

# Exploring concordance and discordance for return of incidental findings from clinical sequencing

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**Purpose:** The aim of this study was to explore specific conditions and types of genetic variants that specialists in genetics recommend should be returned as incidental findings in clinical sequencing.

**Methods:** Sixteen specialists in clinical genetics and/or molecular medicine selected variants in 99 common conditions to return to the ordering physician if discovered incidentally through whole-genome sequencing. For most conditions, the specialists independently considered three molecular scenarios for both adults and minor children: a known pathogenic mutation, a truncating variant presumed pathogenic (where other truncating variants are known to be pathogenic), and a missense variant predicted *in silico* to be pathogenic.

**Results:** On average, for adults and children, respectively, each specialist selected 83.5 and 79.0 conditions or genes of 99 in the known

pathogenic mutation categories, 57.0 and 53.5 of 72 in the truncating variant categories, and 33.4 and 29.7 of 72 in the missense variant categories. Concordance in favor of disclosure within the adult/known pathogenic mutation category was 100% for 21 conditions or genes and 80% or higher for 64 conditions or genes.

**Conclusion:** Specialists were highly concordant for the return of findings for 64 conditions or genes if discovered incidentally during whole-exome sequencing or whole-genome sequencing.

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**Key Words:** incidental findings; whole-exome sequencing; whole-genome sequencing

## INTRODUCTION

There is an increasing consensus that whole-exome sequencing (WES) and whole-genome sequencing (WGS) will continue to improve in accuracy and decline in price and that the use of these technologies will eventually become an integral part of clinical medicine.<sup>1-7</sup> Several recent reports have highlighted the use of WES/WGS in the diagnosis or treatment of patients,<sup>8-12</sup> and there is rapid expansion of Clinical Laboratory Improvement Amendments–approved molecular laboratories now providing, or soon planning to provide these services to clinicians.<sup>13-15</sup> One of the greatest impediments to the immediate application of sequence data to clinical medicine relates to whether, and to what degree, molecular laboratories and clinicians should seek

out, interpret, and communicate incidental or secondary (i.e., unrelated to reasons for ordering) genetic findings.

Whatever the clinical indication for WES/WGS, there is considerable potential in each patient to discover large numbers of variants in genes associated with human disease.<sup>16</sup> Currently, there are no guidelines for return of incidental findings from clinical sequencing, although there have been proposals for lower- and higher-risk categories or “bins” based on clinical validity and actionability.<sup>17</sup> Yet no one has asked whether well-meaning specialists would agree upon incidental findings that would be appropriate to disclose. To explore concordance or discordance that such efforts might face, 16 specialists in genetics independently evaluated 99 common genetic conditions and

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individual genes and selected those they would recommend reporting back to the patient's physician as incidental findings after WGS.

## MATERIALS AND METHODS

A list was generated of all diseases for which testing is clinically available as registered on the GeneTests website.<sup>18</sup> Genes associated with the same disease were combined. The top 88 conditions or genes based on the frequency of laboratory testing were supplemented by adding hereditary breast and ovarian cancer, a condition that was not frequent among laboratories due to patented genes, along with a number of common chromosomal conditions and deletion syndromes currently diagnosed through cytogenetic analysis (Table 1).

The 16 participating specialists were clinical geneticists and/or molecular laboratory directors, most of whom have been involved in early uses of genome-scale data, but there was no attempt to be representative or to include all relevant subspecialists. Each specialist was asked to assume that he/she was serving as a consultant to a laboratory that performs clinical WGS and to decide which variants discovered as incidental findings should be returned in a report to the ordering physician. Specialists were asked to assume that family history was not available, that the patient had no previously recognized clinical features consistent with the disease variant under consideration, that the patient's gender was known, and that it was known whether the patient was an adult or a minor child (under 18 years), but not the exact age. Specialists were asked to assume that the sequencing was perfectly accurate and could detect translocations and repeat expansions perfectly, even though this degree of accuracy is not available through current WES/WGS technologies. Details of the consent process, patient preferences regarding results disclosure, and details about how disclosure of results might be handled by the referring physician were not specified. An additional assumption was that family members of the patient being tested would not have been sequenced or genetically tested for the variant under consideration, thus decisions were made on the basis of the genome findings alone without contextualization by patient medical history or family history.

