

ARTICLE

Not so simple: a quasi-experimental study of how researchers adjudicate genetic research results

Robin Zoe Hayeems^{*1}, Fiona Alice Miller¹, Li Li² and Jessica Peace Bytautas¹

Ethicists contend that researchers are obliged to report genetic research findings to individual study participants when they are clinically significant, that is, when they are clinically useful or personally meaningful to participants. Yet whether such standards are well understood and can be consistently applied remains unknown. We conducted an international, cross-sectional survey of cystic fibrosis (CF) and autism genetics researchers using a quasi-experimental design to explore factors influencing researchers' judgments. Eighty percent of researchers agreed, in principle, that clinically significant findings should be reported to individual participants. Yet judgments about when a specific finding was considered clinically significant or warranted reporting varied by scientific factors (replication, robustness, intentionality, and disease context), capacity of the research team to explain the results, and type of research ethics guidance. Further, judgments were influenced by the researchers' disease community (autism or CF), their primary role (clinical, molecular, statistical) and their beliefs regarding a general reporting obligation. In sum, judgments about the clinical significance of genetic research results, and about whether they should be reported, are influenced by scientific parameters as well as contextual factors related to the specific research project and the individual researcher. These findings call into question the assumption that the conditions under which an obligation to disclose arises are uniformly understood and actionable. Adjudicating the clinical readiness of provisional data may be a responsibility better suited to evaluative experts at arms' length of the provisional data in question, rather than a responsibility imposed upon researchers themselves.

European Journal of Human Genetics (2011) 19, 740–747; doi:10.1038/ejhg.2011.34; published online 16 March 2011

Keywords: research ethics; reporting genetic research results; quasi-experimental

INTRODUCTION

Recent commentaries argue that researchers bear an obligation to report individual genetic research findings to study participants.^{1–6} Supporters of this obligation believe that disclosure honors the principle of respect for a person^{3–5} and the reciprocal nature of a research relationship.^{7,8} Invoking the principle of beneficence, many argue further that it is in participants' best interest to learn this information;⁴ the common suggestion that results should meet some test of clinical significance (varying from clinical through personal utility)^{4–16} to warrant reporting supports this point. Proponents find confirmation for their position in empiric research with research participants, many of whom believe that such information is owed^{3,9,17–24} and/or will have meaning in their lives.^{19,23,25–28}

Others contend that although the principles of respect for persons, reciprocity, and beneficence should be upheld in the context of research, they may neither be well served if results are disclosed nor denied if they are not disclosed.^{7,29–33} Before unpacking the debates about whether or not participants can understand this information and make meaningful decisions about its receipt,^{29–32} careful consideration is owed to the conditions under which the obligation to report arises in the first place.

Informed by qualitative research with investigators engaged in autism genetics research,³³ this study assumed that decisions about exactly *when* genetic research results achieve some standard of clinical

significance and warrant reporting involve a series of complex judgments that are neither limited to narrow interpretations of clinical utility and validity nor, to date, well understood.^{7,33} To better understand a range of factors that might influence how researchers establish clinical significance and reportability, we conducted an international survey of researchers engaged in studies exploring the genetic basis of two distinct conditions: cystic fibrosis (CF), where current research seeks to understand modifiers of the CFTR *gene*, long known to cause CF,³⁴ and autism spectrum disorders (ASD), where, in contrast, current research seeks to identify genetic variants that *may* contribute to the onset of this heterogeneous set of conditions.^{35,36} While this research does not reflect the full spectrum of current genetic research, this approach enabled us to explore how different communities of researchers orient to research results generated in different disease contexts.

METHODS

Sample, recruitment and data collection

To identify a population of investigators sufficiently engaged in CF and ASD genetic research so that they could provide an informed perspective on reporting research findings to participants, we generated a list of authors of scientific publications using keyword searches in Ovid Medline and EMBASE (2005–2008) (eg, *gene**, or *genom** and *mutation*, *mutat**, *cystic fibrosis*, and *autis**, or *autism*) and built

¹Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; ²Department of Statistics, University of Toronto, Toronto, Ontario, Canada

*Correspondence: Dr RZ Hayeems, Department of Health Policy, Management and Evaluation, University of Toronto, 155 College Street, 4th Floor, Toronto, Ontario, M5T 3M6, Canada. Tel: +416 946 5410; Fax: +416 979 7350; E-mail: robin.hayeems@utoronto.ca

Received 21 October 2010; revised 25 January 2011; accepted 28 January 2011; published online 16 March 2011

on author lists of known research consortia.^{35,36} We included only English language papers reporting or reviewing original scientific research in humans, relevant to CF or ASD genetics. To confirm relevance of the publications, we reviewed titles and abstracts and, where necessary, full papers. From the final set of articles, we generated a complete list of all of the authors listed on these articles (1223 ASD and 964 CF authors). We further limited this set of authors to those for whom we could identify publicly available email and postal addresses, generating a final sample of 877 eligible participants (418 ASD, 459 CF).

Following the Dillman-tailored method of mixed-mode survey design,³⁷ we contacted potential participants five times over an 8-week period in spring 2009. Most contacts were by email with a link to the online questionnaire; the fourth contact was by mail and included a paper copy. We provided participants with an opportunity to receive an executive summary of findings as a non-financial incentive.

