Family engagement in autism biomarker discovery

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Abstract

Autism spectrum disorder (ASD) is a life-long neurobiological developmental condition characterized by impairments in social skills and communication, and repetitive behaviour. Biomarker discovery is a major priority in ASD research to improve the lives of affected individuals and their families. Stakeholder engagement in biomarker discovery has been proposed as a solution to overcome challenges in integrating biomarker discovery into the care pathways. Yet there is little consensus on the concepts and methodology needed to effectively engage stakeholders in biomarker discovery, including the target groups, process, and timing of engagement.

The overarching aim of this thesis was to develop and implement a systematic approach for engaging stakeholders in ASD biomarker discovery. Building on a synthesis of existing theoretical frameworks, I proposed a model for stakeholder engagement in ASD biomarker discovery. In this model, I proposed empowerment as an outcome of the integration of biomarker discovery and two modifiers of empowerment: *perceived utility* of biological testing and *knowledge* about ASD.

Manuscript 1 uses a scoping review methodology to assess the extent to which stakeholder engagement has been feasible based on concrete applications from ASD biomarker discovery. The review revealed limited, albeit clear, empirical examples of family engagement, in three areas: 1) understanding the values of a target community; 2) long-term priority setting with the community; and 3) collaboration in research design. I concluded that advancing family engagement in ASD biomarker discovery requires the development of tools that could measure

the outcomes of biomarker discovery along with the predictors and modifiers of these outcomes among a large and representative sample of families within the ASD care pathway.

In Manuscript 2, I adapted a measure of empowerment (the Genetic Counselling Outcome Scale) as a potential outcome of genetic testing, a recently integrated biological testing within routine care pathways. The adapted measure was implemented among a representative sample of families whose child was receiving this biological testing as part of the ASD diagnostic care pathway. The measure demonstrated good face validity and internal consistency. Further, empowerment was inversely correlated with parent stress and distress. The results suggest that empowerment is a relevant outcome for the integration of biomarker discovery in this population.

Finally, in Manuscripts 3 and 4, I examined potential predictors of biomarker discovery: perceived utility of biological testing and knowledge of ASD using new measures I developed and validated. I found that among affected families undergoing the diagnostic care pathway for their child, lower levels of child functioning and higher levels of family functioning correlated with higher perceived utility for biological testing. I also found that higher parental distress was associated with higher levels of knowledge about ASD. Overall the four manuscripts provided converging evidence of the feasibility of family engagement in biomarker discovery and its integration into the diagnostic care pathway.

I demonstrated how the utility of genetic testing can be systematically assessed in the context of routine care pathways. I conclude that establishing the overall utility of biomarker discovery

requires family engagement not only to improve the impact of already integrated biological tests, but also to determine the readiness of biomarker discovery to be integrated into the care pathway of ASD.

Résumé

Le trouble du spectre de l'autisme (TSA) est une condition chronique neurobiologique qui est caractérisée par des troubles au niveau des capacités sociales, de la communication, ainsi de des comportements répétitifs. La découverte de biomarqueurs est une priorité en recherche dans le domaine du TSA. La mobilisation des parties prenantes dans la découverte de biomarqueurs a été proposée pour surmonter les obstacles à l'intégration de la découverte de biomarqueurs au sein des parcours de services. Cependant, il y a peu de consensus sur les concepts et la méthodologie nécessaires pour impliquer efficacement les parties prenantes dans la découverte de biomarqueurs.

L'objectif principal de cette thèse est de développer et de mettre en oeuvre une approche systématique pour impliquer les parties prenantes dans la découverte de biomarqueurs. En me basant sur une synthèse des cadres théoriques existants, j'ai proposé l'autonomisation comme mesure des résultats de la découverte de biomarqueurs et deux modificateurs d'autonomisation : la *perception de l'utilité* des tests biologiques et les *connaissances* du TSA.

Pour le Manuscrit 1, j'ai utilisé un examen de la portée méthodologique pour évaluer la faisabilité des approches basées sur l'engagement des parties prenantes dans la découverte de biomarqueurs en autisme. Cette revue révéla des exemples empiriques, bien que limités, d'engagement de familles dans trois domaines : 1) la compréhension des valeurs de la communauté ciblée, 2) le développement des priorités à long-terme avec la communauté, et 3) la collaboration dans le développement de projets de recherche. J'ai conclu que l'avancement de l'engagement familial au sein de la découverte de biomarqueurs en autisme demande le

développement d'outils pouvant mesurer les prédicteurs, modificateurs, et les résultats de l'engagement parmi un grand échantillon de familles étant au sein du système de soins en autisme.

Dans le manuscrit 2, j'ai adapté une mesure de l'autonomisation "*Genetic Counselling Outcome Scale*" comme résultat potentiel des tests génétiques, un test biologique récemment intégré dans le cadre de procédures de soins de routine. Cette mesure a été utilisée avec un groupe représentatif de familles ayant un enfant recevant ce test dans le cadre des soins de diagnostique d'un TSA. Cette mesure a démontré une bonne validité apparente et une cohérence interne. L'autonomisation était inversement corrélée au stress et à la détresse des parents. Ces résultats suggèrent que l'autonomisation est une mesure des résultats pertinente de l'intégration de la découverte de biomarqueurs, dans cette population.

Finalement, dans les Manuscrits 3 et 4, j'ai examiné la perception de l'utilité des tests biologiques et des connaissances du TSA. Ceci fut accompli en utilisant de nouvelles mesures que j'ai développées et validées. J'ai constaté que des niveaux de fonctionnement de l'enfant plus bas et des niveaux de fonctionnement de la famille plus élevés étaient corrélés à une plus grande utilité perçue pour les tests biologiques. J'ai constaté qu'une plus grande détresse parentale était associée à des connaissances plus approfondies sur les TSA. Dans l'ensemble, ces quatre manuscrits soutiennent la faisabilité de l'engagement de la famille dans la découverte de biomarqueurs, ainsi que son intégration au sein des parcours de services menant au diagnostic.

J'ai démontré comment l'utilité actuelle de tests génétiques peut être systématiquement évaluée dans le contexte du parcours de soins de routine. Je conclus que pour établir l'utilité globale de la découverte de biomarqueurs, il faut un engagement familial, non seulement pour améliorer

l’impact des tests biologiques déjà intégrés, mais aussi pour déterminer si la découverte de biomarqueurs est prête à être intégrée dans le parcours de soins.

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Above all, to my parents: all that I am is because of your love. Thank you for waiting.

Contribution to original knowledge

This dissertation provides an original contribution towards integrating ASD biomarker discovery into the care pathways using stakeholder engagement in health research. This is the first time that existing frameworks in stakeholder engagement beyond the ASD field have been discussed and a common taxonomy developed specifically for integrating ASD biomarker discovery into the care pathways. This dissertation presents the first model for empirically assessing family engagement in biomarker discovery to improve the integration of biological testing into the care pathways of ASD. The scoping review I conducted and presented is the first review of the literature assessing existing engagement efforts in ASD biomarker discovery. I adapted, translated, and validated the Genetic Counseling Outcome Scale, a measure of empowerment, for use among families in the ASD care pathway. This represents the first measure of empowerment to be adapted for this population in this context. I created two novel instruments for assessing perceived utility of biological testing and knowledge of ASD, two candidate modifiers of integration of biomarker discovery. To date, these are the first instruments to assess these constructs in the context of integrating ASD biomarker discovery into the care pathway.

Contribution of authors

This dissertation consists of six chapters that I conceived, drafted, and executed. I revised this dissertation in its entirety with feedback from Mayada Elsabbagh. The contributions of all authors on the four manuscripts in this dissertation are as follows:

In Manuscript 1, I conceived and designed the study, performed the systematic search, charted and analyzed the data, and drafted the manuscript. I interpreted the data and revised the manuscript with critical feedback for important intellectual content from Mayada Elsabbagh.

Data for Manuscripts 2 through 4 were collected from the *Genome to Outcome* cohort which I conceived and designed with feedback from Mayada Elsabbagh and Iskra Peltekova. I collected data with Jennifer Frei and Iskra Peltekova. I implemented study data collection tools on an electronic data capture platform with support from Mayada Elsabbagh, Iskra Peltekova, Tal Savion-Lemieux, Ruth Bruno, and Jennifer Frei. I oversaw the database and codebook development with support from Ruth Bruno. I performed data cleaning and maintained the database for ongoing use.

All data analyses were conducted by myself, with helpful feedback from Ruth Bruno specifically for Manuscripts 3 and 4. I interpreted the data and drafted all the manuscripts. I revised the manuscripts with critical feedback for important intellectual content from all co-authors listed: Iskra Peltekova, Tal Savion-Lemieux, Jennifer Frei, Ruth Bruno, Ridha Joober, Jennifer Howe, Stephen W. Scherer, and Mayada Elsabbagh.

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List of Abbreviations

ACCE	Analytic validity, clinical validity, clinical utility and ethical, legal and social implications
ASD	Autism spectrum disorder
CBCL	Child Behavior Checklist
CBPR	Community-based participatory research
CMA	Chromosomal microarray
CNV	Copy number variant
DD/ID	Developmental delay/Intellectual disability
DT	Distress Thermometer
FAM-III SR-Brief	Family Assessment Measure, self-rating scale, third edition
FBIQ	Family Background Information Questionnaire
G2O	Genome to Outcome
GCOS-24	Genetic Counselling Outcome Scale
GCOS-24p	Genetic Counselling Outcome Scale, adapted for parents
MPOC-20	Measure of Processes of Care, 20-item version
MRI	Magnetic Resonance Imaging
PCA	Principal component analysis
PRO	Patient/person-reported outcome
PSS-10	Perceived Stress Scale, 10-item version
PUB	Perceived Utility of Biotesting
RCT	Randomized controlled trial
SRS-2	Social Responsiveness Scale Second Edition
VUS	Variant of unknown significance

1 Introduction

Autism spectrum disorder (ASD) is a life-long neurobiological developmental condition characterized by impairments in social skills and communication, and repetitive behavior[1]. Global prevalence estimates suggest that 1% to 2.6% of children have ASD[2,3]. Identification of ASD currently relies on recognition of "red flags", typically in early childhood, and appropriate referral to a specialist team for a diagnostic assessment[4,5]. The diagnostic assessment consists of a detailed developmental history from parents, teachers, and/or other caregivers, evaluation of the core characteristics of ASD, and a thorough appraisal of abilities including cognitive and academic ability, functional skills, executive functioning, and mental health[4,5]. This comprehensive assessment is crucial not only for a diagnosis to be ascertained, but also to tailor service provisions the child will receive in early intervention programs and/or in schools[4,5].

The diagnostic process can often be complex not only because of the child's characteristics but also because of the *care pathway(s)* through which the diagnosis will happen. A care pathway describes the essential steps of health or social care centered on a person with a specific condition and extends across specialties and/or settings[6,7]. Although the care pathway involving an ASD diagnosis is important in shaping long term outcomes, this care pathway is often complex, time-intensive, and inconsistently implemented across contexts[8,9]. This is because of barriers to person-centered and coordinated care, a vital component for ASD diagnosis[10] .

As part of the diagnostic care pathway, a child will also undergo biological testing[4,5,11]. Biological testing in ASD routinely consists of genetic testing to rule out the presence of single-

gene disorders like Fragile X Syndrome and Tuberous Sclerosis. Depending on the specific case, it may also include metabolic testing to identify co-occurring disorders such as Phenylketonuria, and/or neurological testing (e.g. electroencephalography) to investigate suspected seizures. Because of advances made in ASD genomics research[12], chromosomal microarray (CMA) has been recently integrated into the diagnostic care pathway to provide an etiological explanation following an ASD diagnosis by identifying known genetic variants associated with ASD[13].

Therefore, genetic testing for ASD[13], was the result of clinical integration of research results in the area of *biomarker discovery* into the diagnostic care pathway where progress in this area will continue to drive changes in clinical practice. Biomarker discovery is a major priority in ASD research which broadly aims to identify the underlying neurobiological mechanisms of the condition and to translate this knowledge into societal benefits, particularly for affected individuals, their families, and for health systems[14]. Beyond etiological testing, it is also hoped that biomarker discovery for ASD could improve upon care pathways beyond diagnosis by accelerating early detection and supporting personalized treatments, which can translate into improved outcomes for autistic individuals and their families[15-17]. My thesis is focused on how to improve the integration of biomarker discovery into the diagnostic care pathway by engaging families undergoing a diagnostic assessment for a child suspected of having ASD.

Understanding how biomarker discovery can improve upon the diagnostic care pathway requires an examination of the process of translating biomarker discoveries into useful clinical applications. In this chapter, I review the current state of research in the area of biomarker discovery, the challenges for translating this discovery into clinical application, and the role of

stakeholder engagement in resolving some of these challenges. I then turn to existing frameworks from broader health research to improve definitions relevant for stakeholder engagement in autism biomarker discovery: 1) the target groups; 2) the phases; 3) the outcomes; and 4) the predictors and/or modifiers of outcomes. Finally, I summarize the main knowledge gaps in stakeholder engagement in ASD biomarker discovery and explain how this dissertation addresses these gaps to advance the field through empirical research.

1.1 Biomarker discovery: progress and challenges

Biomarkers are defined as measurable and objective indicators of a biological state that are associated with a condition, and are stable across individuals[18]. Discoveries from this area can modify care pathways for ASD. Biomarkers can become clinically useful if they fulfill at least one of the following purposes: biomarkers for *susceptibility* can indicate an increased risk for the condition, *pre-symptomatic* biomarkers reflect precursors before the condition presents itself clinically, *diagnostic* biomarkers confirm or assist a diagnosis, and *prognostic* biomarkers predict the prognosis of a condition including responses to treatments[19]. Many candidate biomarkers for ASD are currently in development and have the potential for these different purposes (for reviews, see[19,20]).

One set of putative biomarkers being developed are genetic variants associated with ASD. In the last two decades, there has been a surge of genetic research development in ASD due to increased resolution of genetic identification through the use of chromosomal microarray (CMA). Now more ASD cases can be traced back to a known genetic etiology: 10% can be attributed to single-gene disorders, such as Fragile X Syndrome, Tuberous Sclerosis, and

Phenylketonuria; novel rare candidate genes, such as *NRXN1* or *SHANK3* can be found in approximately 5% of ASD cases; 5% of cases show large chromosomal abnormalities such as maternal 15q11-q13 duplication; and 5% can be explained by rare copy number variants (CNVs) such as the 16p11.2 deletion[12]. While previously used genetic testing, G-banded karyotyping, was only able to rule out existing co-morbidities found in 5% of ASD cases, CMA could now explain the etiology of ASD for up to 20% of ASD cases. Based on these developments, clinical practice guidelines recommended genetic testing using CMA as part of the autism diagnostic care pathway. It is expected that the further progress in biomarker discovery will increase the proportion of cases with a clear genetic etiology.

Despite the clarity of these clinical guidelines for this specific use of CMA in the care pathway, ethical concerns and dissatisfaction have been expressed regarding the future potential utility of CMA especially in the context of prenatal testing. Although prenatal genetic testing for ASD is unlikely to be feasible based on our current understanding of the complex etiology of the condition, ethical debates on this issue continue to fuel the controversy surrounding genetic testing[21,22]. Incomplete penetrance and variable expressivity of the identified genetic variants continue to be a main scientific challenge when considering these variants as biomarkers in general. For example, 40% of rare CNVs associated with ASD are also found in a non-autistic parent[23]. We also know that the CNVs implicated in ASD are shared risk factors among other neurodevelopmental disorders such as developmental delay (e.g. 16p11.2, among others) thus signifying variable expressivity[12].

Table 1-1 contrasts the current vs. potential utility of genetic testing as offering biomarkers when they are integrated into various hypothetical care pathways. The scientific and ethical challenges associated with each biomarker application in Table 1-1 are detailed next. Biomarkers for *susceptibility* indicate a predisposition for a condition. In other conditions like cancer, genetic testing of risk in children is recommended based on personal or family history and where risk-reduction strategies are available or if the condition predominantly develops in childhood[24]. Considering what we know about the genetic architecture of ASD, 80% of autistic individuals have genetic variants that can be found in the general population, i.e., non-specific to ASD[13]. Additionally, depending on the array type (BAC versus Oligo versus SNP Oligo) and the resolution of the array (targeted versus targeted with backbone versus whole genome) used, the yield ranges from 5% to 20%[13].

Table 1-1. Current and potential utility of genetic markers for autism spectrum disorder (ASD) when integrated into hypothetical care pathways.

Biomarker utility	**Definition**	**Can genetic variants currently be considered biomarkers for ASD?**
Susceptibility	Indicate a predisposition for a condition	The majority of individuals who will develop ASD would have genetic variants that are also present in the general population (non-specific to ASD).
Predictive	Identify underlying biological development of the condition before overt behavioural symptoms develop	Genetic testing alone would not allow for ASD identification prior to the manifestation of behavioural symptoms because the phenotypic expression for each genetic variant associated with ASD varies across individuals. Environmental factors also contribute to symptom manifestation.
Diagnostic	Aid decision in diagnosing a condition	If the genetic variants found in a child with ASD are known to be associated with ASD, rare, and not inherited from parents, these variants are likely to be causes of the child's ASD. Using genetic testing aids in providing a likely etiology for ASD for 15-20% of already diagnosed cases. However, using genetic testing alone in *suspected* cases will not provide a reliable diagnosis that differentiates between ASD and another developmental condition due to the shared genetic variants among ASD and other neurodevelopmental conditions.
Prognostic	Anticipate condition progression, prognosis, and response to therapy	Genetic testing cannot predict the response to behavioural treatments, or to predict change in symptomatology within an individual over time. This is because the variability in treatment response and changes in symptomology over time reflect the as of yet unknown effect of environment on phenotypic expression of identified genetic variants.

Note: ASD = Autism spectrum disorder.

Predictive biomarkers would flag an individual developing the condition before overt behavioural symptoms develop. The genetic profiles of individuals with ASD alone cannot predict what behavioural symptoms will appear because the diverse presentations of ASD symptoms from the same genetic variants likely reflect an interaction between those genetic variants and the environmental factors. Phenotypes reflective of the genetic variant, such as neuronal processes linked with quantitative traits like cognition, may be sensitive to these gene-environment interactions[25]. Currently, the lack of mapping on quantitative and observable traits is a serious limitation on the predictive power of a genetic test.

For genetic testing to be *diagnostic*, it would have to aid in confirming ASD for those suspected of having the condition. Multidisciplinary behavioural assessments are currently crucial for access to subsequent services to inform what services would most benefit the person with ASD. Considering that genetic variants are shared among ASD and other developmental conditions like attention deficit hyperactivity disorder (e.g. 16p13, 5p13, 9q33 as reviewed in [26]), using genetic testing alone will not provide a reliable diagnosis that differentiates between ASD and another developmental condition.

Finally, *prognostic* biomarkers would serve to predict the outcome of a condition to allow for tailored and targeted treatments. The presentation of ASD varies across individuals and the outcomes within individuals can also differ across time[27]. Behavioural interventions also have varying effectiveness, again reflecting the heterogeneity of the condition[28]. It is hoped that further understanding of the neurobiology of ASD can inform biological targets for interventions, and that genetic testing can reveal subgroups of those with ASD who will respond

better to certain targets of treatments over others. As it stands currently, genetic testing cannot predict the response to behavioural treatments, nor is it sensitive to the shifting symptomatology within an individual across time.

It is clear that the current understanding of ASD needs to expand further for a reliable biomarker to be developed. A paradigm shift is ongoing, moving research away from narrow behavioral diagnostic criteria which have proven impossible to reliably and universally associate with underlying biology, to quantitative traits that transcend disorder categories[29-31]. For example, significant declines in the distribution of IQ measures have been found in 16p11.2 duplication between noncarriers and carrier relatives with more pronounced declines between carrier relatives and carrier probands [32]. More candidate biomarkers will likely be available for testing with the advent of these new scientific approaches in understanding the effect of genetic variants on measurable phenotypes.

Interlaced with these scientific and clinical challenges are some ethical issues. The *value* of biomarker discovery has been linked to the debate over whether ASD is a difference or a disability. Proponents of *neurodiversity* do not consider ASD a condition that requires treatment[33]. Instead, they believe that research efforts should focus on improving social acceptance and availability of services for autistic individuals rather than labeling or treating them[34]. Thus, biomarker discovery in general, and genetic testing in particular, is perceived as fundamentally inconsistent with their values[35]. However, there are also many autistic individuals and their caregivers, who may disagree with this view and seek value in discoveries that can reduce the burden of the condition.

Taking into account the scientific and ethical challenges alongside the divergent perspectives and values of those affected, how can we ensure that biomarkers discovery and its integration into the care pathway will yield the expected benefits? In the next section, I propose that one way to address this challenge is to expand the empirical research in order to bridge the current gap in stakeholder engagement in biomarker discovery.

1.2 Resolving the debate over value of biomarker discovery: The need for empiricism

Previous literature suggests that one way to accelerate the integration of new discoveries into care pathways is through *stakeholder engagement*[19]. *Stakeholder engagement* is a broad concept used differently depending on the field. In ASD research, Walsh et al. defined a number of stakeholders in ASD biomarker discovery, including the scientific community, policy makers or regulators, community health care providers, and families[19]. They also outlined that engagement in biomarker discovery entails obtaining systematic input from stakeholders regarding their "values and needs in relation to ASD" and an improved understanding of the predictors and/or modifiers of these values and needs.

The Walsh et al. (2011) approach for stakeholder engagement in ASD is consistent with broader frameworks in health research proposing that stakeholder engagement in the research process produces results that are more impactful and in line with stakeholders' values and needs[36-38]. In general, ASD research has continually advocated for increased stakeholder engagement[39]. Yet, the application of robust theoretical frameworks, including those developed in areas other than

ASD, and empirical applications remains lacking. Biomarker discovery is perhaps the best illustration of this gap: my scoping review search strategy (Chapter 2) has highlighted the scarcity of the empirical application of stakeholder engagement by identifying only 7 original research articles, relative to 21 manuscripts with opinions and critical perspectives identified in the same literature search.

The remainder of this chapter aims to define a theoretical framework relevant for the current thesis, including a taxonomy. The latter is needed given the large number of available frameworks that often overlap in concepts, but not always in terminology relevant for stakeholder engagement in ASD biomarker discovery. This taxonomy will help to conceptualize the process of how ASD biomarker discovery can yield health/social impact through the care pathways, and operationally define:

1) who is the target group for whom the impact of biomarker discovery is anticipated?
2) what are the phases through which biomarker discovery could yield the anticipated impact?
3) what is the anticipated impact of biomarker discovery (outcomes)?
4) what factors influence the outcomes (predictors and modifiers)?

1.3 Theoretical frameworks of stakeholder engagement in health research

Consistent with Walsh et al.'s (2011) approach, I define engagement broadly as assessing and/or integrating perspectives of diverse stakeholder groups in informing a particular research agenda[19]. Many frameworks exist to help assess and/or integrate perspectives of stakeholder

groups in research in some way with overlaps in some concepts and distinctions in others. I specifically focused on frameworks that underlie empirical research in areas other than ASD.

Table 1-2 presents six stakeholder engagement frameworks relevant to ASD biomarker discovery: community-based participatory research (CBPR)[40]; patient-oriented research[41-43]; the "analytical validity, clinical validity, clinical utility, and associated ethical, legal, and social implications" (ACCE) model [44]; research utilization/evidence-based practice [45-48]; implementation science[49]; and knowledge translation[37]. The frameworks all assume that research could better impact a group of people, often called stakeholders, if their perspectives regarding the research are obtained and/or integrated in some manner in the research process. The frameworks, however, differ in multiple ways, including the target group, the process of engagement, and the predictors and outcomes of engagement.

The presence of the multitude of terms across different frameworks and their overlap necessitated a taxonomy in which I defined the constructs most relevant to the scope of my thesis focused on the integration of ASD biomarker discovery into care pathways (Table 1-3). I elaborate on this taxonomy in the following section to determine a model for stakeholder engagement in biomarker discovery.

Table 1-2. List of frameworks in health research supporting stakeholder engagement.

