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Genome-Wide Sequencing for Unexplained Developmental Delays and Multiple Congenital Anomalies: A Rapid Qualitative Review

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Abbreviations

ASD	Autism Spectrum Disorder
aCGH	Array comparative genomic hybridization
CMA	Chromosomal Microarray Analysis
GDD	Global Developmental Delay
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing
VUS	Variant of Unknown Significance

Context and Policy Issues

About one half of people living with congenital anomalies have not had a specific cause or diagnosis identified based on their clinical presentation or examination of environmental causes. Such individuals are given a label of “unexplained developmental delay”, and it is not uncommon for them to be subjected to multiple diagnostic tests venturing on what some refer to as the ‘diagnostic odyssey’. Genetic sequencing has the potential to alleviate these diagnostic odysseys and provide definitive diagnoses otherwise undetectable by clinical history, physical examination, and biochemical or metabolic tests, or to do so sooner than current practice.

Next generation sequencing technologies, like chromosomal microarray (CMA) and whole exome sequencing (WES), require patients to undergo a standard blood draw that is sent off to a laboratory for analysis. The sequencing, analysis and interpretation of these technologies, however, is situated within complex bioclinical collectives[1] made up of highly specialized professionals such as molecular analysts, bioinformaticians, and laboratory geneticists. While the sequencing itself is automated, and algorithms do exist to help identify notable mutations, these collectives must collaboratively interpret sequencing results to connect phenotype to genotype and establish whether identified variants should be considered pathogenic.[2] For technologies like WES and CMA, pathogenicity is labeled along a scale from pathogenic to benign. For example, the American College of Medical Genetics (ACMG) has developed and standardized five descriptive reporting categories: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, or benign. Interpretations are based on known phenotypic associations as documented in open access databases (e.g., Online Mendelian Inheritance in Man, Human Gene Mutation Database) as well as group discussions around natural history and clinical presentation.[2]

Unlike single gene or gene panel sequencing methods that focus on single or small sets of genetic material information, next-generation sequencing reads millions of fragments of genetic information in parallel. This makes the process substantially faster, but it also requires those within the bioclinical collective to be broadly familiar with potential genetic variations.[2] This also has the effect of increasing the amounts of variants returned that may be causally relevant to the person’s condition (i.e., VUS), but cannot be determined with certainty.

Test results and subsequent interpretations of pathogenicity confirmed, they are then returned to the clinic and shared with patients and their families who necessarily find ways of incorporating them into their lived worlds. The purpose of this report is to identify and

describe families' and clinicians' experiences with, and perspectives on, using genetic testing when seeking clarity on a person's unexplained developmental delay or multiple congenital anomalies.

Research Questions

1. How have families, and their health care providers, seeking clarity on a person's unexplained developmental delays or multiple congenital anomalies experienced engaging with the processes of whole exome and/or whole genome sequencing as a diagnostic tool? For example, among other things:
    - How have sequencing, and subsequent results, been presented by health care providers as an option for families and individuals seeking this clarity?
    - How have varied results (e.g., diagnostic, semi-diagnostic, uncertain significance, secondary findings) been received, interpreted, articulated and acted upon by individuals and their families?

Key Findings

- Genetic testing is seen by families and clinicians as a valuable tool for determining causal associations for their child's unexplained condition and to help provide closure to lengthy diagnostic odysseys. Results indicating a genetic cause to their child's condition were often articulated as providing an initial sense of relief.
- For some families, simply knowing their child's condition was genetically located was considered an acceptable position to be in, at least for the time being. This acceptance was often couched in a language of medico-scientific progress and contingent on the hope that more would be known about their child's condition in the future.
- Families hoped and expected that genetic testing would provide personalized information about their child's condition that could lead to new treatment regimens or surveillance strategies. These hopes could be frustrated when testing located pathogenic variants, likely pathogenic variants, or VUS without any predefined or known clinical actionability. It is clear that the need to know and understand the cause(s) of their child's condition was rarely the sole goal of families undergoing genetic testing.
- Many families receiving definite or likely genetic diagnoses often considered this to indicate a more serious and permanent condition. This could lead to a sense of resignation further exacerbated by the reality that many diagnoses have limited clinical actionability. Not all families understood the permanence of their child's condition negatively, however, but rather used results to foster a renewed sense of purpose in helping their child achieve their greatest potential.
- Families often articulated an understanding that genetic diagnoses with limited clinical actionability resituated the burden of care squarely on their shoulders as parents. Prior to testing, parents often described their interest in testing as situated within a desire to both know what is causing their child's symptoms as well as to orient them toward potential treatment strategies. While receiving a definite or probable diagnosis was both an appreciated and desired outcome, for

some it could also feel as though the burden of care had become primarily and permanently situated on them, the parent.

