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Hereditary Dementias

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The Psychosocial Effects of Next Generation Sequence Panels for Predictive Testing of Hereditary Dementias

Dina Green

Abstract

The current standard of care in offering predictive genetic testing for neurodegenerative diseases is that individuals wishing to have testing must have a known family mutation or well-documented family history of a specific disease. This model denies testing to individuals in families where the phenotype of the disease is less clear. However, NGS panel testing for many genes with overlapping phenotypes helps alleviate both the cost and tedious nature of a genetic "fishing expedition." Panel testing increases the risk of receiving variants of unknown significance and, therefore, uncertainty. The goal of this research study is to examine the psychological impact of predictive testing of neurodegenerative disease using NGS panels. **Methods:** This pilot study looked at 15 at-risk participants with a family mutation and 8 without a known family mutation. Participants were evaluated serially: before testing, at 1 month and at 6 months after receiving results. Instruments measuring levels of anxiety, depression, ability to deal with uncertainty, coping strategies, perceived personal control, and rumination were used to evaluate the psychological impact of testing on the 2 groups. **Results:** No significant differences were found between the two groups. A noted trend was an increase in uncertainty after testing among those with a known mutation and a small decrease among those without a known mutation. Statistical significance was not observed due to small number of participants. Initial data suggest that predictive testing for neurodegenerative disease in individuals with a family history does not result in psychological distress. The study is ongoing.

Key Words: Genetic Counseling, adult neurogenetics, dementia, predictive testing, asymptomatic

Introduction

The current standard of care for predictive genetic testing for neurodegenerative diseases requires that healthy individuals seeking testing must have a known family mutation or well-documented family history of a specific disease, preferably one that includes autopsy results. This standard means that upon testing a definitive answer can be obtained for the patient. If, however, the phenotype of the disease running in the family is less clear, a series of genetic tests may be necessary to rule out related diseases. (Goldman, 2012) In this case, there is a higher likelihood of receiving both variants of unknown significance (VUS) and false negatives. Panel testing for many genes with overlapping phenotypes can help alleviate both the cost and the tedious nature of a genetic 'fishing expedition'. The limitations to panel testing include the inability to detect repeat disorder and in some labs, duplications, and deletions. (Beck, 2014)

The chance of receiving a VUS increases with the number of genes tested. Many times, the affected family member cannot be tested to identify a mutation, which can leave an at-risk patient who wants testing with limited options. The rise of panel testing and the existence of a proven protocol for the testing of single-gene disorders such as Huntington's disease (HD) raises questions about whether it is still ethical to deny these patients testing. The HD protocol provides a theoretical framework that could serve to help the patient cope with the consequences of testing for severe neurodegenerative disorders when there are no known treatments. A similar protocol could be applied to panel testing and provide informed consent to patients, including information on potential results. There is currently an absence of research examining the use of panels for predictive testing for neurodegenerative diseases.

The HD Protocol as a Model

Due to the life-altering nature and psycho-social implications of testing results, testing for HD includes a multi-step process which is highly recommended for all patients. HD is a progressive neurodegenerative disease with the average onset occurring in the 30-50's. The disease typically begins with a movement disorder and psychiatric symptoms and progresses into dementia and severe neurodegeneration. The disease is caused by a trinucleotide repeat in the *HTT* gene. The expansion is inherited in an autosomal dominant manner and is nearly fully penetrant. Therefore, genetic testing is predictive to a degree that is rare amongst hereditary dementias.

Guidelines for HD testing were first established in 1994 and were updated in 2013. (MacLeod, *et al.*) The process includes: genetic counseling, a psychiatric evaluation, a neurological evaluation, and post-results counseling. The patient is asked to bring a support person to the initial genetic counseling consultation and to the results session. The goal of the process is to ensure that those seeking testing are psychologically equipped to handle the result, that they are informed, and that they have appropriate reasons for testing (i.e. have a relevant family history). Those seeking testing are given the tools to contemplate the ramifications of testing, including the potential implications for loved ones. Anxiety can be present in all cases, even when a negative result is received. (Williams , Erwin, & Juhl, 2010) Some patients from HD families have been shown to experience "survivor's guilt" upon receiving a negative test result. (Hayden & Bombard, 2005) The protocol has largely been found to be successful. (Almqvist, *et al.,* 2003; Dufranse, *et al.,* 2011; Timman, *et al.,* 2004) The HD protocol is recommended for presymptomatic testing for other neurodegenerative diseases as well. A past history of depression or anxiety may signal the need for additional

counseling or referral to a mental health professional. (Reichelt, *et al.,* 2004) It is considered essential for patients seeking presymtomatic testing for conditions such as Alzheimer's disease (AD) and Frontotemporal Degradation (FTD) to receive formal counseling, time and support when making the decision to test. (Loy, *et al.,*2013)

Testing for Hereditary Dementias

Recent gene discoveries and advances in technology are contributing to rapid changes in genetic testing for dementias. The present state of testing is complicated by the variability and overlapping expression of diseases. Genetic testing has the ability to accurately predict a patient's lifetime risk for HD and a limited number of other neurological conditions. This accuracy is rarely available for the majority of dementias. AD and FTD are two of the most common dementias. Each is a prime example of variable and overlapping expressivity with regard to other dementias, and for each condition multiple genes may be implicated by the phenotype.

PSEN1, PSEN2, and *APP* are the only known autosomal dominant AD genes (Goldman, 2012). It is rare that insurance will cover diagnostic testing for dementias and it is even more uncommon that they will cover the cost for predictive testing. (Goldman, 2012; Green and Botkin, 2003) These three genes exist as a panel at a cost of range of several thousand to several hundred dollars. The price then increases with any additional reflex testing. Furthermore, a number of other factors must be considered before testing, including the effect testing will have on other family members, the proband's capacity to consent, and the effect of testing on insurance for unaffected individuals.

