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An ethical analysis of divergent clinical approaches to the application of genetic testing for autism and schizophrenia

E. Morris<sup>1,2</sup>, M. O'Donovan<sup>3</sup>, A. Virani,<sup>2,4</sup> J. Austin<sup>1,2</sup>

<sup>1</sup>University of British Columbia, Department of Psychiatry, Vancouver, BC

<sup>2</sup>University of British Columbia, Department of Medical Genetics, Vancouver, BC

<sup>3</sup>Cardiff University, Division of Psychological Medicine and Clinical Neurosciences, Cardiff, Wales

<sup>4</sup>Provincial Health Services Authority of BC, Ethics Service, Vancouver, BC

Corresponding Author:

Jehannine Austin

e-mail: [jehannine.austin@ubc.ca](mailto:jehannine.austin@ubc.ca) (JA)

## **Abstract**

Genetic testing to identify genetic syndromes and copy number variants (CNVs) via whole genome platforms such as chromosome microarray (CMA) or exome sequencing (ES) is routinely performed clinically, and is considered by a variety of organizations and societies to be a “first-tier” test for individuals with developmental delay (DD), intellectual disability (ID), or autism spectrum disorder (ASD). However, in the context of schizophrenia, though CNVs can have a large effect on risk, genetic testing is not typically a part of routine clinical care, and no clinical practice guidelines recommend testing. This raises the question of whether CNV testing *should* be similarly performed for individuals with schizophrenia. Here we consider this proposition in light of the history of genetic testing for ID/DD and ASD, and through the application of an ethical analysis designed to enable robust, accountable and justifiable decision-making. Using a systematic framework and application of relevant bioethical principles (beneficence, non-maleficence, autonomy, and justice), our examination highlights that while CNV testing for the indication of ID has considerable benefits, there is currently insufficient evidence to suggest that overall, the potential harms are outweighed by the potential benefits of CNV testing for the sole indications of schizophrenia or ASD. However, although the application of CNV tests for *children* with ASD or schizophrenia *without* ID/DD is, strictly speaking, off-label use, there may be clinical utility and benefits substantive enough to outweigh the harms. Research is needed to clarify the harms and benefits of testing in pediatric and adult contexts. Given that genetic counseling has demonstrated benefits for schizophrenia, and has the potential to mitigate many of the potential harms from genetic testing, any decisions to implement genetic testing for schizophrenia should involve high-quality evidence-based genetic counseling.

## **Keywords**

Schizophrenia, autism, genetic testing, copy number variants, ethics

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Not applicable

## Introduction

Autism spectrum disorder (ASD), global developmental delay (GDD), intellectual disability (ID), and schizophrenia can all demonstrate complex and heterogeneous etiologies – that is, they can arise from varied combinations of (mostly) common genetic susceptibility variants (Bray & O'Donovan, 2019; Gaugler et al., 2014) and non-genetic/environmental contributors (Dean & Murray, 2005; Karimi, Kamali, Mousavi, & Karahmadi, 2017). While rare genetic variants of large effect (e.g. CNVs) can also contribute, they typically demonstrate incomplete penetrance and variable expressivity (Bray & O'Donovan, 2019; Kushima et al., 2018), and act in concert with other genetic and/or environmental contributors (Grozeva et al., 2012; Tansey et al., 2016). Exceptions to this exist in the context of ID and global DD (GDD) (sometimes in concert with ASD), which can in some cases, occur due to a single fully penetrant causative genetic condition, albeit with considerable phenotypic variability (e.g. Down syndrome, Smith-Magenis syndrome, males with full expansion FMR1 mutations (Fragile X syndrome) etc.).

Various organizations have endorsed routine genomic investigations (i.e. chromosome microarray (CMA) and exome sequencing (ES) as first-tier tests for GDD/ID as well as for ASD (Manning, Hudgins, & Professional Practice and Guidelines Committee, 2010; Miller, D. T. et al., 2010; Schaefer & Mendelsohn, 2013; Silva et al., 2019; Srivastava et al., 2019; Stravropoulos & Shago, Mary, Canadian microarray user group, 2016; Volkmar et al., 2014). In clinical settings, when schizophrenia occurs together with additional characteristics such as ID (i.e. low (<70) IQ that existed prior to the onset of schizophrenia) and/or multiple congenital anomalies, this should prompt suspicion of a genetic syndrome and therefore genetic testing (Miller, D. T. et al., 2010). A diagnosis of schizophrenia alone,

however, is not, to our knowledge, recognized as an indication for CMA or ES by any medical association, and accordingly, these tests are not routinely performed in a clinical setting for the sole indication of schizophrenia.

Therefore, in the absence of GDD/ID (or multiple congenital anomalies), practice guidelines suggest different clinical approaches to CNV testing for ASD and schizophrenia. Here, we consider bioethical principles (beneficence, non-maleficence, autonomy, and justice), in order to evaluate if genetic testing is justified in people with schizophrenia without additional features such as ID, as is currently the recommendation of some guidelines for those with ASD. As well, we seek to disaggregate the benefits of genetic counseling from those of genetic testing for this population. Thorough exploration of these issues is particularly important given the recent proposition that neuropsychiatric CNVs be included in population-based genomic screening programs (Martin et al., 2020) and it has been proposed that CNV testing for schizophrenia could be potentially incorporated into routine clinical care (Baker et al 2014, Costain et al 2013, Finucane et al 2020, Moreno De Luca et al 2018), although the need for more data about the hazards and benefits of such testing has been emphasised (Sullivan and Owen 2020).

In large studies of schizophrenia where known ID is an exclusion criterion, schizophrenia associated CNVs are detected in around 2.5% of cases (Rees et al., 2014). It should be noted that in a high proportion of people with these variants, the CNVs are certainly associated with schizophrenia, but they do not confer particularly large effects on risk of the disorder, and the overall rate for the same CNVs in controls is around 1%. Studies showing much higher detection rates of “pathogenic” CNVs in schizophrenia have often included a broad definition of what is clinically relevant, and can include variants of

unknown significance (VUSs) as well as others that are classified as pathogenic for other phenotypes, but where the evidence for association with schizophrenia is weak. Moreover, some have included individuals with known ID or congenital abnormalities (Costain et al., 2013; Kushima et al., 2018; Singh et al., 2017; Zarrei et al., 2019), characteristics that are known to enrich for CNVs in schizophrenia (Balakrishna & Curtis, 2019; Lowther et al., 2017; Thygesen et al., 2018; Viñas-Jornet et al., 2018). Given that genetic testing is already recommended for individuals *with* ID, there needs to be careful consideration of the utility of expanding testing to all individuals with schizophrenia *without* ID.

Our review of: 1) the historical context, through which the rationale emerged for CNV testing for ASD, as well as the suggestion of CNV testing for schizophrenia, and 2) the application of bioethical principles via ethical analysis, demonstrate that it is ethically justifiable to offer CNV testing for ASD or schizophrenia when individuals present with GDD/ID and/or congenital anomalies. However, incorporating CNV testing into routine clinical practice for individuals with ASD or schizophrenia in the absence of these additional phenotypes has more limited clinical utility, and is therefore less justifiable. Given ASD's enmeshed history with GDD and ID (see Fig.1), its onset in early infancy, and the benefits of identifying certain genetic syndromes in childhood, genetic testing for ASD (even without additional phenotypes) potentially has more benefit than genetic testing in schizophrenia.

<<Insert Figure 1>>

### **Comparing autism/ASD(s) and schizophrenia**

In order to evaluate the core bioethical principles of beneficence, non-maleficence, autonomy, and justice in the context of providing genetic testing for ASD and schizophrenia, differences (and similarities) between these two conditions need to be considered. Specifically, the potential for benefits and harms arising from testing will relate to characteristics of the natural history and etiology of the condition to which it is being applied. Here we consider: 1) age at onset, 2) natural history and 3) genetic architecture.

### ***Age at onset***

While both ASD and schizophrenia are considered to be at least partially neurodevelopmental in origin, they have very different ages at which symptom onset typically occurs. ASD typically emerges in very early childhood (often <18 months)(Ozonoff, Heung, Byrd, Hansen, & Hertz-Picciotto, 2008), while schizophrenia typically emerges between the late teenage years and early adulthood (Hafner et al., 1994). This difference in age at onset results in different potential benefits of testing (see Beneficence), and differences in who will typically be consenting to testing and receiving results (i.e. adults with schizophrenia vs parents of a child with ASD), which could result in different potential harms of testing and impacts on autonomy (see Non-Maleficence and Autonomy).

### ***Natural history***

In addition to differences in age at onset between ASD and schizophrenia, the course of the conditions also differs. Specifically, ASD is persistent from its onset (albeit the associated features can certainly change across the development), while symptoms of schizophrenia can be more episodic – this difference in course can result in different potential harms of genetic testing (see Non-Maleficence).

## ***Genetic architecture***

Finally, there may be differences in genetic architecture between ASD and schizophrenia. No single genetic variation is known to result in ASD in a fully penetrant manner, but there are a number of fully penetrant genetic syndromes which invariably result in GDD or ID, often in conjunction with ASD or “autistic features” (Kaufmann et al., 2017; Klein-Tasman, Phillips, Lord, Mervis, & Gallo, 2009; Laje et al., 2010; Parisi, Di Filippo, & Roccella, 2015; Rumsey et al., 2014) and the distinction between ASD and GDD/ID in such cases is often complex (Fig.1) (Thurm, Farmer, Salzman, Lord, & Bishop, 2019). In contrast, to date, no instances of schizophrenia or ASD (without GDD/ID) have yet been comprehensively explained by a single genetic variation (e.g. a dominant, recessive or X-linked condition). However, a caveat here is that schizophrenia emerges later in life than ASD. Given genetic syndromes are phenotyped most extensively for manifestations that occur early on in life, and that it is challenging to diagnose schizophrenia in people with severe ID, it may be that just as in ASD, strong relationships between genetic syndromes and schizophrenia do exist, but have not yet been recognized.

<<Insert Table 1>>

Importantly, though rare CNVs which confer susceptibility to neuropsychiatric conditions (e.g. 22q11.2 deletion or 16p11.2 deletions) are considered pathogenic, and occur in some cases of schizophrenia or ASD, they are neither fully penetrant for, nor sufficient to explain the presence of the schizophrenia or ASD phenotype.

