



**Returning genetic
research results in
neurodevelopmental
disorders:
Report and review**

Working Group, ASD and return of results

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About this report

This report originated from discussions at the Annual Brain Development Conference in late 2013 between researchers in the Neuroethics Core and Autism Spectrum Disorders Project of NeuroDevNet. Discussants felt that return of research results is a pertinent issue but that researchers are missing a comprehensive picture of the recommendations, approaches and empirical data related to the return of research results in genetics studies in children, in neurodevelopmental disorders, and specifically in autism.

This report provides an overview of recent genetic studies of autism spectrum disorder (ASD), and reviews the ethical guidance (policies and peer-reviewed literature) and best practices on the return of individual research results in adult and pediatric genetic research. We focus on this case because of the wealth of genetic research being carried out in families and cohorts to explain the etiology of ASD and because there is a burgeoning literature on parental perspectives on the return of results in this case. The empirical perspectives are collected and summarized and provide context with regard to researcher and parent perspectives on the return of genetic results in ASD studies. We conclude by making recommendations about the return of both incidental and ASD-related findings and highlight issues that merit further discussion, including the role of the child or adolescent with developmental disability in decision-making, and the importance of risk communication. We believe that the report will be of use not only for those working in the area of ASD but more broadly in the field of pediatric genetic research and neurodevelopmental disorder research. For example, the publication of new evidence showing that genetic alterations play an important role in the etiology of cerebral palsy in some children means that genetic research may be becoming increasingly common in other areas of the study of neurodevelopmental disorders.

Glossary:

General results: Aggregated findings concerning a group or a cohort of persons, a summary of the research.

Individual research results: Results directly concerning an individual participant that are discovered during the course of research. Individual results can either be related to the condition studied (i.e. Autism Spectrum Disorder) or be an incidental finding. It does not include pre-existing personal information used during research, such as the medical record of the individual.

Incidental findings: Unanticipated discoveries that are outside of the research objectives (i.e. that do not touch upon Autism Spectrum Disorder) but that may be relevant to the individual participant. ¹

ASD-related research findings (or potentially relevant findings): Results directly concerning an individual participant discovered during the course of research, regarding the presence of a variant implicated in Autism Spectrum Disorder.

Personal utility: Quality of the information that can be used on a personal level, namely to understand better the origins of a condition (the *why*) and the reproductive implications associated to the finding.

Clinical utility: Quality of results that provide meaning about the etiology of a child's condition and that are of use for clinicians and families. These results can be used on a clinical level, towards better orienting prevention and therapeutic decisions for an individual.

Clinical validity: Corresponds to the measurement of the accuracy with which a test identifies or predicts a clinical condition. It is defined in terms of clinical specificity, sensitivity and predictive value. ²

Scientific validity (also called analytical validity): Represents the capacity of a test to measure the characteristic it is designed to identify. In particular, this concept includes the capacity that the test will be positive if the genetic characteristic is present (analytical sensitivity), and negative if it is absent (analytical specificity). ³

¹ Inspired by TCPS2, supra note 1 (glossary)

² Inspired by Explanatory Report – Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes, 27 November 2008, CETS 203, at art 5, s 49.

³ Inspired by Explanatory Report – Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes, 27 November 2008, CETS 203, at art 5, s 48.

The complex etiologies of neurodevelopmental disorders as evidenced by the genetics of ASD

The involvement of genetic factors in the etiology of autism spectrum disorder (ASD) has long been presupposed based on the increased concordance of autism among twins and increased incidence in siblings.[1, 2] The chances of having a second child with ASD may be as high as 18%.[3-6] However, the role of specific genetic factors in ASD is still under investigation. In only about 25% of individual cases is a genetic factor present that may explain the presence of ASD (See Box 1). This means that identifiable genetic factors alone are currently unable to account for approximately 75% of cases of ASD. In addition, gene-environment interactions are increasingly recognized as playing a role in ASD.[7, 8] Hence, the justification for advanced genetic research studies to identify the complex relationships between risk, heritability, gene-environment interactions and ASD.

BOX 1: Examples of genetic findings related to ASD

Rare and de novo copy number variants

Features: incomplete penetrance, variation in the phenotype (overlap with disorders such as schizophrenia, Bipolar Disorder), may be inherited but not necessarily inherited in the case of de novo variants, and rare in the general and ASD population (any single variant is only found in 1% of cases of ASD). Found in approximately 10-20% of individuals with ASD

Coding sequence variations in neuronal synaptic genes

Features: mutations of candidate genes found in areas of the genome responsible for specific functions thought to be dysregulated in ASD, such as synapse function. Found in 5-10% of individuals with ASD

Genetic disorders where ASD is secondary

Features: genetic disorders where ASD is secondary (i.e., Fragile X or Rett syndrome)

Informed by Heil and Schaff (2013) [1] and Huguet et al. (2013) [2]

The complex etiologies of neurodevelopmental disorders as evidenced by the genetics of ASD *continued*

Results from a recent large multi-center study of families affected by ASD have confirmed the increased likelihood of rare copy number variants in individuals with ASD compared to controls.[9] The results implicate many candidate genes responsible for neuron signaling and synapse function. These and other data suggest strong endorsement for clinical genetic testing in autism[10, 11] because it may identify needed interventions or provide early awareness of related medical issues where specific genetic factors are recognized. In return, increased clinical genetic testing and the addition of more genetic data from individuals with ASD into clinical genetics databases may also further elucidate genetic components of the disorder. Three persisting issues complicate the interpretation of genetic findings in ASD (See Box 2).

Box 2: Three main issues complicate the interpretation of genetic findings in ASD

Incomplete penetrance of currently identified genetic factors associated with ASD

i.e., the presence of a genetic factor associated with ASD does not necessarily indicate the etiology of ASD (a small set of the population will have the same genetic factor and no ASD)

Variation in phenotype expressivity

i.e., the same genetic variants associated with ASD are associated with other psychiatric disorders and individuals with the same variant may express different phenotypes, for instance schizophrenia or bipolar disorder

Variation in inheritance with de novo variants

i.e., the inheritance of genetic variants may only be understood as a potential cause of ASD in light of information about the role played by the gene in neurodevelopmental processes or in light of the pedigree and phenotype expression of other members of the family

Informed by Heil and Shaff (2013) [1]

The complex etiologies of neurodevelopmental disorders as evidenced by the genetics of ASD *continued*

Genetic research in the area of ASD seeks to gain broader knowledge about the etiology of the spectrum of ASD and the discovery of genetic factors that predict earlier detection of autism, or to identify those at high risk of developing ASD. Data are often gathered from children with ASD and their families through large multi-national projects such as the International Autism Genome Project. The fact that many genetic findings are rare or *de novo* justifies the collection of large data sets and the study of various members of the family.

