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“Not tied up neatly with a bow”: Professionals’ Challenging Cases in Informed Consent for Genomic Sequencing

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Abstract

As the use of genomic technology has expanded in research and clinical settings, issues surrounding informed consent for genome and exome sequencing have surfaced. Despite the importance of informed consent, little is known about the specific challenges that professionals encounter when consenting patients or research participants for genomic sequencing. We interviewed 29 genetic counselors and research coordinators with considerable experience obtaining informed consent for genomic sequencing to understand their experiences and perspectives. As part of this interview, 24 interviewees discussed an informed consent case they found particularly memorable or challenging. We analyzed these case examples to determine the primary issue or challenge represented by each case. Challenges fell into two domains: participant understanding, and facilitating decisions about testing or research participation. Challenges related to participant understanding included varying levels of general and genomic literacy, difficulty managing participant expectations, and contextual factors that impeded participant understanding. Challenges related to facilitating decision-making included complicated family dynamics such as disagreement or coercion, situations in which it was unclear whether sequencing research would be a good use of participant time or resources, and situations in which the professional experienced disagreement or discomfort with participant decisions. The issues highlighted in these case examples are instructive in preparing genetics professionals to obtain informed consent for genomic sequencing.

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Keywords

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Background

Genome and exome sequencing are rapidly being integrated into research and clinical practice in both adult and pediatric populations. Genomic sequencing can examine thousands of genes simultaneously, and is currently most often used to identify the genetic basis of single-gene, Mendelian disorders (Biesecker & Green, 2014). Recent analyses have estimated that exome sequencing has a diagnostic yield for rare disorders of about 25% (Yang, 2013; Yang, 2014). In addition to its diagnostic capability, genomic sequencing can also identify variants categorized as incidental or secondary findings that are unrelated to the indication for testing. The scope of the ethical and legal obligation that laboratory personnel and healthcare providers may have to return incidental findings from genomic sequencing to participants has been a focus of ongoing debate. In 2013, the American College of Medical Genetics and Genomics (ACMG) issued a policy statement stating that laboratories offering sequencing are obliged to seek and return to the ordering provider pathogenic or likely pathogenic variants in 56 genes related to conditions for which treatment or surveillance is expected to significantly improve patient outcomes (Green et al., 2013). The ACMG later amended this policy statement to acknowledge that patients should have the opportunity to opt out of receiving these incidental findings during the informed consent process (ACMG, 2014).

Due to the breadth and unanticipated nature of results that may be returned, genomic sequencing may pose heightened challenges for obtaining informed consent relative to the process of informed consent for other types of genetic testing (ACMG, 2013). The ACMG recommends that informed consent for sequencing include information about the likelihood and types of results that will be returned, including incidental/secondary findings; risks and benefits of testing; limitations of the sequencing technology to detect pathogenic variants; implications of results for family members; and alternatives to sequencing for obtaining a diagnosis. Additionally, the ACMG notes that patients should be informed about and able to opt out of allowing their identifiable results to be shared in databases, and be told about policies regarding re-analysis of their data and the potential for re-contact (ACMG, 2013). Given the impossibility of summarizing every possible results scenario that could occur in the consent session, it has been observed that patients or participants consenting to sequencing are consenting to a test that has many inherent uncertainties (Hooker et al., 2014).

Genetic counselors and other professionals working in settings offering genomic sequencing are tasked with conveying this voluminous and complex information to patients or participants and obtaining informed, voluntary consent for testing. While theoretical and practical guidelines have emerged (Appelbaum et al., 2014a; Appelbaum et al., 2014b; Ayuso et al., 2013; Bunnick et al., 2013; ACMG, 2013), little has been written about the specific kinds of challenges that professionals encounter when obtaining informed consent for sequencing. As the demand for genomic sequencing increases, case examples can be a

valuable teaching tool in preparing genetics professionals to obtain informed consent for this type of testing (Hooker et al, 2014).

There is a limited body of research examining the experiences of professionals who obtain informed consent for clinical testing or research participation. Professionals who consent patients for participation in research have reported ethical challenges because of role conflicts. For example, research coordinators must balance their roles as patient advocates vs. study advocates, and there are situations where these roles conflict (Davis et al., 2002; Fisher et al., 2012). The challenges of balancing these roles may be particularly pronounced for health professionals, such as genetic counselors, who obtain consent for research as well as provide clinical care (Markel & Yashar, 2004), sometimes for the same person.

In 2010, the NIH funded Clinical Sequencing Exploratory Research (CSER) projects to address the critical questions raised by clinical applications of genomic sequencing, including the development of policies and procedures for obtaining informed consent and returning results to families (Manolio 2014). The resulting CSER Consortium (<https://cser-consortium.org/>) includes nine U01 projects and several R01 projects in the United States that are offering exome or genome sequencing collectively to over 3000 pediatric and adult patients with a variety of conditions including cancer, cardiac conditions and, neurodevelopmental disorders. Through the process of consenting these patients who become research participants, investigators in the CSER projects have gained considerable experience discussing sequencing with patients and obtaining informed consent for participation in sequencing research studies.

