Genomic Care in Autism Spectrum Disorder and Related Neurodevelopmental Disorders – Towards a Personalized Approach

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Table of Contents

1. Abstract

Autism Spectrum Disorder (ASD) and related Neurodevelopmental Disorders (NDDs) are clinically heterogeneous conditions that manifest with developmental difficulties in multiple domains. Despite their clinical diversity, NDDs share common genetic aetiologies. Therefore, genetic testing, like chromosomal microarray (CMA), is considered standard of clinical care in the health management of NDDs. As more powerful genetic tests gain traction in clinical care they will introduce greater amount and complexity of genetic information. With the increase in genetic knowledge and testing in NDDs, two issues have surfaced that present challenges to personalized genomic care in NDDs:

1. The impact of clinical genetic testing has mainly been evaluated through measures of clinical utility (e.g. diagnostic yield and clinical care impact). However, there is a limited understanding of the personal utility experienced by families undergoing genetic testing.
2. Clinical genetic information is lagging behind the fast paced genomic discovery research in NDDs. There is an imbalance between genetic knowledge from research and its integration to improve clinical care in NDDs.

The goal of this thesis is to contribute to the integration of research findings into routine clinical care by improving our understanding of the impact of genetic testing on families affected by ASD/NDD. Ultimately, this knowledge will add to the development of more evidence-based and personalized framework for genomic care in NDDs across clinical services.

In Manuscript 1, I examined clinical utility (i.e. diagnostic yield) and personal utility of genetic testing in a population-based cohort of parents of children affected by ASD/NDDs, undergoing clinical CMA. Personal utility was assessed by measuring parental 'empowerment' using a novel tool, the Genetic Counselling Outcome Scale (GCOS)-24 [1]. I also examined

which child, parent and health service factors acted as predictors of parental empowerment. The results showed that the diagnostic yield of CMA in this cohort was lower than reported in the literature, suggesting that the clinical utility of CMA is lower in a sample representative of the clinical heterogeneity of NDDs. The results also demonstrated that parental perception of the provision of general information correlated with and was predictive of parental empowerment at the time of genetic testing. These findings provided further insight into the impact of undergoing genetic testing on affected families.

In Manuscript 2, I used a case series design to examine the return of genetic research results (RoR) to participants from genomic research studies in ASD, and the integration of this information into the participants' health care. To date, there are no accepted research guidelines for RoR. The purpose of this study was to develop a framework, informed by the literature and expert consultation, which guided the RoR process at our research site and facilitated integration of results into existing clinical care. The case-series demonstrated the ethical, clinical and practical difficulties of RoR in ASD genomic studies for participants enrolled as children. Overall, I suggested that optimal use of genetic research results relied on their integration into individualized clinical care pathways for participants.

Ultimately, I demonstrated that personal utility of undergoing genetic testing can be measured using the construct of 'empowerment', in parents of children with NDD, and identified some factors that influence empowerment. I also contributed a novel framework for the integration of research genetic results in healthcare for participants, facilitating a greater intersection between research and clinical care in ASD. I conclude that greater understanding of the impact of genetic testing and effort to integrate genetic research information into clinical care contribute to a more personalized approach to genomic care in NDDs.

2. Résumé

Le trouble du spectre de l'autisme (TSA) et les autres troubles neurodéveloppementaux (TND) sont caractérisés par des difficultés développementales. Malgré leur diversité clinique, les TND partagent une même étiologie génétique. Par conséquent, les tests génétiques, tels que l'hybridation génomique comparative sur micropuce (CGH), sont considérés un standard pour la gestion des TND. Au fur et à mesure que des tests plus avancés deviendront le nouveau standard de soins cliniques, ils offriront une quantité et une complexité accrue d'information génétique. Par conséquent, deux nouvelles problématiques sont apparues dans le domaine des soins génomiques personnalisés pour les TND:

1. L'impact des tests génétiques a jusqu'à maintenant été évalué principalement au niveau de leur utilité clinique. Cependant, nous avons une compréhension limitée de l'utilité subjective perçue par les familles soumises à ces tests.
2. L'information génétique accessible au niveau clinique accuse un retard sur l'évolution rapide des recherches génétiques sur les TND. Il y a donc un déséquilibre entre les connaissances génétiques provenant de la recherche et leur utilisation dans les soins pour les individus avec un TND.

L'objectif principal de cette thèse est de contribuer à l'intégration des données de recherche dans les pratiques cliniques, par une amélioration de notre compréhension de l'impact des tests génétiques sur les familles affectées. Ultimement, cette compréhension favorisera le développement d'une approche davantage personnalisée et basée sur des données probantes, dans les soins aux individus avec des TND.

Dans le premier manuscrit, j'examine l'utilité clinique (le rendement diagnostique) ainsi que l'utilité personnelle subjective des tests génétiques dans les parents d'enfants avec

TSA/TND, qui ont effectué une CGH clinique. L'utilité subjective a été évaluée à l'aide de l'autonomisation (« empowerment ») parentale. Pour ce faire, j'ai utilisé un questionnaire nouveau, le *Genetic Counseling Outcome Scale (GCOS)-24* [1]. J'ai aussi évalué quels facteurs étaient prédictifs du niveau d'empowerment parental. Les résultats démontrent que le rendement diagnostique de la CGH dans notre cohorte, qui est représentatif de l'hétérogénéité clinique des TND, est inférieur à celui rapporté dans la littérature. En plus, la perception parentale de l'information clinique générale corrélait, ainsi qu'était prédictive, de l'empowerment parental. En somme, ces résultats fournissent une vision plus claire de l'impact des tests génétiques sur les familles.

Dans le deuxième manuscrit, j'examine au moyen d'une série d'études de cas, la communication des résultats génétiques de recherche aux participants d'une étude génétique portant sur le TSA, ainsi que comment cette information est intégrée dans les soins offerts aux participants. À ce jour, il n'existe pas de lignes directrices officielles concernant la communication des résultats génétiques de recherche. Cette étude avait pour but de développer une approche d'encadrer la communication des résultats génétiques de recherche, et de faciliter leur intégration dans les soins cliniques déjà offerts. En somme, je propose que l'utilisation optimale des résultats de tests génétiques de recherche repose sur leur intégration dans une approche individualisée de soins offerts aux participants.

En résumé, j'ai démontré que l'utilité personnelle subjective du processus de test génétique peut être mesurée chez les parents d'enfants avec des TND à l'aide du concept d'empowerment parental. J'ai aussi proposé une nouvelle approche pour l'intégration des résultats de recherche génétique dans les soins de santé des participants. Je conclus qu'une meilleure compréhension de l'impact des tests génétiques, ainsi qu'un effort pour intégrer les

résultats génétiques de recherche dans les soins, peuvent contribuer à une approche plus personnalisée des soins génomiques pour les TND.

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4. Contributions to Original Knowledge

This dissertation provides an original contribution towards a more personalized approach to genomic care for individuals and families affected by ASD and related NDDs. This is the first time personal utility from undergoing genetic testing has been quantified in parents of affected children in existing healthcare pathways, through the use of a novel and recently adapted Patient Reported Outcome Measure (PROM) of empowerment. It is also the first time that child, family and health service factors have been explored as predictors of parental empowerment at the time of clinical genetic testing for their affected child. This dissertation also offers practical tools to bridge the gap between research and healthcare in ASD. It is the first to provide a structured framework for the return and clinical integration of research genetic results to participants enrolled as children in genomic studies.

5. Contributions of Authors

This dissertation consists of 11 chapters that I conceived, drafted, and finalized. I revised this dissertation in its entirety with feedback from Afiqah Yusuf and Mayada Elsabbagh. The contributions of all authors for the two manuscripts in this dissertation are as follows:

For Manuscript 1, I conceived and designed the Genome to Outcome cohort study with input from Afiqah Yusuf and Mayada Elsabbagh. I implemented the clinically embedded research protocol for participant recruitment for the Genome to Outcome cohort with assistance from Jennifer Frei and Mayada Elsabbagh. I conceived and designed the study for Manuscript 1 with feedback from Mayada Elsabbagh. I implemented and performed the electronic data collection with help from Ruth Bruno, Jennifer Frei, Tal Savion-Lemieux and Afiqah Yusuf. I analyzed and interpreted the data by myself with feedback from Mayada Elsabbagh and Afiqah Yusuf. I drafted the manuscript and revised it with critical feedback for important intellectual content from all co-authors: Afiqah Yusuf, Jennifer Frei, Tal Savion-Lemieux, Ridha Joober, Jennifer Howe, Stephen W. Scherer, and Mayada Elsabbagh.

For Manuscript 2, I conceived and designed the study with input from Mayada Elsabbagh. I convened and led the workgroup that conceived the Return of Results Framework, consisting of myself, Daniela Buhas, Lara Stern and Mayada Elsabbagh. I carried out the return of genetic research results. I performed data collection and organization. I drafted the manuscript and revised it with critical feedback for important intellectual content from all co-authors: Daniela Buhas, Lara Stern, Emily Kirby, Afiqah Yusuf, and Mayada Elsabbagh.

6. Introduction

Neurodevelopmental disorders (NDDs) are a group of conditions with onset during the developmental period in children, including autism spectrum disorder (ASD), global developmental delay (GDD) and intellectual disability (ID) [2]. These conditions are the result of complex interactions between environmental and genetic factors, many of which converge on gene networks involved in brain development and cell signalling [3, 4]. Current clinical recommendations advocate for the use of genetic tests, namely chromosomal microarrays (CMA), in the clinical care of individuals with NDDs [5]. Genetic testing is used to find a biological aetiology for the clinically established diagnosis of NDD and guide healthcare for the affected individual and family [6].

Genomic technologies and knowledge about the genetic underpinnings of NDDs from research continue to expand at a rapid pace [7]. Genomic research of NDDs employs even more powerful genetic tests than those used in clinical practice, such as exome sequencing (ES) and genome sequencing (GS), for the discovery of genetic variants in ASD and related NDDs [8, 9]. At present, there are hundreds of genetic variants thought to be associated with the development of ASD [7]. In fact, powerful genetic tests, like ES and GS, may soon become part of the routine clinical care of individuals with NDDs [10].

As genomic technologies and knowledge grow, so has the push for a more personalized approach to healthcare for individuals and families affected by NDDs [11]. Two particular challenges to personalized genomic care in NDDs have been a) understanding the personal utility, and therefore impact, of genetic testing on affected individuals and families [12, 13] and b) integrating the rapidly generated genomic knowledge form research into the overall healthcare

for NDDs [14]. There are several complexities to genetic testing that have contributed to these two issues, which I outline herein:

6.1. Utility of genetic testing

Utility is an important aspect of understanding the impact of an intervention, such as genetic testing [15]. The utility (i.e. the usefulness) of clinical genetic testing for ASD and related NDDs has been evaluated mainly through clinical measures, such as diagnostic yield and impact on clinical outcomes [15, 16]. Diagnostic yield is the percentage of individuals who obtained a molecular genetic diagnosis from the genetic test [15]. Initial studies examining the diagnostic yield of CMA in ASD and related NDDs, reported a yield of 10-15 %, based on CMAs performed in clinical genetics referral populations [5, 17-20]. However, other studies in cohorts of individuals with NDDs that may be more representative of the general clinical population are suggesting that the diagnostic yield of CMA may be lower in those populations than expected [18, 19, 21]. This may be due to that fact that NDDs present with significant clinical heterogeneity and a large proportion of individuals with NDD do not demonstrate pathological findings (e.g. obvious dysmorphic features, seizures, congenital anomalies, severe ID, etc.) beyond neurobehavioural differences [2, 22]. In fact, it is now accepted that the genetics of NDDs involve a variety of complex mechanisms, including rare and de novo copy number variants (CNVs), single nucleotide polymorphysms (SNPs), variable expressivity and incomplete penetrance of variants, as well as epigenetic influences [23]. Thus, CMA alone cannot detect the diverse genetic differences that play a role in the manifestation of NDDs.

