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Perceived ambiguity as a barrier to intentions to learn genome sequencing results

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Abstract

Many variants that could be returned from genome sequencing may be perceived as ambiguous—lacking reliability, credibility, or adequacy. Little is known about how perceived ambiguity influences thoughts about sequencing results. Participants (*n*=494) in an NIH genome sequencing study completed a baseline survey before sequencing results were available. We examined how perceived ambiguity regarding sequencing results and individual differences in medical ambiguity aversion and tolerance for uncertainty were associated with cognitions and intentions concerning sequencing results. Perceiving sequencing results as more ambiguous was associated with less favorable cognitions about results and lower intentions to learn and share results. Among participants low in tolerance for uncertainty or optimism, greater perceived ambiguity was associated with lower intentions to learn results for non-medically actionable diseases; medical ambiguity aversion did not moderate any associations. Results are consistent with the phenomenon of "ambiguity aversion" and may influence whether people learn and communicate genomic information.

Keywords

genetic/genome testing; ambiguity aversion; perceived ambiguity; optimism; tolerance for uncertainty; response efficacy

Introduction

Genome sequencing is a major technological advance in that it can provide information about one's genetic predisposition to develop a variety of diseases and other health-related outcomes (Biesecker & Green, 2014). Sequencing results are increasingly available in research and medical contexts (Institute of Medicine and National Research Council, 2010).

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Learning genetic information may be desirable, particularly if the disease in question is preventable or treatable (e.g., heart disease) and genetic information could motivate prevention or early detection. Even if the disease is not preventable or treatable (e.g., Alzheimer disease), learning such risks could have benefits, such as allowing people to plan for negative outcomes or to reassess their priorities (Christensen et al., 2011). When genetic information does confer important and/or medically actionable information, learning this information and sharing it with relatives who may also be at risk may be desirable. For many patients, genomic sequencing is elective, and therefore it is critical to understand patient attributes that are associated with interest in such testing. As we will discuss, despite the promise of genome sequencing, it brings with it uncertainty from both a medical and patient perspective that may dampen patient enthusiasm for this kind of risk information.

In conventional genetic testing settings, people often seek testing based on a known history of disease. For example, individuals with a family history of cancer may undergo genetic testing to learn whether they are at quantifiably increased disease risk and to reduce uncertainty about the nature and source of their disease risk (Cameron & Muller, 2009; Sweeny et al., 2014). In these contexts, low tolerance for uncertainty generally predicts greater uptake (Braithwaite et al., 2002; although uncertainty may not actually be reduced post-testing, Vos et al., 2013).

However, low tolerance for uncertainty may not lead to greater uptake if people perceive the utility of genetic information to be uncertain. Although this can be the case with single-gene testing, genome sequencing holds even greater potential for actual and perceived uncertainty. Participants in genome sequencing studies, like those enrolled in the present study, may be less likely to expect a specific test result upon enrollment and thus could be unsure whether information provided will be useful (cf. Biesecker et al., 2014). Additionally, the science linking genetic variants to disease risk (and optimal treatment) is in a nascent stage (MacArthur et al., 2014). As such, genome sequencing may identify some variants for which there is cause for concern about disease risk but the extent and timing of the risk may be unknown and/or the implications for one's health uncertain. These factors leave open the possibility for individuals to perceive ambiguity in their results.

Uncertainty arising from limitations in the reliability, credibility, or adequacy of information has been defined by decision theorists as *ambiguity* (Ellsberg, 1961; Han, Klein, & Arora, 2011). In the present study, perceived ambiguity of sequencing results was defined as participant perceptions of the accuracy and interpretability of any potential future results (Table 1). Ambiguity causes people to pessimistically appraise risks and choice options and avoid making decisions—a phenomenon known as "ambiguity aversion" (Camerer & Weber, 1992; Ellsberg, 1961). Ambiguity aversion occurs in health domains; for example, people who perceive greater ambiguity in health information perceive themselves to be at greater risk for disease, regard disease as less preventable, report lower engagement in prevention behaviors (Han, Moser, & Klein, 2007) and have difficulty making medical decisions (Hamilton et al., 2013).

Given its breadth and the enormous number of variants with little or no data on clinical validity and utility, genome sequencing data have significant potential to be ambiguous, and

might elicit ambiguity-averse responses in people deciding whether to learn sequencing results. Specifically, if perceiving ambiguity is associated with more negative perceptions of sequencing results, individuals who expect test results to be ambiguous may opt out of learning genetic information even before healthcare providers have an opportunity to address questions about the ambiguous nature of the information. Importantly, because much sequencing information *is* ambiguous, the goal may not be to alter individuals' perceptions of or responses to ambiguity in genome sequencing results. Yet, it is important to acknowledge that people who avoid genomic sequencing results altogether may not receive useful information about well-known diseases with clearly linked genetic variants.

