Genetic Testing, Interpretation, and Communication: Exploration Across Disciplines

by
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Abstract

Technological advances have made possible genomic and genetic testing for a variety of diseases, warranting examination of how we think about the risks and benefits of genetic testing. As genetic tests are increasingly incorporated into both clinical and research settings, it is critical that we understand the implications of such tests for both individuals and their family members. Questions of whether, when, and how to pursue genetic testing, interpret genetic test results, and communicate those results to family members all must be considered and are explored in this dissertation.

This study has two parts: The first part focused on ethical issues raised by genetic and genomic testing. We examined whether, when, and how to pursue genetic testing by gathering opinions on current issues in genetic testing from the first cohort of people to receive presymptomatic testing for Huntington’s Disease (HD), 20-30 years ago, who have lived with the implications of that testing for decades. Additionally, longitudinal risk perception scores, clinic notes, and interview data from this cohort were analyzed to understand how individuals interpret genetic test results as well as what factors contribute to genetic risk perception. Finally, we examined whether, when, and how genetic risk information should be communicated to minor children, through interviews with parent child pairs affected by or at-risk for either HD or hereditary cancer, along with genetic counselors. The second part of the study focused on scientific issues raised by genetic
and genomic testing. We investigated the prevalence of pathogenic germline mutations in known cancer predisposition genes in patients with metastatic breast cancer who were not selected for early age of onset or family history to provide insight into whether germline testing should be performed in the setting of metastatic breast cancer, since test results can have therapeutic implications as well as implications for one’s family members.

Results of the first part of this study, which focused on ethical issues raised by genetic and genomic testing, indicate that genetic testing requires careful consideration both in terms of its availability and the testing protocol. The majority of participants reported the importance of individual autonomy in decisions about whether and when to be tested, the need for formal testing protocols, opposition to direct-to-consumer testing for HD, and returning medically actionable secondary findings. In addition, we found that many people do not interpret genetic test results in the way one would expect. With regard to communicating genetic risk information to children, our data suggested a discrepancy in the amount of information children want and the amount of information parents are giving, a need for parents to take time to process their own result before communicating with children, and a need for additional resources on how to communicate with children about genetic risk information, as well as child-specific resources on various genetic conditions. Finally, results of the second part of this study, which focused on scientific issues raised by genetic and genomic testing, demonstrate the importance of performing germline testing in cases of metastatic breast cancer and potentially other metastatic cancers as well, given the excess of pathogenic germline mutations in known cancer predisposition genes in our population of women with metastatic breast cancer compared
to the general population. This data also suggests that these pathogenic germline mutations in known cancer predisposition genes may be associated with more treatment-resistant forms of disease.

In conclusion, more resources are needed for patients to fully appreciate their genetic risk and genetic test results. More resources and guidance are also needed for patients on how to communicate results to one’s family members, particularly one’s children. Genetic counselors and other health professionals need guidance on how to communicate genetic risk information to family members in order to better assist patients. Our results should also be taken into careful consideration by disease-specific advocacy organizations, such as the American Cancer Society and the Huntington’s Disease Society of America, as well as professional societies, such as the National Society of Genetic Counselors and the American College of Medical Genetics, when considering the availability of genetic testing and testing protocols. Finally, our results should be taken into consideration by health professionals in oncology, where it may be advisable to perform germline testing in the case of metastatic breast cancer, and perhaps other cancers as well, in order to better guide treatment and to advise regarding familial cancer risk.

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Dedication

I dedicate this work to my parents, who sacrificed so much in order to facilitate my own success and happiness. Their selflessness is recognized and forever appreciated.
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Table Of Contents

Abstract ........................................................................................................................................ii
Dedication ......................................................................................................................................v
Acknowledgements ..................................................................................................................vi
Table Of Contents ......................................................................................................................vii
List of Figures and Tables ..........................................................................................................viii

Chapter 1: Introduction ..............................................................................................................1
References Chapter 1..................................................................................................................4

Chapter 2: Perspectives on Genetic Testing and Return of Results from the First Cohort of Presymptomatically Tested Individuals At-Risk for HD.................................................................5
Abstract .........................................................................................................................................5
Introduction .......................................................................................................................................6
Methods ...........................................................................................................................................9
Results .........................................................................................................................................11
Discussion ......................................................................................................................................22
Conclusion ......................................................................................................................................27
References Chapter 2 ..................................................................................................................29
Tables Chapter 2..........................................................................................................................34
Figures Chapter 2.........................................................................................................................36

Chapter 3. Risk Perception Before and After Presymptomatic Genetic Testing for Huntington’s Disease: Not Always What One Might Expect .................................................................38
Abstract .........................................................................................................................................38
Introduction .......................................................................................................................................39
Methods..........................................................................................................................................41
Results .........................................................................................................................................43
Discussion ......................................................................................................................................44
Conclusions .......................................................................................................................................46
References Chapter 3 ..................................................................................................................49
Tables Chapter 3..........................................................................................................................55
Figures Chapter 3 .........................................................................................................................59

Chapter 4: “I wanted more information but I think they were scared I couldn’t handle it:” Whether, When, and How to Communicate Genetic Risk Information to Children.................................................................................62
Abstract .........................................................................................................................................62
Introduction.......................................................................................................................................63
Methods..........................................................................................................................................64
Results .........................................................................................................................................67
Discussion ......................................................................................................................................75
Conclusions .......................................................................................................................................77
References Chapter 4 ..................................................................................................................79
Tables Chapter 4..........................................................................................................................83

Chapter 5: Prevalence of Pathogenic Germline Mutations in Known Cancer Predisposition Genes in Individuals with Metastatic Breast Cancer ......................................................................84
Abstract .........................................................................................................................................84
Background......................................................................................................................................84
Chapter 1: Introduction

As genetic and genomic testing are increasingly incorporated into both research and clinical care, it is vital that we understand the ethical implications of such testing for both individuals and their family members. Understanding whether one should pursue genetic testing, when testing should be performed, whether direct-to-consumer testing is available, whether a formal test protocol is required, what results are returned, how one interprets genetic test results, and how one communicates genetic risk information to his or her family members are vital in determining best practices for medical professionals. Due to the relatively recent introduction of genetic testing into research and clinical care, few such data exist on these particular issues.

In this dissertation, interview data and clinic notes from different cohorts who had experience with genetic testing and/or receiving genetic risk information were used to address questions relevant to current ethical issues in genetic testing. On the clinical side, germline testing was performed in the setting of metastatic breast cancer in order to determine its value in this setting as well as to determine whether pathogenic germline mutations in known cancer predisposition genes are associated with more aggressive forms of disease. While this portion of the study was focused on scientific issues raised by genetic and genomic testing, ethical issues were also raised by germline testing. These ethical issues include return of genetic test results, interpretation of genetic test results, and how one communicates genetic risk information to his or her family members, since germline mutations are relevant not only to the tested individual, but also to his or her genetic relatives.

Ultimately, this work strives to answer questions about best practices in genetic testing
including whether and how genetic testing should be performed, whether and what results should be returned, how results are interpreted by patients/subjects, and whether, when, and how genetic risk information should be communicated to one’s family members, specifically to one’s children.

*Project 1: Interviews with Different Cohorts with Experience with Genetic Testing and/or Receiving Genetic Risk Information*

The work related to ethical issues in genetic testing contained three parts. The first gathered opinions about current issues in genetic testing from the first cohort of people to receive presymptomatic testing for Huntington’s Disease (HD) 20-30 years ago, who have lived with the implications of that testing for decades. During a semi-structured interview, participants were asked open ended-questions on the importance of autonomy in the decision to be tested, whether a formal testing protocol is necessary, whether physician ordering is acceptable in the absence of a formal protocol, whether online direct-to-consumer (DTC) genetic testing for HD is acceptable, and whether incidental/secondary findings should be returned in the context of whole exome/genome sequencing.

The second part analyzed risk perception scores, research clinic notes, and interview data collected from this same cohort to understand how individuals perceive their own genetic risk and genetic test results as well as factors that influence risk perception.

Finally, the third part of this project involved interviews with parents affected by or at-risk for hereditary cancer or HD and their children aged 15-17. Genetic counselors were also interviewed. These interviews were conducted to investigate best practices regarding
whether, when, and how to communicate genetic risk information to children. Currently, our understanding of the consequences of children learning genetic risk information is largely based on research in adults, which may not be relevant to children due to differences in cognition and stability of self-concept between children and adults. Very few studies have involved talking with minors directly or comparisons of what parents think they are communicating with what children say they are hearing.

Project 2: Germline Sequencing in the Setting of Metastatic Breast Cancer Diagnoses

The work related to scientific issues in genetic testing involved a germline testing study in individuals with metastatic breast cancer. In a study by Pritchard et al., 2016, a germline mutation rate of 11.8% in 20 cancer-related genes was found in 692 men with metastatic prostate cancer patients who were not selected for early-age of onset or family history. Our study aimed to expand on this data and investigate whether the prevalence of germline mutations in cancer-related genes in patients with metastatic breast cancer is similar to that observed in patients with metastatic prostate cancer. The present study is the first to investigate the prevalence of germline mutation in patients with metastatic breast cancer and will provide insight into whether germline testing should be performed in the setting of metastatic breast cancer, since test results can have therapeutic implications as well as implications for one’s family members.
References

Chapter 2: Perspectives on Genetic Testing and Return of Results from the First Cohort of Presymptomatically Tested Individuals At-Risk for HD

Abstract

This qualitative study gathered opinions about genetic testing from people who received presymptomatic testing for Huntington’s Disease (HD) 20-30 years ago and have lived with the implications of that testing for decades. During the last section of a semi-structured interview, participants were asked open ended questions about their opinions on the importance of autonomy in the decision to be tested, whether a formal testing protocol is necessary, whether physician ordering is acceptable without a formal protocol, whether online direct-to-consumer (DTC) genetic testing for HD is acceptable, and whether incidental/secondary findings should be returned in the context of whole exome/genome sequencing.

Most – but not all – participants were in favor of an individual’s right to decide whether and when to pursue testing, use of a formal testing protocol, and returning medically actionable secondary findings. However, the majority of participants were opposed not only to physician ordering and DTC HD testing in the absence of a formal protocol, but also to returning a secondary finding of an HD expanded allele.

This study presents the opinions of a unique and extremely well-informed cohort on issues that need to be taken into careful consideration by genetic counselors and other medical professionals who are developing genetic testing protocols, making decisions about the availability of genetic tests, and making decisions about whether and how to return incidental findings.
Introduction

Huntington’s Disease (HD) is a progressive neurodegenerative disease characterized by involuntary movements, abnormal voluntary motor control, cognitive deterioration, and affective symptoms. Many patients experience major affective disorder (e.g., depression) as a manifestation of the illness, typically occurring years before physical symptoms. While some symptomatic treatment is available, there is no cure. The symptoms of the disease are generally recognized in the fifth decade of life and progress over time; individuals survive a median of 18 years after motor onset (Ross et al., 2014).

In 1983, HD became the first genetic disease gene mapped using DNA polymorphisms. Shortly thereafter, linkage tests were developed, enabling presymptomatic testing, which was subsequently offered in the context of two clinical trials. The Johns Hopkins Huntington’s presymptomatic testing protocol (JH HD presymptomatic protocol) began in 1986 and enrolled 180 individuals during the first 10 years of the program.

Learning one’s own genetic status may have serious implications both for the individual and for his or her family. The decision to be presymptomatically tested is not a simple one. While learning one does not carry the disease mutation may relieve anxiety, testing positive for the expanded repeat can lead to loss of hope, major depression, and suicidal thoughts (Hagberg, Bui, & Winnberg, 2010; Kessler et al., 1987; Meissen & Berchek, 1987). The results can also go the other way, leading to alleviation of worry and uncertainty associated either with not knowing, or with being at risk (Codori & Brandt, 1994).
As one of the first two protocols to return presymptomatic test results, the JH HD presymptomatic protocol was carefully designed to avoid adverse outcomes to the extent possible. The protocol included extensive pre-test counseling, with five 90-minute individual counseling sessions with a psychologist to discuss the nature of the genetic test, the various outcomes that might be expected, and the effects that the test results might have on participants’ emotional and family lives. Testing was provided at no cost to participants. Subjects had to be of sound mind and without any evidence of early disease in order to participate. Additionally, all subjects who underwent testing were to have a study partner to serve as emotional support and as a liaison with the project staff in the event of future difficulties. After disclosure, eight in-person follow-up visits were programmed over a three-year period (Brandt et al., 1989).

