ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

"Possibly positive or certainly uncertain?": participants' responses to uncertain diagnostic results from exome sequencing

Debra Skinner, PhD[1], Myra I. Roche, MS, CGC[2], Karen E. Weck, MD, FCAP[3,4], Kelly A. Raspberry, PhD[1], A. Katherine M. Foreman, MS, CGC[4], Natasha T. Strande, PhD[3], Jonathan S. Berg, MD, PhD[4], James P. Evans, MD, PhD[4] and Gail E. Henderson, PhD[5]

Purpose: Clinical genome sequencing produces uncertain diagnostic results, raising concerns about how to communicate the method's inherent complexities in ways that reduce potential misunderstandings and harm. This study investigates clinicians' communications and patient/participant responses to uncertain diagnostic results arising from a clinical exome sequencing research study, contributing empirical data to the debate surrounding disclosure of uncertain genomic information.

Methods: We investigated the communication and impact of uncertain diagnostic results using ethnographic observations of result disclosures with 21 adults and 11 parents of child patients, followed by two semistructured interviews with these same participants.

Results: Participants understood their uncertain results in ways that were congruent with clinical geneticists' communications. They followed recommendations for further consultation, although family testing to resolve uncertainty was not always done. Participants were prepared for learning an uncertain result and grasped the key concept that it should not be used to guide healthcare or other decisions. They did not express regret for having learned the uncertain result; most regarded it as potentially valuable in the future.

Conclusion: This study suggests that uncertain diagnostic results from genome sequencing can be relayed to patients in ways they can understand and consistent with providers' interpretations, without causing undue harm.

Genet Med advance online publication 2 October 2017

Key Words: clinic communication; genetic counseling; genome sequencing; patient response; uncertain result

INTRODUCTION

Genome sequencing (GS) has moved into clinical practice as an effective diagnostic tool for rare Mendelian disorders.[1] While successfully identifying variants that explain the patient's phenotype for about 25% of those referred for testing,[2] this diagnostic testing also produces results of which the clinical interpretation remains uncertain. The occurrence of uncertain results has become increasingly prevalent with the broader use of GS and the amount of information it generates.[3,4] A recent taxonomy delineates the possible sources and ramifications of uncertainty,[5] but empirical work on its production, interpretation, communication, and impact on patients and clinicians is just beginning.[3,6–8]

A critical focus is to characterize ways in which clinicians interpret uncertainty arising from GS, how they communicate it to patients, and how patients understand and respond to it. Some have questioned the value of reporting uncertain results owing to concerns about misinterpretation that could lead to psychosocial and other harms from downstream effects such as unnecessary interventions.[9–11] Proponents who argue for reporting uncertain results contend that this information holds potential value in the future, that nondisclosure can also result in harms, and that harms can be mitigated by appropriate pre- and posttest genetic counseling.[3,12–14] While ambiguous results are not new in medicine,[15,16] the potential for uncertain results and any accompanying harms is much greater in GS owing to the scale of the assay. A recent review of seven genomic sequencing studies of patients with suspected genetic disease reported that, across these studies, 40% learned an uncertain result (range 8.6–51.8%).[2] Key concerns remain about which uncertain results should be returned and how to communicate the inherent complexities to patients in ways that reduce potential misunderstandings and harms.[17]

Thus the expanded use of genome-scale sequencing as a diagnostic tool will inevitably lead to an increasing need to communicate uncertain results. Here we present data from an ethnographic study, embedded in a clinical sequencing project, that observed clinical geneticists' communications about uncertain diagnostic results and interviewed patient/

[1]FPG Child Development Institute, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [2]Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [3]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [4]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [5]Department of Social Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Correspondence: Debra Skinner (debra.skinner@unc.edu)

Submitted 26 April 2017; accepted 1 July 2017; advance online publication 2 October 2017. doi:10.1038/gim.2017.135

participants about the responses they gave on learning them. Findings from this study can inform the debate surrounding the impact of disclosing uncertain genomic information to individuals having diagnostic genome-scale sequencing.

