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Value of Genetic Incidental Findings Related to Cancer Causing Genes

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Abstract Purpose: Generation of incidental findings (IFs) from whole genome and exome sequencing raise several questions about the return of IFs to donors in the research setting. One important aspect that is highly understudied is whether individuals from the general public value the return of IFs and what individual characteristics are associated with these values. Methods: We used a willingness to pay (WTP) survey—an economic tool—to evaluate the values individuals place on the information provided by a genetic counseling consultation providing IFs for cancer causing genes. An online survey was administered through ResearchMatch, a national registry, in June 2015. Along with demographics, attitudinal and health-related questions, survey respondents were asked WTP questions to reveal the values for IFs information specifically for cancer causing genes. Results: The average WTP of 94 respondents was $161 (95% CI: $132-202) for a one-time IF consultation for cancer causing genes. Income was significantly associated with WTP. Respondents with annual household incomes ≥$80,000, on average, were WTP $75 more for a counseling consultation in comparison to those with incomes ≤$39,999 raising concerns for the ability to pay for IFs. The strongest predictor of WTP was respondents' perceptions regarding the importance of genetic health information for preventing diseases. Conclusions: Understanding individuals' value of information on IFs can help guide policy and normative recommendations. Future research should include individual preferences for return of IFs, explore if return of IFs may be harmful, and evaluate how it may impact subsequent treatment, health-related behaviors, non-health-related behaviors, and healthcare disparity. Implications for Cancer Survivors: This research provides insight into how individuals value identification of genetic related risk for cancer. This has important implications for those who may want to know if they are susceptible for re-occurrence risk and risk of family members.

Keywords: *incidental findings, sequencing, willingness to pay, return of results, genetics*

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1. Introduction

Whole-genome and exome sequencing are increasingly used in scientific research [1]. When using next generation sequencing in research, there are possibilities that other genetic findings (e.g., cancer causing genes) not related to the primary purpose of the study are identified — commonly called genomic "incidental findings" (IFs) [2,3]. The National Institutes of Health has expressed support for return of IFs because they carry important health implications especially if the results are clinically actionable [4]. Some arguments favoring return of IFs are based on the principle for respect to persons in that individuals have a right to receive information regarding their health if they so choose [5,6,7,8]. The key arguments against the return of results include uncertainties regarding clinical utility and diagnostic misperception of IFs [9]. Diagnostic misperception is particularly problematic when the results include information on the risk of adult or late onset diseases that may or may not manifest within an individual's lifespan. [10] Other arguments against disclosure include the financial/logistical burden that responsible return of results may impose on a research project [11,12].

Return of IFs is likely beyond the proposed scope of many sequencing research projects unless the return process is incorporated prospectively into the project plan and budget. Prior investigations have suggested that IFs may need to be managed under a fee-for-service model (individuals pay separately) to finance the return of IFs [10]. However, it raises questions about the "ability to pay" and how a fee-for service may create disparities among different socioeconomic groups where the primary research may be designed to represent a cross section of socioeconomic groups. Therefore, it is urgent to evaluate whether individuals value IFs and if they are willing to incur the cost of receiving IFs. Measuring individual values can provide critical information for policy

development related to stewardship of bio-specimens, obligations of researchers to return results, and financing provision of IFs in the future.

To determine value, one way is to estimate individuals' willingness to pay (WTP) [13,14,15,16,17]. WTP is the maximum dollar amount that individuals are willing to forego to receive a health care good/service, and provides a measure of individual preferences or valuation of the service [18,19]. WTP is particularly important for the return of IFs in which there are differences in how much an individual may value an IF based on individual attitudes and knowledge, and the attributes of an IF. The purpose of this study is to assess whether individuals value return of IFs for cancer causing genes—and the value determinants thereof—by implementing a pilot WTP survey. The overall hypothesis is that individual characteristics such as income, and knowledge about health information contained in genes for preventing a disease will be associated with values for return of IFs.

2. Methods

2.1. Study Participants

We recruited participants through the Research Match program—a secure national registry that links volunteer participants with researchers. After receiving IRB approval at the University of Utah, Research Match sent an email in June 2015 to registry participants that described the purpose of the study, risks and benefits, procedures and $20 gift certificate. Research Match randomly selected 800 individuals (out of an estimated national panel of 75,000 participants meeting our project's inclusion criteria) aged 18-91 years to send this email. The first 150 interested individuals who replied were sent a link to the WTP survey. Of the 150 that were sent the link 95 completed the survey (63% response rate among interested participants). For our analysis, we excluded one outlying individual who was 83 years of age at survey; remaining individuals were 18-70 years of age. The final sample size for our analysis was 94.