Specialists provided separate responses as to whether incidental findings should be returned to the physicians of adults and of minor children, and where applicable, in each of three categories of variants: a known pathogenic mutation, a truncating variant presumed pathogenic (where other truncating variants were known to be pathogenic), and a missense variant predicted to be deleterious by *in silico* analysis. For recessive conditions or genes, specialists were asked to specify whether they would return a variant even in a carrier state, or only if the patient were found to be biallelic (for autosomal recessive) or hemizygous (for X-linked), or not at all. For repeat-expansion disorders, specialists indicated whether they would return a finding of a premutation or full mutation, only a full mutation, or neither. For each possible scenario per disease (adult/child, pathogenic/truncating/missense), specialists were also asked if

they had difficulty deciding whether to report the variant. Each specialist could decline to respond due to lack of familiarity with the condition or gene. All of the aforementioned choices were made through pull-down, forced-choice menus. For the purposes of this analysis, conditions or genes were counted if the specialist recommended an affirmative response in the dominant disorders or genes, or in any option of the recessive, X-linked, or expansion disorders or genes.

The specialists did not communicate with each other about their decisions. All 16 specialists are listed as coauthors of this paper. One additional coauthor (S.K.) is a genetic counselor who prepared the lists and assisted with data analyses and manuscript preparation, and a second additional coauthor (A.L.M.) is a contributor in ethics and legal issues who participated in data analyses and manuscript preparation.

## RESULTS

Of the 16 specialists who selected conditions, 13 were MDs with or without an additional degree, and 3 were non-MD PhDs; 9 were primarily clinical geneticists, 3 were primarily molecular laboratorians, and 4 were active both clinically and in the molecular laboratory.

The conditions and genes proposed and the number and percentage of specialists who would recommend return of incidental findings based on these are shown in Table 1 (specialist order does not correlate with order of coauthors). For each of the 99 conditions and genes, an average of 13.5 (s.d. 1.9, range 8–16) specialists suggested incidental genetic findings be returned about adults and 12.8 (s.d. 2.3, range 4–16) suggested findings be returned about children if there was a known pathogenic mutation. For each of 72 conditions and genes (excluding trinucleotide repeat-expansion, chromosomal, and deletion conditions, and conditions caused by only a specific known mutation), an average of 12.6 specialists (s.d. 2.3, range 8–16) and 11.9 specialists (s.d. 2.2, range 7–15) suggested that incidental findings of truncating variants be returned about adults and children, respectively. An average of 7.4 specialists (s.d. 1.5, range 4–10) and 6.6 specialists (s.d. 1.7, range 3–9) suggested that incidental findings of a missense variant predicted to be pathogenic by *in silico* analysis be returned about adults and children, respectively. The concordance in favor of disclosure was 100% for 21 conditions or genes in the Adult/Known Pathogenic Mutation category, 80% or higher for 64 conditions or genes, and at least 50% for all conditions or genes.

Concordance was higher for returning incidental information about conditions that had potential for medical intervention (such as cancer predisposition syndromes) than for those without such potential (such as developmental or neurodegenerative disorders). Concordance was also higher when returning incidental findings about adults rather than about children, and for returning known pathogenic mutations and presumed pathogenic truncating variants rather than missense variants predicted to be pathogenic. The total number of genes or conditions selected by each specialist varied along these