Frameworks	Predictors or modifiers of engagement	Main outcomes of interest targeted by engagement
Community based participatory research (CBPR)[40]	Core values Motivations for participating Personal relationships Cultural identities/humility Individual beliefs Community reputation	System and capacity changes: Health The extent to which interventions are culturally based and sustainable Changes in power relations Community empowerment Cultural renewal Health outcomes: Social/economical conditions Health disparities
Patient-oriented research[41-43]	Training in research Planning of engagement Definition of roles Attitude towards patient-oriented research Relationship between community groups	Health outcomes Securing funding for research Relevance of research topics to patients Patient enrolment and attrition rates in research Relevance of outcomes to patients Fit of study protocol with context Perceived credibility of research reports to patients Dissemination of research results to patients
Genomics – ACCE framework[38,44,50]	Perceived risk of the condition Motivation for test Knowledge of condition and test Disease status Relevance of test Disease-specific worry Age, gender, education	Clinical utility i.e. how likely a test significantly improves patient outcomes

Table 1-2 (*Continued*)

Frameworks	Predictors or modifiers of engagement	Main outcomes of interest targeted by engagement
Research utilization/Evidence-based practice[45,51,52]	Beliefs and attitudes towards research Involvement in research activities Information-seeking Education Position in the organization Knowledge and beliefs about evidence-based practice	Uses of research: Cognitive use Strategic use Instrumental use Resolution of problem/issue or realization of best practice outcomes
Implementation science[49,53]	Knowledge Skills Roles Optimism Beliefs about consequences Intentions Goals Memory, attention, and decision processes Social influences Emotions Behavioural regulation	How likely a new treatment, service, practice, or innovation achieve the following: Acceptability Adoption Appropriateness Feasibility Fidelity Implementation cost Penetration Sustainability
Knowledge translation[37]	Knowledge Attitudes Skills Habits	Practice change to adopt research product

Note: ACCE = **A**nalytic validity, **C**linical validity, **C**linical Utility, **E**thical, legal, and social implications; While *implementation science*, *knowledge translation,* and *research utilization* have been used interchangeably and been consolidated together into a "meta-theoretical" framework[54], they differ in historical roots, field of application, and subsequently in constructs and measurements of the constructs[55]. Hence, there was a need to un-pack these distinct frameworks. Conversely, community-based participatory research (CBPR) was discussed in this dissertation as the over-arching framework encompassing integrated Knowledge Translation (iKT) because of the similarities between iKT and CBPR[56].

Table 1-3. Taxonomy of the integration of ASD biomarker discovery into care pathways.

Category	Construct	*Sub-construct*	Definition
Target group	Community		A group delineated by the common value of ensuring that biomarker discovery have utility for the affected person and family which includes the affected person and family themselves along with researchers and practitioners. Community is often used as a synonym to stakeholders or beneficiaries of biomarker discovery.
		Affected persons	Persons diagnosed with or at-risk for ASD. Affected individuals receiving care in a health care setting from practitioners are also referred to as patients in some frameworks.
		Affected family	A unit of persons looking after and providing for the needs of the autistic person. They encompass parents, siblings, and/or other caregivers of the autistic person.
		Practitioners	Individuals who use or intend to use health applications in their routine practice.
		Researchers	Individuals who develop biomarkers through all phases of biomarker discovery.
Phases	Candidate biomarker discovery		The process by which researchers investigate how well a biological state detects the presence, absence, or risk of ASD.
	Biological test development & validation		Based on an aggregate of research studies demonstrating the *analytic* and *clinical validity* of a test that detects a biological state related to ASD, this biological test for the specific biological state becomes available for a specific purpose within a defined setting.
		Analytic validity	The accuracy and reliability with which a test measures the biological state of interest.
		Clinical validity	The accuracy with which the biological state is associated with ASD in the appropriate clinical setting.
		Diagnostic yield	The proportion of individuals found to have abnormal results from biological testing over the total number of individuals tested. It is considered one measure of clinical validity.

Table 1-3 (*Continued*)

Category	Construct	*Sub-construct*	Definition
	Integration into care pathways		The recommendation of the biological test for integration into care pathways through clinical practice guidelines.
		Care pathways	The essential steps of care across disciplines and settings centered on the affected person and family.
		Clinical practice guidelines	Evidence-based recommendations for practitioners to use a biological test in their routine practice for a specific purpose.
		Uptake	The degree to which a biological test is used by practitioners as per the clinical practice guidelines. It may also be referred to as *adoption.*
Potential outcomes or predictors/ modifiers	Child factors	*Severity of condition*	The presence and extent of autistic symptoms, which refer to the degree of social impairment.
		Child functioning	The child's ability to function in everyday environments, typically measured by the absence of emotional and behavioural problems.
	Family factors	*Knowledge of condition*	The extent to which a person can correctly identify facts from misconceptions about a condition.
		Parent stress	The degree to which a parent perceives the situations in their life as stressful.
		Parent distress	A state of emotional suffering in a parent associated with stressors and demands that are difficult to cope with in daily life.

Table 1-3 (*Continued*)

Category	Construct	*Sub-construct*	Definition
		Empowerment	A person-reported outcome (i.e. an outcome captured directly from the person; PRO) describing the beliefs that an individual can make important life decisions in an informed way (decisional control), has sufficient information about the condition (cognitive control), can make effective use of the health and social care systems for the benefit of the whole family (behavioural control), can manage one's feelings about having a genetic condition in the family (emotional regulation), and can look to the future having hope for a fulfilling family life, for oneself, one's family, and/or one's future descendants (hope).
		Family functioning	Social and structural properties of the global family environment. It includes interactions and relationships within the family, particularly levels of conflict and cohesion, adaptability, organization, and quality of communication.
	Biological test characteristics		The extent to which a biological test leads to net benefits over harms, including clinical, personal, and perceived utility.
		Clinical utility	Objective indicator of net benefit over harm on a health indicator
		Personal utility	Objective indicator of net benefit over harm in psychological, social, and economic indicators.
		Perceived utility	A person-reported outcome describing any form of utility (clinical or personal) perceived by the affected person and family to yield net benefit over harms.
	Health services factor	*Perception of family-centeredness*	A person-reported outcome describing parents' perceptions of the extent to which the health services received are family-centered i.e. respectful of and responsive to the family's preferences, needs, and values.

Note: ASD = Autism spectrum disorder.

1.3.1 Target stakeholder groups of biomarker discovery

Identifying the target stakeholder groups for ASD biomarker discovery is a challenge. Previous research has argued for careful consideration of research methods when representing a unifying view from a pre-defined stakeholder group[19,57]. The conceptual definition of *community* in community-based participatory research (CBPR) suggests that the community in biomarker discovery are those who share the value of biomarker discovery as leading to more benefits than harms on the affected individuals and families [40]. In sum, this definition of stakeholders would include affected persons and families, practitioners, and researchers. A *primary* target group would arguably be the affected persons and families who are the ones receiving the biological test. Therefore, this group was the focus in my thesis.

1.3.2 Phases of biomarker discovery

Stakeholder engagement can occur across different phases of biomarker discovery. For ASD biomarker discovery, the phases include the following: discovery of new candidate biomarkers, development and validation of biological testing to detect the biomarkers, development of guidelines for how these biological tests can be used, and integration of the biological tests into routine care pathways. The process by which CMA became integrated into the diagnostic care pathway, which is a focus of my thesis, illustrates these phases of biomarker discovery. During candidate biomarker discovery, researchers assess the association between genetic variants and ASD (for example[12]). Following this phase, a biological test (i.e. CMA) for these genetic variants is validated by establishing the analytic and clinical validity[58]. Currently, diagnostic yield has been reported as a measure of clinical validity of CMA. Based on this diagnostic yield, clinical practice guidelines were published to recommend that practitioners use CMA in the context of a

post-diagnostic testing for etiology[13]. As discussed earlier, up to 15-20% of cases of ASD, along with developmental delay/intellectual disability (DD/ID) and multiple congenital anomalies, will have pathogenic genetic variants that could explain the conditions.

The final phase involves integrating CMA into the care pathway which is likely to vary across different health systems. The care pathway involving CMA is part of the diagnostic evaluation for ASD, requiring coordination between the primary care physician and the clinical geneticist in follow-up care and genetic counselling prior to and following genetic testing for all individuals[11]. The uptake of CMA in this care pathway has been inconsistent: 80% of families reported never having seen a genetics professional despite having interest in the testing and half of those who had seen a genetics professional had asked for the referral themselves from their child's doctor[59] suggesting that primary care providers are not informing families about genetic testing.

The majority of frameworks would suggest that stakeholder engagement can only occur when a discovery is "ready" to be integrated as a biological test into the care pathways, specifically to improve the uptake of biological testing[37,38,49]. However, this assumption of readiness of discoveries for uptake has certainly not been the case in ASD biomarker discovery. Hence, stakeholder engagement can and should occur in step with ASD biomarker discovery during all of its phases[50].

1.3.3 Outcomes of biomarker discovery

A primary long-term goal of biomarker discovery is to improve the lives of affected individuals and their families. Specifically, the hope is that biomarkers can facilitate detection of ASD by identifying precursors to the condition[15]; aiding behavioural diagnosis[16]; and personalizing

treatments to the individual's biological profile[60], which may ultimately help reduce the condition's symptoms and improve functioning in the affected individuals[61,62]. Moreover, the burden experienced by the affected families can also be mitigated by increasing their knowledge of the condition thus reducing stress and distress and improving family functioning, as seen in the impact of biological testing in other fields[63,64].

A more direct outcome of biomarker discovery is to ensure that biological testing demonstrates *clinical utility*. Biological tests can impact affected individuals and families in many ways well-beyond clinical indicators such as in ending the diagnostic odyssey, providing relief from guilt, and in informing family planning[65]. Further, CMA is already integrated in care pathways without offering preventive or therapeutic interventions for all affected individuals and families. Thus, a broadened definition of clinical utility beyond objective health indicators is critical in the context of ASD.

In my thesis, I propose two forms of utility distinct from clinical utility. The first is personal utility, which refers to consequences on non-health outcomes experienced by individuals following biological test results[66]. In contrast, I defined perceived utility as the extent to which a biological test is perceived by the affected individuals and families to lead to more benefits than harms[66]. Overall, empirical evidence of the differences between these measures of utility are lacking[66,67], especially within ASD biomarker discovery. As detailed in Chapter 4, perceived utility has not been measured in ASD beyond qualitative studies thus limiting the generalizability of the results.

In broader context, evaluating biological testing for a complex condition like ASD relies on measuring patient/person-reported outcomes (PROs), defined as outcomes assessed directly from the person without interpretation of the person's response by anyone else[68]. One PRO, already validated as relevant in the context of clinical genetic testing is the construct of *empowerment*, developed by McAllister et al, to measure the outcome of genetic testing[69]. Related to PROs are complementary constructs of *family-centered care* that can inform how biomarker discovery can be responsive to stakeholders' needs. As will be discussed in Chapter 4, measures of family-centred care already exist (e.g. Measure of Processes of Care)[70], but have rarely been used in the context of ASD biomarker discovery.

The extent to which stakeholder engagement can accelerate the desired outcomes of biomarker discovery can currently only be inferred across the different frameworks. Evaluating the impact of stakeholder engagement on these outcomes of biomarker discovery relies on empirical assessment within an overarching and consistent model which is currently lacking.

1.3.4 Predictors and/or modifiers of biomarker discovery integration

Because ASD is a heterogeneous condition that has a wide-ranging impact on families, one relevant predictor of integration of biomarker discovery is the severity of the condition in the affected individual. Some have speculated that the biomarker discovery is fundamentally misaligned with the values of the ASD community[35]. However, this is in stark contrast to the calls for biomarker discovery and its clinical applications to reduce the burden of ASD for families who are in need of further support[71,72].

In my thesis, I investigate the role of three levels of factors relating to the child, family, and health services on potential outcomes of biomarker discovery. For child factors, it is possible that the severity of the condition and the level of child functioning are predictors of the outcomes of biological testing. For example, those who have a child who has more severe symptoms and are lower functioning would likely benefit more from biomarker discovery. Family factors, including parent knowledge[73], parent stress and distress[73], and family functioning[74], have been found to predict the uptake of genetic testing. Existing attitudes about the discovery are another relevant predictor of the integration of ASD biomarkers into the care pathway[73], which can be operationally measured as the *perceived utility* of biological testing. Finally, for health services factors, namely the degree to which families perceived the care they have received to be family-centered, could also predict biomarker discovery integration as evidenced by the effect of experience with the care pathway on research utilization/evidence-based practice. Despite being proposed by different frameworks (Table 1-2), little evidence currently exists on the interaction between these factors in determining outcomes of biological testing, a gap that my thesis begins to address.

1.4 A model of family engagement in ASD biomarker discovery

In conclusion, although stakeholder engagement is touted as essential for discovery to be respectful and responsive to stakeholders' values, the degree to which engagement is theoretically feasible in biomarker discovery is unknown. It is clear that stakeholder engagement in biomarker discovery and its translation into the care pathways has been under-conceptualized. By drawing from the rich theoretical frameworks of engagement in health research, I have extracted operational definitions of ASD biomarker discovery across frameworks to inform

stakeholder engagement in this field (Table 1-3). Further evidence of the role of engagement on biomarker discovery requires empirical assessment within a consistent model. I present a simplified model in *Figure 1-1* focusing on one outcome of biomarker discovery, empowerment. Advancing this field now requires systematic and empirical validation of this model to understand how stakeholder, and in particular family engagement, can be feasible and to what extent can this engagement eventually lead to families who can be empowered by discovery and care.

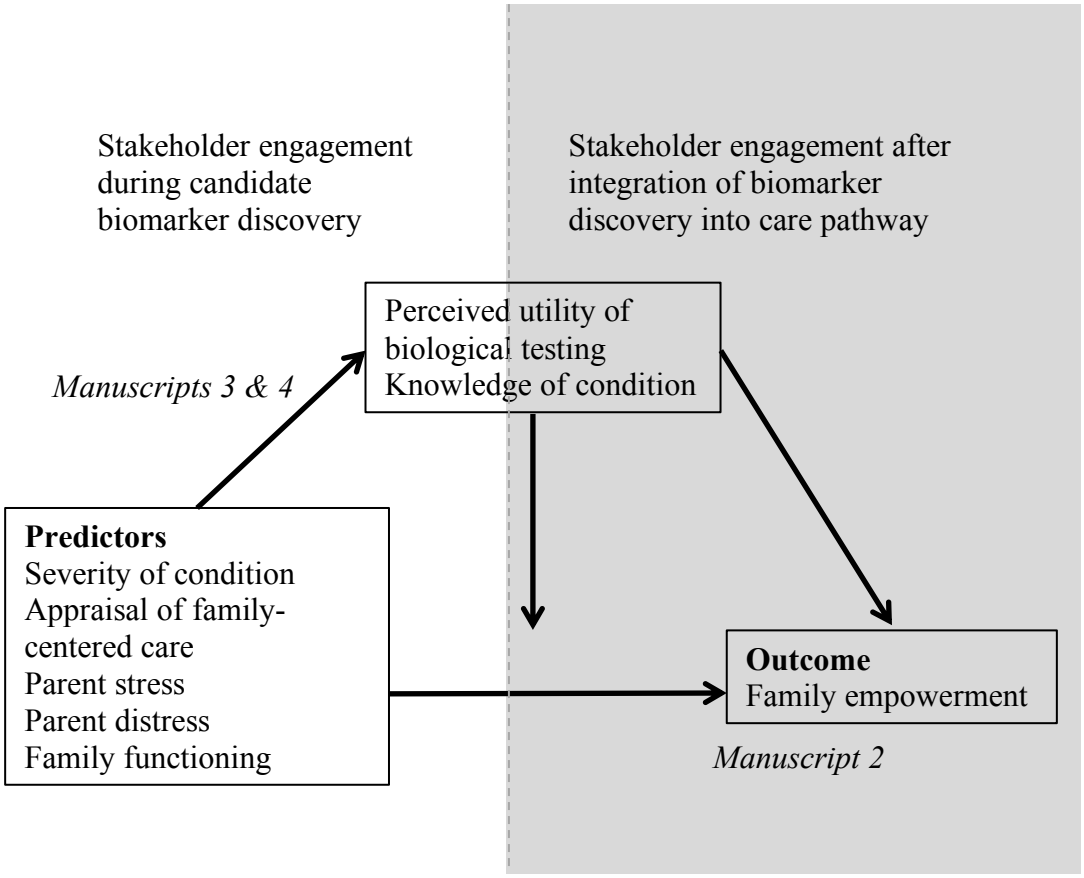

Figure 1-1. Model of stakeholder engagement in biomarker discovery along with contributions of this dissertation to the model.

1.5 Thesis overview and research questions

The overarching goal of this thesis is to develop and implement a systematic methodology for engaging stakeholders in ASD biomarker discovery. While the previously discussed theoretical frameworks of stakeholder engagement in health research have showed that family engagement in biomarker discovery is theoretically feasible, some have suggested that it is practically incompatible for engagement[35]. However, the extent to which this claim is supported by evidence is unknown. Therefore, Manuscript 1 uses a scoping review methodology to answer the first research question: **what is the extent to which stakeholder engagement approaches, namely community-based participatory research, have been feasible, based on concrete applications from ASD biomarker discovery?** I concluded that empirical examples, albeit only a few, exist in three areas: 1) understanding the values of a target community, 2) long-term priority setting with the community, and 3) collaboration in research design. I proposed that overcoming the barriers to family engagement in ASD biomarker discovery requires 1) defining a consistent and meaningful sample of stakeholders as a target of biomarker discovery and 2) developing and implementing the use of tools to measure the predictors, modifiers and outcomes of biomarker discovery. In the remainder of the thesis, I empirically address three knowledge gaps identified from the concrete applications of family engagement in ASD biomarker discovery.

The first gap is the lack of an outcome of biomarker discovery relevant for use among a priority target group defined previously: families of a child with neurodevelopmental conditions within the care pathway, or families undergoing an integrated biological test for a putative biomarker for ASD. Therefore, in Manuscript 2 I advanced the empirical investigation of an outcome of

biomarker discovery, which I proposed to be empowerment. My second research question was as follows: **to what extent can the Genetic Counseling Outcome Scale (GCOS-24) be adapted for use as a measure of empowerment among a representative sample of families with a child with a neurodevelopmental condition undergoing biological testing within the routine care pathway?** I designed and implemented a unique study protocol: *ASD Genome to Outcomes* (Manuscript 2) to capture the integration of a biological test for one type of potential biomarkers, namely genomics into routine clinical care. This provided an ideal sample to validate empowerment as an outcome of biomarker discovery because the families can reflect on future biological testing based on their experience with the recommended CMA. One hundred and thirteen families were enrolled from 2016 to 2018 and were followed as they underwent CMA for clinical and research purposes.

The second gap identified from Manuscript 1 is the lack of validated tools to measure the predictors of biomarker discovery. In Manuscript 3, I developed a measure of perceived utility of biological testing in ASD and implemented it in the *ASD Genome to Outcomes* cohort (defined in Manuscript 2). I examined the model for engagement during candidate biomarker discovery phase by addressing the third research question of this dissertation: **to what extent do child, family, and health services factors predict perceived utility of biological testing among families undergoing such testing in the context of a suspected ASD in their child?**

Manuscript 3 signalled that perceived utility of biological testing could depend on the family's knowledge of ASD. Therefore, I extended the findings in Manuscript 4 to understand knowledge of ASD among families within the care pathway. This objective was achieved by answering the

final research question: **to what extent do child and family factors relate to knowledge of ASD among families undergoing clinical biological testing for ASD?**

In the final chapter, I recapitulate my findings in the context of the goal of this thesis which is to develop and implement a systematic methodology for stakeholder engagement in ASD biomarker discovery. Additionally, I discuss the implications of this thesis for both theory and practice, the limitations of this thesis, and potential future strategies for optimizing engagement in biomarker discovery.

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2 Manuscript 1: At the cross-roads of participatory research and biomarker discovery in ASD: the need for empirical data

2.1 Preface

Drawing from theoretical frameworks of stakeholder engagement in health research, I resolved that family engagement in biomarker discovery is theoretically feasible and I proposed a systematic methodology whereby predictors and outcomes of biomarker discovery are measured among a defined sample of families. Parallel to developing this theoretical foundation, there is also a need to assess the empirical evidence for family engagement in biomarker discovery. Therefore, Manuscript 1 uses a scoping review methodology to assess the extent to which one stakeholder engagement approach, namely community-based participatory research, has been feasible, in relation to concrete applications in ASD biomarker discovery.

Family engagement in biomarker discovery also requires tools to assess predictors, modifiers and outcomes of biomarker discovery. The existence of these tools along with empirical examples of their applications required a review of the literature. Therefore, the scoping review that I completed and published[75] served to not only (1) establish the scope of previous empirical work on family engagement in ASD biomarker discovery but also to (2) assess the availability of tools that could be used to support engagement.

The scoping review identified seven studies that engaged families in ASD biomarker discovery. The review has revealed limited albeit clear empirical examples of family engagement, in three areas: 1) understanding of values of a target community, 2) long-term priority setting with the community, and 3) collaboration in research design. I identified three main knowledge gaps in stakeholder engagement in ASD biomarker discovery: 1) a systematic assessment of predictors, modifiers, and outcomes of engagement measured in a defined target group, representative of the diverse range of stakeholders affected by ASD using validated tools is needed to explain the heterogeneous views of those affected by ASD and advance family engagement in ASD biomarker discovery. This relies on both 2) a defined and representative target group for engagement, which has been indistinct in the literature, and 3) the development and validation of tools that could be used to assess predictors, modifiers, and outcomes of biomarker discovery.

Manuscript 1 was published in *BMC Medical Ethics* in 2015.

At the cross-roads of participatory research and biomarker discovery in autism: The need for empirical data

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2.2 Abstract

Background: Identifying biomarkers for autism can improve outcomes for those affected by autism. Engaging the diverse stakeholders in the research process using community-based participatory research (CBPR) can accelerate biomarker discovery into clinical applications. However, there are limited examples of stakeholder involvement in autism research, possibly due to conceptual and practical concerns. We evaluate the applicability of CBPR principles to biomarker discovery in autism and critically review empirical studies adopting these principles.

Methods: Using a scoping review methodology, we identified and evaluated seven studies using CBPR principles in biomarker discovery.

Results and Conclusions: The limited number of studies in biomarker discovery adopting CBPR principles coupled with their methodological limitations suggests that such applications are feasible but challenging. These studies illustrate three CBPR themes: community assessment, setting global priorities, and collaboration in research design. We propose that further research using participatory principles would be useful in accelerating the pace of discovery and the development of clinically meaningful biomarkers. For this goal to be successful we advocate for increased attention to previously identified conceptual and methodological challenges to participatory approaches in health research, including improving scientific rigor and developing long-term partnerships among stakeholders.

Keywords: Autism, community-based participatory research, biological markers

2.3 Background

A biomarker is a stable and objective indicator of biological state. The search for biomarkers associated with autism spectrum disorder (ASD) is currently underway [15-17]. Among the potential uses of biomarkers are the following: biomarkers for susceptibility indicate a predisposition for a condition such as the presence of a genetic variant associated with ASD [76]. *Presymptomatic* biomarkers can identify an individual developing the condition before overt behavioural symptoms are noticeable. For example, brain imaging techniques such as electroencaphalography are being researched to help distinguish infants at higher risk for ASD before behavioural symptoms manifest [77]. Biomarkers can also be used as a *diagnostic* tool: in ASD, chromosomal microarray analysis has been recommended as a first-tier diagnostic test for ASD to supplement behavioural diagnostic procedures, clarifying the presence of diagnosable genetic conditions [13,78]. Finally, biomarkers may also be *prognostic* i.e. to predict the outcome of a condition to allow for tailored and targeted treatments. All of these biomarkers have the potential to accelerate detection of ASD and access to tailored services for improved outcomes for those with ASD and their families.

There are challenges in translating research on biomarkers in the clinic [19]. Firstly, what precisely should these biomarkers map onto in ASD and at which developmental time-point? Considering the condition's heterogeneity [79-82] and its developmental nature [83] deciding on the impairment at a certain time-point to which a biomarker can predict is challenging. Secondly, a person's position on the spectrum is not fixed throughout life [25,27,62], making biomarker measurement sensitive to a person's development. Finally, discovered biomarkers thus far have poor

sensitivity and specificity when applied to the general population, limiting their utility in community-based care [19].

Such challenges in translating biomarker discovery to clinical applications have been often deliberated in bioethics. This includes discussion of ethical issues related to bio-banking, prenatal or population screening, and direct-to-consumer testing [84-86]. We have previously argued that issues related to translating biomarker discovery are much broader at the intersection of scientific, social, and health systems challenges [19]. Effective knowledge translation in this area relies on engagement of key stakeholder groups, the intended beneficiaries of this research. Engaging stakeholders in this area would inform researchers of questions relevant to stakeholders. Thus, end products of this research would address stakeholders' needs and circumvent potential harms, accelerating appropriate translation of biomarker discoveries. However, the extent to which stakeholders are engaged in biomarker discovery is currently unclear and some have suggested that biomarker discovery is on the whole discordant with stakeholders' needs [35,87]. Our goal is to systematically evaluate these claims.

