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Exome sequencing study in a clinical research setting finds general acceptance of study returning secondary genomic findings with little decisional conflict

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Abstract

The most appropriate strategies for managing secondary genomic findings (SF) in clinical research are being developed and evaluated. We surveyed patients at the National Institute of Allergy and Infectious Diseases (NIAID) to evaluate decisional conflict regarding enrolling in a study that returns SF. Responses were collected using a cross-sectional survey after informed consent but before return of SF. Sixty-six adults of 116 eligible participants responded. No participant explicitly declined because they did not want to possibly receive a SF. Sixty-five of 66 (98%) participants thought it was appropriate to return SFs in research; one participant was unsure. Decisional conflict regarding enrolling in a study returning SF was low overall with 68% of participants reporting a score of less than 10 on a 100-point decisional conflict scale, implying that they felt informed, clear on what they wanted, and supported. Lower genetic literacy was weakly associated with higher decisional conflict (Spearman's rho = −0.297, $p = 0.015$). Six participants reported confusion related to the choices about SFs. Our data suggest that participants in our study feel it is appropriate to receive SF and have little decisional conflict about potentially receiving such information; however, some participants may need further education and counseling.

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Authorship Contributions:

Morgan Similuk, Jia Yan, Michael Setzer, Leila Jamal, Patty Little, Helen Su, and Michael Lenardo all made substantial contributions to the work, as outlined by the International Committee of Medical Journal Editors (ICMJE), including the conception or design of the work and contributing to drafting and revising the work critically for important intellectual content. Morgan Similuk conceived of and designed the study, collected data for the study and drafted the manuscript. Morgan Similuk and Jia Yan conducted the statistical analyses. Morgan Similuk, Jia Yan, Michael Setzer, and Leila Jamal made substantial contributions to the design of the work, the analyses, and interpretation of data for the work. Patricia Little contributed to data collection and provided intellectual content and approval of the work. Michael Lenardo and Helen Su contributed to drafting the work and revising it critically for important intellectual content. All authors provided final approval of the version to be published, and agree to be accountable for all aspects of the work.

Conflict of Interest:

Morgan Similuk, Jia Yan, Michael Setzer, Leila Jamal, Patty Little, Michael Lenardo, and Helen Su declare that they have no conflict of interest.

Keywords

Exome sequencing; secondary findings; clinical research; decision making; literacy; genetic counseling

Introduction

The return of individual genetic results from clinical research varies considerably by study (Wynn et al., 2015). This variability is partly dependent on study context, such as the relationship between investigator and participant, available resources, institutional norms, and investigator preference (Jarvik et al., 2014). For example, a genomic research study where physicians provide individual medical recommendations or administer treatment to participants has different ethical obligations than a research study doing genomic analysis on samples from de-identified biobank participants. One area without consensus is the return of secondary findings (SF) in a research setting (Wolf, Burke, & Koenig, 2015). Return of a selected consensus set of SF is recommended in the clinical setting by the American College of Medical Genetics and Genomics (ACMG) (Green et al., 2013; Kalia et al., 2017).

One way to inform policy on the return of SF in the research setting is to conduct research on patient knowledge and preferences. In one study conducted at the National Institute of Health (NIH) Clinical Center (CC), where the current study was also conducted, Sapp and colleagues interviewed 13 individuals who had recently received a positive SF report. They found that these participants reported minimal psychological distress although four had not yet accessed the recommended follow-up care. This study also surveyed 107 individuals who received negative SF reports and found that most expressed a good understanding of what that result meant for them, although a minority expressed confusion about the difference between primary findings (PF) and SF (Sapp et al., 2018). Other studies show that most (> 95%) research participants opt to receive SF when given the choice (Facio et al., 2013; Loud et al., 2016). While these studies provide some insight that SF may be acceptable and useful to research participants, gaps in our understanding of this issue still exist. These gaps specifically include patient experiences in undergoing consent for the return of SF.