**Table 1** Number (%) of specialists selecting each incidental genetic finding for return

Condition/gene	Known mutation		Truncating variant		Missense variant	
	Adult	Child	Adult	Child	Adult	Child
Cancer						
Hereditary breast and ovarian cancer	16 (100.0%)	12 (75.0%)	15 (93.8%)	11 (68.8%)	9 (56.3%)	4 (25.0%)
Li-Fraumeni syndrome	16 (100.0%)	14 (87.5%)	16 (100.0%)	13 (81.3%)	9 (56.3%)	5 (31.3%)
Lynch syndrome	16 (100.0%)	12 (75.0%)	16 (100.0%)	11 (68.8%)	9 (56.3%)	4 (25.0%)
APC-associated polyposis	16 (100.0%)	15 (93.8%)	16 (100.0%)	14 (87.5%)	9 (56.3%)	7 (43.8%)
MYH-associated polyposis	16 (100.0%)	13 (81.3%)	15 (93.8%)	13 (81.3%)	9 (56.3%)	5 (31.3%)
Von Hippel-Lindau disease	16 (100.0%)	16 (100.0%)	16 (100.0%)	15 (93.8%)	10 (62.5%)	7 (43.8%)
<i>MEN 1</i>	16 (100.0%)	15 (93.8%)	16 (100.0%)	14 (87.5%)	9 (56.3%)	7 (43.8%)
<i>MEN 2</i>	16 (100.0%)	15 (93.8%)	15 (93.8%)	13 (81.3%)	9 (56.3%)	7 (43.8%)
PTEN hamartoma tumor syndrome	16 (100.0%)	16 (100.0%)	16 (100.0%)	15 (93.8%)	8 (50.0%)	5 (31.3%)
Neurofibromatosis 1	15 (93.8%)	15 (93.8%)	15 (93.8%)	15 (93.8%)	7 (43.8%)	6 (37.5%)
Retinoblastoma	16 (100.0%)	16 (100.0%)	16 (100.0%)	15 (93.8%)	8 (50.0%)	7 (43.8%)
Metabolic/storage						
MCAD deficiency	15 (93.8%)	15 (93.8%)	14 (87.5%)	14 (87.5%)	9 (56.3%)	8 (50.0%)
Gaucher disease	16 (100.0%)	15 (93.8%)	15 (93.8%)	14 (87.5%)	10 (62.5%)	9 (56.3%)
Tay-Sachs disease	15 (93.8%)	14 (87.5%)	14 (87.5%)	13 (81.3%)	9 (56.3%)	7 (43.8%)
Phenylketonuria	16 (100.0%)	15 (93.8%)	15 (93.8%)	14 (87.5%)	8 (50.0%)	8 (50.0%)
Galactosemia	16 (100.0%)	15 (93.8%)	15 (93.8%)	14 (87.5%)	9 (56.3%)	9 (56.3%)
Niemann-Pick disease	14 (87.5%)	13 (81.3%)	13 (81.3%)	12 (75.0%)	9 (56.3%)	8 (50.0%)
VLCAD deficiency	15 (93.8%)	14 (87.5%)	14 (87.5%)	13 (81.3%)	9 (56.3%)	9 (56.3%)
Homocystinuria	16 (100.0%)	15 (93.8%)	15 (93.8%)	14 (87.5%)	9 (56.3%)	9 (56.3%)
Tyrosinemia type 1	16 (100.0%)	15 (93.8%)	15 (93.8%)	14 (87.5%)	9 (56.3%)	9 (56.3%)
Pompe disease	16 (100.0%)	15 (93.8%)	15 (93.8%)	14 (87.5%)	9 (56.3%)	8 (50.0%)
Familial dysautonomia	13 (81.3%)	13 (81.3%)	12 (75.0%)	12 (75.0%)	8 (50.0%)	8 (50.0%)
Biotinidase deficiency	15 (93.8%)	15 (93.8%)	13 (81.3%)	13 (81.3%)	8 (50.0%)	9 (56.3%)
Isovaleric acidemia	14 (87.5%)	14 (87.5%)	13 (81.3%)	13 (81.3%)	8 (50.0%)	9 (56.3%)
LCHAD deficiency	13 (81.3%)	13 (81.3%)	12 (75.0%)	12 (75.0%)	8 (50.0%)	8 (50.0%)
Glutaric acidemia type 1	14 (87.5%)	14 (87.5%)	13 (81.3%)	13 (81.3%)	8 (50.0%)	8 (50.0%)
Citrullinemia type 1	15 (93.8%)	15 (93.8%)	14 (87.5%)	14 (87.5%)	8 (50.0%)	8 (50.0%)
Wilson disease	16 (100.0%)	15 (93.8%)	15 (93.8%)	14 (87.5%)	10 (62.5%)	9 (56.3%)
CPT II deficiency	15 (93.8%)	15 (93.8%)	13 (81.3%)	13 (81.3%)	8 (50.0%)	9 (56.3%)
Multiple acyl-CoA dehydrogenase deficiency	14 (87.5%)	14 (87.5%)	13 (81.3%)	13 (81.3%)	8 (50.0%)	8 (50.0%)
SCAD deficiency	13 (81.3%)	13 (81.3%)	12 (75.0%)	12 (75.0%)	6 (37.5%)	6 (37.5%)
GSD type 1a	16 (100.0%)	15 (93.8%)	15 (93.8%)	14 (87.5%)	8 (50.0%)	8 (50.0%)
Metachromatic leukodystrophy	13 (81.3%)	13 (81.3%)	12 (75.0%)	12 (75.0%)	8 (50.0%)	7 (43.8%)
MPS type 1	14 (87.5%)	14 (87.5%)	13 (81.3%)	13 (81.3%)	8 (50.0%)	7 (43.8%)
Methylmalonic acidemia	14 (87.5%)	14 (87.5%)	13 (81.3%)	13 (81.3%)	8 (50.0%)	8 (50.0%)
Maple syrup urine disease	15 (93.8%)	15 (93.8%)	14 (87.5%)	14 (87.5%)	8 (50.0%)	8 (50.0%)
Fabry disease	16 (100.0%)	14 (87.5%)	15 (93.8%)	13 (81.3%)	10 (62.5%)	8 (50.0%)
OTC deficiency	15 (93.8%)	15 (93.8%)	14 (87.5%)	14 (87.5%)	8 (50.0%)	8 (50.0%)
Neurological/neuromuscular						
LIS1 lissencephaly	10 (62.5%)	10 (62.5%)	10 (62.5%)	8 (50.0%)	5 (31.3%)	5 (31.3%)
CMT type 1A	13 (81.3%)	11 (68.8%)	N/A	N/A	N/A	N/A