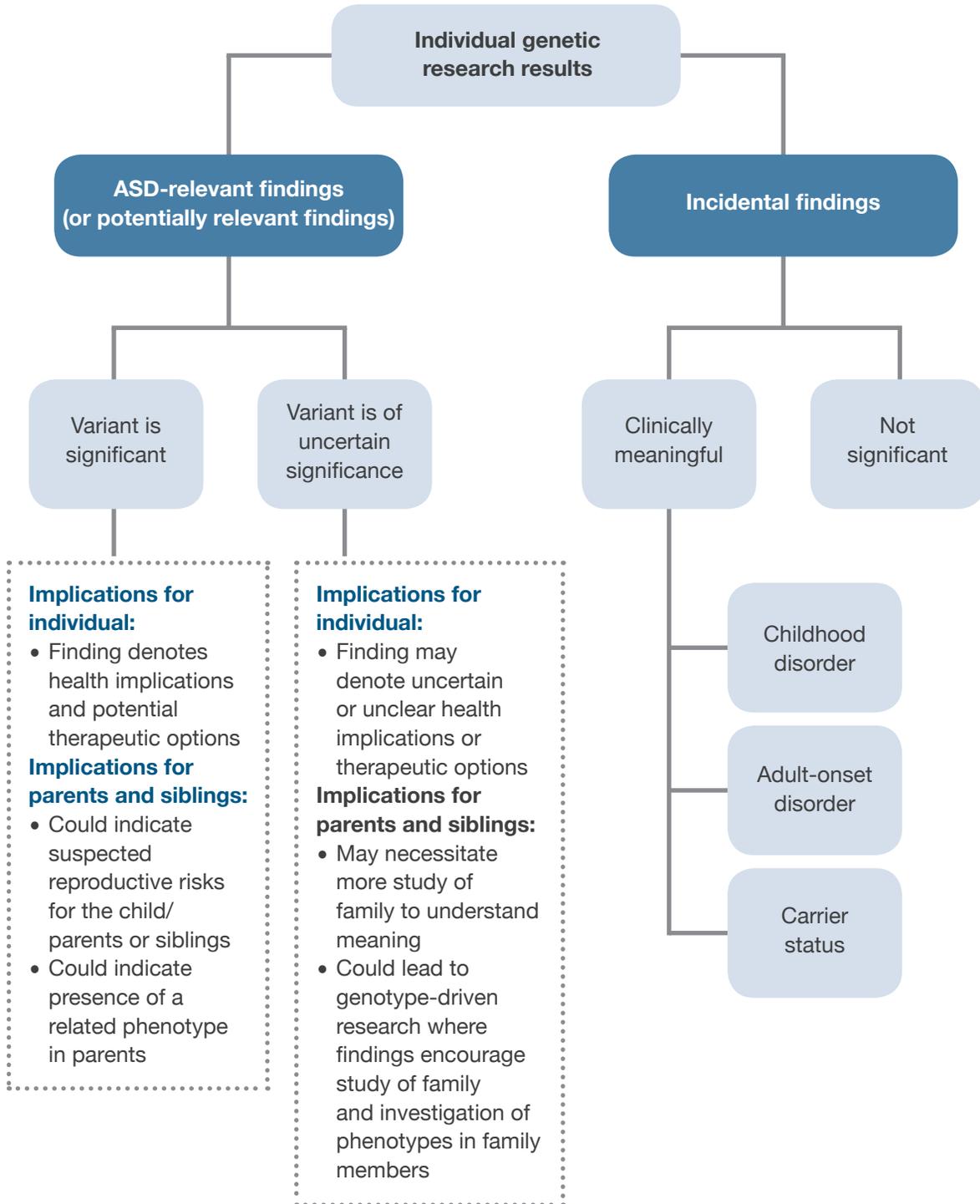
Some of the important considerations emerging with the discovery of ASD-relevant genetic research findings are:

1. A new rare copy number variant is difficult to ascribe meaning to;
2. Detection of a copy number variant associated with ASD may be meaningful beyond the research participant (either because of sibling risk, reproductive risk, or under-diagnosed ASD or psychiatric disorders in family members);
3. Families or individuals involved in research may or may not have already received clinical genetic testing.

These issues indicate the wide-ranging implications of participation in genetic research for families and siblings and hint that the full scope of the meaning of genetic findings in the child may not be understood without context from the family's genetic and phenotypic pedigree (see Figure 1). Furthermore, any genetic research has the potential to generate incidental findings (IFs) that in pediatric participants could reveal genetic findings that are actionable in childhood or that indicate adult-onset disorders or carrier status (Figure 1). The discovery of incidental findings is common with the advent of exome and whole-genome sequencing. There is always a possibility that some genetic variants may be present but remain undetected by a research team.

The complex etiologies of neurodevelopmental disorders as evidenced by the genetics of ASD *continued*

Figure 1: Genetic research results relevant to the discussion of return of individual findings



Genetic research and the return of research results in children

Generally, clinical genetic testing in children for adult-onset conditions has been endorsed only when the results would lead to altered medical management in childhood, emphasizing the importance placed on actionability and the fact that preferences of the adolescent/child should guide decisions about testing once they reach adulthood. [12] Even in the clinical context, recommendations surrounding the return of secondary findings have been followed by intense discussion and even some reversal of position. In 2013, guidelines by the American College of Medical Genetics (ACMG)[13] for genome-scale sequencing suggested that a requisite number of pathogenic genetic mutations had to be tested for and disclosed in adults and in children. This approach brought forward questions about the alignment of ACMG's own policies for predictive testing in children and allowing children to consent to testing at adulthood. General objections soon followed along with criticism that the recommendations set aside patient autonomy.[14] The ACMG has since updated the recommendation such that it is acknowledged that patients should be given the option to opt out of the routine analysis of this predetermined set of genes at the time of sending the sample.[15] With this update, parents also have the opportunity to opt out of testing for their child during the consent process.

In the research setting, researcher obligations and the ethical rationale for returning individual research results have been the focus of thorough discussion, especially in light of the fact that there are important differences between the clinical and research environments (i.e., quality of genetic testing) and obligations towards individual participants (and their families). Many open questions remain such as how are the preferences of parents and children taken into account (at the time of consent and afterwards); to whom should disclosure be made and when, and what are the obligations of researchers to disclose. Challenges, which have been much debated in the field of genetic research, include how to balance researcher obligations for the disclosure of individual research findings with the need to protect participants and parents from undue related harm (e.g., privacy, anxiety). These challenges become more complex in the pediatric context where researchers must take into account the expectations of parents and minors to know, or not know, about these findings.

Genetic research and the return of research results in children *continued*

In this report, we review the ethical foundations for and against the return of research findings and the positions put forward in international guidelines for best practices and by other collaborative or interdisciplinary efforts. The perspectives of researchers and parents, as well as empirical studies of researchers and parents regarding ASD studies specifically are reviewed in an effort to establish the degree of overlap or disagreement with the normative literature about the return of research results. Our review is based primarily off literature searches conducted in July 2013, was informed by ethics policy documents that were already in our library, and was expanded when external peer reviewers with an expertise in this area identified important reference documents. We summarize the findings including the convergences and divergences of these perspectives and policies; and discuss four issues requiring consideration and or evidence to inform best practices for return of genetic research findings in neurodevelopmental disorders:

1. How researcher orientations impact perspectives or practices in the return of genetic findings;
2. How personal utility might meet the needs of the best interest standard for disclosure;
3. The importance of risk communication in neurodevelopmental disorders;
4. The role of the child or adolescent with developmental disability in decision making.

When possible, we describe in detail the applicable Canadian policies and studies.

Ethical guidance regarding the return of research results in genetic studies and in pediatrics

Research ethics policies and guidelines for disclosure of genetic findings

A review of international research ethics policies on the return of individual research results demonstrates a wide variability of recommendations.[16] A common anchor of existing policies is the potential health benefits that may be accrued by the return of clinically significant research findings. Several international policies, but not all, recommend that individual results (or incidental findings) be obligatorily disclosed when relevant to health or quality of life. Guidance issued by the World Health organization on the specific disclosure of individual genetic results further defines that disclosure should be made on the basis of a clear demonstration of clinical benefit and communicated in a way that averts or minimizes harm so long as there is no evidence that the individual would prefer not to know.[16] Levesque and colleagues' (2011) describe how some international guidance leaves room for return of results as an option rather than an obligation.