Scant literature exists about the content and process of informed consent for genomic sequencing, and less about challenges that individual providers face when offering this relatively new type of testing. As part of a collaborative effort between two CSER consortium workgroups (Genetic Counseling Workgroup and the Informed Consent and Governance Workgroup), we interviewed professionals who obtain informed consent for genomic sequencing in research and/or clinical settings to understand their experiences and perspectives. Here, we present some of the challenging case examples described by these professionals, with an aim to identifying unique issues that may be associated with conducting informed consent sessions for genomic sequencing.

Methods

Participants

Study participants were recruited in one of two ways. First, one of the authors contacted a PI or Co-PI from each of the 9 CSER U01 clinical sequencing projects, or from other projects included in the CSER consortium that offer genomic sequencing in a research context, to request names and contact information for 1–3 individuals with the most experience conducting informed consent sessions for their project's study participants. Depending on the protocol for obtaining informed consent for each individual project, these individuals could be genetic counselors, physicians, or trained study coordinators. Second, the authors identified five large clinical centers in the United States outside of the CSER consortium

offering clinical genomic sequencing and contacted one genetic counselor at each center about participating in the project.

Recruitment and data collection

One of the study authors sent an email describing the study to all potential participants and scheduled a telephone interview based on the participant's availability. Interviews were conducted by four of the authors using a semi-structured interview guide that was developed by the study team. Interview topics included: descriptions of the person's clinical experience and responsibilities; the process of consenting study participants and/or patients for genomic sequencing; common questions, concerns, and misperceptions about genomic sequencing raised by patients or study participants; and challenges to obtaining informed consent. As part of the interview, the interviewee was asked to summarize one particularly challenging case involving informed consent. These cases are the focus of this report; other findings from this study will be reported elsewhere.

All interviews were conducted over the phone after obtaining verbal consent from the participant. The interviews lasted between 30 to 80 minutes. Interviews were recorded and all audio files were sent to a professional transcriptionist.

The study protocol was classified as exempt by the Institutional Review Board of the University of Pennsylvania.

Data Analysis

Study investigators read through the transcribed interviews to check for accuracy, completeness, and to redact any identifiable information. De-identified interview transcripts were imported into QSR International's NVivo 10 software for coding and analysis. For the purpose of this study, we collated and examined interviewees' challenging or memorable informed consent case examples to identify groups of common challenges. Interviews in which the participant did not share a challenging case, or where the challenge related to some other aspect of care or research, such as return of results, were excluded from this analysis. When an interviewee shared more than one case example, we included the case or scenario that was more specifically described. Two investigators (AT and DS) independently reviewed the case examples and conducted a content analysis of the primary challenges for each case, with high concordance between the two reviewers. The few discrepancies were resolved by consensus. Investigator AT then grouped challenges according to common themes, which were further reviewed and discussed by a subset of investigators (AT, DS and BB) to ensure trustworthiness. Data from these informed consent cases coalesced into two overarching themes.

Results

Of 35 people contacted, 29 (83%) participated in an interview. Three-fourths of interviewees were genetic counselors, and the remainder were research coordinators. Research coordinators had various educational backgrounds, from bachelor's degrees in biology or psychology to master's degrees in epidemiology, health communication, and biotechnology. Some research coordinators mentioned having been trained to conduct informed consent

sessions by or consulting with genetic counselors working on their projects, and many used genetic counselors as a resource on an on-going basis.

All but one interviewee shared a challenging or memorable case example. Four individuals were excluded from this analysis as their case examples focused on challenges related to return of results, rather than to obtaining consent. The analysis is based on the remaining 24 challenging informed consent cases. Table 1 summarizes the professions, practice settings and experience with informed consent for genomic sequencing of these 24 interviewees.

The challenges described by the interviewees fell broadly into two domains: challenges to participant understanding of the content covered during the informed consent process, and challenges related to facilitating decision-making about undergoing genomic sequencing (Table II).

Challenges to Participant Understanding

General and genomic literacy—Obtaining informed consent for genomic sequencing involves the discussion of complex information, and some interviewees described situations in which they had difficulty assessing participant understanding of the information or tailoring their communication to the participant's needs. For example, a genetic counselor described the challenge of consenting participants with varying backgrounds and levels of genomic literacy (the number in parentheses is the interviewee ID):

We live in a town full of engineers, and so oftentimes with some of them, you do get down into the weeds of genetics and science, but also we have a lot of rural families that come in with very limited background, and parents who only finished eighth grade, and it's challenging to explain exome sequencing to that population, and making sure that they understand it. (04-1)

Three interviewees reported cases in which a person with high genomic literacy wanted to know a lot of information about the highly technical aspects of genomic sequencing. Two of those interviewees, both research coordinators, referred participants to their genetic counselor colleagues who were able to field the more complicated technical questions. The third, a genetic counselor, reported that while the technical questions were a challenge, she worried that one genetically savvy participant who had an advanced degree in molecular genetics was focused on the details and limitations of sequencing rather than the implications of results for herself and her family:

I think at least on the pre-test side if I had to guess, based on how much she was focusing on that, it was almost like a defense mechanism for her. You could already see her skepticism with any results that might come back and whether she would actually believe any of them because she was focused so much on the limitations of the technology and our interpretation.... So it was just difficult because I've never been pushed that hard on the technical aspects by a patient before and I was trying to just remember what were my main goals for her to walk away with... (20-7)

This interviewee struggled with achieving a balance between accommodating the participant's informational preferences and the interviewee's priority that the participant

understood the potential sequencing results and their implications for herself and her family, rather than focusing on the technical details of the testing. Other interviewees described the challenges involved with tailoring their communication of complex information to individuals who had much lower baseline levels of genetic knowledge, as in this genetic counselor's example:

I had one participant who I think stands out in my mind because he was much less educated than many of our participants, but really wanted to participate because he had a strong family history of heart disease. And he was really worried about the future generations in his family and he really felt like this was an opportunity for him to contribute something to them. And it was a real challenge for me to start with him. He had highlighted the consent form very carefully and he highlighted the word 'genome' and he kept saying 'gnome' ...he was like 'What's a gnome? What does that mean?... Is that in my body? Can you take it out of me?' (05-1)

She commented that the experience of consenting that participant helped her to reflect on what participants needed to understand, and how she as a professional could assess their understanding. She described having a mental "minimal list" of points that she felt were important for participants to understand before consenting to the test, which included the breadth and relatively uncertain nature of results. She also employed the strategy of asking participants to explain their understanding of the information to assess their comprehension.

Even within a single family, different individuals may have different levels of education and comprehension of the information provided. This interviewee related her experience consenting a family for pediatric sequencing where the mother had trouble understanding the information:

So I think that the dad was hanging in there in terms of the information, but the mom wasn't. At the end, she finally says, can you tell me in three words or less what we're talking [about]— and I thought, oh God. You hate that when that happens. So I did. And she was fine with that. But it's just, you got different people at different levels. And she's trying to nurse the baby. And chaos, chaos. (10-4)

This concern speaks to the imperative that these professionals feel to adequately inform participants about sequencing and assess their understanding and ability to give informed consent. These challenges to assessing understanding, communicating with individuals at varying levels of literacy, and balancing the participant's information preferences with the professional's priorities were reported by interviewees from across different sites working with different populations.

Managing expectations—Interviewees described the importance of participants' understanding the scope of the testing, including potential results and limitations of the testing. A few discussed challenging cases in which the participant had unrealistic expectations of the testing, and their need to modulate these expectations.

I felt like I needed to absolutely pour cold water on her in the sense that no matter what was stated, she overstated it ... And she was just so far over the top with her own desires for information and I was having a lot of trouble getting her to hear

what was being said and that this was not being promised and that we could not figure all this out. (03-2)

For many individuals or families, sequencing is the newest and possibly the final step in their “diagnostic odyssey” that included previous negative genetic testing results. Consequently, they express considerable hope and optimism about the ability of genomic sequencing to yield results that will have a substantial impact on treatment. This poses challenges for the interviewees as reflected in this excerpt:

I think also from the other side of it is working with patients who don't really know much about what it could do; they're excited to take part in it...just making sure that they really understand that they're not getting their hopes up either, they know that this might not do anything for them, they might not find anything that might give them new treatments, but people ...who are very desperate because they've progressed through all the standard lines of therapy and are looking for some sort of miracle. I think those are definitely the most challenging because you know that the patients definitely have so much invested in this and not to promise anything. (11-3)

For these professionals, helping participants achieve realistic expectations of the testing is an important part of the informed consent process. Unrealistic hopes or expectations can pose a challenge to understanding.

Contextual factors—Some cases focused on the contextual factors that made it difficult to communicate with participants or to gauge their understanding. One interviewee, whose project involves consenting families with very ill children with cancer, remarked on the importance of timing the approach for informed consent so that the family can hear and understand the information:

The one that really taught us timing – because we did have a family and I think we caught them on a day where they were already getting bad news. The oncologist did say it was an okay thing to go ahead and talk to them but it was, I think, more so you might not catch them anytime soon. The mom was extremely withdrawn. The dad was extremely angry. And... he didn't want to hear the consent. They just wanted to sign the paperwork, and of everyone, I think those are the hardest because you really need them to understand. (01-3)

Communication challenges were also observed when multiple family members were present during the session. Some projects request samples from family members who may be present during the consent session and have questions about the implications of results for themselves or other relatives. A few interviewees noted the issues involved when the presence of additional family members made it difficult to communicate information to the primary participant, as in this case:

The more challenging ones are when lots of family members are accompanying the participant and they have a lot of questions, too. Most of them don't have their own agenda, but a lot of times if the participant has questions they want to chime in and

try to answer... Or they'll ask their own personal questions ... 'I have an aunt with this.' So just start taking you off track or telling their own personal stories. (10-1)

