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# Association of researcher characteristics with views on return of incidental findings from genomic research

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## Abstract

Whole exome/genome sequencing (WES/WGS) is now commonly used in research and is increasingly used in clinical care to identify the genetic basis of rare and unknown diseases. The management of incidental findings (IFs) generated through these analyses is debated within the research community. To examine how views regarding genomic research IFs are associated with researcher characteristics and experiences, we surveyed genetic professionals and assessed the effect of professional background and experience on their opinions. Researchers who did not have clinical training, provide clinical care to research participants, or have prior experience returning research results were in general more inclined to offer return of IFs than their colleagues with these characteristics. Understanding this will be important to fully appreciate the impact that policies on return of genetic IFs could have on participants, researchers, and genomic research.

### Keywords

genetics research; genomics; genomic results; incidental findings; return of results; secondary findings; whole exome sequencing

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**Conflict of Interest Statement**

Julia Wynn, Josue Martinez, Jimmy Duong, Yuan Zhang, Jo Phelan, Abby Fyer, Robert Klitzman, Paul S. Appelbaum and Wendy K. Chung declare that they have no conflict of interest

**Informed Consent: For studies with human subjects**

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2000 (5). Informed consent was obtained from all subjects for being included in the study.

## Introduction

Whole exome/genome sequencing (WES/WGS) is now commonly used in research and is increasingly used in clinical care to identify the genetic basis of rare and unknown diseases (Bainbridge et al., 2011; Need et al., 2012). Because of the comprehensive nature of WES/WGS, it has the possibility of identifying incidental findings—i.e., genetic variants or mutations unrelated to the disease of interest (Cassa et al., 2012; Kohane, Masys, & Altman, 2006; Wolf et al., 2008). Whether and which incidental findings should be returned to research participants is now being debated within the genetics community (Green et al., 2012; Jewell, 2012; Klitzman et al., 2013; Lemke, Bick, Dimmock, Simpson, & Veith, 2013; Lohn, Adam, Birch, Townsend, & Friedman, 2013; Townsend et al., 2012), in part stimulated by the release of the ACMG guidelines mandating return of results from 56 genes for all patients receiving clinical WES/WGS (Green, Berg, et al., 2013). Concerns expressed about these guidelines include limitations on patient autonomy, conflict with previous guidelines for genetic testing in children, and availability of well-curated mutation databases to interpret results (Klitzman et al., 2013; Ross, Rothstein, & Clayton, 2013). However, supporters of the guidelines contend that genetic IFs are similar to IFs in other areas of medicine, including radiology, are inherent to the practice of medicine, and should similarly be returned (Green, Lupski, & Biesecker, 2013). The guidelines have since been modified to allow patients to opt out of receiving particular results (American College of Medical & Genomics, 2013), but the discussion in the field continues.

The Presidential Commission for the Study of Bioethical Issues recently released recommendations for the management of IFs generated from clinical, research and direct-to-consumer testing. (Presidential Commission, 2013). This report provides useful guidelines for IFs generated in many contexts but does not address the obstacles specific to research IFs. Many of the arguments for and against returning IFs generated through clinical testing can be applied to the return of IFs from research but there are additional considerations in a research setting. These include the need for clinical confirmation of research findings, the dilemma of how to manage IFs for research participants who had not previously consented to return of IFs, re-identifying samples from biorepositories, and the frequent unavailability of an infrastructure and funding to support disclosure of results (Appelbaum et al., 2013; Jewell, 2012; Johnson, Lawrenz, & Thao, 2012; Klitzman et al., 2013; National Heart et al., 2010; Wolf et al., 2008).

There are numerous stakeholders in the genomic research community with varying views on return of genetic IFs (Jarvik et al., 2014; Meacham, Starks, Burke, & Edwards, 2010). We previously reported our survey of the opinions of genetic researchers regarding return of research-derived IFs, with the majority (95%) of respondents endorsing returning IFs to research participants for highly penetrant disorders with immediate medical implications (Klitzman et al., 2013). There was less consensus about return of other types of IFs, such as those that incur a moderate risk of disease, or about returning IFs from the sequencing of minors and fetal samples (Klitzman et al., 2013). Other surveys of researchers have also demonstrated support for returning or the option of returning IFs ((Jarvik et al., 2014; Meacham et al., 2010; Williams et al., 2012)

