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Patients' views on incidental findings from clinical exome sequencing

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ABSTRACT

This article characterizes the opinions of patients and family members of patients undergoing clinical genomic-based testing regarding the return of incidental findings from these tests. Over sixteen months, we conducted 55 in-depth interviews with individuals to explore their preferences regarding which types of results they would like returned to them. Responses indicate a diversity of attitudes toward the return of incidental findings and a diversity of justifications for those attitudes. The majority of participants also described an imperative to include the patient in deciding which results to return rather than having universal, predetermined rules governing results disclosure. The results demonstrate the importance of a patient centered-approach to returning incidental findings.

1. Introduction

Individualized medicine promises that with a patient's genomic profile, clinicians will be better able to diagnose and tailor treatments, ultimately leading to improved health outcomes and resource utilization. However, genomic medicine foregrounds issues of return of unexpected results, known as incidental findings (IFs), from such tests. As we develop policies for the future of genomic medicine, we must determine how to incorporate patients' values and expectations in a meaningful and ethically robust way.

At this early stage of genomic translational research, it is often unclear whether data generated have clinical significance. A number of studies have examined research participants' expectations and attitudes toward the return of individual research results with potential clinical significance (Beskow et al., 2009; Kaufman et al., 2012; Ormond et al., 2010; Rigter et al., 2013a,b; McGowan et al., 2013; Daack-Hirsch et al., 2013; Townsend et al., 2012; Clarke, 2014; Fernandez et al., 2014; Sapp et al., 2014; Facio et al., 2013; O'Daniel and Haga, 2011; Shalowitz and Miller, 2008). These studies show that research participants want genetic data returned to them. Other studies reveal that many research participants want all of these data regardless of its clinical significance or "actionability" (Bollinger et al., 2013; Harris et al., 2013). Most of these studies were conducted with individuals participating in genomic research studies rather than undergoing clinical genome or exome sequencing. This distinction – research versus clinical – is sometimes pointed out as justification for not necessarily returning a genetic incidental finding unless it reaches a high threshold of urgent clinical meaning (e.g. malignant hyperthermia) (Fabsitz et al., 2010). There have been efforts to 'bin' findings into various categories based on clinical utility, actionability, and clinical urgency (Berg et al., 2011, 2013; Lindor et al., 2013; Bradbury et al., 2014a; Goddard et al., 2013). Some attempts have been made to distinguish between clinical actionability and personal utility (Bunnik et al., 2014) as well as to describe how the general, non-medical public understand and articulate these terms (Graves et al., 2015). While scholars have been discussing the return of incidental findings for more than a decade, (Jarvik et al., 2014; Wolf et al., 2013; Green et al., 2013a; Fullerton et al., 2012; Biesecker, 2013) the debate has intensified with the increasing clinical use of exome sequencing (Green et al., 2013a,b; Fullerton et al., 2012; Bradbury et al., 2014b; McGuire et al., 2013; Ross et al., 2013; McCormick et al., 2014; Yu et al., 2014).

We present results from a qualitative study in which we conducted interviews with patients and family members of patients pursuing exome sequencing in a clinical setting. Our results represent one of the first studies to demonstrate the range of patients' opinions and motivations for those opinions in a clinical setting. Patients expressed a variety of preferences for learning incidental findings from genomic sequencing; however, regardless of the differences they had in personal preference, most agreed that individual choice and participation in the decision making process was critical. These findings highlight the importance of a patient-centered approach to returning findings from clinical exome sequencing. By recognizing how patients' perspectives

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differ or coincide with those of medical experts (e.g., clinical laboratories, professional organizations, healthcare institutions, and providers), it becomes more feasible to develop policies that are capable of respecting all concerns salient to patients during healthcare decision-making.

2. Methods

2.1. Study design and participants

The study was designed to investigate patient attitudes toward genomic medicine. Interview guides and participant contact materials were developed and subsequently approved by the Mayo Clinic Institutional Review Board. We conducted in-depth, semi-structured interviews (Britten, 1995) with patients and their family members engaged in the process of utilizing exome sequencing as a tool for clinical diagnosis or treatment at the Mayo Clinic Individualized Medicine Clinic (IM Clinic). The IM Clinic was established to integrate new sequencing technologies into medical practice (Lazaridis et al., 2014). Patients referred to the IM Clinic during the time of this study either had a cancer that had failed standard treatments or were going through a "diagnostic odyssey," that is, pursuing diagnosis after having exhausted all standard available limited gene panel tests relevant to their phenotype. Diagnostic odyssey participants presented with a range of phenotypes, including those that affect respiratory function, digestion, the musculoskeletal system, the brain and nervous systems, others included immunodeficiencies, or developmental delay. Oncology participants represented a variety of cancers including breast, colon, gastrointestinal, ovarian, kidney, liver, lung, brain, and a number of rare cancers.