In this case, the involvement of other family members made it difficult for her to answer questions, and drove the session off-topic. Another interviewee described a case in which he felt like he was rushing during the informed consent session because of the presence of an uninterested family member:

There was one case where I was speaking to the wife, the patient, and the husband looked so bored and agitated, and wasn't saying anything, but you could tell. And I felt really bad and wanted to speed things up, but then couldn't. (11-2)

One additional contextual challenge was the occurrence of unexpected disruptions, such as medical complications, as experienced by this research coordinator:

I know I've had several where the child...something happens with their [central] line and it gets crazy and out of control... (01-1)

Interviewees reported that contextual factors such as these made it particularly problematic for them to share information with participants and feel confident that the participants absorbed and understood that information.

Challenges in Facilitating Decision Making

Regardless of their level of understanding of the information conveyed, patients or participants must make decisions about whether to participate. A second domain of challenging cases shared by providers involved facilitating participant decisions about whether to agree to sequencing. We found that genetic counselors were somewhat more likely than research coordinators to discuss cases involving decision-making challenges, particularly those related to family dynamics or consideration of the value of sequencing for a particular participant.

Challenging Family Dynamics—Interviewees discussed various research and clinical settings in which they encountered problems facilitating decisions due to complicated family dynamics. In pediatric settings, interviewees recounted cases in which there were disagreements between parents or between parents and children about agreeing to sequencing. Several of the pediatric sequencing sites allow parents to decide whether or not to learn different categories of incidental/secondary findings, and selecting which results to learn was sometimes a point of disagreement within families.

So that was one...the mom was just overly—I shouldn't say 'overly anxious,' but very anxious about the testing in general, about what they might find out about their son, where dad really did want mostly everything back. He thought they would be better equipped to deal with concerns in the future if they knew what to expect somewhat. So I tried as best I could to figure out where each was coming from, try and see what similarities they had between them, what their differences in thinking were and work through the possible ways that the results could come back and see how they would feel. But then again, they ended up calling me back the next week and saying that they totally changed their mind. (06-3)

Another interviewee discussed a similar case of parental disagreement about whether to learn certain types of information from the sequencing:

She wanted to do the sequencing and was of the opinion that she wanted the oncologist to have the information to be able to make decisions but she didn't even want to know anything about the tumor and was basically saying 'If we found out that there was something—a marker related to poor prognosis or predictor of bad response—I can't...I don't want to know that.' And germline...like forget it. And the father was really like 'I want to know everything.' So we discussed it in the room and left it that they would opt out of the germline findings... I don't know. I feel like those ones where people don't agree, I find really challenging... they always feel a little yucky when they're not tied up neatly with a bow. (09-3)

In each of the above cases, the interviewees guided families through discussion and brought out each parent's perspective. The families also had the opportunity to reconsider their decisions after leaving the informed consent session. Two other cases involved disagreement between parents and their children who were old enough to provide assent.

I had one whose parents were very eager; very professional parents, very interested. And the son—he was a teenager, I don't know that he wasn't interested, but the fact that we put so much stake into what he thought of it, he ended up declining and the mom...we had a conversation afterwards because she really wanted him to do it, and said that really the fact that we even asked him was kind of the reason he said no. It was the first time in this whole treatment process that he's really had a say and so he just exercised that because he could, not because he didn't really care so much about the results or getting them. (01-2)

And the child was adopted and there was his adopted relative and he actually declined to learn any incidental findings unrelated to the cancer diagnosis and his adopted mother actually wanted to receive those incidental findings. So, it was an interesting opportunity to use some of our counseling and facilitating decision-making skills to understand what were the reasons why the child did not want the results? What were the reasons the parent did want the results? And is there a way that we could reach an agreement about what to do with those kinds of findings? So it wasn't challenging, but what it did show to me is that genetic counselors are especially skilled. It's what we do every day outside of the research setting is actually opening up the doors and facilitating that decision making, making sure that people understand what are the pros and cons and what's the best way to get to a place where everybody is comfortable with the decisions being made. (09-2)

Interviewees (all genetic counselors) who described memorable cases involving family disagreement generally felt that those cases particularly evoked – or challenged – their counseling skills. While issues related to family disagreement were most commonly discussed by interviewees in pediatric settings, adult settings could also be challenging when multiple family members with different perspectives were present. One interviewee shared a case in which an adult woman who, though cognitively intact, was reliant on her family for transportation and medical care. The session where she was making decisions about learning incidental findings was also attended by her father, who was a healthcare professional and

well versed in genetics. The interviewee described her concern that the power dynamics in the session were such that the daughter might not be making her own decision about incidental findings.