This paper examines how views regarding genomic research IFs are associated with researcher characteristics and experiences for this diverse cohort of researchers. Several studies have started to identify different opinions regarding genomic IFs in different stakeholders. Williams et al. (2012) surveyed researchers and institutional review board (IRB) chairs and found agreement on topics that need to be considered before offering return of IFs, including medical importance of the IF, participant preference, test validity and personnel to disclose results. They also found that while researchers did not express a need for IRB-generated disclosure policies except in rare cases, IRB chairs indicated a need for consistent policies for the return of IFs and emphasized the importance of anticipating and planning for IFs in the consent process. Meacham et al. (2010) interviewed researchers regarding disclosure of research IFs and found support for return of IFs with considerable variety of approaches and considerations. They discussed concern for patient wellbeing, scientific validity of the IFs and adherence to IRB rules. Both of these studies demonstrate a lack of consensus within the research community and the need for further investigation.

In this study, survey respondents were intentionally heterogeneous in their training and their roles in research. Some had clinical training while others did not, and there was similar diversity with regard to whether respondents had direct interaction with research participants. Some played dual roles as both the participants' clinical providers and researchers, while others had no clinical relationship with the participants. Survey respondents also varied in the number of years they had been conducting research and the patient populations they studied. A small percentage had experience returning research-related results or research IFs to participants. We explored the impact of these diverse backgrounds on researchers' opinions..

## Materials and Methods

### Participants

We identified 787 genetic researchers by: 1) searching the NIH online RePORTER database for principal and co-principal investigators of currently funded grants using combinations of key words (e.g., human genetics, human genomics, genetic epidemiology, exome sequencing, whole genome sequencing, genome-wide association); and 2) applying similar criteria to the abstracts from the 2011 American Society of Human Genetics meeting. Only investigators whose research focus was human disease gene identification were included. Email addresses for 734 researchers were identified using online resources. Individuals outside the USA and for whom no email address was found were excluded. A total of 734 researchers received an invitation to the study and 241 (33%) responded to 50% or more of the survey questions

### Instruments

The survey included fixed-response questions and opportunities to enter free-text comments. Questions and response options are shown in Tables I to III. The survey was composed of 25 questions that assessed researchers' characteristics and 31 questions on opinions regarding genomic research IFs. Content was based on a literature review and phone interviews with researchers, and was designed to elicit attitudes and experiences. It was reviewed by 6

researchers, 2 genetic counselors, and 2 research coordinators, with subsequent revisions, and was piloted with 10 researchers. It took 20 minutes to complete. This paper reports the results from 10 questions on returning specific types of IFs to specific populations as related to the researchers' characteristics.

### Procedures

Researchers eligible for the survey were contacted by email to solicit their participation. They were invited to click on a link where they viewed an informed consent disclosure. Email reminders were sent twice to non-respondents. Respondents were offered a $25 gift certificate for participation, and could skip any questions they did not wish to answer. The survey was conducted between August and October 2012. The study was approved by the IRBs of Columbia University Medical Center and the New York State Psychiatric Institute.

### Data Analysis

We analyzed the association of researchers' opinions regarding IFs and their training and characteristics as researchers. Based on their responses to survey questions, researchers were dichotomized with regard to gender, clinical training, provision of clinical care to research participants, amount of research experience (< or > 6 years of research experience), whether they had returned genetic research results, whether they had returned genetic research IFs, and whether they studied children. Researchers with clinical training were defined as those with an MD degree, regardless of the other degrees they held.

Associations between selected researcher characteristics and their survey responses were analyzed with chi squared, Fisher exact tests, and logistic regression models estimated using generalized estimating equations (GEEs) to adjust for within-subject correlation. A p-value of $< 0.05$ was considered statistically significant.

## Results

A detailed description of the 241 respondents has previously been published (Klitzman et al., 2013). Briefly, 64% were male, 34% had clinical training, 22% provided clinical care, 51% had greater than 6 years of research experience, 28% had returned research results, 12% had returned research IFs and 57% had studied children.

