BRIEF REPORT | Genetics inMedicine

How do research participants perceive "uncertainty" in genome sequencing?

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Purpose: The scope of uncertainty in genome sequence information has no rival in health-care delivery. We present data from adults participating in a National Institutes of Health study using this technology, in which perceptions of uncertainty are hypothesized to be key in predicting decisions to learn and act on genome health information.

Methods: We conducted six professionally moderated focus groups with 39 randomly selected ClinSeq participants varying on whether they had coronary heart disease and had received prior sequence results. We elicited perceptions of the uncertainties associated with genome sequencing using written prompts.

Results: Participants perceived uncertainty as a quality of genome information. The majority of participants characterized uncertainty of sequencing information as "changing, fluid, developing, or ground breaking." These responses led to anticipation of more optimistic future outcomes. Fewer participants described uncertainty as "questionable, less accurate, limited, or poorly understood." These perceptions seemed to undermine participants' faith in genome information, leading to feelings of disillusionment.

Conclusion: Our findings suggest that perceptions of uncertainty are related to epistemological beliefs that inform expectations for the information. Interventions that promote realistic expectations of genome sequencing may mitigate negative responses to uncertainty.

Genet Med advance online publication 29 May 2014

Key Words: epistemological beliefs; expectations; genome sequencing; informed choice; uncertainty

Although uncertainty pervades medical information, its scope in genomes may be unprecedented. How patients perceive this uncertainty likely predicts decisions to learn sequence results and to act on the information. Practitioners who obtain consent to genome sequencing from patients face the challenge of conveying these uncertainties to ensure informed choice and mitigate unrealistic expectations.

Despite progress in defining health-related uncertainty and advancing conceptual clarity, limited empirical evidence exists to predict responses to the uncertainties associated with genome sequencing information.[1] Han et al.[1] define uncertainty as the subjective perception of ignorance, in contrast to the state of being ignorant: not knowing what one does not know. Their taxonomy of medical uncertainty identifies three principal sources: probability, ambiguity, and complexity. Probability expresses the indeterminacy of future outcomes; ambiguity describes the lack of reliability or imprecision of risk estimates; and complexity refers to features of available information that make it difficult to understand (e.g., modifying factors). Recipients of genome sequence information may experience uncertainty arising from all these sources. The taxonomy further distinguishes issues from sources of uncertainty: scientific, practical, and personal. How practitioners convey these sources and issues of uncertainty in genomes, and how patients perceive them, are relatively unknown.

A growing body of literature suggests that uncertainty can have a variety of psychological effects.[2–4] Mishel et al.[5,6] describe perceptions of uncertainty surrounding chronic illness as a source of loss, leading to negative outcomes. At the same time, their data also suggest that uncertainty may be interpreted as an opportunity for hope. Yet conveying uncertainty to patients may lower their satisfaction with health-related decisions.[7] Furthermore, patients' responses to uncertainty may depend on their expectations of such information.[8] An accurate awareness of the current state of technology, for example, might facilitate less aversive responses to uncertainties in genome information. However, much remains unknown about the types of uncertainties experienced by recipients of genome sequence information, and their psychological effects.

An important research task, therefore, is to explore people's perceptions, including expectations, of the uncertainties of genome sequencing information. To this end, we conducted a focus group study of research participants to determine how they perceive uncertainty associated with health-related genome information and how their expectations might affect their responses to this uncertainty.

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Submitted 12 November 2013; accepted 21 April 2014; advance online publication 29 May 2014. doi:10.1038/gim.2014.57

MATERIALS AND METHODS

Thirty-nine participants were recruited from the ClinSeq cohort for participation in six focus groups, each ranging in size from four to eight participants. ClinSeq is a longitudinal study of adults with a spectrum of risk for coronary artery disease who have been phenotyped and categorized by cardiac health bins and evaluated by exome sequencing.[9,10] Bins were defined using a 10-year risk of coronary artery disease: bin 1, <5%; bin 2, 5–10%; bin 3, >10%; bin 4, known coronary artery disease.[11] Participants were selected for the focus groups to achieve representation of cardiovascular health risk, sex, general health status, and prior receipt of a result. Participants for two groups were selected randomly from a subset that had not received genetic results and were in bin 1. Participants for three groups were selected randomly from the subset that had not yet received exome results and were in bin 4. Participants for a sixth group were selected randomly from those who had received at least one variant result. Focus group sessions were held on and off the National Institutes of Health campus (located in Bethesda, MD), each lasting about 90 minutes. All sessions were observed by the authors, as well as audiorecorded and transcribed.