## **Applying bioethical analysis in relation to CMA testing in the context of ASD and Schizophrenia**



Ethical analysis, using a systematic framework and application of relevant ethical principles, enables robust, accountable and justifiable decision-making. The following analysis is based on the work of (Jonsen, Siegler, & Winslade, 2002) and utilizes the core bioethical principles outlined in Beauchamp & Childress's work both of which are widely recognized as foundational works in bioethical decision making.

### ***Beneficence***

Beneficence refers to promoting welfare of others, and in medicine, all clinicians have a duty to engage in actions that they believe are in the best interest of a patient's welfare (Kinsinger, 2009).

The evidence that genetic *counseling* can be beneficial for people with conditions like ASD and schizophrenia, and their families (Griesi-Oliveira & Sertié, 2017; Inglis, Koehn, McGillivray, Stewart, & Austin, 2015; McMahon, Baty, & Botkin, 2006; Moldovan, Pinteá, & Austin, 2017; Semaka & Austin, 2019) is sometimes assumed to provide evidence that genetic *testing* is beneficial - indeed conceptually, genetic counseling and genetic testing are often conflated in the broader medical literature (Austin, 2019). Common assumptions, for example, are that genetic testing is required for access to genetic counseling services, and that positive outcomes are dependent on communication of test based risk information (Gershon & Alliey-Rodriguez, 2013; Moreno-De-Luca, Ross, & Ross, 2018); both assumptions are false. While genetic counseling can incorporate genetic testing and risk communication, it is neither defined by, nor limited to these activities (National Society of Genetic Counselors' Definition Task Force et al., 2006). Indeed, genetic counseling in the absence of any genetic testing, both for ASD and for schizophrenia has demonstrated value (e.g. increased empowerment and illness management self-efficacy)(Austin, 2019; Costain

et al., 2014; Hippman et al., 2016; Inglis et al., 2015; McMahon et al., 2006). Similarly, genetic counseling for psychiatric disorders has demonstrated value even without communication about risk for recurrence (Borle, Morris, Inglis, & Austin, 2018).

While genetic *testing* is not required in order for benefits to be achieved from genetic *counseling* in the context of ASD or schizophrenia, testing can provide additional benefits when it:

- 1) provides a causal explanation for the neurodevelopmental/psychiatric condition,
- 2) informs detection and management of associated non-psychiatric/physical phenotypes,
- 3) allows more accurate assessment of risk for recurrence of the neurodevelopmental/psychiatric condition in family members, and/or
- 4) provides information on the prognosis and management of the neurodevelopmental/psychiatric condition itself, or additional neurodevelopmental comorbidities.

In the following sections, we explore the capacity of CNV testing to provide these outcomes in the context of ASD and schizophrenia (summarized in Table 2).

<<Insert Table 2>>

#### *Providing a causal explanation of neurodevelopmental/psychiatric condition*

Genetic testing has the potential to identify variants that explain GDD/ID phenotypes, and that - in the context of a constellation of features that together comprise a genetic syndrome (e.g. full mutations males with Fragile X syndrome, Cornelia de Lange

syndrome, Williams syndrome) - may also be *associated with* autistic features or other psychiatric problems.

Parents of children with ASD with GDD/ID report that receiving molecular confirmation of a genetic syndrome can provide benefit for the family, separate from medical management implications (Hayeems, Babul-Hirji, Hoang, Weksberg, & Shuman, 2016) - in that it can help them to accept their child's GDD/ID and ASD, acknowledge that it is "permanent" and "beyond their control", and mitigate feelings of guilt (Reiff et al., 2015). The molecular confirmation of a genetic syndrome in individuals with schizophrenia and GDD/ID and/or congenital anomalies also been perceived by patients and providers to help with explaining the "complex medical history" (Costain, Chow, Ray, & Bassett, 2012; Kraus et al., 2018).

For individuals who have either ASD or schizophrenia *without* GDD/ID or other features that raise suspicion of a genetic syndrome (e.g. multiple congenital anomalies), CNV testing is less likely to identify a rare genetic syndrome or a susceptibility CNV (Ho et al., 2016; Lowther et al., 2017; Munnich et al., 2019; Tammimies et al., 2015). Indeed, the utility of applying genetic testing in ASD when there is no GDD/ID has previously been questioned (Barton et al., 2018; Chodirker & Chudley, 2008). On the other hand, although genetic testing cannot provide a complete causal explanation for ASD or schizophrenia, it has been suggested that CNV testing could still help families with understanding of these conditions by identifying/labelling a genetic contributor (Finucane, Brenda M., Myers, Martin, & Ledbetter, 2020) (e.g. a susceptibility CNV). However, embarking on genetic testing is not without harms (see Non-maleficence), and many of the same benefits can be achieved without genetic testing by helping families understand neuropsychiatric

disorders and the role of genetic contributors through psychiatric genetic counseling (the benefits of which have been demonstrated (Hippman et al., 2016; Inglis et al., 2015; Semaka & Austin, 2019)). Indeed, the importance of high quality, evidence-based genetic counseling when considering CNV testing for ASD or schizophrenia is highlighted by the need to ensure families understand that although genetic testing may provide a complete explanation for why an individual has a *genetic syndrome*, it cannot, on its own, provide a comprehensive explanation for why the individual has all of *the specific phenotypic features (such as schizophrenia)* associated with the syndrome.

#### *Informing medical management of associated non-psychiatric/physical phenotypes*

Since ASD and GDD/ID emerge during childhood, the identification of an underlying genetic syndrome can sometimes allow for the provision of anticipatory and proactive care for other, physical manifestations of the syndrome (Vorstman et al., 2017) (e.g. cardiac and renal monitoring in the context of Kleefstra (Willemsen et al., 2011) or Williams syndrome (Committee on Genetics, 2001)). Since schizophrenia typically emerges during adulthood, the most well understood major physical manifestations associated with a CNV (e.g. tetralogy of fallot in 22q11.2 deletions) should generally have been detected prior to onset of psychiatric symptoms. Further, clinical recommendations for management of physical issues in adult populations with a CNV are very limited (e.g. calcium monitoring in 22q11.2 deletion (Fung et al., 2015)). Therefore, it follows that there is the potential for greater benefit from applying CNV testing among younger cohorts (e.g. patients with *childhood onset* schizophrenia (Ahn et al., 2014). Of note, most cases of childhood onset schizophrenia often co-occur with ASD and/or other DDs (Rapoport, Chavez, Greenstein, Addington, &

Gogtay, 2009) and when these features are present, routine use of CMA testing is already established – at least in North America. However, we should note two caveats here. First, the early manifestations of CNVs, including their effects on cognitive ability, may be missed, particularly in socio-economically disadvantaged families that are over-represented in those with schizophrenia. Moreover, the characterization of CNV syndromes has focussed on medical manifestations that occur during childhood/adolescence, but much less is known about those that may emerge in later life.

*Enabling accurate recurrence risk estimation of the neurodevelopmental or psychiatric condition*

Identifying a genetic syndrome that is fully penetrant for GDD/ID can help substantially with estimating chances of recurrence for the same syndrome in relatives (Herman et al., 2007; Schaefer, Mendelsohn, & Professional Practice and, Guidelines Committee, 2008). For example, if an individual's GDD/ID is attributable to a fully penetrant dominant syndrome that occurred *de novo* (e.g Williams Syndrome), chances for recurrence of GDD/ID in other relatives is usually estimated to be no greater than general population risks (with the caveat of the rare possibility of germ-line mosaicism). However, when ASD or schizophrenia occurs outside of the context of GDD/ID, recurrence estimates are typically based on a detailed 3-generation family history (Austin, 2019; Borle et al., 2018), and the value of genomic data for predicting risk for these disorders is quite different. Given an affected family member with a relevant CNV, the probability of another family member carrying the same CNV can be determined with a high degree of certainty (e.g. a 50% chance for a child to inherit the same CNV from an affected parent), and from

that, the probability of recurrence of ASD or schizophrenia in those carriers can be estimated using Bayesian statistics, albeit with large confidence intervals. These issues require careful genetic counseling to ensure that psychiatric illness is not regarded as an inevitability for family members without current psychiatric problems in whom CNVs are detected.

The probability of recurrence of ASD or schizophrenia in family members who test *negative* for the CNV is very hard to estimate accurately. Even in individuals with a higher penetrance CNVs such as 22q11.2 deletion, or 16p11.2 (proximal) deletion, other genetic and environmental factors still contribute to the development of schizophrenia or ASD (Rosenfeld et al., 2009; Tansey et al., 2016). Family members without the CNV can then still be expected to have elevated liability (genetic and possibly environmental) for schizophrenia or ASD. Thus, in these cases, genetic counseling to evaluate the CNV in light of the family history is needed to ensure risk estimates are as accurate as possible and to facilitate discussions with families about the limitations of these estimates, and of cascade testing for the CNV. Similarly, when

*Providing information on the prognosis and treatment of the neurodevelopmental/psychiatric condition*

When a genetic syndrome is uncovered during childhood, the accumulated clinical knowledge about its natural history can provide a better understanding of the syndrome-specific psychiatric and behavioural features and neurodevelopmental delay (Oliver, Berg, Moss, Arron, & Burbidge, 2011) (e.g. repetitive self-injurious behaviour associated with Smith-Magenis Syndrome (Finucane, Brenda, Haines Dirrigl, & Simon, 2001), food-related

obsessions observed in Prader-Willi Syndrome (Holland et al., 2003), or lack of social boundaries and inhibition observed in William Syndrome (Klein-Tasman et al., 2009)). Identifying a genetic syndrome during childhood can also provide a better sense of neurodevelopmental prognosis, which can, in turn, allow for mitigation of “unrealistic expectations” for the child (which parents perceive to be a benefit) and/or providing or planning for future supports (Baker, Raymond, & Bass, 2012; Nag, Hoxmark, & Naerland, 2019; Reiff et al., 2015).

While many treatments and management strategies are generally applicable to broad groups of people with childhood neurodevelopmental conditions, some syndrome-specific approaches to treatment are emerging (Vorstman et al., 2017). For example, in Prader Willi syndrome, growth hormone therapy has been suggested to help with not only obesity/food seeking, but can also potentially help address cognitive and behavioural issues (Grugni, Sartorio, & Crinò, 2016). In Smith-Magenis syndrome, the use of melatonin and beta-antagonists can help address some of the sleep and behavioural issues associated with the condition (Poisson et al., 2015).