- Genetic testing and diagnosis have the potential to implicate other family members as potentially living with the, as yet unrealized in them, condition. While this is seen by many families as beneficial in family planning or caring for other children, it can also heighten both clinical and parental surveillance of currently undiagnosed children.
- Even in cases where genetic inheritance was clear, geneticists marked out an ethical space attempting to decouple a causal link from the moralizing language of blame. By highlighting things like the role that chance plays in the transmission of genetic mutations, geneticists attempted to combat stigmatizing effects of genetic diagnoses.
- Interest in receiving incidental findings is often articulated around concerns with clinical actionability, condition severity and perceptions of autonomy. Families articulated the desire to receive all incidental findings that indicated severe conditions that were clinically actionable in childhood. Some families expressed a similar interest in incidental findings that were severe and actionable in adulthood. When incidental findings were not desired, this was largely due to their limited clinical actionability as well as parents' feelings that their child should make their own decisions in adulthood.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, CINAHL, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and qualitative studies. The search was also limited to English language documents published before March 15, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Individuals living with unexplained developmental impairments (or those for whom a diagnosis has subsequently been achieved), as well as their families and primary care providers.
Intervention	Genome-wide sequencing i) whole exome sequencing ii) whole genome sequencing
Context/Setting	Use of whole exome and/or whole genome sequencing at various times in genetic investigations
Outcomes	Issues emerging from the literature that relate to descriptions of experiences engaging with genome wide sequencing for the diagnosis of unexplained developmental delay. This may include, among other things,

	perspectives on the relevance or utility of testing, perspectives on access to testing, perspectives on the sorts of results sequencing provided or may provide, potential benefits and harms of the sequencing process, perspectives of how sequencing fits into the "diagnostic odyssey," and discussions of expectations of sequencing broadly speaking.
Study Designs	Qualitative studies of any design

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or they were duplicate publications.

Data Analysis

A "best fit" framework approach[3] was used to analyze data relating to the perspectives and experiences of people engaging with genome-wide sequencing. The thematic categories identified within Stivers and Timmermans'[4] study exploring how families and their geneticists understood the actionability of exome sequencing results were chosen a priori as the foundational framework. The categories identified therein include those related to the diagnostic implications and subsequent biomedical consequences of exome screening, parental guilt and fear associated with a child's condition, and conversations around disability support services.[4] Where necessary, these categories have been supplemented to include those that emerged throughout this analysis.

One reviewer conducted the analysis. Included primary studies were read and re-read to identify key findings and concepts that mapped onto the framework, which was modified as new concepts emerged. During the reading and re-reading of studies, memos were made, noting details and observations about the study's methodology, findings, and interpretations, and connections to other studies and concepts in the framework. Diagramming was used to explore how emerging concepts mapped across study findings and across concepts. Using these techniques, concepts were re-ordered and organized into thematic categories. Re-reading, memoing and diagramming continued until themes were appropriately described and supported by data from the included publications. During the analysis, issues with transferability and the results of the critical appraisal were reflected on to aid with interpretation.

Summary of Evidence

Quantity of Research Available

A total of 436 citations were identified in the literature search. Following screening of titles and abstracts, 411 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 10 publications were excluded for various reasons, and 14 publications describing 13 studies met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[5] flowchart of the study selection.

Summary of Study Characteristics

Details regarding the characteristics of included studies are available in Appendix 2: Characteristics of Included Studies, and about patient participants in Appendix 3.

Study Design and Data Collection

Two studies reported on in three publications used mixed methods,[6-8] and one study was described as using an interpretive description design.[9] The remaining 10 studies did not state a study design.[4,10-18]

Seven studies reported on in eight publications used a form of thematic analysis.[4,6-8,13,15,17,18] A form of content analysis was the method of data analysis used by four studies.[10,12,14,16] The method of data analysis was not stated in the remaining two studies.[9,11]

Ten studies collected data using interviews.[6,9-16,18] One study used video-recorded consultations.[17] Two studies used more than one method of data collection: one study (reported on in two publications) used self-report questionnaires and interviews,[7,8] and one used interviews and video recorded consultations.[4]

Country of Origin

Six studies reported on in seven publications were conducted in the United States.[4,7,8,12,13,16,17] Two were conducted in Canada[9,18] and another two in the Netherlands.[11,14] One was conducted in each of France,[6] Belgium,[10] and the United Kingdom.[15]

Participant Population

Eleven publications representing 10 studies included parents of patients who had undergone testing.[6-14,16,18] One study included families,[17] and one included families and geneticists.[4] Another study included parents and their young adult children.[15] A total of 348 patients who were children of parent participants were included in this review.

Interventions (and Comparators)

Patients had undergone WES testing in six studies,[4,6,11,14,16,17] CMA in three studies reported on in four publications,[13 7,8,18] and aCGH in two studies.[9,10] One study each focused on genetic testing not otherwise specified,[12] and genetic sequencing not otherwise specified.[15]

The reasons for testing varied with three studies including patients who were tested for developmental delay,[6,10,11] two for Autism Spectrum Disorder (ASD) (reported in three publications),[7,8,12] and one for developmental delay and ASD.[18] One study tested for developmental delay, ASD, and/or congenital anomalies,[9] another for developmental delay, ASD, and/or congenital anomalies and other behavioural or chronic medical concerns,[13] and one for complex pediatric neurologic problems.[14] One study tested patients for undiagnosed disorder,[16] and two did not report the reason for testing.[4,15]

Summary of Findings

<u>Diagnostic Implications</u>

Knowing, understanding and the potential for treatment options

By and large families described the primary motivation for engaging with genetic testing as a desire to know and understand the cause(s) of their child's condition.[4,6,9,12,14,16,18] While parents often understood their child's clinical diagnosis, these had typically been established on the basis of symptomatic markers that were unable to ascribe causal

associations. As such, the potential for genetic testing to provide specificity and clarity regarding their child's condition was highly valued and sought after.