In this study, we aimed to quantify the extent and type of decisional conflict that clinical research participants had about **enrolling in a study that returns** SF, among other relevant variables. We specifically chose to focus on decisional conflict due the uncertain outcomes, risks, and benefits that are inherent when discussing and making decisions regarding SF. We use the term “decisional conflict” to refer to participants feeling: (1) uncertain about which choice is best for them; (2) uninformed, unclear about personal values, or unsupported; or (3) ineffective in their decision making, as conceptualized by the widely-used decisional conflict scale (O’Connor, 1995). We also sought to identify participant attributes associated with such conflict, most notably risk perception and genetic literacy level. Participants’ assessments of how likely they are to receive personally useful genetic information might affect motivation for study participation and subsequent behavior (Biesecker, Schwartz, & Marteau, 2013; Heshka, Palleschi, Howley, Wilson, & Wells, 2008; Tong et al., 2015),

consistent with the broadly-referenced theory of planned behavior (Godin & Kok, 1996). These perceptions can also help us identify potential misunderstandings about study procedures and results.

In a similar manner, patients' literacy levels have been associated with multiple patient-centered outcomes; those with lower literacy often have a greater degree of misunderstanding and confusion about genetic testing (Roter, Ellington, Erby, Larson, & Dudley, 2006; Roter, Erby, Larson, & Ellington, 2007), are less likely to participate in health care decisions (Cooper, Beach, & Clever, 2004) and are less likely to make decisions about genetics that are consistent with their stated values (Dormandy, Michie, Hooper, & Marteau, 2005; van den Berg, Timmermans, Ten Kate, van Vugt, & van der Wal, 2005). Literacy not only reflects one's ability to read and write, but is also associated with one's ability to understand and remember complex information communicated verbally (Institute of Medicine (US) Committee on Health Literacy, 2004; Williams, Baker, Parker, & Nurss, 1998). Given that literacy level is typically a fixed attribute unless one undergoes a targeted intervention, it is an appropriate and relevant variable to consider when assessing a population's response to new genetic information as well as patient education and counseling on genetics. Measures of general literacy tend to be highly correlated with context-specific literacy measures, such as the genetic literacy measure used in this study.

To address our research aim to characterize decisional conflict in regard to participating in a study that returns SF and to explore potential correlates of this decisional conflict, including risk perception and genetic literacy, we administered a cross-sectional survey to patients with immunological disorders *prior* to the return of results of SF analysis. Participants were recruited from studies within the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH CC in order to evaluate genetic causes, i.e., PF, of their immune-related diseases. This specialty population is infrequently the focus of social and behavioral research on genetic testing and represents a novel and interesting group of patients who in many cases have symptoms that arise from the interaction of genetic susceptibility and key pathogen exposures. This study was part of a larger project at the NIH CC focusing on outcomes in genomics.

Methods

Participants

One-hundred-thirty-six participants were enrolled in this study, all of whom were referred for whole exome sequencing (WES) by other studies at NIAID and related collaborations. One individual died and was subsequently enrolled on this study for further genetic analysis following a conversation with that individual's next-of-kin; this participant did not receive SF analysis. The clinical indication for referral included a mixed group of patients with primary immune deficiency (PID) and their relatives ($n = 65$), children diagnosed with pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS) and their relatives ($n = 32$), and patients with familial mastocytosis and their relatives ($n = 39$). All living participants or their guardians provided written informed consent for participating in NIH IRB-approved study protocol 15-I-0113.

Instrumentation

Surveys included four scales with 6–17 items each plus novel items chosen to address additional questions in this population. Genetic literacy was assessed using a previously published modification of the Rapid Estimate of Adult Literacy in Genetics (REAL-G) (Erby, Roter, Larson, & Cho, 2008; Hooker et al., 2014) in order to provide a proxy for overall literacy level as well as anchor to the genetic content of the research questions. Decisional conflict was assessed with a widely-used 17-item scale, which includes sub-scales assessing decision quality related to feeling informed, feeling one's decision is consistent with one's values, experiencing an acceptable degree of uncertainty around the decision, feeling supported, and feeling effective in one's decision making (test-retest reliability coefficient = 0.81; α = 0.78–0.92) (O'Connor, 1995). General self-efficacy was assessed using a short-form, 6-item scale (α = 0.79–0.88) (Brignardello-Petersen, 2017; David et al., 2018; Raghuram Pillai et al., 2020). Lastly, the survey included previously-used questions regarding risk perception (Tong et al., 2015), and seven novel items regarding previously hearing of WES, ability to cope with receiving a PF or SF, and acceptability of returning SF in a research setting.