Technological advances have made genetic and genomic testing possible for a variety of diseases, including those with adult onset (Abdolahi et al., 2014; Hilgart, Hayward, Coles, & Iredale, 2012; Meropol et al., 2011; Trondsen, Boole, Stensland, & Tjora, 2014), warranting examination of how we think about genetic testing and its benefits and risks. Because HD is one of the first diseases for which genetic testing was offered (Hayden, 2003; Hayden et al., 1988; Meissen et al., 1988), early experience with the JH HD presymptomatic protocol cohort influenced collective thinking about key issues related to genetic testing and the return of test results. Nevertheless, it is important to keep in mind that HD is also a “worst-case scenario” for pre-symptomatic genetic testing due to high penetrance and the lack of effective treatment or cure (Brandt et al., 1989).
As increasing numbers of genetic tests are being used to both directly and incidentally assay genes for adult-onset neurodegenerative disease, and as large-scale genetic testing is increasingly integrated into clinical care, it is critical that we understand the perspectives of those who have gone through presymptomatic genetic testing, over both the near- and long-term. Furthermore, given their experience living with such test results, this cohort’s opinions on ethical issues raised by today’s genetic testing procedures and policy may be particularly informative. Because of the relatively recent introduction of presymptomatic genetic testing into clinical care, few such studies exist (Baig et al., 2016; Dufrasne et al., 2011; Gargiulo et al., 2009; Timman, Roos, Maat-Kievit, & Tibben, 2004).

Below we describe a follow-up study with people who were enrolled in the original JH HD presymptomatic protocol between 1986 and 1998. We have examined their opinions on the importance of autonomy in the decision to be tested, whether a formal testing protocol is necessary, whether a physician ordering an HD test in the absence of a formal protocol is acceptable, whether ordering presymptomatic testing for HD online via a DTC (direct-to-consumer) web site is acceptable, and whether incidental/secondary findings (including the presence of genetic risk factors and of an expanded HD repeat) should be returned in the context of whole exome/genome sequencing. The data presented here are based on the opinion questions at the end of a much longer interview; other data obtained in this interview will be reported in a more comprehensive paper on this cohort.
**Methods**

**Participants**

This study was approved by the Johns Hopkins University Institutional Review Board. A total of 278 individuals enrolled in the Johns Hopkins Huntington’s presymptomatic testing protocol between 1986-1998. Of these 278 individuals, 72 dropped out before the disclosure of test results. Of the remaining 206 individuals, 76 were found in the presymptomatic testing protocol to carry an expanded repeat, and 130 were found to carry a normal repeat. Participants were recruited into the current follow-up study through two paths: first, indirectly via fliers posted in the HD clinic, outreach through Huntington Disease Society of America (HDSA) support groups, the HDSA website and trial database ([http://www.hdsa.org](http://www.hdsa.org)) and Facebook; second, direct recruitment using last known address. Through indirect recruitment, six individuals demonstrated interest and four were eligible. Though direct recruitment, 101 letters were sent out, and 60 responses were returned. Fifty-five of these responses indicated willingness to participate in the study. Of these 55, 18 had expanded repeats, 32 had normal repeats, and five dropped out before the disclosure of test results. An attempt to enroll equal numbers of males, females, individuals with expanded repeats, and individuals with normal repeats was made. Sixteen individuals were willing to participate but not interviewed due to an over-abundance of individuals with normal repeats.

Ultimately, 39 individuals were interviewed for the current study. Of these 39 participants, 15 were found in the presymptomatic testing protocol to carry an expanded repeat, 21 were found to carry a normal repeat, and three dropped out before the
disclosure of test results. In seven cases, spouses or caregivers were also present during the interview. The mean age of participants was 59.6. Of those in our study with expanded repeats, the majority (9/11) had been clinically diagnosed with HD at the time of the interview.

**Procedures**

Semi-structured interviews lasting an average of 68 minutes and ranging from 32 to 112 minutes were conducted by four members of the study team. In most cases, two members of the study team were present during each interview, but in five cases, it was only possible for one interviewer to be present. Members of the study team who conducted interviews included one clinical psychologist, one genetic counselor, and two researchers trained in qualitative research techniques. Interview topics included individuals’ testing experience, reasons for testing, communication of test results, and impact of testing on mental health, relationships, and life decisions. The interview concluded with a series of opinion questions about hypothetical scenarios involving the return of genetic test results and incidental/secondary findings following large-scale genetic testing. The opinion questions consisted of five open-ended questions (Table I).

**Data Analysis**

The interviews were audio recorded, transcribed, and scrubbed of all identifying information. A preliminary codebook was developed based on the interview guide. Five study team members read three transcripts and developed a codebook, which was then revised iteratively and used to code all transcripts. Completed interviews recoded accordingly. All interviews were double-coded, and any conflicts in coding were discussed by the two coders, reconciled, and finalized using QSR International’s NVivo.
11 qualitative analysis Software. Codes were refined as more data were analyzed. For each transcript, the interviewer coded both the attributes of the interviewees and the dialogue. Attributes of the interviewees included expanded or normal repeat length and disclosure date. Analysis of opinion questions was done by using QSR International’s NVivo 11 to produce code reports, which were then analyzed to determine the distribution of responses.

**Results**

Data were collected from 15 expanded-repeat, 21 normal-repeat, and three undisclosed participants. Our participants included 20 females and 19 males (Table II). Due to the qualitative nature of this work, not every participant answered every question. One participant with an expanded repeat was too severely affected to answer these questions, which were at the end of an approximately hour-long interview, so responses were recorded from 38 participants. The total number of participants who responded to each question is included with the results. The 18 quotes in this section come from a total of 15 participants.

**Right to Decide**

Participants were asked their opinion on how important it is for an individual to decide whether and when to learn his/her genetic risk status for HD. A majority (31/38) of participants believe it is very important for individuals to decide for themselves whether and when to pursue testing. Many participants believe negative outcomes such as anxiety, loss of hope, and/or suicidal thoughts will occur if individuals do not make this decision for themselves.
“Each person really has to make the decision, because if someone, if we would’ve made it for my sister, she would’ve been miserable. Or if I would’ve, someone said, ‘No, you should wait,’ I would’ve been miserable. So each person pretty much has to make that decision on their own.”

(Female, Normal Repeat)

“I feel that people should be able to make their own personal decisions. I mean I wouldn’t have wanted to get my children tested at three or five or ten and then be able to just tell them. I prefer to let them pick and choose just like with anything else as an adult—make your own choice and decisions. My sisters both seem to be perfectly happy and living wonderful amazing lives without knowing. What if they were forced to know? Maybe that would be bad for them.”

(Male, Expanded Repeat)

A small number of participants (6/38) recognize the importance of individuals deciding for themselves whether and when to be tested but believe all individuals should know their genetic risk status before having children.

“It’s very important...If you want to have children, I think there’s things you can do now. You can do in vitro stuff. So, you can test if kids have it or don’t have it. It’s just sort of—I don’t understand, if someone was at risk, why they wouldn’t get tested if they wanted to have children because they obviously know what they’ve been through. And how could you put a child through that?” (Female, Normal Repeat)
One participant believes it is not important for an individual to decide whether and when to be tested because everyone should know his/her genetic risk status.

“What I think is very simple. I think the more knowledge that you have, the better. Then even if you get to difficulty, anything like that, well, you can endure the difficulty better because it's the truth.”

(Female, Normal Repeat)

Need for Protocol

As discussed above, all participants in the JH HD presymptomatic protocol underwent procedures in a formal protocol before learning their risk status. The protocol required each individual seeking his/her genetic risk status to undergo extensive pre-test counseling as well as follow-up visits after the disclosure event. The protocol also required each participant to have a study partner to accompany him/her to the pre-test and disclosure appointments.

Individuals in the current study were asked their opinion on whether all individuals who want to be tested for HD should be required to go through the same formal protocol as they did in the JH HD presymptomatic protocol. Thirty-seven participants answered this question. The majority of participants (22/37) believe that a formal protocol similar to that of the JH HD presymptomatic protocol should be required.
“It was really good that they prepared me for it and yeah, it gave me—I think I went a week apart for the three times and it gave me a chance to think because sometimes you can ask me a question and I really don’t want to feel pressured to have to answer right away, you know, but also too at the time I mean I had the offer that, hey if you don’t want to know your results even up until the last minute we don’t have to tell you, we’ll just lock them away and that’s that.”
(Male, Normal Repeat)

Other participants believed a formal protocol should be required, but the protocol should be shorter than that of the JH HD presymptomatic protocol.

“I do but maybe if it could be condensed…make that carrot that you’re hanging in with that final answer a little bit more proximal, you know?”
(Male, Normal Repeat)

There were also participants (7/37) who believed that individuals should be able to decide for themselves whether to go through a formal protocol. Only one participant believed that a formal protocol should not be required because barriers should not be placed on people who want to be tested.

“You know, part—I really think that it should be up to the individual to do it and to maybe be given the options that are out there, but make that decision” [about whether to go through a formal protocol].
“We shouldn’t impose restrictions on people from finding out things that they may be perfectly okay and have their own support system and their own capabilities to be able to decide.”

Physician Ordering

Individuals in the current study were asked whether they believe it is acceptable for a doctor to order presymptomatic testing for HD without having a patient go through a formal testing protocol. Thirty-five participants answered this question. A majority of participants (28/35) believe that it is unacceptable for a physician to order a test for HD without having a patient go through a formal protocol. One participant believed physician ordering was unacceptable because insurance might find out about the patient having HD. Most felt that physician ordering in the absence of a formal protocol was unacceptable because patients need education and counseling.

“...I think there should be, there should be some consideration for counseling. Because you don’t know what the results are going to be. I mean everybody’s going to handle the results of that test differently, so I think there needs to be some preparation for what if their test is the expanded repeat...And it’s only for your own, you know, your own peace of mind. I mean, nobody wants to get a, ‘Hey, guess what. You’ve got this disease, and when you turn 37, 38 years old, you’re going to start losing your gross motor skills. Then
you’re going to lose your fine motor skills and you’re not going to remember who your family is, and then you’re going to be balled up into this little, you know, this shell of a person. And somewhere in there is still you, but you’re not going not be able to get that out.’ You need to have somebody you can talk to about that stuff. You know, ‘Hey. Yeah, okay. You’re positive. Yeah, you’re expanded repeat. That’s not the end of the world. We can prep for this. There’s things we can do. We can make your life better even when that time comes.’ I think there needs to be some consideration and preparation for counseling in the chance that it is expanded repeat.” (Male, Normal Repeat)

A small number of participants (5/35) believe that physician ordering is acceptable. Of the participants who fell into this category, three felt a formal testing protocol should be highly encouraged before a doctor orders HD testing, but ultimately the patient should be able to decide whether s/he wishes to go through a formal protocol. One participant felt that it is acceptable for a doctor to order HD testing without having a patient go through a formal testing protocol because the importance of all at-risk individuals knowing their HD status before having children outweighs the need for a protocol; similarly, two participants felt that it is acceptable because it would be easier for people to find out their genetic risk status without the formal protocol.

“I think that probably would have more pluses than minuses, you know what I mean? Because it’s one of those things where at least it’s more affordable for people when, like, you don’t—like I had to travel four hours to get it done, so that would be an—but, ah, yeah, I think it would be [good].”
DTC Testing

Participants were asked their opinion regarding the acceptability of online ordering of genetic testing for HD, without going through a doctor. Thirty-one participants answered this question.

The majority (24/31) of participants believe it is unacceptable for genetic testing for HD to be available DTC on the internet.

“No and having this person who went through it without going through any counseling, I think he’s finding it very difficult. Like he said to me, ‘I wish I had gone through the process,’ because when—going and having it done and finding out you don’t have it is easy. Going through it and finding out you have it, that’s hard. And you need support. You need help. And you need people around you who understand it. And I think the doctors and social workers and psychologists and everyone that’s involved [in a formal protocol], they can help you through it.”

“No! You should be going through a program where they prepare you for everything.”
A small number of participants (3/31) believe that ordering genetic testing for HD on the internet is not ideal but that if such a DTC test is cheaper and/or the only way a patient is able to learn his/her status (e.g., the patient does not have access to a doctor or cannot otherwise afford the test), then DTC testing should be allowed.

Some participants (4/31) believe that DTC testing is acceptable because it is an individual’s right to learn his/her genetic risk status.

“I mean, that's their right! It's just like finding out if you have the gene for cancer. You know, if you want to know, you want to know.”
(Male, Normal Repeat)

**Incidental Findings**

Participants were asked what they think a doctor should do in the case of an incidental/secondary finding of an HD repeat expansion, subsequent to genomic testing. Each participant was given a scenario in which a doctor ordered whole genome sequencing on a cancer patient to see if a genetic cause of the cancer could be identified. Each participant was then asked about two situations. In the first scenario, the participant was asked what the doctor should do if s/he discovers an incidental finding of an HD repeat expansion when testing the patient for a genetic cause of cancer (Figure 1). In the second scenario, the participant was asked what the doctor should do if s/he discovers an incidental/secondary finding of a medically actionable condition (such as
increased risk for heart disease) when testing the patient for a genetic cause of cancer (Figure 2).