Indeed, many families who received test results that located pathogenic or likely pathogenic variants (or sometimes even VUS) expressed feeling an initial sense of relief.[4,6,7,13,16] Even though this meant their child was (likely) living with a genetically defined disorder, identifying pathogenic variants could help to validate or potentially supersede a clinical diagnosis for both parents and geneticists,[4] as well as answer questions perceived to be left unanswered (and unspecified) in a clinical diagnosis.[4,6,7,16] This is not to say that parents were hoping for a pathogenic result, but that even if they "didn't want to have anything come back … having an answer when you never thought you would have an answer is, you know, good." (p. 1547)[4]

Implicit within this dichotomy (i.e., not wanting to find pathogenic variants, but considering knowledge of their presence a "good" thing) is the potential for clinical treatment strategies that a genetic diagnosis may bring about. Often, by the time families were offered genetic testing (particularly new generation testing like WES) they had spent years pursuing an explanation for their child's condition that could orient them toward treatment strategies not already indicated by their clinical diagnosis.[4,9,12,18] This was certainly the case for some families whose pathogenic results helped to open doors to new or different treatment options;[4,16] however, for the large majority of families, results needed to be accepted as providing a name or location for their child's condition without offering other clinically actionable information.[4,6,7,9,14,16]

For some, this was an acceptable position to be in – naming and thus "knowing" what was wrong with their child was considered a satisfactory outcome for the time being as it was one they had never thought they would have.[4] Even so, accepting where they were at presently tended to be couched in a language of a "future knowing" and hope that a deeper understanding of their child's condition may begin to emerge.

> It gave us closure. Did it help us a lot right now? No. But when more information comes out over the next few years when more people are tested in the genetic areas, then I feel when we have a larger pool of people at different age ranges, and then you are going to start to be able to find out okay, this is kind of the pattern we see with these children that carry this syndrome.(p. 1025)[16]

In this case, the hopes regarding potential treatment options and outcomes that families may have carried into testing were not shelved altogether, but rather repositioned and refocused on yet another thing to come in the future.

Others were clearly frustrated by the lack of clinical actionability of their child's test results – especially when they indicated pathogenic or likely pathogenic variants and VUS.[13,14] "I visited our family doctor and asked: 'Do you know what is wrong with our child?' 'No' was his answer. I did not receive any information about the diagnosis. And that annoys me you know, something is found, and he knows nothing about it."(p. 1210)[14] That the family doctor "knows nothing about it" is especially frustrating for these parents as testing was able to conclusively identify a pathogenic variant causing their child's condition.

This calls attention to an important distinction between knowing "of" and knowing "about" that some parents indicated learning only after testing.[9,16] "So I think that was the biggest misconception of genetics for us. … Thinking that genetics could give us a clear point, or move us forward to a cure. As opposed to just saying, OK, this is what went wrong. Cause

this is how I understand genetics now."(p. 301)[9] The assumption that the processes and meanings associated with *knowing* that something exists (i.e. knowing "of" a variant) were equivalent to those associated with *understanding* how that genetic variant works and can be treated (i.e. knowing "about") was a primary source of frustration among families across studies.[4,6,9,13,14,16] While this did not mean that parents completely gave up hope that a treatment would come along,[8,12,16,18] it is clear that the need to know and understand the cause(s) of their child's condition was rarely the sole goal of families undergoing genetic testing. Rather, their goals of genetic testing tended to be articulated in conjunction with hopeful conversations around treatment outcomes, management strategies and prognostic timelines among other things.[4,17]

Permanence and Acceptance

Families across result categories as well as testing technologies tended to approach and interpret test results within frames of (im)permanence. [4,6-8,13,14,18] While children undergoing sequencing or CMA had often already received clinical diagnoses (e.g., GDD, ASD, other congenital anomalies), a genetic diagnosis was understood as providing less space for interpretation, "a black and white, yes or no."(p. 1456)[8] While not every parent articulated a concern with permanence, and even considered their results (largely VUS) as impermanent, [6,8] the majority of families clearly understood them as fixed and immutable.

For some, this understanding of permanence could engender a sense of resignation exacerbated by the realities that these diagnoses often represent rare diseases with little in the way of clear, definitive treatment strategies. "You realize the situation [of the child] will not change. With that muscle disease we thought 'Well, let us give him some medication and he will improve,' and something like that will not happen now."(p.1210)[14] This might help to explain why some families expressed experiencing a sense of relief when testing failed to identify any pathogenic variants or located ambiguous VUS.[6,9,13,14] As one mother put it, "For the moment, we still don't have any answers. [silence] It's long. [silence] but, whatever … I'm happy he's not sick. It's nothing serious."(p. 6)[6] Even though this child had received a clinical diagnosis indicating developmental delay, in the absence of pathogenic genetic results, their condition was understood as "nothing serious".

Though perhaps understood as more serious, this is not to say that these families become wholly incapacitated in their child's care, but rather that it seems to indicate a pivot in the point and primary locus of that care for some. Prior to testing, parents often described their interest in testing as situated within a desire to both know what is causing their child's symptoms (as presented above) as well as to orient them toward potential treatment strategies.[9,12,18] While receiving a definite or probable diagnosis was both an appreciated and desired outcome, for some it could also feel as though the burden of care had become primarily and permanently situated on them, the parent.[8,13,14] "Now I kind of feel like I can't beat it, and I'm not gonna win, but I have to try to get her to the best place in life that I can. …I think I liked it better when I was trying to beat it."(p.1457)[8] Whereas pre-diagnostic hopes may have been articulated in a language of medical management and treatment, a genetic diagnosis could carry the felt responsibility to help their child attain the "best place in life" that they, as a parent, can.

Of course, care for children living with unexplained developmental delays, ASD or other rare disorders is already well situated within the home (even gendered at times[14]), but the seeming permanence of a genetic diagnosis could contribute to sentiments, and resignations, of this being a lifelong journey with their child: "I know what his future is now.

