Once you know it you can't un-know it—irreversibility and uncertainty in genetic testing for cancer risk.

Authors:
NB Henrikson (corresponding author): University of Washington, Institute for Public Health Genetics, Seattle WA, USA. Email: nhenriks@u.washington.edu

SD Ramsey: Fred Hutchinson Cancer Research Center, Seattle WA, USA. Email: sramsey@fhcrc.org

****Work in progress—do not quote without authors' permission****

"When you leave that way you can never go back
A train won't run on a torn up track
Sometimes I wish I'd never roamed, oh no
'cause when you leave that way you can never go home…"

Lyrics by Confederate Railroad; www.cowboylyrics.com

"You can't 'unknow' this information. This is forever. Your whole life changes in 10 minutes."

Genetic Testing Gives Glimpse Into Future
The New York Times, May 4, 1997
by Cynthia Magriel Wetzler

"Once you know you've got the mutation, you can't unknow it," Winship said. "Some people need the certainty and make their life decisions and plans. Other people can't deal with that certainty."

Watt, Emily. When Breast Cancer Runs in the Family; Study to Find Out Why Some Families More at Risk. http://www.apria.com/resources/1,2725,494-217203,00.html

A. AIMS

Since the completion of the Human Genome Project, testing for genetic susceptibility to disease has been a promise of the clinical impact of genomic science. Understanding how people at risk make the decision to get a genetic test or not are essential to public health planning, yet all known tests have significant numbers of refusers.

Irreversibility is the property of a decision that, in lay terms, once done cannot be undone. In economic terms, irreversibility is a property of a decision that reduces the number of options available. We suspect that an individual's decision to undertake genetic susceptibility testing has the property of an irreversible decision, and may be a motivator not to test and may help to characterize groups of refusers of genetic tests. The aim of this research project is to determine if there is evidence that irreversibility affects decision-making about genetic testing for colorectal cancer risk.

We had several research questions for this project. First, what are the attitudes of relatives of people with cancer and controls towards uncertainty and irreversibility? We hypothesized that some proportion of both controls and relatives would report that reducing uncertainty is a motivator in getting a genetic test. We further hypothesized that some proportion of both controls and relatives would report that the irreversibility of genetic information influences their decision-making about getting a genetic test, specifically that those who think that irreversibility is important might increase likelihood of either refusing or deferring the decision to get a genetic test.

Our second research question was: are relatives of people with colorectal cancer or controls more likely to report that irreversibility influences their likelihood of getting genetic susceptibility testing? Thinking that perhaps relatives of people with cancer were more likely to be motivated to get genetic testing regardless of the consequences, we hypothesized that relatives of people with colorectal cancer are less likely to report considering irreversibility in decision-making about genetic testing than controls, and that relatives are less likely to report considering irreversibility in timing of decision-making about genetic testing.

Our third research question was: what predicts intentions of likelihood of considering irreversibility in genetic susceptibility testing decision? Since we had several interesting variables to review in this project, we hypothesized that lower perceived risk, no previous colorectal cancer screening, fewer relatives with cancer, and older age are correlated with increased likelihood to consider irreversibility in genetic susceptibility testing. We thought that accompanying family member through cancer treatment and diagnosis, gender, health, current diet, exercise, and alcohol consumption, attitudes about reducing uncertainty might also influence likelihood of considering irreversibility in genetic susceptibility testing decision.

B. BACKGROUND

Population-based genetic testing for colorectal cancer risk may benefit the public health. At least 145,000 people are diagnosed with colorectal cancer in the United States each year. Since colorectal cancer is the third most common type of cancer in the United States for both men and women (both incidence and death), any successful prevention or early detection program stands to make a large public health impact (1). Although up to 20% of all colorectal cancers occur in individuals with a family history of colorectal cancer, less than 5% are thought to result from high-penetrance, hereditary cancer syndromes such as hereditary non-polyposis colon cancer (HNPCC) or familial adenomatous polyposis (FAP) (2). For the large proportion of colorectal cancer not directly attributable to familial syndromes, much is thought to be from common, lower-penetrance polymorphisms that may contribute to cancer risk. Research into the genetic basis of colorectal cancer risk is fast identifying polymorphisms and their potential association with cancer risk, such as MTHFR667, APC*I1307K, and HRAS1*VNTR, getting closer to a time where genetic testing for cancer risk is in widespread clinical use (3).

For all genetic tests used clinically, there are significant groups of refusers. Most currently used genetic tests for adult cancer risk are for family members of known familial cancer syndromes such as hereditary nonpolyposis colon cancer (HNPCC) and hereditary breast and ovarian cancer (HBOC). We expect lower uptake for tests for diseases that have no known treatment or prevention, such as

Alzheimer disease or Huntington disease. For treatable or preventable diseases, uptake has been lower than expected, from 33% to 75% of eligible people seeking genetic testing, and uptake rates for already affected individuals have been as high as 85% (4, 5) (6). Uptake for tests that involve population-based testing, compared to screening of relatives or already affected individuals, may be somewhere in between, as in one study that found a 56% uptake from people recruited in a waiting room (7). Understanding decision-making is important to public health planning efforts; as population-based screening tests become available we will want to be able to reach as many people as possible. Because most studies of uptake of tests have been cross-sectional, it is unknown whether refusers have permanently rejected genetic testing or have deferred the decision. Although testing uptake is not measured in this project, previous studies suggest that population-based controls may be more likely to refuse or defer testing than relatives or affected individuals.

