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ORIGINAL ARTICLE

Predictive testing for neurodegenerative diseases in the age of next-generation sequencing

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Abstract

The availability and cost of next-generation sequencing (NSG) now allow testing large numbers of genes simultaneously. However, the gold standard for predictive testing has been to test only for a known family mutation or confirmed family disease. The goal of this study was to investigate the psychological impact of predictive testing for autosomal dominant neurodegenerative diseases without a known family mutation using next-generation sequencing panels compared to single-gene testing of a known family mutation. Fourteen individuals from families with a known mutation and 10 individuals with unknown family mutations participated. Participants completed questionnaires on demographics, genetic knowledge, and psychological measures of anxiety, depression, perceived personal control, rumination, and intolerance to uncertainty at baseline and 1 and 6 months after receiving results. Decision regret was measured 1 and 6 months after receiving results. Participants completed a modified Huntington disease genetic testing protocol with genetic counseling and neurological and psychological evaluation. Genetic testing of either the known family mutation or an NGS panel of neurodegenerative disease genes was performed. Semi-structured interviews were performed at 6 months post-results about their experience. Two-sample *t* tests were performed on data collected at each time point to identify significant between-group differences in demographic variables, baseline psychological scores, and baseline genetic knowledge scores. Within-group change over time was assessed by a mixed-effects model. Results of this study indicate that NGS panels for predictive testing for neurodegenerative disease are safe and beneficial to participants when performed within a modified HD protocol. Though significant differences in psychological outcomes were found, these differences may have been driven by genetic results and baseline psychological differences between individuals within the groups. Participants did not regret their decision to test and were largely pleased with the testing protocol.

KEYWORDS

genetic counseling, neurodegenerative disease, next-generation sequencing panels, predictive genetic testing, psychosocial impact, uncertainty

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1 | INTRODUCTION

The use of next-generation sequencing (NGS) panels is now the gold standard for diagnostic genetic testing of neurodegenerative disease. However, the gold standard for predictive testing is single-gene testing of a known family mutation. The efficacy of NGS panels for testing neurodegenerative disease predictively without a known family mutation has not been previously explored. Because of the large number of genes being tested, NGS leads to the possibility of finding variants of unknown significance (VUS) which would be unactionable and leave the patient with the same uncertainty experienced before testing. Whether such uncertainty would cause adverse outcomes is unknown. In a study using an NGS panel for predictive testing of hereditary breast and ovarian cancer, Lumish et al. (2017) found a significant level of distress, avoidance, and intrusive thoughts in participants receiving positive results and VUS.

Predictive testing for neurodegenerative disease has been available since the onset of genetic testing for Huntington disease (HD) in 1993. An international protocol was accepted in 1994 and has been the benchmark ever since (International Huntington Association & the World Federation of Neurology Research Group on Huntington's Chorea, 1994). The goal of the protocol is to promote safe outcomes for the patient. The protocol has been revised several times both in the United States and in Europe, but the fundamental principles still stand (Huntington's Disease Society of America, 2016; MacLeod et al., 2013).

The original HD predictive testing protocol has been applied to pre-symptomatic testing of most other fatal, neurodegenerative diseases. Extensive research on the outcome of predictive testing for HD and other diseases has concluded that the protocol is generally safe and effective. Though depression, suicidal ideation, and anxiety certainly occur in people with positive and negative results, few serious adverse outcomes have been reported when the protocol has been followed (Almqvist et al., 1999; Cassidy et al., 2008; Cohn-Hokke et al., 2018; Crook et al., 2017; Crozier et al., 2015; Decruyenaere et al., 2003; Fanos et al., 2011; Green et al., 2009; Lêdo et al., 2018; Quaid et al., 2017; Steinbart et al., 2001; ; Molinuevo et al., 2005; Tibben, 2007). Those people who are at the greatest risk for post-test adverse outcomes have the highest pre-test distress (Gargiulo et al., 2009; Lêdo et al., 2018; Meiser et al., 2000).

A requirement of the predictive testing protocol is a documented family history of HD or a known family mutation for other autosomal dominant diseases. This requirement ensures that patients who elect to proceed with predictive testing receive a definitive result. Additionally, until recently, full Sanger sequencing of all genes associated with a disease was very expensive and impractical for most patients. Since the advent of NGS, the cost of testing multiple genes simultaneously has declined significantly and is now affordable for many patients.

More people are now aware of the availability of genetic testing, and many are concerned about their risk for Alzheimer's disease or another neurodegenerative condition (Rentería et al., 2020). These individuals may not have access to familial genetic results either because the affected family member has died, is estranged, or declines testing. In our experience, when denied predictive testing because of an unknown family mutation, patients often become frustrated, angry, and anxious. Though the uncertainty of testing without a known mutation is explained, patients claim that this uncertainty would be no worse than their current uncertainty.