A detailed family history spanning three generations is required prior to testing. (Goldman, 2012; Loy, *et al.,* 2013) Sometimes when obtaining a family history, there is a lack of information secondary to adoption, loss of contact with relatives, deceased relatives, misdiagnosis, misinterpretation of medical information, or a lack of discussion about medical issues within the family. (Snider & Buckles, 2013) For these reasons, individuals with a negative family history should still be considered for genetic testing in some circumstances. (Goldman, 2005; 2012) Genetic testing would not change the course of treatment for a condition such as AD, but could confirm or suggest that a patient might be affected from an alternate form of dementia. This could inform relatives of a genetic risk and enable the proband to participate in research studies. (Snowden, Rollinson, & Thompson, 2012)

Unlike other genetic testing clinics, relatives seeking predictive testing are almost entirely self-referred. As opposed to following the recommendation and order of a physician, the request for genetic testing is personally motivated. These individuals come in to identify and understand the possible contribution of genetic factors for a disease that appears to be part of their family history. NGS panels are able to cast a wider net per test for the avid information seeker. These patients are typically unaware of what distinguishes a genetic pattern for particular genes or the potential risks of testing— including chances for a VUS or inconclusive results. Still they are assumed to be vigilant and motivated to find an answer as they are self-referred and therefore, have demonstrated that drive. (Christensen, *et al.,* 2015)

Reasons for Predictive Testing

Since dementias are typically progressive and currently have few treatments, management and long-term care planning can be beneficial. (Hayden & Bombard, 2005) While any genetic testing may produce stress for an individual, testing for diseases with no

reliable preventive path or current cure can be especially psychologically complex. Research suggests that anxiety levels can be mitigated with proper protocols, such as seen with HD. (Garguilo, Lejeune, & Tanguy, 2009)

Another cited reason for seeking presymptomatic testing is to alleviate uncertainty. Assuming the anxiety experienced by an individual seeking genetic testing is, to their mind, worse than the potential anxiety occasioned by a positive or uncertain result, is it ethical to deny testing? Unexpected adverse events such as depression may follow a positive or uncertain result. While there is not, to date, a definitive answer on the balance of these risks, experts have pointed out that the risks are exacerbated when testing for dementias which are not preventable. (Molinuevo, et al., 2005) By way of comparison, most adult-onset cancer syndromes are associated with screening protocols and prophylactic measures. (Frost, *et al.*, 2004)

Family members' genetic testing results have also been identified as a predictor of psychological distress after testing. Post-test distress is highest when results differ between siblings, such as when one is a non-carrier and one is found to have BRCA1/2 mutation. (Loader, *et al.,* 2001) Experience of a loss is another indicator of psychological distress post-testing. Having a relative who died from breast or ovarian cancer causes many to perceive genetic testing as highly significant and reliable. (Thewes *et al.,* 2003) Another study reported that being a member of a high-risk family was perceived as being more upsetting than the anticipation of receiving the result of genetic testing. (Coyne *et al.,* 2003) Studies looking at the psychological effects of presymptomatic testing for HD have followed patients at varying ages over 6 months to 10 years. Each found a rate of approximately 17% of

patients experiencing adverse effects. These were predominately depression and psychological distress. (Lawson, et al., 1996)

Approximately 6-8% of the general population has received genetic testing. (Blendon, Gorski, & Benson, 2016) A 2013 article by Henneman, *et al.* discusses an increase in awareness of genetic testing between the years 1990 and 2004, but suggests that it did not significantly increase between 2002 and 2010. The 2010 Wilde, *et al.* study showed positive attitudes toward genetic testing, mainly among those who have family histories of disease. In 2001, Neumann et al. found that 79% of the general population in a telephone survey indicated that they were interested in predictive genetic testing for AD. Those who responded positively to this hypothetical decision cited the desire to spend time with family, sign advance directives, and purchase long-term care insurance if results were positive.

The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study was designed to assess the impact of susceptibility testing on asymptomatic adult children of AD patients. (Roberts, *et al*, 2003) The strongest predictor of actual testing in this study was the pretest statement of desire to prepare one's family for the possibility of developing AD. Findings also support prior research showing participants citing altruistic motivation for proceeding with genetic testing research. (Geller, *et al*, 1999) In this setting, it has been noted, kin altruism might be the more relevant term. (Batson, 1991) The motivation to increase the welfare of immediate family members clearly plays a part in the decision. It is also of interest to note that a small number of participants cited the use of genetic testing to plan for suicide if results were positive. Follow-up with this group suggested that each was only considering suicide as a viable alternative once they became symptomatic. Risk of suicide has played a more significant role in follow-up after genetic testing programs for

Huntington's Disease. (Almqvist et al., 1999) It should be noted that a predominant motive for choosing predictive HD testing remains to be a means to reduce ambiguity for the individual and his or her children as well as the ability to plan for long-term care. (Duisterhof, Trijsburg, Niermeijer, & Roos, 2001; Garguilo, Lejeune, & Tanguy, 2009)

Impact of Testing

Research studying the impact of predictive genetic testing for late-onset conditions on individuals is limited and has mainly focused on cancer and HD. The cancer studies focus on the clinical utility of the testing; that experience is notably different from dementia testing in that dementias are not currently preventable. Fewer studies have been published on genetic testing results associated with uncertain significance or results that were inconclusive. Frost *et al.* (2004) found women who received unclear variant information often expressed frustration and may have misinterpreted the results. Such a scenario highlights the importance of pre-testing counseling regarding the possibility of uncertain results. Croyle *et al.* (1995) determined that individuals with a high need for certainty may be particularly at risk for psychological distress when faced with uncertain, inconclusive, or delayed results.