Before it was – you're hoping and praying, now I know. I know what I've got. I know that I'm going to have a child until I'm dead. He's going to be with me until I die."(p. 1458)[8]

Typically framed as a form of acceptance,[8,13,14] the sentiments of permanence attached to a genetic diagnosis could also push parents toward a more positive framing of their child's future. Suggesting that the negativity surrounding permanence was due to faulty expectations prior to testing, these parents acknowledged that regardless of a genetic diagnosis their child was living with a condition that prevented them from seeming "normal" and living "normally."[8,13]

> Then people can live – I think, in my opinion, people can have healthier lives and then instead of blaming something we can go ahead and find methods to – reasonable methods to allow these people, like [child] to go ahead and function in the world that wasn't created for them.(p.1458)[8]

Biomedical Consequences

While WES and other genetic tests are not officially indicated to assess appropriateness of current treatment regimens and monitoring strategies, or the accuracy of current prognoses, it is clear that both families and clinicians engage with testing as a way of getting at these concerns.[4,9,16,18] Though test results, even when indicating pathogenic or likely pathogenic variants, rarely changed treatment regimens (as noted above), in some cases they were used to support referrals to new specialists or to support additional monitoring and testing strategies.[4,14] Once engaged with new specialists, it may then become possible for new treatment regimens to be suggested.[4]

Where further testing or retesting was presented as an outcome, some parents seemed confused regarding the afterlife of their child's prior bloodwork, as well as how and when further testing or retesting may occur.[9,13] This was particularly the case for parents whose child had received results indicating VUS – "From what I understand, as new channels of testing become available, they're going to run her blood through that and test for those things. If anything pops up, then we're going to go back and kind of go from there."(p. 108)[13] While this father's apparent confusion indicates a need for geneticists and other clinicians to clearly articulate when and how ongoing monitoring or testing may happen, it also points to the potential movement in parents' (or other participants') views on and experiences with genetic testing. As a field (or fields) constantly in flux and perennially expanding, testing may beget testing, that begets testing, that begets testing. While pathogenic or likely pathogenic (and sometimes VUS) results may delineate a certain sense of permanence among most parents, it is possible that negative results (and sometimes VUS) could be understood or interpreted as creating testing feedback loops where you continually re-enter spaces of simply "go[ing] from there."

Whether already situated in one of these feedback loops, or being testing naïve, surveillance (e.g., monitoring and testing) regimens, suggested for the child being tested, could easily move beyond them and onto current or potential siblings. While this was often dependent upon the type of results and form of primary genetic testing, it was not uncommon for both clinicians and parents to call the potential pathogenicity of other children into question.[7,8,14,16,17]

> I'm waiting for when is the ball gonna drop and she starts having a problem. Right now, you couldn't ask for a more social, friendly, intelligent [child]. … She's so far ahead of other 4 year olds in what she can do … she's incredible. And, actually, I mean, if

> something happens to her, that's going to devastate us … if she just stops talking.(p. 1457)[8]

While this concern was often tempered when results indicated that the pathogenic or likely pathogenic variant(s) (and sometimes VUS) of the primary child being tested was de novo,[7,17] where inherited this could prompt heightened surveillance for siblings both at home and in the clinic.[7,14,17]

This ability of genetic testing to move beyond the child in question through to those who share genetic material was also made clear by the way in which testing was used by both parents and clinicians to engage with conversations around family planning.[4,7,9,12,14,16,18] In cases where a pathogenic or likely pathogenic variant was found, these conversations tended to hinge around inheritance patterns and the risk of transmitting the genetic mutation to another child. When the variant was inherited, as opposed to de novo, parents often used this information to decide against having other children.[4,7,14,16] In some cases where a VUS was returned, parents indicated that these results may not influence their decision making around family planning.

Parental guilt, fear and a seeking a sense of community

In light of the limited clinical utility of some testing results, positive sentiments around testing were often articulated in languages of personal and social utility.[4,17]

Paired with the interest parents expressed in knowing just what was the cause of their child's condition (as explored above), it is not surprising that many parents pursued genetic testing as a way of addressing personal fears that they were the causal agents themselves.[4,6,7,17,18] Whether concerned that they had done something during pregnancy to prompt their child's current condition or that they were carriers of the genetic mutation affecting their child, parents struggled to make sense of causality.

While emotional management is not an accepted reason to undergo genetic testing,[4,17] geneticists were keen to help alleviate parents' fears and outlined fine distinctions between causal variants, environmental factors and assigning blame.

> This sounds like a complete guilt trip that it comes from one of your X chromosomes. The reality is it's not. I mean we all carry mutations. It just happens to be this one that's on your X … No way to know, it's not something that you did, or anything. It was there, it's been probably there for generations on end … Now it happened that it was transmitted to one of your boys, and probably now responsible for his symptoms because he … was a boy. (P.1549)[4]

Even in cases where genetic inheritance was clear, geneticists marked out an ethical space attempting to decouple a causal link from the moralizing language of blame. By highlighting things like the role that chance plays in the transmission of genetic mutations, geneticists attempted to combat stigmatizing effects of genetic diagnoses.

Beyond the bounds of moralizing that typically exist within parenting experiences, many parents described heightened experiences of moralizing in caring for children living with unexplained developmental delay, ASD or other congenital anomalies, which could be especially difficult and personally taxing.