### Overall views on IFs (Table I)

There was near consensus among researchers, regardless of their previous experiences and characteristics, that research participants should be offered the option of receiving IFs. There were no significant differences in responses of researchers dichotomized by clinical training, provision of clinical care to research participants, whether they had returned genetic research results, whether they had returned genetic research IFs, whether they studied children, and gender. The exception was researchers with greater than 6 years of research experience, who were less likely to endorse offering IFs than their colleagues with 6 or fewer years of experience (75% and 88% respectively, p=0.04). There was less consensus and more uncertainty in the responses when researchers were asked about returning IFs from

sequencing of children or fetuses, though again there were no significant differences by researcher characteristics.

### Clinical experience and views on IFs (Table II)

The views of those researchers who endorsed or were uncertain about giving participants the option of receiving IFs were examined in more detail to determine whether there were differences based on clinical experience and clinical role. Responses regarding the return of specific categories of IFs varied depending on the clinical experience of the researcher and age of the participant. Researchers without clinical training were more likely to respond that they would offer to return IFs of high penetrance without available clinical intervention as compared to their colleagues with clinical training (65% vs. 51%, p=0.03). Researchers who had no clinical training or did not provide clinical care to participants were more likely to offer to return a complete list of variants from the entire genome/exome (20% vs. 7% p=0.01 and 19% vs. 6%, p=0.02).

Responses also correlated with researchers' clinical experience when we examined views on returning IFs from sequencing of children. Researchers with clinical training were less likely to support offering most types of IFs from the sequencing of minors, including results related to conditions of high or moderate penetrance without clinical intervention, conditions with reproductive implications, variants of no clinical significance, pharmacogenetic variants, and a complete list of variants. When all categories of IFs were analyzed together, researchers with clinical training were significantly less likely to endorse offering to return IFs of minors than researchers without clinical training (OR=0.62, CI=0.47–0.82, p<0.01). Similarly, researchers who provide clinical care to research participants were significantly less likely to favor returning IFs of minors than those who did not provide clinical care (OR=0.71, CI=0.52–0.96, p=0.03).

Finally, when examining researchers' responses to whether different types of IFs should be returned to participants when fetal samples are studied, there were few differences in opinions related to researchers' characteristics. Researchers without clinical training were more likely to offer to return a complete list of all variants from the entire genome/exome in fetal research than their colleagues with clinical training (17% vs. 3%, p<0.01). Researchers who provided clinical care to their research participants were more likely to offer to return IFs from fetal sequencing that were of modest penetrance and had available clinical interventions (60% vs. 43%, p=0.05).

### Experience returning research results and views on IFs (Table III)

Researchers' experience returning research results or research IFs to participants were not observed to be associated with their views on returning specific categories of IFs. When all categories of IFs were analyzed together, researchers who had experience returning genomic research results were significantly less likely to offer to return IFs from sequencing of minors than researchers who had not had experience returning research results (OR=0.72, CI:0.53–0.99, p=0.04). Researchers who had experience returning research IFs to participants were more likely to offer to return IFs from sequencing of fetal samples for IFs of high or modest penetrance with available clinical interventions and for pharmacogenetic

variants. When IFs were examined in aggregate, researchers with experience returning IFs were 1.9 times more likely to endorse returning IFs from fetal testing (CI:1.14–3.17, p=0.01).

### Other researcher characteristics and views on IFs

Overall, there were few differences in response about whether to return IFs to research participants when other characteristics of researchers were examined, including whether the researcher studied children and the gender and years of experience of the researcher. There were no differences in responses for any categories of IFs when examined by whether the researcher studied children. Male researchers responded that they would be more likely to offer to return a complete list of variants from the entire genome/exome to research participants than female researchers (19% vs. 9%, p=0.04), but there were no other differences when views were examined by gender (data not shown). Finally when all categories were analyzed together, researchers with < 6 years of experience were 1.27 (CI: 1.01–1.59, p=0.04) times as likely to return IFs to participants and 1.37 (CI: 1.04–1.08, p=0.02) times as likely to return results from the sequencing of minors than their colleagues with ≥ 6 years of experience (data not shown).

## Discussion

We surveyed genetic researchers' opinions on returning IFs to research participants and examined whether there were differences in responses based on clinical background, research involvement, and demographic characteristics. When researchers were asked the broad questions of "should participants be given the option of deciding whether they want IFs returned," "should IFs ever be returned when children are the subjects of genomic research," and "would you return IFs from findings of testing being done on a fetus" there was little difference in responses based on the researchers' experience or personal characteristics. However, differences in views emerged with regard to return of specific categories of IFs.