Survey instrument

The survey instrument was developed by the study team drawing on previous research and a review of the literature,^{7,22,33,38,39} and was pre-tested with 10 eligible respondents (who were excluded from the final sample). It included a non-experimental component consisting of 22 items: (i) three demographic questions about the respondent's primary role in research, professional training and gender, (ii) seven practice questions about barriers to care in the respondent's jurisdiction, and the role of the respondent's research team in providing information to participants, and (iii) 12 attitude questions about the respondent's perceived responsibilities toward research participants, beliefs about the potential for harm from provisional scientific information, and beliefs about the role of genes in ASD or CF.

The instrument also included a quasi-experimental component, using vignettes with a factorial survey design. This enabled us to maximize external validity by presenting respondents with true-to-life vignettes, and exploit the principle of random assignment to understand the independent effect of contextual and demographic characteristics, often difficult to achieve with non-experimental designs because of collinearity among these factors.^{40–42} Each vignette contained some combination of the attributes that appeared relevant to the adjudication of research results.^{7,29–33} Each vignette told the story of a genetic research team that was considering how to manage a research finding and presented some combination of the two to six versions (or levels) of each of the 10 attributes. These attributes included features of the science (eg, replication status, robustness of the finding), the research team (eg, capacity of team to explain results) and the research environment (eg, availability of clinical services, research ethics guidance). Of the 10 attributes, seven had 2-levels, one had 3-levels, and one had 6-levels for a total of 2304 possible unique vignettes ($2^7 \times 3 \times 6 = 2304$). Using the fractional factorial technique to reduce the total possible number of vignettes to a number suited to our anticipated sample size and interest in main effects, we developed an orthogonal and balanced matrix, with 48 vignettes specific to CF and 48 specific to ASD.⁴³ (Supplementary Tables 1 and 2 present a sample vignette and attribute list).

Each respondent received two vignettes: one that represented the disease context (CF or ASD) with which they were more familiar and one that represented the other disease context. A series of random numbers was generated and assigned to each vignette to establish the order and pairings of vignettes for each respondent. Each of the unique vignettes was assigned to a respondent once before any one vignette was assigned again.

Following the presentation of each vignette, respondents were asked to consider four judgments. Two of these judgments are the focus of this paper: (1) whether 'the research team can be confident that this research finding is clinically significant,' and (2) whether 'the research team should ensure that information about this genetic variation (as specified in the vignette) is communicated to participants in whom it is identifiable, or their guardians.' Data from responses to other questions are reported elsewhere.^{44,45} Both the attitude questions in the non-experimental component of the questionnaire and the professional judgments elicited in response to each vignette were measured using 5-point *Likert* scales from strongly agree to strongly disagree.

Analysis

Likert scales were dichotomized into agree (agree or strongly agree) versus not (neutral, disagree, strongly disagree) and descriptive statistics were computed for all independent variables. We explored the factors influencing judgments (1) and (2) by first calculating unadjusted odds ratios (ORs) and 90% or 95% confidence intervals (CIs), as appropriate, for selected independent variables (ie, not the attributes embedded in the vignettes). Next, two separate multivariate models were estimated to assess the effect of experimental variables (ie, attributes embedded in the vignettes) and selected independent variables (Tables 3 and 4) on judgments (1) and (2). For the vignette attributes that reflected the scientific robustness of CF (factor C) and ASD (factor D) findings, respectively, specific comparisons were constructed for entry into the model. For both CF and ASD, we constructed a test of scientific robustness (CD1–CD2) and a test of intended versus incidental findings (CD1–CD6). For CF, we constructed a test of phenotypic severity (C1–C3) and for ASD, we constructed a test of methodological approach (D1–D3) (Supplementary Table 1 defines factors C and D). The final main effects models are reported with unadjusted and adjusted ORs and 95 or 90% CIs, as appropriate.

Responses to vignettes were treated as separate observations; thus, the unit of analysis was the judgment provided (N-judgment) and not the individual participant (N-participant). To account for the unknown correlation between the two vignette responses from each participant, we used generalized estimating equations (GEE) with an unstructured correlation structure to fit the parameters of two generalized linear models (binomial, with logit link), and specified the regression models with (Huber–White) sandwich variance estimators for clustered data.⁴⁶ We used the forward selection method to develop the models, removing variables where there was evidence of multicollinearity. As different selection procedures can lead to different final models, we re-introduced all variables of interest into the final model to test their significance at $P \leq 0.1$ (using the Wald statistic). Goodness of fit statistics are limited in the context of GEE models and are not reported in this paper.⁴⁷ Due to missing data, seven participants included in the descriptive analyses were removed from univariate and multivariate analyses. All statistical analyses were completed using R (version 2.10.1, 2009) and geepack (version 1.0–17, 2010) software packages.^{48,49}

Finally, we generated an index to assess the degree to which each potential participant was involved in relevant ASD or CF genetics research, and to assess whether participants and non-participants differed in this regard. We scored each eligible genetics research publication, differentiating between highly relevant (eg, discovery research, research with human subjects or populations) and less relevant publications (eg, incidence/prevalence studies, case studies). Each participant was then assigned a final score depending on the number of publications multiplied by its relevance score (1 or 2). The final index ranged from 1 to 41.