MATERIALS AND METHODS

To provide empirical data on clinicians' communications and patient/participants' subsequent responses, we recruited 21 adult patients and 11 parents of child patients (hence referred to as "participants") who learned uncertain results from exome sequencing (ES) conducted by the North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing (NCGENES; University of North Carolina, Chapel Hill, NC) study. NCGENES studied the diagnostic utility of ES in a clinically diverse set of patients suspected to have an underlying genetic etiology for their condition but in whom no diagnosis had been reached through the usual clinical care. NCGENES results were filtered by a diagnostic list, or lists, of genes selected based on each patient's phenotype. An expert committee made up of clinical geneticists, genetic counselors, clinical laboratorians and PhD-level research scientists decided as a group whether the result to be disclosed should be categorized as diagnostic, possibly diagnostic/uncertain, or negative. Uncertain results were classified based on whether the case was that there was a variant of uncertain significance, an uncertain phase of two pathogenic variants (i.e., in *cis* or *trans*), an uncertain or incomplete phenotypic fit for the participant's condition, or another reason or reasons for uncertainty. Diagnostic and possibly diagnostic/uncertain results were confirmed by Sanger sequencing analysis in the UNC CLIA-certified Molecular Genetics Laboratory and a clinical report was issued.

The 32 participants in this ethnographic study were purposively selected as far as possible to reflect the different disease cohorts and sociodemographic characteristics (gender, age, race/ethnicity, education) of the 169 NCGENES participants who were given uncertain diagnostic results (25.3% of the total 669 enrolled). Participants provided written consent for an ethnographer to observe the study visit at which NCGENES clinical geneticists and genetic counselors disclosed results, and for telephone interviews 4 weeks and 1 year after disclosure. The second interview was conducted because many participants had not yet been given the results from their family testing, nor had they met with a recommended specialist at the time of the first interview. All 32 participants completed the first interview, and 27 (18/21 adults and 9/11 parents) completed the second interview. Of the five participants not re-interviewed, two were lost to recontact, one declined, and two were unable to do the interview owing to illness. Interviews were semistructured and designed to elicit participants' (i) understandings of their uncertain result, (ii) concerns or psychosocial responses related to it, and (iii) plans of action or accounts of actions they had taken based on the result, especially regarding recommendations for further testing or consultations. Study visits and interviews each lasted approximately one hour, and were audio recorded and transcribed verbatim. The university institutional review board approved all procedures and protocols.

The ethnographers (D.S. and K.A.R.) conducted a systematic content analysis of the observation and interview transcripts, employing data display matrices to summarize, categorize (i.e., code), and systematically compare and link findings within and across the 32 cases.[18] We compared the content of clinician communications across all cases for commonalities and variations, and linked these to participants' responses as recounted in interviews, noting especially both congruencies and differences between what clinicians communicated and what participants understood, as well as participants' psychosocial and behavioral responses to their uncertain results.

RESULTS

Participant characteristics

The sample of 32 participants included 21 affected adults and 11 parents of affected children. Sociodemographics of the sample are depicted in **Table 1**. Both parent and adult participants were predominately non-Hispanic white, with adults being more diverse by condition, gender and age. There was some diversity by education, with 56% having a college degree or higher Importantly, 78% reported having previous genetic testing with no molecular diagnosis.

Congruence between clinicians' communications and participants' understandings

NCGENES clinicians had the task of interpreting the clinical reports of uncertain diagnostic results to participants. It is important to note that not all uncertain results were variants of uncertain significance (VUS). In their communications with participants, clinicians attempted to clarify the nature of the uncertainty, the reasons the result was considered an uncertain but possible answer for the condition, and the implications of this uncertainty for participants and their relatives.