The only study on the use of genetic testing to assess genetic risk for a neurodegenerative disease without a known family mutation is the Risk Evaluation and Education for Alzheimer's Disease (REVEAL). REVEAL has studied the outcomes of testing at-risk individuals (due to family history of Alzheimer's disease) for the Alzheimer's risk gene, *APOE*. REVEAL found that their study population of largely well-educated White individuals generally accepted the predicted risk despite *APOE* e4 being neither necessary nor sufficient for the development of Alzheimer's disease (Cassidy et al., 2008; Green et al., 2009). However, numerous individuals who have tested outside this research environment and without genetic counseling have reported adverse outcomes such as acute anxiety and depression (Marshe et al., 2019; Zallen, 2018).

The goal of this study was to investigate the psychological impact of predictive testing for autosomal dominant neurodegenerative diseases without a known family mutation using next-generation sequencing panels compared to single-gene testing of a known family mutation.

2 | METHODS

2.1 | Participants

Participants were selected by continuous enrollment from individuals who self-referred for genetic counseling because of a family history of a neurodegenerative disease. Enrollment was limited to people over the age of 18 without a known diagnosis of dementia. Patients were screened over the phone for an autosomal dominant family history of a neurodegenerative disease. Those individuals who met the above criteria were invited to participate in this study.

Participants were classified into two groups:

Group A: Individuals at risk for a clinically or genetically confirmed monogenetic disease (e.g., HD) or at risk for a specific known family mutation for frontotemporal dementia (FTD), Alzheimer's disease (AD), or Creutzfeldt–Jacob disease (CJD);

Group B: Individuals at risk for an autosomal dominant neurodegenerative disease without a known family mutation.

The original goal for recruitment was 15 individuals/group. However, we had a fixed budget to pay for the genetic testing. Some of this money was used on participants who withdrew after receiving their test results but before completing the study. Therefore, we were unable to reach our original goal. Fourteen individuals in Group A and 10 in Group B completed the study.

2.2 | Procedure and study instruments

All participants who agreed to participate were sent a Columbia University Irving Medical Center IRB-approved informed consent. After signing the informed consent and before coming for genetic counseling, they were asked to complete an initial set of questionnaires, including demographics; extended family history; and items that we created to assess knowledge of genetics (Genetic Knowledge Questionnaire, a non-validated measure). The following validated measures were used: Patient Health Questionnaire-9 (PHQ-9) to assess depression (scores could range from 0 to 27; cutpoints for mild, moderate, moderately severe, and severe depression = 5, 10, 15, and 20) (Kroenke et al., 2001); Generalized Anxiety Disorder 7-item Scale (GAD-7) (scores could range from 0 to 21; cutpoints for mild, moderate, and severe anxiety = 5, 10, and 15) (Löwe et al., 2008); Intolerance of Uncertainty Scale (IUS) (a 27-item survey with a 5-point Likert scale for each question, scores could range from 27 to 135 with low score = less intolerance) (Buhr & Dugas, 2002); Modified Rumination-Reflection Questionnaire (mRRQ) (11-item survey with a 5-point Likert scale, low score = less rumination) (Trapnell & Campbell, 1999); Perceived Personal Control Questionnaire (PPC) (9-item scale, with each item scored as 0 = do not agree, 1 = somewhat agree, and 2 = completely agree) (Berkenstadt et al., 1999); and the Decision Regret Scale (DRS) (a 5-item scale each assessed on a 5-point Likert scale, scores could range from 5 to 25, with low score = less regret) examining how participants felt about their decision to have genetic testing (Brehaut et al., 2003).

Participants at risk for HD, with their study partner (identified by the participant), were seen through the Columbia University Huntington's Disease Center of Excellence, whereby they saw a board-certified genetic counselor (JG), then a psychiatrist, and finally a neurologist (KM) prior to genetic testing.

Participants at risk for non-HD neurodegenerative diseases, with their study partners, were seen at the Columbia University Irving Medical Center CTSA-funded outpatient research center. Their modified HD protocol included genetic counseling with a board-certified genetic counselor (JG), followed by a Mini-Mental State Examination (MMSE) to screen for cognitive impairment, and a neurological examination and psychological evaluation completed by a neurologist (KM) prior to genetic testing.

A blood sample was then drawn and sent to the Personalized Genomic Medicine Laboratory at Columbia University Medical Center where it was analyzed either for the known mutation (Group A) or for a customized next-generation sequencing neurodegenerative disease panel (Group B) consisting of the following genes: *PSEN1*, *PSEN2*, *APP*, *SOD1*, *ANG*, *TARDBP*, *FUS*, *VCP*, *ALS2*, *DCTN1*, *VAPB*, *SETX*, *SMN1*, *UBQLN2*, *MAPT*, *GRN*, *CHMP2B*, *APOE*, *LRRK2*, *GBA*, *PARK2*, *PINK1*, *SNCA*, *UCHL1*, and *PRNP*. Additionally, repeat expansion mutation analysis of intron 1 of *C9orf72* was performed on most samples.