When examining specific categories of IFs, researchers without clinical training and without responsibilities for the clinical care of research participants tended more frequently to endorse returning IFs across multiple categories of IFs and ages of research participants, including return of a complete list of variants from the entire genome/exome. These differences may have been influenced by variation in the researcher's appreciation of the clinical and psychological impact of IFs, ability to gauge the clinical utility of genomic information, and concerns for legal liability if results were not returned—all factors that previously have been documented to affect attitudes on these issues (Clayton & McGuire, 2012; Grove, Wolpert, Cho, Lee, & Ormond, 2013; Klitzman et al., 2013; Lohn et al., 2013; Townsend et al., 2012). The different views may also be related to fundamental differences in opinions about how much access research participants should have to their genomic information and researchers' obligations to research participants, which have also been debated in this community (Miller, Mello, & Joffe, 2008; Townsend et al., 2012).

Greater caution among researchers with clinical training may be based on a higher level of concern regarding negative effects on participants—especially children—whom they may be

more likely to see through a clinical lens. Previous studies have also identified concerns raised by researchers and genetic professionals about the ability of participants to access qualified individuals to interpret returned data and provide appropriate counseling (Grove et al., 2013; Klitzman et al., 2013; Townsend et al., 2012). Researchers who provide clinical care may be especially attuned to these limitations and have greater concern that participants could incorrectly interpret complex genomic information, leading to unnecessary anxiety, inappropriate medical interventions or non-adherence to health maintenance guidelines (e.g., if participants incorrectly interpreted negative results to mean they were not at risk to develop a particular disease).

Some of the most significant differences in responses were observed when researchers were asked about returning results from sequencing of minors. When all categories of IFs were examined together, both researchers without clinical training and those who did not provide clinical care to participants were more likely to endorse returning IFs than their colleagues with these experiences. The possibility of returning IFs from minors has generated considerable debate. The clinical guidelines of the American Academy of Pediatrics and American College of Medical Genetics on predictive genetic testing for minors discourage return of data regarding adult-onset conditions to allow pediatric patients to make decisions for themselves when they reach adulthood (Committee on Bioethics et al., 2013; Ross et al., 2013). Researchers providing clinical care may be more aware of or might place greater weight on these guidelines; other researchers may be more concerned about the possible implications for the child's parents and for their subsequent reproductive choices.

A modest proportion of the researchers surveyed had returned research results or IFs to research participants. In general, these researchers were less inclined to return IFs. This tendency was statistically significant when considering IFs from sequencing of minors. The exception to this trend was that researchers who had experience returning IFs were more likely to support returning IFs from fetal research. As a result of their experience, these researchers may have been more appreciative of the implications of returning this information for pregnancy management, future reproductive options, and the health of the parents.

## Practice Implications

These findings highlight, too, needs for enhanced education regarding these concerns among researchers, their staffs, and patients. In the future, a wide variety of researchers may be in the position to return results to subjects, and may range widely in their understanding of and comfort about the issues involved. Although some of these researchers will have had clinical training and prior experience returning results, others may have had neither. The availability of experienced geneticists and genetic counselors for interpretation and communication of the data will be especially important to these studies. All genomic investigators will need to consider these issues in advance and assemble an appropriate team of professionals to interpret the data and convey their implications to participants. Genetic counselors' unique perspective on these issues will be integral in developing policies and guidelines for genomic research studies.

### Limitations

Among the limitations to this study is that researchers were dichotomized based on a limited array of questions regarding background, role, and personal characteristics. These responses may not reflect all relevant characteristics and experiences of researchers that could influence their decisions about offering to return IFs. In addition, we are limited in our ability to identify the reasons for the differences we identified; additional studies will be required for a more complete understanding of the basis for our subjects' responses.

### Conclusion and Research Recommendation

Researchers are significant stakeholders in determining policies regarding management of IFs from genomic research, since they will be the ones to implement the policies that are ultimately developed. Our results demonstrate that researchers' training and prior experience with returning genetic research results are correlated with their views on how research IFs should be managed. The associations we identified between researchers with greater clinical experience and/or experience returning IFs and less support for returning research IFs suggest a degree of caution in formulating policies for return of IFs. These findings also suggest the need for additional research to understand the basis for these attitudes and their relationship to the impact that policies on return of genetic research IFs could have on participants, researchers, and genomic research.