Option value theory suggests that deferring decision-making may have value. The components of option value theory as stated by Palmer and Smith are: "1. There exists a degree of uncertainty about the future state of the world. 2. The investment entails an essentially irreversible commitment of resources. 3. There is usually some discretion as to the timing of the investment" (8). An irreversible decision is one that "significantly reduces for a long time the variety of choices that would be possible in the future"(9). The concept of irreversibility has been introduced in environmental economics to value the "option" of deferring decision-making in economic modeling for environmental problems (9, 10). A classic example is a choice ("option") of whether to demolish the Notre Dame cathedral to build a parking lot; choosing to demolish is irreversible and preserving the cathedral is not. In health-related decisions, an irreversible decision limits future choices, so may be perceived a negative choice for someone who desires to maintain as much choice as possible. Some health economists have argued that the options approach, including irreversibility of a decision and timing of decision-making, be included in health economic studies [7]. Doing so makes it possible to adjust estimates of benefit to include the value of the permanent loss of the option (ie. demolishing the cathedral permanently eliminates that choice).

Irreversibility and timing of decision-making have been incorporated with success into economic studies of environmental resource management (11) and AIDS therapy (12). In the psychological literature, investigators have examined the idea of finality of surgery, especially sterilization, in studies of anticipated regret and post-decision regret, finding that some voluntarily childless couples avoided or postponed sterilization because of the finality of the procedure (13, 14). Anderson, in a theory of the psychology of decision avoidance, suggests that the reversibility of a decision directly influences the deferring of decision-making (15). A behavioral economic inquiry into the effects of irreversibility to decision-making around genetic susceptibility testing has not been undertaken.

Knowledge of genetic testing results is irreversible and happens under conditions of uncertainty. The decision to undertake genetic susceptibility testing can be considered irreversible, in that once one's inherited genetic makeup is known, it they cannot be unknown or "unlearned." Testing also happens under conditions of uncertainty—a person seeks genetic testing to find out one's risk, and the outcome of a more precise estimate of disease risk is still an uncertain result. Therefore, we think that genetic susceptibility meets the suggested conditions under which option value theory may have some application. This study seeks to explore whether such an effect impacts decision-making, specifically intentions to put off or refuse genetic testing. It is an exploratory analysis to examine the applicability of these ideas to genetic testing.

Conceptual framework

Figure 1 shows a draft conceptual model for how the concepts of uncertainty and irreversibility contribute to a decision to get a genetic test, adapted from a conceptual model that includes previously studied measures and their influence on the testing decision (16). This conceptual diagram adds the concepts of uncertainty and irreversibility and their suggested connection to the testing decision. In the diagram, background factors such as demographics and cancer history are suggested to influence personal factors such as cancer worry, risk perception, and general health, and may also show a differential in terms of knowledge about genetics. These personal factors may, and have been shown to in previous studies, influence intentions to get genetic testing and subsequent testing decisions (17). The new information that this diagram brings is the suggestion that uncertainty and irreversibility also may play into the testing decision, and may also be moderated by background factors. Desire to reduce uncertainty in knowing one's risk has been shown in several studies to influence genetic testing decisions (17). In one study, negative attitudes towards uncertainty were predictive of interest in genetic testing (18). In another, the desire to reduce uncertainty was mentioned in open-ended interview settings (19). Irreversibility is also suggested to influence the testing decision, but in the opposite direction. Whereas reduction in uncertainty is suggested as a motivator for getting testing, we suggest the irreversibility of the testing process as a motivator against getting testing. Several studies modeling aspects of environmental preservation have included a measure of irreversibility, both as relevant to the individual and to a policy-making body (11, 20-22). Some studies have addressed the relevance of the irreversibility of other health choices, most notably in studies of sterilization and in initiation of therapy for HIV (14, 23, 24). No studies we know of have included a measure of irreversibility in a study of decision-making for genetic testing.

C. RESEARCH DESIGN AND METHODS

This research project will use data from a cross-sectional web-based survey whose participants are relatives of people with colorectal cancer and a control sample. The survey's larger goal is to determine quality of life impacts of learning that one carries a polymorphism that increases risk for colon cancer. The analysis in this paper will explore the research questions stated above.

Study population. The study population was drawn from controls and first degree relatives (FDRs) enrolled in the Seattle Colon Familial Registry (CFR), a registry of incident colorectal cancer cases from the Seattle metropolitan area and their first degree relatives. Eligibility requirements for participation in the project described in this project include: age 20-65, English speaking and literate, no personal history of colorectal cancer, and valid phone number and address.

Survey content. The survey is part of a larger project based at the Fred Hutchinson Cancer Research Center (S. Ramsey, PI; NIH/NHGRI RO1 CA114794) called the Genetic Modeling Study (GMS). The aim of the GMS is to develop a state of the art simulation model of colorectal cancer progression including genetic testing to help decision-makers plan for the possible economic and clinical impact of polymorphism tests for colon cancer susceptibility.

The survey aims to estimate quality of life (QOL) effects related to polymorphism and haplotype screening, including family history and effects of learning of carrier status. The survey includes the EQ-5D general health assessment, family history of cancer, demographics, perceived risk for colorectal cancer, diet, exercise, and cancer screening behaviors, and anticipated reactions to positive and negative test results.

Recruitment. Beginning in Spring 2006, CFR staff mailed invitations to participate in the survey to eligible FDRs and controls that include study background, security and confidentiality issues, and web log-in for the survey. Participants were asked to either complete the survey online, or to return a response card indicating their refusal or interest in completing the survey, including their consent to give GMS study staff their contact information. GMS staff followed up three weeks later with a phone call only to those who returned the card expressing interest in participating in the survey. The projected sample size for the study will be about 150 each of controls and relatives.

