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ARTICLE

What is a meaningful result? Disclosing the results of genomic research in autism to research participants

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Developments in genomics research have been accompanied by a controversial ethical injunction: that researchers disclose individually relevant research results to research participants. With the explosion of genomic research on complex psychiatric conditions such as autism, researchers must increasingly contend with whether – and which results – to report. We conducted a qualitative study with researchers and participants involved in autism genomics research, including 4 focus groups and 23 interviews with parents of autistic children, and 23 interviews with researchers. Respondents considered genomic research results 'reportable' when results were perceived to explain cause, and answer the question 'why;' that is, respondents set a standard for reporting individually relevant genetic research results to individual participants that is specific to autism, reflecting the metaphysical value that genetic information is seen to offer in this context. In addition to this standard of meaning, respondents required that results be deemed 'true.' Here, respondents referenced standards of validity that were context nonspecific. Yet in practice, what qualified as 'true' depended on evidentiary standards within specific research disciplines as well as fundamental, and contested, theories about how autism is 'genetic.' For research ethics, these finding suggest that uniform and context-free obligations regarding result disclosure cannot readily be specified. For researchers, they suggest that result disclosure to individuals should be justified not only by perceived meaning but also by clarity regarding appropriate evidentiary standards, and attention to the status of epistemological debates regarding the nature and cause of disorders.

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INTRODUCTION

Recent years have witnessed an explosion of genomic research on complex psychiatric conditions, such as autism.[1–3] Such research is in its infancy, but may in time underpin refined interpretations of disease taxonomy and etiology,[4,5] and support the improvement of treatment modalities. It may also provide genetic information to individual families, to explain the cause of some cases, the associated reproductive risks, and to guide management. Autism genomics research has yet to reveal clinical genetic tests for 'autism' *per se*, but whether to learn about emerging results is a question that already animates those engaged in this research.[6,7]

Developments in genomics research have been accompanied by demands to codify a new ethical obligation, incumbent upon researchers: to disclose the results of research to the individuals whose participation has made such research possible. This obligation encompasses both the suggestion that researchers should make the aggregate results of research available to research participants,[8] and more controversially, that researchers should disclose research results to the individuals for whom the results are individually relevant.[9,10] Debate centers around the moral motivation for such an obligation, and what kinds of findings would trigger it. Proponents argue that the obligation is supported by specific ethical principles, and is widely desired by participants.[11–13] Critics have questioned the coherence of the obligation, and the implications of a uniform duty for the research enterprise as a whole.[14–16]

The obligation to report individually relevant research results to research participants is advanced as a general requirement of research ethics,[10,17] without regard for the specific issues arising in different disease contexts. Yet this omission is substantial, as it is not clear that standards that are sensible in one domain (eg, cancer genetics) make full sense in others (eg, psychiatric genetics). In this paper, we report results from a qualitative study of autism genomics research that explored researchers' and participants' experiences and expectations regarding the disclosure of genetic research results. Our findings have implications for the governance of result disclosure in autism genomics, and raise questions about the viability of a uniform, or context-free, ethical obligation to disclose individually relevant results to research participants.

METHODS

With ethics approval from Hamilton Health Sciences and the relevant hospitals, we conducted a qualitative study in 2006 and 2007 with researchers and research participants involved in autism genomics research. We held 4 focus groups with 34 parents of minor or adult children with autism spectrum disorders (12 mothers, 4 fathers, 9 couples) recruited through relevant research groups in Southern Ontario (cited as FG-M or FG-F, mother or father, respectively). As some parents were unable to attend focus groups or preferred one-on-one conversations, we also conducted 23 semistructured interviews (cited as I-M or I-F, mother or father, respectively); 22 of these interviews were with 25 parents (18 mothers, 1 father, 3 couples) recruited through the same research groups, and 1 interview (1 mother) was with a participant recruited

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through a Canadian autism advocacy organization. Finally, we conducted 23 interviews with researchers (study or site principal investigators), including 11 clinicians (cited as RC) and 12 non-clinicians (cited as R). Researchers were recruited in Canada (n=8), the United States (n=11), and Europe (n=4) through publicly available sources (eg, academic publications, websites) and snowball sampling.

Focus groups and interview discussions explored respondents' (i) involvement with autism genomic research, (ii) expectations regarding providing (for researchers) or receiving (for participants) genetic research results about individual participants, and (iii) beliefs about the circumstances under which participants should be provided with such results. Interviews averaged 1 h, focus groups 2 h; each was tape-recorded, transcribed verbatim and entered into a qualitative database (NVivo, Version 7, Doncaster, Victoria, Australia).

