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How do research participants perceive “uncertainty” in genomic sequencing?

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Abstract

Introduction—The scope of uncertainty in genomic sequence information has no rival in health care delivery. We present data from adults participating in an NIH study using this technology where perceptions of uncertainty are hypothesized to be key in predicting decisions to learn and act on genomic health information.

Methods—We conducted six professionally moderated focus groups with 39 randomly selected ClinSeq[®] participants, varying whether they had coronary heart disease and had received prior sequence results. We elicited perceptions of the uncertainties associated with genomic sequencing using writing prompts.

Results—Participants perceived uncertainty as a quality of the 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 the information, leading to feelings of disillusionment.

Discussion—Our findings suggest that perceptions of uncertainty are related to epistemological beliefs that inform expectations of the information. Interventions to promote realistic expectations of genomic sequencing may mitigate adverse responses to uncertainty.

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Introduction

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

Despite progress defining health-related uncertainty and advancing conceptual clarity, limited empirical evidence exists to predict responses to the uncertainties associated with genomic sequencing information.¹ Han and colleagues defined uncertainty as the subjective perception of ignorance, in contrast to the state of being ignorant: not knowing what one does not know.¹ Their taxonomy of medical uncertainty identifies three principle *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 genomic sequence information may experience uncertainty arising from every source. The taxonomy further distinguishes *issues* from sources of uncertainty: scientific, practical and personal. How practitioners convey these sources and issues of uncertainty in genomics, 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 and colleagues described perceptions of uncertainty surrounding chronic illness as a source of loss, leading to negative outcomes.^{5, 6} At the same time, their data also suggested that uncertainty may be interpreted as an opportunity for hope. Conveying uncertainty to patients may lower their satisfaction with health-related decisions.⁷ Further, patients' responses to uncertainty may depend on their expectations of the information.⁸ An accurate appreciation of the current state of technology, for example, might facilitate less aversive responses to uncertainties in genomic information. However, much remains unknown about the specific types of uncertainty experienced by recipients of genomic sequence information, and the specific psychological effects of these uncertainties.

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

Methods

Thirty-nine participants were recruited from the ClinSeq[®] cohort for participation in six focus groups conducted in Bethesda, MD. ClinSeq[®] is a longitudinal study of adults with a spectrum of risk for coronary artery disease (CAD), 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 CAD: Bin 1, < 5%; Bin 2, 5-10%; Bin 3, >10%; Bin 4,

known CAD¹¹. 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 genetic results and were in Bin 4. Participants for a sixth group were selected randomly from those who had received at least one variant result from the study. Groups ranging in size from four to eight members were held locally on and off the NIH campus, each lasting about 90 minutes. Sessions were observed by the authors, audio-recorded, and transcribed.

Quantitative data from a sample of ClinSeq[®] participants was used to inform the discussion guide.¹² A central theme was assessing preferences for receiving results and perceptions of their value. These data are published elsewhere.¹¹ Focus group participants also explored their perceptions of the uncertainties of genomics and their implications. While Han's taxonomy¹ helped to 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 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: 1) "What does this statement mean to you?" and 2) "How do you feel about this statement?" The moderator then asked participants to discuss their answers, elaborating on their responses to receipt of ambiguous results.

Transcripts were generated verbatim from the written notes and audio recordings of the discussions and coded in NVivo QSR 9.0. An initial codebook was generated from our prior data and expanded using an iterative process. Transcripts were coded by two independent coders (MW, TF) and discrepancies reconciled. A comparative content analysis was used to identify themes and quotes identified to support them. The kappa score generated for inter-coder reliability was 0.95.

The National Human Genome Research Institute IRB 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 both probability and ambiguity (manifest by imprecision in interpreting the pathogenicity of variants) and 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 grp 6, participant 3)

Other participants perceived uncertainty as pertaining to the reliability of the research and/or investigators, stating that “*they [ClinSeq®investigators] are not sure how to interpret the information,*” and one suggested that; “*they [ClinSeq®investigators] do not really know what they are doing.*” Another participant from a separate group stated that he wouldn't “*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 varying expectations regarding uncertainty in genomic information. Most participants perceived such uncertainty as normal and expected. Several participants normalized uncertainty as a routine part of life in 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 grp 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 grp 3, participant 2)

In 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 grp4, participant 2).

Responses to uncertainty

When asked about their feelings regarding the uncertainty in genomic 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 genomic 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 grp 6, participant 3)

This tolerance of ambiguity appeared to influence attitudes toward receiving ambiguous genomic 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 grp 6, participant 1)

In contrast, other participants perceived uncertainty negatively. They predicted feeling *perplexed, uneasy, anxious, or more vulnerable*. These views appeared to relate to expectations of genomic information; one participant described feeling “*disappointed,*” while another reported feeling “*less hopeful.*” These perceptions were also related to a pessimistic view of future information; one participant noted “*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 genomic information with relatives. Some participants expressed an intolerance of ambiguity manifest in a lack of desire for certain genomic information; one participant, for example, stated that she only wanted to learn *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 requested a range of probabilities. One participant sought less ambiguity stating that he desired learning information with a “*higher level of certainty to make decisions..*” (Focus grp 5, participant 4)

Discussion

These 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 genomic information, genomic research, and genomic researchers themselves, described by a few as not knowing what they are doing.

Consistent with theoretical accounts of health-related uncertainty generated by Mishel, our study found a duality in responses to uncertainty, which participants appraised as both an opportunity and a threat.⁵ These dual appraisals have been identified in other studies.^{13, 14} In our study, participants who perceived uncertainty in genomic information as opportunity

reported optimistic feelings about future research and what they may learn from their results. In contrast, those who perceived uncertainty as a loss expressed more pessimistic future perspectives.

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

This contrast in perspectives suggests 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 for uncertainty, resilience, and optimism, and other personality traits also influence responses to uncertainty. While these traits are not subject to interventions by providers, assessing them 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.

Limitations to this study are the exploratory nature of this research among a relatively small number of ClinSeq[®] participants who are not representative of the general population. They are representative of early adopters of genomic technologies; those in the population likely to pursue genetic technology for health reasons, whether they have CAD or not. They are highly educated, earn higher salaries and demonstrate their enthusiasm for this technology^{8, 12}. Additional research is needed to learn if and how perceptions of uncertainty may differ according to whether participants are affected with a disease or choosing to undergo sequencing to make medical decisions. It is expected that genomic sequencing will be used more broadly to generate information about one's health. This cohort is helping us understand how perceptions of the vast nature of the uncertainties associated with genomic sequencing may contribute to making an informed choice, and interpreting and using genomic sequencing information in health-related decisions.

Further, 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 the 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 consenting patients to genomic 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.

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