However, in schizophrenia, the detection of a contributory variant has little implication for treatment, severity, or prognosis, which are generally indistinguishable between those with and without the susceptibility CNV (Bassett & Chow, 2008; Gothelf et al., 1999). Though there have been suggestions to avoid certain psychotropic medications for individuals with 22q11.2 deletions (due to increased risk for seizure (Baker, Costain, Fung, & Bassett, 2014)) there is not compelling evidence to alter psychotropic medication solely based on the presence of a CNV (Dori, Green, Weizman, & Gothelf, 2017). To our knowledge, there is also little evidence for the value of adjunctive treatments for

schizophrenia based on the presence of a CNV, although it should be acknowledged research here is sparse. For example, while there are very preliminary reports of potential interventions (e.g. Omega-3 supplementation for reducing *conversion to psychosis* in patients with 22q11.2 deletion syndrome (Armando et al., 2020)), there is *no evidence* of benefit, especially for those with the syndrome in whom schizophrenia is already established. Similarly, anecdotal reports of behaviour improvement in children have led to some suggestions about the possibility that magnesium supplements may potentially offer benefit in the context of 15q11.2 BP1-BP2 deletion, but there is no suggestion of benefit for schizophrenia (Butler, 2019; Sullivan & Owen, 2020).

### ***Non-maleficence***

Non-maleficence refers to ensuring actions, interventions, or services do not harm the individual. Here, we first compare the potential harms that may arise from 1) identifying a pathogenic variant, 2) failing to identify a pathogenic variant, and 3) identifying a variant of uncertain significance (VUS) in the context of CNV testing for ASD and schizophrenia. Then, we examine the potential harms associated with providing genetic testing to parents of a child with ASD, as compared with providing them to an autonomous individual with schizophrenia themselves (Summarized in Table 2).

#### *Identifying a pathogenic variant*

As described under “Beneficence”, above, for some parents of children with GDD/ID and/or ASD, a genetic diagnosis is seen as an indicator of the “permanence” of a child’s condition – which some see as a benefit. In the context of schizophrenia, where symptoms can be episodic, and full recovery is possible, the potential for a genetic diagnosis to result in families accepting active illness as a permanent state is quite problematic (Kronfeldner,



2009), and would also need to be addressed through the provision of thorough counseling (Austin, 2019).

#### *Failing to detect a pathogenic variant*

In families with GDD/ID or ASD where no pathogenic variant is detected, families often feel that genetics has been “ruled out” as a cause, even when genetic counselling has been provided to explain the limitations of genetic testing (Hayeems et al., 2016; Reiff et al., 2015); this can lead to over attribution of the role of family environmental factors, which in turn can lead to increased parental guilt. It is likely that the same would be true in families with schizophrenia (Miller, R. & Mason, 2005).

#### *Identifying a variant of uncertain significance (VUS)*

Data from non-psychiatric settings (e.g. cancer, cardiology) show that patients often misunderstand VUSs, develop healthcare provider distrust, and experience feelings of fear, stress, helplessness, and persistent distress when a VUS is identified (Makhnoon, Garrett, Burke, Bowen, & Shirts, 2019; O'Neill et al., 2009). Other studies have demonstrated that healthcare providers (including physicians) erroneously use VUSs to guide medical management in both cardiac and cancer settings (e.g. prophylactic mastectomy based on the presence of a VUS, or cessation of cardiac screening/surveillance in family members of someone with a cardiac condition that is suspected to be genetic if they do not have the affected relative's VUS) (Ackerman, 2015; Turner, Rao, Morgan, Vnencak-Jones, & Wiesner, 2019). Given that most VUSs are eventually reclassified as benign (Mersch et al., 2018; Slavin, Manjarrez, Pritchard, Gray, & Weitzel, 2019; Turner et al., 2019), the use of the presence or absence of a VUS to guide clinical decisions has the potential to create harm both for the individual and the system (Hoffman-Andrews, 2018).

While in the context of GDD/ID, parental testing can - at least in some cases - help inform interpretation of the pathogenicity of a VUS (Kearney et al., 2011) and thus decrease the frequency of a VUS result (Miller, D. T. et al., 2010), this is not possible for schizophrenia or ASD without GDD/ID (e.g. Asperger Syndrome). Specifically, given that fully penetrant variants exist for GDD/ID, there is some rationale to use medical geneticists' clinical judgment (based on the clinical presentation of the individual and the genes contained in the region of the VUS) to upgrade a *de novo* variant to "likely pathogenic", and to downgrade a variant inherited from an unaffected parent to "likely benign" (Kearney et al., 2011). Given there are no known CNVs that are fully penetrant for schizophrenia or ASD, distinguishing a VUS from a variant with reduced penetrance and/or variable expressivity is more challenging than in the GDD/ID setting where at least the possibility of a fully penetrant variant exists (Lu et al., 2007).

*Providing genetic test results to a parent of a child with ASD vs. individual with schizophrenia*

Accumulating evidence suggests that there is a greater potential risk of harm associated with providing genetic test results to individuals with pre-existing psychological/emotional distress and/or psychiatric disorders than for individuals without such a personal history (Almqvist, Brinkman, Wiggins, Hayden, & The Canadian Collaborative Study of, Predictive Testing, 2003; Butow, Lobb, Meiser, Barratt, & Tucker, 2003; Esplen et al., 2013; Hamilton, Lobel, & Moyer, 2009; Meiser & Dunn, 2000; Murakami et al., 2004; van Oostrom et al., 2007; Voorwinden & Jaspers, 2016). When comparing how genetic test results may be delivered for children with ASD and people with schizophrenia, this observation has important potential consequences. Specifically, in ASD, given the typical ages at which children are usually tested, consent for genetic testing is provided by, and results are

delivered to, parents rather than the child. In schizophrenia, it is more likely to be the affected individual who would consent to testing, and receive the results, with concomitant greater potential for a negative impact on psychological outcomes. However, this possible harm must be weighed against the opportunity for greater respect for, and promotion of autonomy for people with the disorder, as we discuss below.

### ***Autonomy***

Autonomy is defined as the right of competent individuals to make informed choices about their medical care. Where individuals do not possess capacity to make a certain decision, their substitute decision makers are tasked with making a decision in the individual's best interest which also accounts for an individual's values, belief system and life circumstances. Testing for some types of genetic conditions (e.g. newborn screening for metabolic disorders) is performed without explicit autonomous informed consent (e.g. through an opt out process), and this is justified because of the time frame in which testing needs to occur and the large magnitude of potential benefit and small amount of potential harm (Kelly, Makarem, & Wasserstein, 2016). The utility of genetic testing for ASD is not generally accepted to meet these criteria, and testing therefore is typically considered to require adequate pre-test counselling and informed consent from substitute decision makers. Despite this, studies indicate that pre-test discussions or counseling for CMA actually only occurs half of the time (Godfrey & Clark, 2014), which suggests that even respect for parental decision-making is often not upheld in cases of ASD testing.

If genetic testing is to be recommended to an individual with schizophrenia, informed consent for the test must be obtained, and that individual (or if relevant, guardian) must have the opportunity to decline to have the test. Adults with schizophrenia

may be at particular risk for autonomy violations given that determining capacity for consent when someone is experiencing an episode of psychosis is complex (Hostiuc, Rusu, Negoii, & Drima, 2018). Moreover, given the fluctuating nature of the disorder, diminished capacity at one point in time does not mean that individuals with schizophrenia cannot consent; rather it means that timing of the discussion is important and should coincide with periods of capacity taking into account an individual's long-term values and consistency of opinion over time (Epstein, 1982). Also of concern is that in some countries such as Canada when an individual is detained under mental health legislation, it is felt that their autonomy and capacity is so compromised by their condition that they are no longer allowed to make certain decisions.

Thus, particular care and attention to the process of providing genetic testing and the communication of results is warranted for people with schizophrenia. Moreover, because the genetic test is unlikely to directly influence treatment, there is a need for very careful consideration of whether, if, and how it should be used.

### ***Justice***

In medicine, justice is a broad term and can relate to both procedural and distributive justice. In this context we focus on the latter, particularly as it results to equity in the provision of services whereby individuals with comparable conditions are treated alike. Therefore, fundamental to considering the issue of discordant clinical approaches to genetic testing for ASD and schizophrenia, from a bioethical principle standpoint, is the question of whether these two conditions can be considered comparable. Since presence of GDD/ID is an indication for genetic testing, the real justice related issue arises when considering approaches to genetic testing in schizophrenia and ASD in individuals *without* GDD/ID and/or congenital anomalies. For example, since CNV testing is currently

recommended in numerous practice guidelines for ASD (even without GDD/ID), one could make an equity-based argument that CNV testing should also be part of routine clinical care for people with schizophrenia (even without GDD/ID) (Baker et al., 2014; Moreno-De-Luca et al., 2018). However, those making such an argument should note that in the context of ASD without GDD/ID, genetic testing is: 1) not supported by the FDA (Webb, Scharf, Spear, Edelmann, & Stroustrup, 2015), and 2) has been met with criticism (Barton et al., 2018; Chodirker & Chudley, 2008). It is therefore not evident that CNV testing should actually be applied to all cases of ASD. Indeed, a recent study shows that genetic testing for ASD is inconsistently applied in clinical practice (Soda et al., 2021). It is important to recall that the rationale for implementing genetic testing for individuals with ASD was shaped by the presence of the GDD/ID as a component of ASD diagnostic criteria (Shaffer & American College of Medical Genetics Professional Practice and, Guidelines Committee, 2005) at that time (Fig 1): CNV testing produces higher detection rates and has the greatest benefit in the presence of GDD/ID (Ho et al., 2016; Munnich et al., 2019; Tammimies et al., 2015). Similarly, when CNV testing is applied in the context of schizophrenia, higher detection rates are also found when individuals also had a diagnosis of ID (Lowther et al., 2017; Thygesen et al., 2018; Viñas-Jornet et al., 2018).

Finally, an equity-based rationale for providing CNV testing for people with schizophrenia is diminished by the difference between ASD and schizophrenia in terms of age at onset. Many of the benefits of detecting a CNV are influenced by the age of the patient, which typically differs between ASD (a childhood onset condition) and schizophrenia (typically an adult-onset condition).

## Conclusion

Examination of the historical relationship of ASD to GDD/ID, the difficulties that exist in distinguishing between ASD and GDD/ID (de Giambattista et al., 2019; Rødgaard, Jensen, Vergnes, Soulières, & Mottron, 2019; Thurm et al., 2019), and age at presentation, explain why genetic testing has been proposed as a first-tier test for ASD but not for schizophrenia. However, ethical analysis suggests there is currently insufficient evidence of clinical utility of CNV testing for the sole indications of schizophrenia or ASD. However, when schizophrenia or ASD present with other features (e.g. ID, or congenital anomalies) CNV testing is warranted as there is a much greater possibility to confirm a genetic syndrome which can provide many benefits (Lowther et al., 2017; Viñas-Jornet et al., 2018).