A clinical geneticist and a genetic counselor met with each participant to discuss diagnostic results. Although the eight NCGENES clinicians who disclosed results differed stylistically, the order and content of their communications conformed to the same general pattern. This was largely due to their similar training as clinical geneticists and genetic counselors and their close collaboration as a research team since the beginning of NCGENES in 2011. During the project, they had frequent discussions at project and molecular sign-out meetings about difficult cases, leading to a consensus about the most effective ways to communicate different types of results. In cases in which uncertain results were disclosed, clinicians followed their description of the genetic result with an assessment of the degree to which they believed the variant was a plausible explanation for the patient's symptoms. They described sources of uncertainty, including limitations of the technology, incomplete databases, and rudimentary knowledge of the contribution of pathogenic variants to disease. Clinicians often elicited additional information about

Table 1 Sociodemographic characteristics of interview participants

	Adults (n = 21)	Parents (n = 11)
Gender		
Male	42.9% (9)	9.1% (1)
Female	57.1% (12)	90.9% (10)
Age		
Range/mean	19–84/50 years	NA[1]
Range/mean of child patient		1–16/6.5 years
Race/ethnicity		
Non-Hispanic white	90.5% (19)	72.7% (8)
African American	9.5% (2)	9.1% (1)
Asian	0.0 (0)	18.2% (2)
Education		
High school 12 years or lower	14.3% (3)	0.0% (0)
Some college/associate's degree	23.8% (5)	54.5% (6)
College degree	33.3% (7)	9.1% (1)
Advanced/professional degree	28.6% (6)	36.4% (4)
Had previous genetic testing	71.4% (15)	90.9% (10)
Conditions		
Cancer	23.8% (5)	0.0% (0)
Cardiogenetic disorders	9.5 (2)	0.0% (0)
Neuromuscular or neurogenerative conditions	57.1 (12)	0.0% (0)
Ophthalmological disorders	9.5 (2)	9.1% (1)
Intellectual disability and/or congenital malformations	0.0% (0)	90.9% (10)

[1]Age of parents was not available.

personal or family medical history to better evaluate if these features matched the phenotype expected based on the reported genotype. In some cases, they recommended family testing or other clinical evaluations that could potentially provide additional evidence regarding pathogenicity of the variant. After summarizing key points and addressing questions, clinicians ended by reiterating that reanalysis and advancements in the field could potentially provide a more certain answer in the future. Thus, the premise they communicated was that an uncertain result should not be viewed as a final result but one requiring more information and research. They assured participants that they would continue to search for an answer and contact them with any new information.

Our analysis of participants' understandings of these communications indicates remarkable congruence in almost all cases. Participants demonstrated a wide range of ability to recall specific details with a few participants having only a superficial understanding, but with one exception (discussed below), they understood that the result was uncertain and not a definitive answer. They regarded the uncertainty of the result in ways that were similar to how it was communicated: as being uncertain but likely, uncertain but possible, or uncertain but an unlikely explanation of their symptoms. **Table 2** provides representative examples that illustrate this congruence.

For the majority of the 32 participants, clinicians presented the result as an uncertain but possible answer. For example, a genetic counselor began the study visit with an older male with neuropathy by saying: "We do have something potentially to tell you about or at least to puzzle you with… we did find a genetic change in a gene that we're suspicious about. It's never been seen, and so we call it a variant of uncertain significance." She then described symptoms associated with changes in the gene (*BSCL2*), the variability of the phenotype, and the lack of knowledge about whether or not symptoms of neuropathy were associated with variants in the portion of the gene where the variant was located. She ended this explanation, stating,

> It's enough to make us say, "Well, it's definitely uncertain in its significance." It might have absolutely nothing to do with your neuropathy. One of the ways we can potentially find out about that and try to learn a little bit more is to see if this gene change occurs in individuals in your family who have the symptoms.

In the follow-up interview the participant, who had a science background, said he had learned that they had found "an undiscovered variant in my genome." He did not remember the name of the gene, but understood that it was an uncertain result for which family testing might provide more information.