Canadian research ethics guidelines for human genetic research, as laid out in the Tri-Council Policy Statement (2010), require that researchers plan for managing information revealed through their research. This requirement includes a plan for sharing individual findings with participants.[17] When planning to share findings, researchers are compelled to offer participants the opportunity to indicate their preferences regarding the receipt of such information, and the sharing of this information with family or others.[17] The adult participant must be allowed an informed choice about disclosure, and current guidance reflects that preferences should be respected. The following guidance is offered by the The Network of Applied Genetic Medicine's "Statement of principles on the return of research results and incidental findings" (Quebec):

1. That **material findings** should be offered to an adult participant when, additional considerations and exceptions have been weighed (i.e., anonymization, expectation of participants), REB approval has been obtained, the participant has consented to the return, and the research result has been confirmed;
2. That **non-material findings** may be offered to adult participants, so long as they meet criteria for scientific and clinical validity, REB approval is obtained, the benefits of return surpasses the risks, the participant has consented to the return, and the research result has been confirmed;
3. That results that **do not meet generally accepted criteria of scientific and clinical validity** should not be returned to participants. [18]

Ethical guidance regarding the return of research results
in genetic studies and in pediatrics *continued*

A review of TCPS guidelines can be found in Table 1, including those provisions laid out in the newest edition of the TCPS (2014).[19, 20] The most significant changes include detailing of the unintended harms that may result from disclosing incidental findings such as needless concern, including anxiety, costs or burdens of follow up or affect insurability, and the opportunity that some researchers may request an exemption from the obligation to return material incidental findings (See Table 1).

How the above guidance applies to children participating in research is important. The Network of Applied Genetic Medicine offers the following recommendations when returning results about minors:

1. That results should be returned (and parents should not be able to refuse return) when they meet the generally accepted criteria of scientific and clinical validity, and they have significant implications for the health of the minor, including that there are treatment or prevention strategies available that should be initiated during childhood or adolescence, REB approval has been obtained and the research result has been confirmed.
 2. That results concerning the future adult health of a minor should not be offered except in exceptional circumstances where the validated results are important for the immediate health of a parent or adult-aged sibling. In these cases the assent of the minor should be obtained, and parent consent must have been obtained.
- [18]

Ethical guidance regarding the return of research results
in genetic studies and in pediatrics *continued*

In an effort to draw together best practices for pediatric research, Avard and colleagues (2011) have reviewed international research ethics guidance for policies and practices relevant to children, including the return of research results. The resulting Best Practices for Health Research Involving Children and Adolescents provides a summary of suggested best practices for the return of individual research results in pediatric studies.[21] These best practices are positioned next to the current TCPS guidelines in Table 1. Best practices also include the ways that researchers acknowledge or balance the rights of parents and children not to know about genetic findings. Avard and colleagues (2011) suggest that these include:

- (1) respecting parents and children when they indicate not wanting to know about results;
- (2) overriding preferences not to know when the results have significant health implications for the child;
- (3) extending the right not to know to relatives.[21]

Table 1: Best practices for the disclosure of research results in children and adolescents

**Research ethics guidance
(TCPS(2010) [17]; TCPS(2014) [19])**

DISCLOSURE OF INDIVIDUAL RESULTS**Genetic research:**

- Researchers conducting genetic research shall: a) in their proposal, develop a plan for managing information that may be revealed through their genetic research; b) submit their plan to the REB, and c) advise prospective participants of the plan for managing information revealed through the research (Article 13.2, TCPS (2010) and TCPS (2014))
- When researchers plan to share findings with individuals, researchers shall provide participants with an opportunity to:
 - a) make informed choices about whether they wish to receive information about themselves; and
 - b) express preferences about whether information will be shared with a biological relative, or others with whom the participants have a family, community or group relationships (Article 13.3, TCPS (2010) and TCPS (2014))
- Where researchers plan to share results of genetic research with participants, the research proposal should make genetic counselling available at that time, where appropriate (Article 13.4, TCPS (2010) and TCPS (2014))

DISCLOSURE OF INCIDENTAL FINDINGS**TCPS (2010)**

- Researchers have an obligation to disclose to the participant any material incidental findings discovered in the course of research (Article 3.4, TCPS (2010))
- Material incidental findings include those findings that have been interpreted as having significant welfare implications for welfare for the participant, whether health-related, psychological or social (Article 3.4, TCPS (2010))
- When material incidental findings are likely, researchers should develop a plan indicating how they will disclose such findings to participants, and submit this plan to the REB (Article 3.4, TCPS (2010))
- If researchers are unsure of how to interpret findings or uncertain whether findings are material, they should consult colleagues or refer to standards in the discipline. If researchers are unsure of the most appropriate method for disclosing material incidental findings to participants, they should consult with their REB or with colleagues (Article 3.4, TCPS(2010))
- Researchers should exercise caution in disclosing incidental findings that may cause needless concern to participants. When necessary, researchers should direct participants to a qualified professional to discuss the possible implications of the incidental finding for their welfare (Article 3.4, TCPS (2010))
- In some cases, incidental findings may trigger legal reporting obligations and researchers should be aware of these obligations (Article 3.4, TCPS (2010))

TCPS (2014)

- Researchers have the obligation to disclose to the participant any material incidental findings discovered in the course of research (Article 3.4, TCPS (2014))
- Incidental findings are considered to be material incidental findings if they have been interpreted as having significant welfare implications for the participant . Material incidental findings may appear at any stage of the research (Article 3.4, TCPS(2014))
- If researchers are unsure of how to interpret findings or uncertain whether findings are material, they should consult colleagues or refer to standards in the discipline. (Article 3.4, TCPS(2014))
- Researchers should exercise caution in disclosing incidental findings that may cause needless concern to participants such as participant anxiety, unnecessary costs and burdens of follow-up; or may affect eligibility for employment or insurance. When necessary, researchers should direct participants to a qualified professional to discuss the possible implications of the incidental finding for their welfare (Article 3.4, TCPS (2014))
- When material incidental findings are likely, researchers should develop a plan indicating how they will disclose such findings to participants, and submit this plan to the REB (Article 3.4, TCPS (2014))
- A researcher may request an exception to the obligation to disclose material incidental findings, based on the impracticability or impossibility of disclosing such findings to the participant. The onus is on the researcher to justify to the REB the need for the exception (Article 3.4, TCPS (2014))

Table 1: Best practices for the disclosure of research results in children and adolescents *continued***Best practices****(Taken from Best Practices for Health Research Involving Children and Adolescents (Avard et al., 2011 [21]))****DISCLOSURE OF INDIVIDUAL RESULTS**

- Individual results should be communicated when they are clinically valid and reliable and where there are significant implications for the health of the participant and either prevention or treatment is available
- When parents refuse to know the results, researchers should offer the results to the child when s/he reaches maturity or majority
- When the research involves young children, the information should be disclosed to the parents
- When the research involves school-age children and adolescents, the information should also be delivered to them in a manner appropriate to their development, level of understanding and degree of maturity
- When returning such results, counselling should be offered to the parents and, if appropriate, to the child
- Researchers should also discuss the following considerations: the choices available, the limitations of available clinical services, the accessibility of counselling services, and the familial implications of the information