2.2. Willingness to Pay Survey

Our survey consisted of items including questions on demographics, history of diseases (e.g., cancer), perceptions regarding preventive genetics (respondents rated the importance of gene information for preventing diseases on a scale of 1 [not at all important] to 5 [highly important]), and WTP for the return of IFs for cancer causing genes.

Prior to asking the WTP questions, we provided a brief description of IFs (supplemental Table A). To reduce over-reporting of WTP, we reminded our respondents that they would be paying for return of IFs out of their pockets, leaving less money to spend on other things. The WTP question pertaining to cancer causing genes is reported in Table 4.

A double-bounded WTP format [20] was implemented to elicit willingness to pay for return of IFs. The first question asked N=94 respondents whether they would pay a pre-specified dollar amount (commonly referred as the bid amount) to get results back that may tell them that they are likely to develop cancer. Each respondent randomly received one of three 3 first bids (i.e., $50, $100, $200). Of the total, 20 (21.3%), 57 (60.6%) and 17 (18.1%) respondents received the first bid amount of $50, $100, and $200, respectively. If a respondent agreed to pay the first bid, a follow-up question with a higher bid amount (double the amount of first bid) was asked. In contrast, if a respondent refused to pay the first bid, a follow-up question with a lower bid amount (half the amount of first bid) was asked. The opening bids were selected to reflect the one-time genetic counseling consultation cost, typically between $50 and $250.

Several follow-up questions were asked to evaluate whether their WTP responses will change based on cancer treatment certainty (clinical actionability), diagnosis timing (early or late adult onset) and predictive certainty (highly likely to occur). For example, we asked respondents whether their WTP response will change if there existed an effective treatment for the cancer diagnosed through genetic testing via the IFs. Then we asked them if they would pay more/less toward one-time IF consultation.

2.3. Statistical Analyses

All analyses were conducted in Stata 13.0 (StataCorp LP, College Station, TX). Statistical significance was considered at alpha=0.05 level (two-sided).

Summary statistics of individual characteristics and their perceptions regarding preventive genetics were computed. An interval regression method was used to identify associations between WTP and respondent characteristics [21,22]. Responses to WTP questions were used to create an interval censored dependent variable, that is, WTP≥2*bid (agreed to pay both the first and second bid); BID≤WTP<2*bid (agreed to pay the first bid and refused to pay the second bid); BID>WTP≥BID/2 (refused to pay the first bid and agreed to pay the second bid); and WTP<BID/2 (refused to pay both the first and second bid). This regression modeled the probability that the actual WTP lies within intervals specified above. Independent variables included demographics (sex, age, race, marital status, education, and household income), family history of cancer, and individual's perceived importance of health information through the use of genetics. Regression coefficients indicate variation in WTP across independent variable categories, such as, income categories. The predicted values from this regression were used to estimate mean and median WTP. The 95% confidence interval (CI) for the mean and median WTP were computed via bootstrapping (500 replications).

Finally, we descriptively summarized whether individuals' responses to WTP questions would change based on differences in cancer treatment certainty, diagnosis timing and predictive certainty.

3. Results

3.1. Summary Statistics

Of the 94 respondents, 69.2% were females (Table 1). Over 60% were between 18 and 35 years of age, the remaining 40% were equally split between 36-50 and 51-67 years. The majority (72.3%) were non-Hispanic white

and over one-third were married. Less than one-third had a partial high school education, high school degree or partial college education, about 30% had graduate or professional training and the remaining were college or university graduates. Half of the respondents had annual household incomes (pre-tax) of over $60,000, about 23% had incomes between $40,000 and $59,999 and the remaining 26.7% had incomes ≤$39,999.