Psychological impact of genetic testing is associated more closely with pre-test distress than testing results. (Reichelt *et al.,* 2004) Many researchers suggest that because of the documented relationship between pre- and post-test anxiety, clinicians should identify those individuals with high levels of distress through formal assessment prior to genetic testing.

Next Generation Sequencing

Next Generation Sequencing (NGS) has revolutionized predictive and diagnostic medicine with the ability to sequence individual genes or the entire genome. NGS tests have

been less effective at identifying deletions and duplications, however, labs are beginning to incorporate this option as part of NGS testing. Recent years have provided not only a remarkable improvement in sequencing technologies and capabilities, but also a reduction in the cost of testing. Based on information provided by the National Human Genome Research Institute at the NIH, the cost of sequencing a genome has fallen from approximately $500 million to map the first human genome to approximately $1000. Further reductions can be expected in coming years as new platforms are brought to market. With lower costs on the horizon, genetic testing will be available to a wider range of the population.

While there is a high potential efficacy of an NGS panel for hereditary dementias, this technology has been limited in its detection abilities. The inability to detect repeat mutations is particularly relevant, given their importance in this subset of genetic diseases. A separate test would need to be performed to pick up such mutations. Additionally, variants of unknown significance (VUS) remain a major limitation of NGS. The inconclusive result has the potential to leave the patient with more uncertainty than prior to testing, which they may wrongly interpret as positive or negative.

The psychological impact of predictive Next Generation Sequencing panel testing for hereditary neurodegenerative disease on both affected and unaffected patients requires more study. Identifying the psychological side effects and attitudes will aid in the development of future protocols and may lead to normalization of dementia panels, and potentially easing accessibility for patients who desire the information.

Unaffected patients are uniquely susceptible to a negative psychological impact resulting from genetic testing. While many initially describe the uncertainty of knowing whether they will develop the disease as being worse than a definitive positive response, they

cannot predict response to unknown outcomes. (Molinuevo, et al., 2005) They are often

unaware of the potential of a VUS, or rare secondary panel findings, or of how they will react

to receiving a positive result. (Semaka , Creighton, Warby , & Hayden, 2006) . Testing has

the potential to have profound negative effects on the patient. It remains unclear whether the

patient's psychological posture is weakened after testing.

Methods

  This study aims to document the psychological impact of panel testing for hereditary

dementia on unaffected patients. The protocol for this study was developed by Karen Marder,

MD and Jill Goldman, MPhil, MS, CGC of Columbia University Medical Center (CUMC).

The main study is ongoing and will look at 30 participants over 6 months post-genetic testing

results. This report functions as a pilot study covering a smaller sample over a shorter time

frame.

Participants

  Participants over the age of 18 were recruited and ascertained at CUMC via self-

referral for neurogenetic counseling. Participants were screened for candidacy over the phone

by the genetic counselor. Accepted participants were categorized as either Control (having a

known family mutation for a neurodegenerative disease), or Experimental (having a family

history for disease without a known family mutation).

Study Instruments

  The participants completed the following validated study instruments in the form of a

questionnaire packet: Patient Health Questionnaire (PHQ-9), Generalized Anxiety (GAD-7),

Brief COPE coping scale, Intolerance of Uncertainty (IUS), Modified Rumination-Reflection

Questionnaire (mRRQ), Perceived Personal Control (PPC), Decision Regret Scale (DRS),

Attitudes Toward Genetic Research and Testing (ATT), Genetic Knowledge Questions (KNOW), and a Demographics questionnaire. These questionnaires were administered prior to the testing and the initial genetic counseling session, 1 months after receiving results, and 6 months after receiving results. The DRS was only administered 1 month and 6 months after receiving results. For the purposes of this paper, the KNOW, ATT and 6 month questionnaires were not analyzed. This study is ongoing at CUMC and will be analyzed at a later point when more data is collected.

Six months after receiving results, patients were asked to participate in a semi-structured phone interview. Patients were asked to speak to their experience with genetic counseling and the presymptomatic testing protocol, the impact of the results, and the hypothetical situation in which the participant received the opposite result (Appendix).

Data Collection

Prior to the pre-test counseling appointment, informed consent and HIPAA forms were signed and then a questionnaire pack was completed by the participants. The genetic counseling session included a discussion of the symptoms, course, genetics, and the patient's experience of the disease, reasons for testing, potential results, impacts of potential results, and insurance concerns. Participants underwent a neuropsychiatric evaluation by the neurologist following the genetic counseling session. Genetic testing eligibility was determined by the genetic counselor, who recommended either panel testing or single-gene testing. Genetic test results were given in person by the genetic counselor. Participants were required to bring a support person to this appointment. One month after receiving results, questionnaire packs were completed by the participants. Pre- and post-test questionnaires were compared using one-tailed t-tests. Experimental and Control questionnaires were

compared. Analysis was performed using SPSS software. P values 0.05 or lower are considered significant.

The 6 month follow-up interviews were analyzed anecdotally due to the small sample size. This qualitative information was examined in the context of the observed qualitative trends.

Genetic Testing

All testing was performed at CUMC. The Control participants had targeted genetic testing for mutations previously identified in the family. The experimental group was tested using a custom panel determined by the genetic counselor. The Next Generation Sequencing panels were created from the following list of genes. Some but not all of these were included in every panel:

PSEN1, PSEN2, APP, SOD1, ANG, TARDBP, FUS, VCP, ALS2, DCTN1, VAPB, SETX, SMN1, UBQLN2, MAPT, GRN, CHMP2B, APOE, LRRK2, GBA, PARK2, PINK1, SNCA, UCHL1, PRNP

The panel also included repeat expansion mutation analysis in Intron 1 of *C9orf72* using PCR and Southern blot analysis.