For this paper, we analyzed coded sections of each transcript in which respondents discussed genomic research in autism or the expectations or obligations of researchers and participants regarding genetic research findings. Focusing first on researchers' transcripts, and using writing as an analytic device,[18] we categorized coded sections, seeking to identify thematically coherent interpretations of the meaning arising from autism genetics research or research results. Once we had a preliminary coding scheme (expectations, evidence, epistemology), we reviewed transcripts from parent interviews and focus groups using and revising this scheme. We iterated between groups of transcripts (parents to researchers to parents, and so on), searching for contrary instances and strengthening the coding scheme through exclusion of less robust inferences. Given the richness and depth of some interviews and focus groups, we pursued qualitative saturation both across and within transcripts. Our analysis adopted a modified grounded theory approach.[19] We integrated the iterative and constant comparative analytic method with a reflexive approach to data interpretation to guide us in understanding the data.[20]

In some research groups, clinical genetic testing (eg, Fragile X, MECP2) was routine before research enrollment, with positive results as exclusion criteria. For other groups, however, such results might be unearthed through research-based testing and decisions about their management were sometimes described to us. Although these situations are not without challenge, see Miller *et al*,[21] we focus in this paper on research findings of uncertain clinical significance (eg, susceptibility variants, copy number variants).[22,23]

FINDINGS

By general consensus, the autism genomics research enterprise was not ready, at the time of our study, to permit routine disclosure of genetic research results to individual participants. Correspondingly, researchers had disclosed few such results and few parents had received them. In considering the question of disclosure, then, many researchers identified their 'standard line': that genetic research results in autism are only meaningful in the aggregate and are not reported to individuals. In addition, some researchers focused on the regulatory constraints that impede routine disclosure, such as the need for specific credentials to offer a clinical diagnosis or to report clinical laboratory results (eg, the Clinical Laboratory Improvement Act in the US).

Despite this orientation, parents spoke of their hopes and researchers reflected on specific cases or contexts for result disclosure. Even those researchers facing regulatory constraints identified backdoor processes for ensuring disclosure of 'reportable' results (eg, sending families to licensed facilities to explore 'something'). Thus, though disclosure was not seen as a universal outcome affecting all participants, discoveries with potential relevance to individuals or subsets were considered. Indeed, around the time of our study, several publications reported such findings and reported also on novel and challenging efforts to report these to participants.[6,24] Thus the question remains: what genetic research results would be 'reportable' and why?

A first answer provided by our respondents pertains to the kind of value that research results might provide to participants. Indeed, both researchers and parents offered clear views regarding the kind of meaning that would be desired or warrant reporting. A second answer reflects the standard of proof that results would have to meet in order to be deemed reportable. Researchers were most engaged with this issue, reflecting on the kinds of validity necessary to ensure that a result had meaning. A final answer engaged fundamental debates about the way in which autism is or is not 'genetic.' Here again, researchers were more engaged, though not all reflected on the underlying theories and expectations that informed their work. Although generally distant from the issues of validity and epistemology that underpin the research enterprise, some parents in fact engaged this third theme, reflecting on their expectations about what genetic research, and thus genetic mechanisms or processes, could explain about a disorder of behavior and cognition as complex as autism.

Reportability is related to perceived meaning for participants

Although researchers and parents hoped that genetic research results might secure clinical benefits, respondents emphasized their non-clinical benefits – that research findings might identify reproductive risks and answer the metaphysical question, 'why?' (see Supplementary Table 1 for quotes illustrating themes).

As one researcher stressed, 'understanding why […] their child has Autism is… I mean, it's a big deal.' (2-RC) Perceiving this value, researchers emphasized the importance of reporting such results: 'even if it's just an 'answer' to their case, a solution to what caused this kid's autism. If it's a causal mutation or deletion or something like that then I think it's important that the family gets that information.' (12-R) Parents echoed these expectations. Some supported and others opposed the idea that genetic research might help to identify reproductive risks to avoid the birth of children with these conditions. But most agreed that research offered the possibility of answers. As one parent stated,

> I think for us it was having two older [children] and everything was going very smoothly and all of a sudden we had a [child with autism] and it was, 'Why?' Can we identify why… he's autistic and if it was anything that we had done, bringing him up the way we brought him up, or whether it was a genetic link. And also, now that our [other children] are older, and at some point they'll be having their own families, that if it was a gene, and if it could be identified, that they could have a choice… (4-FG-M)