To achieve this goal, we adopt a framework of community-based participatory research (CBPR) as it relates to ASD biomarker discovery. CBPR aims to support active engagement of the community in research through equitable and sustainable partnerships between researchers and a unit of community [88]. Given that theoretical debates presented have been extensive, we focus on two areas that have not been sufficiently elaborated on before. First, we evaluate the potential challenges in CBPR application to biomarker discovery. Secondly, we systematically assess the

quantity and quality of *empirical* biomarker discovery studies that adopt CBPR principles. We begin with a brief overview of CBPR.

2.3.1 Principles of community-based participatory research

CBPR encompasses a range of approaches that support community involvement in research. These approaches can operate in a wide range of research designs and involve diverse groups and populations [89]. In CBPR, both community and researcher enter into an equitable partnership to address research questions deemed relevant to the target community [88,90].

Historically, the roots of CBPR can be traced back to two periods: 1) research aimed to bridge the theory-practice gap and 2) efforts to empower marginalized groups when the academic institution was critiqued as being too distanced from social problems [91]. The WK Kellogg Community Health Scholars Program was the first to conceptualize a common definition of CBPR, leading to CBPR "foundational books" [90-92]. Within this program, Israel et al. [93] outlined nine specific core principles of CBPR: recognizing a "community" as a unit of identity, leveraging on strengths and resources of both the community and researchers, facilitating collaborative, equitable, and long-term involvement of all partners in a cyclical and iterative manner in all phases of research [93]. CBPR also promotes co-learning and empowering that attends to social inequalities and addressing health from both positive and ecologic perspectives while balancing investments into knowledge and intervention for mutual benefit of all partners. These principles are considered ideal goals to strive toward, concretely built on the following core components of CBPR [94]:

1. Forming a CBPR partnership

2. Assessing community strengths and dynamics

3. Identifying priority local health concerns and research questions

4. Designing and conducting etiologic, intervention, and/or policy research

5. Feeding back and interpreting the findings

6. Disseminating and translating research findings

7. Maintaining, sustaining, and evaluating the partnership

The applications of CBPR are far-reaching and flexibly adapted based on the type of research [89]. The nature of "partnerships" of the community can vary from community representatives acting as an advisory board to researchers [90], to the community directing research projects with researchers only providing technical expertise [95]. CBPR also differs on the intended outcome of the partnership: some partnerships grew to overcome a community's distrust of research groups from previous negative experiences [96], while others were developed to enhance the uptake of findings in the community [89,97].

2.3.2 Conceptual challenges to CBPR as they apply to biomarker discovery in ASD

Despite apparent advantages, CBPR poses significant and previously recognized conceptual challenges in health research. These challenges include ensuring proper representation of a community [98], forecasting long-term impacts of basic research [99,100], and threats to internal validity, specifically concerns for decreased randomization and contamination [101]. We consider how each challenge relates to biomarker discovery and its respective solution.

Stakeholder definition: Among the most frequently recognized challenges to CBPR is how to adequately represent the "community" [101-103]. In participatory research, there is a potential danger

of selection bias, where highly outspoken subgroups may not represent the broader population [101]. We have previously discussed the complexity of defining 'stakeholders' in ASD research, noting that 'stakeholders' have diverse needs, may benefit from research advances differently, and have varying interest in involvement in research [57].

In the case of biomarker discovery, strong claims of an inherent conflict between researchers and 'stakeholders' are presented often without defining who the 'stakeholders' are [87,104]. Homogenizing the stakeholder group is unhelpful because needs faced by individuals with ASD and their families are as heterogeneous as the condition itself [19] and moderated by contextual, geographic, and socio-cultural factors [71,72].

Views differ on what ASD even is: some advocate groups endorsed a search for a "cure" for ASD, a view *neurodiversity* proponents find objectionable because ASD is considered part of "natural human variation" [19,105]. When perceived by some stakeholders as a means to find a"cure", biomarker discovery becomes much more controversial [19]. On the other hand, biomarker discovery is considered a research priority to a geographically and culturally diverse group of stakeholders if such biomarkers were to facilitate identification and timely access to care [71,72]. Moreover, it seems likely that biomarker discovery is a more relevant priority depending on the developmental pathway of the person affected: parents of children suspected of or recently diagnosed with ASD may be more likely to find value in prospective, diagnostic, or prognostic biomarkers relative to families whose children have been diagnosed for several years. Therefore, stakeholder representation is a major challenge in public engagement in ASD research in general [57], applicable to biomarker discovery. The term *stakeholder* is context-dependent, does

not always mean *beneficiary* from research and not *all* stakeholders will want to be or can be adequately represented and engaged [57]. For successful stakeholder engagement to be achieved, a systematic assessment of priorities, needs, and experiences of the stakeholder group is needed.

Forecasting consequences: The second major challenge for CBPR relevant for biomarker discovery lies in foreseeing potential social consequences of any discovery. This is due to the difficulty in predicting the potential ripple effects of understanding the mechanism of a gene, and the fact that knowledge advances in incremental steps by building upon previous discoveries. This general challenge in health research [106] has been previously recognized in ASD biomarker discover. On the one hand, premature involvement of the community in a new discovery before it has proven clinical value would inflate public expectations, leading to a subsequent loss of public trust in science when these hyped promises are not met[19].On the other hand, the *lack* of community engagement has been shown to lead to a loss of public trust in science.

An example comes from the national partnership with Aboriginal representatives, where community representatives expressed that "Aboriginal communities have been researched to death" and unequivocally objected to any further research[107]. After extensive deliberation, representatives agreed that a health survey would be acceptable, but only with an equitable partnership between Aboriginal representatives and researchers in the project. Similarly, Arbour and Cook presented examples of respectful genetic research under the concept of "DNA on loan" in understanding the mechanism of a rare chromosomal abnormality in a First Nations community [96]. The group first discussed the research priorities with the family to develop trust with them. Participating families were then kept updated with the research progress. Later the

group facilitated informed health care and counseling for each family based on their findings. The community and family themselves determined whether or not the specification of First Nations could be used to promote health in the wider community, thus allowing the community to weigh the possibility of stigma with the potential benefit of research for others.

These examples illustrate that the challenge of forecasting research results can be mitigated through active consideration of research priorities and process with participating families. Such involvement also led to benefits for both groups: the community protected themselves from possible stigma and received informed care and counseling, while the research group was able to address their research question and advance knowledge in their field.

Internal Validity: A third major challenge of participatory research is the threat to internal validity. A systematic review of CBPR showed that despite the wealth of studies adopting this approach, limited studies have reported a complete intervention with authors only detailing either their findings or study methodology [101]. This made it difficult to conclude if participatory research is associated with low scientific quality [101]. Nevertheless, concerns of decreased randomization and contamination in CBPR remain [101,108].

This problem is faced especially in randomized controlled trials (RCTs), a methodology with clearly defined standards of scientific rigor. In RCTs, participants randomly allocated to the control group must not be exposed to the intervention and vice versa, causing *contamination.* Because members of the community work closely with each other and with researchers on the

research project in CBPR, the likelihood for decreased randomization and contamination among individuals is high [108].

However, the disappointing results of some non-participatory "high-rigor" RCTs have shown that the improved adherence to interventions found in CBPR along with the unintended benefits of partnerships may outweigh the concern for these threats, all of which can also be mitigated. Authors of a well-designed nationwide RCT (see COMMIT trial [109]) admitted that the lack of community involvement in their trial was the biggest contributing factor in its disappointing outcome, and that "an exclusive focus on risk factors alone may be inappropriate" [110]. In contrast, Andrews et al. worked closely with the community in a tobacco cessation intervention and implemented randomization at the community level to reduce the risk of reduced randomization and contamination [111]. Because of the partnership, they not only showed promising outcomes on smoking cessation, they also reported high retention rates (87%) and improved self-efficacy for both the community health workers implementing the intervention and the participants receiving the intervention [112]. Therefore, as proposed for other areas of health research [101], CBPR has the potential to enhance the quality of conventional research methods for biomarker discovery in ASD by increasing participation rate, lowering drop-off over time where applicable, and increasing capacity for the community and individual to adopt the findings, such as a new test or an intervention.

Taken together, the above considerations suggest that participatory research is neither conceptually nor methodologically in conflict with biomarker discovery in ASD. Nevertheless,

the extent to which there is underlying conflict between biomarker discovery specifically and participatory research is a question that continues to be debated [35].

Despite the wealth of theoretical positions and arguments, what remains largely unknown is whether principles of CBPR have already been adopted in biomarker discovery. Understanding how to achieve participation in this field can resolve these theoretical debates and contribute to future development of biomarker discovery [57].

2.4 Methods

We use scoping review methodology to address the question of how to achieve participation in biomarker discovery. A scoping review methodology [113,114] allows the mapping of key concepts of participation to a complex research area. Unlike systematic reviews that focus on a narrow question with specific study designs decided *a priori*, our use of scoping review methodology would include a broader range of study designs and help us understand the state of the evidence in a field. Therefore, the selected methodology is appropriate considering the lack of knowledge on what exists in participatory approaches in ASD biomarker research.

The goal of the study is to identify previous applications of CBPR in ASD biomarker discovery. Because the state of the science of CBPR in biomarker discovery is unknown and may be limited, we adopt a broad but systematic definition of CBPR as articulated by Israel et al [93]. While not all principles are suitable to all forms of stakeholder engagement, there is general agreement that these principles are likely to characterize ideal partnerships.

Studies were included if they met each of the following criteria:

1. The study should involve one or more of the following key stakeholder groups: a person with ASD, families of individuals with ASD, professionals in the field of ASD, or policy makers. While we had these categories of stakeholders *a priori,* we did not specifically limit the search strategy targeting specific groups to have a higher chance of retrieving relevant articles;
2. To increase the chances of retrieving possible studies, "involvement" of stakeholder groups in research was defined broadly. This would also capture any study that performed *community assessment and diagnosis.* Thus, any study that obtained individuals' views regarding biomarker discovery that could potentially be used to shape future research would be included;
3. The topic of discussion in the study included biomarkers for identification and intervention in ASD, including but not limited to genetic testing and brain imaging;
4. The study was conducted in English;
5. Original empirical research (quantitative or qualitative) were included.

Exclusion criteria were:

1. Reviews and opinion papers;
2. The study involved childhood conditions other than ASD;
3. The study only assessed associations between potential biomarkers and ASD symptoms;

4. The study reported on collaboration between any of the above key stakeholder groups and researchers on topics other than biomarkers for ASD e.g. in implementing interventions.

We searched Medline, CINAHL, PsycINFO, and Embase using a comprehensive list of search terms. Author lists and references were also cross-referenced for potentially relevant articles. Once key articles were identified, we retrieved a list of articles that cited those key articles as well. The search was completed on June 17th, 2014.

Articles were screened first by title and abstract based on the above inclusion and exclusion criteria. Screened articles were retrieved for full text articles. Using a data extraction form, we extracted relevant study characteristics (e.g. document classification, study design, method employed, study population, main outcomes). For quantitative studies, we employed a *narrative method*, wherein results of studies were compiled and organized to form a "composite" understanding of the current state of knowledge [115]. For qualitative studies, the data extraction form contained codes that were recursively applied [116]. In other words, we first developed an initial coding scheme based on the nine CBPR principles articulated by Israel et al [93]. The initial coding scheme consisted of broad categories namely definition of community, outcomes for collaboration, the stage of research at which collaboration occurred, and the evaluation of collaboration. We revised the coding scheme appropriately after applying it to an article; for example, articles that elaborated on the definition of community required additional codes such as community attitudes, awareness and needs. These additional codes were then retroactively applied to all articles [116]. This work conformed to the Declaration of Helsinki and was approved by McGill University Institutional Review Board.

2.5 Results

Our search yielded a total of 342 studies (***Figure 2-1***). After screening the articles first by title and abstract, 73 articles were retrieved for full-text assessment. Out of these 73, only seven examples of original research studies fit with our inclusion criteria. While all possible types of biomarker testing were targeted in the search strategy, all studies captured except for one focused on genetic testing. Similarly, while all possible stakeholders were considered, studies have only involved parents of children with ASD.

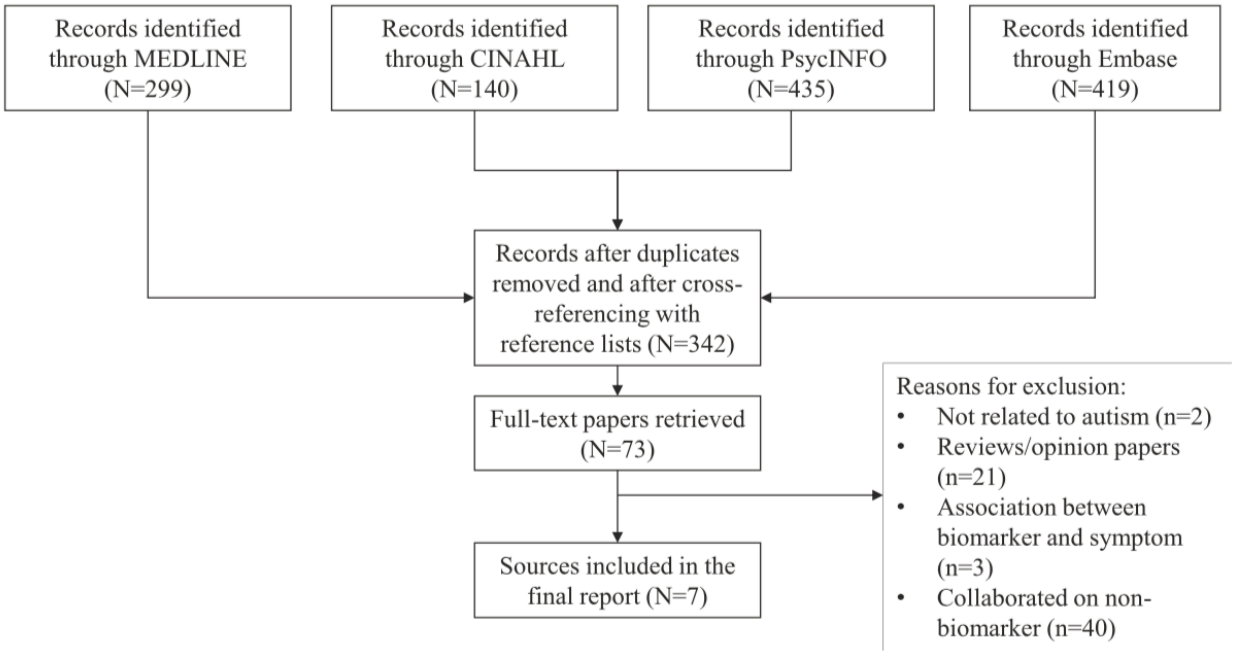

Figure 2-1. Flow diagram of the progression of inclusion of articles.

A synthesis of these seven studies yielded three themes that correspond closely to previously articulated principles and components of CBPR [88,93]. The first is "assessing community strengths and dynamics" by identifying stakeholder attitudes and expectations towards the application of ASD biomarkers in their lives. The second is "identifying priority local health concerns and research questions" by collaborating with stakeholders in setting long-term priorities for ASD

research. The third is in "designing and conducting etiologic research" by collaboration among stakeholders in devising an imaging protocol. In what follows, we synthesize and critically review identified evidence for each of these themes.

2.5.1 Identification of stakeholder perceptions and attitudes

While community assessment by itself is not CBPR, it is an essential component in establishing partnerships with the community prior to initiating CBPR, and in line with one principle of CBPR in defining the community of interest by "assessing community strengths and dynamics" [93]. Considering the dearth of CBPR in the field of biomarker discovery in general, and in the field of ASD biomarkers in particular, we considered what empirical work has previously focused on *community assessments*.

We identified four studies that examined community attitudes towards one biomarker measurement for ASD: genetic testing. They mainly surveyed and/or interviewed parents of children with ASD on their attitudes towards genetic testing, and their experience in and motivation for undergoing testing. On the whole, many parents are 'supportive' of genetic testing for ASD. Using semi-structured interviews (n=42), Chen et al. found that 69% of parents favoured genetic testing for ASD [117]. Another study using an Internet survey (n=25) showed that 80% of parents with a child with ASD would want their younger undiagnosed child tested for an increased risk for ASD even if the test could not confirm or rule out a diagnosis [118]. Those who supported genetic testing do so because they believe it would support early intervention and treatment, help families understand the etiology of ASD, and inform family planning [117]. Parents specifically noted that genetic testing could alleviate guilt and promote acceptance of the condition [119].

While many were in favour of genetic testing, those against did not foresee its value because they perceived ASD as "incurable", they perceived no impact for genetic testing in the child's lives or for future pregnancies, and they have no family history of ASD [120]. Another study found the fear of stigma from testing was also another reason for opposing it [118].

Taken together, these studies have obtained perspectives on genetic testing for ASD through qualitative and quantitative methodologies. Several limitations of the studies hinder the generalizability of their findings. Despite multiplicity of stakeholders in ASD, only parents were the focus. Two of the studies relied on genetics research databases for recruitment, thus there is the possibility of a biased sample. The studies represented views of stakeholders on genetic testing within potentially very different contexts: research versus clinical practice. Moreover, the use of Internet surveys is useful in capturing a large number of respondents, but the survey instrument may only reflect items of interest to the researchers. While two of the studies employed semi-structured interviews, their reporting of results lacks methodological coherence, reflexivity of researcher's role, and method of triangulation [121,122].

In sum, while some studies have attempted to empirically examine stakeholder perspectives, these studies are characterized by methodological limitations, which impacted the generalizability of the findings. To draw valid conclusions about the perspectives of stakeholder groups on biomarker discovery, improved attention to recruitment methods and clarity of constructs assessed are vital.

2.5.2 Collaborative priority-setting

No research projects in ASD biomarker discovery have yet to involve participants in determining research questions directly. However, in line with the CBPR principle of recognizing priorities identified by the community [93], two studies focused on obtaining long-term priorities for ASD research from the community [35,123]. In addition to student group discussions, Higashijima et al. invited a diverse array of community members to monthly public science cafes through a variety of recruitment methods that included parents of children attending nurseries catering to ASD, and employees of childcare services. These community members discussed their views on the relationship between ASD research and society with the guiding question, "Towards the construction of an ASD-friendly society, what is the most impressive/important thing for you after finishing the conversation in today's café discussion?" Discussion points were then analyzed to produce a list of topics that the community would want to discuss further. This list was then used to develop a survey, which was sent out to the larger community to further refine the discussion priorities. Survey results were then presented to researchers in a three-day event dedicated to foster a discussion on creating an "ASD-friendly society." Points included in the final social agenda for ASD research that needs further discussion included the following: ASD research for a cure, definition of ASD, issues surrounding ASD diagnosis and content for dissemination to the public.

Pellicano et al. employed focus groups and survey methodology to obtain views of 1,517 members of the ASD community on the current landscape of ASD research in the UK, along with their research priorities for the future for all fields of ASD research [35]. Many participants called for a more balanced distribution of funding across the different research areas. When

asked about their priorities for future ASD research, participants endorsed research on support and services, efforts to improve public knowledge about ASD, and of greater investment into ASD research in general. The online survey showed that participants unanimously agreed that all research questions are important, with subtle differences (from "moderately important" to "very important") between groups on specific questions. The research questions most frequently endorsed as important by autistic adults, practitioners, and family members are understanding how to improve life skills of autistic adults, how to meet their needs through public services, how autistic people think and learn, and on the future prospects for autistic adults.

The two studies outline the feasibility of setting priorities in a safe and open environment for both scientists and community members. Despite the relatively large samples, both studies present limitations. They employed convenience sampling to maximize participation, without formal consideration of representativeness to a target population, or even a specific definition of what target population was intended. Moreover, groupings of participants with the expectation that most within one group will share the same views is a potentially reductionist approach not reflective of real-world complexity. For example, a "researcher" group is not a meaningful category when properties of the researcher are unknown e.g. the researcher's field of research, career stage, and focus populations.

Other potential risks to generalizability introduced by the two studies are ambiguous content and biased framing of the question. For example, one study asked participants if they were satisfied with the pattern of funding for research. Yet, the categories for research funding were presented as "biology" vs. "intervention", potentially misleading community participants that research in

one area is more likely than the other to directly lead to community benefits. Participants were asked to discuss their research priorities after being presented with the pattern of UK funding. It is possible that participants' perspectives changed after deliberating over an investment "unbalance" in research funding.

Overall, the ongoing considerations highlight the complexity of surveying and/or deliberating research priorities. Notably absent is the use of well-established deliberation approaches abundantly used in global health research, such as the Delphi technique [124] and stakeholder dialogue [125].

2.5.3 Collaboration in research design

One study we identified illustrates feasibility and value of collaboration with the community in design [126], in a way that strengthens conventional research methods and "building on strengths and resources within the community" [93]. Nordahl et al. collaborated with parents in designing a magnetic resonance imaging (MRI) protocol without the use of sedation for their child. Typically, imaging research in ASD requires children to be anesthetized to limit movement during imaging. As a result, imaging research without the use of sedation in ASD is limited to high-functioning children [127], who may not represent others on the spectrum. Nordahl et al. succeeded in obtaining quality scans of 93% of their participants without sedation by collaborating with parents of children who participated. The research team first prepared a handout to describe the MRI protocol to the parents and child. With the parents, they then developed an individualized strategy guided by a questionnaire that assessed the child's sleep patterns. They followed this individualized strategy during the experiment by recreating the child's bedtime routine and sleeping environment at the imaging center. Parents reported positive

feedback on the experience. This study demonstrates that it is feasible to include parents in the design of a study protocol and to ascertain feedback on their experience. Notably, such collaboration allows researchers to better address their research questions while catering to the immediate needs of families.

2.6 Discussion

Our review has revealed that limited albeit clear empirical examples of participatory research in ASD biomarker discovery. Applications of CBPR have addressed three areas: 1) understanding of needs and priorities of a target community, 2) long-term priority setting with the community, and 3) collaboration in research design. Despite the fit of these empirical studies with CBPR principles, it appears surprising that their number is so limited given that biomarker discovery is an area of major investment and the emerging literature advocating the need for community engagement. What our review could not address is whether similar approaches have already been used in biomarker discovery but their findings not published.

What possible barriers might explain the lack of CBPR applications in biomarker discovery? One possible barrier is the sheer complexity of engagement in this area. The condition impacts a multitude of diverse communities, each with a complex group of stakeholders whose attitudes and perspectives are variable. What is clear based on our findings is that previously identified potential challenges of participatory research are more likely whenever the stakeholder group is not defined as a coherent and meaningful sample. Considering that conducting a *community assessment and diagnosis* prior to partnering with the community is a "key factor" in the success of carrying out community-based participatory research generally [88,94,128], defining the

community of interest would then be an essential first step in adopting CBPR in ASD biomarker discovery.

More generally, ASD research is 'reinventing the wheel' in adopting participatory elements, instead of building on experiences and models in similar areas of health research. For example, a group of researchers working with small Alaskan native communities have proposed a CBPR-approach to conducting genetic studies for complex conditions (obesity, diabetes, and cardiovascular disease) and sharing these results to maximize the potential benefit and understanding [129]. The research team held open dialogue sessions between the researchers, the tribal council, and community representatives from their Yup'ik Eskimo study population, in which genetic education workshops were paired with discussions on Alaskan Native culture to create culturally respectful experimental protocols. Community involvement occurred throughout recruitment to prevent group harm and stigmatization. When results were ready, consultations with the community helped produce culturally relevant formats for presentations. Dissemination of the results was made in Yup'ik with the presence of at least one research member to answer questions. Such a format serves as an important framework from which biomarker discovery in ASD could be feasibly adapted.

A further challenge is that the notion of 'conflict' between researchers and the community assumes a false distinction between two groups and suggests that one is expected to yield to the views of the other. Yet, advancement of knowledge does not occur in a vacuum – society is rarely impervious to its long-term benefits and detriments. Contributions by autistic researchers and advocates to debates on research priorities within mainstream scientific journals [130,131] have

also blurred the boundaries between "community" and "researcher". ASD research is vulnerable to funder and public pressure that may undermine the value of scientific discovery and advancement of knowledge [19,57]. Such pressures may be, in part, why scientific priorities were historically driven by what turned out to be simplistic promises, such as a "gene" for ASD [19,57]. Our findings suggest that available data are currently too limited to evaluate the claim that biomarker discovery is indeed misaligned with other stakeholder perspectives [35,87]. Available studies were not only few, but also were characterized by methodological limitations impacting generalizability. When pushed towards polemics, conflicting priorities between *researchers* versus *the public* become a false notion lacking pragmatic real-world value.

