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Informed Consent for Whole Genome Sequencing: A Qualitative Analysis of Participant Expectations and Perceptions of Risks, Benefits, and Harms

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Abstract

Scientific evidence on the extent to which ethical concerns about privacy, confidentiality, and return of results for whole genome sequencing (WGS) are effectively conveyed by informed consent (IC) is lacking. The aim of this study was to learn, via qualitative interviews, about participant expectations and perceptions of risks, benefits, and harms of WGS. Participants in two families with Miller syndrome consented for WGS were interviewed about their experiences of the IC process and their perceptions of risks, benefits, and harms of WGS. Interviews were transcribed and analyzed for common themes. IC documents are included in the supplementary materials. Participants expressed minimal concerns about privacy and confidentiality with regard to both their participation and sharing of their WGS data in restricted access databases. Participants expressed strong preferences about how results should be returned, requesting both flexibility of the results return process and options for the types of results to be returned. Participant concerns about risks to privacy and confidentiality from broad sharing of WGS data are likely to be strongly influenced by social and medical context. In these families with a rare Mendelian syndrome, the perceived benefits of participation strongly trumped concerns about risks. Individual preferences, for results return, even within a family, varied widely. This underscores the need to develop a framework for results return that allows explicitly for participant preferences and enables modifications to preferences over time. Web-based tools that facilitate participant management of their individual research results could accommodate such a framework.

Keywords

Whole genome sequencing; informed consent; results return; participant preferences

INTRODUCTION

Whole genome sequencing (WGS) of individuals and families is a transformative new tool for discovering novel genes and pathways underlying Mendelian disorders and perhaps complex diseases as well. To date, the genomes of several hundred individuals have been

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reported, primarily as a consequence of testing different sequencing platforms, computational approaches, and analytical methods [Levy et al., 2007, Wheeler et al., 2008, Wang et al., 2008, Roach et al., 2010, Schuster et al., 2010, Ashley et al., 2010, Pelak et al., 2010]. Moreover, a recent informal survey of genomics centers suggests that by the end of 2011 more than 30,000 genomes will have been sequenced [Genomes by the thousand, 2010]. Accordingly, use of WGS is already widespread. The rapid growth of WGS in biomedical research is, however, occurring largely in the absence of empirical data on how to most effectively conduct informed consent (IC), much less on participant expectations/perceptions of risks, benefits, and harms of WGS.

Recently, we used exome sequencing (ES) of multiple, unrelated, affected individuals to identify the gene for Miller syndrome [Ng et al., 2010]. Miller syndrome is a rare, autosomal recessive disorder characterized by craniofacial and limb anomalies. In parallel to this effort and in part in case the causal mutation for Miller syndrome was located outside the exome capture target, two families, consisting of both parents and their two adult children with Miller syndrome were also recruited for WGS [Roach et al, 2010]. While both families were recruited for WGS, we anticipated that the members of only one family would undergo WGS, whereas the other family would only be sequenced if the DNA from the first family failed sequencing (e.g., technical failure). WGS of this Miller family began before the causal gene was identified via ES.

As this family would be the first, to our knowledge, with a Mendelian disorder to undergo WGS, developing an IC process posed several challenges, in particular, addressing issues of privacy, data sharing and return of results. This was due in part to the unparalleled scope of genetic risk information to be discovered from each individual, combined with both knowledge of familial relationships and the potential media attention that would be focused on the study because of its novelty.

While the broad ethical principles that should be considered in WGS studies have been presented [Caulfield et al., 2008, McGuire et al., 2008] and several investigators have discussed the IC process that accompanied WGS of individuals [Wheeler et al., 2008, Ormond et al, 2010, McGuire and Lupski, 2010], the processes used for IC and return of results have not been evaluated empirically. Furthermore, while consensus guidelines on WGS from a working group have been reported, development of these guidelines predated the exponential increase in WGS studies and its conclusions do not easily translate into the current landscape in which WGS is being increasingly applied in many genetic studies [Caulfield et al, 2008].

We describe the development of an IC document for WGS and the process used for obtaining IC. Both the IC document and process were designed to reflect the somewhat unique ethical challenges presented by WGS and our limited understanding of possible risks and benefits. In addition, we report the results of a qualitative analysis of interviews conducted with each participant about their experiences with the IC process and their perceptions of the risk associated with sharing of WGS data, as well as their preferences for return of results. Based on our findings, we make general recommendations about IC for WGS studies and discuss issues that we think deserve further investigation.

MATERIALS AND METHODS

Study Population

Two families (A and B), each including both parents and their adult children with Miller syndrome, were recruited to participate in a project in which their whole genomes were to be sequenced. These two families were selected from a larger cohort of families with Miller

syndrome because they each had two affected offspring. Because both families were already enrolled in a related study to find the gene for Miller syndrome, they were somewhat familiar with human genetics research, traditional approaches to gene discovery, and the process of IC. However, the IC process in which they had previously participated did not include an explicit discussion of WGS. Family B also had an unaffected adult daughter who was not included in the WGS study, but who attended the IC conference and participated in the subsequent qualitative interview study. Family A was located in the United States, in a different state than the investigators; Family B was not located in the United States. All individuals were of European ancestry and native English speakers.