> Believe me, people wanna tell me stuff all the time. Everybody and their brother wants to tell me: my kid should eat kale (shakes) or something then she'd be all better you

> know. And I wanna say, 'No, it's a genetic mutation. Unless you can fix the gene, this is not gonna get better.'(p. 1550)[4]

Experiences like these could be demoralizing and play a part in contributing to a pervasive sense of self-doubt for parents. For this reason, parents often indicated appreciating testing as a way of both validating strategies being employed as they cared for their children at home,[4,13,14,16-18] and fulfilling their perceived ethical responsibility to do whatever they could to improve their child's care, even if results were negative or inconclusive.[7,9,16]

> The biggest thing to me was just a relief that I'm not crazy, I'm not a bad mom, that there was something going on with my son. And I think that the biggest thing that I have gained from seeing you guys is the relief that finally, someone, in essence, almost kind of believes me because of the trouble that we had had for the years before that.(p.106)[13]

Even in the absence of a definitive diagnosis, identifying a VUS helped to alleviate the burden of guilt due to self-perceived poor parenting that some parents may carry around for years. The validation was both important personally for some, and it also helped to validate that their child was indeed living with some condition, for which some described that clinicians may have been reticent to accept previously.[7]

Validation that they were not poor parents was furthered when genetic results were able to provide access to a group of families whose children had received similar or the same diagnosis.[13,14,16] Caring for children living with unexplained conditions could be incredibly time consuming and was noted as drawing attention away from building ongoing social connections leaving parents feeling isolated and unsupported.[14,17] For many, a genetic diagnosis helped to open doors and build new social ties by introducing them to families living with similar conditions and experiencing similar difficulties. Others expressed that a genetic diagnosis could be detrimental and promote a sense of isolation among families as results tended to indicate a rare disease, which no or few other child(ren) may be living with.[13,16]

Disability Support Services

While families engaging with genetic testing tended to already be somewhat engaged with disability support services, several families indicated that receiving a pathogenic or likely pathogenic or VUS diagnosis may improve their chances of accessing more direct or appropriate services.[4,7,9,13,17] Though providing a genetic diagnosis for this reason is not an express purpose of genetic testing,[4] having "a label"[4,9] for their child's condition could lend credence to a parent's claim and make service providers "more open to my suggestions and my thoughts."(P. 106)[13] As such, parents indicated providing schools, service providers and even family physicians with the results of their child's genetic diagnosis.

That being said, it was also noted that receiving a clear genetic diagnosis could damage a parent's claim for disability services as their child may no longer be indicated.[4,17] One geneticist warned, "That's a double-edged sword, because sometimes the school, when you get the diagnosis, then feels that the diagnosis which can be severe, then obviates the need for doing anything."(p. 224)[17]

Incidental Findings

Parental decision making

Parents deciding whether or not they would want to receive incidental findings of their child's test considered the types of risky (or not) futures indicated in these results paired with their clinical actionability and concerns for their child's future autonomy.[10,11,15]

As such, where incidental findings were interpreted by clinicians as indicating severe conditions that could be clinically addressed early in childhood, parents uniformly expressed a desire to know and act upon these findings.[10,11,15] This could be complicated, however, if clinical action was not indicated until adulthood or the condition was considered to be less severe. In these cases parents struggled with how this decision might remove their child's possibility for autonomous decision making later in life.[11,15] While several parents indicated an expectation to remain responsible for decisions regarding their child's health into adulthood due to a current condition (e.g., intellectual disability) as reasoning to pursue incidental findings, others either hoped their child's current condition might change or assumed that it would, and chose not to pursue incidental findings for this reason.[11,15] As such, deciding not to know incidental findings was largely situated in parental concerns for their child's future autonomy and could be supported where findings indicated a less severe condition or one that could be addressed later in life.

Parents also highlighted the ways in which receiving incidental findings, regardless of clinical actionability, could be incorporated into daily life to influence their perceived relationships with and obligations to their child as well as to contribute to spaces like reproductive planning (e.g., carrier status) and emotional management.[10,11] In many ways, this is reflective of the social and personal utilities many parents articulated in relation to primary testing results wherein (dis)confirmation of parental ability or care could foreground conversations around clinical actionability.

Associations between guilt, fear and the possibility to have some sort of "knowledge" could act both as a draw to incidental findings as well as a push not to engage with them.[10,11,15] Framed as negotiations with uncertainty, parental desires to know "of" incidental findings that may later become knowing "about" clinically actionable conditions were often articulated from competing perspectives. For some, the draw of knowing "of" incidental findings regardless of their clinical actionability was situated as providing a grip on their child's future and potentially alleviating guilt were a treatment to become available in that future. "The feeling that you want to know predominates" as in the absence of this knowing "you remain in the 'modus of uncertainty' that you want to get out of."(p. 1683)[11] For others, there was a deep concern that knowing "of" would infringe on their ability to enjoy life with their child and thus helped them make the decision not to receive incidental findings. "How can you let them grow up normally … you're going to have a different outlook on life, that's not always going to be positive."(p. 1683)[11] In either case, it is clear that parental decision making around incidental findings is fraught with moralizing judgement calls on what makes a good parent.

Individual decision-making

Where individuals for whom the genetic testing was being performed were making their own decisions regarding the return of incidental findings, their perspectives tended to align with those of parents making decisions on behalf of their child (e.g., primarily around clinical actionability either now or in the future). Where different, concerns with ownership

of personal data and their ability to manage or cope with an adverse prognosis were described as motivations to receive incidental findings and a desire to focus on the primary findings as a reason not to receive them.[15]

Limitations

Included publications were largely focused on families' experiences engaging with genetic testing and subsequent perspectives on the sorts of information provided through testing, the work testing results was able to do (or not) both clinically and personally, as well as how expectations leading into testing were either fulfilled or not through testing. By and large, however, included publications did engage with similar experiences or perspectives among clinicians and other genetic professionals. While this does not limit the strength of understanding families' experiences and perspectives, it does limit the interpretive and analytical capacity to inform an understanding of the ways in which familial and clinical perspectives and experiences interact.