More advanced genomic tests, initially used in research, complement CMA in its diagnostic yield when used in clinical care and improve the identification of genetic variants associated with NDDs in discovery research [4, 17, 24]. For example, a study demonstrated that

relative to CMA, where 9.3% of probands diagnosed with ASD had an identifiable underlying aetiology, the yield from a combined CMA and ES was 15.8% [17]. When GS was used in 85 quartet families affected by ASD, it found mutations associated with ASD in 42.4% of the families [8]. More powerful genomic tests like ES and GS are used in the discovery of new susceptibility variants associated with genetically complex NDDs, by revealing different types and greater resolution of genetic changes [3, 7, 25]. They are also gaining traction in the clinic for improved detection of genetic variants associated with various health conditions, including NDDs [10]. The clinical use of these powerful genomic technologies will generate greater amount and complexity of genetic information for those affected by NDDs. However, diagnostic yield provides only partial insight into the utility of genetic testing in the care for NDDs.

Another measure of the usefulness of genetic testing is clinical utility. Clinical utility is defined as the extent to which the diagnostic test improves health outcomes for the individual, such as access to therapy and services, or preventative care [15]. Studies have shown that clinically significant genetic results in children and families affected by NDDs may inform clinical utility and resource planning in a meaningful way for clinicians and families. For example, genetic results may inform prognosis, medical management and health surveillance of the child [26-29]. They may influence family planning decisions based on recurrence risk analyses [26-28, 30]. Establishing aetiology may end the “diagnostic odyssey” and avoid unnecessary tests for the child [26, 27]. However, clinical utility is directly related to the type of genetic result generated by the genetic test [28]. CMA results are broadly classified by clinical cytogenetic laboratories into “negative/likely benign”, “pathogenic/abnormal” and “variants of uncertain clinical significance” (VUS) [5], based on clinical interpretation guidelines that were

last updated in 2010. Pathogenic/abnormal variants are more likely to elicit changes in clinical recommendations and management, as compared to results classified as VUS [31].

Measures of clinical utility offer insight into the clinical impact of genetic testing on individuals and families affected by ASD and related NDDs. However, clinical utility does not capture the impact of psychological and emotional responses to genetic testing, such as guilt and blame stemming from the heritability of an identified genetic change, disappointment from the mismatch between expected and actual clinical utility of the results, or parental confusion stemming from the complexity of genetic results [26-29, 32, 33]. It also fails to capture the impact of non-actionable genetic results like VUS [29].

Qualitative studies have shown that individuals and families undergoing genetic testing experience another outcome in addition to those typically valued by clinical services (i.e. diagnostic yield and clinical impact), namely personal utility [15, 34]. Personal utility encompasses a broad range of subjective, psychological and non-health related outcomes of genetic testing, such as feelings of control, increased knowledge about oneself or one's family, and future planning [15, 35, 36]. There are relatively few quantitative studies on personal utility of genetic testing for families affected by ASD/NDD [15, 37]. Qualitative studies on this topic identify that the act of undergoing genetic testing can have a personal impact for families, regardless of the results generated by the genetic test. For example, parents who do not report a direct medical benefit of the genetic result still express a benefit from feeling informed [27, 38]. Interviews with mothers of children with ASD who had undergone clinical CMA showed that they identified aspects that were "missing" from the experience of genetic testing that would have helped them understand the value of the test, such as information about genetics and

genomics in general, the genetics of ASD, and use of genetic results and their relevance to life-long care [27, 33].

Capturing the personal utility during the process of genetic testing for families affected by ASD and related NDDs can lead to an improved understanding of the impact of testing. It can provide meaningful information on how to optimize genetic testing with the goal of making that process more person- and family-centered.

Thus, Objective 1 of this thesis is to quantify the personal utility from undergoing clinical genetic testing (namely, CMA) in families of a child with ASD or related NDD during routine clinical care. I address Objective 1 in Manuscript 1. I provide a deeper review of the literature around the personal utility of undergoing genetic testing in the context of NDDs. I discuss the challenges inherent in measuring personal utility. I propose the construct of empowerment, as a measure of personal utility from genetic testing, and demonstrate its use in a population-based cohort of parents of children with ASD and related NDDs undergoing genetic testing in existing clinical care pathways. Based on previous research with other health conditions, I examine specific child, family and service factors as predictors of empowerment (i.e. personal utility).

6.2 Return of genetic research results

ASD is a complex condition implicating numerous genes that produce a clinically heterogeneous phenotype [3]. This complexity makes the return of genetic results (RoR) nuanced, requiring individualized genetic counseling and health management. Recommendations by the American College of Medical Genetics and Genomics from 2010 offer direction on the interpretation and return of results from CMA in clinical settings [5]. More recently, they

published guidance on the interpretation of certain secondary findings and sequence variants from clinical genetic testing [39, 40]. Result classifications are generally based on a combination of factors: (1) the availability of clinical phenotypic and published scientific information about the genetic change, (2) whether it is inherited from a healthy or affected parent, and (3) the structural characteristics of the genetic change (e.g. deletion vs. duplication) [5, 40].

However, existing recommendations regarding result interpretation are currently limited. First, most recommendations are outdated (most recent guideline was published in 2015). Second, they do not take into account the large increase in genomic information about NDDs from research in recent years [41]. Finally and most importantly, no recommendations exist specifically for return of results obtained in large-scale genomics studies to participants and/or their integration into routine healthcare. Existing recommendations offer limited guidance on RoR in the context of NDDs and do not consider for the variability in care pathways within different healthcare systems [42]. Although these recommendations provide an evidence-based approach to result interpretation form clinical genomic testing in general, there is still considerable variation in how clinical laboratories utilize them and there is a continued need for further refinement to improve the accuracy and consistency of genetic result interpretation [43]. Ultimately, this is limiting the access of affected individuals and families to novel genetic information that has the potential to uncover the etiology of the NDD and alter their healthcare [14].

When used in a research context, results from advanced genetic tests, like ES and GS, accelerate discovery of new genetic variants associated with ASD, but are subject to more complex reporting challenges than clinical tests [44]. There are several discussions on the ethical obligations of researchers for RoR in the research context [45, 46]. There are also numerous

opinions regarding the broader process of RoR from research, including ethical considerations, scientific validity and clinical applicability of research results, and criteria for RoR to individuals [46-52]. However, a review of this literature reveals that there are no unifying recommendations on the process of returning and integrating research genetic results into participants' clinical care. Furthermore, approaches may differ across different health jurisdictions and institutions. This lack of practical recommendations for RoR from genetic research may result in variable practices by research teams.

Therefore, Objective 2 of my thesis is to offer a framework for the return of genetic research results to participants affected by ASD and related NDDs, which ultimately leads to their integration into routine healthcare. In Manuscript 2, I provide an in-depth review of the literature on RoR form research. I then outline a framework for RoR form genomic research to participants and illustrate its application through a case series involving RoR to individuals and families participating in genetic research in ASD.

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7. Manuscript 1: Predictors of empowerment in parents of children with autism spectrum disorder and related neurodevelopmental conditions who are undergoing genetic testing

7.1 Preface

Assessing the personal utility of genetic testing in families affected by ASD and related NDDs has been a challenge due to the lack of standardized measures of personal utility. One construct that has emerged from the genetic counselling literature is 'empowerment' resulting from receipt of genetic services. In Manuscript 1, I proposed empowerment as a measure of personal utility from genetic testing in families whose affected child is undergoing clinical CMA for a diagnosis of ASD or related NDD. I utilized a recently adapted and validated tool for quantifying empowerment in this clinical context, and explored child, family and health service factors that may influence empowerment from genetic testing. I found that parental perception of the provision of general health information and of their function in the family correlated with parental empowerment. In a model accounting for all factors, parental perception of the provision of general information was predictive of empowerment at the time of genetic testing for their child. This Manuscript demonstrated the feasibility of using empowerment as a measure of personal utility from clinical genetic testing in NDDs and outlined important areas for future work in making the experience of clinical genetic testing more person-centered, such as tailored pre-test genetic counselling and availability of psycho-social resources at the time of genetic testing.

Manuscript 1 is in the process of submission to Genetics in Medicine.

Predictors of empowerment in parents of children with autism spectrum disorder and related neurodevelopmental conditions who are undergoing genetic testing

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7.2 Abstract

Background: Genetic testing is standard of care in the clinical management of Autism Spectrum Disorders (ASD) and related Neurodevelopmental Disorders (NDDs). Clinical utility is a term often used to describe the impact of clinical genetic testing. However, there is still limited insight and empirical data on personal utility of genetic testing for families of a child with ASD/NDD. The objectives of this study were to 1) assess utility of clinical genetic testing, defined by diagnostic yield and parental empowerment in a population-based sample of parents of affected children undergoing diagnostic assessment; 2) explore child, family, and health services factors as predictors of parental empowerment around the time of genetic testing.

Methods: Families of children diagnosed with ASD/NDD, participating in a prospective genomics cohort between 2016-2019, took part in our study. Families were recruited from a variety of clinics where children were undergoing clinical diagnostic assessments for ASD/NDD. Clinical utility was measured through diagnostic yield of CMA. We also assessed parental empowerment in families undergoing genetic testing for the first time ($N = 69$), using a recently adapted version of the Genetics Counselling Outcome Scale (GCOS)-24. Parents completed additional questionnaires to capture child, family, and health services factors.

Results: The diagnostic yield of clinical CMA was 2.8 % for pathogenic variants and 5.8 % for variants of uncertain significance (VUS) in a representative sample of health systems users. Moreover, we found that personal utility of testing, defined as parental empowerment, was significantly correlated with family functioning, r = -0.391, p = 0.003; and several aspects of perceived family centeredness of care (provision of general information, r = 0.411, p = 0.001; coordinated and comprehensive care, r = 0.440, p = 0.0005; and respectful and supportive care, r = 0.451, p = 0.0005). Overall, the model with all the predictors accounted for 49.8 % of the

variation in parental empowerment around the time of genetic testing, F (10,37) = 3.67, p = 0.002. After accounting for the contribution of all predictors in the model, parental perception of provision of general information remained significantly associated with parental empowerment, F (1,37) = 6.74, p = 0.013.

Conclusions: The informational needs of families, whose children with ASD/NDDs are undergoing genetic testing, play an important role in the empowerment (i.e. personal utility) they derive from genetic testing. Meeting these needs and monitoring empowerment can aid the integration of genomic technologies in the personalized healthcare for ASD/NDDs.

7.3 Introduction

Current clinical recommendations advocate for the use of genetic tests, namely chromosomal microarray analysis (CMA), and more recently exome sequencing (ES), in the clinical care of individuals with neurodevelopmental disorders (NDDs), like autism spectrum disorder (ASD), global developmental delay (GDD) and intellectual disability (ID) [1-6]. These tests are part of standard clinical care and may provide greater genetic information to affected individuals and their families [6]. Despite its widespread use, there is still limited understanding of the impact of clinical genetic testing on families who have a child with an NDD. The impact of clinical genetic testing has traditionally been evaluated based on the extent to which the tests are thought to be safe, effective and/or improve health outcomes [7].