Clinical laboratory companies that provide clinical exome sequencing have their own sets of guidelines for the return of incidental findings (Jamal et al., 2013). The guidelines of the clinical laboratory that the IM Clinic used at the time of this study were reviewed with the patient during the genetic counseling session.

2.2. Data collection

Individuals were invited to participate in this study after they had their initial appointment with an IM Clinic physician. Interested individuals were consented and granted permission for the researchers to access their confidential health information by signing a HIPAA form. Interviews began in December 2012 and concluded in March 2014 and were done either in person or by telephone, depending on the individual participant's preference. Interviews were conducted by KEC (medical anthropologist), CMEH (linguistic anthropologist), and JBMc (molecular biologist trained in empirical bioethics and policy). Interviews lasted between 10 and 50 min, with a mean time of 20 min. We interviewed patients and family members at one or more of four points during the course of their interaction with the IM Clinic. We talked with a number of participants before their initial meeting with the genetic counselor, after that meeting, during the waiting period for testing and analysis, and after the return of testing results. The purpose of conducting multiple interviews was to see how various interactions – with the genetic counselor, with family and friends, and after receiving results – might change their opinions and beliefs regarding testing. There were many complications that prevented us from conducting interviews with the same people at each of these time points. Those complications included attrition due to insurance coverage, health issues, and the often-spontaneous nature of referrals. As exome sequencing can take nearly half a year for results to be returned, we also interviewed many of the participants during the waiting period to gauge attitudinal change. Timing of the interviews depended on the situational context, in particular the availability and health status of the participant.

The team developed an interview guide consisting of four to six open-ended questions, depending on the stage of the process at which the participant was interviewed (interview guides available upon request). All questions included follow-up probes that were used as needed. The interview guide was modified iteratively as data were collected and analyzed and new themes emerged as salient. The general domains covered by the questions included general understanding of genomics and exome sequencing, expectations versus hopes, concerns and challenges, and access to results and incidental findings. Questions probed participants' perspectives on choosing whether to learn clinically actionable incidental findings, optional information like carrier status or pharmacogenomic relevance, and risk for adult-onset dementias. For the purposes of this paper we have chosen to use the general term "incidental findings" (Presidential Commission for the Study of Bioethical Issues (PCSBI), 2013) for terms related to any additional anticipated, unanticipated, secondary, or discovery findings from the application of exome sequencing for diagnostic or treatment purposes.

When interviews included more than one participant – for example a cancer patient undergoing the sequencing and her spouse, or both parents of a diagnostic odyssey patient – all participants consented to be interviewed and signed a HIPAA form. When we had multiple participants in an interview, it was at the request of the participants. Each question was posed to all participants in the group interview. By the conclusion of interview collection, theoretical saturation was achieved for the purposes expressed in the themes of this paper.

2.3. Data analysis

Audio-recordings of the interviews were transcribed, de-identified, and analyzed using standard qualitative methods. All data were stored on a secure server. Team members read the transcripts, and based on this initial review, a coding scheme was developed. A codebook was constructed using aspects of grounded theory and inductive qualitative analysis, which allowed unanticipated themes to emerge from the data (Corbin and Strauss, 2008). At least two study team members analyzed all transcripts, independently using the scheme, and discrepancies were resolved through discussion reaching consensus. The coded text was then compiled for further narrative and manuscript development. The data were analyzed using the standard qualitative data analysis software, QSR NVivo 10.

3. Results

During the timeframe of this study, the IM Clinic had 95 oncology patient referrals and 75 diagnostic odyssey referrals. Individuals representing 37 IM Clinic cases (19 odyssey/18 oncology) were recruited and participated in the study and were interviewed at least once. Relative to participant availability, some were interviewed as many as three times. A total of 55 interviews were conducted. Here we define cases to include patients as well as family members, noting that one case had as probands two siblings with the same genetic condition. Sixteen cases had at least one follow-up interview. The oncology patients interviewed ranged in ages from 29 to 67 years (7 males and 11 females). In some oncology cases, family members joined in the interviews at the request of the proband. Such group interviews were counted as a single interview. The diagnostic odyssey participants were more often parents of the proband, but seven patients, who were old enough and cognitively able to participate, were interviewed individually, though family members occasionally joined at the request of the proband. The diagnostic odyssey patients ranged in age from 20 months to 45 years (12 females and 8 males) (see Table 1). Six of the cases interviewed (three diagnostic odyssey/three oncology) did not proceed with exome sequencing after the initial genetic counseling appointment because of lack of insurance coverage, ineligibility for exome sequencing, or they were not a candidate for surgery for sample acquisition. Twelve of the participants were interviewed after they received their results (7 diagnostic odyssey, and 5 oncology). Individuals are identified as either diagnostic odyssey (Dx) or oncology

Table 1
Participant information.