**Scenario One: Incidental Finding of HD**

Thirty-seven participants answered this question. Approximately half of the participants (18/37) believe that before any genetic testing is performed, the doctor should ask the patient if s/he wishes to be informed of incidental findings and, if so, of which types of incidental findings the patient would and would not like to be informed.

“I think that what would be best suited would be for the doctor to use a genetic counselor before they do any kind of genetic test if they want to go down that route. I think it’s the genetic counselor’s job to then express what’s going to happen and that there’ll be this full sort of information and go through whatever protocol to get a better understanding of if the patient would like to know all the results or just the result for this thing and let the patient make that choice.”

(Female, Normal Repeat)

Many (14/37) participants believe the doctor should simply tell the patient about the HD incidental finding. A small number of participants (3/37) believe that the doctor should tell the patient about the HD incidental finding and then arrange counseling for the patient. One participant was unsure.
“Everybody has that right to know. If you found out something that’s going to affect me, like my death, you—once somebody has that information, I think they’re obliged to tell the person, ‘We have this information if you want it.’”

(Female, Normal Repeat)

Only one participant believed the doctor should not tell the patient about the HD incidental finding.

“And I don’t know that there’s anything that you could do about it either, though. Other than possibly prepare with financial stuff. And it also would make their life very, very difficult as far as obtaining life insurance, and health insurance and all that kind of stuff, because now you’re going to tag them with a diagnosis… if it's Huntington's, ‘now you get to go ahead and wait and see if you start seeing these symptoms, and if you do, we're still not going to be able to do anything about it. You know, we may be able to give some medications to cut down on the ticks, or something like that. But the side effects of most of those medications is horrible!’ You know, so for right now, I would just say that until it's something that can be treated, I'd leave well enough alone.”

(Male, Expanded Repeat)
Scenario Two: Incidental Finding of a Medically Actionable Condition

Of the thirty-six participants who answered this question, only two believe the doctor should not tell the patient about the incidental finding. Some participants (8/36) believe that before any genetic testing is performed, the doctor should ask the patient if s/he wishes to be informed of incidental findings and, if so, of which types of incidental findings the patient would and would not like to be informed. The majority of participants (25/36) believe the doctor should tell the patient about the incidental finding. One participant was unsure.

“I think because it doesn’t have an inevitable death sentence connected to it, and there is a way to prevent it from getting to a further place, yes.”

(Female, Normal Repeat)

“It’s something I could do something about, you know, then I think, yeah. Yeah, then I’d like to know.”

(Male, Expanded Repeat)

Understanding sample sizes were small, there were not notable differences in the way our participants answered most of these questions across gender and repeat status. However, three trends are observed. First, in general, individuals with normal repeats were more likely to see a need for a formal protocol than individuals with expanded repeats. Second,
more men than women felt that while a formal protocol should be encouraged, participation in such a protocol should be up to the patient, though due to the sex skewing in our study population it is unclear whether this difference is more likely due to sex or mutation status. Finally, individuals with normal repeats were generally more interested in returning results of an incidental finding of HD than individuals who carry expanded repeats.

**Discussion**

The goal of this study was to gather insights from a cohort of individuals with experience dealing with genetic test results over many years in order to inform current debates about genetic and genomic testing. This study is one of only a few to assess attitudes on these issues from a population of people who have received genetic testing and have dealt with the results over decades (Baig et al., 2016; Dufrasne et al., 2011; Gargiulo et al., 2009; Timman, Roos, Maat-Kievit, & Tibben, 2004).

Participant responses to the five opinion questions revealed common themes about genetic testing and the testing process. One strong overarching theme is that individuals should have autonomy and be able to make decisions for themselves regarding genetic testing. This finding supports results from decades of research and is in line with typical practice in the field. Guidelines from organizations including the American College of Medical Genetics and Genomics (ACMG), the National Society of Genetic Counselors (NSGC), and the Huntington’s Disease Society of America (HDSA) all emphasize the importance of ensuring that at-risk individuals are able to make a decision about testing freely and without coercion. Furthermore, genetic testing of children is rarely permitted
because of the belief in the importance of preserving the autonomy of the individual in deciding whether to pursue testing (hdsa.org, 2017; Kalia et al., 2017; Lickelderer, Wolff, & Barth, 2008; Quaid et al., 2008).

Our participants considered autonomy essential with respect to an individual being able to decide for himself whether and when to pursue genetic testing. Autonomy is also key to the return of incidental/secondary findings, as many participants felt that before any genetic testing is performed an individual should be asked if s/he would like to be informed (or not) of incidental/secondary findings. This finding, too, is in line with current thinking in the field, as current ACMG guidelines recommend that before clinical genetic testing is ordered, the possibility of incidental findings should be discussed with the patient. A list of 59 genes and associated variants is recommended for return in clinical sequencing, but the autonomy of the patient is preserved by allowing the patient to opt out of receiving these results (Green et al., 2013).

While the majority of our participants felt that a formal protocol should be required and physician ordering without such a protocol is unacceptable, some participants felt the decision to go through a formal protocol and have a physician order the test should ultimately be up to the individual. The same is true for DTC availability. While the majority of participants believed DTC genetic testing for HD is unacceptable, some participants believed it should be allowed, at least in certain circumstances. Thus, even in the context of this serious disease, and among individuals who were at the vanguard of this testing and highly motivated to receive testing, there were both people who believed
that DTC testing should be available and those who felt very strongly that it should not be. Notably, these are not uninformed opinions—they are among the most informed we could ask for.

Current ACMG guidelines on DTC testing require that the test be ordered by a knowledgeable professional, performed in a laboratory accredited by CLIA (Clinical Laboratory Improvement Amendments), and interpreted and delivered by a board-certified genetics professional. Additionally, guidelines state that a genetics expert should be available to help the consumer decide whether the test should be performed and how the results should be interpreted (ACMG Board of Directors, 2016).

DTC testing for HD is not currently available, and predictive testing, in most cases, requires two or more in-person visits to the testing center. In a study by Hawkins, Creighton, and Hayden (2013), distance and inflexibility of the testing process were found to be two major barriers that deter individuals from pursuing predictive testing. Distance relates to time away from work and family, travel time, expense, and the stress of navigating an urban environment. Inflexibility of the testing process relates to the length of the testing process, counseling requirements, and the requirement of a support person. Perhaps rethinking the accessibility of testing would be beneficial, especially in cases where there are barriers to access that prevent individuals from receiving predictive testing. An example of a mechanism to reduce barriers to access is telemedicine, which has been used successfully in many areas of medicine and counseling (Abdolahi et al., 2014; Hilgart, Hayward, Coles, & Iredale, 2012; Meropol et al., 2011; Peshkin et al.,
Possible implementation of telemedicine in the genetic testing process could include options to meet with genetics professionals via Skype or other online videoconferencing tools.

While many participants believe individuals should be able to make decisions for themselves regarding whether to pursue genetic testing and what information they want to receive, a second overarching theme in the interviews is that genetic testing requires careful consideration in terms of its availability and the testing protocol. The majority of participants believe a formal testing protocol should be required and that both physician ordering and DTC testing are unacceptable. These beliefs are in line with both predictive test guidelines for HD (International Huntington Association and Work Federation of Neurology Research Group on Huntington’s Chorea, 1994; MacLeod et al., 2013) and ACMG guidelines (ACMG Board of Directors, 2016). These responses are striking, however, given that our participants are overwhelmingly in favor of genetic testing.

Our findings are concordant with those of a Canadian study (Dufranse et al., 2011) which obtained opinions from individuals who had participated in a presymptomatic testing protocol. While some individuals in this study felt the protocol was too long, the majority of participants understood the importance of the protocol and considered it to be a responsible way of practicing medicine.

The opinions obtained in this study are well-informed, as these individuals have received testing and lived with the consequences over a long period of time. The opinions of our
participants were also varied and did not neatly track with whether they had received an HD result of a normal or expanded repeat. Exploration of more flexible and individualized options for testing and testing protocols that take an individual’s circumstances into account may be appropriate (Hawkins, Creighton, & Hayden, 2012). Nevertheless, careful consideration and more research are needed to properly evaluate these options and avoid adverse effects.

**Study Limitations**

While all individuals in this study have experience with genetic testing, their experience is limited to genetic testing for one disease, HD. Data obtained from populations that have experience with genetic testing for a treatable disease or a disease that exhibits reduced penetrance may reflect more flexibility in the requirement of a formal testing protocol, physician ordering, and DTC availability of genetic tests.

Also of note, individuals in this study represent a population that is fundamentally uncomfortable with uncertainty. These individuals self-selected to be the first cohort of people to undergo presymptomatic genetic testing, resulting in a cohort biased in favor of genetic testing. It is also important to note that the individuals in this follow-up study were a fraction of those who participated in the original study. The individuals in the follow-up study were once again self-selected and therefore are likely biased in favor of those who had a positive testing experience.

While the study team attempted to enroll an equal number of males, females, individuals with expanded repeats, and individuals with normal repeats, it should be noted that there
were more women with normal repeats, and conversely, more men with expanded repeats responded to our recruitment efforts and therefore our sample is somewhat skewed.

**Practice Limitations**

All participants in this study were Caucasian individuals who received testing at no cost as part of a research protocol. In practice, patients may be from a variety of ethnic backgrounds. Cost of testing and follow-up care was not a factor in the decision to be tested in this study. In practice, these considerations may influence an individual's decisions and may cause more people to be in favor of DTC if this method of testing is available at a lower cost than a formal protocol.

**Research Recommendations**

A larger sample representative of many different genetic conditions may be useful in future research. Also, inclusion of individuals from a variety of ethnic backgrounds and socioeconomic statuses would also be useful in creating a less biased cohort.

**Conclusion**

This study presents the opinions of a unique and extremely well-informed cohort on issues that need to be taken into careful consideration by policy makers, genetic counselors, and other medical professionals who are developing genetic testing protocols, making decisions about the availability of genetic tests, and making decisions about whether and how to return incidental findings. Our results offer a unique perspective from individuals who have experience with genetic testing and who have dealt with the results long term.
References

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http://doi.org/10.1038/ejhg.2012.147


Table 2.1 Interview Opinion Questions

| 1. How important do you think it is for an individual to decide whether, how, and when to learn his or her genetic risk status? |  |
2. Do you feel that all individuals who want to be tested for HD should be required to go through the same, formal process as you did?

3. Do you think it is acceptable for a doctor to order testing for HD without having a patient go through the formal testing protocol?

4. In the future, people might be able to buy genetic testing on the Internet, without going to a doctor. Do you think it would be okay to order HD testing this way?

5. A doctor may order testing on a person with a rare cancer to see if they can identify a genetic cause of the cancer. If they do find a genetic mutation that they think explains the disease, they can use that information to test other family members at risk. However, since sequencing looks at all of the patient’s genes, the doctor may not find the cause of the patient’s cancer, but might, for example, learn that the patient is positive for the HD mutation.
   a. Should the doctor tell the patient that s/he is positive for HD?
   b. Does your opinion change if the genetic condition discovered was not HD, but rather a substantially increased risk for heart disease or another condition?

Table 2.2 Sample Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Expanded Repeat (n=15)</th>
<th>Normal Repeat (n=21)</th>
<th>Undisclosed (n=3)</th>
<th>Total (n=39)</th>
</tr>
</thead>
</table>

34
<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (26.7)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (73.3)</td>
</tr>
</tbody>
</table>
Figure 2.1 What should a doctor do if an incidental finding of HD is found when testing a patient for a genetic cause of cancer?
Incidental Finding of an Actionable Condition

- Do not disclose
- Yes, if opt in prior to testing
- Yes
- Unsure

Figure 2.2 What should a doctor do if an incidental finding of a medically actionable condition is found when testing a patient for a genetic cause of cancer?
Chapter 3. Risk Perception Before and After Presymptomatic Genetic Testing for Huntington’s Disease: Not Always What One Might Expect

Abstract

Background
In 1983, Huntington’s Disease (HD) was the first genetic disease mapped using DNA polymorphisms. Shortly thereafter, presymptomatic genetic testing for HD began in the context of two research studies. One of these trials was at the Johns Hopkins University Huntington’s Disease Center.

Methods
As part of the protocol, risk perception (RP) values were collected at 16 time points before and after testing. The current study investigated changes in RP scores before and after genetic testing. Of the 186 participants with pre- and post-testing RP values, 39 also had contemporaneous research clinic notes and recent semi-structured interviews available for analysis.