Similarly, the initial intent of this analysis was to identify the ways in which varied discourses (e.g., clinical, policy, popular culture) surrounding genetic testing may influence how families and clinicians understood, experienced and reflected on testing, no includable publications were identified addressing these issues. Again, while this does not lessen the strength of what was found, it does limit the ability to discern how discourse may contribute to families' desires to access (or not) genetic testing.

For those studies that included patient participants, there was no analysis of differences in experiences by different populations, for example as defined by socio-economic status, geographic location, or ethnicity as factors that may be expected to influence or shape patients' experiences. Such differences may be important to explore as people typically classified as within vulnerable or marginalized populations may require specific considerations not addressed or identified in the included publications or this analysis.

Two studies examined geneticists' experiences providing test results to families, but were located within the United States where conversations around ongoing monitoring, retesting and the use of results for disability support services may not be transferrable to the Canadian setting.

Conclusions and Implications for Decision or Policy Making

This review used a "best fit" framework approach to synthesize results of 14 publications (13 studies) and describes key features of how patients and clinicians understand, use and interpret genetic tests and their subsequent results for a child's unexplained developmental delay, ASD or other congenital anomalies.

Genetic testing is seen by families and clinicians as a potentially valuable tool for determining causal associations for their child's unexplained condition and to help provide closure to lengthy diagnostic odysseys. What the idea of closure means, however, varies and can complicate the generalizable value of genetic testing. While many families articulated an initial sense of relief when testing pointed to a definite or probable genetic diagnosis, the ability of that diagnosis to instigate further clinical action could affect how families incorporated results into their lived worlds.

For some families, simply knowing their child's condition was genetically located was considered an acceptable result, at least for the time being. Of course, clinical actionability

would have been appreciated, but in light of experienced lengthy diagnostic odysseys this diagnosis provided a name and location for their child's condition that they never expected. While acceptance was often couched in a language of medico-scientific progress and contingent on hopes that more would be known about their child's condition in the not-so-distant future, diagnostic closure for these families had been realized.

For others, closure seemed to be closely tied to the ability for a genetic diagnosis to "do." In these cases, the assumption that the processes and meanings associated with *knowing* that something exists (i.e. knowing "of" a variant) were equivalent to those associated with *understanding* how that genetic variant works and can be treated (i.e. knowing "about") and was a major source of frustration. Families hoped and expected that genetic testing would provide personalized information about their child's condition that could lead to new treatment regimens or surveillance strategies. These hopes could be frustrated when testing located pathogenic variants, likely pathogenic variants, or VUS without any predefined or known clinical actionability.

In either case, it is clear that the need to know the cause(s) of their child's condition was rarely the sole goal of families undergoing genetic testing. The ability for families to situate themselves and incorporate results (of any type) into their lives may be, at least partially, contingent on the sorts of conversations families had with clinicians or other specialists prior to testing. Ensuring that these conversations held prior to testing clearly walk families through the possible outcomes of testing, both diagnostic categories and their likelihood for clinical actionability, may help to alleviate frustration for some families. That many families considered their child's definite or likely genetic diagnosis as representing a greater level of severity and permanence, further highlights the importance of having these conversations early and often.

Even in cases where genetic inheritance was clear, geneticists marked out an ethical space attempting to decouple a causal link from the moralizing language of blame. By highlighting things like the role that chance plays in the transmission of genetic mutations, geneticists attempted to combat stigmatizing effects of genetic diagnoses. Emphasizing the importance of framing to specialists engaging with families may help to alleviate feelings of guilt or fear parents often feel when faced with a genetic diagnosis for their child.

Families often articulated an understanding that genetic diagnoses with limited clinical actionability resituated the burden of care squarely on their shoulders as parents. Prior to testing, parents often described their interest in testing as situated within a desire to both know what is causing their child's symptoms as well as to orient them toward potential treatment strategies. While receiving a definite or probable diagnosis was both an appreciated and desired outcome, for some it could also feel as though the burden of care had become primarily and permanently situated on them, the parent.

Genetic testing and diagnosis have the potential to implicate other family members as potentially living with the, as yet unrealized in them, condition. While this is seen by many families as beneficial in family planning or caring for other children, it can also heighten both clinical and parental surveillance of currently undiagnosed children.

Interest in receiving incidental findings is often articulated around concerns with clinical actionability, condition severity and perceptions of autonomy. Families articulated the desire to receive all incidental findings that indicated severe conditions that were clinically actionable in childhood. Some families expressed a similar interest in incidental findings that were severe and actionable in adulthood. When incidental findings were not desired,

this was largely due to their limited clinical actionability as well as parents' feelings that their child should make their own decisions in adulthood.