Item design. We have designed items that elicit attitudes and intentions about genetic testing as it relates to two constructs of interest: uncertainty and irreversibility. We designed the questions using a question format used previously in studies testing the theory of reasoned action, using the theory primarily as a measurement structure guide (25-27). To establish face validity for the questions, we

showed the questions to 12 non-participants inside and outside the academic community. The questions are written at a 7th grade reading level and are listed in the results in Table 3.

Measures.

The survey contained a brief hypothetical description of a genetic test for colon cancer risk that, if positive, would provide a risk of 50% higher than diet, exercise, and family history alone. Using the participant's previously entered risk estimate, it offers a hypothetical risk (see Appendix). Following this hypothetical were questions about anticipated reactions to genetic test results, reducing uncertainty, and the importance of the irreversibility of the genetic test result.

Test property and attitudes on irreversibility: These items asked participants to agree with a statement describing the irreversibility of the decision to get a genetic test, and to rate the importance of this property both in general and to the participant specifically. All item response codes were on a 5-point Likert scale with responses from "strongly agree" to "strongly disagree" or "very important" to "not important at all."

Irreversibility influence on timing of decision: This item asks how the irreversibility of the test influences putting off decision-making about genetic testing: "Because I can't unlearn the results, I would be more likely to put off deciding about the test until later." Respondents choose one answer from a 5-point Likert scale from "definitely true" to "definitely false."

Irreversibility influence on testing intention. This item asks how the irreversibility of the test impacts intentions to get the genetic test. Respondents choose one answer from a 5-point Likert scale from "A lot more likely" to "A lot less likely." For analysis, we recoded this variable as appropriate based on the distribution of results; a likely option is a dichotomous recoding "a lot more likely/likely" versus all other responses.

Attitudes and intentions on reducing uncertainty. There were three questions attitudes and intentions around reducing uncertainty and genetic testing, all given with response choices on a 5-point Likert scale. First, respondents were asked to indicate whether getting the genetic test in the scenario would reduce their uncertainty; second, whether that was good or bad in general; and third, whether it would make them more or less likely to get the genetic test.

Demographics. The survey measured age in years as a categorical variable, gender, and education, which respondents answered by choosing one of nine categories from "did not finish high school" to "PhD or terminal degree."

EQ-5D descriptive system scores. The EQ-5D is a self-administered instrument for measuring health state utilities, and contains descriptive items for five domains (mobility, self-care, usual activity, pain/discomfort, and anxiety depression) as well as a visual analog scale rating of overall health (www.euroqol.org), and provides a universe of 243 possible health states. The EQ-5D was developed by a consortium of researchers in western Europe and has since been applied in U.S. populations (28, 29). This analysis will use both the calculated score and the percentage of respondents indicating a moderate or severe problem in each domain (28, 30).

Perceived risk. Perceived risk is measured in this study with two variables: perceived cancer risk as a percentage and whether that risk is higher, lower, or average compared to people of the same age.

Family history. In the questionnaire, respondents indicated their family history of cancer in father, mother, siblings, children, and grandparents, also indicating which type of cancer. For this analysis, we will calculate the total number of relatives with any cancer.

Closeness to relative during cancer experience. Respondents were asked to think about the relative to whom they were closest to when the relative had cancer, and indicate how close they were to this person during diagnosis and treatment by choosing one response of five in a categorical format from "I accompanied them through diagnosis and treatment" to "we did not speak at all during their diagnosis and treatment." For this analysis, we recoded these responses based on the spread of responses to people who were closest to the relative during diagnosis and treatment versus others.

Colon cancer screening behaviors. Participants indicated if they had ever had colon cancer screening with a dichotomous yes/no question. Follow-up questions asked what type of screening they had last (fecal occult blood test, sigmoidoscopy, or colonoscopy) and when, as indicated by how many years ago. There is an additional variable that asks how sure of their screening history they are by indicating "my recent screening history is described above" or "I have had screening, but I'm not sure when or what type of screen I've had." For this analysis we used only the dichotomous variable of ever had colorectal cancer screening.

Diet, exercise, smoking, and alcohol. Participants were asked about their current diet by indicating one of four categories ranging from "always eat healthy" to "almost never eat healthy." Similarly, they indicated their exercise frequency by one of four choices ranging from "regular exerciser" to "not at all." They indicated whether or not they were a current smoker and chose one of five categories for alcoholic drinks consumed per week: none, 1-2, 3-6, 7-10, or 10+.

Analysis. After recoding variables of interest as necessary, we conducted the following analyses. We

reported results of each question according to relative/control status and conducted tests for correlation between related items. Second, we calculated bivariate summary statistics for all variables by risk group (relative/control) status, including appropriate significance tests such as chi-square and two-tailed t-tests to determine any statistical differences between responses for relatives and controls. Finally, we calculated bivariate statistics on demographic and psychosocial variables to determine preliminary predictors of attitude on irreversibility. Full multivariate modeling to establish predictors of attitude on irreversibility will be conducted when the data collection is complete.

D. HUMAN SUBJECTS RESEARCH

Consent, confidentiality, data integrity and safety procedures are established and are followed according to the Fred Hutchinson Cancer Center Institutional Review Board (IRB file #5804).

E. RESULTS

In June 2006 we completed a preliminary data pull from the research project, which had to that point gathered data on 172 participants, 136 controls and 84 relatives. Table 1 shows the demographic characteristics of the sample. There were few differences in the two groups, except that the relative group on average reported higher numbers of relatives with cancer and were also more likely to have had colon cancer screening. Both of these variables are expected to be higher in the relative group, since they were recruited from high-risk colon cancer families. Both samples were predominantly in the 40-59 age range, were predominantly female, were non-smokers, and had tended to have completed at least a high school education. Both groups reported similar diet, exercise, and alcohol consumption.