Several respondents expected that in answering the question 'why,' genetic information might bring broader positive effects such as 'peace of mind that this is a genetic thing,' (21-I-F) or a reduced sense of blame. Others were skeptical of these benefits: 'I don't know if it gives them peace of mind. I don't think it's, in the long run, it doesn't matter because they still have to live with the disabled child.' (7-R) Similarly, participants wondered whether genetic information might assign blame within families in hurtful ways:

> I struggled with too is, when we were told that it had a strong genetic component of course, it's like, 'Okay, so did the husband bring it into the family or did the wife?' And that's something that we never wanted to investigate – to lay any blame on one side of the family for carrying the defective gene. (15-I-M)

Thus, genetic research on autism – and the results that it might yield – was seen to promise the broad benefits that arise from information more generally. Although several respondents hoped that genetic research might affect clinical care – through information on health risks or for drug development – the dominant expectation was that

genetic research results could answer the question 'why,' and for those who approved of such uses, provide important information about reproductive risks, primarily for siblings and extended family members. Several respondents hoped that this information might also bring benefits in the form of reduced self-blame or peace of mind, but others doubted this outcome. Genetic results, even though they might need to be reported, would not solve the day-to-day challenges of autism and might even evoke blame within families by assigning responsibility for the transmission of genetic risks.

Reportability is related to evidentiary standards

In discussing cases where results might be disclosed to individual participants, researchers identified several principles for adjudicating whether, in a specific case, a result might be 'true' (see Supplementary Table 2 for quotes illustrating themes). As one clinician researcher noted, three different standards of proof existed, defined by three different disciplinary norms:

> …these genetics projects are made up of basically three different disciplines. There's the clinical people, there's the statistical people and there's the molecular biology people. These three groups have a different view of the world. So the molecular biologist says, 'This is abnormal.' The statistician says, 'Yes, but the probability of this in cases verses controls is not increased. It's not statistically significant therefore it's not a true finding.' And the clinician says, 'What am I supposed to do with you two people?' [….] People have very different criteria for what constitutes 'a finding.' (1-RC)

As this researcher suggested, one norm for establishing the truth-value of a finding was biological, arising from evidence regarding inheritance patterns and molecular function. Researchers drew on this evidentiary norm in deciding that some anomalies were 'very real,' for example, because the anomaly, 'was found in both of their children but neither parent, and it affected a gene that… we were pretty convinced it was causing autism.' (10-RC) A second norm drew on clinical conventions: that results with uncertain implications were deemed causal and reportable if associated with clinically suspicious phenotypes or identified through clinical encounters.

These two norms supported a key rationale for reporting genetic research results to individual participants – to provide clinical and biological clues to aid in understanding uncertain results. Researchers reported such results because they wanted families to know. In addition, researchers sometimes made use of result reporting to further investigate, for example, the nature of an individual's clinical phenotype given an identified molecular variant, or to ascertain whether biological family members manifested the expected clinical phenotype in light of the putative heritability of a given variant. As one researcher noted, 'we had a research interest, too, to interact with the kids more to maybe get a more detailed phenotypic assessment to see what their current status was…' (10-RC) Indeed, as another researcher stated,

> It's these atypical cases that really provide the clues we need. […. One case was] very instrumental in our understanding and actually resolving what was going on at the molecular level. (1-R)

The third norm for establishing the veracity of a finding was statistical, relying on evidence in populations of patients. From this perspective, reporting results to resolve biological or clinical causation in individual cases was not valid. Given the relatively small size of most control populations, and the problems of ascertainment bias, where 'what they do with controls is only look at them after they've found something in the cases,'

> …from a statistical point of view there's really no sample size that would allow us to definitively state that a particular very rare variant is truly autism associated or that that variation has got anything to do with autism. [….] So I'm actually … somewhat skeptical that these kind of N of 1 studies should actually be returned to participants because scientifically I have no idea what that means in terms of recurrence risk. (7-RC)

In discussing the disclosure of research results to individual participants, researchers advanced rationales for adjudicating between reportable and non-reportable results. Two rationales, the clinical and biological, supported a practice of reporting results to individuals in order to conduct further research and clarify result meaning. The third rationale – statistical – was incompatible with this practice, seeking clarity only through further study of populations.

