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Experiences With Obtaining Informed Consent for Genomic Sequencing

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Despite the increased utilization of genome and exome sequencing, little is known about the actual content and process of informed consent for sequencing. We addressed this by interviewing 29 genetic counselors and research coordinators experienced in obtaining informed consent for sequencing in research and clinical settings. Interviews focused on the process and content of informed consent; patients/participants' common questions, concerns and misperceptions; and challenges to obtaining informed consent. Content analysis of transcribed interviews revealed that the main challenges to obtaining consent related to the broad scope and uncertainty of results, and patient/participants' unrealistic expectations about the likely number and utility of results. Interviewees modified their approach to sessions according to contextual issues surrounding the indication for testing, type of patient, and timing of testing. With experience, most interviewees structured sessions to place less emphasis on standard elements in the consent form and technological aspects of sequencing. They instead focused on addressing misperceptions and helping patients/participants develop realistic expectations about the types and implications of possible results, including secondary findings. These findings suggest that informed consent sessions should focus on key issues that may be misunderstood by patients/participants. Future research should address the extent to which various stakeholders agree on key elements of informed consent. © 2015 Wiley Periodicals, Inc.

Key words: genetic counseling; genetic testing; genomic sequencing; informed consent; qualitative research

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INTRODUCTION

Genome sequencing is increasingly being performed in both clinical and research settings. Currently, clinical sequencing primarily aids in the diagnosis of individuals who have conditions suspected to have a genetic etiology [Biesecker and Green, 2014]. In such situations, sequencing identifies a pathogenic variant in about 25% of cases [Lee et al., 2014; Yang et al., 2014], occasionally leading to significant changes in clinical management [Worthey et al., 2011; Milligan et al., 2014]. Although currently not in widespread use, clinical genomic sequencing can guide cancer therapy selection and monitoring [Garraway, 2013; McLeod, 2013; Van Allen et al., 2014] and is being applied in many other clinical situations [Bowdin et al., 2014; Dewey et al., 2014]. Despite predicted clinical utility, experts have identified factors that preclude its rapid clinical adoption, and limitations that should be addressed in the informed consent process [Burke et al., 2013; Evans and Khoury, 2013; Manolio et al., 2013; McLeod, 2013;

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Biesecker and Green, 2014; Dewey et al., 2014; Vrijenhoek et al., 2015]. To briefly summarize, technical limitations prevent the identification of all disease-associated variants, and the reliance on incomplete and error-prone variant databases prevents the unambiguous classification of many variants that are identified. Despite efforts to improve and streamline variant capturing and calling, data on genotype-phenotype correlation may be unavailable, and controversy remains about which variants, or categories of variants should be returned to patients. Additional barriers to clinical adoption include limited evidence of clinical validity and utility of test results; the uncertain nature and frequency of adverse psychosocial outcomes resulting from testing; and concern that patients and providers might not understand results or act appropriately on them.

The informed consent process can be used to help patients understand the implications of possible results and the limitations of testing, and make decisions about the return of secondary findings. Lessons learned from experiences in obtaining consent and returning results could guide best practices, potentially preventing some of the possible harms if and when sequencing gains widespread use.

The National Institutes of Health through the Clinical Sequencing Exploratory Research (CSER) Consortium has spearheaded efforts to collect evidentiary data for the successful clinical integration of genomic sequencing. CSER consortium projects offer genome or exome sequencing to participants with a variety of clinical indications to investigate the efficacy, impact and outcomes of testing [Gray et al., 2014]. Cohorts represented in the various CSER consortium projects include healthy adults; adults seeking preconception carrier screening; adults who previously participated in genetic research; and children and adults with suspected genetic conditions, including various types of cancer, cardiomyopathies, or intellectual disabilities. In each of these projects, participants are offered, or randomized to be offered, some secondary findings. Additional information about the CSER projects can be found at https://cser-consortium.org/projects.

Although the offer of sequencing in these projects is governed by site-specific research protocols, there are many direct links to clinical activities. For example, participants are usually recruited by the patients' clinicians; the confirmed, diagnostic results may be entered into the participant's medical record; and clinicians who either assume responsibility for acting on results or making appropriate referrals are members of the research team [Burke et al., 2014]. Thus, the content of the consent process in these projects must address elements relating to research participation as well as the expected risks, benefits and limitations of learning clinically-relevant and non-relevant results, including secondary findings [Scollon et al., 2014].

Policies are also being developed that address clinical integration of genomic sequencing, including informed consent [Manolio and Green, 2014]. The American College of Medical Genetics and Genomics (ACMG) has defined a minimum list of "actionable" genes for which laboratories should report pathogenic variants identified as secondary findings because appropriate clinical action can significantly reduce disease risk [Green et al., 2013]. The initial ACMG statement recommended that, regardless of the clinical indication for sequencing, laboratories should analyze and report mutations found in 56 genes associated with 24 Mendelian conditions [Green et al., 2013]. The revised statement acknowledged that patients should be able to decline secondary findings [ACMG Board of Directors, 2014].