However, such a narrow definition of utility has been insufficient to understand the full impact of genetic testing on families. First, clinical utility has often been defined by the diagnostic yield of the genetic test, i.e., proportion of individuals who obtain a molecular genetic diagnosis as a result of testing. Yet, to date, population estimates of diagnostic yield are not available because most published reports are based on samples of children referred to single subspecialty clinics, resulting in wide variations of reported diagnostic yield [1, 8-10]. Previous work has highlighted that diagnostic yield is not only impacted by representativeness of the sample of healthcare users but it can vary from one healthcare setting to another [11]. Thus, diagnostic yield cannot be the sole measure of impact of genetic testing on families.

Second, other measures of clinical utility are defined based on changes in clinical management as a result of genetic testing [12-14]. However, the studies are increasingly clarifying that individuals and families undergoing genetic testing also experience a different outcome than typically measured in clinical services, namely ‘personal utility’ [7, 15]. Personal

utility encompasses a broad range of non-health related outcomes of genetic testing, including psychological outcomes, e.g. feelings of control, increased knowledge about oneself or one's family, and future planning [7, 16, 17]. Relative to the broader field of medical genetics and genetic counselling, there are relatively few empirical studies on the personal utility of genetic testing for families affected by ASD/NDD [7, 12]. Most of the available information on the impact of genetic testing on families comes from qualitative studies, which are small and have limited generalizability [18-25]. On the whole, the literature suggests that both positive and negative implications of genetic testing for families are possible.

One potential positive impact of clinical genetic testing, as illustrated by interviews with parents of children with congenital abnormalities, ASD and/or developmental delay, is to provide an explanation for their child's challenges, and offer prognosis and direction to caring for their child [18]. Establishing aetiology may end the "diagnostic odyssey" for the child [19, 20]. Some parents reported a sense of comfort in knowing the biologic cause of their child's condition and that knowledge may help clarify the child's strengths and difficulties [21]. In fact, many parents who do not report a direct medical benefit of the genetic result still express a benefit from feeling informed [22, 23].

In contrast, a large percentage of parents have expressed a sense of ambivalence about genetic testing and had concerns about the potential for psychological distress, insurance discrimination, making sense of ambiguous findings, and "managing the weight of inflicted insight" [24]. A qualitative study of parents of children with ASD showed that among those who had taken their children for genetic testing, one-third had negative experiences, such as difficulty understanding genetic terminology and information, lack of family-centeredness, and long wait times to access genetic testing [20]. Interviews with mothers of children with ASD who had

undergone clinical CMA showed that they identified aspects that were "missing" from the experience of genetic testing that would have helped them understand the value of the test, such as information about genetics and genomics in general, the genetics of ASD, and use of genetic results and their relevance to life-long care [21, 22].

There are only a few quantitative studies that have explored the potential impact of genetic testing on families, sometimes in the context of NDDs. They also identified a mix of positive and negative potential impacts. A survey exploring the genetic testing experiences of over 500 parents of children with ASD in the US showed that 37.6% were "unsatisfied" mainly due to lack of perceived testing benefits to their children and unpleasant testing experiences with healthcare providers [26]. A survey of parents of children who underwent clinical ES showed that parents with anxiety and depression experienced the greatest psychological impact [27]. In a large study of psychological outcomes related to ES and GS for a variety of conditions, parents of pediatric patients reported the greatest levels of uncertainty and distress, but also the highest degree of positive experiences [28].

These seemingly contradictory impacts may be explained by the varied contexts in which each family experiences genetic testing. Assessing *personal* utility from genetic testing stems from the child, family and health service factors that may modify the impact of genetic testing in the context of ASD and related NDDs. We recently reported a series of findings from a cohort study of families of children diagnosed with ASD or related NDDs who underwent genetic testing, from a population-based sample representative of clinical services [29-31]. We found that parental distress and ASD knowledge correlated among families undergoing genetic testing [31]. We also showed that child and family functioning correlated with perceived utility for biological testing among these families [30]. A mechanism by which child and family

functioning affect parental experience of genetic testing is that partner interactions may be under greater strain in families who have a child with a chronic condition [32-34] and family conflict is intertwined with parental mental health [35, 36] and child symptomatology [32]. Health services experience may also play a role in the experiences of parents of an affected child during the process of genetic testing. While we did not find a significant correlation between level of family-centered care and perceived utility of biological testing [30], other studies have shown the frustration of families affected by ASD from encountering a broader care system that lacks transparency, fails to provide adequate support and direction, and lacks a family-centered approach [37, 38]. Taken together, our recent findings suggest that interactions between child, family, and health services factors likely modify the impact of clinical genetic testing for individual families.

Personal utility of genetic testing in families affected by ASD and related NDDs has been challenging to measure due to lack of consensus on constructs and limited standardized tools [39]. One outcome that has shown promise in capturing the personal utility from genetic services is 'empowerment' [40]. The World Health Organization defines empowerment as "a process through which people gain better understanding and control over their lives" [41]. More specific to genetic services, McAllisiter *et al.* defined empowerment as the belief that the individual receiving genetic services has "decisional", "cognitive", and "behavioural control", "emotional regulation" and "hope", and that the beneficial effects of genetic information are reflected in these five aspects [40, 42, 43]. The construct of empowerment has been operationally defined and validly measured to describe the potential patient benefits from genetic information and services using a Patient Reported Outcome Measure (PROM) called the Genetic Counselling Outcome Scale (GCSO)-24 [40, 42].

In this study, we extend our previous work [30, 31] by examining the utility of clinical genetic testing in a cohort of families of children with ASD and related NDDs, in routine healthcare pathways. First, we assessed diagnostic yield in a population-based sample of families with an affected child, recruited from a variety of clinical services, as they underwent diagnostic assessment for the child. Second, we examined personal utility among parents of affected children, around the time of clinical genetic testing for the child, using a modified version of the GCOS-24 (mGCOS-24) that we recently adapted and validated for use in parents of children with NDD [29]. Finally, we explored child, family, and health services factors previously proposed as potential predictors of empowerment in the context of genetic testing for ASD and related NDD based on previous studies with other populations [29, 43, 44].

7.4 Participants and Methods

Sample:

Recruitment of participants relied on a clinically embedded protocol (i.e. families were recruited directly from a variety of clinical services as their child underwent routine assessment for suspected NDD), as part of a longitudinal genetic study in Montreal, Canada, called Genome to Outcome. The Genome to Outcome study aimed to assess the standard of care in genetic testing for children with NDDs and contribute to understanding the genetic basis of NDDs. Inclusion criteria for this larger study were: families of a child or youth (age 0-18 years) referred for an evaluation of a NDD for which genetic testing is recommended. Children with previously diagnosed genetic disorders were excluded. The study was approved by the Research Ethics Board of the Research-Institute of McGill University Health Centre.

Clinicians in Child Development clinics (developmental paediatricians, psychologists), Psychiatry clinics (child and adolescent psychiatrists) and Genetic clinics (genetic counsellors) at a quaternary pediatric centre (McGill University Health Centre) and at a specialized mental health centre (Douglas Mental Health University Institute), alerted families who met the inclusion criteria about the Genome to Outcome research study. All participating clinicians were involved in the child's clinical care, either through diagnostic assessment that also included at least some information on genetic testing (i.e. pre-test genetic counseling, or elements thereof, done by a non-genetic specialist) or through formal pre-test genetic counseling that followed the diagnosis of NDD made by another academic or community clinician. The majority of pre-test genetic counseling was not done by a genetic counselor, although in some cases it was. It is important to highlight that information on clinical genetic testing offered by non-genetic clinicians to families varied in content depending on the clinical practice of the clinician. Interested families then spoke with a research assistant over the telephone to learn more about the study. Families that remained interested met with the research assistant, who obtained informed consent and enrolled them into the study.

During the study visit, the 'parent most knowledgeable' (PMK) about the child was introduced to a set of online questionnaires, some of which were completed during the visit and the remainder were completed at home. Typically, the blood draw for the clinical genetic test (CMA) took place on the same day as the research study visit, but in some cases it took place before or after the study visit. As part of the broader Genome to Outcome study, all family members, including the proband, also provided a blood sample for research genetic testing.

For the purpose of the current study, data was analysed only from families whose child had no genetic testing in the past, in order to capture the impact of undergoing clinical genetic

testing for the first time. Among this group of families undergoing clinical genetic testing for the first time, a genetic result was available on average 10.9 weeks after the child's final diagnostic assessment visit - a visit that typically includes the disclosure of the diagnosis of ASD or related NDD to the family, and/or recommendation for clinical genetic testing from the clinical care provider, which may or may not involve some form of pre-test counselling. In all cases, families completed the study questionnaires prior to having knowledge of their child's genetic results.

The sociodemographic data for the overall Genome to Outcome study cohort suggests that the participating families were representative of the general Montreal population (Table 7-1). Approximately 60% of the families reported an annual household income of less than $80,000 (Table 7-1). Forty six percent of the respondents had a high school or college diploma as their highest completed degree, with the remainder holding a university or professional degree (Table 1). Based on the 2016 Canadian Census, the median family household income in Montreal in 2015 was $69,228 [45]. Sixty-one per cent of individuals in Montreal have a high school or college diploma, while 39% hold a university or post-secondary degree (Stats Canada). The majority of PMKs were married or common-law and were biological mothers to a male child with ASD.

Table 7-1. Descriptive data for families enrolled in the Genome to Outcome cohort (*n* = 113). ASD = Autism spectrum disorder; DD/ID = Developmental delay/Intellectual disability; M = Mean; SD = Standard deviation; CMA = chromosomal microarray imaging.