2.7 Conclusion

We suggest that deliberation around the intended outcomes of research, both short- and long-term, would instigate the same progress seen in other areas of health research, while mitigating concerns around participation. We propose that re-conceptualizing biomarker discovery in ASD as participatory would entail clarifying and increasing its social relevance, enhancing rather than undermining its rigor, and accelerating its intended benefits to society. The success of this vision will rest on long-term partnerships among stakeholders to achieve enhanced public trust and engagement in science that would yield benefits to all involved.

2.8 Competing interests

The authors declare that they have no competing interests

2.9 Authors' contributions

AY conceived and designed the study, performed the systematic search, charted and analyzed the data, and drafted the manuscript. Both AY and ME made substantial contributions to interpretation of the data and revision of the manuscript critically for important intellectual content. Both authors have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring the questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

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2.11 Figure legend

***Figure 2-1*. Flow diagram of the progression of inclusion of articles**.

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3 Manuscript 2: Adaptation and validation of the Genetic Counseling Outcome Scale for autism spectrum disorder

3.1 Preface

Manuscript 1 resolved that stakeholder engagement in ASD biomarker discovery must build on a clear definition of the target group for biomarker discovery that is representative of the diverse range of families living with ASD and it must systematically assess predictors, modifiers, and outcomes of biomarker discovery with validated tools. I proposed empowerment as an outcome of biomarker discovery following its integration into the care pathway, namely as biological tests. A measure of empowerment in the context of genetic testing already exists: Genetic Counseling Outcomes Scale (GCOS-24), but it has not been validated in ASD. Thus, the goal of Manuscript 2 is to validate the GCOS-24 for use among the target group of families in ASD biomarker discovery. Achieving a representative sample of families undergoing this type of clinical care requires a research protocol that is embedded within a care pathway where genetic testing is being applied.

In the following manuscript, I describe the implementation of a research study protocol that is integrated within clinical care in two large university health centers. The *Genome to Outcome* cohort was established as a large-scale biorepository capturing both clinical and genomics data

from families affected by a neurodevelopmental condition. This manuscript also describes characteristics of the cohort from whom data was collected for Manuscripts 3 and 4.

Manuscript 2 has been submitted to *Journal of Genetic Counseling*.

Adaptation and validation of the Genetic Counseling Outcome Scale for autism spectrum disorder

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3.2 Abstract

Research advances in the genetic architecture of autism spectrum disorder (ASD) have led to the integration of clinical genetic testing into the ASD care pathway, specifically for known genetic etiologies associated with the condition. However, data to evaluate this testing is limited, with no consensus on relevant outcome measures to capture the range of impacts following clinical genetic testing in ASD. The Genetic Counseling Outcome Scale (GCOS-24) is a validated patient-reported outcome measure for clinical genetics services. However, the GCOS-24 was not validated for ASD. Families seen for their child's evaluation of a neurodevelopmental condition, for whom genetic testing is recommended, were invited to participate in a prospective genomics cohort between 2016-2018. Families completed the GCOS-24p, an adapted version of the original GCOS-24 (n = 111). Internal consistency of the GCOS-24p is acceptable (Cronbach's $\alpha = 0.84$). The GCOS-24p inversely correlates with stress and distress suggesting evidence of convergent validity (rs ≥ 0.39, ps < 0.001). Cognitive interviews suggest that the GCOS-24p has sufficient face validity. The use of the GCOS-24p as an outcome measure of clinical genetic services, such as genetic testing in families affected by neurodevelopmental disorders, will allow for assessment of the impacts of these services.

Keywords: Autism spectrum disorder, neurodevelopmental disorders, patient-reported outcome measures, genetic testing

3.3 Introduction

In the last two decades, progress in genetic research in Autism spectrum disorder (ASD) has uncovered genetic events that could explain the condition in more ASD cases than ever[12,58]. Approximately 10% of ASD cases can be attributed to single-gene disorders, such as Fragile X Syndrome, Tuberous Sclerosis, and Phenylketonuria; 5% of ASD cases present with novel rare changes in genes such as *NRXN1* or *SHANK3*; another 5% of cases show large chromosomal abnormalities such as maternal 15q11-q13 duplication; and 5% can be explained by rare copy number variants (CNVs) such as 16p11.2 deletions[12,58].

Because of these advances, clinical genetic testing as part of the standard diagnostic assessment for ASD, now involves chromosomal microarray (CMA) testing for known genetic etiologies associated with the condition[13]. Integration of CMA in diagnostic care pathways was based on evidence for improved diagnostic yield compared to the previously used G-banded karyotyping[13]. Specifically, a review of 33 studies concluded that CMA can detect "pathogenic genomic imbalances" in 15-20% of patients with ASD, developmental delay/intellectual disability (DD/ID), and multiple congenital anomalies, versus a ~3% yield from G-banded karyotyping[13].

The integration of CMA into routine care pathways in ASD diagnosis introduces challenges reflecting the complexity of the care pathway leading to diagnosis. This pathway relies on the ability of primary care providers to refer to a multidisciplinary team of experts after recognizing symptoms of ASD[5]. This team can then thoroughly examine the child's development, cognitive and academic skills, adaptive functioning, social communication and behaviour, and mental

health[4,5]. As part of this pathway, a child will also undergo biological tests[4,5,11]. Biological testing consists of conventional genetic tests to rule out single-gene disorders, like Fragile X Syndrome. CMA was specifically recommended to identify a possible etiology[13]. Biological testing may also include metabolic tests to identify co-occurring disorders such as inborn errors of metabolism[11].

In clinical practice, CMA offers three categories of results for families with a child with ASD. A *pathogenic* result is found in up to 18% of children with ASD[132] which is when an identified copy number variant (CNV) occurs *de novo*, is associated with a known genetic syndrome, and/or is large. An example of a pathogenic result is the 15q11-q13 duplication, which is also associated with epilepsy[133]. In this case, along with clarifying a likely genetic cause for ASD, the result also impacts the clinical management of the child by prompting for seizure surveillance. Over 80% of diagnosed cases would receive a negative result, whereby no variants known to be pathogenic are found. In contrast, a "*variant of uncertain clinical significance (VUS)"* indicates that the identified CNV is weakly associated with the clinical phenotype and/or affects a gene that has an unknown function. The VUS result offers the greatest challenge for laboratories and clinicians to interpret and thus communicate to families [134]. Therefore, defining the clinical utility of CMA based on diagnostic yield does not capture the complexity of potential impact on families receiving uncertain or negative results.

However, the integration of CMA within care pathway leading to diagnosis has been challenging; despite reporting interest in genetic testing, 80% of caregivers of children with ASD surveyed in the USA had never seen a genetics professional[59]. Fifty-five percent of those who

had seen a genetics professional had requested the referral themselves from their child's doctor, which indicates that primary care providers are failing to inform families of genetic testing.

In addition to integrating testing into routine care, we know very little about the impact of genetic testing for families with an autistic child. To date only a handful of qualitative studies have explored the impact of clinical genetic results on families affected by neurodevelopmental conditions in general[65,135-137]. On the one hand, these studies show that test results may offer clear benefits to affected families of children diagnosed with neurodevelopmental conditions such as relief, access to services, family planning, hope, revised care plans, etiological explanation, and increased understanding.

On the other hand, several actual or perceived risks of genetic testing in neurodevelopmental conditions have also been identified[137]. Negative or VUS results were perceived as adding more uncertainty instead of resolving parents' questions about the condition's etiology. Following pathogenic results, some parents struggled to understand the relevance of the results for their current and future situation. Some parents also expressed guilt because they may have passed on the pathogenic results to their child. It is important to note, however, that these qualitative results have highlighted the potential positive and negative impacts of testing, but their results are not generalizable unless they are empirically evaluated in adequately powered studies with representative samples of health systems users.

The current study seeks to address two major knowledge gaps in ASD genomics research. First, no study to date has recruited a large and representative sample of health systems users in their

sample. Genomics research in ASD have previously relied on either the recruitment of families in the community facilitated by advocacy groups[138] or the recruitment of families from clinical settings for an additional battery of research assessments[139]. This potentially results in increased burden for families when assessments are repeated for both clinical and research purposes. This may explain how genetics research samples in general are likely to be of higher socioeconomic status[140] and are potentially higher functioning (e.g. a mean nonverbal IQ of 80.4 in a genetics study[139] versus 66.3 from a clinical cohort[141]) compared to the clinical population of health systems users. To address this gap and recruit a large and representative sample of health systems users, we designed a research protocol that is integrated within the care pathway that families experience during diagnosis.

A second knowledge gap stems from the mixed evidence on the impacts of genetic results, signalling a need for a comprehensive outcome measure of clinical genetic testing that can capture the impacts of genetic results on families in this population. Fortunately, the broader area of medical genetics and genetic counseling has validated a new patient-reported outcome measure specifically for genetic testing that have not yet been applied to ASD or related neurodevelopmental conditions. Building on focus group and interview data from patients and health professionals in clinical genetics services[142], *empowerment* has been proposed as a multi-dimensional outcome measure of clinical genetics services that takes into consideration the multiple potential risks and benefits of genetic testing[142,143]. McAllister *et al.* defined the construct of empowerment as the belief that the individual undergoing genetic counselling has "decisional", "cognitive", and "behavioural control", "emotional regulation" and "hope"[142-144].

The Genetic Counseling Outcome Scale (GCOS-24)[144] has been validated in recent years as an outcome measure to capture empowerment as an impact of genetic testing. The original GCOS-24 was validated among samples consisting of a majority white British females referred for familial cancer risks who themselves were undergoing genetic counseling[144]. Despite growing evidence for its validity and reliability as an outcome measure to capture the impact of clinical genetic testing, the application of the GCOS-24 for ASD is limited in three ways because genetic testing for a child directly impacts the whole family: 1) parents are the primary decision-makers for the genetic testing on behalf of their child, and thus could be impacted by the outcome of the decision for their child to undergo testing; 2) parents are target recipients of genetic counselling following testing; and 3) genetic results for the child often lead to subsequent testing of parents/siblings, potentially yielding results that impact their health. Establishing empowerment as a valid outcome measure of genetic testing for use among parents requires validating the existing empowerment measure in the context experienced by these families.

The aim of the current study is to validate the Genetic Counseling Outcome Survey (GCOS-24) for use among parents whose child is undergoing genetic testing for ASD by using a large and representative cohort study integrated into routine care pathways. Specific objectives were to (i) adapt the GCOS-24 for use in the family context and (ii) assess face validity, internal consistency, and convergent validity of the adapted measure among parents of a child with ASD undergoing genetic testing. To this end and consistent with the validation process of the original GCOS-24[144], we examined results against measures of caregiver stress and distress.

3.4 Materials and Methods

The multi-site study was approved by the Research Ethics Board of the McGill University Health Centre and the Research Ethics Board of the Douglas Mental Health University Institute.

3.4.1 Participants

Families were recruited into the *Genome to Outcome* (G2O) Cohort. This study aims to understand the role of factors related to the child, family, and health services in moderating the impact of different genetic results on parents and it integrates participation into a large-scale genomics research study[145-148]. Families eligible for the G2O Cohort were those with children between 0 to 18 years of age diagnosed with a neurodevelopmental condition for which CMA testing was recommended. Children with a previously diagnosed genetic condition were excluded.

Referrals to the G2O Cohort were made by 11 clinicians across several departments (Genetics, Child Development, and Psychiatry) in two hospitals: the McGill University Health Center and Douglas Mental Health University Institute. All participating clinicians were involved in a diagnostic care pathway either through comprehensive diagnostic evaluation that includes genetic testing or through referral for genetic testing that followed a diagnosis of ASD from a community clinician.

We implemented a clinically integrated protocol to achieve a representative sample to address the tendency for research samples to be of higher socioeconomic status and functioning compared to the general population[149,150]. Referring clinicians were actively involved in the

design and implementation of the protocol, and a few acted as "champions" to support integration of research within their service.

Families were informed of the research project by one of the referring clinicians during their routine clinical appointment to discuss the child's condition. Those who were interested in participating in the G2O Cohort agreed to be contacted independently by the research team within one week.

3.4.2 Study design

Interested families were invited and consented to blood samples which were collected in the hospital site where they were initially recruited. To substantially reduce burden of participation in research, we integrated the protocol with the routine care pathway by combining the collection of blood samples for research in the same visit with clinical testing when the latter was ordered.

During the same visit, the caregiver considered to be the most knowledgeable about the child underwent an interview and was asked to complete the online self-report measures, detailed below. To reduce burden on the family, another member of the research team was present to support the child with a neurodevelopmental condition and their sibling(s) in the same room while the caregiver was interviewed. To validate the GCOS-24 for our target population of parents of children with ASD undergoing genetic testing, we employed a measure that assesses each of the following constructs: parent empowerment, stress, distress, and sociodemographic characteristics of the family. All data collection tools were available in both English and French.

We examined convergent validity of empowerment as the degree to which empowerment and another construct that theoretically should be related to empowerment, are observed to be related. Parent-reported stress and distress have been widely explored in both neurodevelopmental and genetic conditions. Parents of children with these conditions have higher levels of stress and distress as compared to parents of typically developing children[151-157]. Many affected families also report a significant emotional response to the disclosure of genetic results for their child [135,154,158,159]. Thus, a significant inverse correlation between a measure of empowerment with that of stress and distress would support the convergent validity of the GCOS-24 for use among parents of a child with ASD undergoing clinical genetic testing.

3.4.3 Self-report measures

GCOS-24: *Parent empowerment* was measured using an adapted GCOS-24 [144]. It was developed as an outcome measure to evaluate clinical genetics services. The GCOS-24 was anchored in qualitative studies to ensure that the outcomes of clinical genetics services were endorsed as valuable to both individuals undergoing genetics services and genetic counselors[143]. It was also previously shown to have high internal reliability and test-retest reliability and showed evidence of construct validity; GCOS-24 scores were correlated with scores on the Perceived Personal Control questionnaire and were higher in patients who self-identified as "active in a patient support group" [144]. Higher scores on the GCOS-24 indicate higher levels of empowerment.

Table 3-1 lists items of the GCOS-24 that required revision to adapt the GCOS-24 for our target population of parents of a child with a neurodevelopmental condition.

Table 3-1. Specific items from the GCOS-24 that were revised**.**

Original	Revised
I am clear in my own mind why I am attending the clinical genetics service.	I am clear in my own mind why my family is having genetic testing.
I can explain what the condition means to people in my family who may need to know.	I can explain what the neurodevelopmental condition means to people in my family who may need to know.
I understand the reasons why my doctor referred me to the clinical genetics service.	I understand the reasons why my doctor may have to refer my family to the clinical genetics service.
I understand what concerns brought me to the clinical genetics service.	I understand what concerns brought my family to do genetics testing.

We followed established guidelines to translate the adapted GCOS-24 (GCOS-24p) into French for the target population[160]. This consists of 1) forward translation from English to French by a bilingual health professional familiar with the target population, 2) back-translation from the translated French version into English by another bilingual health professional, blind to the original English version, 3) reconciliation of the original English version, the translated French version, and the back-translated English version of the questionnaires by the two translators for "semantic, idiomatic, experiential and conceptual equivalence"[161], especially for items identified in the back-translation to be problematic or ambiguous, and finally 4) a final proof-reading of the French version by another bilingual health professional.

To examine the face validity of the adapted questionnaire, we conducted a series of follow-up cognitive interviews[162] with a sample of seven parents from the target population to verify that the terms were interpreted consistently across participants. Participants were asked to verbalize their thought process while reading the questionnaire items with the help of verbal probing. Cognitive interviews were completed in-person after the caregiver had completed the online questionnaire at home. The interview was audio-recorded and transcribed off-line. During the interview, probes were used to ensure that all participants were asked the same question consistently. Probes for each item are as follows: (1) *Can you repeat the statement in your own words?* (2) *How did you arrive at that answer?* and (3) *Was this hard or easy to answer?*

Participants of the cognitive interview were all mothers to boys diagnosed with ASD. The median age of the mothers was 35.1 years (range = 28-45). The median age of their child with ASD was 5.8 years old (range = 5-11). Most mothers had a bachelor's degree or higher, and all mothers reported an annual household income of more than $80,000.

Perceived Stress Scale: *Parent stress* was measured using the 10-item version of the Perceived Stress Scale (PSS-10[163]). It measures the extent to which situations in the past month are perceived as stressful. The PSS-10 has been previously shown to have high internal reliability in a sample of the general population (coefficient alphas ≥ 0.84), adequate test-retest reliability, is correlated with life-event scores, and is a better predictor of health and health-related outcomes than life-event scores[164]. Higher scores indicate higher levels of parental stress.

Distress Thermometer: *Parent distress* was measured using the Distress Thermometer (DT [165]). The DT was developed for parents of a "chronically ill child" to identify parents most in need of support in their emotional functioning. The DT consists of a thermometer score ranging from 0 (no distress) to 10 (extreme distress). Respondents are instructed to check the number that best described their overall distress. The thermometer score was shown to correlate with anxiety and depression as measured on the Hospital and Anxiety Depression Scale and showed diagnostic utility. It correctly detected 86% of clinical cases of anxiety and depression among parents and ruled out 67% of non-clinical cases[165].

Sociodemographic characteristics of interest were caregiver age on study visit and education, and annual household income. These variables were assessed by a caregiver interview using the Family Background Information Questionnaire (FBIQ[166]). Diagnostic and medical information on the child with ASD and related conditions was obtained via chart review on standardized forms developed in-house. Specific information collected on participating families included child's age on study referral, gender, diagnosis, and genetic results.

3.5 Results

3.5.1 Participants

Out of the 241 eligible families referred from clinicians, 113 (46.9%) were enrolled into the G2O Cohort. The most common reason reported by families who refused research participation was that they were busy and/or overwhelmed by other demands limiting their participation.

To assess the representativeness of the sample, especially in view of the large proportion of families who declined participation, we independently compared key variables between participating and non-participating families, excluding families who were ineligible for the study. An independent-samples *t* test showed that child's age on study referral was not significantly different between those who declined ($M = 6.02$, $SD = 3.22$) versus those who enrolled in the study ($M = 6.70$, $SD = 3.72$), $t\,(239) = 1.55$, $p = 0.12$. Fisher's exact tests also showed that there were no significant differences in diagnosis and gender between the families who enrolled in the study versus those who declined participation, ps ≥ 0.05 (86% of families who enrolled had a child with ASD versus 76% of families who declined participation; 74% of families who enrolled had a male child versus 76% of families who declined participation).

Sociodemographic characteristics of the *G2O Cohort* ($n = 113$) are presented in Table 3-2. Most survey respondents were biological mothers to a male child with ASD. The proportion of families reporting household incomes and parent education lower than the Montreal average. Based on the 2016 census, the average total income of households in 2015 was $69,047 and 31% reported having completed a bachelor's degree or higher[167], suggests the clinically integrated protocol succeeded in enrolling a representative sample of families.

We identified one potential bias in the sample which is the likelihood of over-representation of families with ASD relative to other neurodevelopmental conditions. It is surprising that this occurred considering that ASD cases typically make up of 60% of referred samples in diagnostic clinics. Because the proportion of those with ASD was not statistically different between families who enrolled versus those who declined participation, a possible explanation is that families with

ASD may be more likely to participate in genetics research studies in general due to increased media coverage on ASD research and services in Quebec in that time period. To address this potential bias, analyses were repeated with an ASD-only sample.

Table 3-2. Sociodemographic characteristics of the *G2O Cohort* (*n* = 113).

Characteristic	**Statistic**
Child's age on study referral in years *M* (*SD*)	6.7 (3.71)
Child's gender *n* (%)	
Male	84 (74.3)
Female	29 (25.7)
Child's diagnosis *n* (%)	
ASD	97 (85.8)
DD/ID	16 (14.2)
Number of child's siblings	
0	31 (27.4)
1	60 (53.1)
2 or more	22 (19.5)
Caregiver's age on study visit in years *M* (*SD*)	39.3 (7.9)
Caregiver'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 (85.0)
Single/separated/divorced	17 (15.0)
Respondent education background *n* (%)	
Diploma or certificate below bachelor level*	53 (46.9)

Table 3-2 ***(Continued)***

Characteristic	Statistic
Bachelor's degree or higher	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 (38.1)
Missing	1 (0.9)

Note: ASD = Autism spectrum disorder; DD/ID = Developmental delay/Intellectual disability; *M* = Mean; *SD* = Standard deviation; *This includes a diploma/certificate from high school, community college, CEGEP, nursing school, University, trade or technical school, or vocational School.

Out of the 113 enrolled families, 111 families completed the GCOS-24p. The distribution of the responses on the GCOS-24p are presented in *Figure 3-1*. The histogram suggests a negatively skewed distribution. Descriptive statistics of the GCOS-24p along with other measures of interest can be found in Table 3-3.

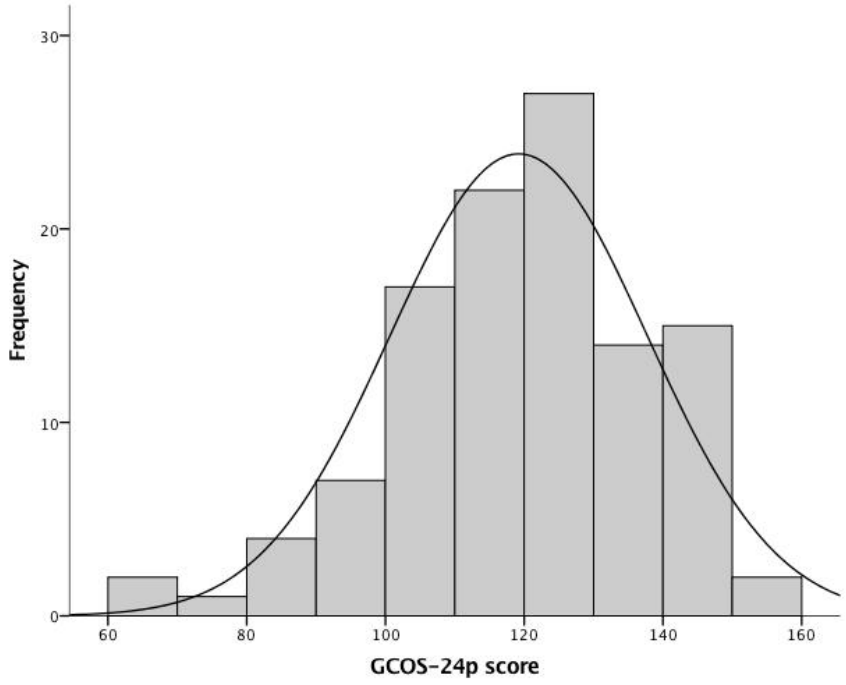

Figure 3-1. Histogram of GCOS-24p total score

Table 3-3. Descriptive statistics of main measures for the current study.

Measure	***n***	**Min-Max**	**Mean (SD)**
GCOS-24p total score	111	61-156	119.2 (18.5)
Distress thermometer	110	0-9	4.0 (2.7)
PSS-10 total score	111	3-32	17.1 (6.7)

Note: GCOS-24p = Genetic Counseling Outcome Scale adapted for parents; PSS-10 = Perceived Stress Scale 10-item version; *SD* = Standard deviation; List-wise *n* = 110.

3.5.2 Face validity

Cognitive interviews of the GCOS-24p showed overall good face validity for the target population of parents of children with ASD. The cognitive interviews confirmed that the questionnaire has adequate readability with parents reporting consistent understanding of the items of the questionnaire. There were no issues from the revised items: parents reported that they understood the term "genetic testing" to be a test to determine if there is something in the DNA or genes that causes their child's neurodevelopmental condition and from which parent(s) the gene or mutation was inherited. They understood the term "neurodevelopmental condition" to mean conditions in which the brain develops differently from others.

3.5.3 Internal consistency

Cronbach's alpha of the GCOS-24p was 0.84 ($n = 111$), which suggests good internal reliability. Cronbach's alpha of the GCOS-24p for the ASD-only sample was 0.85 ($n = 95$).