The ACMG has also outlined points to consider for the informed consent process for genomic sequencing [ACMG Board of Directors, 2013]. Recommended content of informed consent includes the likelihood and types of primary and secondary findings that might be returned; the risks, benefits and limitations of testing; potential implications for family members; whether identifiable results are provided to databases; and policies for re-contacting as new knowledge is gained about the clinical implications of a variant. The ACMG guidelines are thus broad and primarily address the content, rather than the process, of informed consent. Early reports of the consent process for research genomic sequencing described the complexity [Ormond et al., 2010; Rigter et al., 2014], and warned of the large amount of time needed to obtain informed consent [Mayer et al., 2011; Tabor et al., 2012]. It has become clear that, in order to make the process scalable and manageable to both patients and clinicians, alternative strategies are needed that provide important information without overwhelming the recipient [Hooker et al., 2014].

As a first step to examining which content was deemed important to relay, the consent forms being used by the 9 U01 CSER projects were compared [Henderson et al., 2014]. The content showed considerable heterogeneity, an unsurprising finding in light of the differences in the types of patients recruited, the inclusion of results in the medical record, the results eligible to be returned and the degree to which participant preferences influence this decision [Henderson et al., 2014]. It was also noted that the consent forms were generally long (mean number of words was 4588) and used language demanding a high reading level (median Flesch-Kincaid grade level was 10.8). However, the content of consent forms may not be associated with one's level of understanding, as many participants (and patients) sign consent forms without reading them [Joffe et al., 2001; Desch et al., 2011; Robinson et al., 2013]. Even when relatively simple and recognizable language is used in consent documents, gaps in understanding remain [Morgenstern et al., 2014]. The potential discrepancy between consent form content and patient comprehension highlights the critical role played by interpersonal interactions to promote understanding, autonomy and shared decision-making [Schenker et al., 2011; Nishimura et al., 2013; Presidential Commission for the Study of Bioethical Issues, 2013].

Genetic counselors have played a central role in interpersonal interactions during the consent process for genetic testing because of their expertise in educating patients and families about genetics, and counseling them about the risks, benefits and limitations of genetic tests [Markel and Yashar, 2004]. Settings offering genomic sequencing both clinically and under research protocols in the United States rely on genetic counselors to obtain informed consent and participate in the return of results [Iglesias et al., 2014; Rigter et al., 2014; Williams et al., 2014]. Some CSER projects also use research coordinators trained by genetic counselors to obtain consent.

We conducted semi-structured interviews with individuals in the U.S. who are currently among the most experienced at obtain-

ing consent: genetic counselors and research coordinators for the CSER-sites and genetic counselors obtaining consent for clinical sequencing. In this paper, we describe the content and process of informed consent for genomic sequencing as reported by these experienced professionals, and describe factors that influenced the way they conducted consent sessions. These data can be used to inform the development of guidance on the content and process of informed consent for genomic sequencing.

MATERIALS AND METHODS

Participants

We recruited study participants in two ways. First, we contacted a principal Investigator (PI) or Co-PI from each of the 9 NIH-funded U01 CSER projects or from other projects in the CSER consortium that offer genomic sequencing, to request names and contact information for 1-3 individuals (study coordinators, genetic counselors or physicians) with the most experience conducting informed consent sessions for their genomic sequencing project. Second, investigators identified 5 large clinical centers in the United States known to the study team for their experience offering clinical genomic sequencing and contacted 1 genetic counselor at each center about participating in the project.

Recruitment and Data Collection

A study investigator sent an email describing the study to potential interviewees and scheduled a telephone interview. The study team developed a semi-structured interview guide that included open-ended questions followed by probes asking interviewees to describe their clinical experience and responsibilities; the process of consenting study participants and/or patients for genomic sequencing; common questions, concerns and misperceptions patients/participants had raised; how obtaining informed consent for genomic sequencing differed from obtaining consent for other types of genetic tests, and challenges that had arisen and how they responded to them. We also asked interviewees to describe a particularly challenging or memorable case; findings from that part of the interview have been reported elsewhere [Tomlinson et al., 2015].

Interviews were conducted by four study team members (three genetic counselors and one social worker). Each interviewer initially conducted one interview and the transcripts from those interviews were reviewed and discussed by team members. The interview guide was modified slightly after the initial interviews, and feedback was given to standardize the way each interviewer asked questions and the probes used to expand on interviewee responses. After obtaining verbal consent, we conducted digitally recorded phone interviews between March and July, 2014. Each interview lasted between 30 to 80 min, and was later transcribed.