Characteristics of the child	
Mean child age in years at time of study referral (*SD*)	6.7 (3.7)
Diagnosis *N* (%):	
ASD	97 (85.8%)
GDD or ID	16 (14.2%)
Sex *N* (%):	
Male	84 (74.3%)
Female	29 (25.7%)
Characteristics of the PMK	
Age in years at study visit *M* (*SD*)	39.3 (7.9)
PMK's relationship to child *N* (%):	
Biological mother	98 (86.7%)
Biological father	11 (9.7%)
Adoptive mother	4 (3.5%)
Marital Status *N* (%):	
Married/common law	96 (85%)
Divorced/Separated/Single	17 (15%)
Education *N* (%):	
High school or College	53 (46.9%)
University or Post-secondary	60 (53.1%)

Annual household income *N* (%):	
Less than $40,000	34 (30.1%)
Between $40,000 and $80,000	35 (30.1%)
More than $80,000	43 (39.1%)
Missing	1 (0.9%)

Measures:

a) Diagnostic yield:

Diagnostic yield from the clinical CMA was determined by performing a chart review for each child. Yield was calculated as the proportion of pathogenic and likely pathogenic results (as interpreted by the clinical analytic laboratory where the CMA was performed) from all reported results.

b) *Empowerment:*

Further work on the concept of empowerment as an outcome in genetic counselling has led to the creation of the validated PROM, consisting of 24 questions, called the GCOS-24 [43]. It is a PROM of empowerment designed for use in the context of genetic services and measures empowerment as a result of the receipt of genetic information [46]. Psychometric analysis of the GCOS-24, in a population of individuals with genetic conditions, revealed that this tool shows good internal consistency, test–retest reliability, sensitivity to change, and evidence of construct validity [43]. For the purpose of our study, we utilized the adapted version of the GCOS-24, the mGCOS-24, as described above [29]. Higher scores indicate greater degree of empowerment.

c) Sociodemographic and clinical variables of interest:

Family annual income, age and education level of the PMK were assessed using a structured interview at the time of the study visit, the Family Background Information Questionnaire (FBIQ) [47]. Diagnostic and medical information on the child was obtained through chart review, including child's age, biological sex, diagnosis, and genetic results.

d) Child's emotional and behavioural functioning:

Emotional and behavioural functioning in the child were assessed using the Child Behaviour Checklist-2 (CBCL-2), which is a popular standardized measure of a child's emotional and behavioural problems [48]. The CBCL obtains parent ratings of 99 to 113 items on their child's emotional, behavioural, and social problems. The CBCL has been developed for use in children aged 1 ½ - 5 years 6 - 18 years. T-scores were used in this study to summarize scores across both age groups. Higher total scores indicate greater problems in child emotional and behavioural functioning.

e) Family functioning

Parental (PMK) perception of their function within the family was evaluated through a parent self-report tool, Brief form of the Family Assessment Measure, third edition, Self-rating scale, (Brief FAM-III SR) [49, 50]. The Brief FAM-III SR consists of 14 items that allow a person to rate his/her own functioning within the family. The Brief FAM-III SR is a module of the broader Brief FAM-III measure, which is based on the Process Model of Family Functioning. This theoretical model suggests that each family member perceives the level of interaction differently and that relationships within the family change along with an individual's perception of their own functioning. The Brief FAM-III SR assesses the following dimensions of family strengths and weaknesses: task accomplishment, role performance, communication, affective expression, affective involvement, control, and values and norms [50]. The Brief FAM-III has

been used in families of children with chronic conditions and developmental disabilities [50] and is reported to have good internal reliability and test-retest reliability [50]. Higher scores denote lower sense of functioning.

f) Parental perception of family-centeredness of care:

Family-centeredness of care, as perceived by the PMK, was assessed using a 20-item questionnaire, the Measure of Processes of Care (MPOC-20), completed by the PMK. The MPOC-20 was developed to assess parents' perceptions of the extent to which the health services they and their child received over the past year were family-centered. The MPOC-20 captures five dimensions of care 1) Enabling and partnership; 2) Providing general information; 3) Providing specific information about the child; 4) Coordinated and comprehensive care for the child and family; and 5) Respectful and supportive care. The MPOC-20 has been validated in samples of parents with children who have a variety of NDDs [51]. The measure was reported to have good internal reliability and test-retest reliability. Previous studies found that the MPOC-20 correlated with a measure of satisfaction and parental stress [51]. Higher scores reflect parental perception of greater family-centered care.

Because our target population includes French-speaking individuals, we followed established guidelines [52] to translate all measures into French, if no validated translation already exists.

Statistical Analyses:

Bivariate associations between parental empowerment (GCOS-24 scores), sociodemographic variables, and child, parent (PMK) and health services factors, were explored using correlation analyses: continuous variables were analyzed using Spearmen's rho tests while group comparisons were performed using independent *t*-tests. In order to minimize Type I error due to

multiple comparisons, the Bonferonni correction was applied, yielding a more stringent *p* value of 0.005. For the purpose of all statistical analyses, transformed Brief FAM-III SR data was used, by applying the square root transformation, to ensure a normal distribution. To examine the combined impact of different covariates and factors on parental empowerment, we used a general linear model analysis. For the general linear model analyses, we applied a significance level of $\alpha = 0.05$ (two-sided). All statistical analyses were done using the statistical software packages Statistical Package for the Social Sciences (SPSS) 26.0 for Mac (SPSS Inc., Chicago, IL).

7.5 Results

Participants:

A total of 257 eligible families were referred to the Genome to Outcome study between 2016 and 2019. Forty three percent of families agreed to participate ($n = 113$). The most common reason for not participating that families reported was that they were too busy. Further details on the cohort were previously reported by Yusuf et al. [30, 31].

Diagnostic yield

Of all enrolled families ($n = 113$), 105 (93%) had a CMA result available from clinical genetic testing done either before or after study enrolment; this information was missing for 7 families. Of these, 94 (89.5%) had a negative CMA result; 6 (5.7%) had a 'variant of unclear significance' (VUS); 3 (2.8%) had a pathogenic variant; and 2 (1.9%) had a variant classified as 'benign'. Therefore, the overall diagnostic yield of clinical CMA in our population-based cohort of children with NDDs was 2.8% (for pathogenic results) and 8.6% (for pathogenic and VUS results combined), which was lower than the yield typically reported in the existing literature, of 10-15% [1].

Descriptives of predictors and outcome measure

Of the complete sample of 113, 70 families had a child diagnosed with an NDD, and who had not previously had any genetic testing (36 had previous genetic testing and 7 were missing information about availability of a previous genetic result). One family was excluded because their diagnostic assessment occurred over 1 year from the time of genetic testing and study participation. This is because parents' experience of health care services beyond one year cannot be reliably measured using the MPOC-20. Thus, all subsequent analyses were done on a sample of *n* = 69. Table 2 presents descriptive statistics for all standardized measures, including outcome measures and predictors.

Table 7-2. Descriptive statistics for the outcome measures (*n* = 69).

Measure	**Mean (*SD*)**
Outcome	
mGCOS-24 total score (n = 68)	118.9 (*19.2*)
Predictors	
CBCL-2 total *T* score (n = 50)	62.6 (*10.7)*
Brief-FAM-III SR total score (n = 54)	12.2 (*5.9*)
MPOC-20 subscales score (n = 62)	
Enabling and partnership	4.2 (*2.0*)
Providing general info	3.9 (*1.9*)
Providing specific info	4.4 (*1.8*)
Coordinated and comprehensive care	4.4 (*1.7*)
Respectful and supportive care	4.8 (*1.6*)

Exploratory analyses

We first assessed the extent to which child and parent (PMK) sociodemographic variables were independently associated with parental empowerment. After correcting for multiple comparisons, there was no statistically significant association (defined as $p < 0.005$) between any of the demographic factors and parental empowerment around the time of genetic testing (Table 7-3). Due to the uneven split in sample size for child's diagnosis and the PMK's marital status (Table 1), the correlation between these factors and empowerment were not analyzed.

Table 7-3. Correlations of sociodemographic variables with parental empowerment around the time of genetic testing ($n = 69$).

Sociodemographic Factors	**Parental Empowerment (mGCOS-24 Score)**
Child's Age	r (68) = 0.088 p = 0.475
Child's Sex Male vs. Female	t(66) = -0.583 p = 0.562
Parental Age	r (68) = 0.082 p = 0.508
Parental Education High school/Vocational/College University/Professional	t(66) = 2.58 p-value = 0.012
Family Income < $70,000 > $70,000	t(64) = -1.13 p-value = 0.261

We then assessed the extent to which child (child's emotional and behavioural functioning), family (family functioning) and health services factors (perception of family centeredness of care) were independently associated with parental empowerment around the time of genetic testing (Table 7-4). After correcting for multiple comparisons, there was no correlation between child's degree of emotional and behavioural functioning and parental empowerment. There was a significant moderate negative correlation between family functioning and empowerment (i.e. lower perception of function in the family was associated with lower empowerment). There was a significant strong positive correlation between several aspects of perceived family-centeredness of care and parental empowerment, namely, provision of general information, coordinated and comprehensive care, and respectful and supportive care.

Table 7-4. Correlations between child, family, and health service factors, and parental empowerment around the time of genetic testing (n = 69).

Additional Factors	**Parental Empowerment (GCOS-24 Scores)**
Child	
CBCL-2 total *T* score	*r* (50) = - 0.127 *p* = 0.379
Family	
Brief FAM-III SR total score	*r* (55) = - 0.391* *p* = 0.003
Health Services	
MPOC-20 subscales score	
Enabling and partnership	*r* (62) = 0.295 *p* = 0.02
Providing general info	*r* (62) = 0.411* *p* = 0.001
Providing specific info	*r* (62) = 0.301 *p* = 0.017
Coordinated and comprehensive care	*r* (62) = 0.440* *p* < 0.0005
Respectful and supportive care	*r* (63) = 0.451* *p* < 0.0005

* Denotes p < 0.005

Predictors of empowerment

To explore predictors of parental empowerment around the time of genetic testing for their child with ASD/NDD, we used a general linear model with mGCOS-24 total scores as the dependent variable, family income and parental education level as fixed factors, and child's age, child's emotional and behavioural functioning (CBCL-2 total *T* scores), family functioning (Brief FAM-III SR scores), and parentally perceived family-centeredness of care (MPOC-20 subscale scores) as covariates (R^2_{corr} = 0.362). The model explains 49.8 % of the variation in parental empowerment around the time of genetic testing, $F(10,37) = 3.67$, $p = 0.002$, $R^2 = 0.498$; (Table 7-5). Parental perception of provision of general information makes a significant contribution to the model and accounts for significant amount of the variation in parental empowerment, $F(1,37) = 6.74$, $p = 0.013$ (Table 7-5). There is a trend towards significance for parental education level, $F(1,37) = 3.72$, $p = 0.061$ and parental perception of function in the family $F(1,37) = 3.24$, $p = 0.080$, as contributors to the model (Table 7-5). No other factors are predictive of parental empowerment.

Table 7-5. Impact of child, family and health service factors on parental empowerment.

Predictors	**F (*df*)**	**p-value**
Corrected model	3.67 (10)	0.002
Child's age	0.56 (1)	0.461
Child's emotional and behavioural functioning	0.05 (1)	0.818
Family income	2.55 (1)	0.119
Parental education	3.72 (1)	0.061
Family function (Brief FAM-III SR)	3.24 (1)	0.080
Family centeredness of care (MPOC-20)		
Enabling and partnership	0.01 (1)	0.939
Providing general info	6.74 (1)	0.013*
Providing specific info	0.10 (1)	0.754
Coordinated and comprehensive care	0.01 (1)	0.943
Respectful and supportive care	0.02 (1)	0.897

*$p < 0.05$

7.6 Discussion

In this study, we assessed clinical utility of undergoing clinical genetic testing in a population-based cohort of parents with a child affected by ASD or related NDD, recruited from routine clinical care pathways. Data drawn from a cohort representative of the clinical reality is likely to offer information that has greater applicability to understanding and improving the use of genomics in healthcare for NDDs. We assessed clinical utility using two complementary measures: diagnostic yield and parental empowerment, where the latter is a measure of personal

utility for individual families. Diagnostic yield, was 2.6% for pathogenic results and 8.6 % for combined pathogenic and VUS results, which is lower than the typically reported diagnostic yield of 10-15 % in other studies [1, 9, 10, 53, 54]. Since CMA became part of the recommended clinical investigations for the assessment of NDDs about a decade ago [1], several studies have examined the diagnostic yield of CMA in the context of ASD and related NDDs. These recommendations were based on a review of 33 studies and reported an average diagnostic yield of 12.2 % [55]. However, the reviewed studies were mainly done in populations already referred to clinical genetics services, which tend to have more clinical indications (e.g. congenital anomalies and dysmorphic features) and more severe symptomatology (e.g. intellectual disability), leading to higher likelihood of detecting a pathogenic variant by CMA.