Table 2 shows the results for both groups in terms of perceived risk and health status. In the perceived risk questions, we found that relatives were at significantly higher perceived risk, more likely to select 50% or higher as their perceived risk ($p=0.001$). When asked to rate their own risk as higher, the same, or lower than others of their same age, 61% of the relatives chose “higher” compared to 14% of the control group ($p<0.0001$). However, control group participants were much more likely than relatives to have accompanied or remained very close to a relative during the relative’s cancer diagnosis and treatment ($p=0.008$).

Results were not significantly different for anticipated worry immediately after a positive test result or for anticipated relief after negative test result. However, the relative group was more likely to anticipate being “very worried” a year after a positive test result ($p=0.015$). The survey also measured perceived health state in the form of the EQ-5D instrument; scores were slightly higher in the relative group but this difference was not statistically significant.

The results of the eight questions about irreversibility and uncertainty are shown in Table 3. The majority of both groups (79% and 78%) reported that a genetic test would reduce their uncertainty about their overall cancer risk. An even higher proportion reported that reducing uncertainty would be personally either good or very good (88% and 89%). When asked how reducing uncertainty would affect their intention to get the blood test, the majority of both groups also endorsed the "likely" or "a lot more likely" options (88% and 82%). There were no statistically significant differences in response to these questions between the two groups.

The first irreversibility question was a statement for participants to endorse or not that basically described the property of the decision to get the genetic test as irreversible. A majority of both groups endorsed this statement with either "agree" or "strongly agree" (86% and 93%). We then asked two questions relating to the participant's attitude about irreversibility, both in general and for the participant specifically. For the general attitude question, about half of the control group (53%) endorsed the "matters" or "matters a lot" options, compared to 72% of the relative group (72%). There was a non-significant trend toward for this item ($p=0.10$). On the personal attitude question, similar proportions of each group endorsed the "very important" or "important" options (41% and 51%). We asked two questions about how irreversibility would affect participant intentions to either get the test or to put off deciding about the test. For the item probing intentions to get the test at all, the majority of both groups said irreversibility would cause them to be more likely or likely to get the test (64% and 69%). For the item asking about irreversibility influencing intentions to put off the decision until later, a majority of both groups endorsed the "false" option (68% and 72%), while a minority (15% and 10%) endorsed the "true" option. Overall, the response rate for this block of eight questions was 61% in the control group and 80% in the relative group.

We also calculated Pearson correlations between the attitudes and intentions items on uncertainty and irreversibility (Table 4). As expected, the uncertainty items were significantly correlated with one another. The first question on irreversibility (agreement with the property in general) was not correlated with the other irreversibility items. The responses to deferring decision-making because of irreversibility were highly correlated with the responses to intentions of getting the test because of irreversibility and to thinking that irreversibility matters in general. The responses to intentions to getting the test because of irreversibility were not correlated with any of the other items on irreversibility. Questions 5 and 6, general and personal attitudes on the importance of irreversibility were very highly correlated.

Determinants of attitude on irreversibility. Table 5 shows the results of the influence of psychosocial variables in the survey on attitudes about irreversibility. Perceived risk and closeness to a family

member were not determinants in a bivariate analysis of thinking that irreversibility is important. However, anticipated reactions to positive and negative results were highly differential between the two groups. People who indicated that irreversibility is not important were more likely to say that they would not be worried after a positive result, either immediately following the result or one year later, and were more likely to say that they would not feel any different after a negative test result. There were statistically significant trends for these responses. People who thought that irreversibility was not important were also less likely to report being somewhat or extremely anxious on the EQ-5D anxiety/depression scale item ($p=0.01$). The following items were not statistically different between people who did and did not think that irreversibility was important (results not shown): age, gender, number of relatives with cancer, diet, exercise, alcohol use, smoking, closeness to relative during cancer treatment, perceived risk, and perceived risk compared to others of the same age.

Discussion

We conducted a preliminary analysis of data collected from participants in a high-risk cancer registry in the U.S. and control group. Our preliminary results suggest that the irreversibility of the decision to get a genetic test is important to a significant proportion of respondents and that reducing uncertainty is a motivator for intentions to get a genetic test for cancer risk.

The two groups of participants did not differ significantly on the majority of the variables we measured, except for number of relatives with cancer, a difference we would expect considering that the relative group is drawn from a registry of high-risk cancer families. A possibly related difference was in the reported perceived risks of the two groups. Although it is not unusual to find reported perceived risks that are higher than the individual's actual risk, the relative group in this study reported significantly higher perceived risk than the control group, especially in the 50% and higher categories. There was a nonsignificant trend toward significance in this variable predicting attitudes on irreversibility.

In answer to the questions about the importance of uncertainty, both in general and in terms of the participants' own intentions to take the test, the vast majority of respondents indicated that reducing uncertainty about cancer risk was important, good, and would be a motivator for choosing to get the hypothetical blood test. These questions were admittedly specific probes that did not probe for the variety of other reasons why people get genetic tests, such as to inform family members of increased risk. However, these items were so strongly endorsed that we feel that it provides further evidence that the genetic testing decision happens under conditions of uncertainty and that reducing that uncertainty may be a motivator for those undertaking such decisions.

The responses to the irreversibility items suggest that the majority of the respondents in both groups have indicated agreement with the statement of irreversibility as a property of the genetic testing decision. Slightly less, but still a majority, indicated an attitude that irreversibility is also important, both in general and for the participant specifically. This suggests that genetic testing is an irreversible decision and that this concept has applicability in this domain.