CNV testing is already indicated for people with GDD/ID or multiple congenital anomalies (in both children and adults) under current clinical practice guidelines. However, the clinical utility and benefits of CNV testing for the sole indication of schizophrenia are not clear, and the potential harms are not, at present, convincingly outweighed by benefits (see Table 2). We therefore propose that clinical CNV testing remains reserved for individuals with schizophrenia who have additional features (ID, congenital anomalies) until more research has clarified the harms and benefits of testing. Similar considerations apply to variants detected by exome sequencing where there is a much higher likelihood of incidental or secondary findings (Rego et al., 2018). Given emerging enthusiasm for genetic testing, including testing provided by direct to consumer companies, such research is urgently needed.

While the application of CNV tests for *children* with ASD or schizophrenia *without* GDD or ID is, strictly speaking, off-label use (Webb et al., 2015), there may be clinical utility and benefits substantive enough to outweigh the harms associated with failing to identify a pathogenic variant, or identifying a VUS as there is more opportunity for the detection of accompanying physical and co-morbid neuro-developmental disorders and proactive care. It is interesting to note however, that the recent guideline from the American College of Genetics and Genomics about the use of whole genome or exome sequencing in pediatric settings focuses on ID and congenital anomalies, and omits “isolated ASD” from consideration (Manickam et al., 2021). It is important to note that while we recognise that the medical needs of adults with schizophrenia are often neglected (Lambert & Newcomer, 2009; Wey, Loh, Doss, Abu Bakar, & Kisely, 2016), and that more thorough medical management and assessment overall is needed. However, screening for CNVs and indeed other forms of genetic testing, is not necessarily an appropriate or effective way for making up for those shortcomings, particularly in the light of the high rates of physical comorbidities in people with schizophrenia who are not carriers of CNVs.

It is also informative to consider the use of CNV testing in populations of people with ASD and schizophrenia in light of suggestions of including neuropsychiatric CNVs in population-based screening programs (Martin et al., 2020). Population-based screening is driven by a set of well-established principles (Wilson, Jungner, & World, 1968) that have evolved with advances in genetic technology (Andermann, Anne, Blancquaert, Beauchamp, & Déry, 2008). At its core, the ethical implementation of a genetic population screening program requires that:

- the overall benefits of screening outweigh the potential harms, and

- the natural history of the condition and/or “gene carriers” is adequately understood (Andermann, A., Blancquaert, Beauchamp, & Costea, 2011).

With regard to these requirements, first - as discussed above - our exploration of the issues suggests that there is currently not sufficient evidence that benefits of identifying a susceptibility CNV outweigh the harms. Second, since CNV testing is typically performed through whole genome platforms (e.g. CMA), many of the variants that are identified are poorly understood and/or confer only a small effect on risk for schizophrenia. For example, while the natural history of 22q11.2 deletion syndrome is relatively well understood, and confers a large effect on risk for schizophrenia, many of the other CNVs associated with schizophrenia are less well characterized, with clinical significance of some CNVs debated and reclassified over time, and/or often associated with small effect sizes (Chang et al., 2016).

Many of the potential harms associated with CNV testing for schizophrenia could be mitigated by providing testing in a patient-centered and evidence-based manner (i.e. in the context of a genetic counseling protocol (Austin, 2019)); however, further studies on patient reported- and clinical outcomes, and financial costs associated with CNV testing for the indication of schizophrenia are needed before making recommendations to expand CNV testing to all patients with schizophrenia.

Finally, the framework we applied here to analyze approaches to genetic testing could be applied to other situations where there are not clearly established recommendations or differing views on the utility of genetic testing for particular populations.

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## References

Abdul-Rahman, O. A., & Hudgins, L. (2006). The diagnostic utility of a genetics evaluation in children with pervasive developmental disorders. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, 8(1), 50-54. doi:00125817-200601000-00007

[pii]

Ackerman, M. J. (2015). Genetic purgatory and the cardiac channelopathies: Exposing the variants of uncertain/unknown significance issue. *Heart Rhythm*, 12(11), 2325-2331. doi:10.1016/j.hrthm.2015.07.002 [doi]

Ahn, K., Gotay, N., Andersen, T. M., Anvari, A. A., Gochman, P., Lee, Y., . . . Rapoport, J. L. (2014). High rate of disease-related copy number variations in childhood onset schizophrenia. *Molecular Psychiatry*, 19(5), 568-572. doi:10.1038/mp.2013.59 [doi]

Almqvist, E. W., Brinkman, R. R., Wiggins, S., Hayden, M. R., & The Canadian Collaborative Study of, Predictive Testing. (2003). Psychological consequences and predictors of adverse events in the first 5 years after predictive testing for huntington's disease. *Clinical Genetics*, 64(4), 300-309. doi:10.1034/j.1399-0004.2003.00157.x

Andermann, A., Blancquaert, I., Beauchamp, S., & Costea, I. (2011). Guiding policy decisions for genetic screening: Developing a systematic and transparent approach. *Public Health Genomics*, 14(1), 9-16. doi:10.1159/000272898 [doi]

- Andermann, A., Blancquaert, I., Beauchamp, S., & Déry, V. (2008). Revisiting wilson and jungner in the genomic age: A review of screening criteria over the past 40 years. *Bulletin of the World Health Organization*, 86(4), 317-319. doi:10.2471/blt.07.050112
- Armando, M., Ciampoli, M., Padula, M. C., Amminger, P., De Crescenzo, F., Maeder, J., . . . Papaleo, F. (2020). Favorable effects of omega-3 polyunsaturated fatty acids in attentional control and conversion rate to psychosis in 22q11.2 deletion syndrome. *Neuropharmacology*, 168, 107995. doi:S0028-3908(20)30061-7 [pii]
- Austin, J. C. (2019). Evidence-based genetic counseling for psychiatric disorders: A road map. *Cold Spring Harbor Perspectives in Medicine*, doi:a036608 [pii]
- Baker, K., Costain, G., Fung, W. L., & Bassett, A. S. (2014). Chromosomal microarray analysis- a routine clinical genetic test for patients with schizophrenia. *The Lancet.Psychiatry*, 1(5), 329-331. doi:10.1016/S2215-0366(14)70308-6 [doi]
- Baker, K., Raymond, F. L., & Bass, N. (2012). Genetic investigation for adults with intellectual disability: Opportunities and challenges. *Current Opinion in Neurology*, 25(2), 150-158. doi:10.1097/WCO.0b013e328351820e [doi]
- Balakrishna, T., & Curtis, D. (2019). Assessment of potential clinical role for exome sequencing in schizophrenia. *Schizophrenia Bulletin*, doi:sbz057 [pii]
- Baldwin, E. L., Lee, J., Blake, D. M., Bunke, B. P., Alexander, C. R., Kogan, A. L., . . . Martin, C. L. (2008). Enhanced detection of clinically relevant genomic imbalances using a targeted

plus whole genome oligonucleotide microarray. *Genetics in Medicine*, 10, 415.

Retrieved from <https://doi.org/10.1097/GIM.0b013e318177015c>

Barton, K. S., Tabor, H. K., Starks, H., Garrison, N. A., Laurino, M., & Burke, W. (2018). Pathways from autism spectrum disorder diagnosis to genetic testing. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, 20(7), 737-744. doi:10.1038/gim.2017.166

Bassett, A. S., & Chow, E. W. C. (2008). Schizophrenia and 22q11.2 deletion syndrome. *Current Psychiatry Reports*, 10(2), 148-157. doi:10.1007/s11920-008-0026-1

Borg, I., Delhanty, J. D., & Baraitser, M. (1995). Detection of hemizyosity at the elastin locus by FISH analysis as a diagnostic test in both classical and atypical cases of williams syndrome. *Journal of Medical Genetics*, 32(9), 692-696. doi:10.1136/jmg.32.9.692 [doi]

Borle, K., Morris, E., Inglis, A., & Austin, J. (2018). Risk communication in genetic counseling: Exploring uptake and perception of recurrence numbers, and their impact on patient outcomes. *Clinical Genetics*, 94(2), 239-245. doi:10.1111/cge.13379 [doi]

Bray, N. J., & O'Donovan, M.,C. (2019). The genetics of neuropsychiatric disorders. *Brain and Neuroscience Advances*, 2, 10.1177/2398212818799271. doi:10.1177/2398212818799271

Bryson, S. E., Clark, B. S., & Smith, I. M. (1988). First report of a canadian epidemiological study of autistic syndromes. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 29(4), 433-445. doi:10.1111/j.1469-7610.1988.tb00735.x [doi]

- Butler, M. G. (2019). Magnesium supplement and the 15q11.2 BP1-BP2 microdeletion (burnside-butler) syndrome: A potential treatment? *International Journal of Molecular Sciences*, 20(12), 2914. doi:10.3390/ijms20122914
- Butow, P. N., Lobb, E. A., Meiser, B., Barratt, A., & Tucker, K. M. (2003). Psychological outcomes and risk perception after genetic testing and counselling in breast cancer: A systematic review. *The Medical Journal of Australia*, 178(2), 77-81. doi:but10729\_fm [pii]
- Chang, H., Li, L., Peng, T., Li, M., Gao, L., & Xiao, X. (2016). Replication analyses of four chromosomal deletions with schizophrenia via independent large-scale meta-analyses. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 171(8), 1161-1169. doi:10.1002/ajmg.b.32502
- Chodirker, B. N., & Chudley, A. E. (2008). Routine genetic testing for asperger syndrome. *Genetics in Medicine*, 10, 843. Retrieved from <https://doi.org/10.1097/GIM.0b013e31818b0c76>
- Committee on Genetics. (2001). American academy of pediatrics: Health care supervision for children with williams syndrome. *Pediatrics*, 107(5), 1192-1204.
- Costain, G., Chow, E. W., Ray, P. N., & Bassett, A. S. (2012). Caregiver and adult patient perspectives on the importance of a diagnosis of 22q11.2 deletion syndrome. *Journal of Intellectual Disability Research : JIDR*, 56(6), 641-651. doi:10.1111/j.1365-2788.2011.01510.x [doi]