In contrast, clinical genetic testing is recommended for ASD/NDD as a first-tier test, independent of a referral to clinical genetics services, as ASD and related NDDs present with broad and heterogeneous phenotypes, with many autistic individuals showing average or above average cognitive abilities, and no recognizable dysmorphic features or congenital anomalies [56]. Reports based on cohorts external to clinical genetic services showed a CMA yield closer to 9 % [9, 10]. Our cohort may be more representative of the heterogeneous NDD population than these studies and may be more reflective of the clinical care pathways, in which CMA is meant to be implemented. Therefore, the CMA yield in our cohort may be more representative of the reality of CMA testing outcomes in the broader ASD/NDD phenotype across clinical services in general.

In addition to measuring diagnostic yield across the whole sample, we also used the mGCOS-24, to assess empowerment as an outcome of clinical genetic services. The measure allowed us to quantify the personal utility of each parent in the sample around the time of clinical

genetic testing for their affected child with ASD or related NDD. We also assessed child, family and health service factors that may predict parental empowerment. Our results showed that higher parental perception of provision of general information predicted parental empowerment around the time of genetic testing. Interestingly, empowerment was not predicted by sociodemographic or child-specific factors; rather, there is some specificity of the effects on empowerment to factors unrelated to the individual or child characteristics, namely quality of care and family dynamics. A novel finding in the context of ASD/NDD is that empowerment was linked with parental experience of healthcare services, i.e. the extent to which parents think that they are provided with appropriate and relevant information about the child's condition and services [51]. A positive experience with information provision may increase a parent's sense of empowerment around genetic testing because they may align with the constructs inherent in the concept of empowerment, such as "decisional control", "cognitive control" and "behavioural control" [40].

Studies have shown the importance parents place on information about genetic testing [57, 58]. For example, Zhao et al. (2019) demonstrated that most parents (73.7%) of a child with ASD, who was undergoing genetic testing, were interested in receiving health education on genetic testing [57]. The most desired topics for health education included accuracy of genetic testing, cost, relevant benefits of testing, testing procedure, eligibility to undergo genetic testing, potential harms, previous use and experience among individuals affected by ASD, and confidentiality issues [57]. Studies have shown that, when the informational needs of parents were not met, this resulted in negative experiences during genetic testing, such as difficulty understanding genetic concepts and terminology, and difficulty understanding the "value" of the test [20, 21].

The perception of provision of general clinical information by the participating families in our study may be related to the pre-test counselling they received from the healthcare provider, during the clinical visit for their affected child that preceded study enrolment. This in turn may suggest that pre-test counselling plays an important role in the empowerment (i.e. personal utility) that parents derive from genetic testing for their child. Therefore, it will be of great importance that the content and process of pre-test counselling be optimized for what parents finds helpful and relevant around the time of genetic testing. Development of informational tools for parents whose children are undergoing testing may increase effectiveness and potential impact of pre-test counselling. This may include: provision of comprehensive information that is relevant to the child's diagnosis, health and service needs and community resources [59]; provision of information outside of standard clinical venues or modes of dissemination (e.g. through telehealth, on-line modules, print, etc.) [58]; provision of information to family members who may play an important family role (e.g. grandparents, siblings, first-degree relatives etc.) [60, 61]; access to information on peer-support groups and caregivers with similar lived experiences [59].

Our work lays the foundation for using PROMs to optimize and personalize the process of genetic testing, especially as novel genomic technologies are integrated in clinical care in a population where such measures have been scarcely used. Use of outcome measures like empowerment among families of a child who is undergoing more advanced genetic testing, such as GS or ES, may prove particularly useful in enhancing the clinical integration of these tests as the informational needs of families are greater due to the increased complexity of the results generated by these tests.

Our results also suggested that parental perception of their function within the family may also potentially impact parental empowerment around the time of genetic testing for their affected child. Our analysis showed a significant negative correlation between perception of family function and empowerment, although family function was not found to be a significant predictor for empowerment in our sample (but there was a trend to statistical significance). An analysis in a larger sample may offer greater insight into the relationship between family function and empowerment around the time of genetic testing. Overall family function is impacted by the presence of an NDD in a child [62]. Parents of children with ASD report lower family cohesion and adaptability than parents of unaffected children [63]. Partner interactions are under greater strain in parents of children with a chronic or neurodevelopmental condition [32-34].

It will be important to explore further the relationship between family function and personal utility from genetic testing, because if a parent perceives their function within the family to be low, they may not derive the optimal benefits of undergoing genetic care for their child. This means that both the informational needs and the existing family function may have to be taken into account in order to optimize the process of genetic testing for families. Future studies can also shed light on the importance of the intersection between genetic services and mental health services to support families undergoing genetic testing, such as social work, family therapists, counsellors, and peer-support groups, among others.

7.7 Conclusions

Participating families in our study were representative of the general population and our research protocol was embedded in existing clinical care services. This in turn, contributes to

results that are more generalizable and representative of families affected by NDDs and their clinical reality. We showed that the yield of clinical CMA in children with ASD and related NDDs from a general population sample may be lower than the reported CMA yield in the literature. Our study provides insight into the informational needs of affected families whose child is undergoing genetic testing. This knowledge, in turn, can help optimize the process of genetic testing for families, such as offering relevant and individualized pre-test counselling and support to parents. Furthermore, we demonstrate that a PROM assessing empowerment (GCOS-24) can be used as a measure of personal utility from genetic testing. This tool can be used to guide the process of refining the integration of genomic technologies in the healthcare for families affected by ASD and related NDDs.

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8. Manuscript 2: Enhancing the impact of genomics research in autism through integration of research results into routine care pathways – a case series

8.1 Preface

The use of powerful genomic technologies in large genetic studies of ASD has generated large amount of genomic knowledge. However, the translation of research genomic information into clinical care for individuals and families affected by ASD has been slow and presently clinical use of that information lags behind the fast pace of genomic discovery research. Despite many theoretical discussions about the ethical and practical aspects of returning genetic research results to participants in genomic studies of ASD, no unifying approach has been offered to guide the return of genetic results (RoR) form research and integrate them into the participants' healthcare. In Manuscript 2, I offer a framework for RoR from genomic research derived from the existing literature and expert opinion. I illustrate the application of this framework with case series involving RoR to participants from large-scale genomic studies in ASD. This Manuscript offers an evidence-based approach to bridging the gap between genomic research and healthcare in ASD.

Manuscript 2 has been submitted for publication to *Frontiers in Genetics* and is currently under review.

Enhancing the impact of genomics research in autism through integration of research results into routine care pathways – a case series

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Keywords

Return of Research Genetic Results, Autism Spectrum Disorder, Neurodevelopmental Conditions, Clinical Care Pathways

8.2 Abstract

The return of genetic results (RoR) to participants, enrolled as children, in autism research remains a complex process. Existing recommendations offer limited guidance on the practical use of genetic research results for clinical patient care. We highlight current challenges with RoR and illustrate how the use of a guiding framework drawn from existing literature facilitates RoR and the clinical integration of genetic research results. We report a case series (n = 16) involving the return of genetic results to participants in large genomics studies in Autism Spectrum Disorders (ASD). We outline the framework that guided RoR and facilitated integration into clinical care pathways. We highlight specific cases to illustrate challenges that were, or could have been, resolved through this framework. The case-series demonstrates the ethical, clinical and practical difficulties of RoR in ASD genomic studies for participants enrolled as children. Challenges were resolved through the use of pre-established framework to guide RoR and incorporate research genetic results into clinical care. We demonstrate the negative impacts when guidance is lacking. We suggest that optimal use of genetic research results relies on their integration into individualized care pathways for participants. We offer practical tools to bridge the gap between research and healthcare in ASD.

8.3 Introduction

The rapid advancement of genomic research in Autism Spectrum Disorders (ASD) has been supported by the growing participation of affected children and families, and by the use of increasingly powerful genomic tests, such as microarrays, exome and genome sequencing (ES, GS). In the clinic, genetic tests are used to find an etiology for the behaviorally defined diagnosis of ASD, which may guide healthcare for the affected individual or family (1). However, existing

clinical genetic testing recommendations are outdated and do not take into account the large increase in genetic information about ASD (2). They also do not consider the variability in care pathways within different healthcare systems (3). The genetic and clinical heterogeneity of ASD makes the return of genetic results (RoR) complex, requiring individualized genetic counseling and health management (4). Recommendations by the American College of Medical Genetics and Genomics only offer direction on RoR related to secondary finding from clinical genetic testing (5). Existing clinical RoR recommendations lag behind the fast pace of genomic discovery from ASD research and there is limited guidance in the context of neurodevelopmental conditions. This may limit access of affected individuals and families to novel genetic information that has the potential to alter their healthcare (6).

When used in research, results from genetic tests like ES and GS accelerate discovery of new genetic variants associated with ASD, but are subject to more reporting challenges than clinical tests (7). Research participants are interested in receiving their personal or their child's genetic results (8). Researchers may have the responsibility to return genetic results to participants, when these lead to changes in the participants' healthcare (9). There are several recommendations on the ethical obligations of researchers for RoR in the research context (10, 11). There are also numerous discussions regarding the broader process of RoR from research, including ethical considerations, scientific validity and clinical applicability of research results, and criteria for RoR to individuals. Supplementary Table 10-1 provides a summary of the literature on these topics. However, there are no specific recommendations on which research genetic results should be communicated and how to integrate research genetic results into participants' clinical care. Furthermore, approaches may differ across different health systems and institutions (12). Research teams may rely on clinical recommendations, which are limited in

scope. This lack of practical guidance for RoR from genetic research may result in variable practices by research teams (13, 14).

Conventional ethics frameworks for RoR are faced with new challenges stemming from the increasing frequency and complexity of genetic findings from genomic technologies. RoR from genetic studies typically aims to return findings that are actionable for participants (i.e. the finding can guide clinical decision-making) (15). Although this goal is underscored in various recommendations (Table S10-1), none have offered a comprehensive roadmap for RoR. In this report we present 16 cases involving the return of complex genetic research results to participants who enrolled as children, and their families, in large-scale genomic studies in ASD, across two different healthcare jurisdictions in Canada. We highlight specific challenges with the return of research genetic results to participants. We outline the framework that guided our RoR process (Figure 8-1), with the aim to integrate research genetic results into clinical care pathways for participants. We describe five cases in greater detail to illustrate special challenges with the RoR process that were, or could have been, resolved with the implementation of our framework. We suggest that achieving optimal utility of research genetic results for participants relies on their integration in *routine clinical care pathways*. This approach would ensure that research genetic results are maximally utilized, while minimizing potential harm to participants. It may also foster collaboration between research and clinical settings that may contribute to improved interpretation of complex genetic results, up-to-date information on actionable findings, improved care pathways for affected individuals, and accelerated translation of research into clinical care.

8.4 Methods

The cases involved children and their families, who participated in large-scale multi-site genomic studies in ASD between 2007 and 2017, namely, the Simons Simplex Collection (SSC) (www.sfari.org/resource/simons-simplex-collection/) and MSSNG (www.mss.ng), by enrolling through our research site. The SSC recruited children with ASD, their sibling and biological parents. MSSNG continues to recruit children with ASD, siblings and biological parents. Families were recruited from hospital or community clinics where children underwent diagnostic assessments. Once a research genetic result was available for a participant, the primary study site initiated RoR by contacting us (secondary site) to complete the process. There was a time lag between recruitment and RoR, due to lengthy research analyses. Clinical information was obtained by clinical and research charts review. The studies involving human participants were reviewed and approved by the Research Ethics Board of the Research-Institute of McGill University Health Centre. The participants or their legal guardians, if enrolled as children, provided their written informed consent to participate in this study.