DISCLOSURE OF INCIDENTAL FINDINGS

- Researchers should discuss with potential participants and/or parents the likelihood of incidental findings being discovered in the course of research during the informed consent process
- The method of disclosure of these findings should be detailed in the consent form
- If appropriate and possible, incidental findings should be discussed with the REB and, if appropriate, offered to the child and/or parents
- Incidental findings with clear and proximate clinical importance should be disclosed to the child and/or parents
- Non-paternity should be disclosed to the mother only
- When communicating such findings, counselling should be offered to the child and/or parents

Perspectives from the academic normative literature on the ethics of the return of research results

a) Underlying ethical considerations

Generally, recommendations for the return of results imply that the actual return of general (e.g., summaries) or individual research results is supported by three ethical principles.[16]

1. Principle of justice: reciprocity (fairness) is owed to the participant for the knowledge gained during research
2. Principle of beneficence: the benefits of research should be returned more globally to society and to participants through the communication of research results
3. Principle of respect for persons: the communication of results acknowledges the importance of participants as persons in research

Based on these principles, most authors believe that researchers have an obligation to return at least aggregate results but researcher obligations to return individual or incidental findings results have been debated. At a minimum, it may be ethically acceptable for researchers to consider a range of issues such as the actionability of findings discovered, the severity and age of onset of the genetic risk, the effect on the subject of receiving the information and potential structural conditions in place for disclosure (e.g., expertise of the team and access to follow up care) with an emphasis on returning results that are clinically significant or accurate and that lead to important health benefits.[16, 22] Part of the controversy stems from the acknowledgement that there are many practical and conceptual issues that complicate the return of individual research results (see Box 3). One of the more substantial challenges is the fact that genetic findings may not at first appear to be clinically significant but may become so as research progresses. These and other barriers challenge the sequence of responsibilities of researchers.

Perspectives from the academic normative literature
on the ethics of the return of research results *continued*

BOX 3: Barriers to the return of individual research results

Practical barriers

Burden and cost of returning results

Which to return, how and when

Incorporating participant preferences (which can change over time)

Secondary use of biobank data is not linked to information about the participant

Inconsistent ethics guidance on the topic

Theoretical barriers

Incoherence between the goals of research to create generalizable knowledge
and the return of individual findings

Uncertain psychological and medical effects of returning results

View that genetic results are not predictive

Inconsistent perspectives about researcher obligations

Examples pulled from: Levesque et al. (2011) [16]; Hens et al. (2011) [22]; Knoppers et al. (2014) [23];
Di Pietro and Illes (2013) [27]

In pediatric genetic research, additional issues have been acknowledged such as the potential for the return of results to lead to unnecessary and costly investigations or medical interventions, increased parental anxiety or guilt, family stress related to identifying other members of the family who may be at risk, and potential psychological harm when altering a parent's perception of their child.[23] In children particularly, one concern is removing the right to an open future by returning individual genetic results to parents, especially where conditions are adult-onset or have no accepted treatment.[23, 24] These barriers are sometime juxtaposed against the potential benefits to children and families of identifying a potentially serious, medically actionable genetic finding.[23]

Perspectives from the academic normative literature
on the ethics of the return of research results *continued*

b) Recommended approaches for adults

Recommended approaches for the return of research results in capable adults have been developed. Levesque (2011) describes the strengths of an approach that deals with scientifically-oriented concepts rather than vague or confusing ethical principles (Box 4). For the researcher in genetics, such a model may also take into account the broader range of scientific factors that influence ethical decisions and options about the return of research results. Importantly, what becomes clear by looking at this recommended approach is that there is almost no situation where patient preferences or any other ethical, legal, and social (ELSI) issue would override an important clinically significant finding. However, this feature seems to align with other views on the balance of patient autonomy and beneficence; most recommendations state that it would be appropriate to override patient or parent preferences for results that are medically important and actionable.[21, 25] While most academic reflections on the topic have focused on the validity of findings and how to reconcile these with personal preferences for disclosure, an important early reflection offered by Ravitsky and Wilfond (2006) draws attention to how personal meaning can be incorporated into decisions about returning genetic results. In the absence of clear clinical utility, the authors suggest that researchers may consider the personal meaning of results when making decisions about disclosure, although they acknowledge that the broad implications of disclosures for personal utility requires more study.

Perspectives from the academic normative literature
on the ethics of the return of research results *continued*

Box 4: Recommended approach for managing return of individual research results

Rationale:

A flexible framework is needed that recognizes that in many cases disclosure is permissible or advisable, in few it is an obligation.

Criteria for consideration during disclosure:

- Analytic validity (including accuracy of the result)
- Clinical validity (including accuracy with which we can detect the clinical outcome)
- Clinical utility (including how likely the result will impact health)
- ELSI issues (including participant preferences, investigations that may be undertaken, potential for anxiety)

Outcome:

According to the degree to which all four criteria are fulfilled by the findings, return of results:

- Is not recommended (i.e., findings that are uncertain, difficult to interpret or about a benign condition)
- May be recommended
- Is highly recommended (i.e., findings that indicate a high probability of developing a serious illness where there is available treatment)

Levesque et al. (2011) [16]

Perspectives from the academic normative literature
on the ethics of the return of research results *continued*

c) Recommended approaches for children

In pediatric research studies, the controversies about which findings to return and when are complex due to consideration of the ways that children benefit or not from findings that may be medically significant (e.g., actionable or not in childhood). In adults, autonomy is respected by considering patient preferences for disclosure of individual results. However, parental authority does not necessarily dictate the appropriate boundaries of return of results for children.[22, 23] A parent's preference not to know about results may be overridden in the case of clinically meaningful and actionable findings in childhood, and similarly, results may be withheld from parents in cases where the developing autonomy of children may allow them the opportunity to participate in decisions about what they want to know about themselves and when.[22]

Recommended approaches in children favor the return of genetic variants predicting a strong probability of the child being at risk for early-onset treatable or preventable disorders that reflect consideration of the child's best-interests.[22, 23] Parents should not be able to opt out of the return of these findings.[26] In spite of guidance that scientifically valid and clinically useful results should be returned, much more caution should be used when disclosing findings that lack clinical accuracy or confidence and when disclosed these should be accompanied by warnings about acting on findings that are not clinically validated (i.e., possibility of undergoing unnecessary medical tests) as well as other information about what role the researcher can or will play after disclosure.[24] Additional thorny questions arise in considering whether parents have a right to receive all of their child's genetic research results. Although much of the guidance assumes that parents act in their child's best interest in seeking out information that may impact the family, reproductive decisions, and psychosocial wellbeing, the rights of the child or adolescent to voice their own opinion about the disclosure of research results must be given due attention.[23, 26] For this reason, Knoppers et al., (2014) suggest that findings that predispose a child to an adult onset disorder should generally not be returned and decisions surrounding return of results should be delayed until the child can make this decision. This aligns with proposals that recognize the right of the child to an open future.

Perspectives from the academic normative literature
on the ethics of the return of research results *continued*

“Consensus exists ... that indicate parents should not have access to genetic data about their children if there are no known treatments or preventative therapies of immediate benefit to the child”[24]

Other concerns for the return of individual research results in children[22] continue to be reflected upon, including:

- The consideration that should be given to the age of sexual majority in determining when to disclose or when to seek preferences of the participant when it relates to adult onset disorders or reproductive risks.
- If parents could be the gatekeepers for genetic information about their children, and strategies to ensure that parents pass on appropriate information to their children and when.
- What can we do to manage new scientific evidence and follow up over a long term with children and adolescents with evolving capacity to consent to the return of findings?
- How do we manage findings that may have reproductive implications for siblings, parents and child participants?