- Costain, G., Lionel, A. C., Merico, D., Forsythe, P., Russell, K., Lowther, C., . . . Bassett, A. S. (2013). Pathogenic rare copy number variants in community-based schizophrenia suggest a potential role for clinical microarrays. *Human Molecular Genetics, 22*(22), 4485-4501. doi:10.1093/hmg/ddt297 [doi]
- Costain, G., Esplen, M. J., Toner, B., Scherer, S. W., Meschino, W. S., Hodgkinson, K. A., & Bassett, A. S. (2014). Evaluating genetic counseling for individuals with schizophrenia in the molecular age. *Schizophrenia Bulletin, 40*(1), 78-87. doi:10.1093/schbul/sbs138 [doi]
- de Giambattista, C., Ventura, P., Trerotoli, P., Margari, M., Palumbi, R., & Margari, L. (2019). Subtyping the autism spectrum disorder: Comparison of children with high functioning autism and asperger syndrome. *Journal of Autism and Developmental Disorders, 49*(1), 138-150. doi:10.1007/s10803-018-3689-4
- Dean, K., & Murray, R. M. (2005). Environmental risk factors for psychosis. *Dialogues in Clinical Neuroscience, 7*(1), 69-80. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/16060597>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181718/>
- Dori, N., Green, T., Weizman, A., & Gothelf, D. (2017). The effectiveness and safety of antipsychotic and antidepressant medications in individuals with 22q11.2 deletion syndrome. *Journal of Child and Adolescent Psychopharmacology, 27*(1), 83-90. doi:10.1089/cap.2014.0075 [doi]

Epstein, L. I. (1982). Clinical ethics: A practical approach to ethical decisions in clinical medicine. *Journal of Legal Medicine*, 3(3), 490-495. doi:10.1080/01947648209513363

Esplen, M. J., Cappelli, M., Wong, J., Bottorff, J. L., Hunter, J., Carroll, J., . . . Meschino, W. (2013). Development and validation of a brief screening instrument for psychosocial risk associated with genetic testing: A pan-canadian cohort study. *BMJ Open*, 3(3), 10.1136/bmjopen-002227. doi:10.1136/bmjopen-2012-002227 [doi]

Evaluation of automatic class III designation (de novo) summaries. (2019, Sep 30,). *US Official News*

Finucane, B. M., Myers, S. M., Martin, C. L., & Ledbetter, D. H. (2020). Long overdue: Including adults with brain disorders in precision health initiatives. *Current Opinion in Genetics & Development*, 65, 47-52. doi:<https://doi.org/10.1016/j.gde.2020.05.001>

Finucane, B., Haines Dirrigl, K., & Simon, E. W. (2001). Characterization of self-injurious behaviors in children and adults with smith-magenis syndrome. *American Journal on Mental Retardation*, 106(1), 52-58. doi:10.1352/0895-8017(2001)1062.0.CO;2

Flint, J., Wilkie, A. O., Buckle, V. J., Winter, R. M., Holland, A. J., & McDermid, H. E. (1995). The detection of subtelomeric chromosomal rearrangements in idiopathic mental retardation. *Nature Genetics*, 9(2), 132-140. doi:10.1038/ng0295-132 [doi]

Fung, W. L., Butcher, N. J., Costain, G., Andrade, D. M., Boot, E., Chow, E. W., . . . Bassett, A. S. (2015). Practical guidelines for managing adults with 22q11.2 deletion syndrome.

*Genetics in Medicine : Official Journal of the American College of Medical Genetics*, 17(8), 599-609. doi:10.1038/gim.2014.175 [doi]

Gaugler, T., Klei, L., Sanders, S. J., Bodea, C. A., Goldberg, A. P., Lee, A. B., . . . Buxbaum, J. D. (2014). Most genetic risk for autism resides with common variation. *Nature Genetics*, 46, 881. Retrieved from <https://doi.org/10.1038/ng.3039>

Gersh, M., Grady, D., Rojas, K., Lovett, M., Moyzis, R., & Overhauser, J. (1997). Development of diagnostic tools for the analysis of 5p deletions using interphase FISH. *Cytogenetics and Cell Genetics*, 77(3-4), 246-251. doi:10.1159/000134586 [doi]

Gershon, E. S., & Alliey-Rodriguez, N. (2013). New ethical issues for genetic counseling in common mental disorders. *The American Journal of Psychiatry*, 170(9), 968-976. doi:10.1176/appi.ajp.2013.12121558 [doi]

Godfrey, E., & Clark, P. (2014). Developing standards for chromosomal microarray testing counselling in paediatrics. *Acta Paediatrica*, 103(6), 574-577. doi:10.1111/apa.12601

Gothelf, D., Frisch, A., Munitz, H., Rockah, R., Laufer, N., Mozes, T., . . . Frydman, M. (1999). Clinical characteristics of schizophrenia associated with velo-cardio-facial syndrome. *Schizophrenia Research*, 35(2), 105-112. doi:S0920-9964(98)00114-5 [pii]

Griesi-Oliveira, K., & Sertié, A. L. (2017). Autism spectrum disorders: An updated guide for genetic counseling. *Einstein (Sao Paulo, Brazil)*, 15(2), 233-238. doi:10.1590/S1679-45082017RB4020



- Grozeva, D., Conrad, D. F., Barnes, C. P., Hurles, M., Owen, M. J., O'Donovan, M. C., . . . WTCCC. (2012). Independent estimation of the frequency of rare CNVs in the UK population confirms their role in schizophrenia. *Schizophrenia Research*, *135*(1-3), 1-7. doi:10.1016/j.schres.2011.11.004 [doi]
- Grugni, G., Sartorio, A., & Crinò, A. (2016). Growth hormone therapy for prader-willi syndrome: Challenges and solutions. *Therapeutics and Clinical Risk Management*, *12*, 873-881. doi:10.2147/TCRM.S70068
- Hafner, H., Maurer, K., Loffler, W., Fatkenheuer, B., an der Heiden, W., Riecher-Rossler, A., . . . Gattaz, W. F. (1994). The epidemiology of early schizophrenia. influence of age and gender on onset and early course. *The British Journal of Psychiatry.Supplement*, *(23)*(23), 29-38.
- Hamilton, J. G., Lobel, M., & Moyer, A. (2009). Emotional distress following genetic testing for hereditary breast and ovarian cancer: A meta-analytic review. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *28*(4), 510-518. doi:10.1037/a0014778
- Hayeems, R. Z., Babul-Hirji, R., Hoang, N., Weksberg, R., & Shuman, C. (2016). Parents' experience with pediatric microarray: Transferrable lessons in the era of genomic counseling. *Journal of Genetic Counseling*, *25*(2), 298-304. doi:10.1007/s10897-015-9871-3 [doi]

Herman, G. E., Henninger, N., Ratliff-Schaub, K., Pastore, M., Fitzgerald, S., & McBride, K. L. (2007). Genetic testing in autism: How much is enough? *Genetics in Medicine*, 9, 268.

Retrieved from <https://doi.org/10.1097/GIM.0b013e31804d683b>

Hippman, C., Ringrose, A., Inglis, A., Cheek, J., Albert, A. Y., Remick, R., . . . Austin, J. C. (2016).

A pilot randomized clinical trial evaluating the impact of genetic counseling for serious mental illnesses. *The Journal of Clinical Psychiatry*, 77(2), 190.

doi:10.4088/JCP.14m09710 [doi]

Ho, K. S., Wassman, E. R., Baxter, A. L., Hensel, C. H., Martin, M. M., Prasad, A., . . . Butler, M. G.

(2016). Chromosomal microarray analysis of consecutive individuals with autism spectrum disorders using an ultra-high resolution chromosomal microarray optimized for neurodevelopmental disorders. *International Journal of Molecular Sciences*, 17(12), 2070. doi:10.3390/ijms17122070

doi:10.3390/ijms17122070

Hoffman-Andrews, L. (2018). The known unknown: The challenges of genetic variants of uncertain significance in clinical practice. *Journal of Law and the Biosciences*, 4(3), 648-

657. doi:10.1093/jlb/lxx038

Holland, A. J., Whittington, J. E., Butler, J., Webb, T., Boer, H., & Clarke, D. (2003).

Behavioural phenotypes associated with specific genetic disorders: Evidence from a population-based study of people with prader-willi syndrome. *Psychological Medicine*, 33(1), 141-153. doi:10.1017/s0033291702006736 [doi]

Hostiuc, S., Rusu, M. C., Negoii, I., & Drima, E. (2018). Testing decision-making competency of schizophrenia participants in clinical trials. A meta-analysis and meta-regression. *BMC Psychiatry*, 18(1), 2. doi:10.1186/s12888-017-1580-z

Inglis, A., Koehn, D., McGillivray, B., Stewart, S. E., & Austin, J. (2015). Evaluating a unique, specialist psychiatric genetic counseling clinic: Uptake and impact. *Clinical Genetics*, 87(3), 218-224. doi:10.1111/cge.12415 [doi]

Jacquemont, M. L., Sanlaville, D., Redon, R., Raoul, O., Cormier-Daire, V., Lyonnet, S., . . . Philippe, A. (2006). Array-based comparative genomic hybridisation identifies high frequency of cryptic chromosomal rearrangements in patients with syndromic autism spectrum disorders. *Journal of Medical Genetics*, 43(11), 843-849. doi:jmg.2006.043166 [pii]

Jonsen, A. R., Siegler, M., & Winslade, W. J. (2002). *Clinical ethics* (5. ed. ed.). New York [u.a.]: McGraw Hill, Medical Publ. Division. Retrieved from [http://bvbr.bib-bvb.de:8991/F?func=service&doc\\_library=BVB01&local\\_base=BVB01&doc\\_number=009878944&sequence=000002&line\\_number=0001&func\\_code=DB\\_RECORDS&service\\_type=MEDIA](http://bvbr.bib-bvb.de:8991/F?func=service&doc_library=BVB01&local_base=BVB01&doc_number=009878944&sequence=000002&line_number=0001&func_code=DB_RECORDS&service_type=MEDIA)

Karimi, P., Kamali, E., Mousavi, S. M., & Karahmadi, M. (2017). Environmental factors influencing the risk of autism. *Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences*, 22, 27. doi:10.4103/1735-1995.200272

Kaufmann, W. E., Kidd, S. A., Andrews, H. F., Budimirovic, D. B., Esler, A., Haas-Givler, B., . . .