Development of the Informed Consent Document for WGS

Using the basic principles of IC, we identified three key areas of WGS research that were different enough from the original study to warrant modification of the IC document to include: 1) a description of the overall experimental approach; 2) an explanation of the possible risks to confidentiality and privacy from the generation of WGS data and data sharing; and 3) an explicit approach for return of results to each participant that included a description of the types of genetic variants identified accompanied by summary information of their potential clinical utility. Using these core elements as a guide, we developed an IC document for WGS. The final consent form was 9 pages and 4,014 words long (see Supplementary Materials for full IC form).

The consent document defined and described WGS and explained that, in addition to identifying the specific cause of Miller syndrome, a major goal of the research was to study the process of whole genome sequencing in a family, the nature of variation transmitted from parent to offspring, and the ability to *de novo* mutations. It included statements about risks to privacy and confidentiality stemming from the vast amount of variation data generated from each individual and the anticipated deposition of the sequence data into the database of genotypes and phenotypes (dbGaP). dbGaP is a restricted access data repository supported and managed by NIH (Mailman et al., 2007). NIH-funded GWAS studies generally have been required to share genotype and phenotype data to dbGaP, and recently some NIH-funded exome and whole genome sequencing studies have also been required or encouraged to share data via dbGaP. Researchers must apply for permission to gain access to each specific dataset in dbGaP, agree to conditions of use and make guarantees about the security of the data. Data in dbGaP is de-identified, although a recent study demonstrated that is possible to use aggregate frequency data from GWAS studies in dbGaP to determine whether an individual is a member of a study cohort (Homer et al., 2008). Such risks of sharing exome and whole genome sequencing data in dbGaP are discussed in detail elsewhere (Tabor et al., 2011).

For this study, the IC document indicated that the risk of identifiability for the participants would be high for at least three reasons independent of the planned sharing of sequence data in dbGaP or other databases. First, Miller syndrome is extremely rare (i.e., roughly two dozen families reported) and manuscripts describing the clinical characteristics of affected individuals from both families along with photographs of their faces had been published. Although the use of photographs is not a new challenge to privacy and confidentiality in genetic research, this practice increases the risk of linking a research subject to risk variants in WGS data with phenotypic consequences. Second, both families could be more identifiable because each had a unique pedigree among reported families with Miller syndrome. Third, this WGS study was likely to receive increased media attention because of its novelty. The increased risk of inferring the identity of a study participant could facilitate linking them to other genetic or phenotypic data that might be stigmatizing or discriminatory.

The consent document explicitly addressed the return of WGS results, including those both related to and coincidental with Miller syndrome. Results were binned to reflect how they would be summarized for publication and summary results from each bin were offered for return. These bins included (1) a summary of overall variation, (2) variants considered to be "potentially harmful," and (3) variants associated with common diseases, drug response, non-medical and personality traits, and ancestry. The summary of overall variation included the number and proportion of different kinds of variants (e.g., synonymous, missense, nonsense) and the number and proportion of known and novel variants. Participants were given the option to receive or not receive all research results, and the option to revise their decision during the course of the study (Box 1, Supplementary Material – see Supporting Information online).

Compared to targeted approaches (e.g., sequencing candidate genes) and genomic approaches (e.g., array comparative genomic hybridization), the risk of identifying "incidental findings" via WGS is substantially higher. Accordingly, the consent document explicitly described the risk of identifying incidental findings, including possibly undesired or unanticipated information.

IRB Review

The Seattle Children's Hospital Institutional Review Board (IRB) reviewed and approved the protocol to perform WGS as a modification to a "parent" study protocol on limb malformation syndromes, under which both families were originally enrolled. The IRB required that a Research Family Liaison (RFL) be included in the IC process. The RFL is a staff position at Seattle Children's Research Institute whose responsibility is to assist families and to collaborate with members of the pediatric research team to facilitate IC [Salas et al., 2008]. Specifically, the IRB required that the RFL speak privately with each participant to ensure he or she understood the aims of the study and did not feel coerced into participation, particularly by other family members. The IRB also reviewed and approved the protocol for the qualitative interview study.

Informed Consent Conferences

Prior to the consent conference (CC), each family member was sent a copy of the IC document via e-mail to enable advance review. The CC involved a consent team composed of: a study coordinator (MJM), the principal investigator (MJB), a genetic counselor (KMD), and a bioethicist (HKT), one or more family members and an RFL. Members of both families requested the CCs be conducted with more than one family member present, and for one family with all family members present. This request was accommodated for three reasons. First, we wanted to respect the preferences and autonomy of the family about who they wanted present during the interview. Second, by speaking to family members together, we could ensure that they all received the same information, and had the opportunity to hear each other's questions and the corresponding answers. Third, by consenting family members together, we could encourage discussion about risks and benefits among all family members.