IRB Approval

This study received approval from the CUMC Institutional Review Board (Approval on February 11, 2016; Reapproved on November 15, 2016) and from the Sarah Lawrence College Institutional Review Board (Approval on September 26, 2016).

Results

A total of 26 participants were recruited for the study by January 20, 2017; 15 were recruited for the control group and 8 for the experimental group. Table 1 lists the results for the demographic information collected. The pre-counseling questionnaires were sent to all individuals, of which 23 continued in the study. To date, the one-month follow-up questionnaires were sent to 11 participants., and10 participants participated in the 6 month follow-up interview.

The demographic information reflects a fair balance of gender and marriage status. Overall, the religious makeup of the participants is reflective of the New York Metropolitan area. Almost all participants who sought testing had completed a 4-year college. Over half of the participants had completed an advanced degree. Most participants were of Caucasian ethnicity.

One experimental and two control participants did not continue far enough into the study to receive the blood draw for the genetic testing. Both of the control participants were at risk for HD. They had completed the initial genetic counseling session and psychiatric evaluation. It was recommended by the psychiatrist that each see a therapist before receiving genetic testing. The experimental patient halted her participation in the research after the initial genetic counseling session out of respect for her husband's wishes to not pursue genetic testing for hereditary dementia. The data presented does not include information from the 3 participants who did not continue in the study. The data collected on the control group participants who withdrew contained outlier scores for anxiety. These two participants scored a 12 and 19 out of 21 (severe anxiety) for the pre-test GAD-7 (anxiety) scale versus the group average of 3.80. One of these participants had an outlying depression score at 17 out of

27 (severe depression) for the PHQ-9 compared to the group average of 4.33. The stopped experimental participant scored a 0 on both depression and anxiety scales.

Of the control group participants, 4 received a positive test result and three received a negative result. Of the experimental group, all participants have received negative results. In both groups, no VUS's were found.

All participants had a family history of a neurodegenerative disease. Each had an affected family member within two degrees of separation. There was no significant difference between groups in the number of affected family members.

To determine any difference in psychosocial effects between those with known family mutations and those without known family mutations, the pre and post testing scores were compared. First the pre and post testing scores were compared within each group and then between groups.

The control group was not found to have any statistically significant findings among the psychological measures (Table 2a). Chief among the descriptive findings for the control group were decreases in depression and increases in anxiety and uncertainty. Similarly, the experimental group had only one statistically significant finding (Table 2b): an observed decrease in the COPE Venting measure. On average, these participants were found to use venting as a coping mechanism significantly less after receiving test results. Of note, an increase in perceived control was observed as well as decreases in positive reframing and planning as coping mechanisms. The decreases in usage of coping mechanisms may be reflective of the negative testing results received by each participant of the group. Overall, there were few statistically significant pieces of evidence in either group, which reflects the small sample sizes.

The experimental and control groups were similar on all but two of the 19 dependent variables studied. The control group showed higher PPC scores both post and pre-test (Table 3, Table 4), suggesting a higher level of control prior to the genetic counseling session. An evaluation of the background knowledge of the participants may be informative of this result. A higher level of control may be indicative of knowing a family mutation and being familiar with the inheritance and other aspects of the genetics pertaining to the family condition. The change in uncertainty for those with a known mutation was much higher than those with an unknown. Further exploration may reveal that this difference in uncertainty is connected to the ambiguity of disease onset for those in the control group who received positive results. For the other 17 outcome variables, the scores of the control group and experimental group did not show significant differences. This may indicate that any changes observed between pre and 1 month post test testing could be a response to genetic counseling instead of pre-existing differences between the two groups. Alternatively, any observed changes and reactions may reflect the varied personal experiences and context of each participant.

Six Month Follow-Up Interviews

A six month follow-up was conducted. The eleven interviews included five subjects from the experimental group and six from the control group. There was consensus from all that that they did not regret the decision to test, nor would they have changed how each went about the process. One positive HD participant noted that a decision to wait longer may have been preferable. There remained a positive impression of genetic counseling and the presymptomatic process. Some were unhappy with the lack of patient autonomy inherent in the process imposed by the protocol as well as the length of time from beginning the protocol until receiving results. While some participants spoke of the psychiatric evaluation favorably,

others did not find this part of the process necessary. A few reported being "treated like a patient" during this experience despite not being symptomatic.

These interviews revealed a variety of reasons for testing. Planning for the future was an umbrella theme that included concern for securing the appropriate insurance and care, time management, especially as it relates to balancing family and work, financial considerations, and "buying that beach house," as one participant noted. Cited less often as a reason for testing was the ability to know if the disease might be passed down to their children. Some of the subjects who received negative results in the experimental group with no known family mutation expressed relief tempered by the remaining uncertainty of a possible undiscovered genetic cause. This response helps explain the uncertainty noted in the quantitative results.

At this six month interview, almost all subjects testing negative reported that they were coping well, yet indicated that there remained the uncertainty of not knowing their genetic status. This mirrored the low level of anxiety measured throughout the process. The themes that emerged revolved around searching for knowledge. These included understanding one's own genetic information, allowing the pursuit of research, participation in trials, and use of specialists should the result be positive. The majority indicated they would have paid for this testing if the cost was within reason. This statement was clarified to refer to a range of several thousand dollars.