Data Analysis

We reviewed the transcribed interviews to check for accuracy, completeness, and to remove any identifiable information. We imported de-identified interview transcripts into QSR International's NVivo 10 software for coding and content analysis. Study investigators met after reviewing a subset of transcripts to develop a coding system through an iterative process standard for content analysis [Miles et al., 2013]. Initial codes related directly to questions asked during the interviews (for example, common questions that participants/patients raised; length of sessions, challenges, etc.). Eight transcripts were independently coded by two investigators, both of whom are experienced qualitative researchers with considerable coding experience, and differences in coding were resolved by consensus. Because there were so few discrepancies in coding, the remaining transcripts were coded by a single coder. New codes were added to the codebook as needed, after discussion with the study team. After all transcripts were coded, the investigators reviewed the coded data to identify dominant themes. Anticipating that obtaining informed consent in a research setting might differ in important ways from that obtained in a clinical setting, we noted the setting and whether the interviewee was a genetic counselor or a research coordinator while reading the transcripts and summarizing findings. We selected representative quotes to illustrate pertinent findings.

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

RESULTS

Twenty-nine of 35 potential interviewees contacted completed interviews for an 83% participation rate. The majority of interviewees were genetic counselors; about half had at least 6 years' experience (Table I). Thirteen had experience obtaining informed consent for sequencing in clinical settings and nearly all had

TABLE I. Interviewees (n = 29)

	N	%
Profession		
Research coordinator	8	27.6
Genetic counselor	21	72.4
Years of professional experience		
0–2	6	20.7
3–5	8	27.6
6–10	4	13.8
>10	8	27.6
Not reported	3	10.3
Sequencing consenting experience		
Research only	16	55.1
Clinical only	2	6.9
Clinical and research	11	37.9
# Patients/participants personally consented		
<20	5	17.2
21–50	13	44.8
>50	10	34.5
Not reported	1	3.4
Population consented for sequencing		
Children only	5	17.2
Adults only	14	48.3
Children and adults	10	34.5

conducted at least 20 consent sessions for exome or genome sequencing.

We have organized the results of the interviews into findings related to the contextual issues interviewees considered as they structured a consent session, differences between obtaining informed consent for genomic sequencing and for other types of genetic testing, the *process* of consenting, and the *content* of consent sessions. The individuals interviewed are referred to as "interviewees". We use the term "patients/participants" in cases where interviewees referred to patients or research participants interchangeably. Otherwise, those offered sequencing are referred to as either patients or participants. When interviewees referred to consenting a child for sequencing, we frequently use the term "family" because the parents were the primary participants in the informed consent discussion.

Contextual Issues Influencing the Consent Process

Interviewees identified a variety of contextual factors that influenced their approach to conducting consent sessions (Table II). Interviewees considered these factors when structuring sessions and anticipating how different families might weigh the risks and benefits in deciding whether or not to agree to sequencing and/or opt to learn secondary findings. First, interviewees considered whether sequencing was being offered as a part of a research protocol or as a clinical service, and ensured that the patient understood the difference, especially because research testing was frequently offered by the participant's own clinician during the course of a clinic visit. As one research coordinator explained:

> "The very first thing that we do is we make it extremely clear that the clinical visit is over—anything that was discussed in the clinical visit is over and completely separate. We say: "We are now going to embark on a research topic". We stare them right in the face and make sure they get that. (03-2)

Interviewees pointed out that discussion of the return of secondary findings also differed according to the context for offering testing. With research testing, the research protocol dictates which, when and how secondary results would be returned. When testing is offered in a clinical setting, discussion of return of results, including secondary findings is frequently based on policies of the laboratory performing the sequencing. When genomic testing is offered to children in both research and clinical contexts, the fact that some results might be available on parents when trios are tested became an important contextual issue that interviewees considered when obtaining consent. Interviewees also discussed how they varied the consent session when consenting a healthy adult in a research protocol, for whom all findings would be secondary, as opposed to testing an affected child whose parents may have spent years seeking the cause of their child's condition. In those cases, parents frequently have an inflated expectation for an answer from exome or genome sequencing. Additionally, in families with an acute illness, such as cancer, interviewees pointed out that there is an unrealistic expectation that sequencing will lead to modifications in treatment. Because of their preoccupation with their child's serious illness, such families may fail to attend to discussion of secondary findings, or may make decisions about return of such findings based on limited consideration of risks and benefits. Interviewees also explained that they approached informed consent differently depending on how much time the family could devote to the session, how much time they had already spent at the hospital that day, and the amount of time that had elapsed after a diagnosis was made or suggested. When families had limited time available, or were already overwhelmed, interviewees indicated that they might decide to obtain informed consent over two visits. Finally, interviewees considered how much experience a patient or family has had with genetic testing. In families new to genetic testing, for example, when a child is diagnosed with cancer, more explanation of genetics might be included in the informed consent session. When offering genomic sequencing to the parents of a child who had already had multiple genetic tests, interviewees would spend minimal time discussing the basics of genetics, but more time explaining the difference between whole exome sequencing and other tests previously performed, such as chromosomal microarray analysis or testing for mutations in single genes.

