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Perspectives on Genetic Testing and Return of Results from the First Cohort of Presymptomatically Tested Individuals At-Risk for Huntington Disease

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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 for HD, whether a formal HD testing protocol is necessary, whether physician ordering for HD 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 HD testing, use of a formal HD testing protocol, and returning medically actionable secondary findings. However, the majority of participants were opposed not only to physician

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Conflict of Interest

KM Stuttgen, JM Bollinger, RL Dvoskin, A McCague, B Shpritz, J Brandt, and DJH Mathews declare that they have no conflicts of interest.

Human studies and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2000 (5). Informed consent was obtained from all participants included in the study.

Animal Studies

No animal studies were carried out by the authors for this article.

Author Contributions

KM Stuttgen, JM Bollinger, RL Dvoskin, A McCague, B Shpritz, and DJH Mathews made substantial contributions to the acquisition, analysis, and interpretation of this work. KM Stuttgen, JM Bollinger, RL Dvoskin, A McCague, B Shpritz, and DJH Mathews were involved in drafting the work and revising it critically for important intellectual content as well as final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved.

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.

Keywords

Genetic testing; Huntington's disease; Direct-to-Consumer Testing; Incidental Findings; Qualitative Research

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 for HD, 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 for HD 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 implications of the test 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 presymptomatic 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 studies exist that evaluate opinions of a cohort decades after testing rather than years (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 for HD, whether a formal HD testing protocol is necessary, whether a physician ordering an HD test in the absence of a formal HD 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 separate paper on this cohort.

Methods

Participant Eligibility and Recruitment

This study was approved by the Johns Hopkins University Institutional Review Board. To be eligible for this study, individuals must have been enrolled in the JH HD presymptomatic testing protocol between 1986–1998. A total of 278 individuals enrolled in the protocol during this time. Of these 278 individuals, 72 dropped out before the disclosure of test results. Of the remaining 206 individuals, 76 were found in the JH HD 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>) and Facebook; second, direct recruitment using last known address. Through indirect recruitment, six individuals demonstrated interest and four were eligible. Two individuals were not eligible because they were not enrolled in the JH HD presymptomatic testing protocol from 1986–1998. The four individuals who were eligible all had normal repeats and were interviewed. Through direct recruitment, 101 letters were sent out, and 60 responses were returned. Fifty-five of the responses received from direct recruitment 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. Twelve individuals were willing to participate but not interviewed due to an over-abundance of individuals with normal repeats or because they were lost to follow-up.

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. Our goal was to conduct interviews in person, if at all possible. Over half of the interviews were conducted in person, however, if it was not possible to travel to participants, interviews were conducted via video call. In a few cases of technical difficulties with video calls, interviews were conducted via telephone. 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' HD 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 were 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

Ultimately, 39 individuals were interviewed for the current study. Of these 39 participants, 15 were found in the JH HD 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 (SD: 6.9). Of those in our study with expanded repeats, the majority (9/15) had been clinically diagnosed with HD at the time of the interview. 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 for HD 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 for HD 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 HD 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 HD testing protocol. Only one participant believed that a formal HD testing 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].

(Male, Expanded Repeat)

“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.”

(Female, Normal Repeat)

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 HD testing 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 for HD testing 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].”

(Female, Expanded Repeat)

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.”

(Female, Normal Repeat)

“No! You should be going through a program where they prepare you for everything.”

(Female, Expanded Repeat)

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 for HD 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 tics, 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 HD testing protocol than individuals with expanded repeats. Second, more men than women felt that while a formal HD testing protocol should be encouraged, participation in such a protocol should be up to the patient, though due to the sex imbalance between those with expanded and normal repeats 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 fields of medical genetics and genetic counseling. 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 performed 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 him/herself whether and when to pursue HD 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 HD protocol should be required and physician ordering for HD without such a protocol is unacceptable, some participants felt the decision to go through a formal HD protocol and have a physician order the HD 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 presymptomatic HD 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 presymptomatic HD 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 presymptomatic 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., 2015; Trondsen, Boole, Stensland, & Tjora, 2014). 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 HD testing protocol should be required and that both physician ordering for HD and DTC HD testing are unacceptable. These beliefs are in line with both presymptomatic 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 finding that a majority of participants believe a formal HD testing protocol should be required is concordant with those of a Canadian study (Dufranse et al., 2011) which obtained opinions from individuals who had participated in an HD presymptomatic testing protocol. Findings by Dufranse (2011) showed that 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. Unlike the Dufranse (2011) study, we not only asked our cohort for opinions on a formal HD testing protocol but also about other domains, including the importance of autonomy in the decision to be tested for HD, physician ordering for HD in the absence of a formal protocol, DTC testing for HD, and the return of incidental/secondary findings.

The opinions obtained in this study are well-informed, as these individuals have received HD 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 more women with normal repeats, and conversely, more men with expanded repeats responded to our recruitment efforts and therefore our sample is imbalanced with respect to gender.

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.

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Figure 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

Figure 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?

Table I.**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.	<p>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.</p> <p>a. Should the doctor tell the patient that s/he is positive for HD?</p> <p>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?</p>

Table II.

Sample Characteristics

	Expanded Repeat (n=15)	Normal Repeat (n=21)	Undisclosed (n=3)	Total (n=39)
Women--N (%)	4 (26.7)	13 (61.9)	3 (100.0)	20 (51.3)
Men--N (%)	11 (73.3)	8 (38.1)	0 (0.0)	19 (48.7)