Di Pietro and Illes (2013) propose a framework for dealing with the disclosure of incidental findings to competent minors in brain research. They recommend that IFs that are of uncertain significance or of clinical significance be disclosed to both parents and minors, in a manner sensitive to the developmental stage of the participant, without the opportunity to opt out of such findings. In the case of findings of low clinical significance, they suggest that preferences of a competent minor could overrule those of parents for disclosure of the information although researchers should try to reconcile the perspectives of parents and minors.[27]

Perspectives offered from normative ethics and guidelines are helpful, but we must also turn to researcher and parent perspectives on the return of individual results to understand their relationship to recommended best practices.

Researcher and parental perspectives regarding the return of individual research results in genetic studies

a) Researcher perspectives

A handful of empirical studies conducted in the United States have assessed the broad perspectives and experiences of genetics researchers, with an emphasis on the reporting of incidental findings.[28-33] Together, these studies show that researchers are inclined to report the discovery of IFs when they are of clear or probable medical significance[28] or when they are highly penetrant and have immediate medical implications [29]. Researchers typically feel that the return of those findings hinges on a moral obligation to disclose information that could negatively impact participants' health or a right of the participant to the information.[29, 31, 32] In contrast, researchers became more uncomfortable with the return of research results when the medical significance was unknown and this and other reasons formed the basis of decisions to withhold results.[28, 29] Other influential factors reported include:

- Appraisal of the clinical significance of the finding and the information to support this interpretation of significance;
- Availability of expertise to return results appropriately;
- Quality of sequencing results not obtained from a certified clinical genetics laboratory;
- Potential burden imposed on researchers which can hinder the progression of research;
- Possibility that participants may not understand the results;
- Potential loss of confidentiality as a result of disclosure;
- Potential for emotional burden for participants.[28,30,31]

In-depth analysis of the perspectives of researchers reveals that many complex factors shape their views about the return of incidental findings, including the genetic variant identified, the associated disease and penetrance of the variant, actionability of the finding, participant wellbeing, researcher responsibility, and input from institutional ethics bodies.[30]

Researcher and parental perspectives regarding the return of individual research results in genetic studies *continued*

More specifically in pediatric cases, researchers suggested that they would overwhelmingly support (91%) returning research findings in children if it showed a highly penetrant condition that was clinically actionable before adulthood. The findings were not so strong for those conditions that were not actionable until adulthood, where only 68% of researchers would return these findings. Compared to return of incidental findings in adults, researchers were more cautious in general about the return of findings in children. [29]

Generally questions persist about the definition of different concepts such as *actionability*, *high penetrance* or *risk*. [29] Following from this, and other challenges listed above, researchers used dynamic problem solving to deal with individual cases [31]; what Klitzman et al., 2013b describe as judgment calls. [30] Researchers often erred on the side of caution in reporting incidental findings because they feared that participants might take overly aggressive action based on these findings. Their decision-making was complicated by findings that were less published, *de novo* or rare variants. [30]

*“If it’s never been seen before, does that guarantee it’s important?”
(Participant as reported by Klitzman et al., 2013b)*

Most researchers in Klitzman et al.’s study (approximately 82%) believed that participants should be offered the opportunity to express whether or not they want IFs returned. However, respecting this choice was sometimes hampered by numerous competing obligations; for instance a highly penetrant but treatable condition. [29, 30] Respecting patient preferences was also challenged by the fact that participants were perceived not always to have fully considered the impacts of knowing (or not), or the perceived likelihood that they could change their minds about disclosure according to different findings. Nonetheless, patient preferences were often taken into account. However, when these preferences were overridden, researchers and ethics review boards felt justified in doing so. [28-30] In contrast, some researchers felt that they should not be obligated to report results or IFs as long as this is expressly stated in the informed consent form and agreed to by participants. [33]

Researcher and parental perspectives regarding the return of individual research results in genetic studies *continued*

b) Research ethics board perspectives

Studying the perspectives of 34 institutional review board (IRBs) chairs about the management of genomic incidental findings, Williams and colleagues (2012) report a focus of IRB chairs on procedure and study protocols. For instance, one IRB chair suggested that many issues associated with how IFs were to be managed could be dealt with by ensuring that protocols and consent documents were clear on the expected process, leaving researchers to enact the approved process.[28] However, as Kiltzman et al.'s (2013) study of researcher perspective's reveals, researchers often seek IRB members' views on whether and when to return such findings. This emphasizes one difference that Williams et al., (2012) observed between researchers and IRB chairs; researchers viewed the return of IFs on a case by case basis (and may look to IRBs to help them navigate these decisions) and IRBs viewed their return driven by existing policy, study protocol or consent. The variation in institutional policies surrounding IFs is important, and leads to significant variation in the return of IFs that is especially obvious in multicenter research trials.[30] Williams et al. 2012 describe that some IRB chairs reported that the same IF policy is applied to any IF while other IRBs reported having no policy about IF return. Similarly, in a review of a sample of informed consent documents for magnetic resonance imaging research in Canada, Palmour et al. (2011) report various strategies disclosed in consent documents for dealing with IFs in neuroimaging research. These include variations in who will be informed (the participant directly or their physician), and how participant preferences will be taken into account in disclosure (i.e., "subject has the choice to be informed of IF", "subject has the choice for the physician to be informed"). [34] Significant evidence gaps exist for IRB decisions (and decision-making processes) about disclosure of research results or IFs.

Researcher and parental perspectives regarding the return of individual research results in genetic studies *continued*

c) Parent perspectives

Two studies, one Canadian and one American, have examined the perspectives of parents of children with rare diseases regarding the return of genetic research findings. These studies revealed important insights into how parents view the obligations of researchers and their own rights over information about their child. Kleiderman and colleagues (2013) found that most parents wanted genetic incidental findings returned to them and believed that they had a right to be informed of all results about their child's health status. However, parents were less confident about wanting to know about adult-onset life limiting and/or untreatable conditions or the carrier status of their child.[35, 36] Knowing about the carrier status of their child was seen as useful for the future of the child, although most parents felt that they should be able to choose whether to receive this information or not.[35] Similarly, Sapp et al. (2014) found that parents wanted to receive information about findings that indicated an increased risk of preventable or treatable conditions in childhood.

In general, these studies demonstrate that parents see themselves as the guardians of health information about their child, regardless of its uses or severity, and perceive the information as important to maintaining control over their child's health.

Kleiderman et al. (2013) further describe that parents perceived that it was their own responsibility to share information with their child at a time that was appropriate and sensitive to the child's understanding of it. This also included information influencing future planning or reproductive risks and the control of communicating health risks with other family members. Parents considered that researchers had an obligation to divulge incidental findings and expected disclosure as a result of their child's participation. Parental views reflected that information sharing should change with evolving capacity; parents felt that later on their child should be able to decide whether or not they wanted to know about incidental findings.[35] In this case, that seemed to mean that parents should respect the fact that they may know about a child's incidental finding but that the child at maturity has a right to tell the parent they do not want to know about it.