Reportability is related to epistemological commitments regarding the role of genetics in autism

Judgments about the reportability of results identified through individual studies involved more than perceived value and evidentiary standards. Judgments also relied on epistemological commitments regarding the nature of autism and the way in which autism is 'genetic' (see Supplementary Table 3 for quotes illustrating themes).

Epistemological commitments motivated researchers' involvement in autism genetics research. As one researcher noted, '…we are working as hard as we can to identify genes that may confer risk and we believe that we can do it.' (5-RC) Another researcher noted the obligation to make epistemological undertakings explicit in communicating with participants:

> I think that there is an obligation for those of us in research to disclose… our sense of… the general role of genetics in autism. Whether we're ultimately shown to be right or wrong it's what we know. It's what we believe to be true. And I think there still is a lot of confusion and, from our perspective, misinformation about the role of genetics *versus* environment. Part of what we do is try to communicate what we believe to be the truth. (10-RC)

Such commitments also involved abstract hypotheses about what it was possible to learn through genetic research. Indeed, some researchers had been attracted to the field because they thought the genetic characterization of autism would be readily achieved.

Researchers' beliefs and hypotheses regarding the role of genetics in autism were not uniform. Instead, they involved active debates. Arguing that the goal of genetic research in autism should be, 'to understand the mechanisms that are abnormal in, say, brain development or growth, and potentially then to think about ways of intervening,' this researcher argued against,

> …this idea that the genetics of common diseases will be able to be used for personalized risk prediction in the population. And we have no evidence that that's likely to be the case at the moment. I mean, it may ultimately be appropriate for some disorders but I don't necessarily think it's going to be generally applicable, and autism may be one of those cases that is essentially… very poorly suited because it may be that the variations are actually very rare. (7-RC)

Another researcher who adopted a similar perspective argued for caution in predicting the utility of such research:

> You know, frankly it's not really clear to me how these findings will be useful. I mean we hope they will be but until you have the findings, you understand the genetics, how much you're going to be able to do beyond that, whether therapies evolve from it, whether or not you can do prevention… those are all things that are very long-term and not clear to me. (8-R)

Some research participants echoed these uncertainties, emphasizing the complex nature of the disorder and of the ways in which it might be genetic. As one parent noted, 'If someone said to me cystic fibrosis or something like that or a single gene mutation and then I'd say okay fine… but you know this… this is not only a gene. It's the combination of mutations of genes and how they affect behavior.' (15-I-M) As another parent noted, in debating the merits of disclosing uncertain information in the research context,

> …a breast cancer gene is information you can act on but if you have one of three genes that's 20% correlated with something else that… I think that that's more likely with the autism literature is that it's not clear single genes or single relationships or even you know two genes or… you know so that to act on… to pretend that you can do counseling or something, like, I think that gets complicated really fast and like people will not just have anxiety but make bad decisions or potentially bad decisions. (4-FG-F)

Decisions about whether the results of individual studies met a standard of reportability involved more than the kinds of meaning that might be generated, or the types of evidence that could sustain such meaning. They also involved fundamental epistemological commitments regarding the ways in which autism might be appropriately thought of as 'genetic,' with commitments to one or another hypothesis adopted by different researchers. In turn, participants articulated hopes and fears regarding result disclosure that illuminated similar debates about the role of genetics in a disorder as complex as autism. These debates were not resolved by evidence from single studies, but served as overarching uncertainties that were amenable to resolution only through sustained research efforts.

DISCUSSION

Our respondents believed that genetic research results that could explain the cause of autism warranted disclosure. Such results explained 'why,' and could permit the identification and management of reproductive risks. Ethics guidance differs on when individually relevant genetic research results should be disclosed to individuals: when results identify serious and avertable health risks, have significance for life and reproductive planning, or are simply of interest.[15] Our respondents set a standard for reportability that is more specific: a standard that reflects the metaphysical value that genetic information is seen to offer in the autism context.

Yet if our respondents agreed on the kind of meaning that autism genetics research results might fruitfully yield, they differed regarding when this goal might be achieved. They articulated discipline-specific norms regarding validity and paradigmatic differences regarding epistemology – that is, regarding the nature of autism and the way in which it may or may not be thought of as 'genetic.'