Table 1. Characteristics of Survey Respondents

Demographics	**N**	**%**
Sex		
Female	65	69.2
Male	29	30.8
Age		
18-35	57	61.3
36-50	18	19.4
51-67	18	19.4
Race		
White non-Hispanic	68	72.3
Others	26	27.7
Marital Status		
Single/divorced/widowed	60	65.2
Married	32	34.8
Highest School Grade Completed		
Partial high school or graduate or partial college education	25	27.2
Graduate or professional training	28	30.4
College or university graduate	39	42.4
Annual Household Income Pre-Tax ($)		
≤39,999	24	26.7
40,000-59,999	21	23.3
60,000-79,999	18	20.0
≥80,000	27	30.0
History of Disease Information: Anyone in the Family with Cancer[b]		
Yes	63	69.2
No	28	30.8
Perceptions Regarding Preventive Genetics[c]	**Mean**	**SD**
How important is health information from your genes for prevention of a disease?	3.8	1.1
How important is health information for prevention of a disease from a family member?	4.0	1.1
How likely are you to agree that information about your genes will prevent a disease?	3.5	1.2
How likely are you to pursue future testing if you do not have any symptoms of the disease?	2.7	1.4

[a] A total of 94 respondents completed the surveys. Individual "Ns" may not sum to 94 due to missing data.
[b] Negligible numbers of respondents reported a personal history of cancer or other serious illness.
[c] Responses to were asked to rate the importance or likelihood using a 5-point scale: 1 (not at all important) to 5 (highly important). We provide the means rating and standard deviations (SD) for perception based questions.

Close to 70% of the respondents reported having someone in the family with a history of cancer. Over 60% of the respondents reported that health information from their genes is very/highly (rating≥4) important for prevention of a disease (mean ratings=3.8, sd=1.1 in a five-point scale).

3.2. Predictors of Willingness to Pay

Household income was a significant predictor of WTP (Table 2). On average, respondents with annual household incomes ≥$80,000 would pay $75 [95% CI: 4.2-144.9] more towards an IF consultation in comparison to those with incomes ≤$39,999 (p-value=0.04). For other income categories, results were significant at 10% level. The strongest predictor of WTP in our sample was respondents' perceptions regarding the importance of health information for preventing diseases. Respondents who rated information from their genes as very (rating=4) and highly (rating=5) important were willing to pay $195 [95% CI: 75.5-314.8] and $192 [72.1-310.8], respectively, more than those who reported that the information was not important at all (rating=1) (p-values<0.01). No other variables significantly predicted variations in WTP.

3.3. Willingness to Pay and For/Against Reasons

The estimated mean WTP in our sample was $161 [95% CI: 132-202] and the median WTP was $165 [95% CI: 122-206] (not reported in the tables). Table 3 summarizes open-ended reasons stated by the respondents, which influenced their willingness to pay (or not to pay) decisions. Of those individuals who agreed to pay the first bid (N=61), a-quarter reported that they would pay for preventing the development of cancer or taking precautions if they had a cancer gene. About 20% of these respondents reported that early detection was important, and about 15% reported that they had a family history of cancer, which made them more likely to pay for return of IFs. About 13% reported that the bid amount was reasonable. Of those respondents who refused to pay the first bid (N=32), over one-third reported that cancer cannot be prevented/cured if diagnosed or they did not want the results back. About 22% reported that the bid was high or they didn't have enough income to pay for IFs, 9.4% said that they did not have a family history of cancer and 9.4% said that they results would worry them.

Table 2. Interval Regression Results for Willingness to Pay[a]

	Coefficient [95% CI]	p-value
Sex		
Female	Ref	
Male	51.3 [-8.2-110.7]	0.10
Age		
18-35	Ref	
36-50	-10.7 [-82.9-61.4]	0.77
51-70	8.3 [-62.4-78.9]	0.82
Race		
Others	Ref	
White Non-Hispanic	-18.8 [-77.8-40.1]	0.53
Marital Status		
Single/divorced/widowed	Ref	
Married	30.4 [-35.8-96.7]	0.37
Highest School Grade Completed		
Partial high school, high school graduate or partial college education	Ref	
Graduate or professional training	20.8 [-51.8-93.4]	0.57
College or university graduate	37.1 [-26.2-100.2]	0.25
Annual Household Income Pre-Tax ($)		
≤39,999	Ref	
40,000-59,999	**59.9 [-6.4-126.1]**	**0.08**
60,000-79,999	**71.2 [-9.1-151.6]**	**0.08**
≥80,000	**74.6 [4.2-144.9]**	**0.04**
Anyone in the Family with Cancer		
No	Ref	
Yes	-38.2 [-95.6-19.1]	0.19
How important is health information from your genes for prevention of a disease?		
1 (not at all important)	Ref	
2	118.9 [-23.6-261.5]	0.10
3	**116.7 [-1.8-235.2]**	**0.05**
4	**195.2 [75.5-314.8]**	**0.001**
5 (highly important)	**191.5 [72.1-310.8]**	**0.002**

[a]The reference category in each variable is marked as "Ref". Coefficients are interpreted as dollars amounts. The 95% CI intervals were estimated using 500 bootstrap replications.