RESULTS

Response rates and characteristics of respondents

Of 785 eligible surveys, the final response rate was 44% (Supplementary Table 3), with the majority of questionnaires (81%) completed online. Participants were almost two times more involved in more relevant research than non-participants (OR=1.8, CI (1.2, 2.7)). The sample was evenly split among ASD and CF researchers (49%, 51%, respectively). Other participant characteristics are described in Table 1.

General beliefs about reporting research results and provisional knowledge

A total of 80% of researchers agreed that, in general, individuals in whom a genetic variation is identified should be informed of this finding when it is judged to be clinically significant. In contrast, only 23% of CF researchers and 15% of ASD researchers agreed that individuals in whom a genetic variation is identified should be informed of this finding when its clinical significance is uncertain. The majority of CF and ASD researchers (66 and 64%, respectively) also agreed that provisional scientific information is potentially harmful for research participants (Table 2).

Multivariate model 1: what influences researchers' confidence in the clinical significance of genetic research results?

Statistically significant vignette attributes. First, characteristics of the science specified in each vignette influenced researchers' confidence that a result was clinically significant: (a) less well-replicated findings (ie, those that were replicated by the same group or those that had not been replicated at all compared with those replicated by an independent research group) were 45% less likely to engender confidence (OR=0.55, 95% CI (0.3, 0.9)), (b) less robust findings (ie, variants found in non-coding regions that conferred only 1.5-fold increased risk for CF or ASD) compared with more robust findings (variants found in known coding regions that conferred fivefold increased risk for CF or ASD) were half as likely to engender confidence (OR=0.5, 95% CI (0.3, 0.8)), and (c) incidental findings (ie, genetic risk for multiple sclerosis in the context of CF or ASD research) engendered 65% less confidence than an intended finding (OR=0.35, 95% CI (0.2, 0.7)). In addition, (d) ASD findings engendered 35% less confidence than CF findings (OR=0.65, 95% CI (0.5, 0.9)) (Table 3). Other scientific (eg, phenotypic severity, methodological approach) and non-scientific (eg, nature of researcher-participant relationship, availability of clinical services for index condition) attributes were not statistically significant influences (data not shown).

Statistically significant independent variables. General beliefs and characteristics of the researchers themselves were also significantly associated with judgments of clinical significance. ASD researchers were 40% less likely than CF researchers to be confident in a given finding (OR=0.6, 95% CI (0.4, 0.96)), and those with a clinical interpretive role were two times more likely than those without this role to be confident in the clinical significance of a finding (OR=2.2, 95% CI (1.4, 3.4)). Researchers who endorsed the general belief that clinically significant findings should be reported back to individuals were 2.8 times more likely than those who did not endorse this general belief to feel confident that the hypothetical finding was clinically significant (OR=2.8, 95% CI (1.4, 5.8)) (Table 3).

Multivariate model 2: what influences researchers' inclination to report genetic research results to participants?

Statistically significant vignette attributes. First, characteristics of the science specified in each vignette influenced researchers' inclination to

Table 1 Summary of participant characteristics

	Total N(P), %
Total no participants (N(P))	343
<i>Research community</i>	
ASD	168 (49.0)
CF	175 (51.0)
<i>Jurisdiction of research</i>	
North America	190 (55.4)
Latin America	7 (2.0)
Europe	126 (36.7)
Asia	13 (3.8)
Australia and New Zealand	7 (2.0)
<i>Professional qualifications</i>	
Medical degree	180 (52.5)
Doctoral degree – research-based	191 (55.7)
Other ^a	195 (56.9)
<i>Primary role in genetic research</i>	
Molecular analysis	164 (47.8)
Statistical analysis	114 (33.2)
Clinical interpretation	149 (43.4)
Other ^a	119 (34.7)
<i>Gender^b</i>	
Female	160 (46.8)
Male	182 (53.2)

Abbreviation: N(P), Number of participants.

^aOther includes respondents who are none of the aforementioned levels.

^bDenominator=342.

report results to research participants: (a) researchers were half as likely to support reporting less-robust than more robust findings (OR=0.5, CI (0.3, 0.8)), (b) 40% less likely to support reporting incidental rather than intended findings (OR=0.6, 95% CI (0.3, 0.96)), and (c) half as likely to support reporting ASD findings than CF findings (OR=0.5, 95% CI (0.4, 0.7)) (Table 4). Characteristics of the research environment also influenced researchers' inclination to report research results. Specifically, they were 40% less likely to support reporting where research teams lacked the capacity to explain research results and provide medical advice to participants than they were when teams were described as possessing such capacity (OR=0.6, 95% CI (0.4, 0.8)). With respect to research ethics governance, researchers were 40% less likely to agree that a result should be reported when research teams were said to use consent forms that were not specific about how to manage result reporting than when consent forms required that clinically significant findings be reported (OR=0.6, 95% CI (0.4, 0.8)) (Table 4). As above, other vignette attributes were not statistically significant influences (data not shown).