Families A and B lived in locations distant from the research team, making it difficult to conduct CC's in person. This is a common scenario for studies of rare genetic diseases, for which participants are often recruited from around the world. Therefore, we conducted the CC either by telephone or by live streaming video (LSV). The latter required that prospective participants have a computer, access to the internet, and know how/be willing to use this tool. We expected that use of LSV might improve communication, as it would allow us to observe, be sensitive to, and respond to non-verbal cues indicative of confusion, anxiety, and/or frustration during the discussion.

The CC with Family A (CC1) was conducted with the mother, affected son and affected daughter. The GC was present with Family A while the remainder of the research team participated via telephone. A separate CC was conducted with the father in Family A alone and took place via telephone with all members of the consent team (CC2). The CC with Family B (CC3) included the mother, father, affected son, affected daughter, and unaffected daughter. CC3 was performed via LSV with the exception that the GC participated via telephone (Fig 1). In each CC, the GC reviewed each section of the consent document, paraphrasing some parts and reading others, and provided opportunities for family members to ask questions of the research team. As required by the IRB, the RFL spoke with each family member individually after the consent form was reviewed, but prior to participants agreeing to participate, to confirm understanding, and to discuss risks and benefits.

Qualitative Interviews and Analysis

Families were contacted within two weeks of their CC to schedule an interview about the WGS consent process and their perceptions of the risks and benefits of WGS research. All interviews took place via telephone and were audio-recorded and transcribed. Names and other identifiers were redacted. Three members of Family A (mother, affected son, affected daughter) were interviewed together at their request. The father of Family A was interviewed separately. Each member of Family B was interviewed separately.

The interview instrument was semi-structured and open-ended and included questions about five topics: 1) experiences living with Miller syndrome; 2) the study of Miller syndrome; 3) participation in the WGS project; 4) the IC process; and 5) the plan for return of results. Interview questions in these topic areas were designed to elicit perceptions related to aspects of IC including: a) the purpose of the research project and descriptions of research procedure; b) motivations for participation; c) benefits and risks; d) confidentiality; e) return of results; and f) data sharing.

Transcripts were uploaded into the qualitative analysis software program Atlas.ti 6.0. Using a conventional content analysis approach [Hsieh and Shannon, 2005] the coding team developed an initial coding scheme for classifying content based upon topics reflected in interview questions as listed above. Two coding team members (HKT and J. Stock) read the interview transcripts and developed a codebook for themes. Two coding team members (TB and J. Stock) consecutively coded interviews using this codebook, incorporating additional codes for newly identified and emerging themes. The entire coding team (HKT, TB, and J. Stock) met and reviewed the results from both coders, finalized the code list, and resolved any discrepancies through discussion and consensus.

RESULTS

Results are described in five major categories: 1) experiences and opinions about the consent process; 2) participant descriptions of WGS, and whether and how it differs from other types of genetic research; 3) motivations for participation and expectations of the study; 4) concerns about risks related to privacy and confidentiality from WGS and 5) perspectives on return of results.

The Informed Consent Process

Length of Consent Conference—All of the participants in CC3 expressed frustration with the length of time required to obtain IC (2–3 hours). However, they recognized that shortening the process might be challenging given the scope of information that needed to be discussed. They also respected the need for the IC process to be thorough, and the fact that it was a requirement of the research:

> "You had to cover everything that you had to cover. And you had to feel that everybody who was consenting to this study knew what they were consenting to, and were consenting, they were truly giving informed consent. And for me, ethically, that was really important." (Parent 1, Family B)

> "I was very comfortable that the process was crossing all the T's and dotting all the I's, and getting everything absolutely right. The part of me that was saying, 'Hurry up, let's get on with it,' was in conflict with the part of me that says, `Well, this is good, they're doing it properly.'" (Parent 2, Family B)

A member of Family B expressed concern about the consent conference "taking a long time about things that maybe I don't necessarily worry about." She stated that she would have preferred that the process be spread out over several shorter conversations:

> "It was just for me, too much information all at once….I have a poor memory, anyway…Most of it would have been in one ear, and I would have understood it, but it would have been kind of in one ear and out the other at the same time. So I just don't sort of retain a whole lot of information at once. (Affected Offspring 1, Family B)

Live Streaming Video vs. Phone—Parent 1 and Affected Offspring 1 and 2 from Family A found use of a telephone for the CC frustrating. This was in part because both affected offspring use hearing-assist devices, but more importantly because it made it difficult for them to interpret nonverbal cues revealed by the consent team. As one family member explained:

> "Pretty much the majority of what you obtained from me, as far as how I'm feeling, and anything, is mostly going to be a physical body, body language, and what not. Not just my voice answering a question. I mean, obviously, we can change the tone of our voice, but it's still just isn't going to show you if you know, if we're happy, or if we're upset, or whatever. I mean, it's just, it IS impersonal, and it's just not accurate, especially in this day and age. I don't see why it has to be done that way." (Affected Offspring 2, Family A)

Instead, members of Family A would have preferred that the consent conference take place face-to-face: "Obviously, it's a really huge and very, very important study. I mean, it kind of breaks through science. And yet, we don't see each other in person? It's just kind of weird" (Affected Offspring 2, Family A). In contrast, Parent 2 from Family A, who participated in a separate phone CC, did not express any concerns about the use of a phone.