	Oncology	Diagnostic odyssey
Age range of the proband	29 years–67 years	20 months–45 years
Gender (male/female) of the proband	7/11	8/12
Total interviews	30	25
Total cases	18	19 (1 case included siblings as probands)
Did not proceed with exome sequencing	3	3
Interviewed after results were returned	5	7

(O) patients, by their age (0y), and by their sex (F = female, M = Male).

Many participants expressed that they would not like to receive any findings from exome sequencing which were irrelevant to their current condition. Motivations driving this preference were varied, and included religious or personal beliefs, burden of information, anxiety and worry, and concerns about insurance repercussions. In contrast, some wanted to know everything, even if such knowledge would not change treatment. Others believed that having more knowledge about health risks would be valuable to alleviate uncertainty, discover answers, provide information for family members, take preventative measures, insure quality of life, and participate in research. Participants often discussed the importance of choice and their ability to decide which results to learn. We organize these data under three broad domains: (i) wanting to know, (ii) wanting not to know, and (iii) patient choice. The first two domains represent the potential diversity of personal opinions, while the third demonstrates the nearly unanimous belief that all participants are entitled to their own choice and that any choice different from their own should nonetheless be treated with respect.

3.1. Wanting to know

Many patients voiced a desire to receive incidental findings. These participants believed that knowledge of incidental findings could improve their quality of life, aid in their search for answers, and help them to prevent or at least to prepare for future health issues.

3.2. Quality of life

Certain participants felt that the benefits of having access to more information outweighed the burdens associated with that knowledge. When prompted with specific results that have limited or no clinical utility, including variants that indicate a risk for a condition for which no known treatment currently exists, the patients restated that they would like to know. As outlined in Table 1, the IM Clinic currently uses a laboratory that does not return incidental findings related to adult-onset neurological conditions that are not currently clinically actionable. Despite this, some participants in our study considered such results 'actionable' in other areas of their lives. Several participants were disappointed when they found out that they would not have the option to learn that information. One patient's mother asked:

> "If I know she's going to develop Alzheimer's or some future degenerative neurological disorder, do I put her through chemo so she can wait to suffer that? I think treatment is always preserving the ability to access some future quality of life. […] I felt that information would be important in helping us to determine how far to go with treatment. […] It *is* actionable information. For us, for our family, it's actionable." (Mother of Dx18yF)

According to this mother, the prohibited information, which the laboratory had deemed non-actionable, would in fact be useful in making treatment decisions for her daughter.

Another participant described how knowledge from exome sequencing could be used to impact her own quality of life:

> "I would like to know anything that could possibly impact the rest of my quality of life. […] Having an undiagnosed chronic disease since you were a little child, you don't know how to plan things. […] If you don't know how day-to-day life is going to go, you never know exactly what could be coming next." (Dx20yF)

3.3. Finding answers and preparing for the future

Participants repeatedly expressed a desire for information that might illuminate any aspect of their health care now or in the future. Participants recognized that exome sequencing inevitably uncovers variants of uncertain significance (VUSs) that may lead to more questions without providing any answers. One patient's mother described VUSs as potentially "another step forward in someday finding an answer" (Mother of Dx14yM).

Participants speculated that there are other areas in their lives in which they could put genomic data into action. Several mentioned that they would use any information to help prepare for the future. One participant elaborated:

> "I feel like knowing that information can just help me plan for the future […] Maybe there are some lifestyle changes I could make that could benefit me. I think I would want to know […] even if there is no treatment […] to possibly plan for long-term care." (Dx42yF)

Some oncology patients stated that other findings unrelated to their cancer would be helpful in planning their lives. Equally comforting for some was the fact that more information gave them a sense of control. As this participant stated:

> "I think information is power […] It affects your family, home, your children; I mean, it affects everything. […] The more you know, the better off you're going to be." (O57yF)

One participant explained that he would like to be able to learn the variants for untreatable conditions so that he could make sure he was not a burden for his loved ones. He said, "I want to know, because it's going to affect how I live my life, and make sure that I have everything in order, so that I am as little of a burden as I can be if it does happen." (O65yM)

In addition, a few patients mentioned that if they could know results related to untreatable conditions, they would participate in research to help find ways to prevent or treat the condition. The father of a diagnostic odyssey patient put it this way: "It is an opportunity for us to learn more about [the patient] that might benefit her and also benefit other people" (Father of Dx5yF).