Statistically significant independent variables. General researcher characteristics and beliefs were also significantly associated with the disposition to report the findings identified in each vignette. ASD researchers were 40% less likely than CF researchers to support result reporting (OR=0.6, 95% CI (0.4, 0.9)), those with a clinical interpretive role in research were 1.5 times more likely than those without this role to support result reporting (OR=1.5, 90% CI (1.03, 2.1)), and those with a statistical role were 30% less likely than those without

Table 2 Summary of participant's general beliefs

		ASD (N(P), %)	CF (N(P), %)
Total no. of participants		167 (49.0)	175 (51.0)
<i>Individuals in whom a genetic variation is identified should be informed of this finding when researchers...^a</i>			
Judge it to be clinically significant ^b	A/SA	134 (80.2)	141 (80.6)
	D/SD/N	33 (19.8)	34 (19.4)
Are uncertain about its clinical significance ^b	A/SA	25 (15.0)	40 (22.9)
	D/SD/N	142 (85.0)	135 (77.1)
Provisional scientific information is potentially harmful for research participants ^{b,c}	A/SA	107 (64.1)	114 (65.5)
	D/SD/N	60 (35.9)	60 (34.5)

Abbreviation: N(P), number of participants.

^aNB, column % given.

^bResponse from one ASD participant missing from this question.

^cResponse from one CF participant missing from this question.

to support reporting the result (OR=0.7, 90% CI (0.5, 0.99)) (Table 4). Researchers who endorsed the general belief that clinically significant findings should be reported to individuals were five times more likely than those who did not endorse this belief to support reporting the vignette finding (OR=4.9, 95% CI (2.7, 8.9)) and those who endorsed the view that provisional scientific information is potentially harmful for research participants were 60% less likely than those who did not share this view to support reporting results (OR=0.4, 95% CI (0.3, 0.7)) (Table 4).

DISCUSSION

Our findings endorse the view that clinical significance is a key criterion on which to base a decision about reporting genetic research results. This view has been advanced by many in the research ethics community, and informs much of the guidance from Institutional and Ethics Review Boards. This alignment of beliefs between ethicists and researchers may prove helpful where research findings come neatly labeled as clinically significant or insignificant – as happens on occasion. But it is typically the role of research to ascertain significance, whether characterized narrowly as clinical utility or more broadly to include personal utility. For any characterization along this spectrum, a standard of clinical validity is required and, as suggested herein, even this benchmark is contested. In reality, then, researchers must adjudicate both clinical significance and reporting obligations simultaneously in contexts that, by definition, involve scientific uncertainty.

Beyond confirming the importance of clinical significance as a decision-making criterion in principle, our findings provide insight into the factors that influence how researchers approach this putative reporting obligation in practice. Clinical significance and reportability indeed depend on expected parameters related to scientific rigor. Specifically, less sound results were less likely to be judged clinically significant or reported, and unsurprisingly, given the lack of clarity about the genetic underpinnings of the ASD, less confidence in the significance of research findings was asserted in this disease context than in the context of CF. Although this may also be a function of limited clinical utility of current genetic research results in the context of ASD compared with CF (untested in this study), we show that these judgments also depend on non-scientific factors specific to the researchers and the contexts in which their teams operate.

A key feature of the research context that influences decisions to report is the team's capacity to report results properly. It has been recommended that reporting genetic findings in a research context be

done by a health professional with training in human genetics and counseling and accompanied by accurate written information.^{48,50,51} Encouragingly, our respondents were less inclined to agree that results should be reported in contexts where research teams lacked this capacity. Unless necessary clinical supports are in place to explain research results clearly, the results are better left in the laboratory.

A second feature of research context that influences judgments about result reporting is research ethics guidance. We found that teams were less likely to report findings where consent forms were nonspecific than when they indicated that clinically significant results were to be reported. This would seem to be a sensible association, given the importance of adhering to the terms of the research relationship as specified through the consent process. However, this association also suggests that greater reticence to report is the default position. As Institutional and Ethics Review Boards increasingly require that research teams offer the disclosure of clinically significant results to research participants,^{5,6} they may be challenging researchers' potentially appropriate reticence.

Researchers' judgments were also influenced by their professional roles and beliefs. Informed by qualitative work, we suspected that their interpretation of emerging findings might in fact be tied to the evidential assumptions used to generate them.³³ Interpretation in turn, would influence what is owed. Expert respondents, bringing different disciplinary training and roles to bear, indeed viewed the significance and reportability of research results differently. Respondents with a clinical role assigned greater significance to, and were more inclined to report, a given finding than those with a non-clinical role. In addition, ASD researchers were more conservative in their judgments of clinical significance and reportability than CF researchers, irrespective of the disease context in which the hypothetical finding was considered. Recent qualitative work argues that judgments about the meaning of research results relies on more than simple tests of analytic or clinical validity.^{7,33} Miller *et al*³³ found that respondents' judgments of significance relied on contests about appropriate evidentiary standards and on fundamental assumptions about the etiologic role of genes in the disease in question. Our data endorse these qualitative findings and suggest also that different research communities may form distinctive 'cultures' with respect to interpreting and reporting results, highlighting the challenge of achieving uniformity in research ethics guidance and practice.