Further Control Group Analysis

The control group data was further analyzed to shed light on the presymptomatic testing experience. Unlike the experimental group, these participants received a combination of positive and negative testing results (Table 6). Of note, analysis of the 1 month follow-up

scores revealed a minimal mean increase in anxiety for the positive results group from pre-test. Both the positive and negative participants exhibited decreases in depression after undergoing genetic testing, showing a trend toward positive mental effect from testing. The negative group showed a slightly larger decrease in depression than the positive group. Furthermore, the negative group showed a larger decrease in rumination after receiving test results whereas the positive group remained approximately stagnant.

Further examination of the control group reveals a discrepancy between the participants at risk for HD versus other conditions. The separation of the HD data (both including and omitting the stopped participants) from the non-HD data showed increases in almost all scores among the HD patients, including anxiety and depression. A two-tailed t-test revealed no statically significant variables. Of note, a larger increase in uncertainty (mean=8.08, $t(10) = -.51$, p=.67) was observed among the HD participants. The small sample size diminishes the accuracy of these values. This may be attributed to the uncertainty of onset among the HD-positive participants. The removal of the at-risk HD participants perhaps paints a more apt comparison to the experimental group due to the similar makeup of conditions within the families, given the more analogous experience with the nature and the genetics of the disease affecting their family.

Discussion

The aim of this study is to evaluate the differences in psychosocial effects between asymptomatic individuals with a known family mutation and those without. It was anticipated that there would be little difference between these two groups. Since all participants without a known family mutation received negative testing results without any VUS's or positive findings, the pilot data may not be adequate to draw conclusions drawn

about this population. Nearly all measures were found to be comparable between the groups pre-and post-test. No evidence was found to support increased negative psychosocial effects for those without a known family mutation in this pilot sample. The interviews reinforced favorable post-testing experiences. When looking at the interviews overall, this trend may be influenced by the higher proportion of negative results received overall. Reevaluation of these trends in a larger sample of participants may provide more definitive evidence of this trend.

Overall, the patients evidenced little difficulty dealing with their experience of genetic testing. To date, there have not been any VUS results identified from testing, and participants did not report significant uncertainty. While the control group showed an increase in uncertainty over time and the experimental group indicated a small decrease, these differences between pre and post-testing were more extensive in the control group. This may be attributed to the positive results seen in this group. Further exploration into descriptive findings may conclude that residual uncertainty lingers with those who receive negative results in the absence of a known family mutation. If so, this may be due to the feeling that there is some lingering genetic risk that we are not as yet able to detect, even if the risk is minimized by a negative panel result. Uncertainty could remain with highly penetrant known mutations as well, since there are no effective tools available to predict exactly how and when the condition for which they are at risk will develop.

Chief among the concerns about testing asymptomatic people was the possibility of significant increases in anxiety and depression, which were not observed in this pilot sample from either the questionnaires or the interviews. An examination of the associated scales found no difference in depression or anxiety between the experimental and control groups.

This may be attributed to the efficacy of the asymptomatic testing protocol. What data we have support prior reports of the effectiveness of the protocol, and provide no evidence to suggest that testing in this population is an unethical or unsound practice.

The qualitative information from the interviews is supportive of positive attitudes toward the presymptomatic protocol and interest in the availability of testing for hereditary dementia and associated neurodegenerative diseases. This anecdotal information is suggestive of a positive impact from the process of testing. Participants cited specific reasons for testing, most of which were intended to aid in alleviating uncertainty for their own futures and their families. Throughout the study, this knowledge-seeking motivation has been especially apparent in the experimental group. Discussions proved this group to be overall well-educated and exhibit similar personality traits, such as being planning and research oriented, or "type A." This is congruent with what may be expected from a patient self-referred for presymptomatic testing. In an effort to gain a better undertraining of those who seek predictive testing for neurodegenerative disease, tailored questionnaires specific to personality should be included in future studies.

Study Limitations

The primary limitation of this study is the small sample size and lack of data from each participant. Notably, more interviews are needed for a more in depth analysis and to provide potentially important information about presymptomatic testing. This group may be uniquely reflective of the typical patient population at CUMC and further studies are encouraged to include a more diverse participant base. Moreover, the participants in the control group were predominantly at risk for HD. Control and experimental groups at risk for more similar conditions may allow for a more apt comparison.

Going forward, it is important to note that the questionnaire responses may be influenced by outside events during the testing process and results period. Two participants shared that during the time of the follow-up questionnaires, each was under high distress because of their respective parents' worsening conditions. Additionally, there is an ascertainment bias with this study, in that all patient are self-referred. Therefore, there may be an initially higher level of anxiety and uncertainty in this population versus those who did not opt to participate.

Conclusions and Future Directions

The data thus far do not rule out either positive or neutral psychological outcomes of predictive genetic testing. The predictive testing protocol may be involved in mitigating negative effects when properly instituted, however, this cannot be proven in the absence of comparison data. Testing may mentally prepare participants and their loved ones for the future and allow them to take the necessary steps to secure care. Further studies are needed to assess the psychological states of those undergoing panel testing. This study will continue to attempt to understand the psychological impact of presymptomatic panel testing on the at-risk population without a known family mutation. A larger study and more extensive longitudinal look at the effects on patients will help evaluate the lasting impact of the results and process of testing.