CC2 for Family B was conducted by LSV. All participants thought that use of LSV was better than consent via phone because it allowed for nonverbal communication. As Parent 2 explained:

> "I think it was better than a telephone conversation. In that Skype is not as good as being there in that you can't see who's out of camera shot, but it is good to be able to see facial expressions and that sort of thing, as you're going through these things. So, from my point of view, I thought that while the technology isn't perfect, it was still a lot better than just having a telephone conversation" (Parent 2, Family B)

Family B valued the establishment of a visual link through LSV, and thought that this contributed substantially to their trust in the researchers and the research process:

> "But, it was good to be able to see face to face, you know, and to see the people who are actually participating in the project who are doing the work, who are on the ground, and to know that, you know, we're, our samples are entrusted to people that we felt were being honest with us, and just came across as being very genuine

> and very worthy, and very interested in trying to help us as a family." (Parent 2, Family B)

Use of LSV did introduce some minor technical difficulties (e.g., "jerky video") and several family members stated that the call affected their short-term access to the internet: "we have a capped broadband?[1] And so, 2.5 hours, nearly 3 hours on Skype, just about wiped out our whole month's broadband." (Parent 1, Family B)

Research Family Liaison and Genetic Counselor Participation—Participants in Family A focused their concerns about the consent process on the involvement of the RFL. They expressed discomfort with the tone the RFL used during each interview, calling it "uncomfortable," "serious" and "offensive." Parent 1 stated: "I actually felt a little bit like I was being cross examined…like a social security administrator, the people that we deal with from the government [to get services for their affected children]." Affected Offspring 2 from Family B echoed this perspective, stating, "I felt like being put on the spot a bit, taking an impromptu exam type thing."

Parent 1 in Family A acknowledged that while the intent of the RFL's participation was to ensure understanding about risks and benefits of the research, she felt that the process was insensitive to her family's unique experiences and motivations for participation in the research as a family with a rare disease and disability.

> "I just want to say that I do understand. I do understand that they wanted to, that [the RFL] wanted to make sure that we understand what was being done, and that even though we don't understand what can happen, like, when it hits the news,… but she wanted, I guess she was protecting us, to see if we really understood what we were saying "yes" to..And, that, I think that's important. But, our life, our entire existence, is so different than what someone that isn't involved in this type of a life could understand. But that's why it seems unnecessary to us." (Parent 1, Family A)

Three of four members of Family A expressed concern that if they did not answer the questions from the RFL correctly, she might "stop" the research, and it was very important to them for the research to proceed and for them to be allowed to participate. Parent 1 in Family A described the RFL as creating "bad energy" and a feeling of pressure: "We just picked up the energy of how absolutely important it was to do it right, and in a way, to even somehow not get the wrong answer, whatever that was, that might not get approval to do this project. I didn't like that at all."

Affected Offspring 2 from Family A did not understand why the RFL interview was necessary, arguing: "I mean, there's no reason not to do it [the study] in my eyes, and I don't see it as, I just don't see any reason why a signature [on the consent form] can't just answer every question."

In contrast, Parent 2 in Family A was neutral about the involvement of the RFL. Similarly, four out of five family members in Family B felt positive about their experience with the RFL, and thought that interviewing the adult offspring separately protected their autonomy. Parent 2 in Family B stated: "I felt it was quite a reasonable sort of, if you like, check and balance against domination of one of the parents over the children, in the family discussion…to me that was quite a reasonable thing to do."

[1]"Capped broadband" refers to a contract with an Internet Service Provider that allows for a limited amount of data use/transfer over a given period of time, for example a maximum amount of data use/transfer for a month.

Two parents, one from each family, spontaneously stated that they were “impressed” by the IC process, and explained that the length and detail of the consent affected their impression of the research. One parent said, “I remember thinking that a lot of effort is going into this from a lot of pretty smart people. And that it must be important to spend that kind of time and that kind of involvement to do that.” (Parent 2, Family A). The other parent stated: “I was really impressed [with the consent process]. It was very thorough; every avenue was sort of gone into.” (Parent 1, Family B).

Participants expressed positive or neutral perspectives on the involvement of the GC in the consent process. In all three CCs, the GC read the consent document and answered questions. Parent 1, Family A stated that the GC involvement was, “very, very helpful…it was really very nice for me, very personal.” Parent 2 in Family A was unclear what role the GC played but felt neutral about her involvement: “I'm sure there's probably, there is a role for that?…genetic counseling, I'm not sure what that means or what that would be for… through the consent form and stuff, I understand the terminology and all that stuff? But it just seemed normal to me.”