3.5.4 Convergent validity

Pearson's r shows that GCOS-24p scores were significantly inversely correlated with PSS-10 scores ($r = -0.39$, $p < 0.001$, $n = 111$) and with DT scores ($r = -0.47$, $p < 0.001$, $n = 110$). This provides evidence of convergent validity of the GCOS-24p. Pearson's r between GCOS-24p scores and either PSS-10 scores or DT scores were similar in the ASD-only sample ($r_{PSS\text{-}10} = -0.45$, $p < 0.001$, $n = 95$; $r_{DT} = -0.51$, $p < 0.001$, $n = 94$).

3.6 Discussion

The goal of this study is to validate the GCOS-24 as an outcome measure of genetic testing among families who have a child with ASD using a large and well represented sample of health services users. Following adaptation of the GCOS-24 for use among parents (GCOS-24p) and its implementation within a clinically integrated research protocol, we found that GCOS-24p showed acceptable levels of face validity, internal consistency, and convergent validity.

This study puts forth empowerment as a parent-reported outcome measure validated in the context of clinical genetic testing for ASD. We assessed convergent validity of the adapted GCOS-24p by comparing it with parent stress and distress. Both of these constructs were chosen because they have been widely explored in parents of a child with a neurodevelopment condition in general and parents undergoing genetic services in particular. Another measure that could be used for assessing convergent validity is locus of control, similar to the validation of the original GCOS-24. Future work to compare this score with scores on Perceived Personal Control would further contribute to this measure's validation.

The adapted GCOS-24p was meaningful and acceptable to the target population. This is evidenced by the high rate of return among families of a broad range of socioeconomic status. This was also reinforced by the cognitive interviews: families were generally supportive of the instrument and understood the items consistently. Further research to measure other properties related to validity such as sensitivity to change, test-retest reliability, concurrent validity, and divergent validity continue to be needed.

The GCOS-24p was comparable with the original GCOS-24. Specifically, the internal consistency, mean score, and standard deviation were similar to those reported in the original

GCOS-24 (Cronbach's α 0.84 vs. 0.87, mean score 119.2 vs. 104–121, SD 18.5 vs. 8.9–25.8[144]). This is consistent with evidence that the impact of a child's condition on a parent may be similar to the impact of an individual's condition on that individual: the level of parental distress is comparable with the level of individual distress[165]. Additional work to understand the family experience related to a neurodevelopmental condition is needed.

3.6.1 Study Limitations

A main limitation of the study is that we assessed empowerment in the parents, but not in the child with ASD themselves. While individuals with ASD were not the target population of the current study, future research should develop the GCOS-24 to be a family measure by incorporating the perspectives of the individuals with ASD as well. Such work would require further adaptations to the GCOS-24 to be meaningful for this population.

Another limitation of the study is the limited representation of neurodevelopmental conditions other than ASD. While the comparable results with an ASD-only sample suggest that the findings of the study are indeed applicable to ASD, future research would need to confirm if the GCOS-24p can be used among parents whose child is diagnosed with any neurodevelopmental condition that warrants genetic testing with CMA.

Finally, while the sample was representative, the participation rate into the cohort was low. Comparisons of available characteristics between enrolled and non-enrolled families showed no differences on basic characteristics. However, it is unknown if other sociodemographic factors have affected the families' likelihood to enroll in the study. Integrating standardized instruments within the care pathway would provide insight into barriers to research participation. It would

allow the research team to tailor the research opportunity for families interested in participating. This would provide the ideal solution for minimizing the potential burden for families to participate in research and for improving representation in research overall.

3.6.2 Practice Implications

Using the GCOS-24p in the clinical context would allow us to evaluate the role of genetic counseling for neurodevelopmental conditions on parental empowerment. There is evidence that the care pathway for genetic testing is not implemented consistently; some clinicians prepare the families for the likelihood of the limited utility of null or VUS results[168], while others fail to even inform the families of the genetic test referral following diagnosis[59]. The ongoing G2O Cohort will assess how these variations in care can predict empowerment using the GCOS-24p to inform pre- and post-result counselling to optimize parental empowerment and in turn, increase the utility of clinical genetic testing.

The goal of the ongoing G2O Cohort is to assess the impact of genetic testing on parent empowerment and to explore potential moderators of the effect. Candidate moderators include child-related factors such as symptom severity and child functioning, parent-related factors such as parents' knowledge of the condition, their perceived utility of biological testing in general, the level of family functioning, and finally, care-related factors such as the extent to which the care received is perceived to be family-centered. The GCOS-24p is important to ultimately inform the integration of future discoveries into clinical care by contributing to the development of an evidence-based and family-centered framework for genetic results disclosure across the clinical services that utilize genetic testing.

In conclusion, we validated the GCOS-24 for use among parents whose child with ASD was undergoing genetic testing. The GCOS-24p showed good face validity, internal consistency, and convergent validity. Ongoing use of the GCOS-24p within the G2O Cohort would contribute to understanding the factors that affect the utility of clinical genetic testing and ultimately help families be empowered from accessing state-of-the-art clinical care.

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3.8 Conflict of interest statement

All authors have no conflict of interest to declare.

3.9 Data availability statement

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions. Anonymized data may be available by reasonable request to the corresponding author.

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4 Manuscript 3: Perceived utility of biological testing for autism spectrum disorder is associated with child and family functioning

4.1 Preface

Manuscripts 1 and 2 concluded that the overall utility of genetic testing and biological testing ASD could be measured and optimized in the context of *routine care pathways*. Complex interactions between the unique characteristics of each child and family in routine health services will likely determine the outcomes of biomarker discovery. *Perceived utility* is an important construct to measure in family engagement in biomarker discovery because it may be both a short-term outcome of candidate biomarker discovery and a potential modifier of discovery following the integration of biological testing into the care pathway (*Figure 1-1*). In Manuscript 3, I examined the construct of perceived utility by assessing its predictors. I also addressed the absence of a measure of *perceived* utility of biological testing in ASD that can be used in routine services.

Based on previous studies of other health conditions[169-171], I examined predictors of perceived utility within a representative sample of families around the time of their child's diagnosis using a new quantitative measure of perceived utility that I developed. Specifically, I examined the association between the parents' perceived utility of biological testing and their child's severity

of symptoms and functioning, parental stress, family functioning, and appraisal of family-centered care, while controlling for sociodemographic factors, namely parental age and education, and household income. I hypothesized that around the time of diagnosis, higher levels of their child's severity of symptoms and functioning, greater parental stress, and lower levels of family functioning and family-centered care are associated with higher levels of perceived utility of biological testing among parents of a child with ASD[169-171].

I found that perceived utility of biological testing among parents of a child with ASD increases with higher child behavioural and emotional problems and higher family functioning. A likely explanation was that the families' perceived utility for biological testing is driven by knowledge of ASD. However, testing of this hypothesis relies on a measure of ASD knowledge which does not exist.

The current study addressed a major knowledge gap in family engagement in the ASD biomarker discovery by using a measure of *perceived* utility of biological testing in ASD among families. I conclude that establishing the utility of biomarker discovery requires family input not only to improve the impact of current biological tests, but also to determine the readiness of potential biological tests for clinical use. This manuscript has implications in engaging families from candidate biomarker discovery through integration of biological testing into care pathways and subsequently towards improving the health impact of discovery for affected individuals and families.

Manuscript 3 has been submitted to *Research in Developmental Disabilities*.

Perceived utility of biological testing for autism spectrum disorder is associated with child and family functioning

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4.2 Abstract

Introduction

The clinical integration of chromosomal microarray (CMA) testing promises improvements in diagnostic yields in autism spectrum disorder (ASD). While the impact on clinical management is promising for some families, the utility perceived by families, including the majority for whom results are negative, is unclear. With next generation genomic sequencing technologies poised for integration, along with promising ASD biomarkers being developed, there is a need to understand the extent to which genomic and other biological testing would have utility for the target recipients of these tests and their families. The purpose of the present study was to examine the predictors of perceived utility of biological testing among parents of a child with ASD.

Methods

The *Perceived Utility of Biotesting* (PUB) questionnaire was developed based on literature review and integrating family input. Following their child's diagnosis, families participating in an ongoing prospective study completed the PUB questionnaire along with self-reported measures of parent stress, child and family functioning, and family-centered care prior to undergoing genetic testing for both clinical and research purposes.

Results

Based on $n = 85$ families, the psychometric properties of the PUB questionnaire suggest it is a reliable and valid instrument. A stepwise regression analysis revealed that lower levels of child emotional and behavioural functioning and higher levels of family functioning correlated with higher perceived utility for biological testing.

Limitations

A main limitation in the study is the participation rate of 50%, thus the possibility of self-selection bias cannot be ruled out. We chose to assess perceived utility among parents rather than the individuals with ASD themselves thus modifying the questionnaire to capture perceived utility from autistic individuals across their lifespan would prove essential in future studies. Finally, ongoing validation of the PUB by assessing the PUB's discriminant and convergent validity is still needed.

Conclusions

We conclude that the utility of biological testing perceived by families whose child is undergoing genetic testing around the time of ASD diagnosis depends on their unique child and family characteristics. This signifies that engaging families in biomarker discovery for improving the impact of research and care requires systematic input from a representative sample of families.

Keywords

Clinical utility, perceived utility, Autism Spectrum Disorder, genomics, genetic testing, biomarkers

4.3 Contributions to the literature

- Engaging families for improving the integration of biomarker discovery into the care pathways for Autism Spectrum Disorders (ASD) requires understanding the extent to which biological testing would have utility across diverse target recipients of these tests and their families, which is currently unknown.
- We found that the utility of biological testing perceived by families whose child is undergoing genetic testing around the time of ASD diagnosis depends on child and family functioning.

- Our results underscore that engagement efforts in developing and integrating biological tests for ASD requires systematic input from a representative sample of families.

4.4 Background

Prior to integrating biological testing into the care pathway, it is important to demonstrate that the test's potential benefits outweigh its risks i.e. its *clinical utility*[172,173]. While clinical utility has been used across multiple fields for different biological tests[173], the term was primarily developed within the context of genetic testing and it also encompasses "psychological, social, and economic consequences of testing"[174]. The term has since been argued to refer to *health* outcomes exclusively, specifically the "ability [of a test] to prevent or ameliorate mortality, morbidity, or disability"[174] through "preventive or therapeutic options that are available, accessible, or effective"[66].

Biological testing integrated into the care pathways in certain conditions do not necessarily lead to "preventive or therapeutic options that are available, accessible, or effective"[66] for all individuals with the condition. Specifically, biological tests incorporated within the care pathway of Autism Spectrum Disorder (ASD) impact health outcomes by identifying commonly occurring co-morbidities[4,5,11]. Tailoring service provisions for early intervention programs or for schools also relies on a detailed developmental history from parents, teachers, and caregivers, evaluation of the core characteristics of ASD, and a thorough appraisal of abilities including cognitive and academic ability, functional skills, executive functioning, and mental health[5].

The difficulty of establishing the clinical utility of biological tests in the context of ASD highlights the limitation in our collective understanding of what constitutes clinical utility. The restrictive definition of clinical utility to only refer to health outcomes ignores the evidence that information from biological test results affects individuals in many ways, regardless of its impact on health outcomes[175], e.g. a genetic test's results can end a diagnostic odyssey, provide relief from guilt, and inform family planning[137]. Finally, this restrictive definition is also antiquated considering the shift to patient-centered care or "care that is respectful of and responsive to individual patient preferences, needs, and values"[176] and the increasing integration of patient-reported outcome measures in care[68]. Thus, a broader measure of overall utility is needed: one that is centered on the values of the patient, which may include other outcomes besides health outcomes.

For example, Grosse and Khoury suggested evaluating outcomes of biological testing based on the value of the results in understanding the condition[174]. Further, McBride et al. favored a "systematic, phased approach" in identifying determinants of interest in biological tests, drawing focus to *perceived* benefits to the individuals receiving the test[50]. Evaluating the overall utility of a biological test must then include anticipating the benefits and harms following a test, and should there be no other subsequent clinical intervention available for the condition, evaluating the value of the information yielded from the test from multiple perspectives including those of the individuals receiving the test. Assessing the utility of a biological test for ASD would therefore include systematically measuring the utility of the possible benefits and harms of the test as perceived by those receiving the test.

What is the overall utility of routine biological tests used in the ASD care pathway? One frequently measured aspect of clinical utility is 'diagnostic yield' or the proportion of individuals with ASD found to have abnormal variants over the total number of individuals tested[13]. Prior to chromosomal microarray analysis (CMA), genetic testing was used to identify common single-gene disorders and chromosomal abnormalities typically using G-banded karyotyping[177]. CMA has led to the identification of rare genes, such as *NRXN1,* causally implicated in ASD and found in approximately 5% of ASD cases[12]. It can also identify rare copy number variants (CNVs) that occur across multiple known genes, found in ~10% of ASD cases, a number which may decrease or increase based on the clinical complexity of ASD and complications being studied[12,58]. Consequently, CMA can produce a higher diagnostic yield compared to previously used genetic tests[13].

Based on these diagnostic yields, in 2010, clinical consensus guidelines recommended integrating CMA as part of the care pathway to investigate the etiology of ASD, developmental delay/intellectual disability and multiple congenital anomalies[13]. Families undergoing CMA would receive results that pertain to variants that are either normal/null, pathogenic, or "of uncertain clinical significance" (VUS). In the majority of families tested, genetic results would be considered normal/null i.e. no CNVs associated with genetic syndromes are identified. Pathogenic results are when CNVs found are associated with known genetic syndromes, *de novo*, and/or is large. They are detected in 5-20% of ASD cases[13] and could warrant changes in care management e.g. increased monitoring for seizures in the case of a 15q11-q13 duplication[133]. Finally, identified CNVs could be novel, with recent associations with clinical phenotypes: in these cases, families would receive a VUS result. The VUS has been most challenging to return

to individuals with an ASD diagnosis and/or their families[134]. It is hoped that the recent shift towards integrating molecular data for penetrant genes and CNVs rather than a strictly clinically defined ASD would resolve some of these challenges[178].

In the broader context, three general challenges exist in implementing these genetic tests in the ASD care pathway. First, hundreds of different rare genes, and CNV and structural variant loci, have been implicated in the development of ASD (different gene test used in commercial testing and research are presented in[179]). Common genetic variants under a polygenic risk model may also be involved. The most frequently detected CNVs among ASD cases can be found in less than 1% of cases[12]. This etiological heterogeneity complicates overall utility, because due to variable expression, and pleiotropy, the extent to which the different variants impact an individual's outcomes is not always clear. For example, a study found that 26% of individuals with a 16p11.2 deletion met full clinical criteria for ASD[180]. Evidence of impaired behavioural and cognitive domains in individuals with 16p11.2 deletions compared to their non-carrier relatives[32] suggests that CNVs may not be highly penetrant for ASD *per se*, but may impact domains related to neurodevelopment more generally. Finally, the diagnostic yield of CMA has not been static. Clinical recommendations for CMA conclude that the diagnostic yield of CMA is up to 20% of those with ASD[13]. However, in most of the studies reviewed, families had a child already referred for an ASD evaluation or already had "complex" ASD[58]. When replicated in other settings, CMA detected a clinically significant variant in 7%[181] of those tested after a diagnosis, suggesting that research samples may not be representative of the population seen in routine care pathways. Further, evidence of overall utility remains lacking for the vast majority of diagnosed ASD cases with "normal" CMA results. Next generation techniques using exome or

genome sequencing may significantly improve diagnostic yield[148,182], but the same challenges will remain.

Progress in *biomarker discovery* continues to drive much of the changes in clinical practice via clinical practice guidelines for the identification of ASD[19], with advances being made in understanding the underlying neurobiological mechanisms of the condition and integrating into the care pathway as biological testing for benefits for affected families[14]. The goal is that biomarkers for ASD could improve upon the ASD care pathway by accelerating detection and allowing for personalized treatments for better outcomes for autistic individuals and their families[15-17]. While many candidate biomarkers for ASD are currently in development (for reviews, see[19,20]), there are concerns that the aforementioned scientific issues along with ethical issues surrounding biomarkers would hamper its integration into clinical practice and limit the benefits for families [19].

Alongside these scientific challenges are ethical issues inherent to the heterogeneous nature of ASD. Some proponents of *neurodiversity*[33] argued that research efforts should prioritize improving social acceptance and services for autistic individuals rather than biomarker discovery[34,35]. On the other hand, there are also many, autistic individuals and their families alike, who "recognize the value of basic and translational science"[183]. Considering these challenges, to what extent can biomarkers be developed and integrated into the care pathway for purposes that align with stakeholders' values?

We propose that the current and future potential of genetic testing and biological testing in general, can be measured and optimized in the context of routine care pathways for ASD. Complex interactions between the unique characteristics of each child and family in routine care pathways will likely determine the overall utility of genetic testing. In the current study we focus on a major knowledge gap: the absence of a measure of *perceived* utility of biological testing in ASD that can be used in routine care pathways.

4.4.1 Perceived utility versus personal utility of biological testing

Two main methodologies have been used to assess the perspectives of parents of a child with ASD on biological testing in general: quantitative survey methodology and qualitative techniques. Perspectives of parents were sought between two groups of parents: those whose child had recently undergone genetic testing[137] and those who had not[59]. Overall, parents whose child had undergone genetic testing found the testing to be useful in offering an explanation for the condition, influencing family planning decisions, improving access to behavioral interventions and medical care, and receiving more information[137]. On the other hand, some parents also reported negative outcomes such as guilt and blame[137].

Parents of children who had not undergone genetic testing reported overwhelming interest in testing, if offered to them[59]. Moreover, parents were interested in genetic risk assessment testing for a younger, undiagnosed child, even if the test could not establish a diagnosis[118]. One study retrospectively interviewed parents who had already received genetic testing on their expectations for and impact of the test[65]. Similarly, some parents noted positive impact while others experienced uncertainty, frustration, and fear following test results.

In sum, evidence provides a mixed picture of parents' perspectives on genetic testing in ASD, with indications that *perceived* utility i.e. perceived outcomes of a test prior to undergoing the test to be distinct from *personal* utility i.e. experienced outcomes of a test result. The inconsistency of findings can also be attributed to the methodological limitations including over focus on qualitative methods, limiting generalizations. Further, most studies are underpowered, given the heterogeneous nature of the target population[184]. Biases in samples also cannot be ruled out: it is possible that participants recruited from research databases are more likely to show overall support and interest for genetic testing[59] whereas clinically referred samples may be more likely to show mixed results[137]. Most importantly, these studies were not guided by any explicit theory or model related to the overall utility of genetic testing. A consistent and valid measure of perceived utility, and a measure of its relevant predictors, are missing thus far.

Based on previous studies of other health conditions[73,169,171], we examined predictors of perceived utility within a representative sample of families around the time of their child's diagnosis within the routine care pathway using a new quantitative measure of perceived utility. Specifically, we examined the association between the parents' perceived utility of biological testing and child's severity of symptoms and functioning, parental stress, family functioning, and appraisal of family-centered care, while controlling for sociodemographic factors, namely parental age and education, child age and gender, and household income. We hypothesize that around the time of ASD diagnosis, higher levels of child severity of symptoms, lower levels of child emotional and behavioural functioning, greater parental stress, and higher levels of family functioning and family-centered care will be associated with higher levels of perceived utility of biological testing among parents of a child with ASD[73,169,171].

4.5 Methods

4.5.1 Sample

In this cross-sectional study, recruitment of participants relied on a clinically integrated protocol as part of a larger longitudinal genetics study, *Genome to Outcome* cohort (with the major genomic findings published in[145-148]). As part of the clinically integrated protocol aimed at reducing a potential source of selection bias, clinicians involved in the family's clinical care introduced families who met the inclusion criteria to the research project. The clinicians were from several departments (clinical psychology, medical genetics, neurology, and paediatrics) in two hospitals: the McGill University Health Center and Douglas Mental Health University Institute. Inclusion criteria of the *Genome to Outcome* cohort were: children or youth (aged 0-18 years) who had a diagnosis of ASD or a related condition for which chromosomal microarray testing was recommended. Exclusion criteria were children with previously diagnosed genetic disorders.

Once enrolled into the study, the caregiver "most knowledgeable" about the child was introduced to online questionnaires during the study visit and was asked to complete them at home. ***Figure 4-1*** outlines the inclusion of participants into the cohort. A total of 193 eligible families with a child diagnosed with ASD were referred for research participation by their clinician between 2016 and 2018 (***Figure 4-1***). Ninety-seven families agreed to participate, which translates to a participation rate of 50%.

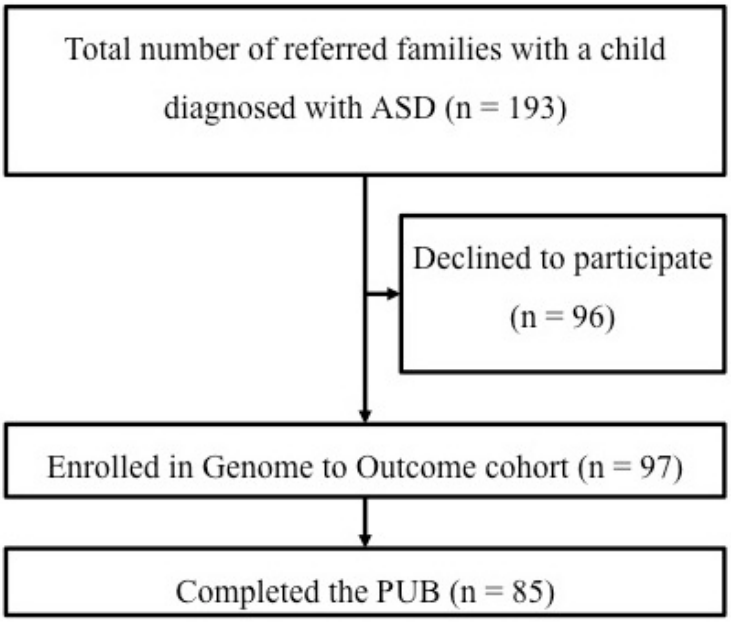

Figure 4-1. Flowchart of participation.

To assess the representativeness of the sample, we compared key variables between participating and non-participating families (Table 4-1). As part of the approved protocol, chart reviews were done for those who declined research participation to obtain basic demographic variables from this population. We found that child's age and gender were not related to enrolment status.

Table 4-1. Comparison between enrolled and declined families with a child diagnosed with ASD.

	Enrolled	**Declined**	***p*-value**
N	97	96	
Child's gender *n* (%)	Male: 75 (77.3%)	Male: 75 (78.1%)	1.00[1]
	Female: 22 (22.7%)	Female: 21 (21.9%)	
Child's age in years	Mean (*SD*): 7.09 (*3.77*)	Mean (*SD*): 6.67 (*3.41*)	0.41[2]
	Range: 2.10 – 17.69	Range: 2.39 – 16.83	

Note: *SD* = Standard deviation
[1]Fisher's exact test
[2]Independent-samples *t* test, $t(191) = 0.81$

Demographics of enrolled families with a child diagnosed with ASD are detailed in Table 4-2 ($n = 97$). The majority of respondents were married or common-law and were biological mothers to a male child with ASD. Forty-two percent of the respondents had a diploma or certificate below a bachelor level as their highest completed level of education and approximately one-third of the families reported an annual household income of less than $40,000.

Table 4-2. Characteristics of enrolled families with a child diagnosed with ASD (n = 97).

Characteristic	Statistic
Respondent age in years *M* (*SD*)	39.0 (7.7)
Respondent's relationship to child *n* (%)	
Biological mother	90 (92.8)
Biological father	7 (7.2)
Marital status *n* (%)	
Married/common law	81 (83.5)
Single/separated/divorced	16 (16.5)
Respondent education background *n* (%)	
Diploma or certificate below bachelor level	42 (43.3)
Bachelor's degree or higher	55 (57.3)
Annual household income *n* (%)	
Less than $40,000	28 (28.9)
Between $40,000 and $80,000	30 (30.9)
More than $80,000	38 (39.2)
Missing	1(1.0)

Note. M mean; *SD* standard deviation

4.5.2 Perceived Utility of Biotesting (PUB) Questionnaire

We developed a new measure, the Perceived Utility of Biotesting (PUB), a questionnaire for parents in our target population (PUB items are presented in Table 4-3). Development of the PUB questionnaire followed established guidelines[185,186]. Each step in the development process is detailed next.

Table 4-3. Item-by-item frequency of responses on the PUB.