And we started talking about that and dad says ‘Well I’ll tell you right now, she wants everything.’ So I had to physically move my chair and look the woman in the face and say ‘So it sounds like you all have maybe talked about this before coming in,’ and she nodded her head at me. And I said, ‘Well what were your thoughts about it?’ ...like really had to purposely engage the participant because their dynamic was just that dad was the decision maker. I don’t think that’s wrong... we talked about it, we debriefed it—me with other counselors—because all of us make decisions in different ways and some of us get advice from people in our family that we think have unique expertise and I do think the daughter felt that dad as a physician did have some insight into this. But it was really clear that had she not wanted that information, I think she still would have ended up requesting it because dad wanted it so much. (10-2)

The interviewee went on to observe that it was challenging to balance her concern for the daughter’s autonomy with respect for the way that decisions are made in the family. This theme was common among those cases that involved family disagreements.

Is sequencing worth it?—Two interviewees discussed cases in which patients questioned whether their participation in sequencing research would be a good use of their time or resources. Because patients at some sites are very ill with terminal conditions, participation in sequencing research may require a lot of time or energy and be unlikely to yield direct benefit. In the following case, the interviewee expressed strong feelings about whether a patient should participate in sequencing research due to health and logistical challenges:

I had one lady who was moving—she’s 31 and has colon cancer and was here house-sitting or something and then she’s moving to [City] the next week and ... she really wanted to be in the study. And she wanted to fly back to [Study site’s city] to do her return visits and clearly, she didn’t have the resources to do that... I was struggling with ‘I don’t want to tell her not to do it’, but she was one where I was like, ‘This is actually what we’re finding for this and I can’t tell you this will be helpful; it hasn’t been helpful for anybody so far.’ So I think I was more frank with her than I am with other people because I was really like ‘this is not a good use of your time; you need to establish care where you’re going and not deal with this’. But I didn’t want to dissuade her; I don’t want to make her feel like it’s less of a good idea than I make it seem to other people. (03-1)

The challenge for this interviewee was in balancing her own feelings about whether participation was useful or feasible for the patient with respect for the patient’s choice to participate. A second interviewee, who also works with terminally ill patients, described a session that was particularly memorable:

And at the time when we met her, it was widely metastatic disease. And we knew that she may not live a long time. So it was memorable because it evolved from

informed consent into discussion about life, everybody's interests, how we deal with difficulties, how we deal with diagnosis, how hopeful it was for them to be able to participate into something that is beyond just their own little world. (10-3)

The interviewee elaborated that she found sessions in which quality of life issues and larger questions leading to careful consideration of the benefits and costs of sequencing particularly memorable and fulfilling for her as a genetic counselor.

Interviewee discomfort with participant decisions—A few interviewees shared cases in which they found themselves uncomfortable with, or even distressed by, a participant's decisions during the informed consent session. One interviewee recalled a case in which she was concerned that the participant did not have adequate time to consider his decision about participation.

So I was going to meet with this participant and it was after hours—it was like after five o'clock—and they called me up and they said '...He missed his enrollment appointment, but are you available to still see him? He's about to get on a plane to go home.' So I ran over and I sat down with him and I went over the consent form with him, and his wife was present... he had seen the consent form before; he had gone over it; ...but having his wife in the room, I think, changed his perspective quite a bit. So he ended up enrolling....and I said 'You know, you don't need to sign this now.' So he was fine with it. His wife was making some noises; like she didn't feel so good about it. But I said 'You don't need to sign this now. You can go home. We'll be enrolling throughout the next year or so; we'll catch you at your next visit—that's fine.' But he said, 'No, no, no. I'm here now. I want to sign it. I'll sign the consent form. Take my blood. I'll do the surveys online when I get home,' etc. So I went through with it. (07-1)

The participant later contacted the study to withdraw, citing concerns about insurance discrimination. In this case, the interviewee had misgivings about whether the participant was making an unpressured, autonomous decision to enroll given the time constraints. She had told the participant that he could take his time and enroll on a future visit, but allowed him to enroll that day despite her concerns about time pressures. The interviewee said that the case influenced her future informed consent sessions in that she made sure to allow adequate time to avoid pressured situations.

Other cases represented situations in which the interviewee's and participant's perspectives differed considerably. One interviewee, who worked on a study that returned all incidental findings to participants, shared a case in which a participant was concerned about the possibility of learning about risk for ALS. The interviewee reflected that she needed to be particularly mindful not to influence the participant's decision despite knowing that there was such a small likelihood of the patient receiving that type of incidental result.

It was hard because I knew that learning about ALS was very, very, very, very unlikely and we were having this whole big conversation about it, about something that probably won't happen. It would be different if it was a likely scenario and we could talk about that, but it seems like a pretty far realm of possibility based on how our report is. And so it was hard to ...adequately educate the person about it,

but then also being careful not to influence him, based on the fact that it was probably not going to happen. (07-3)

The interviewee elaborated that the participant in this case eventually declined to participate, which she felt was an appropriate decision given his concerns. In another case, a mother requested that researchers withhold information about previous research participation from her participating child:

So I would say that the parent I mentioned before who did not want us to assent her child because she didn't want us to talk to him about the original study and explain what that study was about, which again, is not something we necessarily have to say, but it's...she wanted us to agree that we would not mention the original study, which crosses a bit of a line. So that was an interesting conversation and that was certainly memorable. (02-1)

In this case, the researchers felt uncomfortable with this mother's decision and explained that they could not comply with her request. As a result, the family declined to participate in the research study.