Results
The data reveal tremendous diversity in RP. While the RP scores of most individuals change in the way one would expect, 27% of participants demonstrated unexpected changes in RP after disclosure. A significantly higher proportion of individuals who received an expanded repeat result had unexpected changes in RP, compared with those who received normal repeat results.

Conclusions
The data suggest that individuals’ RP is influenced by more than merely the results of genetic testing. This finding is important for genetic counselors and healthcare providers,
as it suggests that even comprehensive patient education and disclosure of genetic test results may not ensure that people fully appreciate their disease risk.

Key Words: Risk perception, genetic counseling, genetic testing, Huntington’s Disease

Introduction

Huntington’s Disease (HD) is an autosomal dominant inherited condition that is caused by a trinucleotide repeat (CAG) expansion on chromosome 4 (at locus 4p16.3). This progressive neurodegenerative condition is characterized by cognitive deterioration, involuntary movements, abnormal voluntary motor control, and affective symptoms. While some symptoms of the disease can be managed with medication, there is no cure.

Genetic testing via linkage analysis became available for HD in 1986, when the Johns Hopkins University (JHU) and Massachusetts General Hospital began research studies to provide presymptomatic testing for those at risk. The JHU trial continued through 1998 but after the isolation of the gene responsible for HD in 1993 (MacDonald, 1993) linkage analysis was replaced by direct mutation analysis (direct testing). Compared to linkage analysis, which was 95-99% accurate, direct testing is certain. Since HD is a fully penetrant condition when more than 39 CAG repeats are present, test results in that range guarantee that individuals will develop the disease should they live until the age of onset. Conversely, test results of a normal repeat means that one definitely will not develop the disease.

How people perceive their risk and their responses to it play an important role in individuals’ decision making processes and psychological well-being. Prior studies have investigated changes in RP before and after presymptomatic testing for hereditary cancer
and Alzheimer’s disease (Aspinwall, Taber, Kohlmann, Leaf, & Leachman, 2014; Butow, Lobb, Meiser, Barratt, & Tucker, 2003; Gurmankin, Domchek, Stopfer, Fels, & Armstrong, 2005; Schüz, Schüz, & Eid, 2013), but, unlike HD, these are not fully penetrant conditions. Additionally, in the case of hereditary cancer, there are steps that can be taken to decrease the chances of developing cancer, including enhanced screening, prophylactic surgery, and chemoprevention (McLaughlin et al., 2007). No steps can be taken to decrease the risk of developing HD. While several studies have explored the effects of presymptomatic HD testing (Brandt, Quaid, & Folstein, 1989; Crozier, Robertson, & Dale, 2014; Meiser & Dunn, 2000), to our knowledge only three studies (Binedell, Soldan, & Harper, 1998; Codori & Brandt, 1994; Decruyenaere et al., 1999) measured individual’s perceived risk for HD before testing and after testing. Findings by Codori and Brandt (1994) showed significant differences between the mean disclosed risk and the mean perceived risk among individuals who received results of an expanded repeat but not among individuals who received results of a normal repeat. Findings by Binedell et al. (1998) showed that at-risk individuals who pursue presymptomatic testing perceive themselves as more likely to carry an expanded repeat than individuals who do not pursue presymptomatic testing. Additionally, findings by Decruyenaere and colleagues (1999) showed that higher pre-test perceived risk for HD is positively correlated with depression.

While never published, individuals’ RP scores were solicited and recorded at each visit -- up to eleven years after testing -- from individuals in the JHU HD presymptomatic protocol. The current study analyzed long-term changes in RP, conducted semi-structured follow-up interviews, and reviewed contemporaneous research clinical notes from
individuals who participated in the JHU HD presymptomatic protocol, to investigate factors that contributed to changes in RP. To our knowledge, this is the first study to measure long-term changes in RP for a genetic disease.

**Methods**

**Editorial Policies and Ethical Considerations**

This study was approved by and conducted in accordance with the policies and procedures of the Johns Hopkins IRB. Written informed consent was obtained from all participants included in the study (both at the time of presymptomatic testing and again for recent interviews).

**Data Collection**

RP was measured using a 100 mm. visual analog scale (Figure 1). The left anchor was labeled “absolutely certain that I will not develop HD,” while the rightmost was labeled “absolutely certain that I will develop HD.” Participants indicated their perceived risk by putting a vertical slash along the horizontal line. RP was calculated as number of millimeters from the left anchor.

RP was collected at baseline, which was the participant’s first research appointment and prior to genetic testing. RP was also assessed at 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, 3 years, and then annually, up to 11 years post-disclosure. The average number of data points available per participant included in the analysis was 7.1, where the minimum number of data points required for inclusion was two—a baseline RP score plus at least one RP score after genetic testing.

**Participants**
RP data were collected on 214 participants who were enrolled in the JHU HD presymptomatic protocol from 1986 to 1998. Of these 214 participants, 28 were eliminated from analysis due an insufficient number of data points. Sample characteristics of the 186 individuals included in the analysis are shown in Table 1. Sample characteristics of the subset of 39 individuals who had contemporaneous research clinic notes and recent semi-structured interviews are shown in Table 2.

**Data Analysis**

Changes in RP were placed in two categories: expected changes and unexpected changes. Expected changes were defined as a decrease in RP after a normal repeat result, an increase in RP after an expanded repeat result, or no change in RP after an uninformative result or no result. Unexpected changes were defined as increased RP after receiving a normal repeat result, decreased RP after receiving an expanded repeat result, no change in RP after receiving a test result, variation in RP after receiving a test result, and change in RP after receiving an uninformative result or no result.

As part of a follow-up study investigating long-term effects of presymptomatic genetic testing, a subset of individuals who were enrolled in the JHU HD presymptomatic testing protocol were interviewed once between 2015 and 2017, which was 20-30 years after presymptomatic testing was performed. These semi-structured interviews lasted approximately one hour, and topics included individuals’ testing experience, reactions to test result, confidence in results, and impact of testing on mental health, relationships, and life decisions. The interviews were audio recorded, transcribed, and scrubbed of all identifying information. Research charts of all participants who were interviewed in the follow-up study were obtained and analyzed. A codebook was developed and included
codes for RP, confidence in result, change in RP after testing, and risk misperception. All interviews and charts were double coded, and any conflicts in coding were discussed by the coders and reconciled. QSR International’s qualitative analysis Software NVivo 11 was used for data analysis, along with manual analysis of data.

Code reports generated from the research charts, research records, and interviews of the 39 individuals who participated in the follow-up study were analyzed for discussion about RP. Coded RP content was classified into one of 13 categories (see Table 3).

**Results**

Fifty-one of 186 (27%) participant’s RP scores demonstrated unexpected changes (Figure 2-A). No significant differences in unexpected changes were observed between females and males. However, a significantly higher proportion of individuals who received an expanded repeat result (27/56; 48%) had unexpected changes, compared with those who received a normal repeat result, uninformative result, or were undisclosed (24/130; 20%) ($\chi^2= 17.4, p=0.00003$) (Figure 2-C, D). Unexpected changes were also observed at a higher rate in individuals tested by linkage (26/79; 33%) than in individuals tested by direct testing (21/74; 21%), but these differences were not significant (Figure 2-E, F).

Factors that appear to influence RP identified in interviews and clinic notes are listed and described in Table 3. Of the participants in the long-term follow-up study (n=39), 27 participants identified one of more of these factors (12 participants did not discuss RP).
Discussion

Unexpected changes in RP were observed in more than 1/4 of the full cohort, indicating perceived risk is influenced by more than genetic test results alone. This finding is concordant with other studies, which have found that RP is complex and influenced by a number of factors that may impair accurate risk comprehension (Croyle and Lerman, 1999; Hopwood, 2000). In a literature review by Sivell et al. (2008), 59 studies presenting data on the way individuals perceive, construct, and interpret risk for a range of diseases were evaluated. Nineteen of the studies investigated how individuals construct RP by considering the factors and beliefs on which people base their RP. These factors included past experiences (d’Agincourt-Canning, 2005; Hallowell, Statham, & Murton, 1998; Kelly et al., 2005; Kenen, Arden-Jones, & Eeles, 2004; Robertson, 2000), environmental factors (Ryan & Skinner, 1999; Sheinfeld, Gorin, & Albert, 2003), occupation as it relates to carcinogen exposure (Liede et al., 2000), diet (Ryan & Skinner, 1999; Wilson et al., 2005), stress and worry (Ryan & Skinner, 1999), physical resemblance to affected relative (Fanos & Gatti, 1999), and genetic and family history factors (Julian-Reynier et al., 1998; Liede et al., 2000; Ryan & Skinner, 1999; Sheinfeld Gorin & Albert, 2003; Wilson et al., 2005). Decruyenaere et al. (1999) also found that parental age of onset of HD informed an individual’s RP.

Analysis of additional data from a subset of the full cohort, including both contemporaneous clinic notes and recent interviews identified both previously published and novel factors that appeared to affect RP. Novel factors included symptomatizing, personality resemblance to affected family member, inability to accept normal repeat result, misunderstanding genetic test results, misunderstanding HD risk, genetic test
results of family members, optimism after results of an expanded repeat, denial after results of an expanded repeat, linkage testing, belief in lab mistake, and hope for a cure. As shown in Figure 3, these factors were discussed by both those with unexpected and those with expected changes in RP. Of note, we are defining ‘factors that appear to influenced RP’ as those factors that seem to have influenced how individuals reported their risk on the visual analog scale (Figure 1). Individual’s self-reported disease risk may be influenced not only by their understanding of their genetic test results, but also by other factors, such as coping mechanisms and anxiety. For example, two participants who received an expanded repeat result demonstrated a lower than expected RP score stated they were hopeful a cure would become available and they would not develop symptoms of HD (Figure 3). Further, three participants who received a normal repeat result demonstrated higher than expected changes in RP stated they worried normal human failures (e.g., dropping keys) were symptoms of HD (Figure 3).

Data from the current study indicate that people often appear to misunderstand their risk. A higher proportion of unexpected changes in those with expanded repeats may indicate denial or difficulty accepting a disease gene-positive result, or rather may be an expression of hope about their prospects in the face of the expanded repeat finding. The unexpected RP scores observed in this population may be a manifestation of coping mechanisms being employed after receiving a very difficult test result. Prior studies have shown that minimization of risk and/or denial are common processing strategies after receiving health risk information (Aspinwall et al., 2014; Mathews et al., 2017; Meiser & Dunn, 2000). Additionally, if the receipt of negative information puts a person in a negative mood, they are less likely to process a health message associated
with a disease and their potential of having the disease (Menon, Agrawal, & Aaker, 2006). Finally, interviews with participants in phase I or II oncology trials revealed that many individuals believe having positive thoughts or expressions will improves one’s chances of personally benefitting from a therapy or cure (Sulmasy et al., 2010). This belief may be shared by individuals who carry expanded repeats for HD.

Individuals undergoing presymptomatic testing for HD typically undergo two pre-test genetic counseling sessions before receiving test results. Individuals in the JHU HD presymptomatic study received pre-test counseling, but since they were the first cohort to be tested presymptomatically, five pre-test appointments were required before receiving test results. The proportion of unexpected changes observed in a cohort well-counseled and well-educated on both HD and genetic testing for HD is surprising.

**Conclusions**

After receiving results of genetic testing, people’s RPs do not always change in the way one would expect. Data from this study and others indicate that an individual’s RP is complex and influenced by a variety of factors which are likely not only disease specific but also specific to an individual’s past experiences and beliefs. Furthermore, RP may play an important role in an individual’s decision-making processes and psychological well-being.

This study suggests that extra steps may be necessary to ensure individuals are processing and adapting well to their test results. Without disabusing people of reasonable hope in the face of difficult news, possible interventions include post-test counseling appointments with discussions about RP and continued education about HD. Further research is needed to investigate factors that influence perceived risk. Findings
from this study should be considered by both genetic counselors and healthcare providers, and efforts should be made to respond to RP in order to improve patients’ experience of testing and overall well-being.

**Study Limitations**

The study population included self-selected individuals who were not representative of all individuals eligible for testing. Claes, Denayer, Evers-Kiebooms, Boogaerts, and Legius (2004) suggested that individuals who present for genetic testing may have a higher perceived ability to understand and cope with genetic test results. Not all participants in the current study were independent, meaning some participants in the study were blood relatives of other participants in the study; this could lead to family-specific effects. Also, individuals in this study were primarily Caucasian; further research is needed to assess possible differences in risk perception across different cultural backgrounds and ethnicities.

Since the factors we identified were not exclusively discussed by individuals with unexpected results, we cannot conclude these factors are solely responsible for the observed unexpected changes in RP. It is also important to note that almost all prior studies that have investigated factors that inform RP have been on hereditary cancer. Therefore, the novel factors identified in this study could be due to differences between hereditary cancer and HD.