Perceiving ambiguity in genome sequencing results may not always reduce interest in obtaining results. People vary in how much uncertainty or ambiguity they can tolerate, both in general (i.e., general tolerance for uncertainty, Geller et al., 1993) and more specifically with respect to medical tests and treatments (i.e., medical ambiguity aversion, Han, Reeve, et al., 2009; Table 1). These individual differences might influence behavior; for example, physicians who were low in general tolerance for uncertainty reported being more likely to withhold ambiguous genetic test results from patients (Geller et al., 1993), and people who were higher in aversion to ambiguity about medical tests had less favorable attitudes toward cancer screening (Han, Williams, et al., 2014). These data, particularly those concerning general tolerance for uncertainty, suggest that these individual differences may exaggerate aversive responses to perceived ambiguity. Genomic testing is particularly interesting because it may provide people with both unambiguous and ambiguous feedback about personal disease risk. Given this mix of potential results, we hypothesized that people who reported a high degree of perceived ambiguity about potential sequencing results would report overall less interest in obtaining any results if they were also low in tolerance for uncertainty or high in aversion to ambiguity about medical tests (see Table 1 for hypotheses). We did not have a hypothesis about whether one of these moderators would be more potent than the other.

Another factor that might influence how people respond to actual or perceived ambiguity is dispositional optimism, which indicates the degree to which individuals have positive expectations about their future (Carver & Scheier, 2002; Scheier & Carver, 1993; Table 1). Prior research has shown that dispositional optimism may moderate the effect of perceived ambiguity by reducing aversion to this ambiguity, such that participants higher in optimism reported lower disease worry when presented with ambiguous information than participants lower in optimism (Han, Klein et al., 2011; Han, Klein, et al., 2009). In focus group research using 39 participants drawn from the larger sample utilized for the present study (ClinSeq®), participants differed in whether they perceived uncertainty (which often arises from ambiguity) in sequencing information as expected and relatively positively (e.g., "developing" or "ground breaking") or more negatively (e.g., "questionable" or "poorly understood;" Biesecker et al., 2014). The authors state that focus group participants perceived uncertainty as "an opportunity or a threat," depending on whether participants were optimistic or pessimistic about the implications of the uncertainties.

The goal of the present study was to evaluate the effects of perceived ambiguity with respect to genome sequencing, as quantitative research has not yet examined the effects of perceived

ambiguity or individual differences that may moderate the effects of perceived ambiguity in this context. Participants in the present study voluntarily enrolled in a clinical study designed to pilot the use of genome or exome sequencing and to identify variants related to heart disease and other genetic risks. We first examined to what extent participants expected genome sequencing results to be ambiguous—unreliable, uninterpretable, and untrustworthy—as little quantitative data exist on this question. Our key variables and associated hypotheses are outlined in Table 1. Our primary hypothesis was that greater perceived ambiguity of future sequencing results would be associated with pessimistic appraisals of sequencing (e.g., lower perceptions of the preventability of gene-related diseases and lower beliefs that sequencing information will help reduce disease risk), consistent with the phenomenon of ambiguity aversion. We also predicted that greater perceived ambiguity would therefore be associated with lower intentions to receive sequencing results and decreased intentions to share sequencing information with relatives. Sharing results with relatives is an important downstream behavior. In prior focus group research, some participants thought that uncertainty reduced the value of sharing genome information with relatives (Biesecker et al., 2014), and uninformative results are shared less frequently than informative results (Stoffel et al., 2008; Wilson et al., 2004).

The second aim of the study was to explore the potential moderating effects of individual differences that might have an impact on how people react to perceptions of ambiguity. Specifically, we hypothesized that the expected associations of greater perceived ambiguity with less positive appraisals of genome sequencing results and lower intentions to receive sequencing results would be strongest for participants high in medical ambiguity aversion, high in tolerance for uncertainty, or low in optimism. We did not have reason to believe that the individual differences of medical ambiguity aversion and tolerance for uncertainty (which reflect general orientations toward perceived ambiguity or uncertainty, but do not assess whether someone perceives a specific type of information to be ambiguous or uncertain) would be directly related to whether participants perceived ambiguity about genome sequencing results, only that these differences might moderate responses to such perceptions of ambiguity.

Method

Study Population and Design

Participants aged 45 to 65 from the Washington, D.C. metropolitan area (*N*=998) were recruited for a longitudinal cohort study piloting the use of genome or exome sequencing, with multiple aims including the assessment of intentions to learn sequencing results and identification of variants related to heart disease (ClinSeq®; Biesecker et al., 2009). Of these, the 962 participants who had been enrolled for at least one month and not received sequencing results were invited to complete a baseline survey. The baseline survey was completed by 551 respondents (55.2% response rate) and included a battery of items assessing attitudes and individual difference measures potentially related to genome sequencing. We report only a subset of items, dispersed throughout the survey, that were pertinent to the present study and include data only from the 494 respondents who completed the majority of these items (51.4% completion rate).[1]

Most participants were White (92.7%) and about half were male (55.9%). Participants were on average 61.0 years old (*SD*=5.50), with 96.5% reporting greater than a high school education. The median household income was > $100,000, reported by 78.2% of the sample. Samples in genetic testing and sequencing studies tend to be high in income and educational level (Hensley et al., 2011). A detailed comparison of survey completers and noncompleters is presented elsewhere (Taber et al., 2014) and indicates that survey completers were more likely to be White, to have an income > 100,000 USD, to be a college graduate or higher, and to be male compared to survey non-completers.