N/A, not applicable.

Table 1 Continued on next page

Table 1 Continued

Condition/gene	Known mutation		Truncating variant		Missense variant	
	Adult	Child	Adult	Child	Adult	Child
CMT type 1B	13 (81.3%)	11 (68.8%)	10 (62.5%)	9 (56.3%)	5 (31.3%)	3 (18.8%)
HNLPP	12 (75.0%)	8 (50.0%)	8 (50.0%)	7 (43.8%)	5 (31.3%)	3 (18.8%)
Early onset primary dystonia	11 (68.8%)	10 (62.5%)	8 (50.0%)	7 (43.8%)	5 (31.3%)	5 (31.3%)
Epileptic encephalopathy infantile 2	9 (56.3%)	9 (56.3%)	8 (50.0%)	7 (43.8%)	5 (31.3%)	5 (31.3%)
Spinal muscular atrophy	13 (81.3%)	13 (81.3%)	10 (62.5%)	9 (56.3%)	7 (43.8%)	5 (31.3%)
Canavan disease	11 (68.8%)	13 (81.3%)	10 (62.5%)	10 (62.5%)	6 (37.5%)	5 (31.3%)
Dystrophinopathies	14 (87.5%)	13 (81.3%)	12 (75.0%)	11 (68.8%)	6 (37.5%)	5 (31.3%)
CMT type X1	12 (75.0%)	11 (68.8%)	10 (62.5%)	9 (56.3%)	5 (31.3%)	3 (18.8%)
ARX-related	11 (68.8%)	10 (62.5%)	N/A	N/A	N/A	N/A
Huntington disease	10 (62.5%)	5 (31.3%)	N/A	N/A	N/A	N/A
Dentatorubral–pallidoluysian atrophy	12 (75.0%)	11 (68.8%)	N/A	N/A	N/A	N/A
Spinal and bulbar muscular atrophy	13 (81.3%)	10 (62.5%)	N/A	N/A	N/A	N/A
SCA types 1, 3, 6, 7	13 (81.3%)	11 (68.8%)	N/A	N/A	N/A	N/A
Myotonic dystrophy type 1	14 (87.5%)	13 (81.3%)	N/A	N/A	N/A	N/A
Friedreich ataxia	12 (75.0%)	13 (81.3%)	N/A	N/A	N/A	N/A
Mitochondrial						
Leber hereditary optic neuropathy	12 (75.0%)	11 (68.8%)	10 (62.5%)	9 (56.3%)	6 (37.5%)	5 (31.3%)
MELAS	12 (75.0%)	12 (75.0%)	9 (56.3%)	9 (56.3%)	4 (25.0%)	4 (25.0%)
MERRF	12 (75.0%)	12 (75.0%)	9 (56.3%)	9 (56.3%)	4 (25.0%)	4 (25.0%)
Leigh syndrome and NARP	12 (75.0%)	12 (75.0%)	10 (62.5%)	10 (62.5%)	5 (31.3%)	5 (31.3%)
Developmental						
Noonan syndrome	12 (75.0%)	12 (75.0%)	11 (68.8%)	11 (68.8%)	5 (31.3%)	5 (31.3%)
Beckwith-Wiedemann syndrome	14 (87.5%)	15 (93.8%)	12 (75.0%)	14 (87.5%)	6 (37.5%)	6 (37.5%)
Sotos syndrome	12 (75.0%)	13 (81.3%)	12 (75.0%)	11 (68.8%)	6 (37.5%)	6 (37.5%)
CHARGE syndrome	12 (75.0%)	13 (81.3%)	12 (75.0%)	11 (68.8%)	6 (37.5%)	6 (37.5%)
MECP2-related disorders	10 (62.5%)	11 (68.8%)	10 (62.5%)	11 (68.8%)	6 (37.5%)	6 (37.5%)
FMR1-related disorders	13 (81.3%)	13 (81.3%)	N/A	N/A	N/A	N/A
Inherited predisposition (noncancer)						
Factor V Leiden thrombophilia	12 (75.0%)	9 (56.3%)	N/A	N/A	N/A	N/A
Prothrombin-related thrombophilia	11 (68.8%)	9 (56.3%)	N/A	N/A	N/A	N/A
Familial hypercholesterolemia	16 (100.0%)	14 (87.5%)	13 (81.3%)	11 (68.8%)	7 (43.8%)	6 (37.5%)
Hereditary hemochromatosis	14 (87.5%)	10 (62.5%)	N/A	N/A	N/A	N/A
MTHFR	9 (56.3%)	8 (50.0%)	N/A	N/A	N/A	N/A
$\alpha$ 1-Antitrypsin deficiency	15 (93.8%)	13 (81.3%)	N/A	N/A	N/A	N/A
Gilbert syndrome	11 (68.8%)	9 (56.3%)	10 (62.5%)	8 (50.0%)	5 (31.3%)	4 (25.0%)
APOE	8 (50.0%)	4 (25.0%)	N/A	N/A	N/A	N/A
Other						
Achondroplasia	12 (75.0%)	12 (75.0%)	N/A	N/A	N/A	N/A
Hypochondroplasia	12 (75.0%)	13 (81.3%)	N/A	N/A	N/A	N/A
Marfan syndrome	15 (93.8%)	15 (93.8%)	13 (81.3%)	13 (81.3%)	7 (43.8%)	7 (43.8%)
Dilated cardiomyopathy	14 (87.5%)	13 (81.3%)	12 (75.0%)	12 (75.0%)	7 (43.8%)	7 (43.8%)
Romano-Ward (long QT syndrome)	16 (100.0%)	16 (100.0%)	14 (87.5%)	14 (87.5%)	7 (43.8%)	7 (43.8%)
DFNA 3 nonsyndromic hearing loss	12 (75.0%)	10 (62.5%)	9 (56.3%)	7 (43.8%)	7 (43.8%)	7 (43.8%)