How Obtaining Consent for Genomic Sequencing Is Different

The genetic counselors interviewed were asked how consenting for genomic sequencing differs from obtaining informed consent for other types of genetic tests. Nearly all interviewees indicated that there are distinct differences, primarily relating to the broader scope of possible results available from genomic sequencing, as well as the greater potential for obtaining uncertain results. As one genetic counselor explained:

> "The scope is so much broader. . .. the possibility [of a VUS] is so much greater and there's so much more that we don't know than we do." (05-1)

Genetic counselors discussed having to change their usual approach of providing in depth education about potential results that might be obtained when testing for single genes or small panels of genes. One interviewee explained how she modified her typical approach:

> "When we first started thinking about doing sequencing, we were overwhelmed just because we had been trained to consent for a single gene test or a panel of tests and since there was less information to talk about, we did a really good job explaining every piece of that. But with sequencing, you can't possibly explain every single outcome. You don't know every single outcome" (07-3)

Given the possibility of secondary findings results, interviewees pointed out that unlike testing for a single condition for which there is a family history, patients/participants may have no experience with the types of conditions they might learn about through genomic sequencing. One genetic counselor said:

TABLE II. Contextual Issues Considered When Approaching Informed Consent

Issue	Reason for importance	Illustrative quotes
Research vs. clinical testing	Expectation of benefit; discussion of study-related procedures; confusion about research testing in clinical setting; types of results returned	*"In clinic, the message is clearer because you're just talking about the test; you're not also talking about all the complexities of research." (10-2)* *"Because we're doing this research project in the clinic. . . they feel like they're getting a medical test"(03-1)*
Pediatric vs. adult	Assent for pediatric testing; availability of results on parents when children are tested (trio testing)	*"So we want to always try to obtain assent when we should, but sometimes they're playing video games. I need to really make sure that they are part of the conversation. " (01-1)* *"Even though we're doing the test on the child we can find out information about the parents." (01-3)*
Healthy vs. affected	All results are incidental in healthy individuals; those affected expect an answer/treatment	*"I think the healthy population usually has more concerns—maybe just because they have more to lose." (07-2)* *"When people are so wanting the information and wanting a potential genetic diagnosis, does that cloud the ability to truly think about secondary findings or to truly think about potential risks that could come from it?" (20-7)*
Type of illness	Individuals with acute illness may expect testing will lead to treatment; In families with an acute illness, genomic testing may be a low priority; diagnostic odyssey for those with chronic illness; less concern about risks for those with terminal illness	*"These parents are concerned with their kid with cancer. That's their number one thing. That's so overwhelming in itself that they really don't stress out, or think so much, about the genetic testing." (01-1)* *"Most of the patients, participants that we see, are coming in so excited about the study that they don't want to listen to any of it, they just want to sign the consent form. Like, okay, where do I sign? I'll sign now." (8-2)* *"Our patients are terminal, and so their motivations for enrolling in these kinds of projects might be different from other groups because they have nothing to lose, at this point." (09-2)*
Timing	Amount of time family has been in clinic; poor attention/comprehension if individual recently became ill/received diagnosis	*"A lot of times they've got four more appointments and they're trying to run to their next appointment, so we definitely go with the flow and are flexible." (01-2)* *"A very common answer would be 'I got my hands full. I'm looking at chemotherapy and I can't handle this.'" (03-2)*
Previous experience with genetic testing	Level of knowledge about genetic testing; need to differentiate exome/genome sequencing from other genetic tests	*"For most people in the study, this is not their first genetic test so they've already been consented for some clinical genetic testing" (10-2)* *"So I think that the biggest challenge is that it does require a pretty in-depth knowledge of genetic information. We're fortunate that the people who are getting to us have often gone through some of that process already, so the baseline level is a little bit higher." (20-8)*

"The hardest part is when you're counseling for a specific gene, people come in with some idea of what this might mean for them because they had some experience with the condition in question. . .[with sequencing] they may have a finding that doesn't make sense to them at all because they don't have any personal experience with it." (09-3)

Because of this, the decision-making process about undergoing testing may differ, as this interviewee explained:

"So it seems like they're almost more thoughtful when it comes to a single gene disorder, which they may experience in their family...I think it's harder, sometimes, to deal with the implications of a known quantity than an unknown quantity" (08-2)

Since patients/participants do not necessarily expect to learn results that are unrelated to their primary indication for testing, several interviewees discussed how they try to prepare patients for

thinking about the broader scope of genomic sequencing before they obtain consent. One genetic counselor offering clinical sequencing explained:

> "It's tough with the optional pieces and they have a lot they need to decide, so I do try to get them ahead of time, before we want to order the test, and give them some time to discuss it with family or think about it instead of right there when they're in front of me". (01-2)

Process of Consenting Patients/Participants

When asked to describe the process by which they obtained consent, interviewees reported a variety of approaches. In clinical settings, the consent process was conducted by a genetic counselor with or without a clinical geneticist and occurred as part of a single clinical visit, or in 2 sessions when insurance pre-authorization was needed. The consent process was integrated into the genetic counseling session to include a discussion of the risks, benefits and limitations of testing. In the research settings, the process of obtaining consent was largely influenced by the specific research design and protocol. As shown in Table III, a physician, usually the patient's clinician, most often introduced the study and explained what participation would entail. In all projects, a research coordinator and/or a genetic counselor explained study components and obtained informed consent. In nearly all studies, patients who enrolled interacted with, or were given the opportunity to interact with, a genetic counselor. In 2 of the 9 CSER sites, participants were always given the consent form or educational materials before the study visit. In 3 additional studies, this access sometimes occurred.