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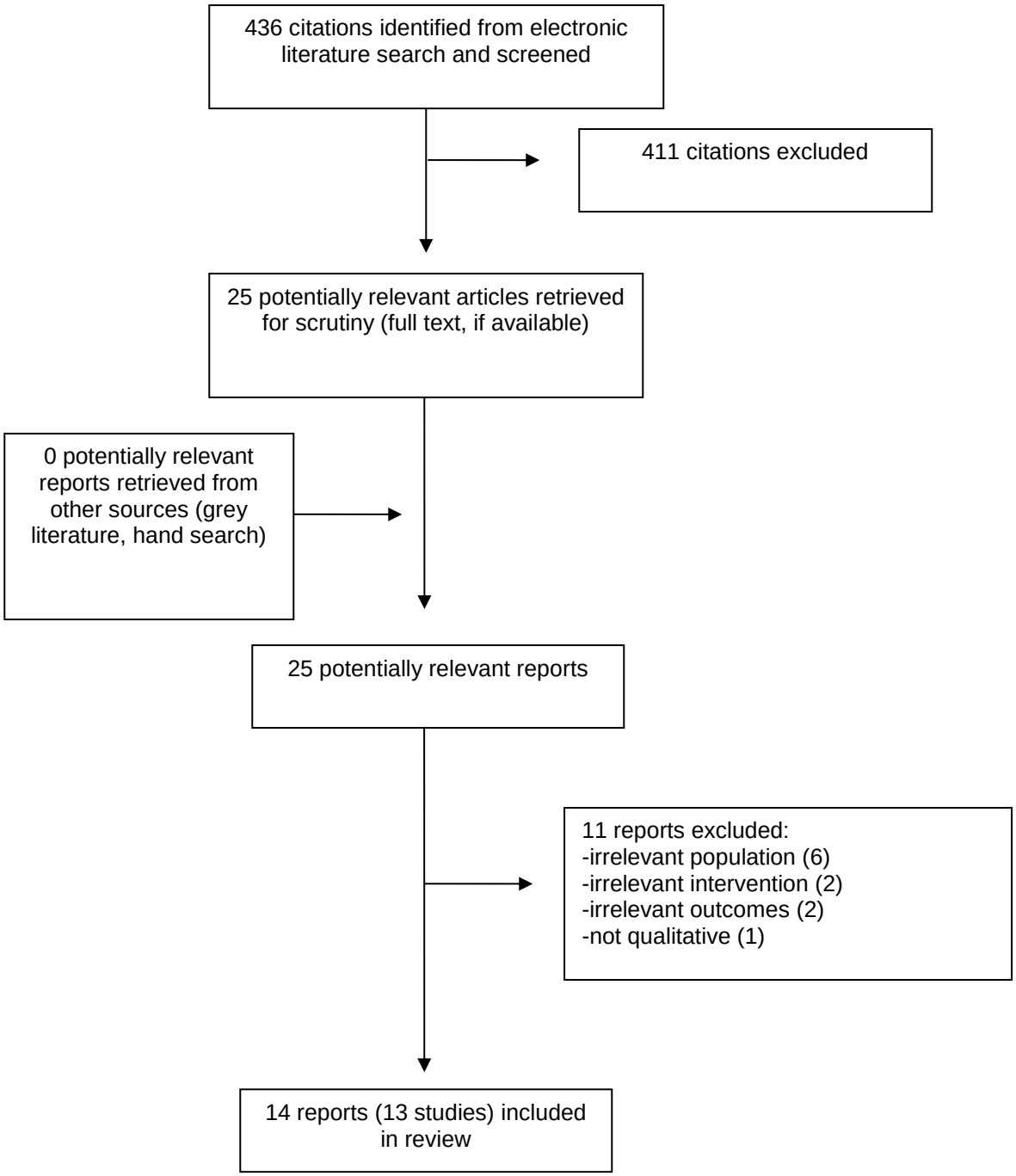
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design; Data Analysis	Study Objectives	Sample Size	Inclusion Criteria	Data Collection
Chassange,[6] 2019, France	Mixed-methods; Quantitative: discrete choice experiment Qualitative: inductive analysis by theme	To explore patients' preferences, expectations and experiences with exome sequencing in order to better understand exome sequencing's move from research to clinical care in France.	57 parents of 30 children	NR	Semi-structured interviews
Tremblay,[18] 2019, Canada	NR; Thematic analysis	To investigate parental understanding and expectations of genetic testing for their child with GDD and/or ASD, when CMA was ordered, but before genetic results were provided.	57 parents of 53 children	CMA ordered by a physician working at CHU Ste-Justine in Montreal (Canada); CMA ordered for ASD and/or GDD; results not yet available; children were aged zero to five years	Interviews
Hanish, [12] 2018, USA	NR; Qualitative content analysis	To explore the decision-making process and experiences of genetic testing from the perspectives of parents of children with ASD.	20 parents Children: NR	NR	Interviews
Mackley,[15] 2018, UK	NR; Thematic analysis	To provide in-depth data on understanding, views and experiences of patients and parents enrolled in genome sequencing studies toward secondary findings (i.e., incidental findings).	10 parents of 10 adult children 6 patients	Adult (18 years of age or older) genome sequencing participants who consented to be contacted	Semi-structured interviews
Timmermans,[17] 2018, USA	NR: Inductive thematic analysis	To examine the presentation of clinical and social implications of exome sequencing findings during patient-geneticist interactions	34 families	Consultations with families where genomic findings were discussed	Video recorded consultations between geneticists and families
Stivers,[4] 2017, USA	NR; Thematic analysis	To explore how genomic test results become actionable in the clinical	Consultations: 38 families; 6 geneticists	NR	Video-recorded consultations