Berry-Kravis, E. (2017). Autism spectrum disorder in fragile X syndrome: Cooccurring conditions and current treatment. *Pediatrics*, *139*(Supplement 3), S194-S206.

doi:10.1542/peds.2016-1159F

Kearney, H. M., South, S. T., Wolff, D. J., Lamb, A., Hamosh, A., Rao, K. W., & Working Group of the American College of Medical Genetics. (2011). American college of medical genetics recommendations for the design and performance expectations for clinical genomic copy number microarrays intended for use in the postnatal setting for detection of constitutional abnormalities. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, *13*(7), 676-679. doi:10.1097/GIM.0b013e31822272ac [doi]

Kelly, N., Makarem, D. C., & Wasserstein, M. P. (2016). Screening of newborns for disorders with high benefit-risk ratios should be mandatory. *J Law Med Ethics*, *44*(2), 231-240.

doi:10.1177/1073110516654133

Keser, I., Luleci, G., & Keskin, V. (1998). Cytogenetic studies among mentally retarded children attending to special classes of MEBARAM in antalya province. *11*, 201-203.

Kinsinger, F. S. (2009). Beneficence and the professional's moral imperative. *Journal of Chiropractic Humanities*, *16*(1), 44-46. doi:10.1016/j.echu.2010.02.006

Klein-Tasman, B., Phillips, K. D., Lord, C., Mervis, C. B., & Gallo, F. J. (2009). Overlap with the autism spectrum in young children with williams syndrome. *Journal of Developmental and Behavioral Pediatrics : JDBP*, *30*(4), 289-299. doi:10.1097/DBP.0b013e3181ad1f9a

Knight, S. J., & Flint, J. (2000). Perfect endings: A review of subtelomeric probes and their use in clinical diagnosis. *Journal of Medical Genetics*, 37(6), 401-409.

doi:10.1136/jmg.37.6.401

Knight, S. J., Horsley, S. W., Regan, R., Lawrie, N. M., Maher, E. J., Cardy, D. L., . . . Kearney, L. (1997). Development and clinical application of an innovative fluorescence in situ hybridization technique which detects submicroscopic rearrangements involving telomeres. *European Journal of Human Genetics : EJHG*, 5(1), 1-8.

Kraus, C., Vanicek, T., Weidenauer, A., Khanaqa, T., Stamenkovic, M., Lanzenberger, R., . . .

Kasper, S. (2018). DiGeorge syndrome : Relevance of psychiatric symptoms in undiagnosed adult patients. *Wiener Klinische Wochenschrift*, 130(7-8), 283-287.

doi:10.1007/s00508-018-1335-y

Kronfeldner, M. E. (2009). Genetic determinism and the innate-acquired distinction in medicine. *Medicine Studies*, 1(2), 167-181. doi:10.1007/s12376-009-0014-8

Kushima, I., Aleksic, B., Nakatochi, M., Shimamura, T., Okada, T., Uno, Y., . . . Ozaki, N. (2018).

*Comparative analyses of copy-number variation in autism spectrum disorder and schizophrenia reveal etiological overlap and biological insights*

doi:<https://doi.org/10.1016/j.celrep.2018.08.022>

Laje, G., Morse, R., Richter, W., Ball, J., Pao, M., & Smith, A. C. M. (2010). Autism spectrum features in smith-magenis syndrome. *American Journal of Medical Genetics.Part C, Seminars in Medical Genetics*, 154C(4), 456-462. doi:10.1002/ajmg.c.30275

- Lambert, T. J. R., & Newcomer, J. W. (2009). Are the cardiometabolic complications of schizophrenia still neglected? barriers to care. *Medical Journal of Australia*, 190(4)
- Lauritsen, M., Mors, O., Mortensen, P. B., & Ewald, H. (1999). Infantile autism and associated autosomal chromosome abnormalities: A register-based study and a literature survey. *Journal of Child Psychology and Psychiatry*, 40(3), 335-345. doi:10.1111/1469-7610.00451
- Lemay, J. F., Herbert, A. R., Dewey, D. M., & Innes, A. M. (2003). A rational approach to the child with mental retardation for the paediatrician. *Paediatrics & Child Health*, 8(6), 345-356. doi:10.1093/pch/8.6.345 [doi]
- Lowther, C., Merico, D., Costain, G., Waserman, J., Boyd, K., Noor, A., . . . Bassett, A. S. (2017). Impact of IQ on the diagnostic yield of chromosomal microarray in a community sample of adults with schizophrenia. *Genome Medicine*, 9(1), 105-z. doi:10.1186/s13073-017-0488-z [doi]
- Lu, X., Shaw, C. A., Patel, A., Li, J., Cooper, M. L., Wells, W. R., . . . Ward, P. A. (2007). Clinical implementation of chromosomal microarray analysis: Summary of 2513 postnatal cases. *Plos One*, 2(3), e327. Retrieved from <https://doi.org/10.1371/journal.pone.0000327>
- Makhnoon, S., Garrett, L. T., Burke, W., Bowen, D. J., & Shirts, B. H. (2019). Experiences of patients seeking to participate in variant of uncertain significance reclassification research. *Journal of Community Genetics*, 10(2), 189-196. doi:10.1007/s12687-018-0375-3

- Manikam, K., McClain, M.R., Demmer, L.A., Biswas, S., Kearney, H.M, Malinowski, J.,  
Massingham, L.J., Miller, D., Yu, T.W., Hisma, F.M., and ACMG Board of Directors. (2021)  
Exome and genome sequencing for pediatric patients with congenital anomalies or  
intellectual disability: an evidence based clinical guideline of the American College of  
Medical Genetics and Genomics. *Genetics in Medicine*. Online Early
- Manning, M., Hudgins, L., & Professional Practice and Guidelines Committee. (2010). Array-  
based technology and recommendations for utilization in medical genetics practice for  
detection of chromosomal abnormalities. *Genetics in Medicine : Official Journal of the  
American College of Medical Genetics*, 12(11), 742-745.  
doi:10.1097/GIM.0b013e3181f8baad [doi]
- Martin, C. L., Wain, K. E., Oetjens, M. T., Tolwinski, K., Palen, E., Hare-Harris, A., . . . Ledbetter,  
D. H. (2020). Identification of neuropsychiatric copy number variants in a health care  
system population. *JAMA Psychiatry*, doi:10.1001/jamapsychiatry.2020.2159
- McMahon, W. M., Baty, B. J., & Botkin, J. (2006). Genetic counseling and ethical issues for  
autism. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*,  
142C(1), 52-57. doi:10.1002/ajmg.c.30082 [doi]
- Meiser, B., & Dunn, S. (2000). Psychological impact of genetic testing for huntington's  
disease: An update of the literature. *Journal of Neurology, Neurosurgery, and Psychiatry*,  
69(5), 574-578. doi:10.1136/jnnp.69.5.574

- Mersch, J., Brown, N., Pirzadeh-Miller, S., Mundt, E., Cox, H. C., Brown, K., . . . Ross, T. (2018). Prevalence of variant reclassification following hereditary cancer genetic testing. *Jama*, *320*(12), 1266-1274. doi:10.1001/jama.2018.13152 [doi]
- Miller, D. T., Adam, M. P., Aradhya, S., Biesecker, L. G., Brothman, A. R., Carter, N. P., . . . Ledbetter, D. H. (2010). Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *American Journal of Human Genetics*, *86*(5), 749-764. doi:10.1016/j.ajhg.2010.04.006 [doi]
- Miller, R., & Mason, S. E. (2005). Shame and guilt in first-episode schizophrenia and schizoaffective disorders. *Journal of Contemporary Psychotherapy*, *35*(2), 211-221. doi:10.1007/s10879-005-2701-4
- Moghe, M., Patel, Z. M., Peter, J. J., & Ambani, L. M. (1981). Cytogenetic studies in a selected group of mentally retarded children. *Human Genetics*, *58*(2), 184-187. doi:10.1007/BF00278708
- Moldovan, R., Pintea, S., & Austin, J. (2017). The efficacy of genetic counseling for psychiatric disorders: A meta-analysis. *Journal of Genetic Counseling*, *26*(6), 1341-1347. doi:10.1007/s10897-017-0113-8 [doi]
- Moreno-De-Luca, D., Ross, M. E., & Ross, D. A. (2018). Leveraging the power of genetics to bring precision medicine to psychiatry: Too little of a good thing? *Biological Psychiatry*, *83*(8), e45-e46. doi:10.1016/j.biopsych.2018.02.013



- Munnich, A., Demily, C., Frugere, L., Duwime, C., Malan, V., Barcia, G., . . . Assouline, M. (2019). Impact of on-site clinical genetics consultations on diagnostic rate in children and young adults with autism spectrum disorder. *Molecular Autism, 10*, 33-2. eCollection 2019. doi:10.1186/s13229-019-0284-2 [doi]
- Murakami, Y., Okamura, H., Sugano, K., Yoshida, T., Kazuma, K., Akechi, T., & Uchitomi, Y. (2004). Psychologic distress after disclosure of genetic test results regarding hereditary nonpolyposis colorectal carcinoma. *Cancer, 101*(2), 395-403. doi:10.1002/cncr.20363 [doi]
- Nag, H. E., Hoxmark, L. B., & Naerland, T. (2019). Parental experiences with behavioural problems in smith-magenis syndrome: The need for syndrome-specific competence. *Journal of Intellectual Disabilities : JOID, 23*(3), 359-372. doi:10.1177/1744629519847375 [doi]
- National Society of Genetic Counselors' Definition Task Force, Resta, R., Biesecker, B. B., Bennett, R. L., Blum, S., Hahn, S. E., . . . Williams, J. L. (2006). A new definition of genetic counseling: National society of genetic counselors' task force report. *Journal of Genetic Counseling, 15*(2), 77-83. doi:10.1007/s10897-005-9014-3 [doi]
- Ning, Y., Roschke, A., Smith, A. C. M., Macha, M., Precht, K., Riethman, H., . . . Brown, W. R. A. (1996). A complete set of human telomeric probes and their clinical application. *Nature Genetics, 14*(1), 86-89. doi:10.1038/ng0996-86
- Oliver, C., Berg, K., Moss, J., Arron, K., & Burbidge, C. (2011). Delineation of behavioral phenotypes in genetic syndromes: Characteristics of autism spectrum disorder, affect

and hyperactivity. *Journal of Autism and Developmental Disorders*, 41(8), 1019-1032.  
doi:10.1007/s10803-010-1125-5

O'Neill, S., C., Rini, C., Goldsmith, R. E., Valdimarsdottir, H., Cohen, L. H., & Schwartz, M. D. (2009). Distress among women receiving uninformative BRCA1/2 results: 12-month outcomes. *Psycho-Oncology*, 18(10), 1088-1096. doi:10.1002/pon.1467