As part of the JHU HD presymptomatic protocol, individuals received extensive pre- and post-test counseling. Thus, results of this study may not be comparable to individuals who receive the current standard of two counseling sessions prior to presymptomatic HD genetic testing. Additionally, individuals in this study underwent
genetic testing between 1986 and 1998. These were some of the first individuals to undergo genetic testing, and trust in genetic test results and understanding of genetic information may be different now than it was at that time. Finally, this study focused on RP in the context of HD, so caution should be used when generalizing these findings to other conditions.
References


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27. NVivo Qualitative Data Analysis Software; QSR International Pty Ltd. Version 11, 2016.


### Table 3.1 Sample Characteristics of 186 Individuals Included in RP Analysis

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Expanded Repeat</th>
<th>Normal Repeat</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(%)</td>
<td>78 (41.9)</td>
<td>108 (58.1)</td>
<td>56 (30.1)</td>
<td>115 (61.8)</td>
<td>15† (08.1)</td>
<td>186</td>
</tr>
</tbody>
</table>

† Consists of individuals who were uninformative by linkage testing and individuals who were undisclosed, meaning they did not receive their genetic test results, but participated in pre-test counseling and appointments over many years at the same time intervals as those who received genetic test results.
Table 3.2 Sample Characteristics of Individuals in Follow-Up Study

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Expanded Repeat</th>
<th>Normal Repeat</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(%)</td>
<td>19 (48.7)</td>
<td>20 (51.3)</td>
<td>15 (38.4)</td>
<td>21 (53.8)</td>
<td>3‡ (07.7)</td>
<td>39</td>
</tr>
</tbody>
</table>

‡Consists of individuals who were uninformative by linkage testing and individuals who were undisclosed, meaning they did not receive their genetic test results, but participated in pre-test counseling and appointments over many years at the same time intervals as those who received genetic test results.
### Table 3.3 Factors that Appear to Influence Risk Perception

<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>Representative Quote</th>
<th>Number of Individuals who Expressed Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatizing</td>
<td>Worry that normal failures (e.g., dropping keys) are symptoms of HD</td>
<td>“I think everybody who is related to somebody that has it, thinks of every time they move their foot, or do a tick, or hesitate with what they're saying, they feel like they have it. At least all the conversations I've had with people. It's just sort of natural. So, I was almost certain that I had it.”</td>
<td>9</td>
</tr>
<tr>
<td>Unable to Accept Normal Repeat Result</td>
<td>Inability to accept that one has a normal repeat and is no longer at risk for HD</td>
<td>“And it wasn’t that I didn’t trust the test result because I really did trust the accuracy and, you know, the things that Hopkins had in place, you know, that it was an accurate test result. It wasn’t that. I just couldn’t believe that that’s what it was.”</td>
<td>5</td>
</tr>
<tr>
<td>Genetic Test Results of Family Members</td>
<td>Test results of family members may be an indication of one’s own test results (e.g., Individual believes it is more likely s/he has an expanded repeat after learning his/her family member has a normal repeat)</td>
<td>“My brother-in-law was very much on the, 'No, she doesn’t have it.' And I was on the over 50 percent, like, 'Yeah, I do.' My sister had been tested, she didn’t have it. What are the chances of both of us not having it? You know?”</td>
<td>4</td>
</tr>
<tr>
<td>Hope for a Cure</td>
<td>Hope for a cure to be developed before one develops symptoms of HD</td>
<td>“There is hope for a cure.” §</td>
<td>3</td>
</tr>
<tr>
<td>Linkage Test Accuracy</td>
<td>Lower accuracy of linkage test (96-99%) compared to direct test (100%)</td>
<td>&quot;After they had identified the gene, they asked to retest me [with the direct test] which they did, and I didn’t ask for the results. Every year when I would come down they would give you the same sort of questionnaires. On one of the questionnaires was just a line on a piece of paper that someone says I have Huntington’s disease and this one says I don’t have Huntington’s disease, and you had to put an x. I could never put my x… it was just beside I don’t think I have it. I could never put it on ‘I don’t have it.’ That’s the only thing I couldn’t do. I got close to there but not – I couldn’t. I never asked for the [direct test] results.”</td>
<td>3</td>
</tr>
<tr>
<td>Physical Resemblance to Affected Family Member</td>
<td>Physical resemblance to an affected family member increases one's likelihood of having an expanded repeat</td>
<td>“I thought, ‘Oh my gosh, if I look my mother, then I must have her gene for Huntington’s.’”</td>
<td>3</td>
</tr>
</tbody>
</table>
| Optimism after Expanded Repeat Result  | Hope that one will not develop HD after receiving results that one carries an expanded repeat | Interviewer: “Can I ask you when they gave you your results, did you think you would get it? Did you believe the results? Or were you optimistic that you wouldn’t?”  
Participant: “I was optimistic I wouldn’t.”                                                                 | 3                                        |
| Personality Resemblance to Affected Family Member | Personality resemblance (e.g., a bad temper) to an affected family member increases one's likelihood of having an expanded repeat | “I always felt like I was like my mother in her values, in her way she was with people. My mother, if you did something to her she held a grudge forever. I felt like I was like her, so maybe I did have some of her.” | 2                                        |
Belief in Lab Mistake | Belief one’s test result is incorrect due to a laboratory mistake | “Yeah, when I first understood I didn’t carry the gene, there’s still always that apprehension, ‘Well, what if the lab was wrong?’” | 2

Misunderstanding Genetic Test Results | Confusion regarding whether “positive” result meant good news or gene-positive (expanded-repeat) | “They said, ‘you tested positive.’ And I literally didn’t know whether that meant that I had the gene or positive like it’s a positive result or a positive outcome.” | 1

Misunderstanding HD Risk | Misunderstanding each child born to a parent affected by HD has a 50% chance of having an expanded repeat, or misunderstanding how HD is passed on in families | “There’s some disease that runs in the family, that turns your brain to mush but don’t worry about it because it skips a generation usually.” | 1

Age of Parental Onset | Increased worry of developing HD as one approaches the age of onset of his/her affected parent | “He has been increasingly worried about developing HD because he is now the age his mother was when she began to show symptoms.” | 1

Denial after Expanded Repeat Result | Inability to accept that one will develop HD after receiving results that one carries an expanded repeat | "How could those tests be positive, there must have been a mistake, those things happen every day, right?” | 1

Table 3. Factors are defined and represented with a quote taken either from clinic notes or interviews. §Quote was taken from visual analog scale; individual with expanded-repeat and lower than expected RP wrote this next to her indicated RP.
Figure 3.1 Visual analog scale. Participant indicated his/her perceived risk on the horizontal line. The line spans 100 millimeters, and a RP percentage was calculated by measuring the distance in millimeters of the marking indicated by the participant from the leftmost side of the line.
Figure 3.2. (A) Total number of expected and unexpected RP changes. (B) Number of expected and unexpected changes in individuals who participated in the follow up study. (C) RP changes in individuals with an expanded repeat. (D) RP changes in individuals with a normal repeat, were uninformative, or were undisclosed. (E) RP changes in individuals tested by linkage analysis. (F) RP changes in individuals tested by direct testing.
Figure 3.3 Factors that appear to influence RP and the number of individuals who discussed each factor.
Chapter 4: “I wanted more information but I think they were scared I couldn’t handle it:” Whether, When, and How to Communicate Genetic Risk Information to Children

Abstract

Objectives

Genetic test results are often relevant not only to persons tested, but also to their children. Questions of whether, when, and how to disclose these results to children can be difficult for parents to navigate. Currently, limited data are available on these questions from the child’s perspective.

Study Design

In this qualitative study, semi-structured interviews were conducted with parents affected by or at-risk for hereditary cancer (N=17) or Huntington’s disease (N=14) and their children aged 15-17. Parents and children were interviewed separately. Genetic counselors (GCs; N=19) were also interviewed.

Results

Most parents interviewed wanted to protect children from genetic risk information (GRI) and feared children would not be able to handle GRI. However, most children reported they did not receive enough information and wished their parent was more forthcoming. Parents recommended taking time to process one’s own test results before communicating with children, and children recommended parents communicate GRI in an honest, hopeful way. Most parents and GCs felt additional resources on communicating with children about GRI and various genetic conditions are needed.

Conclusions
This study includes the experiences and perspectives of a well-informed cohort and results should be taken into careful consideration by parents, GCs, and others who are faced with communicating GRI to children.

**Introduction**

Little research exists on whether, when, and how to inform minors of genetic risk information (GRI). Presently, our understanding of the consequences of children learning GRI is largely based on research on adults. However, research directed at adults may not be relevant to adolescents due to differences in cognition, self-concept, and stability of self-concept between adolescents and adults. While the small number of studies available suggest that children do better when GRI is shared over time in an age-appropriate way, very few of these studies talked with minors directly or compared what parents think they are communicating with what children say they are hearing. As genetic and genomic testing is increasingly incorporated into research and clinical care, a better understanding of how parents and children view genetic risk/status and how it is communicated is vital in order for genetic counselors (GCs) and other health care professionals to provide the best guidance possible, and to help families navigate these conversations. To address this gap, we present qualitative data from interviews with GCs and parent/child pairs from two populations: families at-risk or affected by Huntington’s disease (HD) and families with hereditary cancers (HCs). HD is a dominantly-inherited Mendelian disorder for which there is a highly predictive genetic test, but no cure or highly effective treatment. Like HD, HC mutations can be inherited in an autosomal dominant pattern. However, HD and cancer differ in many significant ways. First, HD exhibits complete penetrance (except in the case of 36-39 CAG repeats, where reduced
penetrance can be observed\(^8\) while cancer exhibits incomplete penetrance.\(^9\) Secondly, while there is no effective treatment for HD and there is no chance of surviving the disease, treatments do exist for cancer, making possible remission and survival. Finally, HD is rarer than many of the HCs. The prevalence of HD is 1:10,000 to 7:100,000,\(^10\) while the prevalence of BRCA mutations is 1:500 to 3:1000.\(^11\)

Both HD and HC populations were included in this study because while HD represents one end of the spectrum for presymptomatic testing, most genetic risk is not nearly so definitive or dire. HD allows us to explore and understand a worst case scenario, while HC provides a useful comparison and broadens the applicability of our findings. GCs were included to gather clinical experiences with communicating GRI to children, opinions on best practices, and current practices in the field of genetic counseling.

**Methods**

**Ethical Guidelines**

This study was approved by the Johns Hopkins University Institutional Review Board and adhered to the Declaration of Helsinki. Informed consent was obtained from all individuals who participated in this study.

**Design**

This qualitative study involved semi-structured interviews with GCs and parent-child pairs. Interviews with parents and adolescents, aged 15-17, were conducted separately and aimed to assess how children understand GRI, to learn about the disclosure event and what information was given to the child, and to evaluate how parents’ perspectives differ from children’s in order to understand factors associated with positive and negative experiences for both parents and children in the communication of GRI. Interviews with
GCs were focused on their experience(s) with advising parents on how to communicate GRI to children and/or communicating this type of information to children directly and suggestions for the future.

**Sample**

Participants in this study were parent/child pairs at-risk for or affected by HD or HC. Parents in the HD population of this study were at-risk for HD, affected by HD, or the spouse/partner of someone living at-risk for or affected by HD. Parents in the HC population of this study had a diagnosis of HC or were the spouse/partner of someone living who had a diagnosis of HC. In this study, HC was defined as a diagnosis of 1) breast/ovarian cancer with genetic testing that indicated a pathogenic BRCA mutation or 2) colorectal cancer with genetic testing that indicated Lynch Syndrome.

Children were at-risk for HD or HC, and of normal cognitive function. The age range of 15-17 was selected because we wanted children to be of similar cognitive ability and at the same stage in development. Additionally, children in this study were those who have had GRI disclosed to them, and we anticipated that it was more likely for a child later in adolescence to have had GRI disclosed to them than a child earlier in adolescence. Normal cognitive function was determined by the absence of an Individual Education Plan (IEP) in the area of cognitive impairment/mental retardation. Parents and children were telephone screened prior to enrollment to confirm their eligibility. Consent was obtained prior to interviews and again before the start of each interview.

Participants in the HD population were recruited through the Johns Hopkins University HD Research Data Base, the Huntington’s Disease Youth Organization, the Huntington’s...
Disease Society of America, and online support groups. Twenty potential HD families demonstrated interest, and 14 were eligible and enrolled. Participants in the HC population were recruited through the Johns Hopkins Colorectal Cancer Registry and online support groups. Thirty potential HC families demonstrated interest, and 17 were eligible and enrolled. GCs were certified by the National Society of Genetic Counselors (NSGC) and had either 1) had a parent ask them (the GC) to communicate GRI to their child or 2) had experience communicating with children about GRI. GCs were recruited through the NSGC website. Twenty-two potential GC participants demonstrated interest, and 19 were eligible and enrolled. Each participant received a $40 gift card for their time.