The return of individual research results in genetic studies of autism

a) Researcher perspectives

Qualitative and quantitative survey studies assessing researcher perspectives on the topic of the return of individual genetic research results in the context of ASD reveal that several practical and conceptual elements factor into researchers' appraisals of the appropriateness of disclosure and the goals of disclosure. All of the following studies were conducted in Canada by the same research group.

*Hayeems and colleagues (2011) report that **80% of respondents** in their sample of international researchers in the areas of cystic fibrosis and autism spectrum disorder **believed that clinically significant findings warranted reporting, while a majority believed that disclosure of provisional findings or findings with uncertain clinical significance was not recommended and could in fact be harmful.***

Their research reveals that the majority of researchers endorsed the obligation to ensure access to clinical services required as a consequence of receiving results, and to updated information about these genetic findings as new research becomes available. [37] Importantly this study revealed several key judgments made by researchers about the clinical significance of genetic findings that impact on willingness to disclose genetic results. Less confidence in the clinical significance of findings was ascribed to/by:

- Less well-replicated findings;
- Less robust findings (those that indicate only a small risk of ASD or CF);
- Incidental findings;
- ASD genetic findings in general, when compared to genetic findings in CF studies;
- Researchers who work in the area of ASD;
- Researchers who don't have a clinical interpretative role.[38]

The return of individual research results in genetic studies of autism *continued*

Interestingly, researchers who reported that the return of clinically significant findings was warranted were more likely to feel confident in the clinical significance of hypothetical genetic findings provided. This is in line with research in the context of ASD that shows that researchers' beliefs about returning individual research results are influenced by their own orientations towards the role of genetics in autism[39] (see below table for more information). As expected, when hypothetical scenarios contained elements diminishing confidence about the clinical significance of findings were presented to researchers, they were less likely to support the disclosure of research results, including half as likely to support reporting ASD findings compared to CF findings.[38] Irrespective of the fact that fewer researchers endorsed the return of ASD genetic findings, they believed that researchers have a duty to follow up any disclosure with updated information about the genetic variation and provide participants access to clinical services.[37] This demonstrates that researchers endorse strong cascading commitments beyond the disclosure of research results, even in the face of potential barriers to accessing clinical care.[37] Earlier research demonstrates that researchers rely on judgments about sufficient "proof" and "truth" of genetic findings in ASD to dictate the appropriateness of disclosure. Some researchers supported the disclosure of individual research findings if it could help to ascertain the meaning of uncertain results, atypical cases or if disclosure would help initiate genotype-driven research within families. Other respondents however, felt that individual results should not be returned based on the assumption that individual case meaning would only exist once statistical evidence had accumulated in populations.[39]

b) Parent perspectives

Studies from the US and Canada on parent perspectives on the return of the individual genetic research results in autism reveal that there are two key drivers to the desire for disclosure [39-41]:

- Genetic research results may answer the question of "why?", provide relief from guilt or better understanding of the etiology of their child's condition;
- Genetic research results could be used for reproductive planning and planning for the future.

Not all parents endorsed these views, with some expressing concerns about the impact of genetic findings on self-blame or the potential for genetic findings to lead to fear, stress and depression among parents without the ability to improve the day-to-day care of their child with ASD. Studies conducted with parents in the context of genetic research in autism are described in further detail in Table 2 and the key findings are reviewed.

Table 2: Parental perspectives on the return of research results in genetic studies of ASD

Article	Publication year	Type of study	Study population
<p>Opinions and intentions of parents of an autistic child toward genetic research results</p> <p>Baret L and Goddard B</p>	2011	Survey	158 parents of an autistic child
<p>What is a meaningful result? Disclosing the results of genomic research in autism to research participants</p> <p>Miller FA, Hayeems RZ and Bytautas JP</p>	2010	Focus group and interview	<p>34 parents of minor or adult children with autism spectrum disorders (focus groups)</p> <p>26 parents of minor or adult children with autism spectrum disorders (interviews)</p> <p>23 researchers (interviews)</p>
<p>Parent perspectives on pediatric genetic research and implications for genotype-driven research recruitment</p> <p>Tabor H, Brazg T, Crouch J, Namey EE, Fullerton SM, Beskow LM and Wilfond BS</p>	2011	Interview	<p>17 parents of children enrolled in genetic studies of autism</p> <p>6 parents of children enrolled in genetic studies of diabetes</p>

Table 2: Parental perspectives on the return of research results in genetic studies of ASD *continued***Key findings**

- Return of research results, as they were, had priority over returning them only once validated and before a prevention or treatment became available
 - 37% of parents thought individual research findings would allow them to make better decisions for the future, 19% to allow them to better inform their family circle
 - 14% would do nothing with genetic results returned but still wished to receive them
 - Impact of receiving positive or negative results was generally positive or neutral (i.e., provided relief or understanding (14%), allowed parents to be prepared for the future (37%))
 - Two profiles of parents in favor of returning individual results were found:
 - A. Those who wanted the knowledge to make reproductive choices and prepare for the future (20% of participants)
 - B. Those who “want to know” (have no intentions about doing anything with the information) (15% of participants)
-
- Parents and researchers emphasized non-clinical benefits of genetic results (i.e., identify reproductive risks, provide an answer to question of “why?”) over any direct clinical benefits
 - Some respondents believed that answering the question “why?” would bring relief or reduce sentiments of blame while others questioned whether genetic findings could increase feelings of self-blame
 - Researchers emphasized that individual results should only be reported if there is sufficient evidence of the result’s importance or significance (including that returning the result would aid in understanding uncertain results and advance knowledge generally as well as provide rationale for studying phenotypes in other members of the family)
 - Researchers have non-uniform beliefs about the genetic factors in autism (i.e., some believe that genetic characterization of autism is possible, while others support the use of genetic factors to understand how the disorder influences neurodevelopment)
 - Beliefs about the role of genetics in autism influenced researcher perspectives on the return of individual research results and the meaning of genetic research findings
-
- Parents anticipated that improved treatment may result from genetic research
 - Parents were not hesitant to participate in more research related to their child’s disease although they expressed a preference that their children only participate in genetic research that was relevant to their family
 - None of the parents felt that there was any possible negative psychological impact of the return of genetic results on their child
 - Parents described the negative psychological impact in general on parents of returning findings with uncertain meaning or where no treatments were available
 - Some parents of children with autism (and not parents of children with diabetes) identified self-blame and guilt as potential negative factors accompanying genetic result disclosure. Other parents discussed opposing perspectives that genetic results removed guilt, provided relief about genetic conditions that were not present, and were empowering
 - Most commonly parents suggested that receiving results could be accompanied by worry, stress, fear and depression
 - Parents desired to choose whether or not they wanted individual research results returned to them
 - Parents of children with diabetes were more likely to discuss direct clinical utility of genetic results. Parents of children with autism discussed more vague clinical uses for the information. Regardless, parents saw genetic findings as knowledge that could be useful now or in the future
 - Parents of children with autism alone stressed the potential of results to inform reproductive planning, although some parents worried that, when used to inform reproductive risks, this information could be harmful to their own children or society
 - Parents of children with autism alone felt that returning genetic research results would be an incentive to participate in future studies. For this reason, some parents expressed a strong desire for disclosure of research findings

Summary of findings and issues for future study

We acknowledge several limitations to this report. Our report is an overview of the literature, both normative and empirical, with regards to the disclosure of genetic findings. Advancements in the study of genetics such as the development of whole genome sequencing are expected to provide more extensive genetic information as well as to increase the possibility of incidental findings being discovered. At the same time, as more genetic variants are identified across research studies generally, the possibility that research participants will feel falsely reassured despite the presence of undetected genetic findings is also increased. In order to be effective in offering guidance to researchers, we must keep in mind the primary goals of research to contribute to generalizable knowledge.