Participants were not financially compensated for participation in the study. They were told that some medically useful results would be routinely returned (e.g., blood chemistries and echocardiograms) and that they may have the opportunity to receive sequencing results if they desired. Other data show that respondents were motivated to participate in this study by both altruism and the potential to learn personalized genetic information (Facio et al., 2011), although intentions to receive multiple types of results were high (Facio et al., 2013).

Prior to the baseline survey, participants completed the consent process. Part of the purpose of the consent was to accurately convey the level of scientific ambiguity so that participants could make informed decisions about whether to enroll in the study. For example, the informed consent stated that, “Our plan is to sequence most of your genes. This analysis will take months or years to complete. This is because genome sequencing is difficult to do. It is also because we have much to learn about the genes we will be sequencing and the gene variants we find.” The informed consent also stated that, “We may find gene variants that are novel and of uncertain clinical importance…We will only report this type of gene variant to you if we can learn enough about it to make us believe that it can cause or contribute to disease.” Participants completed the informed consent process with a trained staff member. Research among a different subset of ClinSeq® respondents demonstrated overall improvement in knowledge of the limitations of sequencing following the informed consent procedure, although accurate understanding was not universal (Kaphingst et al., 2012). The National Human Genome Research Institute’s Institutional Review Board reviewed and approved the study.

Measures

Perceived ambiguity about genetic sequencing results—*Perceived ambiguity* about one’s sequencing results was assessed as the average of agreement with five statements (α =.743) about the interpretability, trustworthiness, and accuracy of personal sequencing results that participants may subsequently receive in this study, on a scale from 1 (*Strongly disagree*) to 5 (*Strongly agree*). Higher scores indicated greater perceived ambiguity. These items were developed based on prior research by the authors in this domain (Hamilton et al., 2013; Han, Klein, & Arora, 2011). Sample items for these and other constructs appear in Table 1.

[1]Different hypotheses concerning predictors of intentions to learn sequencing results in this sample have been tested and reported elsewhere. Other than intentions to receive and share sequencing results (Ferrer et al., 2014; Taber et al., 2015), the only measure currently included in other manuscripts is dispositional optimism, which was examined as a moderator of the effect of perceived risk on intentions to learn and use sequencing results (Taber et al., 2014). Descriptive statistics for the survey respondents are reported in Lewis et al., (2014) and Taber et al., (2014).

Individual difference measures—*Medical ambiguity aversion* was assessed using the 6-item Ambiguity Aversion in Medicine scale (AA-Med; Han, Reeve et al., 2009; α=.792) which assesses aversion to medical tests or treatments about which experts have conflicting opinions. Items were scored on a scale from 1 (*Strongly disagree*) to 5 (*Strongly agree*) and averaged. Higher scores indicate greater ambiguity aversion.

General tolerance for uncertainty was assessed using the 7-item Tolerance for Ambiguity scale (Geller et al., 1993; α =.797), which assesses the extent to which individuals are comfortable with uncertain situations. Items were scored on a scale from 1 (*Not at all characteristic of me*) to 5 (*Entirely characteristic of me*). Higher scores indicate lower tolerance for uncertainty. We refer to this scale as a measure of uncertainty, because it does not assess "ambiguity" as previously defined (see Ellsberg, 1961; Han, Klein, & Arora, 2011).

Dispositional optimism was assessed as the average of three items from the LOT-R (α =. 845) from 1 (*Strongly disagree*) to 5 (*Strongly agree*; Scheier, et al., 1994). Dispositional pessimism was not assessed.

Cognitions about sequencing results—*Perceived response efficacy* for reducing disease risk was assessed as the average of agreement with four items (α =.904) indicating that results would help reduce chances of developing 1) common disease(s), 2) heart disease, 3) cancer, and 4) relatives' chance of getting a genetic condition, from 1 (*Strongly disagree*) to 5 (*Strongly agree;* e.g., "My results will help reduce my chances of getting cancer.")

Perceived health value of results was assessed as the average of three items (α=.865) indicating agreement with statements that sequencing results would be valuable for maintaining future health, one's family's future health, and that results would be useful to physicians, from 1 (*Strongly disagree*) to 5 (*Strongly agree*; e.g., "My sequence results will be valuable for maintaining my future health.")

Perceived health benefits of results was assessed by two items (r=.369) assessing participants' beliefs that they would be likely to experience health benefits (e.g., "How likely is it that you will experience health benefits from learning sequence results?" and "How likely is it that you will experience health benefits from receiving standard medical care (beyond learning sequence results)?), from 1 (*Extremely unlikely*) to 7 (*Extremely likely*).