For five participants, clinicians presented the result as an uncertain but likely cause, as in the case of a girl who had kidney problems and skeletal dysplasia. The clinical geneticist began the study visit with the father: "We actually did find something we think explains what is going on." He added that it was a rare change, not reported before, and thus there was insufficient evidence to prove its pathogenicity but that he was reasonably confident it was the answer "because of what we know about this gene [*WDR19*] and because of what we know about [your daughter] and how well that those match together. That makes it much more likely this is the cause." The father reported in the first interview that he and his wife believed this result was very likely the answer for their daughter's condition, and they were looking for more information on the gene and associated syndromes. As this case suggests, many participants engaged in further activities that could shed light on their results, such as searching the internet for additional phenotypic aspects that might or might not match their own experience. These efforts were encouraged by NCGENES clinicians, who told participants that they were "a part of the team" and welcomed participants

Table 2 Congruency between clinician communication and participant understanding of an uncertain result

Case	Excerpt of clinician's communication	Excerpt of participant's understanding
Female in her 60s who had early-onset breast cancer	"We found a change in your genes that may help explain why you developed breast cancer at a young age and may help explain your family history…but none of us feels it explains the whole story."	"I learned that I had one—I had a gene that was variant—variation in it … It's BARD. BARD1…. I understood them to say they couldn't tell me that that definitely caused it, but that could have been a contributing factor to it."
Middle-aged male with cardiomyopathy	"We did identify something which we say has potential diagnostic value [long discussion about reasons the result is uncertain]…We really don't know whether this variant is related…this gene has been associated, but we don't know about this particular change."	"It wasn't a negative, but it's not truly a positive detection either…I didn't really consider it a positive diagnosis. So for me it was kind of "Yeah. I got a maybe." It's nothing really to worry about yet. Again I'd like to meet with the doctor and discuss the results and see if in his mind it's anything."
Middle-aged woman with neurological problems	"Your results came back solidly in that maybe category. So we do have something to share with you today which is a possible answer for what's going on, but there's simply not enough data yet about what we found to know for sure that it's an answer."	"To me it seems unlikely that this gene could be causative because I looked at patient advocacy groups' information, some of the clinical reports online of people who have this very specific type of hereditary motor neuropathy, and it seems like most of the cases typically are very progressive in nature, which doesn't really seem to match up with my symptoms, although there's a lot of heterogeneity between cases even within families. So it looks like it now has sort of an incomplete penetrance as well so I guess there could be potentially some multiple phenotypes that could come arising from this one particular mutation, but it's hard to explain…that's kind of a mixed bag as far as what the result means."
Elderly male with neuropathy	"The bottom line is it does not look like we found a reason for your neuropathy. We are reporting out one variant but I want to emphasize very strongly that I and the rest of the team do not feel that this is what's responsible for it. We report it out because it just barely squeaked into the category 'Well, maybe we ought to report this out.'"	"Big question mark. Unknown. Remains unknown. There may or may not be a mutation of one or more genes contributing to the inherited peripheral neuropathy. There may, but there's no indication that for sure that that is the cause…[This result] means to me that the science is still vague."
Mother of daughter with congenital malformations	"What we found is a possible explanation for [child's] underlying condition…We can't say this is for sure an explanation, in part or mainly because this particular change isn't something that's been seen before… Although this [report] is written as uncertain….I think that it is quite likely that this change explains [your daughter's] underlying condition."	"So the research said she most likely has it, or it's questionable…It's a new mutation. Since it's not been reported they cannot say for sure…[The clinician] explained it to us why he thought it's most likely that she would have it even though it was just a possible. He actually was very, very helpful in helping us understand why it's different, not something they'd seen before. So those are all things maybe that we wouldn't have known if they just gave it to us. He did take time to explain all of those to us."
Mother of young son with multiple neurodevelopmental problems	"We found a possible explanation for [your son's] issues. I can by no means say this is the answer. I think that doing some more investigation will help. It would help at some point to get you and [son's] father's blood so we can compare some things…(and) I think it makes a lot of sense for him to be seen by [his pediatric geneticist] with this result in mind."	"[The clinician] said that it's definitely no slam dunk, but that me and dad being tested would help it, but also for me to go online and look at what this syndrome entails and the whole symptoms and them things and see how I thought it fit [my son]. And so he said that no one would know better what [son] goes through day to day than me, but when I looked I definitely think that there's something there to even talk further to [pediatric geneticist] about."

to inform them of any new information that could potentially help resolve uncertainty.