Item	Disagree strongly *n*	Disagree *n*	Agree *n*	Agree strongly *n*
1. Biological tests would help me understand why my child has a condition.	2	4	59	20
2. I would feel reassured for my child to have biological testing, regardless of the results.	1	11	50	23
3. As long as a condition cannot be treated, I don't want a biological test for my child. *[reversed]*	0	6	37	42
4. I want to know about biological test results that relate to my child's health later in life.	4	4	29	48
5. I want to know about biological test results that relate to my health later in life.	2	0	31	51
6. Biological tests would tell me about other conditions that my child could develop.	1	3	43	38
7. Biological tests would tell me the chances of my other children developing a condition.	0	3	51	31
8. Biological tests would help me decide whether or not to have more children.	22	17	29	17
9. I would want to know the chances of a baby developing a health condition during a pregnancy.	5	9	39	32
10. Biological test results would help me prepare for my child's future.	2	11	44	28
11. Biological tests would help me stay on top of future treatment options.	1	4	47	33
12. Biological tests would help doctors improve health care for my child/family.	1	4	46	34
13. Biological tests would prevent my child from developing other health problems.	6	33	28	18
14. Biological tests would deprive me of the freedom to control my health. *[reversed]*	4	2	48	31

Table 4-3 ***(Continued)***

Item	Disagree strongly *n*	Disagree *n*	Agree *n*	Agree strongly *n*
15. Biological test results can stigmatize my family. *[reversed]*	3	9	54	19
16. Biological test results would cause problems between me and my (ex)partner. *[reversed]*	0	9	46	30
17. Biological test results would put my mind at ease about my other children's risk of the condition.	2	23	49	11
18. Biological testing would make me more watchful for symptoms in my other children.	2	10	46	27
19. I would feel guilty that I might have passed on a biological risk to my children. *[reversed]*	10	31	27	17
20. Biological tests would make me live with uncertainty. *[reversed]*	4	11	45	25
21. Biological test results would make me focus on the condition instead of what life has to offer. *[reversed]*	6	14	43	22
22. More biological knowledge would de-stigmatize health conditions.	3	16	41	25
23. Research on biological tests would help families like mine.	0	0	28	57

Item generation

We reviewed the literature on perspectives of individuals on biological testing to ensure that the items for the PUB have content validity. The literature review resulted in 32 unique tools. Supplementary Table 1 summarizes the reviewed tools by the condition of the target population. When available, psychometric properties of these tools were also reviewed. All items identified from these questionnaires were compiled into an item bank. "Redundant items", i.e. similar items

with minor phrasing differences were identified and removed by AY and ME, which resulted in 65 items in total. The items were compiled into a single questionnaire tool and minimally adapted for the target population of parents of children undergoing genetic testing, e.g., removal of inappropriate questions and changing phrasing of some questions.

Linguistic adaptation

Considering that the questionnaire is intended for use with a sample of families in Quebec, a French-language version was also developed based on established adaptation guidelines[160]. A French-English bilingual clinical researcher translated the questionnaires into Quebec French. They were then back-translated into English by another bilingual clinical researcher, blind to the original questionnaire. The two translators compared the English versions to reconcile discrepancies in the questionnaires. Items were revised or regenerated as needed. The translated questionnaire was finally revised by a bilingual health professional for the final iteration of the French version.

Follow up cognitive interviews

To examine face validity of the questionnaire, we conducted a series of follow-up cognitive interviews[187,188] with a sub-sample of seven parents from the target population to verify that the terms were interpreted consistently across participants. Respondents were asked to verbalize their thought process while reading the questionnaire items, with the help of verbal probing. Cognitive interviews were completed in-person, after the respondent had completed the online questionnaire at home. The interview was audio-recorded and transcribed off-line. During the interview, probes were used to ensure that all participants were asked the same question

consistently. Probes for each item are as follows: (1) *Can you repeat the statement in your own words?* (2) *How did you arrive at that answer?* and (3) *Was this hard or easy to answer?* Seven mothers from the overall sample participated in the cognitive interview. All have a boy diagnosed with ASD. The median age of the mothers was 35.1 years (range=28-45). The median age of their child with ASD was 5.8 years old (range = 5-11). Most mothers had a Bachelor's degree or higher, and all mothers reported an annual household income of more than $80,000.

The final version of the questionnaire appears in Additional File: Figure S1. Respondents would respond on a scale of 0 to 3 (0 = Disagree Strongly, 3 = Agree Strongly) the extent to which they agree to each of the 23 statements. Scores could range from 0 to 69 with higher scores corresponding to higher perceived utility.

4.5.3 Psychometric properties of PUB

We first assessed psychometric properties for the Perceived Utility of Biotesting (PUB) questionnaire. A total of 85 out of 97 enrolled families completed the PUB questionnaire, a response rate of 87.6%. This indicates a high rate of return and thus minimizes the possibility of non-response bias. Table 3 summarizes the item-by-item responses in the PUB questionnaire.

Cronbach's alpha for the questionnaire is 0.80, which suggests good internal reliability. ***Figure 4-2*** is a histogram of PUB scores in our sample of $n = 85$, which demonstrates a normal distribution.

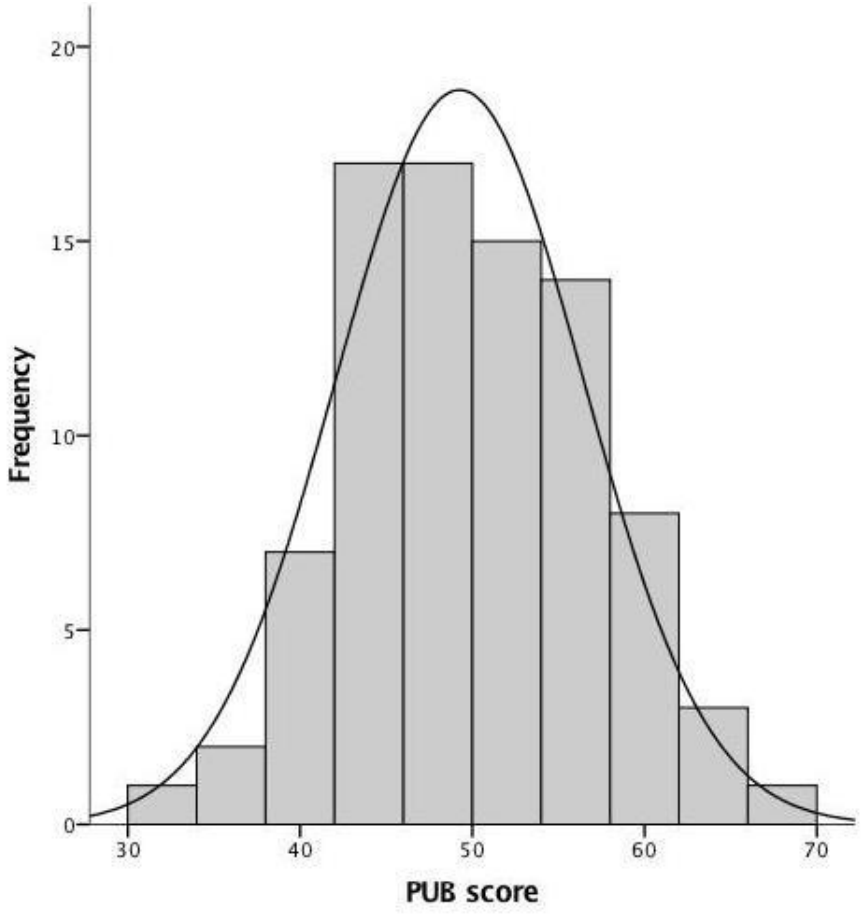

Figure 4-2. Histogram of PUB scores.

Principal Component Analysis

To examine the factor structure underlying the PUB, we conducted a Principal Component Analysis (PCA) followed by orthogonal (varimax) rotation. Kaiser-Meyer-Olkin Measure of Sampling Adequacy is 0.73 which indicates that sampling is adequate. Bartlett's Test of Sphericity is significant, $\chi^2(253)=725.14$, $p<0.001$.

The most reliable method for determining the number of factors to extract in PCA is parallel analysis [189]. First, random datasets with the same number of cases and variables as the real dataset were generated. The eigenvalues from the 95th percentile of the distribution of these

random datasets were then compared to the actual eigenvalues. The number of factors retained correspond to the *i*th eigenvalue from real data that was greater than the *i*th eigenvalue from the generated data.

We randomly generated 1000 data matrices, each with 85 cases and 23 variables using SPSS syntax[189] in IBM SPSS Statistics[190]. The first 7 eigenvalues from both the real and random datasets are presented in Table 4-4. Only the first two eigenvalues exceeded the corresponding random data eigenvalues. This indicates that a two-factor solution is optimal. Thus, two factors were extracted and rotated.

Table 4-4. Eigenvalues from the random datasets along with eigenvalues from the real dataset and the associated percentage of variances.

Component number	**95th percentile eigenvalues from randomly generated data matrices**	**Eigenvalues from the real dataset**	**Associated percentage of variances from the real dataset**
1	2.27	5.55	24.1
2	2.01	3.06	13.3
3	1.85	1.65	7.2
4	1.71	1.37	6.0
5	1.58	1.31	5.7
6	1.48	1.23	5.3
7	1.38	1.10	4.7

To examine if the two factors exist under one factor "perceived utility", we conducted a higher order factor analysis as per a previously published validation of a patient-reported outcome measure [144]. Participant's scores on the two extracted factors were calculated and submitted to another PCA. The eigenvalues (and associated percentage of variances) were 1.25 (62.5%) and 0.75 (37.5%). Parallel analysis revealed that only the first eigenvalue exceeded the eigenvalues that emerged from the randomly generated datasets (the first and second eigenvalue from the 95th percentile of the random datasets are 1.21 and 0.99, respectively). This indicates that the two factors exist under a single higher order construct, 'perceived utility'.

Cognitive interviews

Follow up interviews showed overall good face validity for the target population of parents of a child diagnosed with ASD. The cognitive interviews confirmed that the questionnaire has adequate readability, with parents reporting consistent understanding of the items of the questionnaire.

4.5.4 Summary of development and validation of the PUB

In summary, the development of the Perceived Utility of Biotesting followed established guidelines. Items were generated from the literature, ensuring content validity. Cognitive interviews confirmed the face validity of the PUB. There was adequate internal reliability. A higher-order PCA is consistent with the notion that the PUB items load on a single underlying construct. Thus, we contend that the total PUB score reflects perceived utility of biological testing.

4.5.5 Predictors of perceived utility

The predictors of interest in the current study to perceived utility of biological testing were as follows: severity of ASD symptoms and emotional and behavioural functioning in the autistic child, parent stress, family functioning, appraisal of family-centered care, and sociodemographic factors namely child age and gender, parental age and education, and annual household income. Measures pertaining to each of the predictors are detailed next.

ASD severity of social symptoms was measured using the Social Responsiveness Scale Second Edition (SRS-2 [191]). The SRS-2 is a 65-item parent/caregiver rating scale that provides a picture of a child's atypical social behavior. Higher total scores indicate greater severity of social symptoms specific to ASD. The SRS-2 total score has been shown to have good test–retest reliability ($r \geq 0.88$) and internal consistency (coefficient alpha of 0.95) in clinical samples of children with ASD[191].

Child emotional and behavioural functioning was measured using the Child Behavior Checklist (CBCL), which is a widely used standardized measure of a child's emotional and behavioural problems[192,193]. The CBCL obtains parent/caregiver ratings of 99-113 items on their child's emotional, behavioural, and social problems. The CBCL has been developed for use in children aged between 1½-5 years and those aged between 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.

Parent stress was measured using the 10-item version of the Perceived Stress Scale (PSS-10[163]). It measures the extent to which situations in the past month are perceived as stressful. The PSS has been previously shown to have high internal reliability in a sample of the general population (coefficient alpha = 0.85), adequate test-retest reliability, is correlated with life-event scores, and is a better predictor of health and health-related outcomes than life-event scores[163]. Higher scores indicate higher levels of parent stress.

Family functioning was measured using the Brief form of the Family Assessment Measure, Self-rating scale, third edition (FAM-III SR-Brief [194]). The FAM-III SR Brief provides a total score from 14 items consisting of items on the following dimensions measuring family strengths and weaknesses: task accomplishment, role performance, communication, affective expression, affective involvement, control, and values and norms. The FAM-III was reported to have good internal reliability (coefficient alpha of 0.86 to 0.95) and good test-retest reliability[194]. The FAM-III scores were also sensitive to family therapies[194]. Higher scores correspond to lower levels of family functioning.

Appraisal of family-centered care was assessed with the 20-item Measure of Processes of Care (MPOC-20)[70]. The MPOC-20 was developed to assess parents' experiences and perceptions of family-centered behaviours of service providers experienced in the past year[70]. The MPOC-20 captures five dimensions of care. This study focused on the dimension of care in providing general information. The measure was reported to have good internal reliability (coefficient alphas ranging from 0.77 to 0.88) and good test-retest reliability[70]. The MPOC-20 was also

found to be correlated with a measure of satisfaction and parental stress[70]. Higher scores reflect higher levels of family-centered care.

Sociodemographic variables of interest are: child's age and gender, respondent age and education, and annual household income. These variables were assessed using the Family Background Information Questionnaire (FBIQ[166]).

4.6 Results

4.6.1 Independent relationships between predictors and perceived utility

We first assessed the extent to which each of the sociodemographic variables independently predicted perceived utility of biological testing. Age of the autistic child was found to be positively correlated with PUB scores. None of the other sociodemographic variables correlated with perceived utility (Table 4-5).

Table 4-5. Sociodemographic variables assessed as potential predictors of PUB.

Variable	***n***	**Mean PUB (*SD*)**	**Statistic**	***p*-value**
Child age	85	-	Pearson's $r = 0.23$	0.03
Child gender	85		$t\ (83) = 0.21$	0.83
Female	19	49.3 (7.2)		
Male	66	48.9 (7.4)		
Parent age	85	-	Pearson's $r = 0.18$	0.10
Parent education level	85		$t\ (83) = 0.75$	0.45
Diploma or certificate below bachelor level	36	49.9 (7.9)		
Bachelor's degree or higher	49	48.8 (6.6)		
Household income	84		$F\ (2, 81) = 0.44$	0.65
Less than $40,000	25	48.1 (7.7)		
Between $40,000 and $80,000	22	49.6 (7.6)		
More than $80,000	37	49.8 (6.8)		

Note: *SD* = Standard deviation.

The descriptive statistics of all variables measured are presented in Table 4-6. The relationship between the potential predictors and perceived utility was each assessed using Pearson's *r* (Table 4-6). Higher scores on the CBCL and lower scores on the FAM-III SR-Brief were associated with higher scores on the PUB. The PSS-10, SRS-2, and MPOC-20 general info scores did not correlate with the PUB.

Table 4-6. Descriptive statistics of all variables measured and the correlation between potential predictors and PUB.

Variable	*n*	Min-Max	*M* (*SD*)	Pearson's *r* with PUB
PUB total score	85	31-67	49.3 (7.2)	-
SRS-2 total raw score	79	27-176	91.8 (30.5)	0.15
Social awareness		4-21	11.8 (3.76)	-
Social cognition		1-33	18.2 (6.68)	-
Social communication		9-59	30.7 (9.89)	-
Social motivation		2-31	13.9 (6.08)	-
Restricted interests and repetitive behaviour		4-33	17.5 (7.37)	-
Social communication and interaction		19-143	74.3 (24.4)	-
CBCL Total T score	82	37-87	62.7 (10.3)	0.22*
Internalizing Behaviour T score		41-85	62.0 (9.75)	-
Externalizing Behaviour T score		34-82	57.8 (11.23)	-
PSS-10 total score	85	5-32	18.0 (6.63)	-0.01
FAM-III SR-Brief total score	84	2-28	11.8 (5.65)	-0.34*
MPOC-20				
Providing general information	85	0-7	3.5 (1.91)	-0.13
Enabling and partnership	85	0-7	4.1 (2.04)	-
Providing specific information	85	0-7	4.3 (2.05)	-
Co-ordinated and comprehensive care	85	0-7	4.2 (1.79)	-
Respectful and supportive care	85	0-7	4.6 (1.78)	-

Note: PUB = Perceived utility of biotesting; SRS-2 = Social responsiveness scale; CBCL = Child behaviour checklist; PSS-10 = Perceived stress scale 10-item version; FAM-III SR-Brief = Family Assessment Measure, Self-rating scale, third edition; MPOC-20 = Measure of Processes of Care; *SD* = Standard deviation; * $p < 0.05$.

4.6.2 Multiple regression model

To explore the combined effect of potential predictors on perceived utility of biotesting, we entered the following as predictors of interest in a stepwise regression model predicting perceived utility: respondent age, education, household income, child gender and age, child severity of social symptoms, child emotional and behavioural problems, parent stress, family functioning problems, and family-centered care. The best-fitting model accounts for 19% of the variance in perceived utility of biotesting, $F(2, 74) = 9.90$, $p < 0.001$, R^2-*adjusted* = 0.19. The predictors significant to perceived utility were child emotional and behavioral functioning and family functioning (Table 4-7). Specifically, lower child emotional and behavioral functioning and higher family functioning predict greater perceived utility. No other factors were associated with perceived utility.

Table 4-7. Regression model predicting PUB score.

Predictors	***B***	***SE***	**95% CI *B***	***t***	***p*-value**
(Constant)	41.77	4.62	32.6, 51.0	9.0	1.41×10^{-13}
CBCL T-score	0.22	0.07	0.1, 0.4	3.0	0.004
FAM-III SR-Brief	-0.5	0.13	-0.8, -0.3	-3.9	0.0002

Note: CBCL = Child behaviour checklist; FAM-III SR-Brief = Family Assessment Measure, Self-rating scale, third edition; *B* = unstandardized beta; *SE* = Standard error of unstandardized beta; CI = Confidence interval; *SD* = Standard deviation.

4.7 Discussion

We examined parents' perceived utility of biological testing for ASD using a new quantitative measure. Our sample consisted of a relatively large number of families mostly recruited from

routine care pathways coupled to genomic research studies following a diagnostic assessment for their child with suspected ASD. Our results showed that higher levels of caregiver-reported problems in child emotional and behavioral functioning and higher levels of family functioning correlated with higher perceived utility for biological testing. We did not find any association between perceived utility and parental stress, ASD symptom severity, or family-centered care. Further, socio-demographic factors such as caregiver age, education, and household income were not associated with perceived utility.

Previous research in the broader genetic testing field have focused on models in which the health behavior outcome was frequently conceptualized as whether or not patients undergo or intend to undergo medical care, rather than the extent to which the mandated care they receive was useful to them[73]. In contrast, our data showed that among families who complied with the recommended clinical genetic testing, there was variation in its perceived utility as determined by the families' unique characteristics. This suggests that the "uptake" or "intention" of genetic testing is uninformative when evaluating the utility of a test implemented in routine health care. Rather, an assessment of perceived utility is required to capture the range of utility of testing, even if the target group complies with the recommended test. Future research is still needed to assess if families who opt out of testing also show varied perceived utility depending on these characteristics similarly to those who comply.

Our results were only partially consistent with previous research on predictors of genetic testing uptake. Specifically, when analyzed in a constraint model, parent stress along with socio-demographic factors did not predict perceived utility of biotesting. Appraisal of family-centered

care, a predictor only previously examined in the context of general health behavior[171], was also not associated with perceived utility of biotesting. Wydeven et al. found that while primary care under-referrals predicted lower utilization of genetic services, the under-referrals did not affect interest in and perceived benefits of genetics services among families with a child with ASD[59]. No other study has examined the role of health care services in perceived utility of genetic testing either in ASD or in the broader genetics field. Our results suggest families who have a child with more emotional and behavioural problems may be more likely to expect testing to address these needs but that the care received has no effect in tempering these expectations. It is possible that addressing misconceptions instead may temper unrealistic expectations for biotesting, pending empirical evidence of the role of ASD knowledge on perceived utility.

In contrast to previous findings predicting genetic testing uptake[73], we failed to see a signification association between parent stress and perceived utility. Past studies have shown that individuals with more "condition-specific distress/worry" are more likely to show interest in or undergo genetic testing[73]. This points to a distinction between the construct of condition-specific distress/worry experienced by at-risk individuals with that of stress experienced by parents of a child with an already diagnosed condition. The financial cost of testing for the family for this study should not be a factor[195] since this was a fully-supported research study, but this might also need to be considered in other designs.

The relationship between family functioning and perceived utility found in this study seems at first incongruent. However, studies have shown that cohesive families are more likely to pursue health-promoting behaviours[196] and are more likely to undergo genetic testing[169]. It is possible

that higher levels of family functioning may reflect more resource-seeking behavior for a family, which in turn predict higher perceived utility for biotesting.

Our results have significant implications for the current clinical implementation of genetic testing. Understanding a family's expectations for genetic test results prior to undergoing genetic testing is important because of the potential effect of expectations on the impact of the results[197]. It is possible that families who have high expectations for genetic testing are more likely to become disappointed and subsequently less likely to comply with clinical recommendations. The study results could be indicative of the potential need for tailored pre-test genetic counselling with psycho-educational elements, especially among families who are experiencing greater behavioural and emotional problems in their child. Further work is needed to establish clinical cut-off scores for the PUB that can guide such pre-test counselling.

Measuring the perceived utility of biotesting can also inform the development of future biological testing. Identifying biomarkers for ASD has been a major investment in the past decade. However, challenges in translating these discoveries into practical impact are also grounded in differences in how ASD is perceived and managed among diverse individuals[19]. Family engagement in biomarker discovery "to understand their values and needs in relation to ASD" could overcome these challenges. The results support this approach to measuring "stakeholder priorities and values": we assert that a quantitative measure of perceived utility of biotesting and assessing its determinants in large and representative samples is necessary to engage families in biomarker discovery.

4.7.1 Limitations

A number of limitations of the study need to be addressed in future research. First, half of the eligible families did not participate in the study. While the clinically integrated protocol succeeded in enrolling families with a diverse range of incomes and education levels, we cannot rule out the possibility that the families who could not participate may represent those most in need of support and/or may systematically perceive lower utility from biological testing. Targeted recruitment is needed in the future to ensure that these families are well represented.

We did not assess perceived utility of biological testing among the children with ASD themselves, but only their parents. We targeted parents for this study because they are legal decision-makers in genetic and other biological testing for their child. The perspectives of adults with ASD would be valuable because they can reflect on the use of testing based on their experience. Perspectives of children with ASD undergoing testing would also be crucial considering that testing affects them directly. Establishing the content validity of the questionnaire to account for the heterogeneous experiences of autistic individuals across the lifespan would prove essential in future studies.

We have developed the PUB so that a total score would encompass a comprehensive range of perceived utility of biotesting. Further work in examining the PUB's discriminant and convergent validity is still needed, while acknowledging the dearth of research to inform which constructs are dis/similar enough from "perceived utility" that can be used as reference constructs.

4.8 Conclusions

The current study addressed a major knowledge gap in the measure of overall utility of biological testing in neurodevelopmental conditions by using a measure of *perceived* utility of biological testing in ASD among families. By identifying how characteristics of each child and family affect the perceived utility of genetic testing, we demonstrated how the current and future potential of genetic testing in particular and biological testing in general can be systematically assessed in the context of routine care pathways. We purport that establishing the overall utility of biomarker discovery requires family input, not only to improve the impact of current clinical genetic tests but also to determine the readiness of potential biological tests for clinical integration. This signifies a step in engaging families in the development and integration of biological testing, and subsequently towards improving the relevance and impact of research and care for families.

4.9 List of abbreviations

ASD: Autism spectrum disorder

CBCL: Child Behavior Checklist

CMA: Chromosomal microarray imaging analysis

CNV: Copy number variant

FAM-III SR-Brief: Family Assessment Measure, self-rating scale, third edition

FBIQ: Family Background Information Questionnaire

MPOC-20: Measure of Processes of Care, 20-item version

PCA: Principal component analysis

PSS-10: Perceived Stress Scale, 10-item version

PUB: Perceived Utility of Biotesting

SRS-2: Social Responsiveness Scale Second Edition

4.10 Declarations

4.10.1 Ethics approval and consent to participate

The study was approved by the Research Ethics Boards of the Research-Institute of McGill University Health Centre and of the Douglas Mental Health University Institute. Written informed consent was obtained from participants. The study was performed in accordance with the Declaration of Helsinki.

4.10.2 Consent for publication

Not applicable

4.10.3 Availability of data and materials

The dataset supporting the conclusions of this article is available from the corresponding author on reasonable request. The dataset is not publicly available as participants did not provide informed consented for broad sharing of the data collected.

4.10.4 Competing interests

The authors declare that they have no competing interests.