Quantitative data from a sample of ClinSeq participants were used to inform the discussion guide.[12] A central theme was to assess patients' preferences in receiving results and their anticipated value. These data are published elsewhere.[11] Focus group participants in this study explored their perceptions of the uncertainties of genomes information and their implications. Although the taxonomy of Han et al.[1] helped frame our conceptualization and analysis, general open-ended questions, rather than taxonomy-based prompts, were used to explore perceptions of uncertainty. A professional moderator asked the participants to consider the statement, "There will be a significant degree of uncertainty associated with the majority of sequence information that you may receive," and to write responses to two questions: (i) "What does this statement mean to you?" and (ii) "How do you feel about this statement?" The moderator then asked the participants to discuss their responses to receipt of ambiguous results.

Reviewers asked for distinction between what was written versus what was discussed. Transcripts were generated verbatim from the written notes and audio recordings of the discussions and coded in NVivo QSR 9.0 (QSR International). An initial codebook was generated from our prior data and expanded using an iterative process. Transcripts were coded by two independent coders (M.F.W. and T.C.F.), and discrepancies were reconciled. A comparative content analysis was used to identify themes and quotes identified to support them. The kappa score for intercoder reliability was 0.95.

The National Human Genome Research Institute institutional review board approved this study.

RESULTS

Perceptions of uncertainty

Most participants perceived uncertainty as a quality of the information, describing it variously as changing, fluid, developing, or ground breaking. A few referred to its value as questionable, less accurate, limited, or poorly understood.

Some participants focused on fundamental sources of uncertainty, including probability and ambiguity (manifest by imprecision in interpreting the pathogenicity of variants), as well as scientific issues (what constitutes a variant):

> "There would be probabilities that the sequence was associated with a certain health outcome or situation. So uncertainty would be that range of probability that might matter to us. … [also] there might be a lot of uncertainty about the sequence itself, so we wouldn't know what the association was of that sequence with health outcomes." (focus group 6, participant 3)

Other participants perceived uncertainty as pertaining to the reliability of the research and/or investigators: "they [ClinSeq investigators] are not sure how to interpret the information"; one suggested that "they [ClinSeq investigators] do not really know what they are doing." Another participant from a different group stated that he would not "think less of them [ClinSeq investigators] if they don't know" (focus group 2). A participant from focus group 4 clarified that "just because they do not know what they're doing doesn't mean they're not credible."

Expectations of uncertainty

Participants' comments revealed a diversity of expectations regarding uncertainty in genome information. Most participants perceived such uncertainty as normal and expected. Several participants normalized uncertainty as a routine part of life by stating that "We deal with uncertainty every day, all the time."

> "There's so much uncertainty and change already in life and it's just part of life. … We don't know that we're not going to drive out of here tonight and get hit by a bus." (focus group 6, participant 3)

Similarly, another participant noted that uncertainty was an expected part of scientific research:

> "I think it's pretty clear with any scientific endeavor that our ability to comprehend what we're studying changes day-to-day. … There is a learning curve that is uncertain. We don't know when we're going to know what we know. Of course it's going to be uncertain." (focus group 3, participant 2)

By contrast, a participant registered disappointment at the notion of significant uncertainty.

> "[Significant uncertainty means that] I may not know what to do or what I actually know once you give me the information. [I would feel] disappointed. … I wish there would be more certainty. … It's as much medical art as it is science." (focus group 4, participant 2).

Responses to uncertainty

When asked about their feelings regarding uncertainty in genome information, some participants responded in an affectively neutral or even positive manner, using terms such as "unsurprising," "fine," "reality," "the truth!," "fair," or "acceptable." These participants perceived uncertainty as an expectation of the science and a source of opportunity for the future. These perceptions were tied to optimism that better information would become available in the future. As one participant stated, "We'll just keep finding and discovering more and more new information." Another commented that he was curious to see "how far they get with my genetic make-up before I die."

Optimism about better information in the future also appeared to manifest a broader tolerance for ambiguity in genome information.

> "Suppose you take that piece of ambiguous information and you read some months or years later in *Scientific American* about something and you go, "Wait a minute, this isn't so ambiguous any more." … I think that's entirely possible that we would make connections with that ambiguous information because it's personal; because it was delivered to us about our health and our genes. We could contribute in a whole different way by calling the researchers and saying "What about this?" That could be fun. There's value in that." (focus group 6, participant 3)

This tolerance of ambiguity appeared to influence attitudes toward receiving ambiguous genome information:

> "If it's that ambiguous I would still want to know, but I wouldn't necessarily change my lifestyle, or be upset or bothered by it." (focus group 6, participant 1)

By contrast, other participants perceived uncertainty negatively. They predicted feeling "perplexed," "uneasy," "anxious," or "more vulnerable." These views appeared to relate to expectations of genome information; one participant described feeling "disappointed," and another reported feeling "less hopeful." These perceptions were also related to a pessimistic view of future information; one participant noted that "more questions may be raised by the research than answers" and another that she may therefore "not know what to do with the information." Some participants felt that uncertainty could undermine their faith in the study and reduce the value of sharing genome information with relatives. Some participants expressed an intolerance of ambiguity manifest in a lack of desire for certain genome information; one participant, for example, stated that she wanted to learn only "valid information."