At the time of the first interview, only one participant had imbued an uncertain result with a more definitive interpretation than the one which the clinicians presented. Clinicians reported a novel heterozygous missense variant in *SLC1A3* as a possible but uncertain cause of the adult participant's seizure-like episodes. However, the participant talked about it as "a life-changing result":

> Even if there is no treatment for it, it's extremely significant to me because it's redemptive after all these years of not knowing. I've had a lot of good doctors, but I've had a lot of just horrible treatment by doctors too, and just saying, "Wow. This is what I have." Just having a name to something when you've suffered for so long is just an amazing relief …it's been really redemptive with all that I've gone through.

This case is a useful reminder that even when clinicians stress the uncertain nature of a result, participants make meaning of diagnostic results in light of their own experiences and their need for an explanation. Yet this participant's understanding of her result changed after family testing showed her unaffected father had the same variant, making it much less likely that it was causative. In the second interview, she interpreted the result more in line with the clinicians, saying, "It is still the case there is no answer." As this example indicates, both clinician and participant interpretations can change because of new information such as results from family testing, additional clinical evaluations, and reanalysis and reinterpretation using improved databases.

Behavioral and psychosocial responses

NCGENES participants could give or withhold their consent to the placing of clinically confirmed diagnostic results into their electronic medical record (EMR). Almost all of the participants enrolled in NCGENES elected for results to be placed there. Of the 32 participants in the ethnographic study with uncertain results, 18 of 21 adults and all 11 parents consented to placement. Of the 3 who declined, one was concerned about insurance discrimination, another about misinterpretation, and the third saw no advantage to having it in his EMR. Three-fourths of those who consented did so primarily because they perceived that the result might be valuable to their doctors now and/or in the future. Five participants specifically cited that a desire to have the result documented and accessible to their physicians was the key reason for consenting.

Although 38% saw no disadvantages to this placement, 40% said they were aware of possible insurance discrimination but did not believe it would happen to them, or said that the result would not increase the risk because their disorder was already detailed in their EMR. Others mentioned the possibility of job discrimination or "leaks" of the information, but thought the advantages of having the result in the EMR outweighed potential disadvantages. With two exceptions, participants said they had informed their specialists and/or primary care providers about the result, and had sought their doctors' opinions about whether the result fit with their or their child's condition and what implications it might have for care. Two of the three individuals who did not put the result in their EMR nonetheless reported talking with their doctors about it.

Family testing was recommended for 8 children and 12 adults, to help with interpretation of uncertain results. At least 1 parent of the 8 children, but only 5 of the 12 adults, completed this testing. This difference was in part due to convenience, as parents could provide consent and a sample at the time the results were disclosed, but could also be attributed to their expressed interest in finding an answer. Adults faced more barriers to pursuing family testing. Participants gave a variety of reasons for not following up on family testing. Some thought it unlikely that such testing would result in the acquisition of any significant information, or "it fell off the radar", or they did not want to pressure family members. Others were keen to pursue it, but their relatives refused to be tested, or they were not able to have blood drawn owing to illness or other problems.

Those who pursued family testing and/or consultation with specialists said they were not worried while waiting for any additional results. Several parents explicitly stated that there was no reason to be concerned until they knew the outcome of the testing because they had been through this process before. For example, one mother learned that her son had a variant that could indicate Coffin-Siris syndrome, but she was awaiting the results of parental testing and a consultation with her pediatric geneticist before coming to any conclusions. She commented that uncertainty was nothing new; her son had previously received an uncertain result from a microarray analysis.