Table 3. Reasons For and Against Willingness to Pay

	N	%
Individuals who agreed to pay the first bid (Total=61)[a]		
To prevent development of cancer and take precautions	15	24.6
Early detection of cancer is important	12	19.7
Have a family history of cancer	9	14.7
The bid amount was reasonable	8	13.1
Individuals who refused to pay the first bid (Total=32)		
Cannot prevent/cure cancer or do not want results back	11	34.4
Price is high or don't have enough income to pay for return of IFs	7	21.9
Do not have a family history of cancer	3	9.4
Test results will worry me	3	9.4
Return of IFs should be free	2	6.3

[a] We asked respondents about the most important reasons that influenced their willingness to pay decision. In this table, we summarize the main themes/reasons separately for those who agreed and refused to pay the first bids.

3.4. Attributes of Cancer Diagnosed via IFs and Willingness to Pay Responses

Of the total, 45.7% of the respondents said that their WTP decision would change if there were effective treatments available for cancer (Figure 1), and of these, 100% reported that they would pay more towards IF consultation. Similarly, 44.6% and 18.5% reported that their decision would change if the cancer is developed earlier in life and later in life, respectively. For earlier in life cancer, 92.5% of the respondents would pay more and for later in life cancer, the majority of respondents (82.3%) would pay less. Lastly, 58.1% of the respondent said that their WTP decision would change if it was known that they would develop cancer and of these, 92.3% would pay more.

4. Discussion

The current research assesses general attitudes about willingness to pay for a genetic counseling return of incidental findings (IFs) for cancer causing genes. The strongest predictor for WTP was the belief that health information from return of IFs could prevent cancer. Thus, our research highlights some of the complexities of health beliefs about genetics and should be further examined to understand how individuals value return of IFs for prevention and/or treatment of diseases.