Many interviewees explained that they initially had conducted sessions by closely following the order of topics in the consent form but, as they gained more experience, they began to summarize the main topics and re-order topics discussed according to the desires of participants. Both genetic counselors and research coordinators reported modifying their sessions in this way. This change led to much less rigidly structured sessions guided largely by the individual patient/participant's level of knowledge, interests and concerns. As one interviewee said:

> "When I first started, I stuck to the consent form more. Now I've developed my own way to explain it in an easier way to understand. It also depends on the participant; I kind of change the way I speak based on how informed they are on the topic." (07-2)

This restructuring allowed for more family engagement in the discussion. Also, with more experience, interviewees reported that they gained more of a sense of the kinds of questions a family might be expected to ask, and guided families to ask them if they were not voiced during the session. One interviewee explained:

> "I'm able to say 'some people want everything back; some people don't want anything back.' Just having experienced some questions or concerns that other families have brought up before, I can incorporate that into the session if the families aren't really talking much or if they don't have a lot of questions." (06-3)

Interviewees reported session length varying between 10-70 minutes with 30 minutes being the most common length reported. In general, informed consent sessions for sequencing offered as a part of a research protocol were slightly longer than those for clinical sequencing because of the need to discuss the procedures involved with research participation. In both settings, the factor most often reported to increase the session's duration was a family's increased interest and engagement. Other factors associated with longer sessions were less familiarity with the genetic testing process, lack of participants' previous exposure to the consent form and/or the educational materials, less previous discussion about the study or about sequencing by clinical or study personnel, the presence of a disruptive child, and the need for a language interpreter.

Content of Informed Consent Sessions

The content of sessions also varied and was largely determined by the context for testing and patient/participants' questions and concerns, and their underlying knowledge and expectations of their potential sequencing results. Most interviewees indicated that

TABLE III. Components of the Informed Consent Process Used by CSER U01 Projects

	Study number								
Informed consent component	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
MD introduces study	+	+	+	+	+	+	+	+	
IC form/educational materials sent ahead	+/−	+/−		+		+/−			+
RC contact by phone before IC session		+/−		+	+				+
RC consents		+							
RC consents/GC provided					+				
RC consents/GC offered								+	
GC and/or MD consents	+					+			+
GC or RC consents			+						
GC and RC consent				+			+		

IC, Informed consent; RC, Research coordinator; GC, Genetic Counselor. + = always done in study +/− = sometimes done in study.

the main educational challenge to obtaining informed consent for genome sequencing stemmed from the patient/participants' unfamiliarity with the broad scope of results that could be returned, including multiple variants of uncertain clinical significance (VUS), and their blurring the distinction between diagnostic and secondary findings related to health. In addition, the participant's or parents' need to make decisions about whether or not to learn about various categories of secondary findings led to consent sessions that were different from those addressing other types of genetic testing. Interviewees observed that many patients/participants clung to the unrealistic expectation that their results would illuminate not only the condition for which sequencing was indicated, but also any possible future health problems. This commonly-held belief led interviewees to emphasize the limitations of sequencing in order to help patients/participants to develop realistic expectations about the types and utility of results that might be learned.

Interviewees who conducted research consent sessions described the difficulty of maintaining participants' attention as they tried to review the content of the consent document, facilitate understanding of the types of results that could be returned, and help participants make decisions about which secondary findings to request. With more experience, both genetic counselors and research coordinators began to paraphrase or only briefly review study-related items contained in the consent document. They also placed less emphasis on educating participants about genomics and sequencing techniques, focusing instead on describing the kinds of results that could be learned and their implications. Much of the variability of the content stemmed from differences between research protocols about topics such as how results would be returned, which types of secondary findings could be learned, and the inclusion of results in the medical record. For example, in some CSER projects, results were returned spanning two separate visits, in some, participants could choose to learn about many types of secondary findings, and in some projects, all or a portion of results were automatically included in the medical record.

The Patient/Participants' Perspective—Which Questions, Concerns and Misperceptions Influence the Content of the Consent Session?