Procedures

Participants or their guardians gave consent to WES with SF disclosure. Consent discussions were conducted by a genetic counselor (MNS) and generally included discussion of the indication for genetic testing, collection of a family history, basic education about genetics and genetic testing, discussion of PF and SF as possible results from genetic testing coupled with numerical risk estimates, and elicitation of participant questions or concerns. Participants were made explicitly aware of other sequencing studies where SF were not returned as part of the exploration of their opinions on that element of the study. Risk-benefit assessment and alternatives to participation were also covered, in addition to an explanation of the survey research. The majority of participants being evaluated for PID had prior negative PID gene panel DNA testing. The validity of novel PFs were established by the peer review process. SFs were analyzed by an experienced, board-certified molecular geneticist using the ACMG variant interpretation and SF guidelines (Kalia et al., 2017; Richards et al., 2015).

Participants 12 years of age and older were invited to participate in the survey after consent was completed and remained eligible for survey participation until they received their results at about 6 months after consent. Electronic and pen-and-paper versions of the survey were offered. The electronic administration of surveys was performed using a secure extension of our institute's electronic medical record. Participants who did not initially respond to the survey invitation were sent two reminders.

Survey data was analyzed using SPSS V26 (SPSS Inc., Chicago, IL). The primary analyses regarding decisional conflict were conducted using bivariate models and intended to be primarily descriptive. Only data from adult participants were used in analyses, as the survey instruments were not well validated in adolescents. Descriptive statistics were presented as percentages or means. Bootstrapping was used to derive robust estimates of confidence intervals using resampling with replacement from the original dataset. We derived 95%

confidence intervals (CI) reflecting the 2.5th and 97.5th percentiles of the bootstrap values as the lower and upper bounds of the interval derived based on 1000 bootstrap samples. Spearman's rank correlation coefficient, rho, with the associated *p*-value was used for bivariate correlations between continuous variables. Student's *t*-tests – when the assumption of equal variances between two groups could be met – and Welch's test for equality of means – when two or more samples had unequal variances – with their associated *p*-values were used for comparisons of means. The limited sample size precluded more complex modeling and sub-group analyses.

Results

WES Results

PFs for participants ($n = 4$ families) have been reported separately including both known and novel contributions to disease related to pathogenic variants in *ADA2* (Arts et al., 2018), *CARD8* (Mao et al., 2018), *STAT3* (Natarajan et al., 2018), and *NCKAP1L* (Cook et al., 2020.). None of the participants reported here was found to carry reportable SF as defined by the ACMG. All results returned to participants were confirmed in a CLIA laboratory.

Survey

One-hundred thirty-six participants were enrolled on this protocol, of which 116 were eligible for the survey. Seventy-six participants returned the survey between 1 day and 6 months after consent for a response rate of 66%. Sixty-six of these were adults. All surveys were completed prior to return of results. Survey participants were primarily white (82%), not Hispanic or Latino (79%), female (54%), and affected (73%, in contrast to unaffected relatives). See Table 1. Adult respondents were not significantly different from adult non-respondents in sex ($X^2(1, n = 102) = 0.25$, $p = 0.617$); disease affection status ($X^2(1, n = 102) = 0.756$, $p = 0.385$; or age ($t(66.05) = -0.969$, $p = 0.336$). Due to the limited size of our sample, we did not have enough power to assess differences in race and ethnicity between respondents and non-respondents.