One of the daughters of an oncology patient expressed her hope that they could contribute to future research and be a part of the process of discovery: "Who knows what they are going to discover soon, and so, if you know about it now, you know, you can always be watching [and] participate in studies" (Daughter of O67yM).

After receiving her non-definitive results from sequencing, one patient began a petition with others who share her rare disease in order to raise the funds for more research to be done. She

characterized the advocacy she has undertaken as "really empowering" (Dx45yF).

3.4. Wanting not to know

As discussed in the previous section, patients often expressed a desire to receive results that are not typically returned. However, many participants also expressed a desire not to learn certain types of IF. These participants explained that the burden of learning additional information would outweigh any benefit of knowing those results.

3.5. Religious beliefs

Some participants highlighted religious beliefs against learning incidental information. For example, regarding the option to learn her daughter's carrier status, one mother ruminated:

> "So that means her future spouse would have to be a carrier, and then religiously with our beliefs, we wouldn't do anything with that anyhow. Is that knowledge really necessary? That was a difficult one for me." (Mother of Dx17yF)

Another example of how personal and religious beliefs influence such decisions was the view that we are not meant to know certain things. As one patient suggested:

> "I just question: With our religion or beliefs […] are we supposed to know that I'm going to have Alzheimer's in another 50 years? I don't know if I'm supposed to know that. […] I don't think we were meant to know what will happen and what we are going to be given in our life." (O34yF)

In both these instances, religious beliefs were given as a reason to decline disclosure of certain results. Although both interviewees were party to an active search for specific genetic information, they wanted explicitly to avoid other (unrelated) information.

3.6. Burden of knowledge

Several other participants articulated similar perspectives about learning indicators for their future health but without the religious framing. For these patients there was a pragmatic concern about undue stress.

> "I don't know if I even want to know this, honestly. […] It's like, I don't go to a palm reader, either, so they can tell me what my future is going to be. I don't want to know that, because then you worry about it." (O41yF)

Participants were concerned that incidental information would cause additional anxiety. One participant expressed that "not knowing might even be a blessing" (O61yF). And another thought that learning anything other than a potential targeted treatment was "irrelevant" (O64yM). He mentioned that if his healthcare team found a treatment and his condition improved, he might want to know, but that was not his focus or his goal at the moment.

A few parents of diagnostic odyssey patients did not want to learn other findings, especially regarding results such as adult-onset neurological dementias. They did not want the additional worry and were thankful that this had not been an option provided. According to one mother, such information would be a "ticking time bomb" (mother of Dx6yM). Along similar lines, another participant explained, "It would cause more anxiety. Worrying about him having Alzheimer's in sixty to seventy years would just be more detrimental to the way we would treat him. […] I wouldn't want to know that" (Mother of Dx14yM).

3.7. Future repercussions

Some patients were concerned with how the incidental information would affect insurance eligibility and coverage in the future. One participant explained:

> "The biggest concern I have is down the line, in the future, how this may affect my children with insurance, you know, confidentiality. […] You never know what the future is going to hold for our healthcare and insurance companies and payment and jobs, and [whether it is] going to be used to be discriminated against with my children." (Dx45yF)

In fact, several others worried about privacy and insurance repercussions for their children or other family members in the future. Voicing these concerns, one of the participants noted:

> "It is going to open a can of worms. Let's say that the genetic sequence of my tumor shows a predisposition to a terminal situation that I don't even know that I have. […] Are insurance companies going to deny treatment based on DNA sequencing?" (O61yF)

Though patients elected to participate in genomic testing for their indication, some were wary that any incidental information revealed in the process could potentially raise considerable risks for insurance coverage in the future and that it could lead to unnecessary anxiety.

3.8. Patient choice

There was a general belief that individuals should be allowed greater involvement in deciding which results they would receive. They respected that some individuals do not want to learn anything more than necessary for their presenting condition. On the other hand, they recognized that others might want as much information as possible. Furthermore, many participants explicitly stated that patients with different opinions should be allowed to make their own decisions.

Some participants expressed a sense of inherent ownership of their genomic information and presented this as the basis for their right to decide what they do and do not learn. For example, one woman noted, "You feel like if there is information out there that somebody finds out about your genes, you should have the right to know it, right? You should have the choice because it is *yours*" (Mother of Dx6yM).