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**Table I**

nces of whether genetic IFs should be returned research participants, returned when samples from a child are
m a fetus are studied.

| training | | Provide clinical care to research | Do not provide clinical care to | | Returned results related to research | Not returned results related to | | Has returned research IFs | Has not returned research IFs | | Study children | Do not study children | | Male | Female | | < 6 years experience | ≥ 6 years experience | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n=160 | p-value | n=53 | n=188 | p-value | n=68 | n=157 | p-value | n=30 | n=192 | p-value | n=137 | n=103 | p-value | n=155 | n=86 | p-value | n=122 | n=119 | p-value |
| 82% | 0.52 | 83% | 81% | 0.94 | 82% | 80% | 0.86 | 87% | 80% | 0.66 | 82% | 81% | 0.52 | 81% | 81% | 0.16 | 88% | 75% | **0.04** |
| 3% | | 4% | 4% | | 4% | 4% | | 3% | 4% | | 3% | 6% | | 6% | 1% | | 2% | 6% | |
| 15% | | 13% | 15% | | 13% | 16% | | 10% | 16% | | 15% | 14% | | 13% | 17% | | 10% | 19% | |
| n=160 | p-value | n=52 | n=183 | p-value | n=66 | n=153 | p-value | n=30 | n=186 | p-value | n=133 | n=101 | p-value | n=150 | n=85 | p-value | n=120 | n=119 | p-value |
| 63% | 0.72 | 63% | 62% | 0.73 | 71% | 58% | 0.14 | 80% | 59% | 0.07 | 67% | 56% | 0.21 | 62% | 62% | 0.43 | 66% | 58% | 0.49 |
| 13% | | 10% | 14% | | 12% | 13% | | 10% | 13% | | 10% | 16% | | 15% | 9% | | 12% | 14% | |
| 24% | | 27% | 25% | | 17% | 29% | | 10% | 28% | | 23% | 28% | | 23% | 28% | | 23% | 28% | |
| n=160 | p-value | n=52 | n=183 | p-value | n=66 | n=153 | p-value | n=30 | n=186 | p-value | n=133 | n=101 | p-value | n=150 | n=85 | p-value | n=120 | n=119 | p-value |
| 51% | 0.16 | 40% | 49% | 0.35 | 48% | 44% | 0.15 | 57% | 44% | 0.42 | 47% | 49% | 0.42 | 46% | 49% | 0.70 | 50% | 44% | 0.61 |
| 16% | | 25% | 17% | | 24% | 16% | | 17% | 19% | | 17% | 22% | | 18% | 20% | | 17% | 21% | |
| 33% | | 35% | 34% | | 27% | 40% | | 27% | 37% | | 37% | 30% | | 36% | 31% | | 33% | 35% | |

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**Table II**

Percentage of researchers with different clinical experiences who indicated categories of IFs should be offered to research participants of different ages. Only researchers who responded yes or uncertain in Table 1 are included in this analysis. Logistic regression analysis of all categories is shown with odds ratio (OR) and upper and lower confidence intervals (CI).