Perceived health harms of results was assessed with the same two items (r=.480) assessing perceived health benefits, with "harms to your health" substituted for "health benefits," from 1 (*Extremely unlikely*) to 7 (*Extremely likely*).

Intentions to learn sequencing results—*Intentions* were assessed about three types of sequencing results: medically actionable disease results (described as "a gene variant that predisposes you to a disease that can be prevented or treated"), non-medically actionable disease results (described as "a gene variant that predisposes you to a disease that cannot be prevented or treated"), and carrier status results for recessive conditions (described as "a

gene variant that does not affect your health, but that may be important to the health of other relatives, such as your children"). Two items assessed intentions to learn ("I intend to learn such a result"; 1=*Definitely no* to 5=*Definitely yes*) and likelihood of learning ("How likely is it that you will choose to learn about such a result?"; 1=*Extremely unlikely* to 7=*Extremely likely*) each of the three types of results (medically actionable, r=.247; non-medically actionable, r=.730; carrier, r=.491). Because the restricted range of responses influenced the correlations among items, items were standardized and then averaged to form independent scales for medically actionable disease, non-medically actionable disease, and carrier status, respectively.[2]

Intentions to share sequencing results—*Intentions to share sequencing results* were assessed as the average of six standardized items (α =.884) assessing intentions to share (1=*Definitely no* to 5=*Definitely yes*) and likelihood of sharing (1=*Extremely unlikely* to 7=*Extremely likely*) sequencing results for medically actionable disease, non-medically actionable disease, and carrier status results with family members.

Participants also reported their age, gender, race/ethnicity, education level, and average household income.

Overview of Analyses

After assessing bivariate correlations among all measures, we conducted linear regression analyses to determine whether perceived ambiguity, medical ambiguity aversion, and general tolerance for uncertainty predicted cognitions about sequencing results and intentions to learn and share results. These three variables (i.e., perceived ambiguity, medical ambiguity aversion, and general tolerance for uncertainty) were entered simultaneously in regression analyses to account for any shared variance among them, as preliminary analyses demonstrated that two out of three (see Results) of the correlations among these items reached statistical significance. Next, we tested whether the individual difference measures of medical ambiguity aversion, general tolerance for uncertainty, and dispositional optimism moderated the effect of perceived ambiguity on cognitions and intentions (Hayes, 2013). All regression analyses controlled for the sociodemographic factors of age, gender, income, education, and race. Predictor variables were mean-centered prior to inclusion in regression analyses. Statistical significance was defined as $p < .05$.

Results

Means and standard deviations of survey items are reported in Table 2. Of note, perceptions of genome sequencing results were generally favorable: participants perceived a relatively low degree of ambiguity about sequencing results,[3] moderate response efficacy, high perceived health value, high perceived health benefits of test results, and low perceived health harms of test results. Participants reported relatively high intentions to receive all types of sequencing results and high intentions to share test results with family members.

[2]Log transformations were applied to normalize the distribution (for medically actionable intentions: original kurtosis=2.72 and skew= −1.73, transformed kurtosis= −0.12 and skew= 1.11; for non-medically actionable intentions, original kurtosis=2.07 and skew= −1.60; transformed kurtosis= −0.52 and skew= 0.92; for carrier status results: original kurtosis=4.02 and skew= −1.92, transformed kurtosis= 0.07 and skew= 1.07).

Correlations among study variables are also displayed in Table 2. Of note, the correlations among the ambiguity-related constructs are associated with small to medium effect sizes (Cohen, 1992), suggesting that perceived ambiguity, medical ambiguity aversion, and general tolerance of uncertainty represent distinct constructs.

Associations of Ambiguity-related Constructs with Cognitions about Sequencing Results

We further examined multivariate associations among ambiguity-related constructs and cognitions about sequencing results. Hierarchical linear regression analyses were conducted with perceived ambiguity, medical ambiguity aversion, and general tolerance for uncertainty entered as simultaneous predictors of health cognitions, controlling for sociodemographic factors.

As shown in Table 3 and consistent with our first hypothesis, participants who perceived greater ambiguity about their sequencing results reported lower perceived response efficacy, lower perceived health value, lower perceived health benefits, and higher perceived health harms. Consistent with treating the individual difference measures as moderators, medical ambiguity aversion was inconsistently related to cognitions about sequencing results, and general tolerance for uncertainty was not significantly associated with any cognition.

Associations of Ambiguity-related Constructs with Intentions to Learn and Share Genome Sequencing Results

In linear regressions controlling for medical ambiguity aversion, general tolerance for uncertainty, and sociodemographic factors, perceiving greater ambiguity about sequencing results was associated with lower intentions to learn results and share results with family members (Table 4). Although this effect did not reach statistical significance for intentions to learn medically actionable disease results, the pattern is consistent with the phenomenon of ambiguity aversion. Of note, participants higher in medical ambiguity aversion also reported lower intentions to learn all three types of results, although this effect did not reach statistical significance for intentions to learn medically actionable disease results. Medical ambiguity aversion was not significantly associated with intentions to share sequencing results. General tolerance for uncertainty was not significantly related to intentions to learn or share sequencing results.