Finally, we found that researchers' belief that clinically significant results should be reported to individual participants influenced their assessment of the significance of the result itself. In short, the ethical

Table 3 Factors that influence researchers' confidence in clinical significance

	Confident in clinical significance of vignette finding		Unadjusted OR (95% CI; 90% CI where indicated)	Adjusted OR (95% CI)
	SA/A N(J), %	SD/D/N N(J), %		
<i>The science^a</i>				
<i>Replication status^a</i>				
Not replicated (F3)	75 (21.01)	282 (78.99)		0.562 (0.340, 0.930) ^b
Replicated by same research group (F2)	40 (25.16)	119 (74.84)		0.557 (0.343, 0.902) ^a
Replicated by independent research group (F1) (ref)	59 (37.82)	97 (62.18)		1.00
<i>Robustness^a</i>				
Non-coding region, 1.5-fold increase risk for severe lung disease CF/ASD phenotype (CD2)	35 (32.11)	74 (67.89)		0.489 (0.284, 0.840)
Known coding region; fivefold increased risk for severe lung disease CF/ASD phenotype (CD1) (ref)	48 (38.71)	76 (61.29)		1.00
<i>Intended vs incidental^b</i>				
Incidental finding of variant known to be assoc w/ MS (CD6)	22 (19.82)	89 (80.18)		0.356 (0.177, 0.712)
Intended finding in known coding region; fivefold increased risk for severe lung disease CF/ASD phenotype (CD1) (ref.)	48 (38.71)	76 (61.29)		1.00
<i>Disease context</i>				
ASD	74 (22.02)	262 (77.98)	0.666 (0.508, 0.875)	0.657 (0.494, 0.875)
CF (ref.)	100 (29.76)	236 (70.24)	1.00	1.00
<i>The researcher</i>				
<i>Disease community</i>				
ASD	71 (21.65)	257 (78.35)	0.647 (0.430, 0.972)	0.633 (0.407, 0.984)
CF (ref.)	103 (29.94)	241 (70.06)	1.00	1.00
<i>Role</i>				
Molecular interpretation	87 (26.85)	237 (73.15)	1.101 (0.733, 1.654)	
Non-molecular (ref)	87 (25.00)	261 (75.00)	1.00	
Statistical interpretation	46 (20.54)	178 (79.46)	0.646 (0.441, 0.946) ^d	
Non-statistical (ref)	128 (28.57)	320 (71.43)	1.00	
Clinical interpretation	99 (33.67)	195 (66.33)	2.050 (1.362, 3.096)	2.113 (1.356, 3.287)
Non-clinical (ref)	75 (19.84)	303 (80.16)	1.00	1.00
<i>Qualification</i>				
Medical degree	106 (29.94)	248 (70.06)	1.571 (1.044, 2.366)	
Non-medical degree (ref)	68 (21.38)	250 (78.62)	1.00	
Research doctoral degree	92 (24.60)	282 (75.40)	0.859 (0.572, 1.292)	
Non-research doctoral degree (ref)	82 (27.52)	216 (72.48)	1.00	
<i>Gender</i>				
Male	89 (25.00)	267 (75.00)	0.906(0.604, 1.359)	
Female (ref)	85 (26.90)	231 (73.10)	1.00	
<i>Perceived barriers to clinical services</i>				
Present	79 (24.23)	247 (75.77)	0.845(0.564, 1.266)	
Not present (ref)	95 (27.46)	251 (72.54)	1.00	
<i>General beliefs</i>				
Clinically significant results should be provided (agree, strongly agree)	156 (28.78)	386 (71.22)	2.514 (1.344, 4.711)	3.101 (1.467, 6.172)
Clinically significant results should be provided (disagree, strongly disagree, neutral) (ref)	18 (13.85)	112 (86.15)	1.00	1.00
Provisional scientific information is potentially harmful for research participants (agree, strongly agree)	105 (23.97)	333 (76.03)	0.754 (0.500, 1.137)	
Provisional scientific information is potentially harmful for research participants (disagree, strongly disagree, neutral) (ref)	69 (29.49)	165 (70.51)	1.00	

Abbreviation: N(J), number of judgments.

^aVignette attribute; in the interests of space, we report only the vignette attributes that were retained in the final model.NB: there is no interaction between *type* and *robustness* so we considered them together in making pre-determined comparisons of specific levels.^bF2->F1.^cF3->F1.^d90% CI.

Bold values indicate significant association.