N/A, not applicable.

Table 1 Continued on next page

Table 1 Continued

Condition/gene	Known mutation		Truncating variant		Missense variant	
	Adult	Child	Adult	Child	Adult	Child
DFNB 1 nonsyndromic hearing loss	13 (81.3%)	11 (68.8%)	10 (62.5%)	8 (50.0%)	8 (50.0%)	7 (43.8%)
CFTR-related disorders	15 (93.8%)	14 (87.5%)	13 (81.3%)	12 (75.0%)	8 (50.0%)	7 (43.8%)
Familial Mediterranean fever	15 (93.8%)	14 (87.5%)	11 (68.8%)	10 (62.5%)	8 (50.0%)	7 (43.8%)
$\beta$ -Thalassemia	14 (87.5%)	13 (81.3%)	12 (75.0%)	11 (68.8%)	7 (43.8%)	6 (37.5%)
Hemoglobin SS	14 (87.5%)	13 (81.3%)	N/A	N/A	N/A	N/A
Bloom syndrome	14 (87.5%)	15 (93.8%)	13 (81.3%)	13 (81.3%)	7 (43.8%)	6 (37.5%)
Fanconi anemia ( <i>FANCC</i> -related)	15 (93.8%)	15 (93.8%)	12 (75.0%)	12 (75.0%)	7 (43.8%)	5 (31.3%)
Kallmann syndrome 1	12 (75.0%)	12 (75.0%)	10 (62.5%)	10 (62.5%)	7 (43.8%)	7 (43.8%)
Ichthyosis, X-linked	13 (81.3%)	13 (81.3%)	11 (68.8%)	11 (68.8%)	7 (43.8%)	7 (43.8%)
Could reveal unexpected chromosomal sex						
46,XX testicular DSD	12 (75.0%)	12 (75.0%)	N/A	N/A	N/A	N/A
Congenital adrenal hyperplasia	14 (87.5%)	15 (93.8%)	11 (68.8%)	12 (75.0%)	7 (43.8%)	7 (43.8%)
Androgen insensitivity syndrome	13 (81.3%)	13 (81.3%)	11 (68.8%)	11 (68.8%)	7 (43.8%)	8 (50.0%)
46,XY DSD and 46,XY CGD	11 (68.8%)	12 (75.0%)	N/A	N/A	N/A	N/A
Other chromosomal or deletion syndromes						
Turner syndrome	12 (75.0%)	13 (81.3%)	N/A	N/A	N/A	N/A
Turner mosaic syndrome	12 (75.0%)	13 (81.3%)	N/A	N/A	N/A	N/A
Klinefelter syndrome	12 (75.0%)	13 (81.3%)	N/A	N/A	N/A	N/A
47,XYY syndrome	12 (75.0%)	12 (75.0%)	N/A	N/A	N/A	N/A
Y-chromosome deletion	12 (75.0%)	8 (50.0%)	N/A	N/A	N/A	N/A
22q11.2 deletion	13 (81.3%)	14 (87.5%)	N/A	N/A	N/A	N/A
Wolf-Hirschhorn syndrome	12 (75.0%)	13 (81.3%)	N/A	N/A	N/A	N/A