Individual Differences as Moderators of the Influence of Perceived Ambiguity on Cognitions about Sequencing Results and Intentions

We next tested whether the associations of perceived ambiguity on all measures of cognitions and intentions were stronger among individuals higher in medical ambiguity aversion, lower in general tolerance for uncertainty, or lower in dispositional optimism. A series of linear regression analyses included sociodemographic factors (Step 1), the main

[3]Although paired *t* tests indicated that all five items assessing perceived ambiguity significantly differed from one another, qualitatively, participants on average reported greater endorsement that test results might be difficult to interpret ("I think scientists won't be able to interpret much of my sequencing results," *M*=2.10, *SD*=0.96; "It seems like my sequencing results will be interpreted in many different ways," *M*=2.92, *SD*=0.95, and "I don't think my sequencing results will give clear answers about my future health," *M*=2.69, *SD*=0.93) than beliefs that results would not be trustworthy (*M*=1.68, *SD*=0.69) or accurate (*M*=1.72, *SD*=0.72). A subscale of only the former three items assessing interpretability had an unacceptable alpha of .641, and we therefore retained the 5-item scale with higher reliability (α =.743).

effects of perceived ambiguity, medical ambiguity aversion, and general tolerance for uncertainty, and optimism if included as a moderator (Step 2), and the interaction of perceived ambiguity with a) medical ambiguity aversion, b) general tolerance for uncertainty, or c) optimism (Step 3). Contrary to our hypotheses, medical ambiguity aversion did not moderate the effect of perceived ambiguity on any measure of cognitions or intentions, indicating that perceived ambiguity was not more problematic for individuals who were higher in aversion to ambiguity in medical contexts. However, we describe four significant interaction effects involving general tolerance for uncertainty and optimism below.

Consistent with predictions, general tolerance for uncertainty moderated the effect of perceived ambiguity on perceived response efficacy (unstandardized $\beta = -0.17$, $SE=0.08$, $p=0.044$) and intentions to receive results for non-medically actionable disease ($\beta = -0.05$, $SE=0.02$, $p=.018$), but not any other outcomes. Simple slopes analyses showed that greater perceived ambiguity was associated with lower intentions to learn non-medically actionable results only when individuals reported low (one *SD* above the mean; $\beta = -0.10$, $SE=0.02$, $p<.001$) but not high tolerance for uncertainty (one *SD* below the mean; $\beta = -0.02$, $SE=0.02$, $p=.305$), and the pattern was similar for perceived response efficacy.

Consistent with prior research showing that dispositional optimism moderated the effect of perceived ambiguity on cancer worry (Han, Klein, et al., 2011), optimism moderated the effect of perceived ambiguity on intentions to learn results for non-medically actionable disease ($\beta=0.04$, $SE=0.02$, $p=0.045$)[4] and carrier status results ($\beta=0.04$, $SE=0.02$, $p=0.054$), but not on any other outcomes. Simple slopes analyses showed that greater perceived ambiguity was associated with lower intentions to learn non-medically actionable results only when individuals reported low ($\beta = -0.09$, $SE=0.02$, $p<.001$), but not high levels of optimism ($\beta = -0.03$, $SE=0.02$, $p=.257$), and the pattern was identical for carrier status results.

Discussion

In the present study, higher expectations that one's future sequencing results would be ambiguous— that is, greater endorsement that results would be difficult to interpret, inaccurate and untrustworthy—were associated with less enthusiasm for these results. Specifically, participants who perceived greater ambiguity reported that sequencing results would be less likely to result in health benefits and more likely to harm health, would be less medically useful, and would be less likely to reduce disease risk. Greater perceived ambiguity was also associated with lower intentions to learn sequencing information and to share this information with family members. This pattern of associations is largely consistent with predictions based on the phenomenon of ambiguity aversion, in which people report lower intentions to engage in preventive action when they perceive it to be associated with greater ambiguity (Han, Moser, & Klein, 2007; Han, Kobrin, et al., 2007).

[4]This interaction was further qualified by race (3-way interaction: $\beta = 0.22$, $SE=0.12$, $p=.045$), such that optimism mitigated the effect of perceived ambiguity on intentions to learn results for non-medically actionable disease for White respondents, but not for respondents of other races.

Of note, the association of greater perceived ambiguity of sequencing results with lower interest in learning sequencing results is not necessarily a manifestation of ambiguity aversion, as individuals who are ambiguity-averse could also seek out sequencing information to lessen their perceived ambiguity. This would be particularly true for high penetrance genetic variants. Nevertheless, such a pattern did not emerge in the present study.