The most common patient/participant questions, concerns and misperceptions reported by interviewees are shown in Table IV. Other than questions about practical aspects of research participation or testing, the majority of research participants raised few questions spontaneously during the consent sessions. Interviewees attributed the scarcity of questions to: patients'/participants' previous experience with genetic testing or with research participation; the extent to which they had already interacted with study personnel; their access to study materials, including educational pamphlets and the consent form prior to the session; being overwhelmed by the informed consent process or by their or their child's current illness; and/or the novelty of genomic testing. Although some patients/participants raised concerns about privacy, confidentiality and the potential for insurance discrimination, in most cases, questions or concerns were raised only after these topics had been introduced. Interviewees frequently attributed the apparent lack of concern about risks of testing or study participation to the patient/participants' primary focus on getting an answer to the health problem prompting sequencing, or because the option of sequencing had been introduced by a trusted physician.

Most of the misperceptions reported related broadly to patient/participant naiveté about the limitations of genomic sequencing. One genetic counselor explained that many patients have high expectations that genomic sequencing will provide a great deal of clinically useful information:

> "I think sometimes people think we have trust in our ability to interpret the genome more than they should. So they believe that this information will be really useful to their healthcare or provide them with information that could change their lives." (07-2)

Another genetic counselor pointed out that patients/participants frequently believe that sequencing will provide a definitive answer about the cause of their own or their child's condition:

> "They believe that if we don't find an answer maybe it's not genetic or that if it's genetic we should find an answer every time. I think it's probably hard for a lot of people to understand how much we don't know." (10-1)

The Professional's Perspective—What Content Information Should People Understand in Order to Provide Informed Consent?

In an open-ended question, interviewees were asked to identify the elements that they believed were most important for patients/participants to understand in order to provide informed consent. Twenty elements were mentioned by at least one interviewee (Table V). The most common ones included promoting understanding about the types of results that could be returned, the limitations of testing, especially when negative results were returned, and the implications of the results for the individual. Less commonly mentioned were implications for relatives, the requirements of study participation, privacy protections, and the potential for genetic discrimination. Research coordinators were more likely than genetic counselors to mention research-related items as important.

Several interviewees who were genetic counselors stated that, as they gained more experience reviewing, interpreting, and returning results, they modified their consent sessions to provide more specific and explicit descriptions of the range, prevalence and examples of possible results. As one genetic counselor stated:

> "We're not finding secondary findings in every family, and so that's something I've started making more clear during informed consent...from going through the variants and seeing the types of results that we're giving back also can give me some examples that I use when I'm talking about types of result that we give back." (04-1)

TABLE IV. Common Patient/Participant Questions, Concerns and Misperceptions

Common questions and concerns	Illustrative quotes
Practical details of study	*"I think, honestly one of the main things is the logistics of the blood draw for the kid and how – what kind of involvement that they need to have. (1-03)*
	"There are questions about does the child have to come back to the return visit? How long will it take? Will we get a copy of the results?" (04-1)
Probability of finding an answer	*"I think most commonly, "what are the chances. . .?". . .like "what is the chance that this is gonna find the answer?" (20-7) "*
Possible results	*"A lot of people are asking about kind of multi-factorial conditions. Like is this going to tell me about diabetes?" (08-1)*
Privacy/ confidentiality	*"Privacy issues—how is my information going to be kept private? Is it possible to keep it private? That kind of thing."* (07-1)
	"We also talk about sharing data with DbGap. . .a lot of people are concerned about privacy and aren't that comfortable sharing that information with this public database." (20-6)
Effect on other family members	*"Generally there are questions about what impact this might have for their family. . . "if you do find something, does that mean my family should come back in here?"* (03-2)
Anticipated response to results	*"There have been people who we've been worried about how they might respond to getting testing results back and have not enrolled because it just seemed like too big of a risk to their mental health" (05-1)*
Insurance discrimination	*"I find that most people have no idea about GINA even though it's in the consent form. . .And so that tends to be the thing that I bring up that actually does give people pause during the consent process" (05-1)*
Impact of results on management	*"The question comes up about if it is positive, is there a cure? Is there a treatment?" (06-3)*
Common misperceptions	
Negative results mean a "clean bill of health"	*"I think one misperception that I've heard is some people say well, I hope that this Genome Report tells me that I'm healthy, gives me a good prognosis." (07-3)*
Negative result means not genetic	*"When we're giving negative results, the idea that what they're doing here is kind of the ultimate genetic test that's gonna identify all genetic causes – if we don't find something, that it's gonna rule out genetic conditions, and mean that their child doesn't have one. (04-1)*
Report will contain many incidental findings	*"They're surprised when there's not anything to tell them. They're surprised if they get just a couple pharmacogenetic results. . . people think that their exomes, or genomes, are gonna be more interesting than they actually are. "* (03-1)
Sequencing will identify the cause of a condition	*"A lot of parents put so much hope into this, especially when their kids have been through so much and they've had so many different tests that they – their expectations are very, very high"* (20-2),
Expect incidental results to explain diagnosis in absence of diagnostic findings	*". . .so the biggest [misperception] is that incidental findings are either going to hold a secret to the answer for their diagnosis or are going to interact in a meaningful way with their diagnosis. ..folks definitely think that the incidental findings are going to be more medically meaningful for them than we think they have the potential to be." (10-2)*
Results will be certain	*"The idea that genetic information might give you a "due date" or something like that. . .or you'll get something back that'll say you're definitely gonna get stomach cancer or you're definitely gonna get Alzheimer's when you're fifty." (02-1)*
Genome will change over time	*"Some people will ask "well for the reanalysis do you have to take blood again?" because they think that things might change, or an answer might appear, because their genes have changed" (10-2).*
Results will be predictive of future health	*"I think that somehow they feel like we are going to open this Pandora's box and answer every possible question for them. . .They just think it's so exciting and that we can predict the future with it." (08-1)*