N/A, not applicable.

axes (**Supplementary Table S1** online and **Supplementary Figure S1** online) whereas the discomfort that specialists felt in making the decision varied inversely along the same axes (**Supplementary Table S2** online).

## DISCUSSION

This report presents an exploratory description of concordance and discordance around specific conditions and genes with respect to incidental findings in the context of clinical WGS/WES. There were 21 conditions or genes in which all 16 specialists agreed that known pathogenic mutations should be disclosed if found incidentally in adults, and 4 conditions for which all 16 specialists agreed that known pathogenic mutations should be disclosed if found incidentally in minor children (**Supplementary Table S3** online). There was considerable concordance among all 99 conditions or genes for known pathogenic mutations, with a majority of specialists selecting nearly every condition or gene for return as an incidental finding.

Substantial discordance was observed across two major domains. First, some specialists were more reluctant than others to disclose incidental findings. For example, even within the category of adult/known pathogenic mutations, one specialist reported that he or she would recommend disclosure of only 30.3% of the identified genes or conditions, whereas

two others thought 100% should be disclosed. Second, there was discordance in judgments about the relative value of different criteria when making decisions about disclosures. For some, whether the result pertained to a child or an adult seemed to be the most relevant factor driving the decision to disclose, whereas for others, the established pathogenicity of the variant was the most important factor. These criteria also influenced whether contributors found a particular decision to be difficult. Additional research is needed to better understand the source of this discordance; for example, whether it reflects primarily differences in clinical or ethical judgment or, in the case of the potential pathogenicity of variants, whether specialists were fully aware of the limited accuracy of *in silico* prediction tools for missense variants.

These data have a number of limitations. The specialists were not representative and were of varying degrees of expertise. Each specialist responded independently and without interaction that would characterize formal consensus building. Specialists were asked to assume that no information was available about family history or knowledge of signs or symptoms in relatives of the proband, which is a somewhat artificial situation.

The degree of discordance observed suggests that whether considering incidental findings in research subjects or incidental findings in clinical WES/WGS, it may be difficult to reach



consensus on a specific list of variants that meet a threshold for disclosure, as called for in various consensus statements on incidental findings. However, in an actual consensus group, experts on a subset of disorders would educate the rest of the group and likely increase concordance. Plans that attempt to factor in subject or patient preferences (which were excluded in this exercise) could make consensus easier or more difficult. In this exercise, the choice was whether to provide such information in a report to the ordering physician, not to the patient. This may have provided comfort to the specialists who were wavering because the ordering physician would have the ability to seek preferences from the patient about how much information to share, as well as the ability to contextualize the report by integrating personal medical history, family history, symptoms and signs, or by referring the patient. The variability in responses surrounding issues for which consensus has already been achieved and published (such as the unreliability of *in silico* prediction of variant significance) also highlights the need for greater education, even among specialists, as well as the need for extensively curated clinical-grade databases.

In summary, there was considerable concordance and considerable discordance in choices about return of incidental genomic information among specialists queried for this report. The variability in responses suggests that a relatively small panel of specialists is unlikely to embody all of the necessary expertise to achieve consensus about the vast number of genetic variants that will be identified by WES/WGS, especially if additional variants are considered that are less well characterized than those we selected. Modifications to a typical consensus approach may need to be considered, such as collaboration among multiple expert panels, with each panel being composed of specialists in a more narrow focus of expertise. It appears that even genetic specialists are a heterogeneous group and may not be yet fully prepared to deal with the implementation of new genetic technologies.

## SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/gim>

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## DISCLOSURE

The authors declare no conflict of interest.

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