4.10.5 Funding

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4.10.6 Authors' contributions

AY, ME, IP, and SWS made substantial contributions to the conception and design of the work. AY, JF, and IP were responsible for the acquisition of data. AY and RB were responsible for data analysis. AY, ME, IP, and TSL were responsible for the interpretation of data. AY drafted the manuscript. All authors critically revised, read, and approved the final manuscript.

4.10.7 Acknowledgements

Not applicable

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5 Manuscript 4: Higher distress is associated with higher knowledge about autism in parents of children with autism spectrum disorders

5.1 Preface

Based on the model of family engagement in ASD biomarker discovery proposed (*Figure 1-1*), knowledge of ASD is a potential modifier of biomarker discovery. Results from Manuscript 3 also suggested that knowledge of ASD could explain the relationship between child and family functioning on perceived utility. An assessment of this construct relied on a validated measure of ASD knowledge, which was lacking in the field. The final research objective was to develop a measure of knowledge of ASD and assess predictors of knowledge for use in the care pathway (Manuscript 4).

Manuscript 4 resulted in a measure of ASD knowledge usable among parents[198]. I found that higher distress is associated with higher knowledge among parents following their child's diagnosis of ASD. Implications from this Manuscript include optimizing pre-test counselling in clinical care. Specifically, the Manuscript suggests that counselling prior to genetic testing should entail either emotional or informational support depending on the family. Broadly, the study allows for future research to assess the model of family engagement of ASD biomarker discovery proposed e.g. by examining the extent to which knowledge together with perceived

utility of biotesting could modify the relationship between predictors of engagement and empowerment within a constraint model.

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Association between distress and knowledge among parents of autistic children

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5.2 Abstract

Background: Understanding the overall utility of biological testing for autism spectrum disorder (ASD) is essential for the development and integration of biomarkers into routine care . One measure related to the overall utility of biological testing is the knowledge that a person has about the condition from which he/she suffers. However, a major gap towards understanding the role of knowledge in overall utility is the absence of studies that have assessed knowledge of ASD along with its predictors within a representative sample of families within the context of routine care. The objective of this study was to measure knowledge of ASD among families undergoing routine biological testing in ASD by examining the association between knowledge with potential correlates of knowledge namely sociodemographic factors, parental stress and distress, and time since diagnosis among parents whose child with ASD is undergoing clinical genetic testing.

Methods: Parents of a child diagnosed with ASD (n = 85, M_{age} = 39.0, SD = 7.7) participating in an ongoing prospective genomics study completed the ASD Quiz prior to undergoing genetic testing for clinical and research purposes. Parents also completed self-reported measures of stress and distress.

Results: Parent stress and distress was each independently correlated with knowledge of ASD, rs ≥ 0.26, ps < 0.05. Stepwise regression analysis revealed a significant model accounting for 7.8% of the variance in knowledge, F (1, 82) = 8.02, p = 0.006. The only factor significantly associated with knowledge was parental distress, β = 0.30, p = 0.006. Parental stress, time since diagnosis, and sociodemographic factors were not significant predictors in this model.

Conclusions: We concluded that families require tailored support prior to undergoing genetic testing to address either knowledge gaps or high distress. Ongoing appraisal of the testing

process among families of diverse backgrounds is essential in offering optimal care for families undergoing genetic testing.

5.3 Introduction

Biomarkers are indicators of a biological state that are measurable, associated with a condition, and stable across individuals[18]. It is hoped that biomarkers for Autism spectrum disorder (ASD) could improve upon the identification of and intervention for ASD[15-17]. Biomarker discovery is a major priority in ASD research, with advances being made in understanding the underlying neurobiological mechanisms of ASD, It is hoped that biomarker discovery can be integrated into biological testing that could yield benefits for affected individuals and their families[19]. Currently, biological testing is integrated as part of the routine diagnostic care pathways for ASD. A care pathway describes the essential steps of health or social care centered on a person, with a specific condition, and extending across specialties and/or settings[6,7]. For ASD, the typical care pathway leading to a diagnosis, i.e. the routine diagnostic care pathway. consists of genetic testing to rule out the presence of specific single-gene disorders, like Fragile X Syndrome and Tuberous Sclerosis[4,5]. In some cases, it may also include metabolic testing or neurological tests. As a result of developments in our understanding of the genetic architecture of ASD[58], chromosomal microarray (CMA) testing has also been integrated into clinical practice to provide an etiological explanation for ASD[13].

The genetic architecture of ASD is complex, with numerous underlying genetic etiologies[12]. The advent of CMA testing has allowed us to detect copy number variants (CNVs) i.e. segments of the DNA that vary in copy number. CNVs are thought to explain between 7% to 18% of ASD cases[58,132,181]. However, different CNVs have different penetrance; some CNVs, like the 15q11–q13 duplication, are associated with severe phenotypes such as seizures, “hypotonia, global developmental delays with specific deficits in speech and language” and severe intellectual

disability[133]. Other mutations have less penetrance and most likely have an impact in combination with other factors[199].

Despite this incomplete penetrance, CMA still provides some degree of clinical utility and is currently used in clinical services. CMA provides three categories of results: 1) *"abnormal"*, when an identified CNV is associated with known genetic syndromes, is *de novo*, and/or is large, (e.g. the 15q11-q13 duplication is both associated with ASD epilepsy[133], which prompts for both the monitoring of seizures and provides a likely genetic cause for the ASD), 2) *"normal"*, when either no clinically significant CNV was found or any identified CNVs are known to benign, and 3) "*variant of uncertain clinical significance (VUS)"*, when identified CNVs are novel, and may be associated with clinical phenotypes. The result of a VUS offers a challenge to interpret and communicate to families [134]. Thus, the utility of CMA can only be ascertained by understanding the impact to families receiving these results, which is thus far unclear.

This gap in understanding the impact of CMA results to families highlights the limitation in the current conceptualization of *clinical utility*. Clinical utility of a biological test is defined on the basis of a set of criteria to be met prior to integrating that test into clinical practice[172] and has primarily been defined in the literature as benefits versus harms of a test on health outcomes in particular[174]. With the increased availability and access to genomics information, there is a need to expand the concept of "clinical utility" to overall utility that includes the utility of genomic information from the perspective of those affected by testing, regardless of its clinical use or health impact[174].

One way genomic information would have utility to individuals affected by testing is by increasing their knowledge of the condition, i.e. the extent to which a person can correctly identify facts from misconceptions about a condition. A systematic review found that genetic risk assessment services in cancer increases knowledge of the condition and of genetics [200]. In ASD, recent qualitative studies found that one of the outcomes of CMA in ASD is providing an etiological explanation to the condition to the parents[135-137,201]. This outcome could partly explain feeling *empowered* from attending clinical genetic services i.e. by increasing a sense of control from having information[142]. In sum, knowledge of a condition may have an important role towards the overall utility of genomic testing specifically and biological testing in general. However, a major gap towards understanding the role of knowledge in overall utility is the absence of studies that have assessed knowledge of ASD along with its predictors within a representative sample of families within the care pathway.

In this study, we examined knowledge of ASD among a representative sample of families undergoing clinically recommended CMA by assessing the potential predictors of knowledge, including sociodemographic factors, parental stress and distress, and time since diagnosis. Previous research has shown that higher levels of stress reduced the effectiveness of genetic risk counseling on improving risk comprehension among individuals at risk for a condition[202] while greater time since diagnosis of a condition consistently predicted more knowledge of the condition[203]. We thus hypothesized that lower parental stress and distress, and longer time since diagnosis would correlate with greater knowledge of ASD.

5.4 Materials and Methods

5.4.1 Ethics statement

The study was approved by the Research Ethics Board of the McGill University Health Centre and the Research Ethics Board of the Douglas Mental Health University Institute. Written informed consent was obtained from participants. The study was performed in accordance with the Declaration of Helsinki.

5.4.2 Participants

Recruitment of participants relied on a multi-site clinically integrated protocol as part of a larger longitudinal genomics study, *Genome to Outcome* (with major genomic findings published in [145-148]). Clinicians involved in the family's clinical care introduced families who met the inclusion criteria to the research project. Inclusion criteria of the Genome to Outcome study were: children or youth (aged 0-18 years) who were referred for an evaluation of ASD or a related neurodevelopmental condition, or had a confirmed diagnosis of ASD or a related condition for which CMA was recommended. Exclusion criteria for the Genome to Outcome study were: children with previously diagnosed genetic disorders (e.g. chromosomal or cytogenetic abnormalities, such as Trisomy 21, Duchenne Muscular Dystrophy, Angelman Syndrome, William's Syndrome, etc.). The current study included a sub-sample of the Genome to Outcome study, specifically only the individuals who were diagnosed with ASD. There were no other exclusion criteria.

Enrolled families provided informed written consent. The caregiver "most knowledgeable" about the child was asked to complete online questionnaires at home. A subset of the questionnaires was completed during the study visit to help respondents familiarize themselves to the format of the online questionnaires.

Figure 5-1 outlines the inclusion of participants into the current study. A total of 193 eligible families with a child diagnosed with ASD were assessed for interest in research participation by their clinician between 2016 and 2018 (***Figure 5-1***). Paediatricians referred the most families (*n* = 92/193, 48%). Ninety seven families agreed to participate (50%).

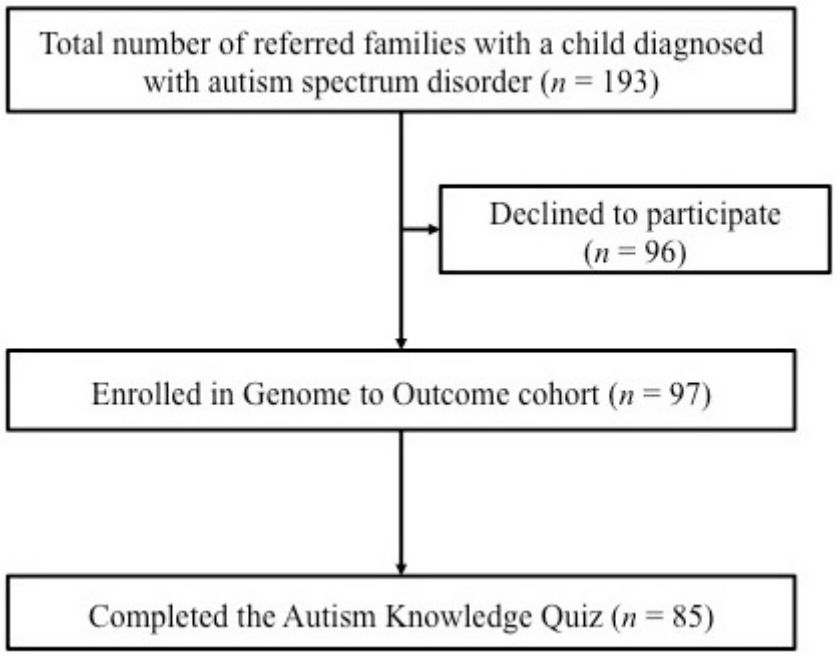

Figure 5-1. Flowchart of enrollment into the study.

The demographics of enrolled families are detailed in

Table 5-1. The majority of respondents were married or common-law and were biological mothers to a male child. Forty-two percent of the respondents had a diploma or certificate below bachelor level as their highest completed level of education and approximately one-third of the

families reported an annual household income of less than $40,000. The median time since diagnosis for the enrolled families was 150 days, with a range of 16 days to 13 years and 4 months.

Table 5-1. Characteristics of enrolled families (n = 97).

Characteristic	**Statistic**
Respondent age in years *M* (*SD*)	39.0 (7.7)
Respondent's relationship to child *n* (%)	
Biological mother	90 (92.8)
Biological father	7 (7.2)
Marital status *n* (%)	
Married/common law	81 (83.5)
Single/separated/divorced	16 (16.5)
Respondent education background *n* (%)	
Diploma or certificate below bachelor level°	42 (43.3)
Bachelor's degree or higher	55 (57.3)
Annual household income *n* (%)	
Less than $40,000	28 (28.9)
Between $40,000 and $80,000	30 (30.9)
More than $80,000	38 (39.2)
Missing	1(1.0)

Note. °This includes a diploma/certificate from High School, Community College, CEGEP or Nursing School or University, or Trade, Technical or Vocational School; *M* = Mean; *SD* = Standard deviation

5.4.3 The Autism spectrum disorder (ASD) Quiz

Assessing knowledge in the context of biological testing requires assessing knowledge of the neurobiology of ASD and the feasibility of biological testing in ASD. In the ASD field, few knowledge instruments are validated, and existing validated knowledge instruments primarily concern with knowledge of ASD features and development [204]. Thus, we developed this ASD Quiz to incorporate concepts related to neurobiology of ASD and the feasibility of biological testing in ASD. Briefly, guided by established methodology [185,205], the development of the ASD Quiz consisted of first, an initial generation of 12 items on the heritability of ASD and the feasibility of biological testing in ASD integrated with items retrieved and adapted from a literature review of questionnaires assessing parents' knowledge of genetics and heritability of any neurodevelopmental condition. Following expert validation of items for accuracy and clarity and translation of the questionnaire to French, we conducted cognitive interviews among parents from the target population. Each step in the development process is detailed in Supplementary material for Manuscript 4.

The questionnaire items are provided in Supplementary Table 2. The ASD Quiz is composed of 19 statements rated either *True* or *False*. A knowledge score was calculated as the percent of correct statements chosen. Higher scores reflect greater knowledge of ASD.

Validity and reliability of the ASD Quiz

Cognitive interviews suggested overall good face validity of the ASD Quiz for the target population: the questionnaire has adequate readability, with parents reporting consistent understanding of the items of the questionnaire.

A total of 85 out of 97 enrolled families completed the quiz, a response rate of 88%. This indicates a high rate of return and thus minimizes the possibility of non-response bias. The item-by-item responses in the quiz are summarized in the S1 Table. ***Figure 5-2*** is a histogram of quiz scores, which demonstrates a negative skewed distribution. This suggests a possible ceiling effect of knowledge among parents of a child on the ASD spectrum.

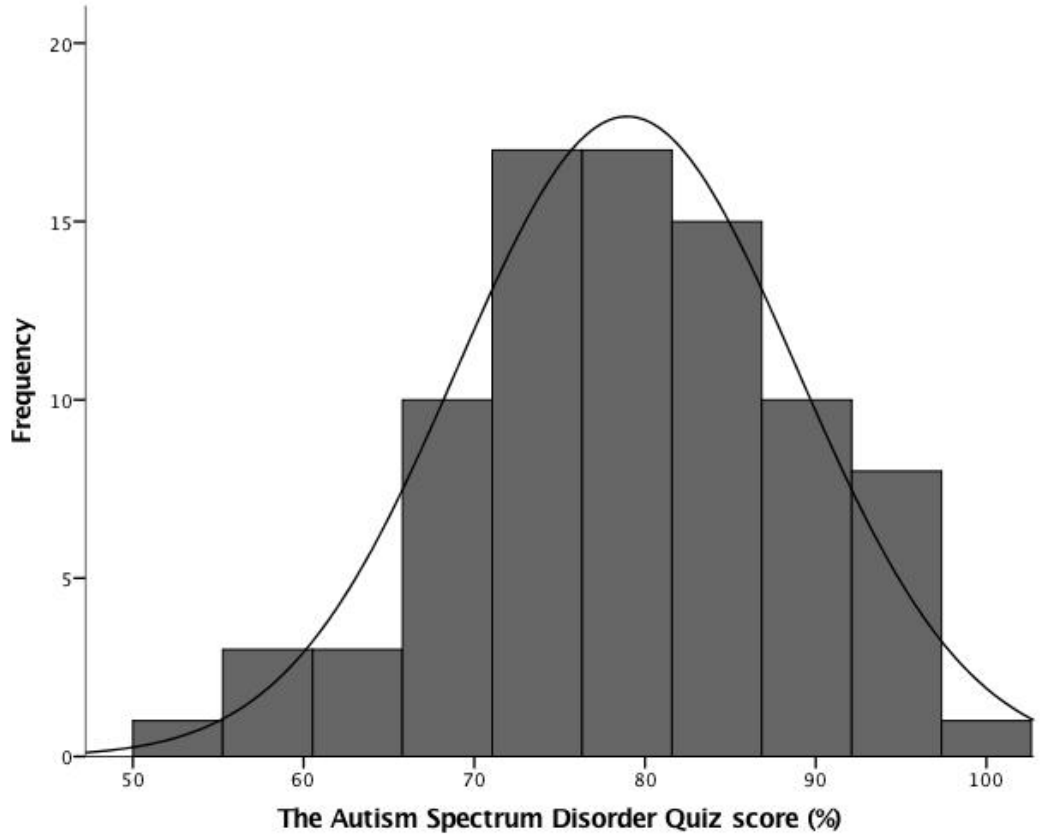

Figure 5-2. Histogram of the Autism spectrum disorder scores

The long-interval temporal stability of the ASD Quiz is supported by the significant correlation between ASD Quiz scores at baseline versus after chromosomal microarray results became available, Pearson's $r = 0.58$, $p < 0.001$ ($n = 41$). The average time between the two time-points was 25.1 weeks ($SD = 10.3$, $Min = 3.3$, $Max = 51.0$).

5.4.4 Correlates of knowledge of ASD

The correlates of knowledge assessed are as follows: parental stress and distress, time since diagnosis, and sociodemographic factors, such as parental age and education, child age and gender, and annual household income. Measures pertaining to each of the correlates are detailed next.

Parent stress was measured using the 10-item version of the Perceived Stress Scale (PSS-10)[163]. It measures the extent to which situations in one's life in the past month are perceived as stressful. The PSS-10 has been previously shown to have high internal reliability in a sample of the general population (coefficient alpha = 0.85), adequate test-retest reliability, is correlated with life-event scores, and is a better predictor of health and health-related outcomes than life-event scores[163]. Higher scores indicate higher levels of parental stress.

Parent distress was measured using the distress thermometer (DT)[165]. The DT was developed "to detect distress in parents of a chronically ill child". The DT has been shown to have good internal consistency (Cronbach alpha ≥ 0.90). The DT was able to predict clinical levels of anxiety and depression and was associated with parental stress[165]. Higher scores on the DT reflect higher parental distress.

Sociodemographic variables of interest are: respondent age, education, and annual household income. These variables were assessed using the Family Background Information Questionnaire (FBIQ)[166].

5.5 Results

5.5.1 Independent relationships with knowledge

We first assessed the extent to which each of the sociodemographic variables is independently associated with knowledge of ASD. The extent to which knowledge differs by child and parent age was assessed using Pearson's r correlation, and the relationship between time since diagnosis and knowledge was assessed with a Spearman's ρ correlation. The effect of parent education level, household income, and whether or not families had already undergone genetic testing for ASD on knowledge was examined using independent-samples *t* tests or a one-way analysis of variance, when applicable. None of the factors significantly correlated with knowledge (Table 5-2). The average knowledge score was 6.4% and 5.3% lower in families reporting an annual household income of less than $40,000 compared to those reporting between $40,000 and $80,000 and those reporting more than $80,000, respectively (***Figure 5-3***). However, these differences were not statistically significant (Table 5-2).

Table 5-2. Sociodemographic variables and time since diagnosis as independent correlates of knowledge.

Variable	***n***	**Mean Knowledge % (*SD*)**	**Statistic**	***p*-value**
Child age	85	-	Pearson's r = -0.01	0.92
Child gender	85	-	t (83) = -0.41	0.68
Female	19	78.1 (11.4)	-	-
Male	66	79.2 (9.6)	-	-
Parent age	85	-	Pearson's r = -0.07	0.52
Parent education level	85	-	t (83) = 1.52	0.13
Diploma or certificate below bachelor level	36	77.0 (9.8)	-	-
Bachelor's degree or higher	49	80.3 (9.9)	-	-
Household income	84	-	F (2, 81) = 3.08	0.052
Less than $40,000	25	74.9 (11.0)	-	-
Between $40,000 and $80,000	22	81.3 (7.9)	-	-
More than $80,000	37	80.2 (9.9)	-	-
Have undergone genetic testing for ASD	85	-	t (83)= 0.13	0.90
Yes	25	79.2 (10.6)	-	-
No	60	78.9 (9.8)	-	-
Time since diagnosis	63	-	Spearman's ρ = -0.001	1.00

Note. ASD = Autism spectrum disorder; *SD* = Standard deviation

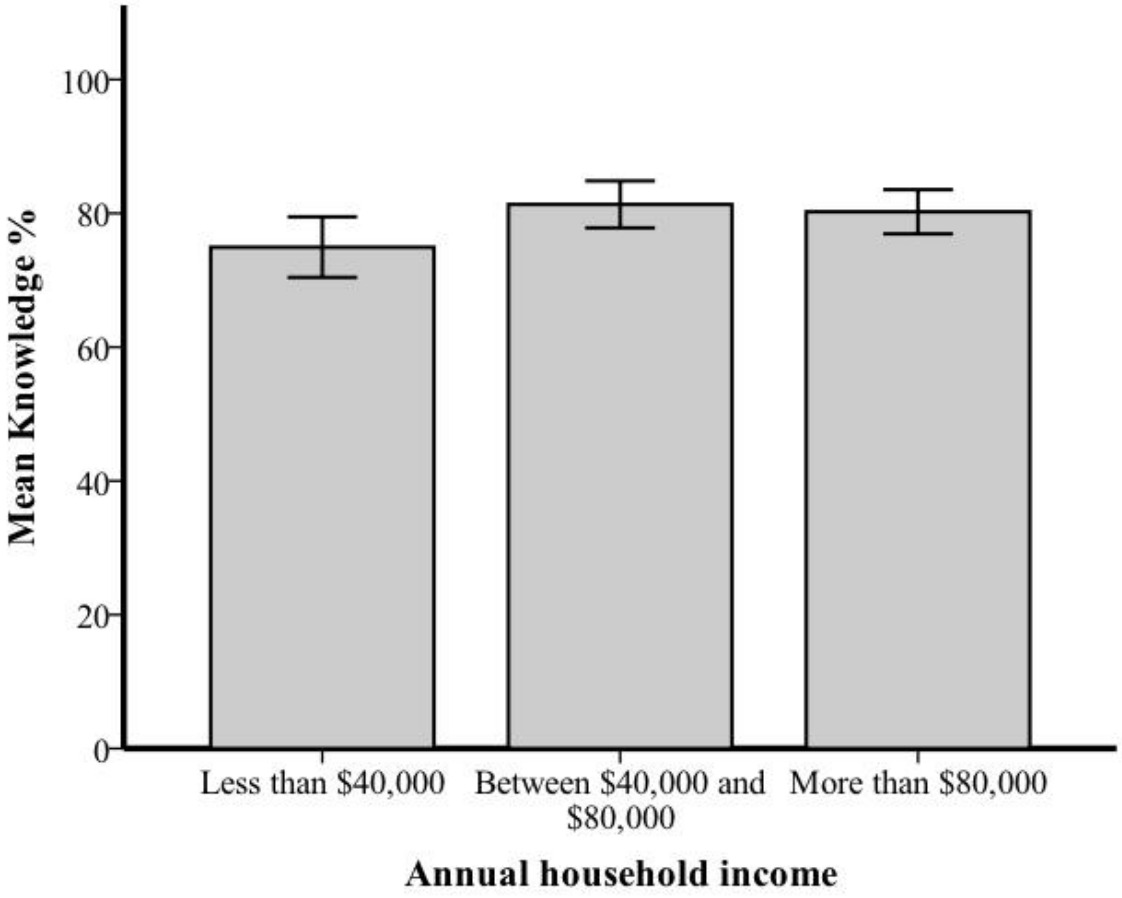

Figure 5-3. Mean knowledge score (%) for each annual household income level. Error bars represent standard errors.

The descriptive statistics of potential predictors are presented in Table 5-3. The relationship between parent stress, parent distress, and knowledge was each assessed using Pearson's *r* (Table 5-3). Higher scores on the DT and on the PSS-10 were moderately associated with higher scores on the ASD Quiz. PSS-10 was strongly correlated with DT.

Table 5-3. Descriptive statistics of potential correlates of ASD knowledge along with bivariate correlations between factors and knowledge.

Variable	*n*	Min-Max	*M* (*SD*)	Pearson's *r* with Knowledge score	Pearson's *r* with PSS-10
PSS-10 total score	84	5-32	17.9 (7.0)	0.26*	-
DT	84	0-9	4.2 (2.8)	0.30*	0.70*

Note. PSS-10 = Perceived Stress Scale 10-item version; DT = Distress Thermometer; *M* = Mean; *SD* = Standard deviation.
*$p < 0.05$

5.5.2 Multiple regression model

To explore the combined effect of correlates on knowledge, we entered the following as predictors of interest in a stepwise regression model predicting knowledge: respondent age, education, household income, whether or not the family has undergone genetic testing for ASD, time since diagnosis, parental stress, and parental distress.