Discussion

In this study, we interviewed professionals who likely are among the most experienced in the United States at obtaining informed consent for genomic sequencing. Through their recounting of their most memorable or challenging cases, we have highlighted potential issues for professionals working in genetics as sequencing technology becomes more commonplace. Though their circumstances of sequencing and practice settings vary, the challenges encountered by these professionals fall broadly into two categories: ensuring understanding of information conveyed during the consent process, and facilitating decisions about testing.

Given that disclosure of information about procedures, risks, benefits and alternatives; participant comprehension of that information; and voluntary participation are essential elements of informed consent (Belmont Report, 1979), it is unsurprising that these case examples highlighted concerns about participant understanding of sequencing or the voluntariness of decisions. It has been recommended that an informed consent process for sequencing should include a discussion about the types of results available and their implications for the participant and family members, the likelihood of obtaining certain results, and the limitations of the testing (ACMG, 2013). Cases in which the participant had a low literacy level and appeared to struggle to understand information presented in the informed consent session were challenging for interviewees. This concern aligns with empirical work from other fields documenting frequent misperceptions and deficits in understanding among participants consenting for participation in clinical research studies, especially among subjects with less education (Joffe et al., 2001; Kripalani et al., 2008). A recent systematic review found that simplified consent forms and extended consent discussions significantly improve participant understanding after informed consent for research (Nashimura et al., 2013), and similar approaches to enhancing understanding or

increasing deliberation should be evaluated with respect to informed consent for genomic sequencing.

As acknowledged by some of the study interviewees, the complexities and uncertainties of genomic information are likely to create even more challenges to the informed consent process, especially among populations with low genomic literacy. Informed consent sessions will need to be carefully tailored to meet the personal needs of each patient or research participant through an open exchange with the patient aimed at identifying individual misperceptions, preferences and concerns (Hooker 2014). To supplement face to face counseling, innovative approaches to provide education and support decision-making are being developed and evaluated (Bradbury 2014; Hurle 2013), including e-learning approaches (Birch 2014). To address the challenge of adequate understanding, consensus about what participants should understand, and at what level of detail is needed (Bradbury 2014). Beskow et al (2014) has shown recently how through the use of a Delphi process, the views of multiple stakeholders can be used to develop consensus on critical elements of informed consent.

Interviewees also highlighted the challenges of working with participants with extremely high expectations for diagnostic results from sequencing, which are out of alignment with published estimates of sequencing diagnostic yield (Yang et al., 2014). Interviewees responded to this challenge by directly addressing these unrealistic expectations. Previous research has found that the public tends to overestimate the benefits of genomic sequencing, particularly for diagnostic applications (McGowan et al., 2013; Wade, Tarini & Wilfond, 2013). Public education addressing genomics generally and the limitations of genomic testing specifically may lead to more realistic expectations of genomic testing (Hurle, 2013).

Several interviewees, particularly those trained as genetic counselors, found themselves challenged by situations involving family discord, coercion or disagreement in decision making. Because genomic sequencing results impact families, and because the testing is often offered in settings where multiple family members are involved in the decisions, it can be challenging for professionals to navigate among competing interests. Our findings suggest that genetic counselors may be particularly attuned to these issues relative to research professionals from other backgrounds. Recognizing that genomic test results also impact relatives, Minari et al. (2014) have suggested that a “family consent” model of informed consent be used. With such a model, conflicts and agenda differences among family members would serve as a basis for opening lines of communication within the family. While helping families reach consensus about decisions could sometimes be challenging for professionals in this study, it also speaks to their ability to effectively facilitate decision-making by creating an environment in which varying viewpoints could be shared and discussed. Given their training, genetic counselors involved with sequencing research may be especially well positioned to foster this kind of environment and help all parties understand the research process and make decisions about participation (Hooker et al., 2014).

Informed consent for genomic sequencing may involve many decision points, such as whether to participate, selection of any optional findings offered as part of sequencing, and

decisions about future use and storage of data; consequently, there are many opportunities for disagreement among parties who may participate in the decision-making process. Because of their training, genetic counselors obtaining informed consent for sequencing likely find themselves balancing professional principles of non-directiveness with the moral imperative to protect the autonomy of patients or their surrogates. Those obtaining consent in pediatric settings need to respect the perspectives and decision-making processes of individual families by acknowledging that the child's role in decision-making will vary (Geller et al., 2003; Miller & Nelson, 2006). Interviewees occasionally found themselves uncomfortable when facilitating patient decisions, especially in cases where patient preferences were in conflict with their own personal feelings or sense of professional responsibility. In a few situations, genetic counselors expressed the desire to sway participants who had terminal conditions or considerable resource limitations away from participation. This was perceived to be at odds with their professional commitment to non-directiveness, which resulted in internal struggle or distress. Interviewees reported that they navigated these situations as best they could, and often reflected on lessons learned for future consent sessions. Bernhardt et al. (2010) also found that many distressing situations experienced by genetic counselors arose from a sense of obligation to be non-directive in situations where the counselor held strong opinions about the patient's best interests. Given these experiences, particular attention to the potential for role conflicts for genetic counselors who are involved in both patient care and research enrollment may be warranted (Markel & Yashar, 2004).