Similarly, our understanding of the genetics of neurodevelopmental disorders is in flux as each new large set of genetic data is analyzed and published. These discoveries may impact our understanding of which genetic findings are clinically significant and should be disclosed in studies seeking to directly identify their presence. Lastly, important international perspectives of researchers and parents are missing from the predominately North American literature on the return of research findings. We must acknowledge that international teams are often involved in large scale studies of genetics and this implicates different international research ethics policies guiding return of results as well as suggests that we need a better understanding of cross-cultural perspectives on the return of research findings.

Summary of findings and issues for future study *continued*

1. Convergences and divergences between ethics policies, scholarly perspectives and empirical data on the return of genetic results

Box 5: Disclosure of incidental genetic findings: major recommendations and observations from ethics policies, literature, and empirical studies

A. Disclosure of actionable and material findings (meeting clinical and scientific validity criteria) is generally supported

- TCPS (2010, 2014) describes an obligation to return material incidental findings, and other international policies identify that findings relevant to a participants' health status should be disclosed (CIOMS, Council of Europe) [16]
- Other policies generally support the offer of disclosure (rather than obligation) of material research results, including incidental findings under certain conditions [18]
- In pediatric participants, an obligation to disclose results that have significant health implications, and that could lead to prevention or treatment is emphasized [18, 21-23]
- Some guidance and authors recommend that parents should not be able to opt out from receiving such information (that which has significant health implications or is actionable in childhood) [18, 26]
- Research on parental perspectives generally supports the return of research results, without specifically dealing with the issue of incidental findings [35, 40, 41]

Box 5

Disclosure of incidental genetic findings: major recommendations and observations from ethics policies, literature, and empirical studies

continued on next page

Summary of findings and issues for future study *continued*

1. Convergences and divergences between ethics policies, scholarly perspectives and empirical data on the return of genetic results *continued*

Box 5: Disclosure of incidental genetic findings: major recommendations and observations from ethics policies, literature, and empirical studies

B. Disclosure of non-actionable or non-material findings is debated

- Generally, findings with unclear scientific or clinical validity should not be returned [18] and the TCPS (2014) urges researchers to exercise caution in returning results which may cause needless concern[19]
- For non-material incidental research findings, researchers may consider actionability, participant preferences, and clinical significance in deciding whether or not an incidental finding will be disclosed [18] ⁴
- In pediatric studies, results concerning the future health adult health (non-actionable in childhood) of the minor should generally not be disclosed [18, 24], although it has also been suggested that findings without clear and proximate clinical importance should be discussed with the REB and, if appropriate offered to the child/or parents [21]
- Researchers should consider the possibility that in longitudinal research, incidental findings that are non-material or non-actionable in childhood could be withheld until such a time that participants reach the age of maturity and can offer their preferences about disclosure [21]
- Empirical evidence shows that researchers are inclined to report incidental findings when they are of clear or probable medical significance or are highly penetrant and have immediate medical implications. Those results where medical significance is unknown are subject of more case by case analysis, and may be consulted on by REBs [28-30]
- Parents have described the negative psychological effects of returning findings with uncertain meaning or where no treatments are available [41], and are not entirely certain that they want to know about fatal adult-onset conditions or the carrier status of their child [35, 36]

⁴ Best-practices highlight a graded strategy as it relates to the disclosure to young children, school-aged children, and adolescents where developing capacity is acknowledged and disclosure practices aligned (for young children disclosure should be to parents, for school aged children they should be included in developmentally appropriate ways and when results have not been provided to parents they may be provided at the age of maturity to the participant) (Avard best practices). In the case of neurodevelopmental disorders, researchers will want to consider the potential for participants, at the age of maturity, to participate in a developmentally appropriate manner to discussions about disclosure preferences, and the ramifications of withholding such information from parents at an earlier time if they are already intricately involved in their child's care (i.e., would the patient be able to enact their own preferences without the parent being involved and therefore is anything gained by waiting to determine the child's preferences). Depending on this reflection, and the nature of the relationship with the research team and the recruited families, it may be appropriate to use parent preferences to guide the return of non-actionable, non-significant incidental findings. In these cases, parents should act with their child's best interests in mind when requesting or refusing information.

Summary of findings and issues for future study *continued*

1. Convergences and divergences between ethics policies, scholarly perspectives and empirical data on the return of genetic results *continued*

Box 6: Disclosure of ASD-related genetic findings: major recommendations and observations from ethics policies, literature, and empirical studies

A. Disclosure of general research results overwhelmingly supported in a way that is accessible to adult participants, parents, and if appropriate children [16, 18, 21]

B. Disclosure of individual research results depends on context

- Participants should be asked about their preferences related to the disclosure of individual research results [18, 19]
- Material results should be offered to adults when additional considerations are weighed (including their preferences and practical considerations such as the availability of genetic counselling support) [18]
- Disclosure of pediatric individual research results is encouraged when individual research results are reliable and valid and have important implications for the participant's health [21]⁵
- Researchers hold differing views on the definitions of concepts such as actionability, high penetrance and risk, that lead them to case-by case analysis when considering disclosure of research results [29]
- Researcher decision-making about the return of IRR is complicated when results are less published, de novo or rare variants [30]
- Researchers generally support the return of clinically significant findings but not of uncertain or provisional findings [38]
- Researchers have differing views themselves about the role that genetic information plays in ASD and that impacts their views on disclosure [39]⁶
- Disclosure of individual results in autism might be seen as appropriate if it allows for genotype-driven research with families or clarification of uncertain variants [39]
- Parents whose children participate in ASD genetic research, generally desire that results be returned. They justify this on the basis that it provides personal utility in the form of assisting reproductive decisions and answering questions about why the child has ASD [39-41]
- Parents describe that returning individual research results creates an incentive to participate in genetic studies [41]

⁵ Although guidance related to the return of incidental findings may be a starting point for considering the appropriate return of ASD-related genetic findings, the fact that many ASD-related genetic findings have uncertain meaning, or are non-actionable, puts a greater emphasis on the challenges facing researchers in dealing with decisions about the disclosure of non-material or uncertain findings.

⁶ Researchers of ASD studies expressed a reluctance to disclose results relative to medical conditions that have stronger genetic links, for instance more penetrance. This is discussed further below but there is a need for researchers in the field of ASD to engage in further deliberation about their own differing views about the genetics of ASD and the meaning of genetic research results. As is identified generally by genetic researchers, questions of certainty and actionability are still active and ongoing but this can seem to conflict with research ethics policies and REB practices that treat the issue as very routine with seemingly clear guidance (i.e., if X is uncertain than do not disclose). It is not a surprise then that researchers report seeking REB advice to deal with individual cases; particularly because issues of context are important (i.e., what expertise is on the team, are genetic counsellors available). This underlines what Eriksson and colleagues (2008) have described as the *interpretation problem*, the fact that “there will always be a gap between the rules and the practice they are meant to regulate” and “an agent must always interpret the rules in order to assess their applicability in a particular situation”. [42]

Summary of findings and issues for future study *continued*

2. Issues requiring consideration and or evidence to inform best practices for return of genetic research findings in neurodevelopmental disorders

The potential for researcher orientations towards genetics to impact perspectives or practices in the return of genetic findings of ASD

The return of research results is influenced heavily by context and not all genetic findings are considered equal. For instance, researcher perspectives on the return of results are highly contingent on factors such as the accurateness of the result, or clinical utility of the result. Importantly, beliefs about the role of genetics in ASD also influence perspectives about disclosure. Contextual elements impacting the disclosure of research results are impossible to capture in general ethics policies, and there is likely to be a lack of specific contextual expertise to contribute to decisions made by REBs about when to disclose results.