Members of Family B expressed no strong opinions about the participation of the GC, and felt that her role met their expectations:

> “I guess I didn't think about it in any special way. I guess my view was that if the research team wanted a genetics [sic] counselor involved, so be it. I didn't feel any particular need to have a genetics [sic] counselor as part of the conversation, for me personally. I can't speak for the others on that. But I didn't have any problem with it.” (Parent 2, Family B)

Comprehension of Consent Process—Participants differed somewhat in their self-assessed understanding of the consent process content. All participants responded affirmatively when asked if the process was clear; they felt that enough information was provided, and that all of their questions had been answered:

> “I felt like my understanding was very clear of what they were going to be doing, why they were doing it, the pros and cons, if you'd like, unique experiences there might be, like around media attention and things like that. So it was really thorough. And that was really good.” (Parent 1, Family B)

One participant from each family indicated that the information about the study was complicated. They felt that some of the information was beyond their understanding. However, they did not consider this a major concern and thought that they did not need to understand it better:

> “I'm not going and looking up and thinking up questions, and finding out, there's nothing I need to know. I'm not as, aware of everything that, as you, as all of you people [research team] are. Being involved in that stuff. So it's so big and it's so, probably important, and so way over my head, as far as technical stuff…” (Parent 2, Family A)

Comprehension of WGS Approach—One parent from each family was able to describe in some detail the goals and approach of WGS. Parent 1 in Family A described the process as creating a “map” of the genome from each family member and comparing their maps to a reference map:

> “and they see all the common sites on the map. And then they look at all the things that aren't common, and they say, you know, “I wonder if any of these things that aren't common could possibly be the Miller gene?” Or maybe they find genes in an

> area that it's at the limb, on the legs, or the bones, and they look in that area. But, and then the bottom line is, they're just trying to find the Miller gene…" (Parent 1, Family A)

Parent 1 from Family B described the nature of the information that would be examined in WGS:

> "they're looking at the whole package of genes, from me, personally, and that they would be able to, if I wanted to get information about it, that they could find information about a lot of different aspects of my genetic code, that might point to things like, whether I might have a predisposition to a particular illness, or whether I carry any other genetic conditions that I could perhaps pass on to someone else, or that I might come down with myself." (Parent 1, Family B)

More than half of family members interviewed (n=5) indicated that they found it difficult to understand and or explain WGS, even after the GC reviewed the topic and purpose of the study. For example, one participant who described WGS as technically "different," explained that it was difficult for him to answer one of questions asked by the RFL: "[She asked] `What's your understanding of what we're trying to achieve?' And it was a very hard question to answer" (Parent 2, Family B) One of the affected offspring stated: "It [WGS] is such a broad subject that, unless you are really in the field and know the lingo of how to explain, it's just, it's kind of like, you know, explaining gravity in a way. It's just complicated" (Affected Offspring 2, Family A). Parent 2 from Family A simply said, "It's so, still far over my head."

Motivations for Participation and Expectations about the Study

The primary motivation of each participant to consent to WGS was to "identify the gene that causes Miller syndrome." In part, this stemmed from a desire for a greater understanding of why they or their family members have Miller syndrome: "I mean, for me…it's really important to get an answer as to why, you know, because we have this huge void…I just kind of want that "why" answer" (Affected Offspring 2, Family A). Participants also expressed altruism as a motivating factor, and a hope that finding a gene for Miller syndrome could help other families who might have or be at high risk for the same or a similar syndrome: "We really feel strongly that if some other human being can benefit from us participating in this study and finding out the missing link that satisfies us at a very deep level" (Parent 1, Family A). She also described the satisfaction that her adult children would get from making a unique contribution to science and society that only they could make because of their disability:

> "When you think about all of the things that people with normal bodies, and normal talents get to do, to feel important—like, if you're a good golfer, you can feel important—and when you have limitations, numerous limitations, what you get to do to feel important is very limited. So this is a great opportunity to feel important, and something that other people can't do, because they weren't born with these bodies, they weren't born with Miller Syndrome…" (Parent 1, Family A)

In general, family members expressed high hopes but low expectations that WGS would identify the gene for Miller syndrome. This was based in part on past experiences with genetic studies of Miller syndrome that had failed to find the gene: "I expect nothing from it, and hope that they'll [the investigators] get something" (Affected Offspring 2, Family A). Despite their hopes, participants were unsure how any result would be translated into a direct benefit for them: "Identifying [the gene] is one thing, but if there's anything that can be done with it, I think that's what's important…" (Parent 2, Family A). Members of Family B noted that identification of the gene would allow for testing of carrier status for their unaffected child/sibling and facilitate family planning. An affected offspring from Family A

also expressed an interest in information for reproductive decision-making "I've always thought about, my offspring, and how that would be affected" (Affected Offspring 2, Family A).

Family Decision-Making about Participation in WGS Study—All members of Family B described the important role of family discussion and consultation in their decision about whether or not to participate in the WGS study. They preferred to participate in the CC together, and insisted that their unaffected adult child, who was ineligible to participate, be present to hear about the study and ask questions:

> "We actually talk about things as a family very much here. We're very much a family, there's no secrets in our family. And we talk about things together. So she [the unaffected adult child] needed to be a part of that, because it's [Miller syndrome] been a long part, large part of her life, too." (Parent 1, Family B)

> "It worked for us because we were all pretty much in tune before we started. And nobody in the family was afraid, if they had a dissenting view, to put it forward." (Parent 2, Family B)