The questions that asked about participants' intentions to get genetic testing considering the irreversibility of the decision, however, were more difficult to interpret. Contrary to our hypothesis, the majority of respondents indicated that since they couldn't unlearn the test results they would be *more* likely to get the genetic test. These responses are inconsistent with what one would expect considering the testing decision as an irreversible commitment of resources and to the responses to the more general questions about attitudes on irreversibility. In fact, if a population considers irreversibility important it would be reasonable to expect that they would report making them less likely, not more, to either put off or refuse to get the test. It may be that this question was poorly worded and thus misunderstood by respondents; the lack of correlation between any of its surrounding items supports that hypothesis. However, in that case one might expect a more even spread across the response answers. It is also a possibility that this is a valid, unexpected finding and reflects a high level of intention to pursue a hypothetical genetic test as described here. Perhaps the severity of the disease and the available surveillance and early detection methods for colorectal cancer are stronger motivators for testing than the irreversibility of the decision is against it.

Further, compared to the proportion of respondents who indicated that irreversibility was important to them personally, fewer indicated that they would be likely to put off deciding about the test because of its irreversibility. One interpretation is that the hypothetical case described in the survey, one that describes a test with a modest ability to predict actual risk above and beyond what non-genetic risk factors offer, was not a compelling enough scenario for the irreversibility of the decision to play a major factor. It is worth noting that the hypothetical was constructed with the express intent of being a realistic picture of what genetic testing for cancer risk at the population level (versus testing in families with known familial cancer syndromes associated with a single gene) might one day look like. Considering that, perhaps this particular scenario, albeit one that stands to affect public health the most, is not one where irreversibility can be expected to play a large role in decision-making.

In accordance with our third research question, it appears that thinking that irreversibility is important is highly associated with anxiety/depression, with anticipated worry after a positive test result, and with anticipated relief after a negative test result, and not associated with any of the classically measured demographic variables or variables in the survey that we hypothesized might be relevant in

explaining this relationship. This is a somewhat unexpected finding since we had thought that a wider variety of variables would be predictors of attitudes on irreversibility.

Considering irreversibility from an options approach, the value in deferring decision-making is tied to an increase in information that can be achieved by putting off a decision to a later date. Our study was intended as a preliminary look into whether the idea of refusing or deferring a genetic testing decision was relevant for people facing a genetic testing decision, and did not go into detail about why they might do so. To further explore the idea of a value in timing of decision-making, future studies should explore potential benefits of deferring decision-making, such as waiting for a treatment or certain prevention to become available. Also, we asked about changes in likelihood of change in intentions and not a single question about intentions to get genetic testing, largely because previous studies have shown that stated intentions to get a genetic test are not necessarily a good predictor of actual uptake behavior. As such, an ideal study design to study the impact of irreversibility on decision-making would take place in the context of prospective tracking of uptake for an actual test. Perhaps as population-based tests for adult cancer risk become available studies of these kind will become possible.

The response rates to the questions about irreversibility and reducing uncertainty were incomplete in both relatives and controls, but seemed significantly higher in the relative group, a difference that did achieve statistical significance. It will be interesting to see if these findings hold one data collection is complete, and if so to explore potential predictors of that difference. Likewise, if the response rate for this set of questions is relatively low in subsequent data collection it would be interesting to speculate on potential reasons for refusal, such as to find out if the questions were considered a burden to answer in the context of the larger survey.

Limitations. There are several potential limitations to this project. First, we did not conduct cognitive debriefing on the items developed for this survey. Therefore, we have limited information on the reliability and validity of the items; specifically, if we find no evidence that irreversibility is used in decision-making we will not know if it was the fault of the item design. However, we used a theory-based question format validated in previous studies; that combined with the face validity process we conducted should lessen the chance for poor or difficult to answer questions. Second, this study does not measure all possible motivators and barriers for decision-making about genetic testing. Therefore we will not be able to speak to the contributions of uncertainty and irreversibility relative to any other potential reasons. We feel that since this is an exploratory study that has never been applied to genetic testing, it is appropriate to probe for the concept of interest to characterize the constructs. Third, there may be some limits to generalizability of the results of the GMS survey since it is a web-based survey and people with easier internet access or higher motivations to participate may be more likely to

complete the survey. A main caveat in this paper is the preliminary nature of the data collection, especially in recruitment of relatives. We anticipate that at the final data collection there will be a more balanced number of relatives compared with controls; with larger numbers we will be able to do more accurate analyses.

Conclusion

Our preliminary analysis of early data in this study provides the first evidence that irreversibility is important to people in individual decision-making about genetic testing for cancer risk and provides confirmation that reducing uncertainty is a motivator in that decision. Considering a particular scenario of a hypothetical population-based genetic test for colorectal cancer, a small but perhaps meaningful proportion reported that they would defer decision-making about genetic testing because of the irreversibility of the decision. These data provide interesting preliminary information about the applicability of the components of an options approach to genetic susceptibility testing and suggest direction for follow-up studies that might provide further evidence. Analysis of the data at study completion, including multivariate predictions of attitudes on irreversibility, should provide some insight into the characteristics of the subgroup of individual decision-makers for whom irreversibility is an important part of the decision to get, not get, or defer a genetic test.

##

TABLES

Appendix Scenario of genetic test for colorectal cancer risk

Some of the risk for colon and rectal cancer is due to our habits

People who consume a diet high in alcohol and red meat, and low in calcium and folate (a B vitamin found in green vegetables), are more likely to develop colon cancer. Smoking cigarettes may increase risk of colon cancer.

Some of the risk for colon and rectal cancer is in our genes

Researchers have found variations in our genes that affect our risk of getting colon or rectal cancer. The gene variations are common-some are present in more than 1 out of four people. These gene variations increase the risk of getting cancer, but not so much that everyone who has them will get cancer.