Ozonoff, S., Heung, K., Byrd, R., Hansen, R., & Hertz-Picciotto, I. (2008). The onset of autism: Patterns of symptom emergence in the first years of life. *Autism Research : Official Journal of the International Society for Autism Research*, 1(6), 320-328.  
doi:10.1002/aur.53

Parisi, L., Di Filippo, T., & Roccella, M. (2015). Behavioral phenotype and autism spectrum disorders in cornelia de lange syndrome. *Mental Illness*, 7(2), 5988.  
doi:10.4081/mi.2015.5988

Poisson, A., Nicolas, A., Cochat, P., Sanlaville, D., Rigard, C., de Leersnyder, H., . . . Demily, C. (2015). Behavioral disturbance and treatment strategies in smith-magenis syndrome. *Orphanet Journal of Rare Diseases*, 10, 111. doi:10.1186/s13023-015-0330-x

Rapoport, J., Chavez, A., Greenstein, D., Addington, A., & Gogtay, N. (2009). Autism spectrum disorders and childhood-onset schizophrenia: Clinical and biological contributions to a relation revisited. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48(1), 10-18. doi:10.1097/CHI.0b013e31818b1c63

- Rees, E., Walters, J. T., Georgieva, L., Isles, A. R., Chambert, K. D., Richards, A. L., . . . Kirov, G. (2014). Analysis of copy number variations at 15 schizophrenia-associated loci. *The British Journal of Psychiatry : The Journal of Mental Science*, *204*(2), 108-114. doi:10.1192/bjp.bp.113.131052 [doi]
- Rego, S., Dagan-Rosenfeld, O., Zhou, W., Sailani, M. R., Limcaoco, P., Colbert, E., . . . Snyder, M. P. (2018). High-frequency actionable pathogenic exome variants in an average-risk cohort. *Cold Spring Harbor Molecular Case Studies*, *4*(6), a003178. doi: 10.1101/mcs.a003178. Print 2018 Dec. doi:10.1101/mcs.a003178 [doi]
- Reiff, M., Giarelli, E., Bernhardt, B. A., Easley, E., Spinner, N. B., Sankar, P. L., & Mulchandani, S. (2015). Parents' perceptions of the usefulness of chromosomal microarray analysis for children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *45*(10), 3262-3275. doi:10.1007/s10803-015-2489-3 [doi]
- Rødgaard, E., Jensen, K., Vergnes, J., Soulières, I., & Mottron, L. (2019). Temporal changes in effect sizes of studies comparing individuals with and without autism: A meta-analysis. *JAMA Psychiatry*, *76*(11), 1124-1132. doi:10.1001/jamapsychiatry.2019.1956
- Rosenfeld, J. A., Coppinger, J., Bejjani, B. A., Girirajan, S., Eichler, E. E., Shaffer, L. G., & Ballif, B. C. (2009). Speech delays and behavioral problems are the predominant features in individuals with developmental delays and 16p11.2 microdeletions and microduplications. *Journal of Neurodevelopmental Disorders*, *2*(1), 26-38. doi:10.1007/s11689-009-9037-4

- Rumsey, R. K., Rudser, K., Delaney, K., Potegal, M., Whitley, C. B., & Shapiro, E. (2014).  
Acquired autistic behaviors in children with mucopolysaccharidosis type IIIA. *The Journal of Pediatrics*, 164(5), 1147-1151.e1. doi:10.1016/j.jpeds.2014.01.007
- Santos, C. B., Boy, R. T., Santos, J. M., Silva, M. P. S., & Pimentel, M. M. G. (2000).  
Chromosomal investigations in patients with mental retardation and/or congenital malformations. *Genetics and Molecular Biology*, 23, 703-707.
- Schaefer, G. B., & Lutz, R. E. (2006). Diagnostic yield in the clinical genetic evaluation of autism spectrum disorders. *Genetics in Medicine*, 8(9), 549-556.  
doi:10.1097/01.gim.0000237789.98842.f1
- Schaefer, G. B., Mendelsohn, N. J., & Professional Practice and, Guidelines Committee. (2008). Clinical genetics evaluation in identifying the etiology of autism spectrum disorders. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, 10(4), 301-305. doi:10.1097/GIM.0b013e31816b5cc9
- Schaefer, G. B., & Mendelsohn, N. J. (2013). Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genetics in Medicine*, 15, 399. Retrieved from <https://doi.org/10.1038/gim.2013.32>
- Semaka, A., & Austin, J. (2019). Patient perspectives on the process and outcomes of psychiatric genetic counseling: An “Empowering encounter”. *Journal of Genetic Counseling*, 0(0) doi:10.1002/jgc4.1128

- Shaffer, L. G., & American College of Medical Genetics Professional Practice and, Guidelines Committee. (2005). American college of medical genetics guideline on the cytogenetic evaluation of the individual with developmental delay or mental retardation. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, 7(9), 650-654. doi:10.1097/01.gim.0000186545.83160.1e
- Shen, Y., Dies, K. A., Holm, I. A., Bridgemohan, C., Sobeih, M. M., Caronna, E. B., . . . Autism Consortium Clinical Genetics/DNA, Diagnostics Collaboration. (2010). Clinical genetic testing for patients with autism spectrum disorders. *Pediatrics*, 125(4), e727-e735. doi:10.1542/peds.2009-1684
- Silva, M., de Leeuw, N., Mann, K., Schuring-Blom, H., Morgan, S., Giardino, D., . . . Hastings, R. (2019). European guidelines for constitutional cytogenomic analysis. *European Journal of Human Genetics*, 27(1), 1-16. doi:10.1038/s41431-018-0244-x
- Singh, T., Walters, J. T. R., Johnstone, M., Curtis, D., Suvisaari, J., Torniainen, M., . . . Barrett, J. C. (2017). The contribution of rare variants to risk of schizophrenia in individuals with and without intellectual disability. *Nature Genetics*, 49(8), 1167-1173. doi:10.1038/ng.3903 [doi]
- Slavin, T. P., Manjarrez, S., Pritchard, C. C., Gray, S., & Weitzel, J. N. (2019). The effects of genomic germline variant reclassification on clinical cancer care. *Oncotarget*, 10(4), 417-423. doi:10.18632/oncotarget.26501 [doi]
- Soda, T., Pereira, S., Small, B. J., Torgerson, L. N., Muñoz, K. A., Austin, J., . . . Lázaro-Muñoz, G. (2021). Child and adolescent psychiatrists' perceptions of utility and self-rated

knowledge of genetic testing predict usage for autism spectrum disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, doi:10.1016/j.jaac.2021.01.022

South, S. T., Lee, C., Lamb, A. N., Higgins, A. W., Kearney, H. M., & Working Group for the American College of Medical Genetics and Genomics Laboratory Quality Assurance Committee. (2013). ACMG standards and guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: Revision 2013. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, 15(11), 901-909. doi:10.1038/gim.2013.129 [doi]

Srivastava, S., Love-Nichols, J., Dies, K. A., Ledbetter, D. H., Martin, C. L., Chung, W. K., . . . the NDD Exome Scoping Review, Work Group. (2019). Meta-analysis and multidisciplinary consensus statement: Exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. *Genetics in Medicine*, 21(11), 2413-2421. doi:10.1038/s41436-019-0554-6

Stravropoulos, J., & Shago, Mary, Canadian microarray user group. (2016). *CCMG guidelines for genomic Microarray testing*. ().CCMG, Laboratory Practice Committee. Retrieved from [https://www.ccmg-ccgm.org/images/Guidelines/CCMG Guidelines for Genomic Microarray Testing FINAL.pdf](https://www.ccmg-ccgm.org/images/Guidelines/CCMG%20Guidelines%20for%20Genomic%20Microarray%20Testing%20FINAL.pdf)

Sullivan, P. F., & Owen, M. J. (2020). Increasing the clinical psychiatric knowledge base about pathogenic copy number variation. *Ajp*, 177(3), 204-209. doi:10.1176/appi.ajp.2019.19040335

Tammimies, K., Marshall, C. R., Walker, S., Kaur, G., Thiruvahindrapuram, B., Lionel, A. C., . . .

Fernandez, B. A. (2015). Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum

DisorderMolecular diagnostic yield of genetic tests in children with AutismMolecular diagnostic yield of genetic tests in children with autism. *Jama*, *314*(9), 895-903.

doi:10.1001/jama.2015.10078

Tansey, K. E., Rees, E., Linden, D. E., Ripke, S., Chambert, K. D., Moran, J. L., . . . O'Donovan, M.

C. (2016). Common alleles contribute to schizophrenia in CNV carriers. *Molecular Psychiatry*, *21*(8), 1085-1089. doi:10.1038/mp.2015.143

Thurm, A., Farmer, C., Salzman, E., Lord, C., & Bishop, S. (2019). State of the field:

Differentiating intellectual disability from autism spectrum disorder. *Frontiers in Psychiatry*, *10*, 526. Retrieved from

<https://www.frontiersin.org/article/10.3389/fpsy.2019.00526>

Thygesen, J. H., Wolfe, K., McQuillin, A., Viñas-Jornet, M., Baena, N., Brison, N., . . . Vogels, A.