Both the parents and offspring in Family B stated that their family dynamics helped them to consider and discuss participation, while respecting the opinions and autonomy of each family member, especially the adult affected offspring. Parent 2 described how the family talked about the study and their participation extensively before the CC, and compared it to the way their family has made decisions about other issues, including medical issues and education:

> "That's the way we've pretty much always done things….What we did worked well for us, because everybody understood and understands that none of us were trying to put pressure on the others to do any particular thing…I think you need to understand that if we didn't do it that way, we'd all have to spend the time informing ourselves, sometimes. And then, we sort of share information within the family to come to, sometimes to an agreement to disagree. And that goes for everything here, not just the medical stuff. It's really worked when we were talking about schooling, it's how we worked it, how we work it on a day-to-day basis, really." (Parent 2, Family B)

Confidentiality and Privacy—Participants were asked whether or not they were concerned about risks to confidentiality and privacy, and if so to describe their concerns. All nine of the participants stated that they were not concerned about possible risks to confidentiality and privacy. In part, they said, any risk of participation paled in comparison to everyday life concerns: "there's more things to be worried about in our life right now than whether we might be known or not, in a study" (Parent 1, Family B).

Parents from both families explained that their lack of concern was also related to their unique perspective as members of families previously described in published reports: "We've never kept our kids hidden…our kids have been published. Our life has been published…it's there for people to see, and it's there for other medical professions to be involved with" (Parent 1, Family B). One of the affected offspring perceived the risk of both being identified in medical literature and databases of genetic data to be low: "It doesn't sort of really worry me, because there are lots of other things that are in medical journals…And so mine would just be in a pool with all the other information really" (Affected Offspring 1, Family B).

Three of four of the parents explained that their diminished concern about risks to confidentiality and privacy was due to their existing lack of privacy because of the

noticeable physical features of Miller syndrome. One parent felt that researchers did not understand this perspective:

> "They [researchers] don't understand what little privacy we have, every day we step out the door. When I'm with…[my adult children], I have no privacy as far as people staring….[My adult children] can't go anywhere and be incognito, or invisible. So again, our perception of privacy is a lot different than, than somebody who has a normal body." (Parent 1, Family A)

One of her adult children added: "I would want as much attention as possible," in part because he thought it might attract publicity for his business. (Affected Offspring 2, Family A).

Parent 1 in Family B explained that before agreeing to participate they investigated whether any genetic information identified in the study could affect their insurance or access to medical care. This parent also was interested in whether there was an obligation to disclose results from the study to medical or insurance agencies. Affected Offspring 2, Family B expressed some concern about potential media attention because of the novelty of WGS, "I'm not one for giving it out to Life Magazine," but stated that this did not affect his decision to participate.

Members of both families acknowledged the possible increased risk to their privacy due to their participation. This risk was tempered by their shared experiences of the public's response to their craniofacial abnormalities. Additionally, they did not perceive the risk to be greater than the risks to which they had been exposed because of their participation in other studies. Moreover, they thought the potential benefit(s) of identifying the gene for Miller syndrome outweighed potential risks: "I understand the amount [of privacy protection]…. And beyond that, nobody can control anything. So it's worth the risk." (Affected Offspring 1, Family A) Another parent suggested that while the issue was discussed among family members, it was not a major concern:

> "I think there was some small concern raised within the consent form and the process itself about the small number of participants in the study making it potentially relatively easy for somebody to identify the participants. And, within the family, we sort of had some sort of discussion about that. I think the children were perhaps more concerned than [other parent] or I, but I don't think, at the end of the day, personally, I didn't have a big issue, because I spent twenty years as a [profession] and telling the media to go run and jump was part of daily life. So I can do that if I need to!" (Parent 2, Family B)

Return of Results

Participants expressed a very strong desire to learn about genes discovered for Miller syndrome. Affected Offspring 1 in Family B explained that such information was part of her identity, and that learning about the gene itself would satisfy a long-held desire to know what caused the disease:

> "I guess I've always wanted to know about the gene [that causes Miller syndrome] …the other [genetic information]…just doesn't really worry me one way or another?…I guess the gene is, you know, it's kind of…it's kind of me, isn't it? The gene is my makeup, so it'd be quite interesting to know about that. But the other stuff, I could really care less about, really." (Affected Offspring 1, Family B)

Participants did not think that the information about a gene for Miller syndrome would have a substantial impact on their lives. Affected Offspring 1 from Family B said, "Unless there's something that you can do with it…it's not like, say, finding a cancer gene in the hopes they

try to get rid of it." However, he indicated that he would be concerned about results that suggested he might be more likely to "markedly deteriorate at some point."

In contrast to the unanimous desire to receive information about the gene for Miller syndrome, participants were ambivalent about whether they wanted to receive results about other genes or conditions. In part, they were unsure as to what kind of information might be returned and what impact it might have on their lives. Parent 2, Family B explained: "One part of me says, `Yes, let's find out everything there is to know about me,' and the other part of me says, `Well, I am what I am, just let it be.'" Their child had a similar perspective: "I've gotten this far in life without knowing, or worrying. I go to the doctor when I'm sick, and that's the way it's always been." (Affected Offspring 1, Family B).