The potential for personal utility to meet the best interests standard for disclosure of research results

Return of research findings related to ASD for reasons of personal utility requires us to think more about the ways that this meets the obligation of parents to act in their child's best interest. Because personal utility (i.e., answering the question of why), rather than clinical utility, seems to be important to many parents participating in genetic studies of ASD, disclosure of individual results on that basis respects the values upheld by parents but it is unclear how they relate this to the best interests of their children. Provided that there is transparency about what the return of research results achieves, a disclosure for reasons of personal utility may be appropriate as long as the parents' desire for information is aligned with best interests of the child. The Network of Applied Genetic Medicine, for instance, suggests that under exceptional circumstances a genetic result that is not actionable in childhood may still be returned based on a favorable balance between benefits and risks (i.e., where the information has significant consequences for the health of the parent's, the siblings). In general, policies about the disclosure of research results lack broad consideration of issues of personal utility. Rather clinical utility has often been the standard by which disclosure and best interests have been established based on immediate health benefits. Furthermore, clinical utility has often been described in a narrow fashion (i.e., results that are clinically actionable or indicate the need for treatment or monitoring). A broader conception of clinical utility would be results that provide meaning about the etiology of a child's syndrome and are of use for clinicians and families. When clinical utility is seen broadly, and where we remain sensitive to a family centered model of best interests, personal and clinical utility are evidently more closely related.

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Summary of findings and issues for future study *continued*

2. Issues requiring consideration and or evidence to inform best practices for return of genetic research findings in neurodevelopmental disorders *continued*

Some may argue that disclosure for reasons of personal utility – with increased potential for feelings of guilt or anxiety when ASD is genetically “explainable” (see below for further discussion of the importance of risk communication) – pose substantial risks to the child and family unit. Further, as it relates to reproductive knowledge, some parents fear that genetic findings could discourage their child with ASD from later having biological children of their own. This hints at unintended harms that may accompany disclosure. One study has shown that regardless of receiving results, families participating in ASD genetic research still found the act of participating valuable.[43]

The importance of risk communication in genetic studies of neurodevelopmental disorders

Different philosophies about the return of research results pit a protective/restrictive model (“only disclose results that are actionable and clinically significant in childhood”) against a more libertarian model of communicating risk information with parents or even minors. As in other instances of risk communication, inadvertent harms are thought to be inherently important to evaluate. These include arousing fear and worry, causing blaming or stigmatizing reactions or inciting guilt, suggesting that actions be taken that are not in an individual’s best interests, and detrimentally impacting on the individual’s identity.[44] The magnitude of these harms is important in evaluating the appropriateness of policies surrounding return of research results although empirical data might be lacking to demonstrate clearly if there are resulting harms. In addition, the magnitude of harms associated with communicating risk related to an “expected” finding (related to ASD) might be significantly different than the magnitude of harms associated with communicating risk related to an incidental or unexpected finding. Empirical evidence suggests that many parents, at least, find the return of research findings useful for reasons of personal utility when they relate to explaining (or not) the presence of ASD. At the same time, researchers have shared with us their personal experiences suggesting that communicating the meaning of a genetic finding related to ASD can be extremely difficult, complex and thorny because of issues identified early on in this review (i.e., incomplete penetrance, non-Mendelian genetics, de novo mutations, differences in phenotypic expression). In empirical studies, parents express more worry about the disclosure of incidental findings, particularly when they indicate life-limiting diseases of adult-onset that lack effective therapy. However, the fact that parents are outwardly more positive about wanting the disclosure of ASD related findings may not reflect the true experience of parents when they are on the receiving end of results that may be confusing, complex, and nuanced, and that may lead to unanswered questions about risk (or heredity, phenotype) for other family members. Additional philosophical and empirical work is needed to further understand harms as a result of risk communication as well as to devise rational explanations that favor one model over another.

Summary of findings and issues for future study *continued*

2. Issues requiring consideration and or evidence to inform best practices for return of genetic research findings in neurodevelopmental disorders *continued*

The role of the child or adolescent with developmental disability in decision making

Current best practices regarding the inclusion of the minor participant in disclosure practices stresses the need for different levels of involvement based on the child's developmental maturity. For young children, information should be disclosed to parents, and parent preferences for disclosure respected, where they are presumed to make these decisions in the best interests of their child. For school-aged children and adolescents, information about findings should be communicated in a way that is developmentally appropriate with consideration of their level of understanding and maturity. However, when to involve or respect minor's preferences with regards to disclosure of research results has seen less attention. Di Pietro and Illes (2013) describe that as long as a minor has capacity, he or she should be involved in decisions about whether to disclose/share results or not. In these cases, they should be asked to consent to the disclosure of results and their preferences should be respected for findings that are of low significance. For minors with ASD who may lack capacity or developmental maturity, parental preferences may guide disclosure. However, an emphasis should be placed on the right of the child to participate actively in these decisions by giving assent or dissent, and parents should be encouraged to revisit disclosure preferences in light of their child's expressed preferences. Moreover, parents should be encouraged to think about future disclosure to the child at the age of maturity or in a developmentally appropriate manner at the time that, for instance, reproductive decisions may become important. An evidence-base relative to the developing capacities of youth with ASD to consent to research does not exist to our knowledge. Without such important empirical questions answered, there will be an evidence gap in understanding effective and appropriate ways to involve youth with ASD in research decisions. The practical implication of such a gap might be a high burden placed on the researcher (i.e., directive to involve youth in developmentally appropriate ways that are time consuming and may not even be effective), or paternalistic practices that exclude the potential involvement of youth with ASD despite their ability to be involved in meaningful ways (i.e., paternalistic restriction placed on vulnerable persons participating in research). These concerns should be examined in more detail.

Summary of findings and issues for future study *continued*

Conclusions

Although in some areas there is little debate (i.e., that parents should not be able to opt-out of receiving information about actionable, material research findings), in many more areas there exist variations in recommended best-practices for the return of research results in pediatric studies (i.e., who should be asked about preferences for disclosure, how and when should findings be disclosed, should parents be offered all genetic results about their child). In many instances, this variation reflects sensitivity to the fact that researchers have different proximity to patients involved in their research, have different systems in place to handle disclosure, and operate under different institutional bodies granting ethical approvals. By reviewing the international ethics policies, normative literature and stakeholder perspectives on this topic, we have discussed convergences and divergences regarding best practices for the return of genetic research results and examined unresolved issues in the return of genetic findings in neurodevelopmental disorders. We remain cognizant of the fact that new evidence or argument about a range of issues could sway or impact best practices in the future. Families who participate in research are leading the charge in the development of new knowledge and treatment options and in doing so they shoulder a significant burden when considered alongside the day to day challenges they may encounter. For this reason it demonstrates deep respect to consider how research can fulfill the broad goals of families participating in research. One way to fulfill these goals may be to return individual research results.

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Working Group, ASD and return of results

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