For example, say there is a gene variant that increases the risk of getting cancer by 50 percent. That may sound like a lot, but if the original risk is small, then a 50 percent increase can still be a rather small risk. For example, a 50% increase risk would raise a 1.0% risk to a 1.5% risk. On the other hand, if the original risk is large, then a 50 percent increase would mean that those with the gene variation have a much larger risk of getting cancer.

A new blood test to determine your risk for colon cancer

Imagine there is a simple blood test that can find the gene variations that affect one's risk of getting colon cancer. This test does not tell you if you have colon cancer, only what your risk is for getting cancer in the future. Let's say that if it is positive, the risk increases by 50 percent. If it is negative, we would say that the person has the same risk they did before the test was done. For example, if someone has a 4 percent risk before the test was done and the test was positive, their risk is now 6 percent, since 50 percent of 4 is 2 and 4+2=6.

You said your risk was X percent, so if you took this hypothetical test and it was positive test it would mean your risk of getting colon or rectal cancer is X + X/2 = Y%

Table 1 Demographics

	Controls (%)	Relatives (%)	Valid n	p-value
Age			172	0.13
20-29	2.2	2.8		
30-39	4.4	13.9		
40-49	33.8	41.7		
50-59	39.0	33.3		
60+	20.6	8.3		
Female	66.2	63.9	172	0.80
Education			171	0.08
HS or less	11.0	20.0		
Some college/associate degree	28.7	42.9		
Bachelors degree	39.7	20.0		
Post-graduate degree	20.6	17.1		
Current smoker	6.7	11.1	170	0.38
Relatives with cancer			167	<0.0001
0	9.2	0		
1	32.8	11.1		
2	35.9	25.0		
3+	22.1	63.9		
Ever had colon cancer screening	62.2	80.6	171	0.04
Current diet			170	0.40
Always healthy	33.6	27.8		
Sometimes healthy	65.7	69.4		
Rarely/almost never healthy	0.7	2.8		
Current exercise			170	0.11
Regular	47.8	33.3		
Occasionally	33.6	55.6		
Rarely/not at all	18.6	11.1		
Alcohol drinks/week			170	0.87
None	38.8	41.7		
1-2 or 3-6	50.0	50.0		
7-10 or 10+	11.2	8.3		

Table 2 Perceived risk and health status

	Controls (%)	Relatives (%)	Valid n	p-value
Perceived cancer risk			169	0.001
0%-5%	57.1	25.0		
6%-14%	14.3	22.2		
15%-49%	15.8	13.9		
50%	9.8	25.0		
Higher than 50%	3.0	13.9		
Perceived risk is			172	<0.0001
Less than other people of same age	35.1	5.6		
Equal to people of same age	50.0	33.3		
Higher than people of same age	14.9	61.1		
Accompanied or was very close to family member during diagnosis/treatment	58.5	33.3	154	0.008
Perceived worry immediately after positive test result			170	0.12
Wouldn't be worried	13.4	5.6		
Would be somewhat worried	71.6	66.7		
Would be very worried	14.9	27.8		
Perceived worry one year after positive test result			170	0.015
Wouldn't be worried	17.9	11.1		
Would be somewhat worried	74.6	63.9		
Would be very worried	6.7	25.0		
Perceived relief after negative test result			170	0.41
Would be very relieved	37.3	30.6		
Would be somewhat relieved	43.3	55.6		
Would not feel different	19.4	13.9		
Somewhat or extremely anxious or depressed (from EQ5D)	28.7	36.1	172	0.39
	Mean±SD	**Mean±SD**		
EQ5D index	0.087±0.13	0.905±0.09		0.16
EQ5D visual analog rating (% of perfect health)	83.0±12.3	84.6±9.6		0.47
Perceived cancer risk (% chance)	13.7±18.2	29.6±26.8		<0.0001
Relatives with cancer	1.88±1.25	3.03±1.23		<0.0001

Table 3 Attitudes and intentions items

Question	Response	Controls (n=84)	Relatives (n=29)	p-value
Reducing uncertainty				
1 Getting this blood test would reduce my uncertainty about my overall cancer risk.	Unlikely	3.6	7.1	0.71
	Neutral	16.7	14.3	
	Likely	79.8	78.6	
2 For me, reducing uncertainty about my overall cancer risk would be …	Good	88.1	89.7	0.82
	Neutral	11.9	10.3	
	Bad	0	0	
3 Reducing my uncertainty about my cancer risk would make me ____ to get the blood test.	Likely	88.1	82.8	0.26
	Neutral	10.7	10.3	
	Less likely	1.2	6.9	
Irreversibility				
4 Anyone who gets this blood test would always know if they carry a cancer risk gene. In other words, they could never unlearn the results.	Agree	86.9	93.1	0.58
	Neutral	9.5	3.4	
	Disagree	3.6	3.4	
5 That no one can unlearn the results of the test	Matters	53.0	72.4	0.10
	Neutral	16.9	3.4	
	Doesn't matter	30.1	24.1	
6 For me, that I couldn't unlearn the test results is	Important	41.0	51.7	0.52
	Neutral	21.7	13.8	
	Not important	37.3	34.5	
7 Because I can't unlearn the results, I would be _____ to get the blood test.	More likely	64.6	69.0	0.41
	Neutral	32.9	24.1	
	Less likely	2.4	6.9	
8 Because I can't unlearn the results, I would be more likely to put off deciding about the test until later.	True	15.7	17.2	0.78
	Neutral	15.7	10.3	
	False	68.7	72.4	
Responded to these questions		61.8	80.6	0.04