**Data Collection**

Semi-structured interviews lasting an average of 20 minutes (9 minutes to 54 minutes) were conducted by one or two members of the study team. The full interview guides are available as supplementary material. Interviews were conducted via telephone, with the exception of one parent/child pair, who were interviewed in person.

**Data Analysis**

Interviews were audio-recorded, transcribed, and scrubbed of all identifying information. A preliminary codebook was developed based on the interview guide. After reading five transcripts, the codebook was refined, and revised iteratively throughout the interview process. The final codebook was used to code all transcripts. All interviews were double-coded, and any coding conflicts were discussed by the two coders (KS and AM), reconciled, and finalized using NVivo 11 (QSR International, Melbourne, Australia). Codes were refined as more data were analyzed. Analysis of opinion questions was done
using NVivo 11 to produce code reports, which were then analyzed to determine the distribution of responses and identify emergent themes.

**Study Limitations**

Parents and children in this study self-selected to participate and share their experience communicating about GRI, resulting in a cohort biased in favor of sharing GRI with minor children. Also, our cohort may be biased in favor of parents and children who had positive experiences communicating about GRI, if parents and children who had negative experiences were less willing to participate in the study. Other limitations include recall bias.

**Results**

Eighty-five individuals were interviewed (see Table 1). Due to the qualitative nature of this work, not every participant answered every question.

**Whether to Disclose**

When asked if parents in other families should talk to their kids about genetic risk, all (34/34) children interviewed responded “yes,” and when children were asked if they were happy their parent had disclosed GRI to them, all children who responded answered “yes.” Of note, one parent in the sample intentionally did not disclose GRI, but their child learned the information nonetheless. All parents who did disclose GRI to their children reported they were happy they had done so.

“I think it’s the responsibility of your parents to share that information with you if it’s going to affect you or affect your family. I think that it’s irresponsible not to talk to your kids about that in whatever way that you may need to.”

Child, HC
“I just don't think it would be possible for me to not know something was going on. And I think it would be really awful to see these changes happening to my dad and having no answer for it and everyone else knew something was going on and I would just be in the dark. It was good to know just what was going on, so I wasn't shut out from the rest of the family.”
Child, HD

“I feel like if they had just not told me about this risk [...] and just told me now, then that'd be super-upsetting, because this could be a big deal in the future, and I feel like there's no point in hiding it, and, sure, it might seem scary in the beginning or when you first hear about it, but if you don't hear about it and don't understand these risks and you end up developing it and not knowing that you could have it I feel like that's a whole lot worse.”
Child, HC

Additionally, 17/34 children reported they could sense something was going on in the family before the parent disclosed GRI but did not know what it was. In these situations, children often reported they felt scared and assumed the situation was worse than it actually was. 10/19 GCs reported that kids are perceptive and able to understand more than we give them credit for, and would therefore benefit from having conversations about GRI.

“Even at nine I knew and I think it helped I knew because instead of worrying, wondering, like, if she took a pill or, like, a shot or something, I knew why. I kind of--before that I was kind of wondering, like, ‘Why? Why do you do that?’”
Child, HC
“So there's been times especially in the cancer setting where the parents have asked the children to not be in the room, which I think probably worries them more. It makes them more anxious than maybe the reality of the situation if they actually heard the information, because if they're just left to wonder what's going on their minds could even run further.”

GC

When to Disclose

Participants were asked when parents should disclose information to children. 17/32 parents reported that a parent should not communicate information right after they learn of their own genetic risk or mutation status and should take time to process their own results before communicating to a child. In response to the same question, 2/19 GCs stated that parents should take time to process their own results before communicating GRI to a child.

“I think telling your kids right away when you first get the diagnosis is in my opinion a mistake, because I think you have to allow yourself to deal with the fear and the sadness and the anxiety and sit with it for a little while and process it and try to come out on the other side of it, because otherwise you're going to communicate your fear and your anxiety to your kids, and so that was the only reason why I wanted to wait a little while to tell my kids, because I wanted them to see that I was okay.”

Parent, HC

Common responses from parents, children, and GCs included the importance of taking the maturity of the individual child and the family situation into consideration when considering the timing of disclosure.
“Everyone's a little bit different, some kids tend to mature a little bit faster than others, and can take in more information more readily than others. So I really think it's dependent on the child, and I wouldn't set the age limit to it.”

GC

“I would say take into account each child's personality and how they handle serious topics. And also take into account what's happening in the family. [If] the kids are seeing [Lynch syndrome’s] impact going on around them, then they-- the parents should explain to the kids why this is happening. And not just leave them not knowing and wondering and making up explanations that might be more horrible than what the reality is.”

Parent, HC

Furthermore, 15/19 GCs and 20/32 parents felt it was best to start disclosing GRI to the child at a young age to normalize the information, and to give the child age-appropriate information gradually over time. 15/34 children reported something that “went well” in their experience with learning GRI was that they were told at a young age and learned more details as they got older. Children reported having first learned about GRI as young as age eight.

“I knew that my mom had it because it was genetic. But I didn’t know that there was a risk that we would also have it because she did. But they kind of shared that information as we went on. And I’m glad they did that. I think if they had told me everything [as a preteen] all at once, it would have been a lot for me.”

Child, HC

“I think providing age-specific information, or age-targeted information can be helpful. As long as you set the stage for early enough, at each point you bring the information in,
it's not going to be blindsiding them, but they're just getting a bit more, a few more pieces to that puzzle so they can comprehend the whole picture.”

GC

**How to Disclose**

18/19 GCs felt that the parent should first disclose, as opposed to a doctor or GC. One GC felt a GC should first disclose to kids. Nearly all parents (31/32) and all children interviewed also felt that the parent should first disclose the information.

15/19 GCs and 18/32 parents felt that parents should seek counsel from a doctor or GC before disclosing information to kids. Additionally, 15/19 GCs, 31/32 parents, and 31/34 children felt parents and children should seek follow up with a GC after the parent initially discloses the information if either the parent or child(ren) feels it is necessary.

When children were asked how parents should communicate information, almost all children (28/34) stated that the parent should communicate the information honestly in a way that does not scare the child. 18/34 children reported that the parent should convey the information with a positive, hopeful attitude.

“*You can’t sugar coat it. You just have to tell them exactly what it is. If you tell them everything’s 100-percent perfect and just about won’t affect them, it’s not true. I’d rather know the full truth.*”

Child, HC

“*My mom, when she first told us she spoke very calmly and explained it in depth and she didn't get too emotional about it, which helped us not immediately freak out and assume that the worst was going to happen.*”

Child, HC
“Just be more on the positive side, like that you have a 50-percent chance, also, of not having it [HD].”

Child, HD

All children interviewed felt parents should have conversations with children about GRI not just once, but several times over months or years. Additionally, 20/34 children reported they desire open communication and the ability to bring up the topic of GRI comfortably with their parent.

“I think they did a really good job of making me feel like it was something that was okay to talk about. And they made me feel like I was part of that conversation and that they wanted to explain it to me.”

Child, HC

**Amount of Information**

Most parents (21/32) reported anxiety and apprehension about communicating GRI to their children. Parents reported wanting to protect the child from the information and fear that their child would not be able to handle the information.

“It's kind of the first thing for me that I have no way of protecting them from. There's nothing, nothing I can do to protect them from this [disease].”

Parent, HD

“I don’t want to scare them and I don’t want to, you know, they’re kids, so they don’t have, like, the brain capacity for the whole picture yet.”

Parent, HC
14/34 children reported they did not receive the information necessary to understand their risk, and 21/34 children reported they wished their parent had given them more information. Zero children reported that their parent gave them too much information.

“I think my father assumed that a lot of it, I wouldn’t understand, and he didn’t want to tell me. And I would go out and find that information some other ways, and then I would talk to him about it. I’d say, ‘Well, Dad, I found out about this [other information about HD]. Why didn’t you tell me [that]?’ And he would just say, ‘Well, I just didn’t think you would understand.’”

Child, HD

“Well, I feel like they didn't explain it enough. I mean, they didn't make me feel scared, but they didn't explain it enough for me to fully grasp it. I didn't really understand the full concepts of this mutation and how it might affect me.”

Child, HC

Resources

16/19 GCs and 26/32 parents wanted additional resources on how to communicate GRI to kids as well as child-specific resources on various genetic conditions.

“Having maybe a resource of information through [...] [American College of Medical Genetics and Genomics] or NSGC or something, where counselors have access to pamphlets of some type of information on different conditions and how to explain that to a child and different points of interest of; like, when to tell-- when-- an age range of when to tell the child and why it's important and information like that to give to a parent that might need to go home and explain that to their child. So having kind of a database of all of that in one spot rather than having to try to go and search everywhere and to try to
find all of this information on our own.”

GC

“I know that there are books out there that are written for children that can explain general genetic concepts. And I’m wondering if they could have anything similar to that for more specific conditions, or generally for hereditary cancers, but also having a complementary guide for parents.”

GC

“... I just didn't feel like there was great I guess guidance on that, and I hate having to Google information and stuff. It's like you want to make sure you're getting good accurate information and so I felt like I had to do a lot of that kind of research myself going into that.”

Parent, HC

13/25 parents with either HD or Lynch Syndrome also wanted more information on their genetic condition and reported their doctor was not knowledgeable about their condition. This was reported by 1/7 parents with BRCA.

While most parents 26/32 reported they consulted the internet, most children 23/34 reported they did not consult the internet and relied on their parent as their sole source of information.

Factors Associated with Negative Experiences

6/32 parents, 6/34 children, and 4/19 GCs reported situations where the child initially learned of their genetic risk from a source other than the parent. These situations involved circumstances in which the child learned of their risk by hearing or reading information
that was not intended for them. In all situations where this occurred, negative outcomes were reported.

“My sister found out, actually, not through my parents. She found out through an email, which is through an email saying that my dad had HD, and so that's why she had been so upset, just because she was very confused and it was just really shocking for her.”

Child, HD

“A lot of the time the genetic counselor offers to write a letter to the family or something and I have heard of like a child opening the mail or seeing in their parents' e-mail about it. It's really, really scary for the child to really not know all the details and not be able to process it with the ability to ask questions.”

GC

No differences were identified between males and females. The 23 quotes in this section came from 22 participants.

**Discussion**

Our study reveals a discrepancy in the amount of information parents wish to communicate to children and the amount of information older adolescents want communicated to them by parents. We know that the reason parents are not comfortable providing more information is due, at least in part, to the need for parents to take time to process their own result before communicating GRI to children. Our study also highlights the need for more resources on how to communicate with children about GRI as well as child-specific resources on various genetic conditions.

Data indicate children want (and often seek) more information than is originally provided by their parents. Considering this along with findings that most children do not consult
the internet or other sources and instead rely on their parent as the sole source of information, indicate the importance of parents providing both adequate and accurate information.

No negative experiences were reported from parents communicating GRI to children. Instead, negative experiences that were reported were related to parents not communicating GRI to children and children learning his or her risk from a source other than the parent. These findings raise the possibility that children are better able to handle GRI than many parents believe.

The majority of parents felt it was important to take time to process one’s own results before communicating with kids and that doing so allowed the information to be communicated in a calmer, less emotional manner. Time to process may allow parents to better meet the emotional needs of children, who desire GRI to be communicated in a calm, positive, and hopeful way that does not make them feel scared. Time to process may also allow parents to consult resources, such as advice from a GC, on how to best communicate GRI to children. During initial disclosure, it is likely topics including one’s own prognosis, what the results mean for one’s child(ren), and whether other family members need to be tested take precedence over the issue of communicating genetic test results to children. As such, a follow-up appointment with a GC months after the initial disclosure appointment may be beneficial.

Both GCs and parents reported a desire for resources on how to communicate with children about GRI as well as child-specific resources on various genetic conditions. While rare in the breast cancer population, approximately half of parents in the HD and Lynch Syndrome populations also reported a desire for more resources on their genetic
condition and questioned their doctor’s knowledge and ability to treat their condition. This was the only difference observed between the HD and HC populations in the study. This may be related to an increase in breast cancer awareness in recent years, due to factors which include the “Angelina Jolie effect.” Patients may benefit both from more frequent and immediate referrals to specialists and from more disease-specific resources provided by healthcare professionals, since a patient’s lack of knowledge about their medical condition and uncertainty regarding a health professionals’ knowledge about their condition can have adverse psychological effects.

Our findings are similar to previous studies in suggesting that children should be informed of GRI and that the information should be communicated by the parent, starting at a young age to normalize information, gradually over time, and using age-appropriate information.