Table 4 Factors that influence researchers' inclination to report results

	Ensure vignette finding communicated to the participant		Unadjusted OR (95% CI)	Adjusted OR (95% CI; 90% CI where indicated)
	SA/A N(J), %	SD/D/N N(J), %		
<i>The Science^a</i>				
<i>Robustness^a</i>				
Non-coding region, 1.5-fold increase risk for severe lung disease CF/ASD phenotype (CD2)	50 (45.87)	59 (54.13)		0.525 (0.310, 0.883)
Known coding region; fivefold increased risk for severe lung disease CF/ASD phenotype (CD1) (ref.)	67 (54.03)	57 (45.97)		1.00
<i>Intended versus incidental^b</i>				
Incidental finding of variant known to be assoc w/MS (CD6)	59 (53.15)	52 (46.85)		0.592 (0.353, 0.989)
Intended finding in known coding region; fivefold increased risk for severe lung disease CF/ASD phenotype (CD1) (ref)	67 (54.03)	57 (45.97)		1.00
<i>Disease context</i>				
ASD	137 (40.77)	199 (59.23)	0.542 (0.431,0.682)	0.539 (0.389, 0.657)
CF (ref)	188 (55.95)	148 (44.05)	1.00	1.00
<i>The research environment^a</i>				
<i>Capacity</i>				
Research team does not have capacity to explain result and provide medical advice (J2)	142 (43.69)	186 (55.31)		0.624 (0.462, 0.843)
Research team has capacity to explain the result and provide medical advice (J1) (ref)	183 (52.74)	164 (47.26)		1.00
<i>Ethics guidance</i>				
Consent form is not specific about how to manage reporting (G2)	148 (42.77)	198 (57.23)		0.616 (0.457, 0.832)
Consent form states that clinically significant findings will be reported (G1) (ref)	176 (53.99)	150 (46.01)		1.00
<i>The researcher</i>				
<i>Disease community</i>				
ASD	142 (43.29)	186 (56.71)	0.672 (0.469, 0.963)	0.618 (0.415, 0.921)
CF (ref)	183 (53.20)	161 (46.80)	1.00	1.00
<i>Role</i>				
Molecular interpretation	155 (47.84)	169 (52.16)	0.960 (0.670, 1.377)	
Non-molecular (ref)	170 (48.85)	178 (51.15)	1.00	
Statistical interpretation	92 (41.07)	132 (58.93)	0.643 (0.435, 0.951)	
Non-statistical (ref)	233 (52.01)	215 (47.99)	1.00	
Clinical interpretation	160 (54.42)	134 (45.58)	1.542 (1.069, 2.223)	1.455 (1.034, 2.048) ^b
Non-clinical (ref)	165 (43.65)	213 (56.35)	1.00	1.00
<i>Qualification</i>				
Medical degree	186 (52.54)	168 (47.46)	1.426 (1.054, 1.929) ^b	
Non-medical degree (ref)	139 (43.71)	179 (56.29)	1.00	
Research-based doctoral degree	162 (43.32)	212 (56.68)	0.633 (0.440, 0.910)	
Non-research-based doctoral degree (ref)	163 (54.70)	135 (45.30)	1.00	
<i>Gender</i>				
Male	170 (47.75)	186 (52.25)	0.949 (0.663, 1.359)	
Female (ref)	155 (49.05)	161 (50.95)	1.00	
<i>Perceived barriers to clinical services</i>				
Present	169 (51.84)	157 (48.16)	1.311 (0.914, 1.879)	
Not present (ref)	156 (45.09)	190 (54.91)	1.00	
<i>General beliefs</i>				
Clinically significant results should be provided (agree/strongly agree)	299 (55.17)	243 (44.83)	4.923 (2.829, 8.585)	4.855 (2.691, 8.758)
Clinically significant results should be provided (disagree, strongly disagree, neutral) (ref)	26 (20.00)	104 (80.00)	1.00	1.00
Provisional scientific information is potentially harmful for research participants (agree, strongly agree)	176 (40.18)	262 (59.82)	0.383 (0.262, 0.561)	0.445 (0.292, 0.679)
Provisional scientific information is potentially harmful for research participants (disagree, strongly disagree, neutral) (ref)	149 (63.68)	85 (36.32)	1.00	1.00

Abbreviation: N(J), number of judgments.

NB: there is no interaction between *type* and *robustness* so we considered them together in making pre-determined comparisons of specific levels.

^aVignette attribute; in the interests of space, we report only the vignette attributes that were retained in the final model.

^b90% CI.

Bold values indicate significant association.

imperative to disclose appears to be bolstering researchers' judgments of scientific relevance, perhaps reflecting the traction that this ethical imperative has gained in the scientific community. Yet although it is appropriate for research ethics to govern the conduct of human subjects research in pursuit of scientific knowledge, it seems inappropriate for it to alter the calculus of scientific judgment. Not only is this a surprising influence, it is not without the possible consequence of over-attributing meaning to research results, in turn triggering potentially unwarranted disclosures.

Two key messages emerge from our findings. The first is that researchers endorse clinical significance as a key criterion for deciding upon an obligation to report a research result to the individual in whom it has been identified. The second is that although researchers endorse this criterion in principle, judgments about what, in practice, actually (a) constitutes clinical significance and (b) warrants reporting to participants are complex and context-specific. This has been demonstrated qualitatively³³ and now, quantitatively. These findings call into question the apparent simplicity of a clinical significance criterion and imply that the criterion itself, and judgments about when it is met, may be too variable and idiosyncratic to guide a universally actionable ethical imperative.

In conclusion, it is perhaps unsurprising that a complex web of contextual factors are brought to bear when researchers are asked to adjudicate their own provisional data. It may be instructive to recall that what fueled the evolution of the health technology assessment discipline, in part, was the need for impartial evidence evaluation.⁵² In the realm of clinical research more generally, it is a comprehensive process of health technology assessment – not the researchers themselves – that typically decides the real-time readiness for uptake of new knowledge. Although it is beyond the scope of our findings to advocate for an analogous process for adjudicating the clinical readiness of genetic research results, the potential applicability of this model of evidence evaluation may warrant consideration in the context of this debate.