Overall, most participants reported not previously hearing or being unsure if they had previously heard about WES ($n = 38$, 58% and $n = 5$, 7.6%, respectively). None of the participants approached for this study explicitly declined due to this study returning SF or asked to opt-out of SF receipt. When asked generally about genomic research projects, 98% of survey participants reported thinking it was appropriate to return SF ($n = 65/66$; 10-point Likert scale ranging from strongly disagree to strongly agree, mean = 9.35 with bootstrapped 95% CI = 9.08 – 9.59); one individual was unsure. When asked about the sources for this generally positive appraisal of SF disclosure for research studies, participants reported their opinions were based on their perceptions of what is in their best interest, what is best for others, and what is the best use of research resources (mean = 8.15; 6.39; 7.71 with 95% CI = 7.62 – 8.61; 5.74– 6.97; 7.12– 8.24, respectively).

Decisional conflict regarding enrolling in a study returning SF was low overall with 68% of participants reporting zero or low decisional conflict ($n = 22$ and $n = 23$, respectively; "low" being a score of less than 10 on a 100-point scale). Most participants reported agreeing

or strongly agreeing (score ≤ 25 on a 100-point scale) with statements related to decision quality such as feeling informed (n = 53, 80%), feeling that their decision was consistent with their values (n = 53, 80%), experiencing an acceptable degree of uncertainty around the decision (n = 60, 91%), feeling supported (n = 64, 97%), and feeling effective in their decision making (n = 64, 97%). Self-efficacy was not associated with decisional conflict (Spearman's rho = −0.096, p = 0.443).

Higher decisional conflict was weakly associated with lower perceived appropriateness of receiving SF (Spearman's rho = −0.296, p = 0.016). Higher decisional conflict was also weakly associated with lower perceived likelihood of receiving SF (Spearman's rho = −0.298, p = 0.015) and lower genetic literacy (Spearman's rho = −0.297, p = 0.015). Decisional conflict was not associated with perceived likelihood of receiving PF (Spearman's rho = −0.231, p = 0.063). Lower genetic literacy was associated with multiple sub-variables of decisional conflict, corresponding to higher decisional conflict regarding effectiveness, i.e., feeling satisfaction and confidence in making an informed choice (Spearman's rho = −0.293, p = 0.017), support, i.e., feeling of having enough advice, support, and independence to make a decision (Spearman's rho = −0.285, p = 0.020); informed, i.e., knowing the risks, benefits, and options available (Spearman's rho = −0.280, p = 0.023); and values, i.e., being clear about what is most personally important in regard to the decision (Spearman's rho = −0.400, $p = 8.8\times10^{-4}$). Genetic literacy was not correlated with the decisional conflict uncertainty subscale, i.e., feeling sure about the decision (Spearman's rho = −0.119, p = 0.343). Lower genetic literacy was also associated with lower reported capacity to "deal with" receiving a PF and SF (Spearman's rho = 0.505, $p = 1.5\times10^{-5}$; Spearman's rho = 0.350, p = 0.004, respectively).

A notable minority of participants reported confusion about basic aspects of study participation, such as being unsure when asked later if they did in fact opt to receive SFs by participating in this study (n = 6/66, 9.1%). Overall decisional conflict was not significantly different between the group of participants with confusion and the group of participants who did not report confusion about whether the study returned SF (t(5.118) = −2.226, p = 0.075; mean difference = −24.74; 95% CI = −53.12, 3.64). Having previously heard of WES was not associated with participants' reported decisional conflict (F(2,10.67) = 2.853, p = 0.102).

Participants reported a high perceived likelihood of receiving a positive result, with 46% and 39% of participants reporting it was "likely" or "very likely" that they would receive a PF or SF, respectively. Risk perception for PF and SF were correlated (Spearman's rho = 0.421, $p = 4.3\times10^{-4}$). The most common likelihood estimate, however, for both PF and SF was "neither likely or unlikely" (46% and 42%, respectively).