It is important to note that, although a few voiced disappointment at not getting a definitive molecular diagnosis, only one of the participants expressed distress related to the uncertain result. The majority were not concerned with the uncertainty surrounding the result, but rather with the challenge of not getting a definitive diagnosis, and therefore remaining uncertain about the progression of the disease and the risks for their children. Participants were aware of and accepted an uncertain result as a possible outcome of study participation and, except in those few cases where it was returned as a likely answer, they appropriately viewed it as "not an answer," "inconclusive," "an unsolved mystery," or "not very significant." No one expressed regret at learning the uncertain result and, instead, many noted its value and potential usefulness in the future. It was a "piece of the puzzle," something "to file away" until more became known. Most expressed sentiments that were similar to this adult who learned an inconclusive result: "They can return anything they want to me. Where I would be disappointed is if they didn't return it. What about in seven years if they find something?"

This potential of genomics to find answers in the future was a significant factor in shaping participants' valuing of and reactions to the uncertain result. They were optimistic about

future answers and valued their ability to contribute to the research that could lead to these advancements. They recognized that even if the uncertain result was not informative to them now, the information could help build data- and knowledge bases. One participant summed up this widely-shared view of the promise of genomics:

> Once exome sequencing becomes more available I think that a lot of other people or a fair number of people will be diagnosed with it, and then when there's more people diagnosed with it, then there will be more money put into research for not only what I have, but for things that affect other people because then more money will be spent for research, and treatments will be developed, and there will be more studies done.

In summary, participants understood uncertain results in ways that were congruent with the NCGENES clinicians' communications. They followed the clinicians' recommendations for further consultation, although family testing that might have resolved the uncertainty was not always carried out. Participants were prepared for an uncertain or uninformative result, and after learning it, did not act in ways that caused harm. They did not express regret for having learned the uncertain result; rather, most regarded it as potentially valuable in the future.

DISCUSSION

In this study, we found that that there was general congruence between how clinicians explained an uncertain result and participants' interpretations of this uncertainty. Two characteristics of participants in this study probably played a large role in this high level of congruence. First, the majority (78%) reported having had previous genetic testing that had not revealed a molecular diagnosis for their or their child's condition, leaving them uncertain about its etiology and family implications. Participants were thus accustomed to ambiguity, as they had already lived with and experienced uncertainties related to their own or their child's medical conditions. Second, during the informed-consent process, genetic counselors specifically addressed the likelihood of obtaining uninformative or uncertain results, thus tempering participants' expectations of getting a definitive answer (details on this process are provided in **Supplemental Information** online). Others have advocated that managing participants' expectations about results in this way should be generally recommended as best practice.[19]

That participants' interpretations largely coincided with clinicians' communications may seem contrary to what has appeared in the existing literature about how patients misunderstand genetic information,[20,21] but may be explained by our specific focus on participants' understanding of the significance of their result and what actions, if any, they should take. Although some participants' comprehension of other genetic information, such as genetic risk and inheritance patterns, may not be precisely congruent with that of clinical geneticists, they grasped the key concept that the diagnostic result was uncertain and should not be used to guide healthcare or other decisions.

Uncertain medical results are often viewed as harmful, but this uncertainty can hold hope and promise.[22] In NCGENES, genetic counselors prepared participants at the time of enrollment for the likelihood that their diagnostic results would be uncertain or uninformative.[19] When results were disclosed, clinicians not only explained the possible reasons for and sources of the uncertainty, they also stressed that, by disclosing variants with uncertain meaning, they were enabling those variants to be reconsidered in future interpretations. As found in a sociological examination of the central role of potentiality for NCGENES participants who learned negative results[6] as well as in other studies,[3,7,23,24] such explicit communication helped participants contextualize the uncertain result and mitigated adverse responses to it, while promoting optimism for potential certainty in the future.