Testing limitations are important for participants to understand, but there was some consensus that patients/participants could gain a sufficient appreciation of these after a relatively minimal amount of education about the technical aspects of genomics and sequencing. One interviewee explained:

> "I give people the 20,000-foot view—that we're going to be looking at their genetic information, comparing it to a standard sequence, and we're looking for differences and changes between theirs and the standard and then trying to hone down on the changes that we think are relevant for their health. . .. And then I usually say 'I'm happy to talk about the details of how we do that, if it's important for you'. I've maybe had a handful of people who have said 'yes, I'd really like to understand that'." (5-1)

Interviewees reported that they used a variety of methods to assess the degree to which participants understood the content of

TABLE V. Elements of Informed Consent Mentioned as Most Important for Patients/Participants to Understand

Informed consent element	# Interviewees mentioning
Results	
Limitation of testing/meaning of negative result	13
Implications of results for individual tested	10
Which results are non-optional	5
Implications of results for family members	4
Which results are placed in medical record	3
Possibility of uncertain results	3
Re-annotation of sequence data	1
Research-related items	
"Everything" included on consent form	5
What participation involves (surveys, interviews, etc.)	5
Study goals	2
Participation is voluntary	3
Study/testing risks	
Privacy	6
Genetic discrimination	6
Psychological risks	3
Discovery of non-paternity	1
Understanding of test	
How sequencing is different from other genetic tests	3
What is genome/exome sequencing?	2
What is an exome?	1
Rationale for requesting parental samples	1

the consent discussion. Several genetic counselors noted that they used their traditional genetic counseling skills to obtain consent and gauge participant understanding. Interviewees assessed participant engagement through non-verbal cues such as eye contact or head nods, or through the number and types of questions asked by families. Some interviewees assessed understanding by asking personalized questions, or by doing understanding "checks" during sessions, such as this research coordinator who said she asks participants:

> "If you did join this research, why would you?". . . And if they say it's because they don't want to get breast cancer and they think that this will help them, then we've gone south some place and need to regroup." (03-2)

DISCUSSION

The general population has been observed to exaggerate the benefits of genomic sequencing [Caulfield et al., 2013; McGowan et al., 2013; Wade et al., 2013], a belief most likely driven by media reports that hype both the predictive and therapeutic value of genomic information [Caulfield et al., 2013]. Through our interviews with professionals experienced in conducting informed consent sessions in both clinical and research settings, we learned that many patients and research participants being offered genomic sequencing held these same beliefs. As a result of this widespread misperception of the likely benefits of sequencing, obtaining informed consent requires the adoption of strategies to manage unrealistic expectations about the range and utility of information that may be learned.

The need to modulate expectations led most of the professionals we interviewed to structure consent sessions by engaging patients/participants in a wider discussion to emphasize the types of results that they might learn and what a "negative result" really means in light of technological limitations of sequencing. The process and content of the sessions were influenced by a number of contextual issues. One factor was the extent to which the patient/participant was cognitively and emotionally prepared to discuss the testing, which in turn was influenced by previous contact with study or clinical staff, exposure to the consent document and/or educational materials, and/or previous experience with genetic testing. Other contextual factors influencing sessions were whether the person being sequenced was an adult or a child, the indication for sequencing, the current state of their illness, and the timing of the consent session. Interviewees reported that, during their initial consent sessions, they generally followed the order of the content of the consent forms fairly closely. As they developed strategies to promote family participation in sessions and as they became familiar with the range of questions, concerns and misperceptions held by patients or participants about genomic sequencing, interviewees reported that they began to conduct sessions in a less structured and more conversational manner, a style that they believed promoted better understanding and engagement.

Consistent with the conclusions of previous research [Joffe et al., 2001; Robinson et al., 2013], interviewees recognized that most patients and participants cannot attend to, let alone understand, all of the information contained in the consent documents. Interviewees recognized that it would not be feasible to devote two to six hours to informed consent sessions, as had been previously reported [Tabor et al., 2012; Rigter et al., 2014], nor was this amount of time necessary. Interviewees came to restructure the session to focus on communicating content that they learned through experience was most important for patients or most likely to be misunderstood. What became key information was the explication of the types of results that could be returned and their implications. This informational focus loosely aligns with recommendations of the ACMG relating to informed consent [ACMG Board of Directors, 2013], but study interviewees were quick to point out that session content varied considerably according to individual patient and family needs, as recommended by Siegal et al. [2012] so as to shift control of the informational process to patients.