Limitations

Our findings can be viewed as only exploratory in nature because of the complexity of the design. Specifically, given the number of attributes and embedded levels that we sought to test, our lower-than-expected response rate limited our power to detect all potentially relevant effects and limited our ability to interpret two-way interacting effects. In addition, the scientific and clinical vignette variables that were assessed for their influence on judgments of clinical significance were more relevant to judgments of 'clinical validity' than 'clinical utility'. This reflects the reality of much genetics research, but limits the generalizability of our findings to other and perhaps more complicated constructions of clinical significance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank our study participants for taking the time to complete our survey as well as Genome Canada for funding this project. We also thank our clinical collaborators in the context of cystic fibrosis genetic research (Drs Peter Durie, Julian Zielenski, and Mary Corey) and autism spectrum disorders genetic research (Drs Stephen Scherer, Peter Szatmari, Wendy Roberts, and Lonny Zweigenbaum). Fiona A Miller is supported by a New Investigator Award from the Canadian Institutes of Health Research (80495). Robin Z Hayeems is supported by a CADRE Postdoctoral Fellowship from the Canadian Institutes of Health Research and the Canadian Health Services Research Foundation. Sponsors' support for this work should not imply endorsement of the conclusions, for which the authors retain sole responsibility.

- 1 Shalowitz D, Miller F: The search for clarity in communicating research results to study participants. *JME* 2008; **34**: e17.
- 2 Shalowitz D, Miller F: Communicating the results of clinical research to participants: attitudes, practices, and future directions. *PLoS Med* 2008; **5**: e91.
- 3 Shalowitz D, Miller F: Disclosing individual results of clinical research: implications of respect for participants. *J Am Med Assoc* 2005; **294**: 737–740.
- 4 Ravitsky V, Wilfond B: Disclosing individual genetic results to research participants. *AJOB* 2006; **6**: 8–17.
- 5 Fernandez C, Kodish E, Weijer C: Informing study participants of research results: an ethical imperative. *IRB* 2003; **25**: 12–19.
- 6 Knoppers B, Joly Y, Simard J, Durocher F: The emergence of an ethical duty to disclose genetic research results. *Eur J Hum Genet* 2006; **14**: 1170–1178.
- 7 Miller FA, Christensen R, Giacomini M, Robert J: Duty to disclose what? Querying the putative obligation to return research results to participants. *JME* 2008; **34**: 210–213.
- 8 Bookman EB, Langchorne AA, Eckfeldt JH *et al*: Reporting genetic research results: Summary and recommendations of an NHLBI working group. *Am J Med Genet* 2006; **140A**: 1033–1040.
- 9 Fernandez C, Weijer C: Obligations in offering to disclose genetic research results. *AJOB* 2006; **6**: 44–46.
- 10 Clarke A, English V, Harris H *et al*: Ethical considerations. *Int J Pharm Med* 2001; **15**: 89–94.
- 11 Rothstein MA: Tiered disclosure options promote the autonomy and well-being of research subjects. *AJOB* 2006; **6**: 20–21.
- 12 Ormond KE: Disclosing genetic research results: examples from practice. *AJOB* 2006; **6**: 30–32.
- 13 Manolio TA: Taking our obligations to research participants seriously: disclosing individual results of genetic research. *AJOB* 2006; **6**: 32–34.
- 14 Sharp RR, Foster MW: Clinical utility and full disclosure of genetic results to research participants. *AJOB* 2006; **6**: 42–44.
- 15 Banks TM: Misusing informed consent: a critique of limitations on research subjects' access to genetic research results. *Sask L Rev* 2000; **63**: 539–580.
- 16 Lavrier RR, Garner SA: Ethical considerations in the communication of unexpected information with clinical implications. *AJOB* 2006; **6**: 46–48.
- 17 Knoppers B, Chadwick R: Human genetic research: emerging trends in ethics. *Nat Rev Genet* 2005; **6**: 75–79.
- 18 Dressler L, Juengst E: Thresholds and boundaries in the disclosure of individual genetic research results. *AJOB* 2006; **6**: 18–20.
- 19 Partridge A, Winer E: Informing clinical trial participants about study results. *J Am Med Assoc* 2002; **288**: 363–365.
- 20 Partridge A, Burstein H, Gelman R, Marcom P, Winer E: Do patients participating in clinical trials want to know study results? *J Natl Cancer Inst* 2003; **95**: 67–68.
- 21 Partridge A, Wong J, Knudsen K *et al*: Offering participants results of a clinical trial: sharing results of a negative study. *Lancet* 2005; **365**: 963–964.
- 22 Godard B, Marshall J, Laberge C: Community engagement in genetic research: results of the first public consultation for the Quebec CARTaGENE project. *Community Genet* 2007; **10**: 147–158.
- 23 Murphy J, Scott J, Kaufman D, Geller G, LeRoy L, Hudson K: Public expectations for the return of results from large-cohort genetic research. *AJOB* 2008; **8**: 36–43.
- 24 Wendler D, Pentz R: How does the collection of genetic test results affect research participants? *Am J Med Genet A* 2007; **143A**: 1733–1738.
- 25 Hoeyer K, Olofsson B, Mjorndal T, Lynoe N: Informed consent and biobanks: a population-based study of attitudes towards tissue donation for genetic research. *Scand J Public Health* 2004; **32**: 224–229.
- 26 Snowdon C, Garcia G, Elbourne D: Reactions of participants to the results of a randomised controlled trial: exploratory study. *BMJ* 1998; **317**: 21–26.
- 27 Schulz C, Riddle M, Valdimirdottir H, Abramson D, Sklar C: Impact on survivors of retinoblastoma when informed of study results on risk of second cancers. *Med Pediatr Oncol* 2003; **41**: 36–43.
- 28 Hayeems R, Miller F, Christensen R *et al*: The Canadian consortium for cf genetics studies reporting cystic fibrosis (CF) modifier gene effects to study participants: pilot survey. American Society of Human Genetics: Philadelphia, 2008.
- 29 Meltzer L: Undesirable implications of disclosing individual genetic results to research participants. *AJOB* 2006; **6**: 28–30.
- 30 Parker L: Best laid plans for offering results go awry. *AJOB* 2006; **6**: 22–23.
- 31 Ossorio P: Letting the gene out of the bottle: a comment on returning individual research results to participants. *AJOB* 2006; **6**: 24–25.
- 32 Dixon-Woods M, Jackson C, Windridge K, Kenyon S: Receiving a summary of the results of a trial: qualitative study of participants' views. *BMJ* 2006; **332**: 206–210.
- 33 Miller F, Hayeems R, Bytautas J: What is a meaningful result? Disclosing the results of genomic research in autism to research participants. *Eur J Hum Genet* 2010; **18**: 867–871.
- 34 Kerem B, Rommens J, Buchanan J *et al*: Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989; **245**: 1973–1980.
- 35 Szatmari P, Paterson AD, Zwaigenbaum L, Roberts W, Brian J, Liu X-Q: Mapping autism risk loci using genetic linkage and chromosomal arrangements. *Nat Genet* 2007; **39**: 319–328.
- 36 Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R: Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J Med* 2008; **358**: 667–675.