Researchers reported several disciplinary logics that established different standards of proof. Two of these logics – the clinical and biological – found support in individual cases. From this perspective, the disclosure of specific research results could be a tool for advancing knowledge, allowing researchers to explore the clinical sequelae of genetic variations, or strengthen the index of suspicion for candidate genes. In these cases, informing families of a suggestive research finding seemed to both answer the family's need for meaning, however uncertain, and provide researchers with additional data to fuel investigation. This rationale was disputed by the third logic – statistical – which sought proof in populations. From this perspective, disclosing results for research made little sense. Large control populations, avoidance of ascertainment bias, and statistical tests of significance were needed if results were to have meaning for researchers or families. Indeed, these differences in standards of proof render illusory the seeming consensus regarding the 'meaning' that results might usefully achieve.

Underpinning these debates about standards of proof in specific instances were fundamental theories about the role of genetics in autism, and to a lesser extent, the nature of autism itself. Whether specific genetic research results were likely to explain cause was a function of respondents' epistemological stance. Those who expected genetic information to guide personalized risk prediction would attribute greater meaning to specific findings than those who questioned this hypothesis, irrespective of the standard of proof brought to bear. Less evident in respondents' comments, though highly relevant to the interpretation of research findings, is the status of autism as one or a multiplicity of disorders. Biomedical research does not simply explain the cause of given disorders, it also explains their nature – lumping or splitting disease categories and establishing or denying biological, clinical and social affinities.[5,25] Autism is currently defined by a complex set of behavioral and cognitive signs and symptoms, with a broad spectrum of types and degrees of disorder. Whether autism can be adequately defined by a set of common biological pathways or is better conceived as a heterogeneous collection of disparate conditions remains to be seen.[4]

Yet epistemological debates about the nature of autism and the role of genetics in its causation are not resolved by single studies. Indeed, it may be that researchers are not always conscious of the ways in which their theories and assumptions about the nature and cause of a psychiatric disorder as complex as autism inform their judgments about validity or potential meaning. Resolving such paradigmatic commitments is the role and obligation of biomedical research. Yet this requires that studies contend with each other over time in order to establish or contest the 'truth' about the nature or etiology of disease. It requires also that researchers be clear and transparent about the extent of their disagreements – over epistemology, standards of proof, or standards of meaning. Finally, it requires that research participants be engaged not simply at the level of meaning – what kinds of results they would like to receive – but also at the more contested and complex levels of validity or epistemology. Efforts to honor participants' desires for meaningful information are surely misplaced if the purported meaning rests on unspoken or contested methodological or epistemological foundations.

These findings have implications for two different audiences. For research ethics, these findings suggest that establishing a context-free set of obligations for reporting research results to individual research participants may be beyond our grasp. This is not to say that no obligations exist, but that to imagine that standard ethical norms can be established for research results, as they can be established for research processes, is to confuse and conflate the one with the other. Psychiatric genetics research asks fundamental questions: What is the nature of a disorder? What is the role of genetics in its causation? Researchers differ in their preferred answers to these questions and

differ also in the standards of proof required to support their answer. Given these differences, achieving consensus to avoid idiosyncrasy in disclosure standards across research teams would be difficult indeed. Yet even if consensus could be achieved, disclosure standards would remain specific to disease context because the meaning that the 'best' results can provide differs by research domain: in cancer genetics this meaning will be prediction linked to prevention/treatment, but in autism genetics this meaning may only be knowledge of causation, full stop.

For members of the research community who struggle to conform to emerging ethical imperatives, these findings should give pause. Disclosure of results to individuals to support further research or out of a desire to 'help' families cannot be a sufficient rationale. Disclosure must be justified by clarity regarding what evidentiary standards are appropriate, and due consideration to the status of real-time epistemological debates regarding the nature and cause of a given disorder.

For both research ethicists and researchers, the goal of consistent and ethically defensible standards for reporting research results faces significant feasibility challenges. Can researchers be transparent and achieve consensus about matters of methodological and epistemological contention? Can ethical guidance help to resolve these disagreements? Further, will researchers serve their own interests in attending to an obligation to disclose research results, and will their interests align with those of research participants? Does the emphasis on hoped-for meaning – what participants want – distract all stakeholders from attending sufficiently closely to the questions of methodology and epistemology that are necessarily at issue in research contexts? Finally, even if we manage these technical and substantive challenges, fundamental normative questions remain: Is it the role of research to adjudicate clinical meaning or the actionable status of genetic results, and can it be the role of research to ensure appropriate access to such clinical goods? In our view, until the debate on disclosure of research findings engages the complexities of the research encounter more fully, the intention to report individual genetic research results to research participants must remain a consideration rather than a uniform or universal obligation.[16]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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