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Appendix 1: Tables

Variable	Category	N	%
Gender	Male	6	40
	Female	9	60
Age Range	18-29	4	26.67
	30-39	7	46.67
	40-49	1	6.67
	50-59	2	13.33
	60-69	1	6.67
Marriage Status	Married	8	53.33
	Single	7	46.67
Education	High School	0	0
	4 Year College	5	33.33
	Advanced Degree	9	60
Ethnicity	African American/ Black	1	6.67
	Asian	1	6.67
	White/ Caucasian	12	80
	Mixed Ethnicity	1	6.67
Religion	Catholic	3	20
	Protestant	1	6.67
	Muslim	1	6.67
	Jewish	5	3.33
	Mixed	0	0
	None	1	6.67
	Other	2	13.33
Indication	HD	9	60
	ALS	3	20
	CJD	1	6.67
	FTD	2	13.33

Table 1a. Sociodemographic Variables: Control Group

Variable	Category	N	%
Gender	Male	4	50
	Female	4	50
Age Range	18-29	0	0
	30-39	5	62.5
	40-49	2	25
	50-59	1	12.5
	60-69	0	0
Marriage Status	Married	5	62.5
	Single	3	37.5
Education	High School	0	0
	4 Year College	2	25
	Advanced Degree	6	75
Ethnicity	African American/ Black	0	0
	Asian	0	0
	White/ Caucasian	7	87.5
	Mixed Ethnicity	1	12.5
Religion	Catholic	1	12.5
	Protestant	2	25
	Muslim	1	12.5
	Jewish	0	0
	Mixed	1	12.5
	None	3	37.5
	Other	0	0
Indication	AD	4	50
	FTD/ALS	1	12.5
	AD/FTD	3	37.5

Table 1b. Sociodemographic Variables: Experimental Group

Table 2a: Control Group Score Differences Between Pre-Test and One Month Follow-up

	PRE-TEST MEAN (N=15)	1 MO. FOLLOW-UP MEAN (N=7)	MEAN DIFFERENCE	T	P LEVEL*
GAD-7 ANXIETY	2.71	4.14	+1.42	-1.18	0.14
PHQ-9 DEPRESSION	4.43	3.14	-1.29	1.49	0.09
PPC CONTROL	15.57	15.86	-0.29	-0.26	0.40
MRRQ RUMINATION	26.57	25.14	-1.43	0.61	0.28
IUS UNCERTAINTY	45.14	52.71	+7.57	1.07	0.16
COPE SELF-DISTRACTION	4.43	3.57	-0.86	1.16	0.14
COPE ACTIVE COPING	5.29	4.29	-1.00	1.08	0.16
COPE DENIAL	2.00	2.57	-0.57	-1.33	0.11
COPE SUBSTANCE USE	2.43	2.00	-0.43	1.00	0.18
COPE EMOTIONAL SUPPORT	5.00	4.43	-0.57	1.00	0.18
COPE INSTRUMENTAL SUPPORT	4.00	4.57	+0.57	-0.93	0.18
COPE BEHAVIORAL DISENGAGEMENT	2.29	2.86	+0.57	-1.08	0.16
COPE VENTING	4.14	4.43	-0.29	-0.33	0.37
COPE POSITIVE REFRAMING	3.43	4.71	+1.28	-1.59	0.08
COPE PLANNING	5.86	5.00	-0.86	0.78	0.23
COPE HUMOR	3.14	4.14	+1.00	-1.73	0.06
COPE ACCEPTANCE	6.00	6.43	+0.43	-0.37	0.36
COPE RELIGION**					
COPE SELF BLAME	2.14	2.14	0.00	0.00	1.00

*for one-tailed test
**Religion could not be computed as the scores were the same with 0 standard deviations

Table 2b: Experimental Group Score Differences Between Pre-Test and One Month Follow-up

	PRE-TEST MEAN (N=8)	1 MO. FOLLOW-UP MEAN (N=4)	MEAN DIFFERENCE	T	P LEVEL*
GAD-7 ANXIETY	2.50	2.50	0.00	0.00	1.00
PHQ-9 DEPRESSION	1.50	1.50	0.00	0.00	1.00
PPC CONTROL	9.50	11.50	+2.00	-0.59	0.30
MRRQ RUMINATION	27.25	25.25	-1.75	1.48	0.12
IUS UNCERTAINTY	46.50	46.25	-0.25	0.05	0.48
COPE SELF-DISTRACTION	4.00	3.25	-0.75	1.00	0.19
COPE ACTIVE COPING	4.50	4.00	-0.50	1.00	0.19
COPE DENIAL	2.25	2.00	-0.25	1.00	0.19
COPE SUBSTANCE USE	2.00	2.00	0.00	0.00	1.00
COPE EMOTIONAL SUPPORT	4.25	3.50	-0.75	1.56	0.15
COPE INSTRUMENTAL SUPPORT	3.50	3.00	-0.50	1.00	0.19
COPE BEHAVIORAL DISENGAGEMENT	2.50	2.00	-0.50	1.00	0.19
COPE VENTING	3.50	2.50	-1.00	2.45	0.04
COPE POSITIVE REFRAMING	5.00	3.75	-1.25	1.67	0.09
COPE PLANNING	5.86	5.00	-0.86	0.78	0.23
COPE HUMOR	3.25	3.00	-0.25	1.00	0.19
COPE ACCEPTANCE	5.50	4.75	-0.75	1.57	0.15
COPE RELIGION**					
COPE SELF BLAME	2.25	2.50	+0.25	-1.00	0.19