First Author, Publication Year, Country	Study Design; Data Analysis	Study Objectives	Sample Size	Inclusion Criteria	Data Collection
		encounter.	Interviews: 15 families		between geneticists and families Interviews
Cornelis,[11] 2016, the Netherlands	NR; NR	To gain insight into parental considerations favoring acceptance or decline of unsolicited findings (i.e., incidental findings) pertaining to their child.	34 parents of 20 children	Parents who had undergone pretest counseling for WES; gave consent for WES for their child before the interview; had not yet received results	Interviews
Hayeems,[9] 2016, Canada	Interpretive description; NR	To explore parents' experiences with aCGH in the pediatric setting and how they make meaning of various types of test results.	21 parents of 21 children	Parents of children with developmental delay, ASD and/or congenital anomalies for whom microarray testing was undertaken following a clinical consultation in the Division of Clinical and Metabolic Genetics at SickKids in 2010.	Semi-structured interviews
Kiedrowski,[13] 2016, USA	NR; Descriptive thematic analysis	To investigate the interpretation and impact of genetic test results of uncertain significance in the context of pediatric chromosomal microarray analysis.	14 parents of 14 children	Families of children who underwent CMA through the Michigan Medical Genetics Laboratories at the University of Michigan Health System and received genetic counseling for a CMA VUS at the University of Michigan Health System's Pediatric Genetics clinic.	Semi-structured interviews
Krabbenborg,[14] 2016, the	NR; Content analysis	To explore the psychosocial aspects of	26 parents of 15 children	NR	Semi-structured

First Author, Publication Year, Country	Study Design; Data Analysis	Study Objectives	Sample Size	Inclusion Criteria	Data Collection
Netherlands		WES results for parents and how these results impact daily life.			interviews
Rosell,[16] 2016, USA	NR; Directed content analysis	To explore key factors contributing to the process of empowerment in parents of children who had undergone WES for an undiagnosed disorder.	19 parents of 19 children	NR	Semi-structured interviews
Reiff,[7,8] 2015, USA	Mixed Methods; Quantitative: Descriptive analysis Qualitative: Thematic analysis	To examine parents' experiences with genomic testing of children diagnosed with ASD, and their perspective of the usefulness of test results.	Quantitative: 50 parents of 50 children Qualitative: 57 parents of 57 children	Adult parents (18 years of age or older), English speaking, one or more children diagnosed with ASD, remembered their child having CMA	Self-report questionnaires and interviews
Christenhusz,[10] 2014, Belgium	NR; content and narrative analysis	To understand what motivates parents to want to know or not know secondary variants (i.e., incidental findings) returned through aCGH testing for a diagnosis of their child's developmental delay.	32 parents of 16 children	Dutch-speaking parents whose children had undergone aCGH for developmental delay	Semi-structured interviews

aCGH = array based comparative genomic hybridization; ASD = Autism Spectrum Disorder; CMA = chromosomal microarray analysis; DCE = Discrete Choice Experiment; GDD = global developmental delay; NR = Not Reported; VUS = variants of uncertain significance; WES = Whole Exome Sequencing;

Appendix 3: Characteristics of Patient Participants

Table 3: Characteristics of Patient Participants who Underwent Testing

First Author, Publication Year, Country	Sample Size (Patients)	Sex (% male)	Age range in years	Reason for testing	Screening Technology	Screening Results[1]
Chassagne,[6] 2019, France	30	47%	0-20 Mean = 8	Developmental delay	WES	Positive (n=10) Uncertain (n=6) Negative (n=14)
Tremblay,[18] 2019, Canada	52	NR	NR	Global developmental delay; autism spectrum disorder	CMA	Normal (n=46) Abnormal (n=5) VUS (n=1)
Hanish, 2018,[12] USA	20	94%	1-12	Autism spectrum disorder	"genetic testing"	NR
Mackley,[15] 2018, UK	12	NR	NR	NR	GS	Positive (n=4) Negative (n=3) No results yet (n=9)
Timmermans,[17] 2018, USA	34	52%	NR	"Serious disabilities"	WES	NR
Stivers,[4] 2017, USA	38	47%	NR	NR	WES	NR
Cornelis,[11] 2016, the Netherlands	20	45%	0-17	Developmental delay	WES	NR; conversations around parental desire to receive secondary findings
Hayeems,[9] 2016, Canada	21	NR	3-21 Mean = 5.4	Developmental delay, autism spectrum disorder, and/or congenital anomalies	aCGH	Clinical significance (n=8) Uncertain significance (n=7) Benign (n=6)
Kiedrowski,[13] 2016, USA	14	50%	3-19	Developmental delay, autism, congenital anomalies, behavioral and other chronic medical concerns	CMA	VUS (n=14)
Krabbenborg,[14] 2016, the Netherlands	15	NR	NR	"complex pediatric neurological problems"	WES	Definitive diagnosis (n=6) Possible diagnosis (n=5) No genetic diagnosis (n=4)

First Author, Publication Year, Country	Sample Size (Patients)	Sex (% male)	Age range in years	Reason for testing	Screening Technology	Screening Results[1]
Rosell,[16] 2016, USA	19	NR	NR	"undiagnosed disorder"	WES	Definite/likely diagnosis (n=11) Possible diagnosis (n=3) No diagnosis (n=5)
Reiff,[7,8] 2015, USA	57	46%	0-15	Autism spectrum disorder	CMA	Pathogenic (NR) VUS (NR) Negative (NR)
Christenhusz,[10] 2014, Belgium	16	38%	0-3	Developmental delay	aCGH	NR; hypothetical conversations around secondary findings

WES = whole exome sequencing; aCHG= array based comparative genomic hybridization; NR= not reported; CMA = chromosomal microarray analysis; VUS = variants of uncertain significance; GS = genome sequencing; NA = Not applicable

[1] Screening results are presented in this table as they are identified in each study rather than according to standardized result categories, as for example offered by the American College of Medical Genetics and Genomics (ACMG).