The best-fitting model accounted for 7.8% of the variance in knowledge, F (1, 82) = 8.02, p = 0.006, R^2-*adjusted* = 0.078. The predictor significant to knowledge was parental distress, β = 0.30, t = 2.83, p = 0.006. Specifically, higher distress is moderately associated greater knowledge. No other factors were associated with ASD knowledge.

5.6 Discussion

We examined parents' knowledge of ASD among a relatively large number of families mostly recruited from routine diagnostic or medical care services. Our results showed that, in a constraint model, higher parental distress correlated with greater ASD knowledge. We did not find an association between knowledge with parental stress or time since diagnosis. Further, socio-demographic factors, namely parental education, and parent age and gender, were not associated with knowledge. The association between income and knowledge, was not statistically significant at the $p < 0.05$ threshold.

In contrast to the hypothesis, distress positively correlated with baseline knowledge of biological testing in ASD. Past studies have shown that greater distress predicts more help-seeking [206]. It is possible that parents with greater distress have also sought more information on ASD because of this help-seeking behavior. Alternatively, it is also possible that greater knowledge leads to greater distress because more unmet concerns are generated. This would suggest that knowledge could have a detrimental impact if families lack appropriate support in navigating the needs generated by that knowledge. Further research assessing both help-seeking behavior along with quality of care in examining the relationship between distress and knowledge is needed to inform this question.

Our results signify the need to control for both baseline knowledge and distress in studies examining the effect of an educational intervention in genetic testing. Specifically, it is possible that those present with higher distress also had higher baseline knowledge, which would be less

likely to improve after an intervention due to a ceiling effect. This may explain previous results on the effect of worry on "reducing" the effectiveness of a genetics risk intervention [202].

5.6.1 Limitations and future directions

To ensure face validity, the ASD Quiz was developed with input from experts and families in addition to being informed by the literature. We have also provided evidence of this measure's stability. Future use of the ASD Quiz to distinguish the general population from ASD experts would provide further evidence of its validity. Other aspects of validity are also valuable, such as discriminant validity to examine if knowledge of ASD is distinct from knowledge of other concepts, like general genetics.

The questionnaires were implemented in a sample of families recruited via a clinically integrated protocol. The integrated protocol was successful in recruiting a more representative sample of families compared to previous research, as shown by the range of incomes and educational levels of families participating in the study. At the same time, there was a high rate of non-participation. We could not rule out the possibility that families who agreed to participate in a genetics project could have a higher knowledge than those who refused. Targeted recruitment and integrating the quiz in clinical assessments is important to address this possible bias.

The results of the study have implications in tailoring genetic counseling prior to undergoing testing. Parents who reported lower levels of distress could benefit from an information-driven counseling session, whereas those reporting higher levels of distress may profit from more psycho-emotional support during counseling rather than an information-focused session. Further research among parents who have a child with a neurodevelopmental condition regarding how

genetic counseling affects knowledge, distress, and perceived utility of biological testing, similar to that done by Lerman et al. [202], is a needed next step in understanding how to improve the overall utility of biological testing in ASD and related conditions.

5.7 Conclusions

The current study characterized the knowledge of biotesting in ASD among parents in routine care pathways for their child on the ASD spectrum. We demonstrated how parents' knowledge increases with higher parental distress. We concluded that families would require tailored support prior to undergoing genetic testing to address either knowledge gaps or high distress. With the advent of next-generation sequencing in standard care, parents are poised to receive more uncertainties in their genomics results. Ongoing appraisal of the informed consent process and its effects on the overall utility of biological testing among diverse backgrounds of families is necessary to ensure that optimal care is offered to families.

5.8 Funding

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5.9 Data Availability Statement

Data cannot be shared publicly because participants did not provide informed consent for broad sharing of the data collected. Data are available from the Azrieli Centre for Autism Research Data Access Committee (contact via acar-dac.mni@mcgill.ca) for researchers who meet the criteria for access to confidential data.

5.10 References

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6 General discussion

Stakeholder engagement in ASD biomarker discovery can resolve challenges relating to the integration of biomarker discovery into routine care pathway. Although the principles of stakeholder engagement in biomarker discovery and its integration are thoroughly described in the literature across different fields, consensus on the methodology was still outstanding. My thesis resulted in concrete tools to facilitate the engagement of specific stakeholder groups, beginning with families, in ASD biomarker discovery. Building on existing frameworks of engagement across diverse research fields, I presented a model for family engagement in ASD biomarker discovery (*Figure 1-1*), which I used as a foundation to formulate the different research questions addressed in this thesis.

In this overall discussion, I first summarize the main results of the studies contextualized within the presented model. Next, I discuss the implications of the thesis on both clinical care and biomarker discovery. I conclude with an examination of limitations and suggestions for further research.

6.1 Summary of Findings

The first study in this thesis examined the overlap between community-based participatory research (CBPR) and ASD biomarker discovery. Using scoping review methodology, I found limited empirical data. However, available studies showed clear instances of community engagement in assessing needs, setting global research priorities, and in research design. Moreover, progress in family engagement in biomarker discovery in particular was likely

hindered by the lack of tools that could be used to accelerate biomarker discovery through engaging well-defined and representative samples of families affected by ASD.

The subsequent empirical studies in my thesis began to address the following gaps:

(1) I adapted and validated the *Genetic Counselling Outcome Scale* (GCOS-24) to measure *empowerment*, a relevant outcome of a biological test for ASD that was recently integrated into routine care based on advances in biomarker discovery.

(2) I developed and validated the *Perceived Utility of Biotesting* (PUB) questionnaire, a new tool to measure *perceived utility* of biological testing. The PUB can complement *diagnostic yield*, the previously prevalent measure of clinical utility, by incorporating perspectives of individuals and families in ASD biomarker discovery.

(3) I developed and validated the ASD Quiz, a tool to assess ASD *knowledge*, as an important predictor of utility of biological testing when integrated into the care pathway.

Across these three empirical studies, my approach was novel because it accounted for the unique interactions that a representative sample of health systems users have with health services. First, I showed that empowerment is a relevant and measurable outcome of clinical genetic testing within this representative sample. Second, I found that perceived utility of biotesting among parents of a child with ASD increases with higher child behavioural and emotional problems and higher family functioning. Contrary to my initial prediction, parent stress, previously shown to be associated with both child behavioural and emotional problems and family functioning[207,208], was not a significant predictor of perceived utility. This suggests that perceived utility is not determined by parents' characteristics per se, but by the impact of their child and family

functioning. I proposed that perceived utility may also be related to the parent's knowledge of ASD. The final empirical study allows for this question to be addressed by understanding the potential predictors of knowledge of ASD. When formally measured using the newly developed ASD Quiz, I found that higher levels of ASD knowledge were associated with higher distress among parents whose child was undergoing clinical genetic testing for ASD. This indicates that optimizing pre-test counseling could entail either emotional support or informational support, or both depending on the family.

In sum, my thesis advanced the methodology needed to engage families in biomarker discovery within the routine care pathway. I developed and validated tools necessary to support engagement by measuring predictors, modifiers, and outcomes of biomarker discovery. I designed a cohort who served as a highly relevant target group for biomarker discovery: families simultaneously undergoing genomics testing both for research and clinical purposes. Within this cohort, I implemented the tools to assess constructs important for testing the model of family engagement in biomarker discovery (*Figure 1-1*). The implications of these findings on both the care pathway and candidate biomarker discovery are discussed next.

6.2 Implications for the care pathway

Recommendations for chromosomal microarray imaging (CMA) for ASD and related conditions have been based solely on diagnostic yield, i.e., the proportion of cases identified using the test as pathogenic (currently 15-20%)[13]. As discussed above, diagnostic yield fails to consider benefits and risks experienced by families following results from CMA, especially for the proportion of families who receive null results and for those receiving a result of unknown

clinical significance. With the advent of whole exome sequencing, families are poised to receive even more information in the latter categories. An understanding of the families' expectations and hopes regarding their genetic test results has also been highlighted as a critical component of future clinical management[209]. I propose that empowerment and perceived utility are important factors to consider as a potential outcome and predictor, respectively, of biological testing. These tools can allow us to empirically assess if modifying parents' perceived utility would affect the experienced impact of test results in empowerment and subsequently, the families' interaction with further care management in the care pathway. Thus, these measures, used within routine care pathways, can inform how the care pathway could be optimized to integrate future genetic testing like next-generation sequencing.

Recommendations for integrating a biological test (such as those completed by the Evaluation of Genomic Applications in Practice and Prevention Working Group[13]) need to be updated to include these measures, especially in complex and multigenic conditions like ASD. Newer biomarkers have been proposed but not yet integrated into clinical practice e.g. measures of electroencephalography[15] . Future studies can help clarify if the model presented in this thesis is applicable for integrating all putative biomarkers or if it is specific to the integration of genomic testing. Engagement in biomarker discovery can ensure that discovery is integrated appropriately into the care pathways. In that vein, future research must continuously evaluate the integration of discovery into routine care from multiple perspectives to ensure that the long-term impact of discovery benefit those for whom they are intended to benefit.

My thesis also brought forth questions about the extent to which families are sufficiently supported prior to undergoing testing, Shared decision-making is an important element of patient-centered care[210 211]. Use of the standardized measures would assist clinicians in potentially tailoring services around biological testing, including pre- and post-test counselling. Future research remains to evaluate modifiable factors that can improve shared decision-making in genetic testing, such as increasing trust with health professionals and improving adherence to subsequent health recommendations.

6.3 Implications for future biomarker discovery

Shared decision-making as a form of engagement can also be applied for engagement in earlier phases of biomarker discovery, including the search for candidate biomarkers. While the distinction between biological testing for research versus clinical purposes is theoretically clear, it is unknown if families perceive the same distinction in utility, especially in light of the availability of uncertain information from clinical testing. What further research can identify is the extent to which such support would lead to families who are more engaged in research. Specifically, studies can expand on the relationship between perceived utility, knowledge, and empowerment in the context of family engagement with biomarker discovery. Would increasing perceived utility and knowledge lead to more empowered participants in research and thus increased engagement in biomarker discovery? Or would increasing perceived utility and knowledge lead to more disappointment when biomarker discovery cannot fulfill those utilities? There are evidence for both hypotheses: a systematic review on predictors of satisfaction in health care suggest contradictory evidence on the relationship between expectations and satisfaction[212]. Future research in ASD biomarker discovery can assess the long-term effects of

modifying perceived utility and knowledge on research participation, empowerment, and ultimately on the relevance of research to address these important questions.

Prior attempts at measuring the relevance of research in ASD have compared the value of biomarker discovery with other fields of research like intervention research by surveying broadly defined stakeholder groups on which types of research most valued by them[35]. This line of research has been arguably unproductive because it relies on comparing hypothesized long-term applications of basic research versus short-term impacts of intervention research, namely on those families who have access to intervention research or its applications. Here, some of the tools I developed such as the PUB could support future priority-setting in research among different stakeholder groups by clarifying (1) what families anticipate as useful from a biomarker, and (2) how those expectations are modified by families' unique characteristics and interactions with care.

Evidence from my thesis suggests that the proposed "misalignment" of values between families versus researchers is unsupported when valid measures are used within a clearly defined target group. Perceived utility is a complex construct. Some families perceive greater utility than others depending on their child and family characteristics. This is in stark contrast to claims that there is inherent conflict between biomarker discovery and proponents of neurodiversity[35]. Hence, priority-setting for ASD research must include families and individuals representative of the spectrum. Future work in validating the PUB for individuals with ASD across a diverse range of contexts would pragmatically advance the methodology for empirically improving the relevance of research.

6.4 Limitations and suggestions for future research

As mentioned in previous chapters, a main limitation of the thesis is the risk for self-selection bias. Care was taken to minimize this with the clinically integrated protocol, which resulted in significantly improved representativeness of families compared to other studies. At the same time, families who are fundamentally opposed to biological testing are perhaps unlikely to participate in a genomics study or in complying with the clinically recommended CMA. A future step is to understand if a parent's decision to have biological testing for their child moderates perceived utility. This could 1) further inform the construct of perceived utility and ultimately the model of family engagement in biomarker discovery and 2) ensure that the diverse views of all families are represented.

Another limitation of the thesis is that the PUB and ASD Quiz were novel instruments validated in this sample. Further studies are still needed to establish the clinical significance of both measures. This can be done by comparing perceived utility with empowerment along with other validated measures found to be correlated with empowerment such as health locus of control and perceived personal control among others[144].

Further analyses of data from the *ASD Genome to Outcomes* cohort is planned after completion of a longitudinal follow up. Such data can strengthen evidence for the directionality of the relationships found in the current thesis. Specifically, future research needs to examine the relationship between child and family functioning and perceived utility longitudinally. It is unlikely that perceived utility could impact child and family functioning but studies have shown that parent factors like stress can interact with child emotional and behavioural problems to

exacerbate each other over time[207]. Additionally the relationship between perceived utility and child and family functioning also suggests that perceived utility is a modifiable factor rather than a stable personality trait like optimism. Longitudinal studies on perceived utility are needed to address this question.

Another limitation of the thesis is that the clinically integrated protocol was susceptible to significant variation within routine care. While the cohort was meant to capture this variation, I could not statistically control for unanticipated potential confounders across all studies, such as time since diagnosis, whether or not the family has undergone genetic testing previously, or as elaborated below, type of neurodevelopmental condition. Future studies need to be larger in size to have sufficient power enough to statistically control for the effect of care variation on the examined relationships.

Finally, the sample was biased towards ASD families: only 14% of families had a child without ASD, which is lower than the rates of referral to the participating clinics. The cohort aimed to be inclusive of families with all neurodevelopmental conditions such as developmental delay/intellectual disability (DD/ID) because the care pathway involving CMA also implicates families with DD/ID[13]. However, clinicians involved in the study referred more families with ASD than with DD/ID. It is unknown why this occurred. Therefore, potential biases in the clinical context cannot be ruled out. Due to the focus of the thesis on ASD, I removed non-ASD families in subsequent analyses in Manuscripts 3 and 4. Future research would need to examine if findings from this study can be generalized to neurodevelopmental conditions other than ASD.

6.5 Conclusions

In summary, through clarifying the concept of family engagement and appropriate methodology to evaluate family engagement, I have demonstrated that the challenges relating to the integration of biomarker discovery into the care pathways can be anticipated. By highlighting the feasibility of family engagement through the use of standardized tools in a representative sample, it is hoped that candidate biomarker discovery can become consistent with stakeholder values. Ensuring science is reflective of societal values depends on a deliberate and systematic methodology that ensures collaboration amongst all stakeholders involved.

6.6 References

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7 Appendices

7.1 Supplementary material for Manuscript 3

Supplementary Table 1. Summary of reviewed tools used for generating items for the PUB.

Condition of target population	First author, Year	Cronbach's alpha
Alcohol use disorders	Strobel, 2013 [213]	-
Alzheimer's disease	Akinleye, 2012 [214]	0.82
Autism spectrum disorders	Chen, 2013 [117]	-
	Narcisa, 2013 [118]	-
	Trottier, 2013 [119]	-
	Wydeven, 2012 [59]	-
	Reiff, 2015 [137]	-
Cancer	Gray, 2012 [215]	-
	Ramirez, 2015 [216]	0.74-0.75
Familial amyotrophic lateral sclerosis	Fanos, 2011 [217]	-
Fragile *X* syndrome	Li, 2013 [218]	-
Huntington's disorder	Scuffham, 2014a [219]	-
Hypertension	Taylor, 2013 [220]	0.66
Inherited eye diseases	Ganne, 2015 [221]	-
Inherited hearing loss, eye disease, and neurological disorders	Etchegary, 2012 [222]	-

Lynch Syndrome	Dewanwala, 2012 [223]	-
	Esplen, 2011 [224]	0.93
Mood disorders	Erickson, 2014 [225]	-
None (general population)	Botoseneanu, 2011 [226]	0.60
	Haga, 2013 [227]	0.63-0.80
	Henneman, 2013 [228]	0.70-0.78
	Jallinoja, 2000 [229]	-
	Taylor, 2011 [230]	-
	Vermeulan, 2014 [231]	-
	Wolff, 2011 [232]	0.56-0.79
Parkinson's disease	Falcone, 2013 [233]	-
	Scuffham, 2014b [234]	-
Post-traumatic Stress Disorder	Dedert, 2012 [235]	0.86
Sickle cell trait	Ross, 2011 [236]	-
Smoking cessation	Quaak, 2012 [237]	-
Treacher Collin's Syndrome	Wu, 2012 [238]	-
Bipolar disorder	Meiser, 2008 [239]	-

Biological testing uses different types of tests to look at many aspects of the human body. For example, blood tests, like genetic tests and brain scans are part of biological testing. Currently, some biological tests for childhood conditions are already used in clinics, while others are being researched. We are interested in your views on how biological tests could be useful or not useful for you and your family. Please rate how much you agree or disagree with the following statements.

	Disagree strongly	Disagree	Agree	Agree strongly
1. Biological tests would help me understand why my child has a condition.	☐	☐	☐	☐
2. I would feel reassured for my child to have biological testing, regardless of the results.	☐	☐	☐	☐
3. As long as a condition cannot be treated, I don't want a biological test for my child.	☐	☐	☐	☐
4. I want to know about biological test results that relate to my child's health later in life.	☐	☐	☐	☐
5. I want to know about biological test results that relate to my health later in life.	☐	☐	☐	☐
6. Biological tests would tell me about other conditions that my child could develop.	☐	☐	☐	☐
7. Biological tests would tell me the chances of my other children developing a condition.	☐	☐	☐	☐
8. Biological tests would help me decide whether or not to have more children.	☐	☐	☐	☐
9. I would want to know the chances of a baby developing a health condition during a pregnancy.	☐	☐	☐	☐
10. Biological test results would help me prepare for my child's future.	☐	☐	☐	☐

	Disagree strongly	Disagree	Agree	Agree strongly
11. Biological tests would help me stay on top of future treatment options.	☐	☐	☐	☐
12. Biological tests would help doctors improve health care for my child/family.	☐	☐	☐	☐
13. Biological tests would prevent my child from developing other health problems.	☐	☐	☐	☐
14. Biological tests would deprive me of the freedom to control my health.	☐	☐	☐	☐
15. Biological test results can stigmatize my family.	☐	☐	☐	☐
16. Biological test results would cause problems between me and my (ex)partner.	☐	☐	☐	☐
17. Biological test results would put my mind at ease about my other children's risk of the condition.	☐	☐	☐	☐
18. Biological testing would make me more watchful for symptoms in my other children.	☐	☐	☐	☐
19. I would feel guilty that I might have passed on a biological risk to my children.	☐	☐	☐	☐
20. Biological tests would make me live with uncertainty.	☐	☐	☐	☐
21. Biological test results would make me focus on the condition instead of what life has to offer.	☐	☐	☐	☐
22. More biological knowledge would de-stigmatize health conditions.	☐	☐	☐	☐
23. Research on biological tests would help families like mine.	☐	☐	☐	☐

Supplementary Figure 1. The Perceived utility of biotesting (PUB) questionnaire.

7.2 Supplementary material for Manuscript 4

The development of the Autism Spectrum Disorder (ASD) Quiz followed established methodology [185,205], consisting of item generation integrating expert input and literature review, linguistic adaptation, and cognitive interviewing. Each step in the development process is detailed next.

7.2.1 Item generation

Two authors (AY and ME) generated items guided by two main concepts: the heritability of ASD and the feasibility of biological testing in identifying ASD in different contexts. We generated 12 items in this initial stage.

We then reviewed the literature on parents' knowledge of genetics and heritability of neurodevelopmental conditions. We retrieved questionnaire items from 22 articles. These articles assessed knowledge related to the following conditions: Autism (n = 7) [204,240-245], Batten disease (n = 1) [246], breast cancer (n = 1) [247], Cystic Fibrosis (n = 4) [248-251], Down's syndrome (n = 1) [252], Inherited Bone Marrow Failure Syndromes (n = 1) [253], Sickle Cell (n = 2) [254,255], Neurofibromatosis Type 1 (n = 1) [256], Attention Deficit Hyperactivity Disorder (n = 1) [257], Hemochromatosis (n = 1) [258], general psychiatry (n = 1) [259], and Parkinson's Disease (n = 1) [260]. When available, psychometric properties of the tools were also reviewed. All items identified from the questionnaires were compiled into an item bank. AY and ME reviewed each item for relevance for biological testing in ASD. Ten relevant items from the review plus the 12 items generated by the authors were compiled into a single questionnaire tool and adapted for the target population of parents of children undergoing genetic testing, e.g., modifications of relevant questions relating to the application of biological testing in ASD and changing phrasing of some

questions. Expert validation was conducted as part of the adaptation: a medical geneticist and a genetics counsellor reviewed the items for accuracy and clarity.

7.2.2 Linguistic adaptation

Considering that the questionnaire was intended for use with a sample of families in Quebec, a French-language version was also developed based on established adaptation guidelines [160]. A French-English bilingual clinical researcher translated the questionnaires into Quebec French. They were then back-translated into English by another bilingual clinical researcher, blind to the original questionnaires. The two translators compared the English versions to reconcile discrepancies in the questionnaires. Items were revised or regenerated as needed. The translated questionnaires were finally revised by a bilingual health professional for the final version of the French version.

7.2.3 Follow up cognitive interviews

To examine the face validity of the questionnaire, we conducted a series of follow-up cognitive interviews [187] with a sub-sample of parents from the target population to verify that the terms were interpreted consistently across participants. Research on cognitive interviewing as an approach to establishing questionnaire validity has argued that cognitive interviewing is crucial in ensuring relevance and clarity of questionnaire items that would be problematic otherwise [261]. In this study, respondents were asked to verbalize their thought process while reading the questionnaire items, with the help of verbal probing. Cognitive interviews were completed in-person, after the respondent had completed the online questionnaire at home. The interview was audio-recorded and transcribed off-line. During the interview, probes were used to ensure that all participants were asked the same question consistently. Probes for each item included: (1) *Can*

you repeat the statement in your own words? (2) *How did you arrive at that answer?* and (3) *Was this hard or easy to answer?*

Seven mothers from the overall sample participated in the cognitive interview. All mothers have a boy with ASD. The median age of the mothers is 35.1 years (range=28-45). The median age of their child with ASD is 5.8 years old (range=5-11). Most mothers had a Bachelor's degree or higher, and all mothers reported an annual household income of more than $80,000.

7.2.4 Summary of development and validation of the ASD Quiz

In summary, the development of the ASD Quiz followed established guidelines. Items were generated based on the literature and integrating expert review, ensuring content validity. Cognitive interviews confirmed the face validity. There was adequate long-term temporal stability. Thus, we contend that the total ASD Quiz score reflects knowledge of ASD.

Supplementary Table 2. Items of the Autism Spectrum Disorder Quiz listed by percentage of participants correctly answering each item

Item	% Correct
If one child in the family has autism then all other children in that family will develop autism too. *[false]*	97
Instead of one unique condition, there are probably many 'autisms' with different biological causes and different rates of developmental progress. *[true]*	94
The MMR vaccine causes autism. *[false]*	93

A doctor can use a genetic test to diagnose a child with autism instead of examining the child's behaviour. *[false]*	93
With the proper treatment most children with autism eventually outgrow autism. *[false]*	92
A test can be done during pregnancy to find out whether or not the foetus will develop autism in the future. *[false]*	92
A genetic risk factor found in people with autism can never be found in people who developed typically. *[false]*	89
A genetic risk factor found in people with autism can also be found in people with other developmental disorders. *[true]*	89
Autism occurs in equal numbers among boys and girls. *[false]*	88
People with autism have a lesion in a specific part of the brain. *[false]*	85
Researchers know how genes and environment interact to cause autism. *[false]*	84
A genetic test can sometimes explain why a person has autism. *[true]*	78
Autism changes the way the brain develops. *[true]*	74
A doctor can use a genetic test to know which children in the community very likely have autism. *[false]*	69
A doctor can use a genetic test to identify possible medical issues in a child with autism. *[true]*	69
Scientists have found an "autism gene". *[false]*	62

A doctor can use a genetic test to advise the family on the chances of their other children developing autism. *[true]*	58
A doctor can use brain imaging to find any neurological problems in children suspected of having autism. *[true]*	48
Many children who have genetic syndromes also have autism. *[true]*	46

7.3 References

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