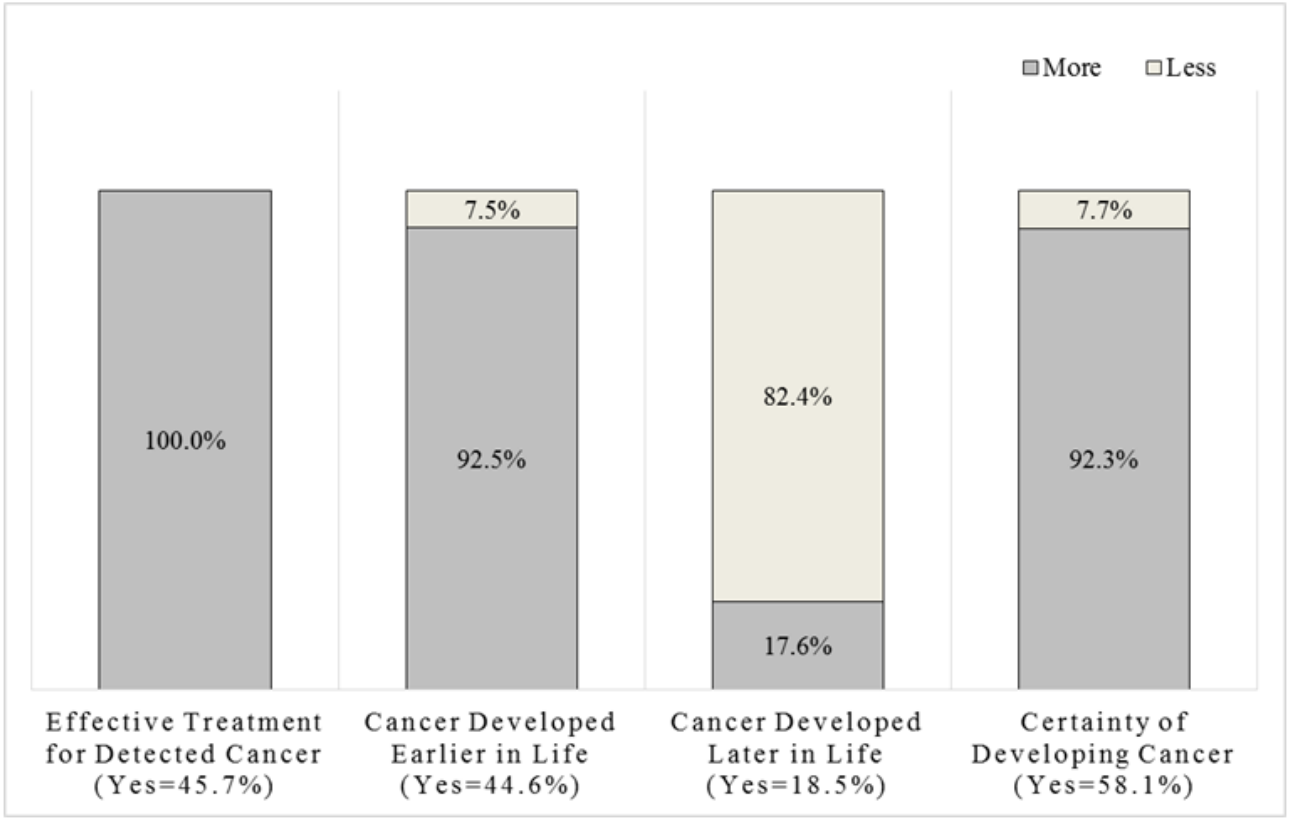

Figure 1. Incidental Findings Attributes and Willingness to Pay Responses[a]

[a] We asked respondents whether their WTP responses would change if there were effective treatments available for the detected cancer genes. Of the total, 45.65% said that their responses would change and of these respondents, 100% said that they would pay more. Similarly, in separate questions we asked if their responses would change if the cancer is developed earlier in life, later in life and if it was known that they would develop cancer.

Table 4. Willingness to Pay Questions Included in the Survey

We are asking you questions about whether certain types of results of the research should be given to people who participate in research studies. We are focused on the kind of results called "incidental findings," which are results that become available from the study, but weren't the original purpose of the study. These results are generated during the process of trying to identify the cause of a person's medical condition. Today, genetic research is more likely to find "incidental findings" because researchers now look at all of a person's genes when searching for genes related to a particular condition. When they do, they are able to find out other things about a person, such as whether they are more likely to develop other diseases. Some of those diseases may be preventable, but others are not, and some are serious and others are less serious. Now I like to ask you a final set of questions about how much you value return of results for CANCER. Remember that this money would be coming out your pocket and that would mean there would be less money for you to spend on other purchases that you might like to make. Please note that insurance does not cover the costs of return of results and in order to understand the results you will need to meet with a genetic counselor to interpret the results. Genetic counseling on average costs about $X per session. Would you be willing to pay $X to get results back that may tell you are likely to develop cancer? Remember that this money would be coming out your pocket and that would mean there would be less money for you to spend on other purchases that you might like to make **If yes ask:** would you be willing to pay $2X per session? **If no ask:** would you be willing to pay $X/2 per session? **Follow-up willingness to pay question for yes or no response:** What was the most important reason that influenced your willingness to pay decision?

The current project used WTP for assessing the values associated with the return of IFs. However, contingent valuation studies may also evaluate individuals' willingness to accept (WTA), which is the dollar amount that is needed to compensate an individual to forego a good/service. Both WTP and WTA are quantitative measures that determine how much an individual values a specific good/service. Yet, a previous health care-related study found that WTA may significantly exceed WTP. [23] While WTP is constrained by income, WTA is not, which can create this difference. Moreover, there are other reasons why WTA may exceed WTP including endowment effects and having substitutes. To avoid overstatement of values, therefore, we used WTP. However, we recommend that future studies evaluate the difference between WTA and WTP for the return of IFs to fill this scientific gap.

Our results also show that income is a strong predictor of WTP for IFs. This raises concerns with respect to the "ability to pay" toward and equity in access to important health information contained in IFs. While earlier research has proposed a fee-for-service (FFS) model for covering the cost of IFs [10], our research demonstrates that it may be high income individuals who are willing to pay that cost of providing IFs. Moreover, this could raise important disparity issues since income may be strongly correlated

to other socio-economic indicators, such as, race and ethnicity. In our data, we had very few Hispanic/Latino (<5% of the sample) and black (<9% of the sample) respondents; therefore, we could not establish this disparity link. Future studies should evaluate whether a FFS model for IF could potentially lead to healthcare disparities.