Current practices in genetic counseling and healthcare focus on the patient in front of the provider, but not on the family unit. Time limitations on GCs and other healthcare providers make it difficult to broaden this focus. However, it is clear that more resources and support are needed for both families and professionals.

Conclusions

This study includes the experiences and perspectives of a well-informed cohort and our results should be taken into careful consideration by parents, GCs, and other medical professionals who are either advising parents on whether, when, and how to communicate GRI to minor children or involved in direct communication of GRI to minors. Our results suggest that communication of GRI could be improved through the development and availability of resources on how to communicate GRI to children, time in appointments
with GCs and other professionals designated specifically to educating parents on best practices in communicating GRI to children, research conducted with parents and children at risk for a wider variety of diseases, and research conducted with children younger than 15.
References


7. Wilkins EJ, Archibald AD, Sahhar MA, White SM. “It wasn’t a disaster or anything”: Parents’ experiences of their child’s uncertain chromosomal microarray result. American


Table 4.1 Participant Demographics

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Chapter 5: Prevalence of Pathogenic Germline Mutations in Known Cancer Predisposition Genes in Individuals with Metastatic Breast Cancer

Abstract

This study aimed to determine the prevalence of pathogenic germline mutations in patients with metastatic breast cancer who were not selected for early age of onset or family history. A total of 100 individuals from Johns Hopkins Sidney Kimmel Comprehensive Cancer Center and Johns Hopkins Sibley Memorial Hospital received CLIA-grade testing through Color Genomics on a panel of 30 genes associated with hereditary cancer. Of 100 total individuals, 11 (11%) were found to have a pathogenic mutation, three (3%) were found to have a “likely pathogenic” mutation, and 20 (20%) were found to have a VUS. Results indicate that germline testing in cases of metastatic breast cancer may be appropriate because if current family history guidelines are followed to determine the appropriateness of genetic testing, pathogenic mutations in cancer susceptibility genes, some of which are therapeutically targetable, will be missed. Additionally, at-risk relatives may also miss opportunities to partake in cancer screening and prevention strategies.

Background

Tumor genome sequences are used to identify driver mutations likely to respond to targeted therapies. The utilization of genomic sequencing is rapidly changing the field of oncology and cancer care (Garraway, 2013; Mody et al., 2015; Roychowdhury et al., 2011), however the utilization of tumor mutational profiles is not novel. Since the 1990s, clinicians have used hormone receptors and HER2 in breast cancer care (Seeger et al., 1985; Wolff et al., 2013). In the past, clinical genomic testing of patient tumors has been
limited by lack of knowledge of relevant genomic biomarkers (De Gramont et al., 2015), but that knowledge has rapidly grown in the past several years and has expanded the scope of cancer genomic testing. Current sequencing practices range from single-gene, to targeted panels, to whole-exome and whole-genome sequencing. Genomic analyses of tumors allow identification of tumor-specific mutations for which targeted therapies may be available.

Genomic analysis also has the potential to identify non-tumor-specific (germline) mutations, which are relevant to both individuals and their family members (Catenacci et al., 2015; Green et al., 2013). Hereditary mutations in cancer-predisposing genes can guide the patient’s clinical care as well as outline additional family members that could benefit from cancer screening.

Some previous studies have suggested the rate of pathogenic mutations in known cancer susceptibility genes in individuals with metastatic cancers not selected for early age of onset or family history of breast or other cancers might be higher than previously expected. In a study by Jones et al. (2015), 815 tumor-normal paired samples from patients of 15 tumor types were evaluated. Results of tumor-normal paired samples identified germline alterations in cancer-predisposing genes in 3% of patients with apparently sporadic cancers (Jones et al., 2015). In a study by Shindo et al. (2017), 33 of 854 (3.9%) of patients with pancreatic cancer had a deleterious germline mutation and only three of these patients reported a family history of pancreatic cancer. Most notably, in a study by Pritchard et al. (2016), a germline mutation rate of 11.8% in 20 cancer-
related genes was found in 692 metastatic prostate cancer patients. Furthermore, mutation frequencies did not differ by age of diagnosis or by family history. These results suggest that individuals who are more resistant to therapies may be those who carry germline alterations.

This study aimed to expand on data by Pritchard et al. (2016) and investigate the incidence of germline mutations in metastatic breast cancer patients by performing germline sequencing on a panel of 30 known cancer predisposition genes (Table 1). We hypothesized that the rate of pathogenic mutations in these known cancer predisposition genes in patients with metastatic breast disease not selected for early age of onset or family history of breast or other cancers would be a rate of 10% or higher based on previously published data from Pritchard et al. (2016).

Data obtained in this study may provide insight into whether germline mutations in known cancer predisposition genes are associated with more resistant forms of disease. Additionally, this study will provide data on whether performing germline testing on all patients diagnosed with metastatic breast cancer is justified. Our study is novel in the sense that we will be the first, to our knowledge, to evaluate the prevalence of germline mutations in patients with metastatic breast cancer but not enriched for age of diagnosis or family history of breast or other cancers.

Methods
Ethical Considerations

This study was approved by the Johns Hopkins University Institutional Review Board and adhered to the Declaration of Helsinki. Informed consent was obtained from all individuals who participated in the study.

Participants

Participants were 18 years or older. All patients of Johns Hopkins Sidney Kimmel Comprehensive Cancer Center and Johns Hopkins Sibley Memorial Hospital during the enrollment period who had a diagnosis of metastatic breast cancer and either 1) had no prior genetic testing or 2) had limited prior genetic testing (defined as a panel of <10 genes) that was negative, were invited to join the study. Participants were not selected for early age of onset or family history. 142 patients were informed of the study, and 100 patients were ultimately enrolled and completed the study. Of the 42 who were informed but did not complete the study, 14 patients were not interested in participating and 28 patients enrolled but did not complete the study because they were either lost to follow-up or passed away during the study. Participant demographics are shown in Table 2.

Data Collection

Patients were approached at the time of their regularly scheduled clinic visit and informed of the study. If patients were interested, consent was obtained. Diagnosis of metastatic breast cancer was confirmed histologically by a member of the study team who viewed the patient’s diagnostic pathology report, after obtaining consent from the patient to do so. A saliva sample was collected in test kits provided by Color Genomics and sent in for Clinical Laboratory Improvement Amendment (CLIA)-grade sequencing,
which is the standard of sequencing that must be used to diagnose or treat any disease or impairment of, or the assessment of health of, human beings. No follow up was performed, unless the patient chose to opt-in to receiving sequencing results or chose to opt-in to receiving genetic counseling. Both genetic testing and genetic counseling were provided to participants free of charge.

Due to clinician time restraints, it was not always possible to consent and collect saliva from individuals during regularly scheduled clinic visits. In these cases, after a patient expressed interest in the study when informed during a regularly scheduled clinic visit, a member of the study team contacted the patient via telephone at a later time to obtain consent as approved by the IRB protocol. A saliva collection kit was then mailed to the patient, who provided a saliva sample and mailed the test kit back.

Data Analysis

CLIA-grade sequencing was performed by Color Genomics. Reports provided by Color Genomics indicated whether a patient had no mutations, a variant of unknown significance (VUS), or a pathogenic mutation.

Results

Of 100 total individuals, 11 (11%) were found to have a pathogenic mutation, three (3%) were found to have a “likely pathogenic” mutation, and 20 (20%) were found to have a VUS. A summary of the pathogenic mutations, likely pathogenic mutations, and VUS identified are shown in Table 3. Notably, 5/11 (45%) of pathogenic mutations identified were in the BRCA2 gene.
**Discussion**

We observed a higher rate of pathogenic germline mutations in known cancer susceptibility genes in patients with metastatic breast cancer than what might have been previously expected. Current guidelines for genetic testing in breast cancer recommend using personal health history, family history, age of onset, and other parameters outlined in the National Comprehensive Cancer Network (NCCN) guidelines (Anderson et al., 2017) to identify individuals most likely to benefit from genetic testing (Nelson et al., 2013). However, results of this study indicate that if these current guidelines are followed to determine the appropriateness of genetic testing, pathogenic mutations in cancer susceptibility genes, some of which are therapeutically targetable, will be missed. Additionally, at-risk relatives may also miss opportunities to partake in cancer screening and prevention strategies.

While the potential to benefit those with actionable gene mutations might seem to justify performing germline testing on all patients with metastatic breast cancer, it is important to note that doing so would present challenges. Genetic testing has the potential to cause adverse events when performed without adequate counseling, and therefore most experts recommend individuals receive genetic counseling before genetic testing is performed (Kinney et al., 2014). However, there is currently a shortage of genetic counselors to provide these services (Armstrong et al., 2015). One solution is for nurses trained in genetic counseling to provide this service (Percival et al., 2016). Another challenge is that some patients do not have access to genetic counselors due to distance, which includes time away from work and family, travel time, expense, and the stress of navigating an
urban environment. One solution to reduce barriers to accessing genetic counselors, or other clinicians providing genetic counseling services, is to utilize telemedicine (Hilgart, Hayward, Coles, and Iredale, 2012).

Study Limitations

First, this study utilized a panel of 30 genes and therefore we were not able to identify all pathogenic germline mutations in known cancer predisposition genes. Second, family history was self-reported and obtained from the medical record. Third, we were not able to determine if detecting these mutations resulted in clinical benefit to patients or their family members. Additionally, more data are needed to determine what genes are of highest priority when performing germline testing on individuals diagnosed with metastatic breast cancer.

Conclusions

We observed a higher rate of pathogenic germline mutations in known cancer susceptibility genes in patients with metastatic breast cancer who were not selected for early age of onset or family history of breast or other cancers than what might have been previously expected. Routine germline testing of patients with metastatic breast cancer may be clinically beneficial to patients and their family members.

References


Table 5.1

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<td>BRCA1</td>
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Table 5.2
Participant Demographics

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<td>Females</td>
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Table 5.3 Mutations Identified
### Pathogenic Mutations

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<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Description</th>
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<tbody>
<tr>
<td>APC</td>
<td>c.3920T&gt;A</td>
<td>(p.Ile1307Lys)</td>
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<td>APC</td>
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<td>ATM</td>
<td>c.6404_6405insTT</td>
<td>(p.Arg2136*)</td>
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<tr>
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<td>c.688delAG</td>
<td>(p.Glu23Valfs*17)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>c.1813dupA</td>
<td>(p.Ile605Asnfs*11)</td>
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<td>(p.Arg643Glufs*15)</td>
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<td>c.5576_5579delTTAA</td>
<td>(p.Ile1859Lysfs*3)</td>
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<td>BRCA2</td>
<td>c.6450dup</td>
<td>(p.Val2151Serfs*25)</td>
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<td>c.7681C&gt;T</td>
<td>(p.Gln2561*)</td>
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<td>BRIP1</td>
<td>c.1429del</td>
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<td>CHEK2</td>
<td>c.4707T&gt;C</td>
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### Likely Pathogenic

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<th>Gene</th>
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<tr>
<td>APC</td>
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### VUS

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<td>(p.Arg2161His)</td>
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<td>ATM</td>
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<td>(p.Thr2921Lys)</td>
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<td>BAP1</td>
<td>c.1217A&gt;T</td>
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<td>(p.Gly1371Arg)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>c.388G&gt;A</td>
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Table 5.4 Mutations Identified by Participant Age

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<th>VUS Participant Ages</th>
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Chapter 6: Conclusions

In the first study, we identified the importance to research participants of 1) autonomy in individuals’ decisions about whether and when to be tested, 2) a formal protocol, and 3) returning medically actionable secondary findings. We also identified opposition to physician ordering, DTC testing for HD, and returning secondary findings of an HD expanded allele. Additionally, we found that many people do not interpret genetic test results in the way one would expect. In the case of HD, an expected change is a perception of decreased risk after a normal repeat result, or a perception of increased risk perception after an expanded repeat result. Finally, with regard to communicating genetic risk information to children, we identified a discrepancy in the amount of information children want and the amount of information parents are giving, a need for parents to take time to process their own result before communicating with children, and a need for additional resources on how to communicate with children about genetic risk information as well as child-specific resources on various genetic conditions.