Discussion

This study assesses patient acceptance and understanding of receiving SF analysis in a heterogeneous cohort of immune disease patients. We found that the majority of our participants reported that it was appropriate to return SF, with overall low or zero decisional conflict regarding their decision to enroll in a genomic sequencing study that returns SFs. This was reflected in the observation that most participants reported feeling informed and

effective in their decision to participate, and that their decision was in line with their values and conferred an acceptable degree of uncertainty. We also found a few important correlates of decisional conflict: lower genetic literacy, lower perceived appropriateness of receiving SF, and lower perceived likelihood of receiving SF were correlated with higher decisional conflict. Furthermore, a proportion of participants was unsure whether they had decided to receive SF. Risk perception of receiving a positive PF and SF was relatively high. Finally, the PFs are consistent with prior reports that WES is useful for discovering genes responsible for immune-mediated phenotypes (Yska et al., 2019). Our participants, especially those with suspected PID, had been undiagnosed by previous genetic testing and the diagnoses by WES in this study were either recently described or novel.

To date, the literature on SF disclosure in research has primarily focused on whether individuals should have this data returned to them (Jarvik et al., 2014; Wolf et al., 2015) and what participants elect (Facio et al., 2013; Loud et al., 2016). In this study, we went further by examining when participants elected to receive SF, how did they feel about that decision, and what the correlates of conflict related to decision making were. Overall, the survey data show that most participants reported thinking it was appropriate to include SF in results returned from research studies, particularly from the perspective of what they perceived to be in their best interest. Our findings present a novel facet of factors in play when individuals make decisions about participating in genome sequencing research that returns SFs, adding to the body of prior research (Facio et al., 2013; Loud et al., 2016). Specifically, most participants in our study reflected positively on the quality of their decision to participate in a study returning SF and reported feeling informed, supported, effective, and unlikely to regret their decision. Consistent with the theory of planned behavior (Godin & Kok, 1996), those who judged the likelihood of receiving clinically relevant genetic information as higher had the least conflict about participation. Additionally, genetic literacy emerged as an important factor in decisional conflict. Participants who had more limited genetic literacy (although still functionally literate), were slightly less confident in their decision-making.]

Accordingly, this study revealed areas needing further attention. A minority of participants expressed confusion about options related to SF in this and other studies. Overall, this is consistent with numerous studies examining misunderstandings of clinically relevant information, especially among those with limited literacy (Flory & Emanuel, 2004; Montalvo & Larson, 2014; Tamariz, Palacio, Robert, & Marcus, 2013). Indeed, genetics is relatively new to clinical care and quickly changing. Genetics discussions can also include terminology and numeracy skills unfamiliar to the average patient (Roter et al., 2007). That lower genetic literacy was correlated with higher decisional conflict in this research study highlights the important need for supporting literacy across clinical and research settings.

Another important finding to consider is that participants' risk perceptions were largely overestimated, consistent with prior literature (Lupo et al., 2016; Roberts et al., 2018). This is perhaps partially due to participants not having the option of choosing "I don't know" or "unsure" when asked about risk in this study, and instead choosing "neither likely or unlikely", potentially creating a systematic overestimation of risk perception in our data (Ellis, Ferrer, & Klein, 2018; Ellis, Ferrer, Taber, & Klein, 2018). Nonetheless, it

is necessary to consider that participants may have simply overestimated their chances of receiving a either a PF or SF. A novel finding in our study is that higher perceived likelihood of receiving a result were associated with lower decisional conflict about participation. Notably, a lower perceived likelihood of a SF was correlated with higher decisional conflict regarding participation in a study that returned SF. Particularly in the context of PF, one should not discount the influence of optimism bias, or unrealistic beliefs, which seem to be beneficial for both quality of life and overall mortality, despite being inaccurate (Chida & Steptoe, 2008; Larson, 1998). In this case, patients may be expressing their hope that this test, or most suggested tests for that matter, might end up being helpful. Such optimism may be linked to slightly easier research participation decisions in this study.