*for one-tailed test

**Religion could not be computed as the scores were the same with 0 standard deviations

Table 3a: Pre-Test Score Differences Between Control and Experimental Groups

	CONTROL MEAN (N=15)	EXP MEAN (N=8)	MEAN DIFFERENCE	T	P LEVEL*
GAD-7 ANXIETY	3.80	2.13	-1.67	1.53	0.14
PHQ-9 DEPRESSION	4.33	1.88	-2.45	1.88	0.08
PPC CONTROL	14.60	11.00	-3.60	2.84	0.01
MRRQ RUMINATION	27.67	25.13	-2.54	0.68	0.50
IUS UNCERTAINTY	47.13	39.88	-7.25	1.26	0.22
COPE SELF-DISTRACTION	4.07	4.00	-0.07	0.11	0.91
COPE ACTIVE COPING	5.27	4.75	-0.57	0.58	0.58
COPE DENIAL	2.20	2.13	-0.07	0.26	0.75
COPE SUBSTANCE USE	2.20	2.00	-0.20	0.77	0.48
COPE EMOTIONAL SUPPORT	5.33	5.13	-0.20	0.30	0.77
COPE INSTRUMENTAL SUPPORT	4.07	4.50	+0.43	-0.57	0.57
COPE BEHAVIORAL DISENGAGEMENT	2.33	2.25	-0.08	0.29	0.77
COPE VENTING	3.87	3.38	-0.49	0.73	0.47
COPE POSITIVE REFRAMING	4.07	4.88	+0.81	-1.04	0.31
COPE PLANNING	6.07	5.63	-0.44	0.74	0.47
COPE HUMOR	3.07	2.75	-0.32	0.52	0.61
COPE ACCEPTANCE	5.60	5.88	+0.28	-0.39	0.70
COPE RELIGION	3.87	4.13	+0.26	-0.24	0.82
COPE SELF BLAME	2.27	2.13	0.14	0.62	0.54

*For one-tailed test

Table 3b: One Month Follow-up Score Differences Between Control and Experimental Groups

	CONTROL MEAN (N=7)	EXP MEAN (N=4)	MEAN DIFFERENCE	T	P LEVEL*
GAD-7 ANXIETY	4.14	2.50	-1.64	0.73	0.48
PHQ-9 DEPRESSION	3.14	1.50	-1.64	0.53	0.17
PPC CONTROL	15.68	11.50	-4.36	2.65	0.03
MRRQ RUMINATION	25.14	25.50	0.36	-0.06	0.96
IUS UNCERTAINTY	52.71	46.25	-6.46	0.57	0.58
COPE SELF-DISTRACTION	3.57	3.25	-0.32	0.31	0.76
COPE ACTIVE COPING	4.29	4.00	-0.29	0.24	0.82
COPE DENIAL	2.57	2.00	-0.57	0.98	0.35
COPE SUBSTANCE USE	2.00	2.00	0.00	**	**
COPE EMOTIONAL SUPPORT	4.43	3.50	-0.93	0.93	0.37
COPE INSTRUMENTAL SUPPORT	4.57	3.00	-1.57	1.16	0.27
COPE BEHAVIORAL DISENGAGEMENT	2.86	2.00	-0.86	1.44	0.20
COPE VENTING	4.43	2.50	-1.93	1.86	0.10
COPE POSITIVE REFRAMING	4.71	3.75	-0.96	0.64	0.54
COPE PLANNING	5.00	4.00	-1.00	-0.69	0.51
COPE HUMOR	4.14	3.00	-1.14	0.90	0.39
COPE ACCEPTANCE	6.43	4.75	-1.68	1.37	0.20
COPE RELIGION	2.86	3.50	+0.64	-0.41	0.70
COPE SELF BLAME	2.14	2.50	+0.36	-0.87	0.41

*For one-tailed test
**could not be computed because S.D.=0

Table 4: Comparison of Score Differences from Pre-Test and One Month Follow-up Between Control and Experimental Groups

	CONTROL MEAN (N=7)	EXPERIMENTAL MEAN (N=7)	MEAN DIFFERENCE	T	P LEVEL*
GAD-7 ANXIETY	-1.42	0	-1.42	-0.82	0.43
PHQ-9 DEPRESSION	1.28	0	1.28	1.06	0.32
PPC CONTROL	-0.28	-2	1.71	0.59	0.57
MRRQ RUMINATION	1.43	1.75	-0.32	-0.1	0.9
IUS UNCERTAINTY	-7.75	0.25	-7.82	-0.77	0.46
COPE SELF-DISTRACTION	0.86	0.75	0.11	0.09	0.93
COPE ACTIVE COPING	1	0.5	0.5	0.38	0.71
COPE DENIAL	-0.57	0.25	-0.82	-1.35	0.21
COPE SUBSTANCE USE	0.43	0	0.43	0.74	0.48
COPE EMOTIONAL SUPPORT	0.57	0.75	-0.18	-0.21	0.84
COPE INSTRUMENTAL SUPPORT	-0.57	0.5	-1.07	-1.18	0.27
COPE BEHAVIORAL DISENGAGEMENT	-0.57	0.5	-1.07	-1.34	0.21
COPE VENTING	-0.29	1	-1.28	-1.06	0.32
COPE POSITIVE REFRAMING	8.14	8.75	-0.61	-0.24	0.81
COPE PLANNING	0.86	1.5	-0.64	-0.41	0.69
COPE HUMOR	-1	0.25	-1.25	-1.56	0.15
COPE ACCEPTANCE	-0.43	0.75	-1.17	-0.73	0.87
COPE RELIGION	0	0	0	0	1
COPE SELF BLAME	0	0	0	0	1

*For one-tailed test

Negative values denote an increase in score for Table 4.