Preferences for communicating uncertainty

Participants expressed varying preferences for information on uncertainty. Some preferred that investigators define the degree of uncertainty when discussing any results. Several of them requested a range of probabilities. One participant sought less ambiguity, stating that he desired information with a "higher level of certainty to make decisions." (focus group 5, participant 4)

DISCUSSION

The focus group participants reported an array of perceptions of uncertainty, characterizing it as developing (fluid), unstable (changing), new (ground breaking), and natural (normal). Their perceptions also addressed information quality, including its value (questionable and limited). Participants most often identified probability and ambiguity as sources of uncertainty. Few respondents discussed complexity. They perceived uncertainty as pertaining to genome information, genome research, and genome researchers themselves, who, as a few respondents allege, do not really know what they are doing.

Consistent with the theoretical accounts of health-related uncertainty generated by Mishel,[5] our study found a duality in responses to uncertainty, which participants appraised as both an opportunity and a threat. These dual appraisals have been identified in other studies.[13,14] In our study, participants who perceived uncertainty in genome information as an opportunity reported optimistic feelings about future research and what they may learn from their results. By contrast, those who perceived uncertainty as a loss expressed more pessimistic future perspectives.

Perhaps the most significant finding of our study is that participants' responses to the uncertainty of genome sequencing information appear to reflect their prior epistemological beliefs—i.e., their beliefs about the nature of genome knowledge. Those who perceived uncertainty in genome information as normal or expected exhibited more optimistic attitudes and greater tolerance of ambiguity. They viewed uncertainty positively, as a source of opportunity. By contrast, those who did not expect uncertainty exhibited more pessimistic attitudes and greater aversion to ambiguity, perceiving uncertainty as a threat. For them, uncertainty was a disappointment that left them disillusioned about their participation.

These contrasting perspectives suggest that epistemological beliefs, from which expectations arise, are important determinants of responses to uncertainty. Assessing and modifying these beliefs—through the provision of an epistemological intervention—may be a key to enhancing informed choice and mitigating negative responses to the uncertainty.[15] More work is needed to explore and confirm these hypotheses and to examine how other factors—including tolerance of uncertainty, resilience, and optimism, as well as other personality traits—also influence responses to uncertainty. Although these traits are not subject to interventions by providers, assessing such traits in conjunction with clients' expectations may help to identify those more likely to appraise the uncertainty as a threat and to mitigate negative affective responses.

A limitation of this study is the exploratory nature of this research using a relatively small number of ClinSeq participants who are not representative of the general population. They are early adopters of genome technologies and represent those in

the population who are likely to pursue genetic technology for health reasons, whether they have coronary artery disease or not. They are highly educated, earn higher salaries, and demonstrate enthusiasm for this technology.[8,12] Additional research is needed to learn whether and how perceptions of uncertainty may differ according to whether participants are affected by a disease or choose to undergo sequencing to make medical decisions. It is expected that genome sequencing will be used more broadly to generate information about a person's health. This cohort is helping us to understand how perceptions of the vast nature of the uncertainties associated with genome sequencing may contribute to making an informed choice and interpreting and using genome sequencing information in health-related decisions.

Furthermore, we framed our inquiry using the descriptor "significant uncertainty," which is most accurate in depicting the scope of uncertainty associated with sequencing information. As such, we were intentionally nonspecific about the sources of uncertainty. Had the uncertainty descriptor been more specific, it may not have led as frequently to perceptions of threat. Nonetheless, the frequency of responses likening uncertainty to opportunity was remarkable.

In conclusion, our findings have direct implications for patients consenting to genome sequencing, facilitating decisions to learn information gleaned from sequencing and decisions to act on the information. Our findings suggest that prior beliefs, and thus expectations, may predict responses to the sources of uncertainties associated with sequencing information: probability, ambiguity, and complexity. Additional research is needed to assess this proposed causal relationship. Exploring these variables with patients may help to maximize informed choice and mitigate negative outcomes.

ACKNOWLEDGMENTS

We thank the focus group participants; Chanza Baytop and Barbara Rosenthal for moderating the groups; and Chris Anderson for help with the references. The Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health, funded this research.

DISCLOSURE

L.G.B. has an unpaid consulting relationship with Illumina and receives royalties from Genentec. The other authors declare no conflict of interest.

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