Parent 2, Family A was concerned about the uncertainty associated with some results: "So you're going to find out something that, it isn't like you're going to read in a textbook. It's something unknown. You don't know what it is and…can that unknown information affect the way you live?" Family members also admitted that because so many potential results were possible, they could not anticipate their own preferences about whether or not to receive results until they were returned: "Whatever answers or information that they do give, that's what I will start asking about, `cause obviously, now, I don't even know what to be asking for" (Affected Offspring 2, Family A).

Several unaffected family members recognized that, despite the long conversation about results, they had not really considered carefully what results they did or did not want, or why, until it was discussed in the study interview. The unaffected offspring from Family B explained: "I think I'd just be happy in general to get results back…I've never really thought about what I wouldn't want to know." Similarly, Parent 1 in Family A stated that she had not considered how she might react to results other than those related to Miller syndrome:

> "I honestly don't know how I'm going to feel…if I'm told I have a gene for Alzheimer's…I have no idea how I'll feel about it until it happens. So, I may not want to just like say, "okay, everybody. Bye, I'm going to go back to work now"…I just think I didn't realize how I would want it until right now." (Parent 1, Family A)

Parent 1 from Family B was unsure about how she would feel about results unrelated to Miller syndrome, and preferred to receive such results via her physician. She also stated that she would prefer to receive results about which she could be proactive, and work together with her doctor to implement appropriate actions or behaviors. All of the parents stated that they knew that variants influencing risk for complex diseases were not deterministic and are influenced by both genes and environmental factors. Therefore, they remained unsure about whether such information would be useful to them.

Because of their ambivalence about the majority of WGS results, several participants believed that it was important to them to be able to change their preferences for receiving results. In this way, they expressed an understanding that the individual meaning and relevance of genetic information in a given person will change over time:

> "We wanted to know kind of what the time frame was, and the process. We needed to know a little bit, we wanted to know a little bit more about what specifically they would be looking, and doing…could we change our mind, you know, if we'd said `yes,' and then decided, `no,' …Or, if we said, `no,' could we change our mind and said `yes.'" (Parent 1, Family B)

Parent 2 from Family A went so far as to change his preferences during the study from receipt of no results to return of all results.

Family members preferred different processes for receiving different kinds of results. They all wanted to receive results about Miller syndrome together with their family members. However, three out of the four parents, preferred to receive results unrelated to Miller syndrome in private. Additionally, they wanted both a verbal and written explanation of results as they anticipated the information would be complex and difficult to understand, and a written explanation could be reviewed again at their convenience.

DISCUSSION

We developed a protocol for obtaining IC for WGS of individuals and families, and subsequently investigated fundamental elements of both the process used to obtain consent and participant preferences for return of results. The aim was to use the information collected to improve the framework for IC and return of results from WGS studies and to identify key research questions for which empirical data would provide further guidance. Analysis of interview data revealed several major findings: (1) concerns of participants in WGS studies about privacy or risks from loss of confidentiality might be different than frequently anticipated; (2) existing guidelines for return of results have not adequately anticipated specific features of WGS studies that will challenge their implementation; and (3) simple extrapolation of conventional approaches to obtaining IC can result in excessive and undue burden on participants in WGS studies.

Risks to confidentiality and privacy from WGS or the sharing of WGS data with other researches were unexpectedly of little concern to participants. This attitude may be due to their previous participation in genetic research that included publication of identifying photographs, the ease with which they are recognized to have a disorder affecting their appearance, or a combination thereof. Perhaps more importantly, they considered the potential benefits of making WGS data widely available to outweigh potential harms related to lack of privacy. This perspective is counterintuitive to the concerns of many IRBs and policy makers about the risk of sharing WGS data. It seems likely that research participants from a more general population or with less recognizable characteristics may have different, more conservative perspectives, but our results suggest that harms related to data sharing may be of overall lower priority to participants in certain research contexts.

There are several challenges to return of results for WGS studies compared to traditional approaches, including: the large number of results available, the increased number of findings of potential clinical utility, the need to interpret novel or private mutations that could be functionally deleterious, and the change in clinical implications over time. When research results are returned, the approach used is typically based on a clinical-service model of genetic testing. A certified GC returns a result to a participant, explains its implications, provides psychosocial support and guidance, and is available to answer questions. While this might be the optimal approach, it would be both impractical and extremely costly for large-scale WGS studies. Moreover, the large number of results of potential clinical utility will likely surpass the capacity of the GC workforce in North America, and the “clinical significance” associated with variants identified by WGS will change frequently, potentially requiring repeated GC consultation.

We found that participants preferred to be given a range of options about which results to receive. However, each participant was interested in receiving results about Miller syndrome even though such results might have little, if any, clinical utility. As other investigators have recognized, research results without clear clinical utility are often of interest to individuals with specific conditions or diseases because of participants' “need to know more about their disease process” (McGuire and Lupski, 2010). Participants had a wider range of perspectives about receiving genetic results unrelated to Miller Syndrome: what they wanted

to receive, why, and how they would want to receive it. Return of results unrelated to the primary goals of the study, identification of the gene for Miller syndrome, is one of the major challenges of IC for WGS (Wolf et al., 2008). We, and others, have addressed this issue, particularly the changing nature of so-called “incidental findings” in greater detail elsewhere (Tabor et al., 2011, Sharp 2011).