- 37 Dillman D, Smyth J, Christian L: *Internet, Mail, and Mixed-Mode Surveys: The Tailored Design Method*. 3rd edn John Wiley & Sons, Inc: Hoboken, New Jersey, 2009.
- 38 Beskow L, Burke W, Merz J: Informed consent for population-based research involving genetics. *J Am Med Assoc* 2001; **286**: 2315–2321.
- 39 Klitzman R: Questions, complexities, and limitations in disclosing individual genetic results. *AJOB* 2006; **6**: 34–36.
- 40 Taylor B: Factorial surveys: using vignettes to study professional judgement. *Br J Soc Work* 2006; **36**: 1187–1207.
- 41 Wallander L: 25 years of factorial surveys in sociology: a review. *Soc Sci Res* 2009; **38**: 505–520.
- 42 Ludwick R, Wright M, Zeller R, Dowding D, Lauder W, Winchell J: An improved methodology for advancing nursing research: factorial surveys. *ANS Adv Nurs Sci* 2004; **27**: 224–238.
- 43 Xu H: An algorithm for constructing orthogonal and nearly-orthogonal arrays with mixed levels and small runs. *Technometrics* 2002; **44**: 356–368.
- 44 Miller FA, Hayeems RZ, Li L, Bytautas JP: One thing leads to another: ensuant obligations when researchers report genetic research results to study participants. *J Law Med Ethics*, (Under review).
- 45 Miller FA, Hayeems RZ, Li L, Bytautas JP: What does 'respect for persons' require? Attitudes and practices of genetics researchers in informing research participants about research. *Am J Med Genet*, (Under review).
- 46 Schwappach DLB, Koeck CM: What makes a error unacceptable? A factorial survey on the disclosure of medical errors. *Int J Qual Health Care* 2004; **16**: 317–326.
- 47 Pan W: Goodness-of-fit tests for GEE with correlated binary data. *Scand Stat Theory Appl* 2002; **29**: 101–110.
- 48 R version 2.10.1 (2009-12-14): Copyright (C). The R Foundation for Statistical Computing, 2009. ISBN 3-900051-07-0.
- 49 Yan J, Højsgaard S, Halekoh U: Generalized Estimating Equation Package. Geepack version 1.0-17 dated 28-01-2010.
- 50 Burke W, Atkins D, Gwinn M *et al*: Genetic test evaluation: Information needs of clinicians, policy makers, and the public. *Am J Epidemiol* 2002; **156**: 311–318.
- 51 Meacham MC, Starks H, Burke W, Edwards K: Reserachers perspectives on disclosure of incidental findings in genetic research. *J Empir Res Hum Res Ethics* 2010; **5**: 31–41.
- 52 Hailey DM: Health technology assessment in Canada: diversity and evolution. *Med J Aust* 2007; **187**: 286–288.

Supplementary Information accompanies the paper on European Journal of Human Genetics website (<http://www.nature.com/ejhg>)