Several of the associations identified here are novel and expand our understanding of ambiguity aversion as a pattern of responses to the perception that information is ambiguous. In the present study, perceiving greater ambiguity was associated with reporting that sequencing results would be less beneficial in reducing disease risk and less medically useful, consistent with prior findings that greater perceived ambiguity is associated with perceiving disease as less preventable (Han, Moser, & Klein, 2007). A downstream implication of these associations that was newly identified here is that participants not only expressed less interest in learning this information, but also reported lower likelihood of sharing the information with their relatives. Communicating genetic information to one's biological relatives is desirable because it allows relatives to learn of their own potentially elevated risk and to respond in a medically-appropriate manner, and can be an important source of social support that can buffer negative effects of stress associated with learning potentially negative health information (Stoffel et al., 2008; Wilson et al., 2004).

Another novel contribution is that the negative association between perceived ambiguity and intentions to learn non-medically actionable disease results was not present when individuals were either high in tolerance for uncertainty or high in optimism. Surprisingly, the general measure of tolerance for uncertainty moderated these effects, whereas the more specific measure of aversion to ambiguity in medical domains did not. One explanation is that individual differences in attitudes toward information overall (regardless of domain) may simply be more potent than differences in attitudes toward information in a specific (even relevant) domain. Another explanation is that medical ambiguity aversion is too similar to ambiguity aversion as a behavioral/psychological response and therefore cannot moderate the effect. Although participants who reported greater medical ambiguity aversion also reported lower general tolerance for uncertainty, the moderate correlation (r=.299) demonstrates that these are distinguishable constructs.

Dispositional optimism also moderated the association between perceived ambiguity and intentions to learn non-medically actionable disease results. Non-medically actionable disease results were likely perceived as being of less certain utility and more threatening than medically actionable disease results. Substantial research has also shown that psychological resources, such as optimism, self-affirmation, or social support can reduce information avoidance or lessen the influence of factors that increase information avoidance (Howell et al., 2014; Taber et al., 2015). Optimism may provide people with the resources to cope with potential threats and may also allow people to construe the information in a more abstract, future-oriented manner rather than focusing on the potentially negative concrete, short-term consequences (Nussbaum et al., 2006).

Clinical Implications

In the present study, perceived ambiguity of sequencing results was present but relatively low. We expected perceived ambiguity to be higher, based on focus group research in which ClinSeq® participants reported that they expected ambiguous and uncertain results from sequencing (Biesecker et al., 2014). The low perceptions of ambiguity are consistent with Bollinger et al.'s, (2012) focus group research in which there was "an underlying expectation that any (individual research result) returned would and should be well understood" (p. 8).

The association of greater perceived ambiguity with lower expected benefits and intentions may be clinically undesirable, because perceiving sequencing results as ambiguous represents a barrier to learning potentially beneficial health information. Moreover, people who perceive ambiguity in genomic sequencing might also avoid any research or clinical trials involving sequencing, especially if they have to provide prior consent acknowledging that researchers are obligated to disclose information about disease risk obtained from the sequencing. Thus, this avoidance could be a barrier to advancement of knowledge about sequencing.

Of course, it is also possible that the association of greater perceived ambiguity with lower expected benefits is desirable, because it represents an accurate understanding of the limitations of sequencing information. There is some evidence that people do not have fully formed attitudes about and do not fully comprehend the limitations of genome sequencing information (Biesecker et al., 2014; Wright et al., 2014). For example, participants who are more optimistic think they will be able to act on sequencing information, even for non-medically actionable disease results (Taber et al., 2014). These positive expectations can be problematic if disconfirmed, as they can lead to greater negative affect and disappointment (Sweeny & Shepperd, 2010). For participants who expect genomic information to be unambiguous and consequently expect greater benefits, specific interventions might be developed to temper these unrealistic expectations.

Ultimately, the goal is for participants to make informed decisions about whether to learn results based on their values and preferences. There is not a "right answer" as to whether people should receive sequencing results, particularly for diseases that are not medically actionable but may hold personal (if not clinical) utility (Foster et al., 2009). The goal may not be for people to perceive overall high or low ambiguity, but rather to understand and carefully consider which aspects of sequencing information are ambiguous and to decide for themselves whether sequencing makes sense. Communicating about the actual ambiguity of sequencing results in a nuanced manner should improve the ability to make fully informed decisions (Han, 2013). Our data suggest that this communication should begin when individuals are contemplating whether to undergo sequencing, rather than merely accompanying receipt of results.

Limitations

Participants in this study were likely proponents of the promise of genome sequencing, given that a different subset of the same sample reported enrolling either because they were

altruistically motivated to contribute to science or because they expected personal health benefits (Facio et al., 2011). Given this positivity, it is unknown whether the findings reported here would generalize to the general public. However, the sample was representative of those who currently will be actually facing receipt of sequencing results, and even among this sample with relatively low perceived ambiguity, perceived ambiguity was still associated with lower interest in learning sequencing results. We expect that perceptions of ambiguity would further hinder enrollment in genome sequencing research in a sample more typical of the U.S. population. The sample was of high socioeconomic status, with survey completers higher in education and income and more likely to be White than survey noncompleters. However, the sample was comparable to samples in other studies of genetic testing, and again is likely representative of the portion of the population that will ultimately make decisions about whether to learn sequencing results. Additionally, cost of living is high in the Washington, D.C. area from which participants were recruited, such that D.C.-area government jobs are paid at 24.22% more than comparable government jobs in other locations (Office of Personnel Management, 2014), suggesting that the income of the current sample is somewhat inflated.