Our findings suggest that researchers may need to develop tools to frame options that help participants consider the range of results that may be offered (for example, only clinically significant and actionable results in many studies), and the possible risks and benefits of anticipated and unanticipated information. In other words, whether an individual wants results returned will sometimes not be a simple “yes/no” answer. Instead results return should be considered a multi-dimensional dynamic process that accounts for a range of participant preferences about return of different kinds of results and that facilitates the evolution of both participant preferences and the clinical utility of results over time. This need for explicit framing of result categories and options for return will be a new challenge for WGS studies. Web-based tools that facilitate participant management of their individual research results could accommodate such a framework.

We found that simple extrapolation of conventional approaches to informed consent may not be appropriate for WGS, and may result in excessive and undue burden on participants. The IC process was long, lasting two to three hours in length, and all nine participants disliked the length of the CC. Several factors contributed to the length of the CC: a desire to thoroughly describe WGS, the review of options about return of results, the IRB requirement that the RFL separately interview each family member, and simultaneous participation of several members of the same family in the session.

These findings were not wholly unanticipated, and indeed it will be challenging to develop consent documents and processes for WGS that provide enough information about a complex experimental approach to ensure that a participant can make an informed decision about participation, while minimizing the burden of the IC process itself. Researchers, in collaboration with bioethicists and IRBs, will need to develop more efficient and innovative ways to explain the benefits and risks of WGS and assess participant understanding. Research participants do not need to understand the technical details of WGS and how it differs from other genetic approaches. Rather, they need to understand the goals of the research, and the risks and benefits of their participation. The participants we interviewed thought they had an adequate understanding of the relevant information and that their questions had been answered. Yet they also thought that details of the experimental approach were still difficult, and perhaps more importantly, unnecessary, for them to understand.

The development of IC protocols for WGS will benefit from the participation of GCs and bioethicists with expertise in informed consent and human genomics research. GCs may be important resources for participants as they consider their options for receiving results, though novel approaches for considering preferences and options for return of results will need to be developed because the size of the workforce of GCs is relatively small compared to the scale at which genome sequencing is likely to take place.

In our study, it was unclear that involvement by the RFL was necessary or beneficial to the CC. In fact, involvement of a RFL elicited a strong negative response from several of our participants, suggesting that this component of the consent process may have been counterproductive. These findings suggest that alternative, perhaps less invasive, approaches to mitigating the risks of coercion are needed. Indeed, most institutions are unlikely to have RFLs available on staff, making their involvement broadly impractical or impossible.

As of yet, there is no consensus as to whether WGS requires an IC document or process that differs from that typically used for conventional genetic studies. Key differences of WGS include the increased likelihood of identifying results with clinical utility that could be returned to study participants and the increased risk of identifiability as a result of sharing WGS data. Addressing the possible benefits and risks resulting from these differences required us to develop a new process for IC and we think that addressing these issues in new consent documents for prospectively collecting samples is optimal. This does not necessarily mean that researchers must universally commit to re-consenting participants for WGS. They should, however, accurately describe the (1) likelihood that results of clinical utility will be identified, (2) plans for returning results, and (3) plans for WGS data sharing including concomitant risks related to privacy and confidentiality.

The results from the two families studied differed in several important ways. Family A was, in general, interested in receiving all possible results, whether related directly or not to Miller Syndrome. Members of Family A were negative about the RFL but positive about the GC. Members of Family B were less interested in receiving results unrelated to Miller syndrome. They were positive about the consent process and the roles of both the RFL and the GC. It is difficult to generalize from these differences, or determine to what extent differences were influenced by family membership and/or their shared CC experience. However, they do suggest that perspectives about data sharing, confidentiality, and return of results might be quite varied both within and between families.

This study has several important limitations. The analysis of the IC process was limited to two families with the same rare multiple malformation syndrome. These results may not be generalizable to individuals (or WGS research participants) with other diseases, or to the general population. It is also possible that families with a rare Mendelian disease, or families that have participated previously in genetic research, may be more knowledgeable and savvy about genetics, genetic research, and possible risks and benefits. They may also be more likely to want to receive results from the research, both related and unrelated to their disease, than the general population. Also, because family members participated in the IC process together, their perspectives may have influenced each other, and their views may not be independent.

Use of WGS to study families with rare Mendelian diseases, cohorts with common complex traits and “healthy” populations is becoming increasingly commonplace. Empirical analysis of participant experiences with IC and return of results for WGS across a range of studies and participant populations is needed to provide data and a framework around which investigators can develop IC processes appropriate to their research programs. To some extent, these efforts could be facilitated if not complemented by national coordination among stakeholders (e.g., federal funding agencies, policy makers, advocacy groups, professional organizations) to develop consensus guidelines and general recommendations for researchers and IRBs. To this end, public sharing (e.g., via supplementary data) of IC documents and protocols among investigators could be helpful and expedite development of best ethical practices for WGS research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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