In addition to the clinicians' nuanced explanations about an uncertain result, this framing results in a future promise of genomic discovery was found to be key to participants' understanding.[25] NCGENES clinicians promised to keep looking for the answer, adding new genes to diagnostic lists, and reanalyzing novel variants. Most participants referenced this promise in their interviews. They understood that uncertainty was part and parcel of this new enterprise, driving the research that might resolve uncertainty in the future. Some participants may not have had a realistic timeline of when science could produce those answers, but hoped that their children and others would benefit if answers did not come in time for them. They viewed the continued efforts of genomic researchers and clinicians as the best chance of finding a definitive genetic diagnosis, and took seriously the clinicians' promise to "keep looking" for the answer.

Findings from this study indicate that uncertainty in diagnostic GS results is accepted and understood by patients when carefully and adequately explained. Concerns have been raised about the potential harms of returning uncertain results from GS[4]; however, genomic medicine is not exceptional in this regard. Much as in other fields of medicine, the biggest risk of returning an uncertain result is likely to be its misinterpretation as a true positive result and subsequent downstream consequences, such as risks of overtreatment. We would argue that greater harm is caused when laboratories overcall variants of uncertain significance as "likely pathogenic" (classifying them as "positive" results) than in characterizing a variant as uncertain and disclosing it appropriately to the patient. However, there is also the concomitant risk that uncertain diagnostic results will be interpreted as negative and be ignored, thus preventing appropriate clinical action.[26] It is important in large-scale GS to convey to participants the potential for uncertain results and to clarify that these are neither positive nor negative, but will remain uncertain until more knowledge is attained.

There are limitations to the current study. Findings may not be generalizable to other clinical or research settings that differ by population characteristics, the level of participant education, and clinical communication practices. The participants in this study had already undergone diagnostic odysseys, with the majority having exposure to the genetic testing process, and many had previously experienced uninformative or uncertain results. Their expectations of definitive results had been tempered by the NCGENES consent and pretest counseling process, and by clinicians' contextualization of the uncertain result. Participants' optimism about future answers could reflect a bias specific to research participants and may not be representative of patients undergoing clinical GS. However, even clinical GS candidates are likely to have had similar experiences. Longitudinal studies in other contexts are needed to determine if and when harms arise from uncertain diagnostic results, and the factors that amplify or ameliorate such harms.

In spite of these limitations, the current study suggests that uncertain diagnostic results from GS can be relayed to patients in ways they can understand and consistent with providers' interpretations, without causing undue harm.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