Table 5: Comparison of Control Group 1 Month Follow-up Scores: Positive versus Negative Testing Results

	POSITIVE MEAN (N=3)	NEGATIVE MEAN (N=4)	MEAN DIFFERENCE
GAD-7 ANXIETY	4.33	4.00	0.33
PHQ-9 DEPRESSION	3.66	2.75	0.91
PPC CONTROL	17.00	15.00	2.00
MRRQ RUMINATION	25.67	24.75	0.92
IUS UNCERTAINTY	53.33	52.25	1.08
COPE SELF-DISTRACTION	3.67	3.50	0.17
COPE ACTIVE COPING	4.33	4.25	0.08
COPE DENIAL	2.00	3.00	1.00
COPE SUBSTANCE USE	2.00	2.00	0.00
COPE EMOTIONAL SUPPORT	5.33	3.75	1.58
COPE INSTRUMENTAL SUPPORT	4.00	5.00	1.00
COPE BEHAVIORAL DISENGAGEMENT	3.33	2.50	0.83
COPE VENTING	4.00	4.75	0.75
COPE POSITIVE REFRAMING	6.33	3.50	2.83
COPE PLANNING	5.67	4.50	1.17
COPE HUMOR	5.33	3.25	2.08
COPE ACCEPTANCE	7.33	5.75	1.58
COPE RELIGION	2.00	3.50	1.50
COPE SELF BLAME	2.00	2.25	0.25

Table 6: Comparison of Control Group HD and Non-HD

	PRE-TEST HD MEAN (N=9)	1 MO. FOLLOW-UP HD MEAN (N=3)	MEAN DIFFERENCE HD PRE TO 1 MO. FOLLOW-UP	MEAN DIFFERENCE NON-HD PRE TO 1 MO. FOLLOW-UP	PRE-TEST NON-HD MEAN (N=6)	1 MO. FOLLOW-UP NON-HD MEAN (N=4)
GAD-7 ANXIETY	4.63	4.33	-0.3	1.33	2.67	4.00
PHQ-9 DEPRESSION	6.13	4.00	-2.13	-0.33	2.33	2.00
PPC CONTROL	14.63	17.00	2.37	--0.5	14.50	15.00
MRRQ RUMINATION	31.13	30.67	-0.46	-3.5	24.50	21.00
IUS UNCERTAINTY	48.25	56.33	8.08	3.67	46.33	50.00
COPE SELF-DISTRACTION	4.63	4.67	0.04	-0.42	3.17	2.75
COPE ACTIVE COPING	5.88	4.00	-1.88	0.17	4.33	4.50
COPE DENIAL	2.00	2.00	0	--0.5	2.50	3.00
COPE SUBSTANCE USE	2.38	2.00	-0.38	0	2.00	2.00
COPE EMOTIONAL SUPPORT	5.54	6.00	0.46	-1.25	4.50	3.25
COPE INSTRUMENTAL SUPPORT	4.64	6.00	1.36	0.33	3.17	3.50
COPE BEHAVIORAL DISENGAGEMENT	2.28	3.33	1.05	0.17	2.33	2.50
COPE VENTING	4.00	5.33	1.33	0.25	3.50	3.75
COPE POSITIVE REFRAMING	4.63	6.33	1.7	0.17	3.33	3.50
COPE PLANNING	6.13	5.33	-0.8	-1.25	6.00	4.75
COPE HUMOR	3.13	4.67	1.54	0.58	3.17	3.75
COPE ACCEPTANCE	5.25	7.33	2.08	-0.25	6.00	5.75
COPE RELIGION	4.13	4.00	-0.13	-1.67	3.67	2.00
COPE SELF BLAME	2.25	2.33	0.08	-0.33	2.33	2.00

Introduction: In this interview, we will be asking you about your experience with genetic counseling and testing. First we will address your reactions to your actual results, then we will ask you some hypothetical questions, then we will ask you for suggestions about the counseling and testing process, and finally a few demographic questions.

As you remember, you were tested for _____ through (a single gene test) (a panel of gene tests). Your results indicated that you (carry) (do not carry) (have a result of unknown significance in) the gene(s) ( ) that cause(s) _____. Now I would like to ask you some questions about this about this testing and result.

1. Now that you are 6-months out from receiving test results, how do you feel about your decision to do genetic testing for the disease in your family?

2. How did you feel while going through the predictive testing protocol (genetic testing and neuropsychiatric evaluation)?

3. Have you or another family member previously experienced genetic counseling and/or testing? If so, how did this experience compare?

4. After being counseled about possible results of unknown significance (an uninterpretable result), what kind of concerns did you have, if any?

5. If you received a result of unknown significance, how are you dealing with the uncertainty?

6. Talk about anything we discussed during the genetic counseling session that made you think about your situation differently than when you called for your appointment or anything you reflected on afterwards.

7. How did you first react upon receiving results?

8. With whom (spouse/partner, children, siblings, friends, employer) did you share results and how did they react? Did you talk about your testing before getting results or only after?

9. How do you feel that you are coping with the results now (any anxiety, depression)?

10. If you received any results of unknown significance, how are (would) you dealing with the uncertainty?

11. How will the result affect your everyday life?

12. How will the result effect your future?

13. How will the result affect your use of the healthcare system or medications?

Now we will ask you some what if questions about having received the opposite result or a result of unknown significance.
14. If you had received the opposite result (state negative or positive), how would it have affected your everyday life?

15. If you had received the opposite result (state negative or positive), how would it have affected your future?

16. If you had received the opposite result (state negative or positive), how would it have affected your use of the healthcare system or medications?

17. If you had received a result of unknown significance, do you think you would be able to deal with the uncertainty? Why?

Now we are going to ask you about your experience with the research and the predictive counseling process.
18. If you were starting the process all over, would you do anything differently? For example, would you have chosen to enter this research project or instead go through clinically testing without the research? Would you have chosen to go to a doctor who would have tested you without genetic counseling?

19. We asked you to think about obtaining life and long-term care insurance prior to testing. Did you do so? How did it make you feel to have to think about future care?

20. Do you feel that your decision to be tested was influenced by the fact that it was free if you participated in this research? Would you have tested if you had to pay for it out of pocket?
21. What suggestions would you make to improve the process of predictive testing?