Prior to commencing RoR, we convened a workgroup of local experts from Montreal Children's Hospital and McGill University to develop a site-specific protocol for RoR to research participants. The workgroup consisted of a geneticist, a child and adolescent psychiatrist, a developmental pediatrician and a researcher (site investigator in the multi-site study). Ongoing consultation was sought from an ethicist. By reviewing cases as they arose and the existing literature (Table S10-1), the workgroup iteratively developed the proposed framework presented in Figure 8-1. The workgroup held in-person and virtual discussions on initial cases of return of results to research participants at our site, resulting in an initial framework for RoR. The framework was refined with subsequent cases, based on informal

feedback from the research staff and participants involved in the actual RoR process, and as new RoR situations arose. The goal was to develop a RoR framework that provided guidance on key aspects when a research genetic result was available, with the intent of result integration into the participant's clinical care pathway, irrespective of healthcare jurisdiction. The framework involves five principles to guide RoR (Figure 8-1):

1. *Relevance of genetic result to current and future care:* genetic and personal health information should be synthesized to determine if the research result is actionable.
2. *Participant/family expectations, preferences and decisions*: preferences for receipt of research result should be elicited from the individual/family, at the time of consent and when an actionable result is available.
3. *Person/family-centeredness:* the research team should collaborate with the Most Responsible Clinician (MRC) (primary care or specialist) for the individual/family receiving the genetic result, to foster personalized healthcare pathways.
4. *Care coordination*: routine health services (e.g. access to genetic specialist) should be actively engaged to ensure that resulting care pathways are clear and accessible.
5. *Benefits and risks*: potential positive and negative impacts of the genetic result on the participant/family and on clinical care pathways should be considered and managed.

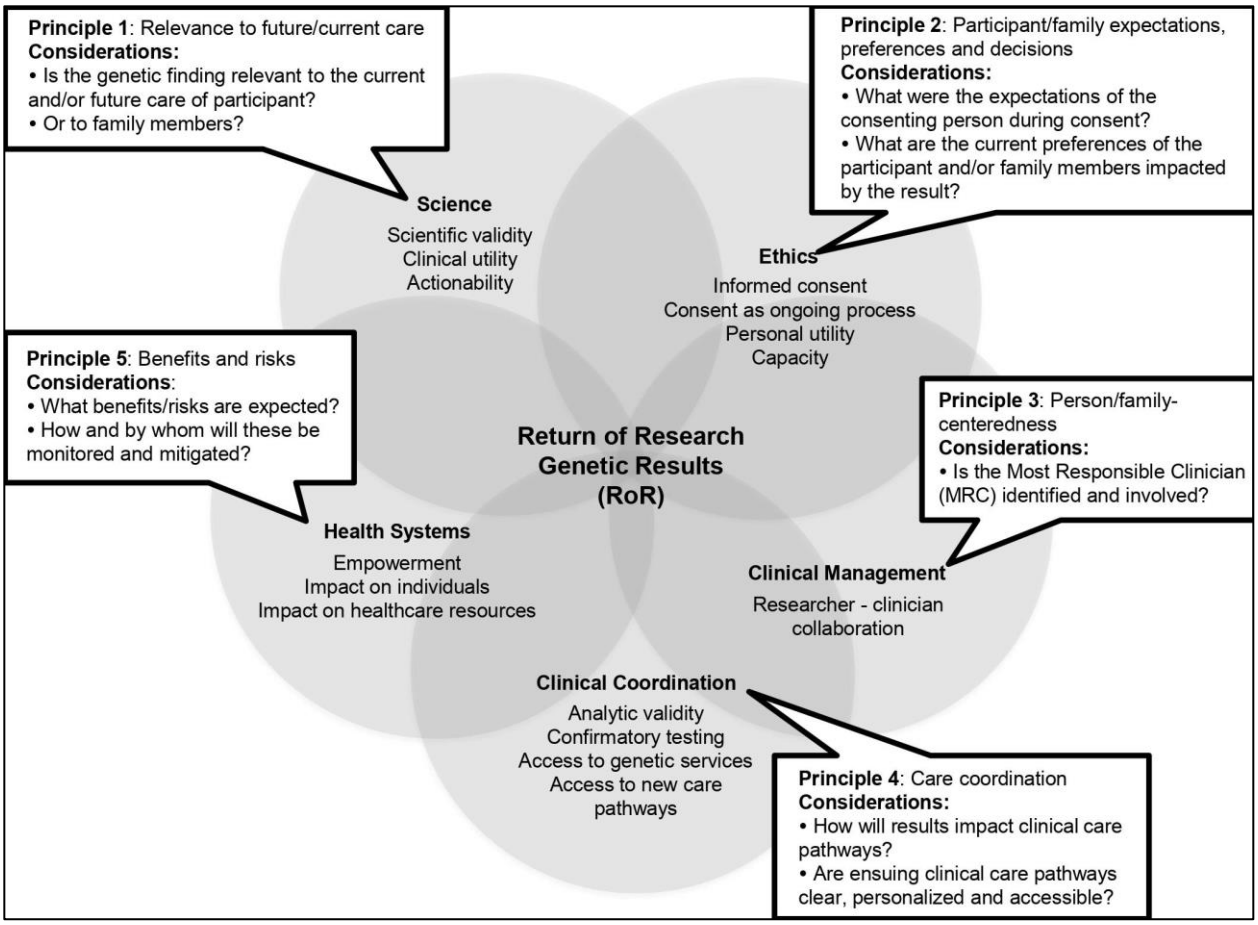

Figure 8-1. Summary of the proposed RoR framework and principles, and their alignment within ethical, scientific and healthcare domains.

8.5 Results

Our research site received genetic research results for 16 participants, who enrolled as children. The average time between enrollment and genetic result availability was 5.5 years. Efforts were made to contact families by all means available. Three participants (cases 7, 11 and 16) lost to follow up and could not be re-contacted. In two cases, genetic results were returned to the family prior to RoR by our site: for case 3, the result was returned by another research study that the family participated in; for case 10, the result was identified on routine clinical genetic

testing. Characteristics of the participants and relevant genetic information are summarized in Table 8-1. The majority (n=14) of cases involved a male participant and all were probands except for one (unaffected sibling). Five of the participants had reached adulthood by the time of RoR. The caregivers who provided consent at enrollment were contacted to facilitate contact with the now adult participants. Of the genetic results, 12 were CNVs, 4 were SNVs and 1 was aneuploidy. Most genetic changes were on chromosomes 1, 15 and 16. Of the CNV results, 6 were deletions (at 9q21.13, 15q11.2, 15q13.1, Xp22.31, and two at 16p13.11) and 6 were duplications (two at 1q21.1, 15q13.1, and 16p11.2; one at 1q43). The majority of genetic changes (n = 10) occurred *de novo*. In the following section, we outline five cases in greater detail in order to highlight specific challenges in the RoR process and illustrate the application of our guiding framework to resolve or circumvent these.

Table 8-1. Characteristics and genetic findings of participants for whom a genetic research result was available.

Case	Sex	Affected Region	Type	Inheritance	Clinical significance	Age at RoR	Outcome of RoR
1	M	hg19 chr1: g.[5663T>G]	SNV	De novo	*mTOR* involvement	6 years	Result returned Clinical care provided
2	F	hg19 chr2: g.[230701696G>A]	SNV	De novo	*TRIP12* involvement Nonsense mutation	24 years	Result returned Clinical care provided
3	M	hg19 chr10: g.[89692908C>T]	SNV	De novo	*PTEN* involvement Known missense effect Characterized syndrome	10 years	Result returned Clinical care provided
4	F	hg19 chr16: g.[2131695C>T]	SNV	De novo	*TSC2* involvement Missense mutation Characterized syndrome	19 years	Result returned Clinical care provided
5	M	1q21.1	CNV dup	De novo	1.4Mb del. of 10 genes Characterized	14 years	Result returned Clinical care provided

					syndrome		
6	M	1q21.1	CNV dup	De novo	1.4Mb del. of 10 genes Characterized syndrome	15 years	Result returned Clinical care provided
7	M	9q21.13	CNV del	De novo	4.8Mb del. of 18 genes	12 years	Lost to follow up
8	M	15q11.2	CNV del	Maternal	VUS 512.4kb del. of 4 genes	11 years	Result returned Clinical care provided
9	M	15q13.1 1q43	CNV dup CNV dup	Maternal De novo	VUS 254kb dup. in 1 gene VUS 28.6kb dup. in 1 gene	12 years	Result returned Clinical care provided
10	M	15q13.2	CNV del	Unknown	1.59Mb del. of 5 genes Characterized syndrome	10 years	Results previously identified on clinical genetic testing
11	M	16p11.2	CNV dup	Paternal	561kb dup. of 30 genes Characterized syndrome	20 years	Lost to follow up
12	M	16p11.2	CNV dup	De novo	633kb dup. of 31 genes Characterized syndrome	12 years	Result returned Clinical care provided
13	M	16p13.11	CNV del	Paternal	1.2Mb del. of 13 genes Characterized syndrome	14 years	Result returned Clinical care provided
14	M	16p13.11	CNV del	De novo	921kb del. of 9 genes Characterized syndrome	20 years	Result returned Clinical care provided
15	M	Xp22.31	CNV del	Maternal	1.6Mb del. of 5 genes Characterized syndrome	22 years	Result returned Clinical care provided
16	M	XXY	Aneu-ploidy	De novo	Characterized syndrome	22 years	Lost to follow up

Case 3

JD is a 10-year old male with ASD and intellectual impairment, who was enrolled in the genetic study at age 4. He was subsequently enrolled in a second genetic study based in a different country. The second research study identified a WES result showing a *de novo*

missense SNV in the *Phosphatase and Tensin Homolog* (*PTEN)* gene, mutations in which are associated with hamartoma tumor syndromes (MIM 607028) (16). The *PTEN* hamartoma tumor syndrome is associated with macrocephaly, developmental delays and autism (16). The variant was classified as pathogenic. Its health implications made it clinically actionable and necessitated disclosure.

The second research site, which was in a different healthcare jurisdiction than the family, communicated the result in a letter to the participant's mother, before the RoR process from first research site where the family enrolled (our site). The mother was encouraged to seek help from local health services but access to those was not facilitated. The family's preferences about the management of the research genetic result were not elicited. The letter triggered significant distress in the mother. She had no guidance on accessing and navigating clinical services within their jurisdiction. The family contacted several researchers and clinicians outside their circle of care to seek guidance. After significant delays, the family obtained access to clinical genetic counseling in their region.

The case illustrates the negative impacts of RoR arising from the absence of a clear pathway for the integration of actionable research genetic findings into clinical care. This contributed to family distress, delays in service provision, and inefficient use of healthcare resources. It also demonstrates the need to monitor the risks and benefits from RoR. The application of our guiding framework could have potentially circumvented these issues.

Case 4

JM is a healthy 19-year-old female whose adult sibling has ASD. As children, the siblings enrolled in the genetic study, along with their parents. Research microarray and ES

analyses were performed for all. The ES for JM revealed a *de novo* missense SNV in the *Tuberous Sclerosis 2* (*TSC2)* gene. Mutations in *TSC2* may cause Tuberous Sclerosis Complex (TSC) (MIM 191092), an autosomal dominant disorder characterized by hamartomas in several organ systems (17). TSC is associated with developmental and learning difficulties, central nervous system tumors and renal problems (17).