We assessed intentions to receive test results rather than actual results. Interest in receiving genetic test results was likely high because it was one possible perceived benefit (of several) that one could obtain by enrolling in the study. The cross-sectional nature of the study limits our ability to draw conclusions about causality, although because several important variables (medical ambiguity aversion, general tolerance for uncertainty, and dispositional optimism) were individual differences, we can be fairly confident that these factors did in fact predict cognitions and intentions regarding sequencing results, rather than the reverse.

Conclusion

Predictive medicine (also described as personalized medicine, individualized medicine, or precision medicine) is based on the premise that patients will desire and seek genome risk information that will allow them and their physicians to use this information to modify their health care to improve longevity and well-being. This theoretical approach to health care should be more successful if patients expect the genomic information to be valuable. Although in the present study perceptions of genome sequencing results were generally favorable, participants who expected sequencing results to be ambiguous reported more pessimistic appraisals of sequencing and had less interest in learning their genetic results. From a clinical perspective, it is as yet unclear whether these perceptions of ambiguity are desirable, although ideally perceptions of ambiguity would “match” the actual degree of medical ambiguity so that participants averse to ambiguity could opt out of learning ambiguous results. The “actual” degree of ambiguity in genome sequencing, however, is debatable, and it is arguably inescapable that genome results will be ambiguous to some degree, primarily because of the substantial scale and scope of genome results and the nascent status of the field. As such, and given that a patient’s individual tolerance of uncertainty may influence how he or she copes with ambiguous genetic sequencing information, it may be more appropriate for clinicians to focus on addressing *responses* to perceived ambiguity rather than on reducing perceived ambiguity itself, and on enabling patients to adopt a thoughtful, deliberative approach to decisions about sequencing. It is

therefore a critical challenge for the field to precisely define the types of ambiguity and uncertainty associated with this testing and to accurately assess patient attitudes and intentions to use potentially ambiguous risk information.

All procedures were reviewed and approved by the National Human Genome Research Institute Institutional Review Board. Informed consent was obtained from all patients for being included in the study.

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Table 1

Characteristics of predictors as assessed in the present study

	Description	Individual difference or perception	Specific to medical context	Specific to genetic sequencing	Sample items	Hypotheses
Perceived ambiguity	Perceptions of the interpretability, trustworthiness, and accuracy of sequencing results that may be learned in the future. "Actual" ambiguity is present when a sequencing result is in fact low in interpretability and accuracy.	Perception	Yes	Yes	• I think scientists won't be able to interpret much of my sequencing results • I don't believe my sequencing results will be accurate • I don't think my sequencing results will give clear answers about my future health	Greater perceived ambiguity would be associated with: **1** Pessimistic appraisals of sequencing (e.g., lower perceptions of the preventability of gene-related diseases and beliefs that sequencing information will help to reduce disease risk) **2** Lower intentions to receive sequencing results **3** Lower intentions to share results with family members
Medical ambiguity aversion	The extent to which individuals are averse to medical tests or treatment about which experts have conflicting opinions. Items are from the Ambiguity Aversion in Medicine scale.	Individual difference	Yes	No	• I would not have confidence in a medical test or treatment if experts had conflicting opinions about it • I would avoid making a decision about a medical test or treatment if experts had conflicting opinions about it • I would not be afraid of trying a medical test or treatment if experts had conflicting opinions about it	Moderation such that: The expected associations of greater perceived ambiguity with less positive appraisals of genome sequencing results and lower intentions to receive sequencing results would be *stronger for participants high in medical ambiguity aversion*.
General tolerance for uncertainty	The extent to which individuals are comfortable with uncertain situations. Items are from the Tolerance for Ambiguity scale.	Individual difference	No	No	• If I am uncertain about the responsibilities involved in a particular task, I get very anxious • I am often uncomfortable with people unless I feel that I can understand their behavior	Moderation such that: The expected associations of greater perceived ambiguity with less positive appraisals of genome sequencing results and lower intentions to receive sequencing results would be *stronger for participants low in tolerance for uncertainty*.
Dispositional optimism	General orientation toward the future	Individual difference	No	No	• I'm always optimistic about my future	Moderation such that: The expected associations of greater perceived ambiguity with less positive appraisals of genome sequencing results

	Description	Individual difference or perception	Specific to medical context	Specific to genetic sequencing	Sample items	Hypotheses
					• In uncertain times, I usually expect the best • Overall, I expect more good things to happen to me than bad	and lower intentions to receive sequencing results would be *stronger for participants low in optimism*.