| | With clinical training | Without clinical training | | Provide clinical care to research participants | Do not provide clinical care to research participants | |
|---|---|---|---|---|---|---|
| **If you were going to return IFs, which of the following would you consider offering?** | n=81 | n=160 | p-value* | n=53 | n=188 | p-value* |
| High penetrance, without clinical intervention | 51% | 65% | **0.03** | 53% | 62% | 0.22 |
| High penetrance, with clinical intervention | 98% | 94% | 0.20 | 94% | 95% | 0.73 |
| Modest penetrance, without clinical intervention | 37% | 43% | 0.41 | 42% | 40% | 0.89 |
| Modest penetrance, with clinical intervention | 81% | 78% | 0.54 | 87% | 77% | 0.13 |
| Reproductive implications for prospective parents | 78% | 80% | 0.69 | 79% | 79% | 1.00 |
| Reproductive implications for children of participants | 60% | 68% | 0.24 | 66% | 65% | 0.93 |
| Potentially relevant, no clinical implications (ancestry) | 16% | 24% | 0.17 | 13% | 23% | 0.11 |
| Data on pharmacogenetic variants | 48% | 58% | 0.17 | 45% | 57% | 0.13 |
| List of all variants from entire genome/exome | 7% | 20% | **0.01** | 6% | 19% | **0.02** |
| **Logistic regression analysis of all categories** | **OR** | **Lower CI** | **Upper CI** | **p value** | **OR** | **Lower** | **Upper CI** | **p value** |
| | 0.82 | 0.64 | 1.04 | 0.10 | 0.87 | 0.66 | 1.15 | 0.33 |
| **When subjects are children, which of the following do you think should be offered?** | n=71 | n=140 | p-value* | n=48 | n=163 | p-value* |
| High penetrance and clinically actionable before adulthood | 93% | 89% | 0.39 | 90% | 91% | 0.78 |
| High penetrance and actionable only in adulthood | 62% | 71% | 0.20 | 65% | 69% | 0.59 |
| High penetrance, without clinical intervention | 35% | 58% | **<0.01** | 42% | 53% | 0.18 |

| | With clinical training | Without clinical training | | Provide clinical care to research participants | Do not provide clinical care to research participants | |
|---|---|---|---|---|---|---|
| Modest penetrance, without clinical intervention | 21% | 39% | **0.01** | 25% | 35% | 0.20 |
| Reproductive implications for prospective parents | 48% | 67% | **<0.01** | 48% | 64% | **0.04** |
| Data on pharmacogenetic variants | 42% | 59% | **0.02** | 42% | 56% | 0.07 |
| Potentially relevant, no clinical implications (ancestry) | 11% | 24% | **0.03** | 13% | 21% | 0.17 |
| List of all variants from entire genome/exome | 7% | 20% | **0.01** | 8% | 18% | 0.11 |
| **Logistic regression analysis of all categories** | **OR** | **Lower CI** | **Upper CI** | **p value** | **OR** | **Lower** | **Upper CI** | **p value** |
| | 0.62 | 0.47 | 0.82 | **<0.01** | 0.71 | 0.52 | 0.96 | 0.03 |
| **If you would return IFs from testing being done on a fetus, what would you return?** | | n=62 | n=135 | p-value* | | n=40 | n=157 | p-value* |
| High penetrance, with clinical intervention | | 60% | 60% | 0.97 | | 65% | 59% | 0.46 |
| High penetrance, without clinical intervention | | 40% | 52% | 0.13 | | 45% | 49% | 0.65 |
| Modest penetrance, with clinical intervention | | 48% | 45% | 0.68 | | 60% | 43% | **0.05** |
| Modest penetrance, without clinical intervention | | 21% | 27% | 0.39 | | 23% | 25% | 0.70 |
| Reproductive implications for the fetus | | 37% | 41% | 0.56 | | 43% | 39% | 0.73 |
| Data on pharmacogenetic variants | | 24% | 34% | 0.16 | | 23% | 33% | 0.19 |
| Potentially relevant, no clinical implications (ancestry) | | 13% | 22% | 0.12 | | 20% | 19% | 0.90 |
| List of all variants from entire genome/exome | | 3% | 17% | **<0.01** | | 5% | 15% | 0.10 |
| **Logistic regression analysis of all categories** | **OR** | **Lower CI** | **Upper CI** | **p value** | **OR** | **Lower** | **Upper CI** | **p value** |
| | 0.78 | 0.52 | 1.17 | 0.23 | 1.00 | 0.65 | 1.55 | 0.99 |

*chi square analysis and Fisher exact tests

**Table III**

Percentage of researchers with and without experience returning research results who re who indicated different categories of IFs should be offered to research participants of different ages. Only researchers who responded yes or uncertain in Table 1 are included in this analysis. Logistic regression analysis of all categories is shown with odds ratio (OR) and upper and lower confidence intervals (CI). odds ratio (OR) and upper and lower confidence intervals (CI).