ACKNOWLEDGMENTS

The research on which this study is based was funded by the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH) under Award Number U01 HG006487-01; the Center for Genomics and Society at the University of North Carolina-Chapel Hill, funded by the NHGRI/NIH under Award Number 2P50HG004488, and TraCS Institute from the Clinical and Translational Science Award program of the National Center for Advancing Translational Sciences, National Institutes of Health under Award Number 1UL1TR001111. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. *N Engl J Med* 2014;370:2418–2425.
2. Strande NT, Berg JS. Defining the clinical value of a genomic diagnosis in the era of next-generation sequencing. *Annu Rev Genom Hum Genet* 2016;17:303–332.
3. Biesecker B, Klein W, Lewis KL, et al. How do research participants perceive "uncertainty" in genomic sequencing? *Genet Med* 2014;16:977–980.
4. Clarke A. Managing the ethical challenges of next-generation sequencing in genomic medicine. *Brit Med Bull* 2014;111:17–30.
5. Han PKJ, Umstead KL, Bernhardt BA, et al. A taxonomy of medical uncertainties in clinical genome sequencing. *Genet Med* 2017;19:918–925.
6. Skinner D, Raspberry KA, King M. The nuanced negative: meanings of a negative diagnostic result in clinical exome sequencing. *Sociol Health Illn* 2016;38:1303–1317.
7. Stivers T, Timmermans S. Negotiating the diagnostic uncertainty of genomic test results. *Soc Psychol Q* 2016;79:199–221.
8. Timmermans S, Tietbohl C, Skaperdas E. Narrating uncertainty: variants of uncertain significance (VUS) in clinical exome sequencing. *BioSocieties* 2016; https://doi.org/10.1057/s41292-016-0020-5.
9. Bonadies DC1, Brierley KL, Barnett RE, et al. Adverse events in cancer genetic testing: the third case series. *Cancer J* 2014;20:246–53.
10. Cheon JY, Mozersky J, Cook-Deegan R. Variants of uncertain significance in BRCA: a harbinger of ethical and policy issues to come? *Genome Med* 2014;6:121.
11. Timmermans S, Stivers T. The spillover of genomic testing results in families: same variant, different logics. *J Health Soc Behav* 2017;58:166–180.
12. Jez S, Martin M, South S, et al. Variants of unknown significance on chromosomal microarray analysis: parental perspectives. *J Community Genet* 2015;6:343–349.
13. Moret C, Hurst SA, Mauron A. Variants of unknown significance and their impact on autonomy. *Am J Bioethics* 2015;15:26–28.
14. Newson AJ, Leonard SJ, Hall A, Gaff CL. Known unknowns: building an ethics of uncertainty into genomic medicine. *BMC Med Genomics* 2016;9:57.
15. Kiedrowski LA, Owens KM, Yashar BM, Schuette JL. Parents' perspectives on variants of uncertain significance from chromosome microarray analysis. *J Genet Couns* 2016;25:101–111.
16. Reiff M, Bernhardt BA, Mulchandani S, et al. "What does it mean?": uncertainties in understanding results of chromosomal microarray testing. *Genet Med* 2012;14:250–258.
17. Strande, NT, Booker JK, Foreman AKM, et al. Clarity in the face of uncertainty: a nuanced classification of uncertain exome cases. ACMG Annual Clinical Genetics Meeting, Phoenix, AZ, 21–25 March 2017.
18. Miles MB, Huberman AM, Saldaña J. *Qualitative Data Analysis: A Methods Sourcebook*, 3rd ed. Sage: Los Angeles, CA, 2013.
19. Bernhardt B, Roche MI, Perry D, et al. Experiences with obtaining informed consent for genomic sequencing. *Am J Med Genet A* 2015;167:2635–2646.
20. Haga SB, Barry WT, Mills R, et al. Public knowledge of and attitudes toward genetics and genetic testing. *Genet Test Mol Biomarkers* 2013;17:327–35.
21. Vos J1, Oosterwijk JC, Gómez-García E, et al. Perceiving cancer-risks and heredity-likelihood in genetic-counseling: how counselees recall and interpret BRCA 1/2-test results. *Clin Genet* 2011;79:207–218
22. Whitmarsh I, Davis AM, Skinner D, Bailey DB. A place for genetic uncertainty: parents valuing an unknown in the meaning of disease. *Soc Sci Med* 2007;65:1082–1093.
23. Amendola LM, Lautenbach D, Scollon S, et al. Illustrative case studies in the return of exome and genome sequencing results. *Per Med* 2015;12:283–295.
24. Timmermans S, Buchbinder M. (2012) Expanded newborn screening: Articulating the ontology of diseases with bridging work in the clinic. *Sociol Health Illn* 2012;34:208–220.
25. Haase R, Michie M, Skinner D. Flexible positions, managed hopes: the promissory bioeconomy of a whole genome sequencing cancer study. *Soc Sci Med* 2015;130:146–153.
26. Genomics Law Report (Conley, J). http://www.genomicslawreport.com/index.php/2017/01/26/williams-v-athena-motion-to-dismiss-hearing-sc-supreme-court-may-be-asked-to-decide-whether-a-diagnostic-laboratory-qualifies-as-a-healthcare-provider. Posted 26 January 2017. Accessed 4 April, 2017.