Participant likelihood estimates for PF and SF in our study were also moderately correlated. While the PF versus SF distinction is meaningful in the world of clinical genetics, it is possible some participants merge these abstract categories into a single idea of ‘clinical relevance’. Indeed, much prior work has shown the extent to which patients reinterpret communication about genetics in a personally meaningful way, embedding the information in their lived experience. This reinterpretation mediates risk-perception accuracy and subsequent behavior, even when one can correctly recall what was told to them by their provider (J. Vos et al., 2011; Joël Vos, Gómez-García, et al., 2012; Joël Vos, Oosterwijk, et al., 2012; Joël Vos et al., 2008). Further, it has also been well-characterized that individuals very frequently use heuristics or cognitive shortcuts to arrive at a decision, rather than taking a detailed, deliberative approach based on all available information for all decisions (Blumenthal-Barby & Krieger, 2015; Marewski & Gigerenzer, 2012).

Study Limitations

This study has several limitations. First, the small sample size precluded multivariate analyses or clinical sub-group analyses which may have provided more nuance. For example, unaffected relatives and affected study probands were combined in these analyses although the perceptions and priorities of these groups may systematically differ. Second, only participants who choose to take part in the study agreed to the survey, although the sequencing and survey were presented separately. Specifically, individuals who were contacted for this study remotely but who were lost to follow up without enrolling and who may have had concerns about SF were not available for study. None of the individuals approached in-person declined. Third, some participants might not have felt they had a real choice about receiving SF or not, due to the way participants were enrolled. Fourth, the wide variation in time between consent and survey completion may have confounded the data. This information was not systematically recorded, and thus cannot be controlled for in the presented analyses. Fifth, there also may be limits to the generalizability of the NIH population compared to other clinical groups of patients with immune disorders, based on possible differences in their range of experiences. Finally, importantly, pre-test counseling in this study occurred via an in-person visit with a certified genetic counselor. Findings from this study should be interpreted within the context of a face-to-face informed consent process that may be distinct from other approaches with varying levels of individualization. Additional exploration of alternative approaches to informed consent, including chatbots

and combinations of chatbot and in-person or tele-consent models – and their effect on decisional conflict regarding enrolling in studies returning SFs – are warranted.

Conclusions

Taken together, despite the study limitations, these data suggest implications for practice and for future research. These data add to the literature on the general acceptability from the patient perspective of SF return in a clinical research setting and demonstrate that the described approach allows most patients to make a decision that they reflect upon positively. Clinically, these findings, along with a broad literature on patient education and counseling, underscore the importance of communications skills which meaningfully engage and clearly impart the most important information to the patient. To do so, these skills should be based upon the rich context of the patient's personal experiences and insights, identify areas of potential misunderstandings, and proactively prevent poor health outcomes related to misunderstandings (Roter & Hall, 2006). This type of tailored communication is needed for all patients; certain patient factors, including but in no way limited to literacy level, can guide such tailoring. Indeed, future research should investigate work to better understand the origins and consequences of overly-high risk perceptions or confusion about PF versus SF, as well as develop communication or other interventions aimed at addressing such issues.

Human Studies and Informed Consent:

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 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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Table 1.

Survey Participant Characteristics

Demographics (n = 66)	***n*,%**
White	54, 81.8%
Not Hispanic or Latino	52, 78.8%
Female	36, 54.5%
Affected	48, 72.7%
Descriptive results (n = 66)	*n*,%
Previously heard of exome sequencing	23, 34.8%
Reported returning SF is appropriate	65, 98.5%
Zero or low decisional conflict about SF	45, 68.2%
Unsure if they are in a study disclosing SF	6, 9.1%
Correlations with decision conflict (n = 66)	Test statistic, *p*-value
Unsure if they are in a study disclosing SF	$t = -2.226$, $p = 0.075$
Perceived appropriateness of returning SF	*Spearman's rho* = −0.296, $p = 0.016$
Perceived likelihood of receiving a PF	*Spearman's rho* = −0.231, $p = 0.063$
Perceived likelihood of receiving a SF	*Spearman's rho* = −0.298, $p = 0.015$
Genetic literacy level	*Spearman's rho* = −0.297, $p = 0.015$