By contrast, unless explicitly requested by the patient/participant, interviewees generally spent less time discussing genomic principles or technological aspects of sequencing, except for what they believed was necessary for patients/participants to understand how the results were generated and interpreted, including the meaning of negative results. Interviewees' experiences in returning results led to their providing more explicit examples about the types of diagnostic results and the range and characteristics of secondary findings that could be returned. With increasing expe-

rience, the verbal content of the sessions tended to become much more personalized and responsive to the patient/participant's informational needs with a corresponding diminished emphasis on some content. Importantly, as recommended by Merrill and Guthrie [2015], rather than providing the type of in-depth pre-test counseling about a specific condition that occurs when testing for a single gene, interviewee provided more global counseling before testing, and more in-depth counseling after testing, based on test results.

Consensus from a variety of stakeholders, including patients and members of the general public will be needed to outline which kinds of information should be presented to patients or participants to provide valid informed consent and to resolve the potential discrepancy between the views of patients/participants and those of scientists or IRB members [Beskow et al., 2010]. Required elements of informed consent for research participation as summarized by Joffe et al. [2001] include items such as an explanation of the purpose of the research; a description of any benefits to others; a description of confidentiality of records; an explanation that medical treatments are available if injury occurs; and an explanation of whom to contact for answers to pertinent questions about the research. Although considered essential by regulatory bodies, interviewees generally did not consider these elements essential for them to verbalize during the session in order to obtain informed consent. As a way to address similar discrepancies, Beskow et al. [2014] recently used a Delphi process to enable a diverse group of expert stakeholders, including biobank participants, to identify a concise set of key points to be included in consent documents and consent sessions that prospective participants should understand in order to provide informed consent for biobank participation. A similar exercise could be done with potential and past patients/participants to identify a minimum set of information that they would want before consenting to genomic sequencing. The initial list could include the elements identified here with additions from other experts and patients/participants [Ayuso et al., 2013].

Because patient/participants' increased familiarity with information about genetic testing or study participation resulted in shorter session lengths, future research should identify innovative ways of providing different levels of details about genome sequencing and its potential outcomes and impacts as desired by individual patients/participants. Ideally, this would lead to a personally tailored approach to informed consent in which patients identify and select the information that is important to their decision-making process [Siegal et al., 2012]. In addition, because decision aids can support decision-making about genetic testing [Kaphingst et al., 2010], more study is needed to assess the extent to which the use of decision aids improves understanding and align decisions with personal values and preferences [Khan et al., 2015].

It should be noted that none of the interviewees in this study reported doing any formal assessment of patient/participant understanding as a part of the informed consent process. Although an instrument to assess genomic knowledge has been developed [Kaphingst et al., 2012] additional tools are needed to help clinicians assess patient/participants' priorities and values, and their understanding of other critical pieces of information [Beskow et al., 2010; Khan et al., 2015]. It is especially important to develop ways to judge understanding of topics that often do not surface unless specifically raised by the clinician, such as the potential for the emergence of unexpected genetic information and the implications of results for obtaining long-term care, disability or life insurance, or for other forms of genetic discrimination [Prince and Roche, 2014].

Limitations

This study represents a description of the current process and content for obtaining consent for genomic sequencing as practiced by individuals with extensive experience conducting consent sessions. However, several limitations should be acknowledged. First, even though we interviewed a substantial subgroup of the genetic counselors and research coordinators conducting consent for genome sequencing in both research and clinical settings in the U.S., they may not represent the experiences of others doing such work, including those in countries outside the U.S. In addition, we did not study actual visits where informed consent was obtained, and we did not seek out the viewpoints of patient/participants. Thus, the list of elements of informed consent mentioned by interviewees as the most important for patients/participants to understand is not intended to be a comprehensive or an ordered list.

CONCLUSIONS

Despite these limitations, because we interviewed a group of professionals with considerable experience conducting informed consent sessions, our findings have important implications for the development of guidelines for informed consent for genomic sequencing as it moves into clinical care. In our study, a subset of key items emerged to become the main focus of informed consent sessions. Our interviewees independently chose the potential results from sequencing to be the main focus of the session. They placed special emphasis on elements relating to this central topic that were likely to be misunderstood including the range and uncertainty of information that could be learned, and the implications of both positive and negative results for the patient. Topics such as sequencing techniques and genomics were relegated to supplementary roles. Future research should address the views of various stakeholders on the key elements of informed consent that this study has identified, and link the process and content of informed consent with outcome measures, such as participant understanding, response to sequencing results, decision satisfaction and utilization of healthcare resources after results disclosure.

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