Limitations

Limitations of these findings stem from the small sample size and the clinical and research settings included, in that challenges described in some case examples are specific to the population consented by interviewees (e.g. adults vs. children, healthy vs. ill populations). Additionally, most interviewees were involved in projects focusing on the process of offering and evaluating genomic sequencing, and experience of these interviewees may not mirror usual clinical practice. Importantly, all interviewees had experience consenting patients or participants for sequencing in the United States, and professionals' experiences in other countries may vary. Findings from this study are not meant to be generalizable. Nonetheless, some challenges encountered by professionals interviewed in this study, such as ensuring participant understanding, supporting decision-making, varying subject literacy and family disagreements, were commonly referenced across settings and are likely to be encountered broadly in both research and clinical settings.

Practice Implications

Many of the informed consent challenges reported by interviewees in this study are not novel and will be familiar to professionals who have consented patients for other types of genetic testing. However, the complexity of genomic sequencing, the variety and uncertainty of potential results, the broad implications of those results, and the elevated expectations of personal benefit from genomic sequencing create some new or amplified challenges for informed consent. As the field begins to recognize informed consent challenges unique to or heightened by genomic technology, case examples may be a valuable training tool for practitioners who are new to obtaining informed consent for sequencing. These case

examples could be incorporated into online interactive learning modules aimed at training genetic counselors to provide education, facilitate decision-making and obtain informed consent for genomic sequencing (Hooker 2014). Issues cited by providers in these case examples may be a jumping-off point for preparing the genetics field to adapt existing techniques and consent processes to the new demands of genomic sequencing.

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References

- ACMG Board of Directors. ACMG policy statement: Updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*. 2014 Published online 13 November 2014.
- ACMG Board of Directors. Points to consider for informed consent for genome/exome sequencing. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*. 2013; 15(9): 748–749.10.1038/gim.2013.94 [PubMed: 23970068]
- Appelbaum PS, Parens E, Waldman CR, Klitzman R, Fyer A, Martinez J, Chung WK. Models of consent to return of incidental findings in genomic research. *The Hastings Center Report*. 2014; 44(4):22–32.10.1002/hast.328 [PubMed: 24919982]
- Appelbaum PS, Waldman CR, Fyer A, Klitzman R, Parens E, Martinez J, Chung WK. Informed consent for return of incidental findings in genomic research. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*. 2014; 16(5):367–373.10.1038/gim.2013.145 [PubMed: 24158054]
- Ayuso C, Millan JM, Mancheno M, Dal-Re R. Informed consent for whole-genome sequencing studies in the clinical setting. Proposed recommendations on essential content and process. *European Journal of Human Genetics: EJHG*. 2013; 21(10):1054–1059.10.1038/ejhg.2012.297 [PubMed: 23321621]
- Belmont Report. The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research. 1979. Retrieved November 7, 2014, from [hhs.gov/ohrp/humansubjects/guidance/belmont.html](https://www.fda.gov/ohrt/humansubjects/guidance/belmont.html)
- Bernhardt BA, Silver R, Rushton CH, Micco E, Geller G. What keeps you up at night? Genetics professionals' distressing experiences in patient care. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*. 2010; 12(5):289–297.10.1097/GIM.0b013e3181db82d9 [PubMed: 20386316]
- Beskow LM, Dombeck CB, Thompson CP, Watson-Ormond JK, Weinfurt KP. Informed consent for biobanking: Consensus-based guidelines for adequate comprehension. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*. 2014 Epub ahead of print.
- Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. *The New England Journal of Medicine*. 2014; 371(12):1170.10.1056/NEJMc1408914 [PubMed: 25229935]
- Birch PH. Interactive e-counseling for genetics pre-test decisions: where are we now? *Clinical Genetics*. 2014; 2014 Epub ahead of print.
- Bunnik EM, de Jong A, Nijsingh N, de Wert GM. The new genetics and informed consent: differentiating choice to preserve autonomy. *Bioethics*. 2013; 27(6):348–355.10.1111/bioe.12030 [PubMed: 23718722]
- Bradbury AR, Patrick-Miller L, Long J, Powers J, Stopfer J, Forman A, Domchek SM. Development of a tiered and binned genetic counseling model for informed consent in the era of multiplex testing for cancer susceptibility. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*. 2014; 2014 Epub ahead of print.