At the time of enrollment, JM was a healthy child, with no neurologic or developmental difficulties. The variant in JM was not previously reported in the literature. The central study site reported the finding as a variant of uncertain clinical significance (VUS), possibly pathogenic. The predicted clinical impact was deemed actionable, warranting disclosure to the participant. Clear health surveillance guidelines for TSC exist (18), along with specialized clinics in JM's community.

JM's mother was contacted, as she consented to JM's research participation at enrollment, to inform her that a genetic result from was available. JM was an adult so her preferences regarding the receipt of the result were obtained. JM expressed desire to learn about the genetic finding. With her permission, the research team collaborated with her MRC (family doctor) on integration of the research result into JM's healthcare. The MRC referred JM to her local genetics clinic for confirmatory clinical genetic testing and counseling. The case demonstrates the integration of novel genetic information from research into the clinical care of a research participant, by considering actionability of findings and preferences of the participant. Collaboration between research and clinical services resulted in clear and person-centered healthcare pathways.

Cases 8 and 9

NM and DM are siblings, 11 and 12 years old, respectively, who have ASD. They enrolled with their parents in the genetic research study. Few years later, during a clinical work-up of NM, a maternally inherited deletion at 15q11.2 was found. The parents were informed of the result by the ordering clinician, but were unable to obtain genetic counseling. Soon after, research microarray results became available for both siblings from the genetic study: NM had the previously identified maternally inherited deletion; DM had a maternally inherited duplication at 15q13.1 and *de novo* duplication at 1q43. The mother did not have any neurodevelopmental conditions.

Deletions in the 15q11 region have been associated with developmental and neurologic issues, with variable penetrance and expressivity (19). The deletion at 15q11.2 was deemed a VUS by the research laboratory. The duplication at 15q13.1 overlapped exons of the *Amyloid Beta Precursor Protein Binding Family A Member 2* (*APBA2*) gene, variants in which have been reported in ASD and psychiatric conditions (20). The 1q43 duplication encompassed the intronic region of *Phospholipase D Family Member 5* (*PLD5*) gene, variants in which have not been reported in ASD. Both CNVs in DM were classified as VUS by the research laboratory. Genetic counseling was recommended for the siblings as the genetic results had a possible link to their neurodevelopmental condition and health implications for them and their family. The genetic findings had relevance to their current and future healthcare and necessitated disclosure.

The research team contacted the family to obtain their preference for accessing the information. With the family's permission, the MRC (pediatrician) was contacted. The MRC facilitated confirmatory clinical genetic testing for DM (clinical microarray was already available for NM) and referred the family to the regional clinical genetics clinic. The case

highlights how a collaborative approach to RoR, by implicating the MRC, facilitated clinical integration of research genetic results and access to routine clinical care.

Case 15

At enrollment, TZ was a 15-year old male with Asperger's Syndrome, enrolled with his family in the genetic study. Research microarray showed a maternally inherited deletion at Xp22.31, affecting several genes, including *Steroid Sulfatase* (*STS*). Mutations in *STS* have been associated with X-linked ichthyosis (MIM 308100) (21). Affected individuals may have extra-cutaneous manifestations (22), ASD and other neurodevelopmental conditions (21). The research laboratory classified the result as likely pathogenic and genetic counseling was recommended. The genetic finding was relevant to TZ's neurodevelopmental diagnosis and other health aspects, so it required communication.

TZ had reached adulthood since enrollment, which took place seven years prior to the availability of the genetic result. The research site notified the family that a research result was available. TZ was an adult capable of making personal health decisions. His mother was also a participant in the study and a carrier of the genetic change. Both had the opportunity to independently express their preferences to learn about the result. TZ had never had clinical genetic testing. He chose not to pursue the matter further. However, his mother expressed interest in learning about the genetic result and its implications for her and TZ's unaffected sibling. With the mother's permission, the research team contacted the MRC (family doctor) and collaborated on the care coordination for the mother and sibling. The MRC referred them to the genetic clinic in their healthcare jurisdiction for confirmatory testing and counseling. This case underscores the importance of eliciting the expectations and preferences of research participants

for whom a research genetic result is available. Personal choice about the receipt of results may differ, even among family members. Genetic results may impact family members differently, based on several factors, including carrier status and clinical profile.

8.6 Discussion

The interpretation of genetic findings in ASD requires careful consideration of existing genetic information in a highly individualized context. Current clinical RoR recommendations do not offer ASD-specific guidance and lag behind novel information from genomic studies. Within research, various RoR recommendations focus on specific topics, but do not present a practical roadmap for the return of genetic findings to participants in ASD research. Our case-series illustrate the complexity of RoR from genetic research studies in ASD. We demonstrate that RoR entails an overlap of ethical issues, complex science, clinical considerations and health systems (Figure 8-1). We utilized a framework of principles derived from the literature (Table S10-1) to guide RoR from research, in order to resolve challenges and integrate genetic research results into clinical care pathways for participants. This approach facilitates a mutually beneficial partnership between clinical and research domains and an application of research genetic results for individual care. The framework we propose steers the RoR process and the clinical integration of genetic research findings in ASD.

Genomic discovery research casts a wide net in order to capture the numerous genes involved in brain development and function, maximizing the chance of actionable findings. Existing ethics recommendations state that researchers must outline if and how their expected genetic results will be returned to participants (10, 11, 23, 24). Return of *actionable* genetic findings is now accepted as standard ethical conduct (10, 23-26). However, interpreting the

actionability of genetic findings can be challenging (6). Recommendations for the interpretation and reporting of results from *clinical* genetic tests have offered broad classification (5, 27, 28). However, the onus is on clinical laboratories and geneticists to make an informed decision about actionability of the results. In research, clinical guidelines are even less applicable, as they do not account for novel information generated by advanced genetic tests. We suggest that research teams consider the participants' personal factors in determining the actionability of a research result. This may be achieved by collecting detailed health data for a contextual interpretation of the genetic research result. Thus, during the RoR process, researchers must synthesize genetic and personal information in order to determine the actionability of research findings.

Ethics recommendations favor clear communication at the time of consent of the researcher's plan for returning results (11, 24). Adult participants should be offered the choice to opt out of receiving personal genetic results (10, 26). A study showed that although most participants valued receiving incidental findings from research, personal utility depended on the type of finding and not all participants wanted to receive results (29). This suggests that a "one-size-fits-all" approach in RoR is not ideal. The timing of RoR also influences personal utility. A study of the return of actionable results to cancer research participants showed that timing of RoR within the individual's current life experiences was important (30). The perspectives of the person/family receiving the results must be considered, which are modified by time and their healthcare journey. Consent should be an ongoing process (11), which is especially important given the time lag between research consent and RoR. The participant's decision at consent about the return of research results should be confirmed before RoR (11). This also ensures that the preferences of adult participants, enrolled as children, are taken into consideration.

Effective RoR from research relies on active engagement of routine health services to ensure that resulting care pathways are personalized, clear and accessible. This at a minimum includes confirmatory testing of the research result at a certified clinical laboratory (26) and the involvement of genetic specialists. The integration of genetic research results into clinical care raises the issue of impact on health system resources. Concerns have been expressed about the practicality, infrastructure and costs of such integration (31). The integration of genetic research results in the healthcare of participants is not meant to replace clinical genetic testing. It is meant to enhance the participant's healthcare if an actionable genetic research result is identified. Moreover, technologies used in genomic research may soon become standard of clinical care (32). Thus, RoR from research can provide valuable insights into the integration of complex genetic information in personal healthcare. This knowledge may help with the implementation of more powerful genetic tests in clinical care for neurodevelopmental conditions.

Collaboration between the research team and the MRC can foster person/family-centered healthcare pathways from the return of genetic research results. Primary care providers desire increased knowledge, closer ties to genetics specialists and access to reliable resources about personalized medicine (33). Models of RoR where the research team takes on aspects of clinical care, like genetic counseling, run in parallel to existing healthcare pathways. They may not address all of the individual's needs and may lack longitudinal involvement. We propose that the research team collaborate with healthcare providers on the integration of genetic research results into clinical care. The MRC can support the individual/family through the receipt of genetic results and ensure that they navigate relevant services. A collaborative model between research teams, healthcare providers and genetic specialists offers continuity and person/family centered care.

Qualitative studies suggest that genetic results can have both positive and negative effects on families. For example, genetic results may inform the prognosis, medical management and health surveillance of a child (34, 35). Some parents report a sense of comfort in knowing the biologic cause of their child's condition, and that genetic results improve access to services (1, 34, 35). On the other hand, parents may have high levels of uncertainty about the meaning of the genetic result for their child or family (35, 36). They may have negative emotional responses, like guilt or blame, about the heritability of a genetic finding, and disappointment with the lack of meaningful impact on services (34-36). We suggest that there should be an effort by research teams to weigh the potential positive and negative impacts when making decisions about RoR. An important goal should be to actively monitor and minimize negative effects on participants receiving genetic research results, in collaboration with the MRC and/or clinical genetic services if required.

The proposed framework for RoR (Figure 8-1) offers practical guidance on returning complex genetic results to research participants and integrating them into individual clinical care. It serves as a scaffold for a systematic approach to RoR, bridging the gap between research and healthcare. The ultimate goal is to maximize the application of genetic knowledge in the care of people with ASD, through a tailored process at the level of the individual and their health system. The identification of a genetic etiology in a participant may have implications for family members who are carriers, but who are unaffected or have traits of the broader ASD phenotype. The RoR framework may also apply to contexts beyond ASD, such as intellectual disability, given the genetic overlap between neurodevelopmental conditions. Further research should focus on understanding the impact of RoR on the individual and broader system level, such as through patient reported outcome measures, measures of clinical utility, and assessments of resource and

economic impact. This will allow the refinement of the RoR process as genetic discovery research continues to enhance our understanding of neurodevelopmental conditions.

8.7 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

8.8 Author Contributions

IP and ME conceptualized the study. IP carried out all data gathering, analyses, initial manuscript preparation and subsequent revisions; ME provided advice on methodology and analyses, and revised the manuscript. DB, LS and EK provided advice on methodology. AY assisted with data collection. DB, LS, EK and AY revised the manuscript.

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9. General Discussion

Genomic technologies have greatly advanced over the past decade and have revealed a large amount of information about the genetic underpinnings of ASD and related NDDs [1]. The genomic factors contributing to NDDs entail a lot of complexity [2]. CMA is now considered standard clinical testing for the investigation of individuals with ASD and related NDDs [3]. More advanced genomic technologies, like ES and GS, are already utilized in some clinical settings and may soon become routine clinical investigations for NDDs [4, 5]. As these genomic technologies gain traction, there is a need for a comprehensive, efficient and personalized approach to integrating genetic testing and up-to-date genomic information into the healthcare of individuals and families affected by NDDs. My thesis offered insight and tools for quantifying and understanding the impact of genetic testing on affected families, and for integrating relevant genetic information from research into clinical care.

9.1 Summary of Findings

In the first study of my thesis (Manuscript 1) I prospectively evaluated the utility of genetic testing (CMA) in a cohort of families with a child affected by ASD or a related NDD. I quantified both diagnostic yield and personal utility of parents whose child with NDD was undergoing genetic testing, in order to gain a better understanding of the impact of genetic testing on affected families. I utilized the modified Genetic Counseling Outcome Scale (GCOS)-24 [6], to measure parental empowerment as a proxy for personal utility derived from undergoing the process of genetic testing for their affected child. I examined if child, family or service factors as predictors of parental empowerment around the time of genetic testing. My approach to this topic is novel for several reasons: 1) I quantified diagnostic yield and personal

utility (via empowerment) in a sample of participants representative of the general population and of the clinical heterogeneity of NDDs; 2) I measured parental personal utility using a novel and recently validated patient reported outcome measure (PROM) in the context of NDDs (ref); 3) I am the first to explore the association between empowerment from genetic testing and child, family and health service factors.