Table 4 Correlations between intentions and attitudes items

		02 Uncertainty	03 Uncertainty	04 Irrev	05 Irrev	06 Irrev	07 Irrev	08 Irrev
01 Uncertainty	Pearson Correlation	.305(**)	.254(**)	-0.085	0.059	0.053	.226(*)	-0.110
	Sig. (2-tailed)	0.001	0.007	0.371	0.536	0.582	0.018	0.250
	N	112	112	112	111	111	110	111
02 Uncertainty	Pearson Correlation	1	.701(**)	-0.059	-0.037	-0.096	.495(**)	-.442(**)
	Sig. (2-tailed)		0.000	0.531	0.699	0.315	0.000	0.000
	N	113	113	113	112	112	111	112
03 Uncertainty	Pearson Correlation		1	-0.124	-0.156	-0.155	.514(**)	-.426(**)
	Sig. (2-tailed)			0.189	0.100	0.104	0.000	0.000
	N		113	113	112	112	111	112
04 Irrev	Pearson Correlation			1	-0.113	-0.144	-0.066	-0.058
	Sig. (2-tailed)				0.238	0.130	0.492	0.540
	N			113	112	112	111	112
05 Irrev	Pearson Correlation				1	.709(**)	0.039	.304(**)
	Sig. (2-tailed)					0.000	0.686	0.001
	N				112	112	111	112
06 Irrev	Pearson Correlation					1	0.048	.282(**)
	Sig. (2-tailed)						0.615	0.003
	N					112	111	112
07 Irrev	Pearson Correlation						1	-.482(**)
	Sig. (2-tailed)							0.000
	N						111	111
08 Irrev	Pearson Correlation							1
	Sig. (2-tailed)							
	N							112

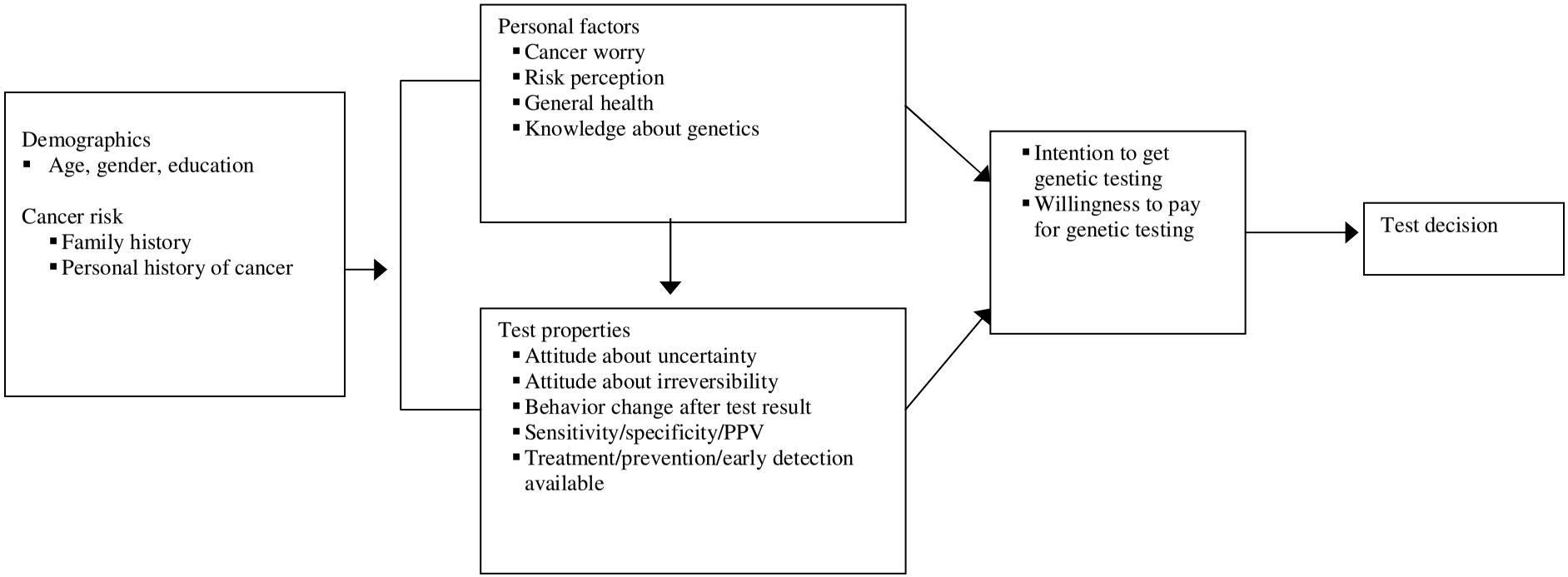
**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 5 Correlates of attitude toward irreversibility

	Irreversibility is important	Irreversibility not important	Valid n	p-value
Perceived cancer risk			108	0.18
0%-5%	46.0	41.7		
6%-14%	25.4	12.5		
15%-49%	9.5	18.8		
50% or higher	19.0	27.1		
Perceived risk is			111	0.67
Less than other people of same age	20.8	22.2		
Equal to people of same age	47.9	39.7		
Higher than people of same age	31.3	38.1		
Accompanied or was very close to family member during diagnosis/treatment	51.1	42.9	101	0.41
Perceived worry immediately after positive test result				
Wouldn't be worried	4.2	17.5	111	<0.0001
Would be somewhat worried	60.4	74.6		
Would be very worried	7.9	5		
Perceived worry one year after positive test result				
Wouldn't be worried	4.2	25.4	111	<0.0001
Would be somewhat worried	68.8	68.3		
Would be very worried	27.1	4.8		
Perceived relief after negative test result			111	0.02
Would be very relieved	50.0	28.6		
Would be somewhat relieved	41.7	46.0		
Would not feel different	8.3	25.4		
Somewhat or extremely anxious or depressed (from EQ5D)	40.8	19.0	112	0.01