There are additional complexities besides type of disease that complicate the return of IFs due to variation in the predictive power, early or late on-set, treatment options as well as individual health beliefs. Respondents in this study reported that their responses toward WTP for genetic counseling would change if the disease developed earlier in life and had a higher predictive power to cause to disease. As normative and professional guidelines are developed, including the opinions of the public and the characteristics of IFs the public most value will be important for effective and equitable decision-making on what IFs should, if at all, be returned and payments for this information.

From a healthcare perspective, return of IFs can be assumed that the information returned is valued only to the extent it can help individuals make better medical decisions [24,25]. Individuals may value return of IFs even when the information does not have treatment options [26]. Some individuals may find value in knowing that a disease is unlikely to happen or they are not at risk. As such, return of IFs can be valuable because it may reduce uncertainty. However, return of IFs may cause harm if the disease is not treatable, individuals seek unnecessary medical treatment or the results create increased anxiety [27]. Future research should address these potential negative impacts as well as the ability to refuse return of IFs.

There are limitations with this study. This survey focused on one type of disease, cancer, and future research should include other disease categories where genetic testing can yield IFs. Another study assessed WTP for predictive tests without immediate treatment implications across several diseases, and found that WTP was the highest for prostate cancer and lower for Alzheimer's disease [28]. This indicates that the type of disease may impact value of IFs. Finally, WTP may also be sensitive to hypothetical bias. However, taking precautionary measures such as reminding respondents about their budget constraint and describing the scenario as if they were real can reduce the magnitude of this bias [29,30].

We could not include information on health outcomes (e.g., self-perceived health status, last doctors' visits etc.) in our analysis due to data unavailability. It is possible that individuals with poorer self-perceived health may be more likely to value return of IFs (i.e., due to lower health confidence), and that health status may be associated with other variables, such as, sex, age and income, which may also influence the coefficient estimates in our WTP model. Future studies should do more detailed investigations of WTP predictors of IFs to identify potential confounding and interaction effects.

In summary, this study explored individual preferences for the return of IFs specifically for cancer causing genes. We implemented the willingness to pay methodology to evaluate how individuals value return of IFs and identified individual characteristics associated with WTP for IFs and attributes of IFs that could potentially affect individual responses to WTP questions. While careful interpretation of genomic findings is important for the responsible return of IFs [1], our research showed that in a FFS model for IFs, only the wealthy may be willing to pay for IFs if there is a high cost of provision of this information. Further, given uncertainty about how individuals will interpret the genetic information and concerns about whether the information is actionable suggests pragmatic provision where recipients may be viewed more as a partner and receive professional interpretation of the results are imperative.

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Compliance with Ethics Standards

Disclosure of potential conflict of interest: The authors declare they have no conflict of interests.

Research involving human participants: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study."

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Supplemental Table A. Willingness to Pay Questions Included in the Survey

We are asking you questions about whether certain types of results of the research should be given to people who participate in research studies. We are focused on the kind of results called “incidental findings,” which are results that become available from the study, but weren’t the original purpose of the study. These results are generated during the process of trying to identify the cause of a person’s medical condition.

Today, genetic research is more likely to find “incidental findings” because researchers now look at all of a person’s genes when searching for genes related to a particular condition. When they do, they are able to find out other things about a person, such as whether they are more likely to develop other diseases. Some of those diseases may be preventable, but others are not, and some are serious and others are less serious.

Now I like to ask you a final set of questions about how much you value return of results for CANCER. Remember that this money would be coming out your pocket and that would mean there would be less money for you to spend on other purchases that you might like to make.

Please note that insurance does not cover the costs of return of results and in order to understand the results you will need to meet with a genetic counselor to interpret the results. Genetic counseling on average costs about $X per session.

Would you be willing to pay $X to get results back that may tell you are likely to develop cancer? Remember that this money would be coming out your pocket and that would mean there would be less money for you to spend on other purchases that you might like to make

If yes ask: would you be willing to pay $2X per session?

If no ask: would you be willing to pay $X/2 per session?

Follow-up willingness to pay question for yes or no response: What was the most important reason that influenced your willingness to pay decision?