- Burke W, Evans BJ, Jarvik GP. Return of results: Ethical and legal distinctions between research and clinical care. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*. 2014; 166(1):105–111.10.1002/ajmg.c.31393
- Davis AM, Hull SC, Grady C, Wilfond BS, Henderson GE. The invisible hand in clinical research: the study coordinator's critical role in human subjects protection. *The Journal of Law, Medicine & Ethics: A Journal of the American Society of Law, Medicine & Ethics*. 2002; 30(3):411–419.10.1111/j.1748-720X.2002.tb00410
- Fisher JA, Kalbaugh CA. Altruism in clinical research: coordinators' orientation to their professional roles. *Nursing Outlook*. 2012; 60(3):143–8. 148.e1.10.1016/j.outlook.2011.10.002 [PubMed: 22083045]
- Geller G, Tambor ES, Bernhardt BA, Fraser G, Wissow LS. Informed consent for enrolling minors in genetic susceptibility research: A qualitative study of at-risk children's and parents' views about children's role in decision-making. *Journal of Adolescent Health*. 2003; 32(4):260–271.10.1016/S1054-139X(02)00459-7 [PubMed: 12667730]
- Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL. American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*. 2013; 15(7):565–574.10.1038/gim.2013.73 [PubMed: 23788249]
- Hooker GW, Ormond KE, Sweet K, Biesecker BB. Teaching genomic counseling: preparing the genetic counseling workforce for the genomic era. *Journal of Genetic Counseling*. 2014; 23(4): 445–451.10.1007/s10897-014-9689-4 [PubMed: 24504939]
- Hurle B, Citrin T, Jenkins JF, Kaphingst KA, Lamb N, Roseman JE, Bonham VL. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*. 2013; 15(8):658–663.10.1038/gim.2013.14 [PubMed: 23448722]
- Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent in cancer clinical trials: a cross-sectional survey. *Lancet*. 2001; 358(9295):1772–1777. S0140-6736(01)06805-2. [PubMed: 11734235]
- Kripalani S, Bengtzen R, Henderson LE, Jacobson TA. Clinical research in low-literacy populations: using teach-back to assess comprehension of informed consent and privacy information. *IRB*. 2008; 30(2):13–19. [PubMed: 18512655]
- Manolio TA, Green ED. Leading the way to genomic medicine. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*. 2014; 166(1):1–7.10.1002/ajmg.c.31384
- Markel DS, Yashar BM. The interface between the practice of medical genetics and human genetic research: what every genetic counselor needs to know. *Journal of Genetic Counseling*. 2004; 13(5):351–368. NY00000403 [pii]. [PubMed: 15604636]
- McGowan ML, Glinka A, Highland J, Asaad G, Sharp RR. Genetics patients' perspectives on clinical genomic testing. *Personalized Medicine*. 2013; 10(4):339–347.10.2217/pme.13.32 [PubMed: 24955098]
- Miller VA, Nelson RM. A developmental approach to child assent for nontherapeutic research. *The Journal of Pediatrics*. 2006; 149(1 Suppl):S25–30. S0022-3476(06)00373-8 [pii]. [PubMed: 16829238]
- Minari J, Teare H, Mitchell C, Kaye J, Kato K. The emerging need for family- centric initiatives for obtaining consent in personal genome research. *Genome medicine*. 2014; 6(12):118.10.1186/s13073-014-0118-y [PubMed: 25593596]
- Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. *BMC Medical Ethics*. 2013; 14:28-6939-14-28.10.1186/1472-6939-14-28 [PubMed: 23879694]
- Wade CH, Tarini BA, Wilfond BS. Growing up in the genomic era: implications of whole-genome sequencing for children, families, and pediatric practice. *Annual Review of Genomics and Human Genetics*. 2013; 14:535–555.10.1146/annurev-genom-091212-153425
- Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of Mendelian disorders. *New England Journal of Medicine*. 2013; 369:1502–1511.10.1056/NEJMoa1306555 [PubMed: 24088041]

Yang Y, Muzny DM, Xia F, Niu Z, Person R, Ding Y, Eng CM. Molecular Findings Among Patients Referred for Clinical Whole-Exome Sequencing. *Journal of the American Medical Association*. 2014; 312(18):1870–1879.10.1001/jama.2014.14601 [PubMed: 25326635]

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Table I

Interviewees (N=24)

	N	%
Profession		
Research coordinator	8	33
Genetic counselor	16	66
Years of professional experience		
0–2	6	25
3–5	7	29
6–10	3	13
>10	6	25
Not reported	2	8
Sequencing consenting experience		
CSER research only	13	54
Non-CSER research only	1	4
Clinical only	1	4
Clinical and research	9	38
# patients/participants personally consented		
20	2	8
21–50	11	46
>50	10	42
Not reported	1	4
Population consented for sequencing		
Children only	5	21
Adults only	11	46
Children and adults	8	33

Table II

Primary Challenge in Each Case

Primary Issue/Challenge	Number of cases (n=24)
Challenges related to participant understanding	13
General and genomic literacy	6
Managing expectations	2
Contextual factors	5
Challenges related to facilitating decision-making	11
Challenging family dynamics	6
Is sequencing “worth it”?	2
Discomfort with participant decisions	3