Figure 1: Conceptual framework



References

1. Cancer Facts and Figures 2006. Atlanta: American Cancer Society; 2006.
2. Rowley PT. Screening for an inherited susceptibility to colorectal cancer. Genet Test 2004;8(4):421-30.
3. de la Chapelle A. Genetic predisposition to colorectal cancer. Nat Rev Cancer 2004;4(10):769-80.
4. Lerman C, Shields AE. Genetic testing for cancer susceptibility: the promise and the pitfalls. Nat Rev Cancer 2004;4(3):235-41.
5. Roberts JS, Barber M, Brown TM, Cupples LA, Farrer LA, LaRusse SA, et al. Who seeks genetic susceptibility testing for Alzheimer's disease? Findings from a multisite, randomized clinical trial. Genet Med 2004;6(4):197-203.
6. Meijers-Heijboer H, Brekelmans CT, Menke-Pluymers M, Seynaeve C, Baalbergen A, Burger C, et al. Use of genetic testing and prophylactic mastectomy and oophorectomy in women with breast or ovarian cancer from families with a BRCA1 or BRCA2 mutation. J Clin Oncol 2003;21(9):1675-81.
7. Anderson RT, Press N, Tucker DC, Snively BM, Wenzel L, Ellis SD, et al. Patient acceptability of genotypic testing for hemochromatosis in primary care. Genet Med 2005;7(8):557-63.
8. Palmer S, Smith PC. Incorporating option values into the economic evaluation of health care technologies. J Health Econ 2000;19(5):755-66.
9. Henry C. Investment decisions under uncertainty: the "irreversibility effect". American Economic Review 1974;64(6):1006-1012.
10. Arrow K, Fisher A. Environmental preservation, uncertainty, and irreversibility. Quarterly Journal of Economics 1974;88:312-319.
11. Kovats RS, Campbell-Lendrum D, Matthies F. Climate change and human health: estimating avoidable deaths and disease. Risk Anal 2005;25(6):1409-18.
12. Lasserre P, Moatti JP, Soubeyran A. Early initiation of highly active antiretroviral therapies for AIDS: Dynamic choice with endogenous and exogenous learning. J Health Econ 2005.
13. Callan VJ. Voluntary childlessness: early articulator and postponing couples. J Biosoc Sci 1984;16(4):501-9.
14. Baum F. Voluntary childlessness and contraception: problems and practices. J Biosoc Sci 1982;14(1):17-23.
15. Anderson CJ. The psychology of doing nothing: forms of decision avoidance result from reason and emotion. Psychol Bull 2003;129(1):139-67.
16. Glanz K, Grove J, Lerman C, Gotay C, Le Marchand L. Correlates of intentions to obtain genetic counseling and colorectal cancer gene testing among at-risk relatives from three ethnic groups. Cancer Epidemiol Biomarkers Prev 1999;8(4 Pt 2):329-36.
17. Gooding HC, Organista K, Burack J, Biesecker BB. Genetic susceptibility testing from a stress and coping perspective. Soc Sci Med 2006;62(8):1880-90.
18. Braithwaite D, Sutton S, Steggles S. Intention to participate in predictive genetic testing for hereditary cancer: the role of attitude toward uncertainty. Psychology and Health 2002;17(6):761-772.
19. Press NA, Yasui Y, Reynolds S, Durfy SJ, Burke W. Women's interest in genetic testing for breast cancer susceptibility may be based on unrealistic expectations. Am J Med Genet 2001;99(2):99-110.
20. Batabyal AA, Yoo SJ. Indivisibility and divisibility in land development over time and under uncertainty. J Environ Manage 2005;76(2):185-90.

21. **Isik M. An experimental analysis of impacts of uncertainty and irreversibility on willingness to pay. Applied Economic Letters 2006;13:67-72.**
22. **Purvis A, Boggess W, Moss C, Holt J. Technology adoption decisions under irreversibility and uncertainty: an "ex ante" approach. American Journal of Agricultural Economics 1995;77(3):541-551.**
23. **Hardy E, Bahamondes L, Osis MJ, Costa RG, Faundes A. Risk factors for tubal sterilization regret, detectable before surgery. Contraception 1996;54(3):159-62.**
24. **Lasserre P, Moatti JP, Soubeyran A. Early initiation of highly active antiretroviral therapies for AIDS: Dynamic choice with endogenous and exogenous learning. J Health Econ 2006;25(3):579-98.**
25. **Glanz K, Rimer BK, Lewis FM. Health behavior and health education: theory, research, and practice. 3rd ed. San Francisco: Jossey-Bass; 2002.**
26. **Andrykowski MA, Beacham AO, Schmidt JE, Harper FW. Application of the theory of planned behavior to understand intentions to engage in physical and psychosocial health behaviors after cancer diagnosis. Psychooncology 2005.**
27. **Ajzen I. Constructing a TpB Questionnaire: Conceptual and Methodological Considerations. 2002 2006 [cited 2005 March]; Available from:**
28. **Johnson JA, Coons SJ. Comparison of the EQ-5D and SF-12 in an adult US sample. Qual Life Res 1998;7(2):155-66.**
29. **Lubetkin EI, Jia H, Franks P, Gold MR. Relationship among sociodemographic factors, clinical conditions, and health-related quality of life: examining the EQ-5D in the U.S. general population. Qual Life Res 2005;14(10):2187-96.**
30. **(AHRQ) AfHRaQ. Calculating the U.S. Population-based EQ-5D Index Score, February 2005. In. Rockville, MD; 2005.**