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Table 2

Bivariate correlations among study variables.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Perceived ambiguity of sequencing results	–	*.124***	*.057*	*−.108**	***−.124*****	***−.285*****	***−.278*****	***.197*****	***−.100****	***−.176*****	***−.159*****	***−.224*****
2. Medical ambiguity aversion		–	*.299***	*−.169***	***.092****	***−.050***	***−.019***	***.215*****	***−.132*****	***−.142*****	***−.163*****	***−.137*****
3. General tolerance for uncertainty[a]			–	*−.218***	***.033***	***−.042***	***−.027***	***.106****	***−.036***	***−.116****	***−.101****	***−.125*****
4. Optimism				–	.106*	.187**	.143**	−.052	.040	.116*	.125**	.132**
5. Perceived response efficacy					–	.428**	.309**	.011	−.010	.106*	.043	.058
6. Perceived health value						–	.426**	−.141**	.135**	.228**	.206**	.247**
7. Perceived health benefits							–	−.251**	.212**	.193**	.186**	.241**
8. Perceived health harms								–	−.170**	−.173**	−.187**	−.169**
9. Intentions, medically actionable disease									–	.546**	.629**	.217**
10. Intentions, non-medically actionable disease										–	.836**	.335**
11. Intentions, carrier status											–	.357**
12. Intentions to share results with family members												–
13. Age	−.044	.024	−.036	.019	.038	.090*	.074	−.047	.000	.020	.032	.088
14. Education	.060	−.123**	−.100*	.012	−.037	−.081	−.006	.030	.076	−.056	−.021	−.025
15. Income	.069	−.040	−.076	.065	−.101*	−.117*	−.062	.044	−.008	−.009	−.010	.052
16. Male[b]	−.008	−.088*	−.008	−.043	.062	.005	−.065	−.015	−.033	.053	.035	.037
17. Race[c]	−.088	−.110*	−.120**	−.038	−.114*	−.023	.041	−.155**	.076	.025	.068	.042
Mean	2.22	2.48	2.62	3.78	2.88	3.94	5.35	2.30	4.64[d]	4.39[d]	4.63[d]	4.47[d]
Response range	1–5	1–5	1–5	1–5	1–5	1–5	1–7	1–7	1–5	1–5	1–5	1–5
Standard deviation	0.60	0.64	0.78	0.73	0.93	0.83	1.00	1.06	0.69	0.92	0.78	0.58

** p<.01,

* p<.05

[a] Higher scores indicate lower tolerance for uncertainty

[b] 0=Female, 1=Male

[c] 0=non-White, 1=White

[d] Values reported are for items indicating whether participants "intend to learn [share] results" prior to standardization and transformation. Mean values for responses to whether participants reported being "likely to learn [share]" results (prior to standardization and transformation) are as follows, on a scale from 1 to 7: medically actionable disease, *M*=6.48, *SD*=1.13; non-medically actionable disease, *M*=6.19, *SD*=1.33; carrier status, *M*=6.57, *SD*=0.92; share results with family members: *M*=6.25, *SD*=0.83).

Note: Italic includes correlations among ambiguity-related constructs, bold includes correlations among ambiguity-related constructs and cognitions about sequencing results, and bold italics includes correlations among ambiguity-related constructs and intentions to learn and share sequencing results.

Table 3

Multivariate associations of perceived ambiguity, medical ambiguity aversion, and general tolerance for uncertainty with cognitions about sequencing results.

	Perceived response efficacy		Perceived health value		Perceived health benefits		Perceived health harms	
	β	***SE***	***β***	***SE***	***β***	***SE***	***β***	***SE***
Perceived ambiguity of sequencing results	−0.24**	0.07	−0.37**	0.06	−0.47**	0.08	0.25**	0.08
Medical ambiguity aversion	0.19**	0.07	−0.02	0.06	0.01	0.08	0.30**	0.08
General tolerance for uncertainty	−0.04	0.06	−0.03	0.05	−0.03	0.06	0.05	0.06

** $p<.01$

Note: All analyses controlled for sociodemographic factors (e.g., age, gender, income, education, and race).

Table 4

Multivariate associations of perceived ambiguity, ambiguity aversion, and tolerance for uncertainty with intentions to learn sequencing results and share sequencing results with family members.

	Intentions to learn sequencing results							
	Medically actionable disease		Non-medically actionable disease		Carrier status		Intentions to share sequencing results with family members	
	β	***SE***	***β***	***SE***	***β***	***SE***	***β***	***SE***
Perceived ambiguity of sequencing results	−0.03^	0.02	−0.06**	0.02	−0.05**	0.02	−0.28**	0.06
Medical ambiguity aversion	−0.03^	0.01	−0.03*	0.02	−0.03*	0.01	−0.08	0.06
General tolerance for uncertainty	0.06	0.01	−0.02^	0.01	−0.02	0.01	−0.09^	0.05

** $p<.01$

* $p<.05$

^ $p<.10$

Note: All analyses controlled for sociodemographic factors (e.g., age, gender, income, education, and race).