Regardless, participants recognized that making decisions about what to learn or not to learn should not be taken lightly, as this participant thoughtfully articulated:

> "I absolutely believe this is all about choice. […] It has potential to be a great choice, but yet it may tell me more than I am comfortable knowing right now. So I think it is absolutely a choice and it is all about the choice, but it doesn't mean it is an easy choice." (Husband of O34yF)

Considering that this participant and his wife, the patient, were not interested in learning incidental findings that were irrelevant to the patient's presenting condition and treatment, choice itself was notably important regardless of their current opinions. One participant, who was disappointed that she would not learn findings related to untreatable dementias, fervently asserted that people should be able to have a choice:

> "I don't think you can make a blanket legislation like that. I don't think you can blanket people like that. I think this is the Individual Medicine program for a reason. Everything has to be on a case by case by case basis because this is serious information and there are many patients who could not handle that information. […] I think

the patient should always have the choice under the proper instruction of a medical geneticist. I would never want someone else to decide that for me." (Dx20yF)

As this participant advocated, the individual context and patient's individual preferences should be central to the practice of *individualized* medicine.

4. Discussion

Though there was considerable diversity of nuanced opinions in our study's population regarding what should or should not be returned, the importance of personal choice and participation in the decision was articulated by a majority of our participants. In addition to these findings, our research provides novel data for why individuals in a clinical setting desire to be able to choose *not* to receive certain results. These data help clarify why it is critical to allow patients to opt out of receiving certain results (American College of Medical Genetics and Genomics (ACMG), 2014).

Anecdotally, it is not uncommon to hear from clinicians the assumption that a diagnostic odyssey patient will want to learn all results from genetic testing, because these tend to be patients seeking answers. They are assumed to want any and all information they can obtain. On the other hand, oncology patients are regularly assumed to have focused concerns on only their current malignancy. Our data however, indicate that this is not always the case. Our findings demonstrate that even within these two different patient populations there is diversity in views about what is important to learn or not learn from genomic testing.

Participants felt that as the individuals who are impacted by the genetic finding, they should have a voice in decisions about what results are returned. We heard several patients express frustration about their not being able to receive findings they believed would be useful for them. In their opinion, incorporating notions of personal utility into decisions about what to return is as important as considerations of clinical utility. This particular finding points to a possible tension between patients' values and regulatory policies implemented in a one-size-fits-all approach. More empirical research is needed to describe how patients and their families, health care providers, and even insurers distinguish and apply the notion of personal utility.

While our study offers rich, qualitative data regarding participants' opinions on the return of incidental findings from genomic testing, it does have limitations. First, we conducted a limited number of interviews. An in-depth interview method was used, and therefore the number of participants was limited. Further studies, both qualitative and quantitative, are needed to gather additional empirical data. While our goal was to interview participants at multiple time points during their journey through the IM Clinic, this was not uniformly achieved due to the health of participants and loss to follow-up. Due to the timing of the study, there was a limited number of participants who were interviewed after the return of testing results (see Table 1). Prior to being interviewed, many of our participants had undergone at least one genetic counseling session about what would be returned from genomic sequencing; this knowledge may have influenced their responses. Ideally, all participants would have been interviewed prior to their first encounter with an IM Clinic genetic counselor. However, this goal was not achieved, as referrals to the IM Clinic were often spontaneous and therefore there was variability in when participants could be recruited. There was also variability in when the interviews were conducted during the process, as many participants traveled to Mayo Clinic from distant locations and the interviews were set up according to the convenience of the participants, either when they were at Mayo Clinic for other appointments or when they were available via telephone. Not all the participants in the group interviews participated in the follow-up interviews, as these were often conducted over the phone with the proband or parent of the minor proband. Although our participants represented patients who both agreed to and declined testing, more research should be done in order to evaluate how the trends demonstrated in our data correspond to preferences in other populations, particularly in populations with less critical health concerns.

Despite our limited sample, our data imply that shared decision making may need to be better integrated into the delivery of clinical genomic technologies. Shared decision making in health care delivery has received increased attention in the last several years, and several groups have demonstrated how appropriate uses of shared decision making can improve health outcomes and healthcare delivery overall (Stacey et al., 2014). Within this context, being sensitive to how to deliver genetic findings to patients is also critical, especially if the patient has expressed a desire to remain focused only on his/her current condition. We know much about what patients and research participants think they want to learn. More data are needed to understand the diversity of reactions from patients undergoing exome sequencing and their families upon learning about additional, potentially devastating, genetic risks.

Patients' perspectives of risks and benefits of knowing genomic information are personal and contextual. It will be important to continue examining the diversity of patients' and other stakeholders' perspectives as genomic technologies are increasingly used in the clinical care. Empirical studies like the one we describe here are critical to ensuring that the translation of genomic technologies into clinical practice happens in a socially and ethically responsible manner.

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