(2018). Neurodevelopmental risk copy number variants in adults with intellectual disabilities and comorbid psychiatric disorders. *British Journal of Psychiatry*, *212*(5), 287-294. doi:10.1192/bjp.2017.65

Turner, S. A., Rao, S. K., Morgan, R. H., Vnencak-Jones, C. L., & Wiesner, G. L. (2019). The

impact of variant classification on the clinical management of hereditary cancer syndromes. *Genetics in Medicine : Official Journal of the American College of Medical*

*Genetics*, *21*(2), 426-430. doi:10.1038/s41436-018-0063-z [doi]

- van Oostrom, I., Meijers-Heijboer, H., Duivenvoorden, H. J., Brocker-Vriends, A. H., van Asperen, C. J., Sijmons, R. H., . . . Tibben, A. (2007). Prognostic factors for hereditary cancer distress six months after BRCA1/2 or HNPCC genetic susceptibility testing. *European Journal of Cancer (Oxford, England : 1990)*, *43*(1), 71-77. doi:S0959-8049(06)00770-2 [pii]
- Viñas-Jornet, M., Esteba-Castillo, S., Baena, N., Ribas-Vidal, N., Ruiz, A., Torrents-Rodas, D., . . . Guitart, M. (2018). High incidence of copy number variants in adults with intellectual disability and co-morbid psychiatric disorders. *Behavior Genetics*, *48*(4), 323-336. doi:10.1007/s10519-018-9902-6
- Volkmar, F., Siegel, M., Woodbury-Smith, M., King, B., McCracken, J., State, M., & American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). (2014). Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(2), 237-257. doi:10.1016/j.jaac.2013.10.013 [doi]
- Voorwinden, J. S., & Jaspers, J. P. (2016). Prognostic factors for distress after genetic testing for hereditary cancer. *Journal of Genetic Counseling*, *25*(3), 495-503. doi:10.1007/s10897-015-9894-9 [doi]
- Vorstman, J. A. S., Parr, J. R., Moreno-De-Luca, D., Anney, R. J. L., Nurnberger, J. I., Jr, & Hallmayer, J. F. (2017). Autism genetics: Opportunities and challenges for clinical translation. *Nature Reviews Genetics*, *18*(6), 362-376. doi:10.1038/nrg.2017.4 [doi]



- Wassink, T. H., Piven, J., & Patil, S. R. (2001). Chromosomal abnormalities in a clinic sample of individuals with autistic disorder. *Psychiatric Genetics*, *11*(2), 57-63.
- Webb, B. D., Scharf, R. J., Spear, E. A., Edelman, L. J., & Stroustrup, A. (2015). Evaluation of the affymetrix CytoScan(®) dx assay for developmental delay. *Expert Review of Molecular Diagnostics*, *15*(2), 185-192. doi:10.1586/14737159.2015.975213
- Wey, M. C., Loh, S., Doss, J. G., Abu Bakar, A. K., & Kisely, S. (2016). The oral health of people with chronic schizophrenia: A neglected public health burden. *Aust N Z J Psychiatry*, *50*(7), 685-694. doi:10.1177/0004867415615947
- Willemsen, M. H., Vulto-van Silfhout, A. T., Nillesen, W. M., Wissink-Lindhout, W., van Bokhoven, H., Philip, N., . . . Kleefstra, T. (2011). *Update on kleeftstra syndrome* doi:10.1159/000335648
- Wilson, J. M. G., Jungner, G., & World, H. O. (1968). *Principles and practice of screening for disease / J. M. G. wilson, G. jungner*. Geneva: World Health Organization; World Health Organization. Retrieved from <https://apps.who.int/iris/handle/10665/37650>
- Yeargin-Allsopp, M., Rice, C., Karapurkar, T., Doernberg, N., Boyle, C., & Murphy, C. (2003). Prevalence of autism in a US metropolitan area. *Jama*, *289*(1), 49-55. doi:10.1001/jama.289.1.49
- Zarrei, M., Burton, C. L., Engchuan, W., Young, E. J., Higginbotham, E. J., MacDonald, J. R., . . . Scherer, S. W. (2019). A large data resource of genomic copy number variation across

neurodevelopmental disorders. *NPJ Genomic Medicine*, 4, 26. doi:10.1038/s41525-019-0098-3

Figure 1

Timeline of the evolution of diagnostic criteria for “autism” and its relationship to developmental delay and/or intellectual disability.

**Development delays (DDs):** defined as delay (prior to age 3) in language (or total lack of language), and/or adaptive functioning. **Global developmental (GDD):** defined as significant delay in 2 or more developmental domains in children under the age of 5 (Srouf & Shevell, 2015) **Intellectual disability (ID):** formerly referred to as mental retardation, typically applied if the criteria for GDD are met after the age of 5

\*(>70%) met criteria for a co-morbid diagnosis of GDD/ID (Bryson, Clark, & Smith, 1988; Yeargin-Allsopp et al., 2003).

Box 1 – Historical overview of the diagnostic criteria and genetic testing in autism

### History of autism diagnosis

The diagnosis of “autism” first appeared in the DSM-III in 1980 as “infantile autism” - a diagnosis that included DDs (e.g. profound delay in or lack of speech, and/or significantly delayed adaptive functioning) as an integral feature of the condition (Bryson et al., 1988).

With the introduction of the DSM IV in 1994, “autism” was officially recognized as a group of disorders (i.e. Autism Spectrum Disorders (ASDs) (rather than a single condition) that encompassed four distinct diagnoses; GDD was an integral component of one (Autistic disorder), but an exclusion criterion for another (Asperger syndrome).

In 2013, with the introduction of the DSM-5, these four separate diagnoses were grouped together again into a single unified diagnosis “Autism Spectrum Disorder” (ASD), for which DDs were no longer a defining feature (Lai et al., 2014). Thus, without additional phenotypic information, it became impossible to determine whether an individual with a diagnosis of ASD had GDD or no

### History of autism genetic testing

The diagnostic criteria for autism have evolved over time, together with ideas about the relationship between DDs and autism/ASD, and simultaneously, genetic testing has advanced (Summarized in Fig.1).

In clinical genetics settings in the 1980’s, when a child presented with DDs, ID or multiple congenital anomalies, cytogenetic investigations (e.g. karyotyping, which microscopically detects large scale copy number variants (>3-5Mb) including aneuploidies and structural rearrangements, testing for Fragile X syndrome) were often performed. Therefore, these investigations were often routinely applied when a child had infantile autism (DSM-III) or autistic disorder (DSM-IV) (Lemay, Herbert, Dewey, & Innes, 2003; Wassink, Piven, & Patil, 2001) (See Fig 1). Under these circumstances, cytogenetic investigations could provide a specific etiological explanation for a child’s delays (e.g. Down syndrome, or Fragile X syndrome) (Keser, Luleci, & Keskin, 1998; Moghe, Patel, Peter, & Ambani, 1981; Santos, Boy, Santos, Silva, & Pimentel, 2000; Wassink et al., 2001).

In the 1990s, fluorescence *in-situ* genomic hybridization (FISH) analyses (which can detect submicroscopic CNVs) began to be implemented clinically to identify genetic syndromes in individuals with DDs or ID (Knight et al., 1997; Ning et al., 1996) *Targeted* FISH testing (using a gene/locus specific probe) was performed when clinical suspicion was high that a patient with GDD/ID had a particular genetic syndrome (e.g. when clinical

features were suggestive of Williams Syndrome) (Borg, Delhanty, & Baraitser, 1995; Gersh et al., 1997); and *subtelomeric* FISH (a less targeted approach) was used for individuals who presented with nonspecific or “idiopathic” DDs/ID phenotypes (Flint et al., 1995; Knight & Flint, 2000).

In 2005, an American College of Medical Genetics (ACMG) practice guideline introduced the use of cytogenetic evaluations (G-banded karyotype and FISH (targeted- or subtelomeric)) as standard of care (Shaffer & American College of Medical Genetics Professional Practice and, Guidelines Committee, 2005). Based on early studies, which reported a 5% diagnostic yield from karyotype and FISH analyses in children with “autism” defined by DSM-III/DSM-II-R criteria (i.e. those with DDs) (Lauritsen, Mors, Mortensen, & Ewald, 1999) the guideline also mentioned the diagnostic utility of the same testing approach for autism when it presents “in association with MR/GDD” (Shaffer & American College of Medical Genetics Professional Practice and, Guidelines Committee, 2005).

By the mid-late 2000s, the field of clinical genetics had embraced CMA in GDD/ID clinical care for its ability to detect submicroscopic CNVs across the entire genome in a single test (Kearney et al., 2011). CMA had the potential to reduce the time lag to reaching a diagnosis for patients with GDD/ID, because it could be applied even prior to the emergence of the full phenotypic presentation that historically would have prompted specific FISH testing for conditions such as Prader-Willi Angelman syndrome, Williams-Beuren syndrome, Potocki-Lupski syndrome, Smith-Magenis syndrome, or Kleeftstra syndrome (Jacquemont et al., 2006; Schaefer & Lutz, 2006). It was for this reason that in 2010, CMA was recommended as a “first-tier test” by the ACMG, Canadian College of Medical Genetics (CCMG), and the European Society of Human Genetics for individuals with “global developmental delay, intellectual disability, or ASDs (DSM-IV)” as well as for those with multiple congenital anomalies (Manning et al., 2010; Silva et al., 2019; Stravropoulos & Shago, Mary, Canadian microarray user group, 2016).

The rationale for including ASDs in this recommendation was based on data showing a detection rate for pathogenic variants of ~10% in this population (Abdul-Rahman & Hudgins, 2006; Baldwin et al., 2008; Lu et al., 2007; Schaefer et al., 2008; Shen et al., 2010). Though Asperger syndrome (i.e. autism without DDs) fell under the DSM-IV’s ASDs umbrella, and was, therefore, technically included when CMA was recommended as a first tier test for ASDs, the utility of CMA for Asperger syndrome has been debated (Chodirker & Chudley, 2008), because the rate with which pathogenic CNVs were detected was often much lower (e.g. 8% for individuals with autistic disorder (i.e. not Asperger syndrome), vs. 0% of individuals with Asperger syndrome (Herman et al., 2007; Shen et al., 2010)) This lower rate with which pathogenic CNVs were detected for Asperger syndrome is thought to be attributable to the absence of DDs from the phenotype (Chodirker & Chudley, 2008; Herman et al., 2007; Jacquemont et al., 2006; Shen et al., 2010) (See Fig 1).

Indeed, studies examining the use of CMA in children with DSM-5 defined ASD have found higher rates of pathogenic CNVs in those with ASD *and* DDs and/or congenital anomalies than in those with ASD alone (Ho et al., 2016; Tammimies et al., 2015). Therefore, the currently available evidence suggests that the diagnostic and clinical utility of CMA testing in children with “autism” is greater in the presence of DDs or ID (Barton et al., 2018; Munnich et al., 2019).

Accordingly, in 2015, when the affymetrix CytoScan Dx Assay platform became the first FDA-approved microarray technology, its “indications for use” were listed as:

“developmental delay, intellectual disability, congenital anomalies, or dysmorphic features” (Evaluation of automatic class III designation (de novo) summaries.2019; Webb et al., 2015). Similarly, when the Aligent GenetiSure Dx Postnatal Assay was approved in 2017, it was with the same stated indications for use. **Therefore, in the US for example, under current FDA approval parameters, CMA for Asperger syndrome (DSM-IV) or DSM-5 defined ASD (for which DDs are not part of the diagnostic criteria) without an additional, co-morbid, diagnosis of DDs or ID (or congenital anomalies); is actually currently considered “off label” use (South et al., 2013).**