This study showed that the diagnostic yield of CMA in a sample of children with ASD and NDDs representative of the general population, and thus heterogeneous in its clinical presentation, was lower than typically reported in studies assessing the diagnostic yield in populations from specialty clinics that may be more prone to referral bias. It also showed that the information needs of parents, as part of the clinical care they receive prior to genetic testing, play an important role in the personal utility (i.e. empowerment) they derive from genetic testing. The family function of parents may also impact their personal utility. My study demonstrated that, contrary to what some literature may suggest [7-10], sociodemographic and child-specific factors do not impact the empowerment parents experience at the time of undergoing genetic testing for their child. This may be because personal utility of genetic testing at that time in a family's healthcare journey may be more closely tied to quality of care and family dynamics rather than factors external to these.

The second study of my thesis (Manuscript 2) provided a summary of the existing literature on the return of results (RoR) from genomic research and offered a framework for RoR to research participants in genomic studies of ASD. The framework was informed by the literature and expert opinion, and provided a systematic approach to RoR with the aim of genetic result integration into the individual's healthcare. I illustrated the application of this framework through a case series involving RoR to research participants from large-scale genomic studies in

ASD. Despite numerous existing discussions on different aspects of RoR from research, this is the first study to offer a practical roadmap for RoR to research participants, specific to ASD and related NDDs. I am also the first to extend the RoR process to include genetic result integration into the participant's existing healthcare in a personalized manner. In Manuscript 2, I offer one approach to enhancing the greater cross-talk between the research and clinical realms in order to facilitate the application of the rapidly generated genetic knowledge form research into clinical care for individuals and families with ASD.

Overall, my thesis offers further insight into the impact of genetic testing on families affected by ASD and related NDDs, and provides tools to enhance the integration of genomic care in NDDs. I next discuss the implications of this information for personalized genomic care in NDDs.

9.2 Implications for personalized genomic care in NDDs

The use of genetic testing in the clinical investigation of NDDs has already transformed care for some affected individuals and families by providing a biological etiology and ending the "diagnostic odyssey", altering health surveillance and access to services, or informing family planning [11, 12]. However, determining the full value and ensuring greater personalization of genomic technologies require metrics that extend beyond laboratory-based performance and clinical outcomes. Patient reported outcome measures (PROMs) have the potential to assess another aspect of genetic testing, namely the personal utility derived by affected individuals and families. I propose and demonstrate that personal utility from undergoing genetic testing can be assessed through the construct of empowerment, and non-clinical factors, such as informational needs and family function are associated with it. The use of PROMs, like the GCOS-24

questionnaire that measures empowerment, can be a valuable tool for capturing the impact of genetic testing and genetic services, including pre- and post-genetic counseling, in a variety of clinical settings external to typical genetic clinics. This may be a valuable tool for optimizing the integration of genomic technologies in a variety of clinical services, given that genetic testing is now routinely offered by specialists other than geneticist, e.g., developmental pediatricians, psychiatrists, etc. [13]. Information from my thesis lays the basis for further work on the optimization and tailoring of more advanced genomic technologies, like ES and GS, which soon will be part of the clinical care of those affected by NDDs.

My thesis highlights that the informational needs and family function of parents experiencing genetic testing for their affected child play an important role in the empowerment, and hence personal utility, they derive form the process of genetic testing. This in turn suggests that tailoring the pre-test counseling process and meeting the information needs of families may allow them to derive greater personal utility from genomic technologies, in general.

As scientific knowledge of the genetic contributors to ASD and related NDDs expands, clinical recommendations need to be updated to reflect the rapid expansion of genomic information and its implications for clinical care of affected individuals and families. My thesis offers a pragmatic approach for integrating genetic information generated from research into the clinical care of research participants that relies on collaboration between the research and clinical realms. The framework for return of genetic research results I propose relies on a person- and family-centered approach to the process of returning genetic results from research.

Future research should focus on evaluating personal utility form genomic technologies in variety of contexts and settings, as well as refining the RoR process from more advanced genomic tests in NDDs.

9.3 Limitations and future research

My thesis utilized different methods for each study presented in the individual manuscripts. In Manuscript 1, I utilized questionnaires in a cohort of families recruited from clinical services, whose affected child with NDD was undergoing clinical genetic testing. One challenge with this study was the possibility of self-selection bias. Families who chose to participate in the study may be primed to experience greater personal utility than families who did not participate. That being said, the reason for not participating cited by the majority of non-participating families was lack of time, so they may be poised to experience similar personal utility from genetic testing as participating families, even though this was not captured in my study.

Another challenge was the loss of data, because some parents did not complete all questionnaires. This may have led to a less powered analysis. I attempted to circumvent this issue by analyzing the entire Genome to Outcome study cohort and compare the results with the analysis of only families who had no previous experience with genetic testing, which revealed the same results.

One other issue was the variability in the time elapsed between the clinical appointment during which parents received counselling on clinical genetic testing for their child and the study enrolment. This may have contributed to an underestimation of parental empowerment or perception of family centeredness of care, as more time would have elapsed between the receipt of relevant clinical information and the completion of the questionnaires.

Lastly, there likely are other parental, child or service factors that contribute to parental empowerment at the time of genetic testing that have not been explored, such as mental health and quality of life.

The information from Manuscript 1 offers leads into several areas of future research. I demonstrated that the general health information received by families prior to genetic testing is associated with their empowerment from genetic testing. Therefore, future research should explore how to optimize the content and process for delivering general health information in the context of family-centred care for NDDs, as well as genetic information in the context of pre-test counselling. Another area for future research is the use of PROMs, such as the GCOS-24, to evaluate the personal utility of affected individuals and families receiving genetic services, such as pre- and post- genetic counselling and genetic testing, in different clinical settings (e.g. genetic clinics, developmental pediatric clinics, general pediatric clinics, psychiatric clinics, etc.). This information can be valuable in refining and personalizing the patient experience. Furthermore, the GCOS-24 can be used to assess empowerment in families undergoing more advanced genetic testing, like ES and GS.

In Manuscript 1, I demonstrate that family function may be another potential factor impacting empowerment from genetic testing. Further research is needed to validate this finding in larger cohort of families who are undergoing genetic testing for the first time. It will be of importance to investigate ways of integrating allied health services to support families undergoing genetic testing, such as social work, family therapists, counsellors, and peer-support groups.

In Manuscript 2, I offer a systematic RoR framework for the return of genetic research results and their integration into routine clinical care, and illustrate the application of that framework through case series. Although a case series was a reasonable starting point given that few empirical studies exist, the study findings are not generalizable. In addition to the small sample size, there was no comparison to a group of participants who received genetic research

results using other strategies. Thus, an area of future research may be to prospectively investigate the utility of the RoR framework both from a researcher and a research participant perspective, and for a variety of NDDs beyond ASD, such as ID and GDD. Further research should also focus on understanding the impact of RoR from research on the individual and broader system level, such as through validated PROMs, measures of clinical utility, and assessments of resource and economical impact. This will allow refinement of the RoR process and may contribute to more meaningful recommendations for RoR from research.

9.4 Conclusions

Overall, my thesis work has made important contributions to the personalization of genomic care for individuals and families affected by ASD and related NDDs. I contributed to clarifying the impact on affected families of undergoing clinical genetic testing by examining an important aspect of that impact - personal utility – and factors associated with it. I put forth and demonstrated the feasibility of a framework for returning research genetic results to research participants and integrating genetic knowledge generated by research into their clinical care. Ultimately, the information from my thesis may contribute to the development of an evidence-based and person-centered approach to integrating genomic research and genomic care into the health care for individuals and families affected by NDDs.

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10. Appendices

10.1 Supplementary material for manuscript 1

Table 10-1. Summary of existing recommendations and discussions on return of genetic results.

RoR Theme	Applicable Questions	Relevant References
RoR process	Formulated with aid from an independent advisory committee?	Fabsitz et al. 2010
	Explicitly stated in the study protocol approved by Ethics Board?	Caulfield et al. 2008 Miller et al. 2010 Pres. Commission. 2013 Tri-council Policy 2014 Sénécal et al. 2015 Thorogood et al. 2019
	Consistent with legal and ethical frameworks?	Fabstitz et al. 2010 Wolf et al. 2012 Zawati et al. 2014 Thorogood et al. 2019
	Current and future specific tests (e.g., microarray, WES, WGS) characteristics considered?	Fabstitz et al. 2010 Zawati et al. 2014 Thorogood et al. 2019
	Family context considered?	Knoppers et al. 2013 Zawati et al. 2014 Sénécal et al. 2015 Thorogood et al. 2019

	Management of incidental/secondary findings considered?	Wolf et al. 2008 Pres. Commission. 2013 Green et al. 2013 Tri-council Policy 2014 Thorogood et al. 2019
	Expertise available to aid result interpretation?	Caulfield et al. 2008 Wolf et al 2012 Green et al. 2013 Tri-council Policy 2014 Holm et al. 2014 Zawati et al. 2014 Sénécal et al. 2015
Individual preferences	Preferences for RoR of individual?	Caulfield et al. 2008 Wolf et al. 2008 Fabsitz et al. 2010 Wolf et al. 2012 Green et al. 2013 Knoppers et al. 2013 Pres. Commission 2013 Tri-council Policy 2014 Jarvik et al. 2014 Holm et al. 2014 Zawati et al. 2014

		Sénécal et al. 2015 Thorogood et al. 2019
	Process of RoR for minors (whose guardians are consented)?	Wolf et al. 2008 Green et al. 2013 Jarvik et al. 2014 Zawati et al. 2014 Sénécal et al. 2015
	Preferences for re-contact for results and/or further studies?	Wolf et al. 2008 Thorogood et al. 2019
	Involvement of Most Responsible Clinician in RoR process?	Wolf et al. 2008 Sénécal et al. 2015
Criteria for RoR in individual cases	Is the finding primary, secondary or incidental?	Wolf et al. 2008 Pres. Commission.2013 Green et al. 2013 Thorogood et al. 2019
	Does it have current and/or future health implication?	Caulfield et al. 2008 Wolf et al. 2008 Fabsitz et al. 2010 Green et al. 2013 Knoppers et al. 2013 Sénécal et al. 2015 Thorogood et al. 2019
	Is it clinically actionable?	Caulfield et al. 2008

		Fabsitz et al. 2010 Wolf et al. 2012 Green et al. 2013 Knoppers et al. 2013 Jarvik et al. 2014 Sénécal et al. 2015
	Does it have therapeutic benefit?	Caulfield et al. 2008 Wolf et al. 2008 Fabsitz et al. 2010 Green et al. 2013 Knoppers et al. 2013 Jarvik et al. 2014 Sénécal et al. 2015
	Is it analytically valid?	Caulfield et al. 2008 Wolf et al. 2008 Fabsitz et al. 2010 Wolf et al. 2012 Knoppers et al. 2013 Jarvik et al. 2014 Holm et al. 2014 Sénécal et al. 2015 Thorogood et al. 2019

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