| | Returned results related to research | Not returned results related | | Has returned research IFs | Has not returned research IFs | |
|---|---|---|---|---|---|---|
| **If you were going to return IFs, which of the following would you consider offering?** | n=68 | n=157 | p-value* | n=30 | n=192 | p-value* |
| High penetrance, without clinical intervention | 56% | 61% | 0.46 | 47% | 62% | 0.11 |
| High penetrance, with clinical intervention | 100% | 94% | 0.29 | 97% | 95% | 0.66 |
| Modest penetrance, without clinical intervention | 43% | 38% | 0.53 | 37% | 41% | 0.68 |
| Modest penetrance, with clinical intervention | 82% | 76% | 0.28 | 87% | 78% | 0.26 |
| Reproductive implications for prospective parents | 72% | 81% | 0.14 | 77% | 79% | 0.76 |
| Reproductive implications for children of participants | 59% | 66% | 0.29 | 63% | 65% | 0.89 |
| Potentially relevant, no clinical implications (ancestry) | 15% | 24% | 0.11 | 17% | 22% | 0.48 |
| Data on pharmacogenetic variants | 49% | 57% | 0.22 | 60% | 54% | 0.52 |
| List of all variants from entire genome/exome | 12% | 18% | 0.25 | 17% | 15% | 0.83 |
| **Logistic regression analysis of all categories** | **OR** | **Lower CI** | **Upper CI** | **p value** | **OR** | **Lower CI** | **Upper CI** | **p value** |
| | 0.88 | 0.68 | 1.14 | 0.33 | 0.96 | 0.66 | 1.40 | 0.83 |
| **When subjects are children, which of the following do you think should be offered?** | | n=137 | p-value* | | n=27 | n=167 | p-value* |
| High penetrance and clinically actionable before adulthood | 90% | 90% | 0.96 | 96% | 89% | 0.25 |
| High penetrance and actionable only in adulthood | 62% | 69% | 0.34 | 78% | 66% | 0.22 |
| High penetrance, without clinical intervention | 38% | 51% | 0.10 | 41% | 49% | 0.42 |

| | Returned results related to research | Not returned results related | | Has returned research IFs | Has not returned research IFs | |
|---|---|---|---|---|---|---|
| Modest penetrance, without clinical intervention | 22% | 34% | 0.09 | 26% | 32% | 0.54 |
| Reproductive implications for prospective parents | 52% | 62% | 0.17 | 59% | 60% | 0.90 |
| Data on pharmacogenetic variants | 42% | 58% | **0.03** | 59% | 53% | 0.53 |
| Potentially relevant, no clinical implications (ancestry) | 12% | 23% | 0.07 | 19% | 20% | 0.82 |
| List of all variants from entire genome/exome | 15% | 16% | 0.85 | 19% | 14% | 0.58 |
| **Logistic regression analysis of all categories** | **OR** | **Lower CI** | **Upper CI** | **p value** | **OR** | **Lower CI** | **Upper CI** | **p value** |
| | 0.72 | 0.53 | 0.99 | **0.04** | 1.05 | 0.70 | 1.57 | 0.83 |
| **If you would return IFs from testing being done on a fetus, what would you return?** | n=52 | n=132 | p-value* | | n=25 | n=157 | p-value* | |
| High penetrance, with clinical intervention | 65% | 55% | 0.18 | | 80% | 55% | **0.02** | |
| High penetrance, without clinical intervention | 44% | 46% | 0.81 | | 64% | 44% | 0.06 | |
| Modest penetrance, with clinical intervention | 50% | 42% | 0.31 | | 72% | 41% | **<0.01** | |
| Modest penetrance, without clinical intervention | 21% | 23% | 0.82 | | 32% | 22% | 0.25 | |
| Reproductive implications for the fetus | 33% | 39% | 0.45 | | 52% | 36% | 0.13 | |
| Data on pharmacogenetic variants | 25% | 32% | 0.36 | | 48% | 27% | **0.03** | |
| Potentially relevant, no clinical implications (ancestry) | 17% | 17% | 0.99 | | 20% | 17% | 0.73 | |
| List of all variants from entire genome/exome | 8% | 14% | 0.22 | | 16% | 11% | 0.52 | |
| **Logistic regression analysis of all categories** | **OR** | **Lower CI** | **Upper CI** | **p value** | **OR** | **Lower CI** | **Upper CI** | **p value** |
| | 0.98 | 0.64 | 1.51 | 0.94 | 1.9 | 1.14 | 3.17 | **0.01** |

*chi square analysis and Fisher exact tests