In the second study, we found the prevalence of pathogenic germline mutations in known cancer predisposition genes in women with metastatic breast cancer to be much higher than the prevalence of such mutations in the general population. This data supports germline testing in cases of metastatic breast cancer and potentially other metastatic cancers as well. It also suggests that these pathogenic germline mutations in known cancer predisposition genes may be associated with more treatment-resistant forms of disease.
In conclusion, genetic testing must be carefully considered in terms of its availability, testing protocol, and how to return incidental findings. Furthermore, because individuals do not always interpret genetic test results in the way one would expect, and risk perception is influenced by more than merely the results of genetic testing, more comprehensive patient education and more discussion with patients about how they are interpreting their risk may be necessary. Additionally, communication of genetic risk information could be improved through the development and availability of resources on how to communicate genetic risk information to children and designated time in medical genetics appointments focused on educating parents on best practices in communicating genetic risk information to children. Finally, performing germline sequencing in the setting of metastatic breast cancer may improve outcomes for patients and their family members by identifying possible targeted therapies for patients and allowing family members who may benefit from genetic testing and/or preventative screening to be identified. These findings are important for patients who are considering or have already received genetic testing, as well as genetic counselors, healthcare providers, policy makers, and parents.
Genetic Counselor Interview Guide

1) Can you tell me a bit about the kind of counseling you generally do, and what sort of institution you work at?
   a) How long have you been there?
   b) How long have you been a GC?

2) We are particularly interested in how families with known genetic disease risk talk with their children about that risk. Do you have experience counseling families with children who are at risk?

3) How often do parents ask you for advice on how to share genetic information like this with their children?
   a) Can you tell me a bit about these experiences?
      i) Are there similarities among the families who generally ask you for advice like this?
         (1) For example, are these requests more common from families with certain types of genetic conditions than others?
         (2) Is it more common for parents to ask you when their children are of a certain age?
   b) Do you ever hear how the disclosure went?
      [If yes]
      i) Can you tell me a bit about that?
ii) Do you know how the parents shared the information or how the child reacted?

4) Has a parent ever asked you to disclose genetic risk information directly to their child(ren)? [If yes, proceed to questions below.]
   a) How often do parents ask you to have that conversation?
   b) Can you tell me a bit about these experiences?
      i) Are there similarities among the families that generally ask you to do the disclosure?
         (1) For example, are these requests more common from families with certain types of genetic conditions than others?
         (2) Is it more common for parents to ask you when their children are of a certain age?
   c) When you are the one disclosing information to the child, how do those conversations go?
      i) What do you say?
      ii) How does the child generally react?
      iii) Is the parent always in the room? If so, how does s/he generally react?

5) In an ideal world, how do you think this information should be shared with children, if you think it should be shared?
   a) When should information be shared?
b) What information should be shared?

c) How should information be shared? (all at once, gradually, by parent, by professional)

6) Are there things you or families can do to make this process go better?

7) Are there ways of doing this that you’ve seen generally don’t work, or tend to go badly?

8) Do you have any sense of whether the genetic information parents tell their children is mostly accurate?

9) What are the pros and cons of disclosing information about genetic risk to children?

10) [If they are generally pro-disclosure] Are there any situations where you think it’s better not to share this kind of information with kids?

11) Do you think children are generally able to understand the genetic information they’re getting?

12) In this last section, we’d like to ask a few more questions about existing resources on disclosing genetic risk information to children.
13) I know that the ACMG has a set of guidelines – are there any other materials that you refer to?

14) Are these materials helpful to you? If so, how? If no, why not?

15) Is there any information or resource about disclosing genetic risk information to kids that is not currently available and would be helpful to you in practice?

16) Do you have any sense of how others in the field are approaching these situations?

17) As you know, we are also conducting interviews with adolescents ages 15-17 and their parents about genetic risk information. Are there any questions that you would want to ask these folks?

18) Any other thoughts/comments about whether, when, and how to disclose genetic risk information to adolescent children.

Child Interview Guide

1) Can you tell me a bit about when you first learned about HD/HC?
   a) How old were you?
   b) How did you find out?
   c) Who told you?
   d) What did they say?
e) How did you react?

2) How much did you know about HD/HC when [X told you about the family risk]?

3) [If learned before parents disclosed info] When did your parent(s) first talk to you about [your family’s risk of X]?
   a) What did they tell you?

4) Did your parents talk to you about it just once, a few, or a bunch of times?

5) When your parents talked to you about it, what location were you in? Were you at home, in the car, at the doctor, or somewhere else?

6) Did a doctor, genetic counselor, or other health professional ever talk to you about it?

7) Did you ever talk to friends about it?
   [If yes]
   a) Did you find that your friends were understanding and supportive?
   b) Were any of your friends familiar with [disease X] or had any of them had experience with [disease X] in their families?

8) When you were learning about genetic information was there a book or website that was helpful to you?
9) When you were learning about genetic information did you consult google or a different internet search engine?

   [If yes]
   a) Did you find the internet helpful, or do you regret using the internet?

10) In general, would you say your family talks a lot about feelings and emotions, or tends to keep things to themselves?

11) Do your parents typically include you in decisions about health matters?

12) Do your parents let you talk to your doctor alone?

13) In general, are you happy your parents talked to you about [your family’s risk of X]?

14) Do you feel like you got all the information you needed to understand your family’s risk?

   [If no]
   a) What information would be helpful for you?

15) Do you think parents in other families with the same kind of risks should talk to their kids about it?
16) Do you have any advice for other parents about how they should talk to their kids about genetic information?
   
a) What kinds of things should parents say and not say?
   
b) Should parents talk about it once, a few times, or a bunch of times?

17) Do you have any advice for parents about when to start having these conversations?

18) Do you think genetic counselors and/or other health professionals should help parents talk to kids about genetic risk info?

19) Do you have any advice for other kids who are just learning this kind of information?

20) Do you think it would be helpful to talk with other kids who are in similar situations?

21) Can you think of anything your parents did really well when they talked to you about genetic risk info?
   
a) Do you think they talked to you at the right time?
   
b) Did the way [X] explained things to you make sense at the time?

22) Can you think of anything your parents could have done better when they talked to you about genetic risk info?
23) Is there anything else you think we should know about your experience with learning about [your family’s risk of X]?

**Parent Interview Guide**

1) Do you remember when you learned that you were at-risk for HD/HC?
   a) How did you find out?
   b) Who told you?

2) [For HD]: Have you been diagnosed with HD? [If yes]: When were you first diagnosed?
   a) Have you been tested and found to have the expanded repeat?
   b) Have you been clinically diagnosed?

3) Did anyone talk to you about how HD is passed on in families?

4) [For HC]: When were you first diagnosed with hereditary cancer?
   a) Did you have genetic testing?
   b) Did anyone talk to you about how [X cancer] is passed on in families?

5) How many kids do you have?

6) How old are they?
7) [Do math of when tested/diagnosed and how old kids are. If the timing is close]: Did you have your children before or after receiving your diagnoses?
   a) Are all of your children genetically related to you?

8) Can you tell me a bit about how you shared information about [disease X] with your kids?
   a) How old were they when you told them?
   b) What information did you give them?
   c) Was it something that came up once, or did it come up several times over months or years?
   d) Was a genetic counselor or another health professional involved?

9) How did your child(ren) react?
   a) Did they seem to understand?
   b) Did they ask a lot of questions?
   c) Did they tell you how they felt about the family risk?

10) In general, would you say your family talks a lot about feelings, emotions, and challenges, or do they tend to keep things more to themselves?

11) In general, are you happy you decided to talk with your child(ren) about [your family’s risk of X]?
12) Do you think other parents should talk to their kids about genetic risk in the family?

13) Do you have any advice for other parents about how to talk to their kids about genetic information?

14) Do you have any advice for parents about when they should start having these conversations? How old should kids be when they first learn?

15) Do you think genetic counselors and/or other health professionals can and should help parents talk to kids about genetic risk information?

16) What do you think went well when you talked to your kids about [your family’s risk of X]?
   a) Do you think you talked to your kids at the right time?
   b) Do you think you explained the information well?
   c) Were there any challenges?

17) Do you feel like you had the resources you needed to help you have that conversation/those conversations?
   [If yes]
   a) What resources were helpful?
   [If no]
b) What resources would have been helpful?

18) If you could go back and do it all over again, is there anything you would do differently?

19) Did you feel like there were genetic counselors and/or other health professionals available to help you talk to your kids about genetic risk information?

20) Is there anything else you think we should know about your experience with talking to kids about genetic risk information?
Curriculum Vitae

Born
St. Joseph’s Hospital, Marshfield, WI
June 11, 1994

Education
Johns Hopkins School of Medicine, Baltimore, MD
Ph.D. Program, Human Genetics – June 2015-present

University of Wisconsin Eau Claire, Eau Claire, WI
Bachelor of Science in Biology, Chemistry Minor
GPA: 3.8 – 2011-2015

Experience
6/15 – present
Doctoral Degree Candidate
Johns Hopkins School of Medicine, Baltimore, MD

Genetic Risk: Whether, When, and How to Tell Adolescents
Authored administrative supplement and conducted research, under the guidance of Dr. Debra Mathews, designed to improve understanding of communicating genetic risk information to adolescents (R01HG008045-04S, PI: Dr. Debra Mathews)
Families At Risk: Long-term Impact of Huntington’s Presymptomatic Genetic Testing

Collected and analyzed data for study designed to improve understanding of the impact of presymptomatic genetic testing for Huntington’s disease on families over time

(R01HG008045, PI: Dr. Debra Mathews)

Prevalence of Germline Mutations in Individuals with Recurrent Metastatic Breast Cancer

Designed and conducted research under the guidance of Dr. Ben Ho Park (PI: Dr. Ben Ho Park)

9/18
Teaching Assistant

Johns Hopkins School of Medicine, Baltimore, MD

Pathobiology Graduate Course, Supervisor: Kathy Gabrielson

7/18
Course Instructor

Johns Hopkins School of Medicine, Baltimore, MD

Miracles of Modern Medicine Summer Course, Supervisor: Yuejin Li

Designed and conducted lectures for gifted high school students on CRISPR/Cas9, assisted reproductive
technology, and related ethical, legal, and social issues associated with both technologies

11/17 – 2/18 **Teaching Assistant**

*Johns Hopkins School of Medicine, Baltimore, MD*

Bioinformatics Graduate Course, Supervisor: Sarah Wheelan

1/15 – 5/15 **Teaching Assistant**

*University of Wisconsin Eau Claire, Eau Claire, WI*

Chemistry 104, Supervisor: Roslyn Theisen

9/13 – 5/15 **Independent Study Research Assistant**

*University of Wisconsin Eau Claire, Eau Claire, WI*

*Mayo Clinic Health Systems, Eau Claire, WI*

Advisors: Dr. Julie Anderson & Dr. Edgar Hicks

Designed and conducted an independent research study on the incidence of *Propionibacterium acnes* infections in rotator cuff repair surgeries and the course of antibiotics associated with the lowest infection rates

9/14 – 12/14 **Research Assistant**
University of Wisconsin Eau Claire, Eau Claire, WI

Department of Biology, Advisor: Dr. Dan Janik

Assisted in a study which investigated the effects of circadian rhythm disruption on organ weights in mice

9/12 – 5/15 Tutor

University of Wisconsin Eau Claire, Eau Claire, WI

Tutored undergraduates in sciences

Honors and Awards

- Administrative Supplement Grant Support (R01HG008045-04S1), 2017-present
- First Prize Annual Maryland Genetics, Epidemiology, & Medicine Poster Competition, 2017
- University of Wisconsin Eau Claire Dean’s List, 2011-2015
- University of Wisconsin Eau Claire Honors Student, 2012-2015
- Peterson Scholarship, 2012-2015
- Ralph Duxbury Scholarship, 2014-2015
- David and Alice Katz Scholarship, 2013-14

Professional Society Memberships

- American Society of Human Genetics, 2016-present

Presentations
March 2018 – Presentation
Johns Hopkins Institute of Genetic Medicine Journal Club – Baltimore, MD
Metaphase II Oocytes from Human Unilaminar Follicles Grown in a Multi-step Culture System

February 2018 – Poster
Maryland Genetics, Epidemiology, and Medicine Research Day – Baltimore, MD
Risk Perception Before and After Presymptomatic Testing for Huntington’s Disease:
Not Always What One Might Expect

September 2017 – Presentation
Johns Hopkins Institute of Genetic Medicine – Baltimore, MD
Genetic Risk: Whether, When, and How to Tell Adolescents

February 2017 – Poster
Maryland Genetics, Epidemiology, and Medicine Research Day – Baltimore, MD
Perspectives on Genetic Testing and Return of Results from the First Cohort of Presymptomatically Tested Individuals At-Risk for Huntington’s Disease

October 2016 – Poster
American Society of Human Genetics Annual Meeting – Vancouver, BC
Perspectives on Genetic Testing and Return of Results from the First Cohort of Presymptomatically Tested Individuals At-Risk for Huntington’s Disease
September 2016 – Presentation

Johns Hopkins Institute of Genetic Medicine – Baltimore, MD

_Germline vs. Somatic Mutations in Breast Cancer: A Case Study_

January 2016 – Presentation

Johns Hopkins Institute of Genetic Medicine – Baltimore, MD

_Ethical Issues Related to Genetic Testing_

Publications