All participants with their study partner came in person to receive results at a post-test genetic counseling session. One month and 6 months after receiving test results, participants were asked to complete the following questionnaires: Genetic Knowledge Questionnaire, PHQ-9, GAD-7, IUS, mRRQ, PPC, and DRS. Additionally, at 6 months post-results, a semi-structured interview about the genetic testing process was administered by telephone (DG). This interview explored feelings about the genetic testing process, how they now feel about their decision to test, reactions and feelings regarding actual and hypothetical results (including receiving a VUS), any changes in lifestyle since receiving results, and suggestions for improving the testing process (Questions available in Appendix S1).

2.3 | Data analysis

The two null (research) hypotheses tested in this study were as follows: (a) There is no difference in the change scores on psychological measures or knowledge items between baseline and 1 or 6 months after receiving test results *between* Groups A (known mutation) and B (unknown mutation); (b) there is no significant change *within* each group between baseline and 1 or 6 months after receiving test results.

Descriptive statistics for demographic characteristics of the mutation known group (A) and unknown group (B) were calculated. Chi-square tests for categorical variables and 2-sample *t* tests for continuous variables were performed to determine any significance *between* groups in demographic variables, baseline psychological scores, or baseline genetic knowledge score.

Differences in the psychological scores between the baseline and post-result assessments *within* each mutation group were determined by a mixed-effects model. Linear mixed-effects model, treating change score as continuous outcome, adjusting for baseline score, genetic results, gender, age, education, and race (White vs. non-White) was used for all tests. Only those participants completing the study were included in the analysis. In analyses which controlled for positive or negative genetic results, the two participants with *APOE4* and *VUS* were excluded. All statistical analyses were performed by SAS version 9.4. The type I error rate was set to be 0.05, all tests were two-sided, and a 95% confidence interval was used.

We conducted a post hoc power analysis (computed by G*Power 3.1) for baseline score and the change score between follow-up visit and baseline visit based on the sample size of our study to determine the minimum detectable effect size.

Two-sample *t* test was used for the mean difference of baseline score between groups A and B. Assuming $\alpha = 0.05$, power = 80%, and sample size of Group A = 14 and sample size of Group B = 10 at the baseline visit, the minimal detectable effect size is Cohen's $d = 1.214$, which is considered a large effect size.

We also used two-sample *t* test for the mean difference of change scores (follow-up visit vs. baseline visit) between groups A and B. Assuming $\alpha = 0.05$, power = 80%, and sample size of Group A = 14 and that of Group B = 8 (some subjects did not complete

the study), the minimal detectable effect size is Cohen's $d = 1.305$, which is considered a large effect size.

Telephone interviews were conducted by co-author DG. Interview summaries were reviewed by two of the authors (DG, JG). Responses were coded by reaction type. Specific emotions were defined as 'present' or 'not present'; attitudes about the testing protocol, test results, the possibility of a VUS, and the effect of testing on life choices were defined as 'positive' or 'negative'; and lifestyle changes were defined as 'change' and 'no change'. The type of responses was further analyzed by whether the participant was in Group A or B and whether their result was positive, negative, or a VUS.

2.4 | Genetic analysis

HTT, *C9orf72*, and the NGS 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*) were analyzed by standard methodology (see Appendix S2 for details). Allele classification of HTT testing followed American College of Medical Genetics and Genomics (ACMGG) Standards and Guidelines for Huntington Disease (Bean & Bayrak-Toydemir, 2014). Sequence variants of genes analyzed by NGS were reported using HGVS nomenclature, 2016 update (den Dunnen et al., 2016), and the joint consensus recommendations of the ACMGG/AMP for variant interpretation (Richards et al., 2015).

3 | RESULTS

Of the 31 individuals who consented, eight withdrew leaving the final number of participants completing the study at 14 in Group A and 10 in Group B (Figure 1). Of the seven who withdrew, two Group A participants were advised to curtail participation by the team psychiatrist because of considerable depression and anxiety. There were no significant demographic differences between the two groups (Table 1).

Nine pathogenic variants were found in Group A and one in Group B. One VUS and an *APOE* ε3,4 result were also reported in Group B (Table 2). *APOE* ε3,4 was reported as a risk factor not a pathogenic variant.

Genetics knowledge and psychological measures: (means and standard deviations can be found in Appendix S3).

At baseline, the two groups (A and B) did not differ on genetics knowledge score or any psychological measures except the PPC (Appendix S3). Group A members had a greater sense of personal control about genetic testing at baseline (Group A: mean PPC = 14.5, $SD = 2.8$; Group B: mean PPC = 9.6, $SD = 3.7$).

Significant differences between the two groups' change scores were found on the GAD, PHQ-9, and the IUS (Table 3). Within-group analyses demonstrated that anxiety scores significantly increased from baseline to 1 month post-results in Group A and then decreased with no significant difference from baseline to 6 months post-results, while no significant changes from baseline to 1 or 6 months post-result were found for Group B. Depression change scores from baseline to 1 or 6 months post-result were significant in Group B, indicating lower scores over time, and resulted in a significant difference in change between groups at both time periods. Group A had significant increase in perceived personal control scores at 1 and 6 months relative to baseline, with little change for Group B. The mMRQ change scores were not significant either between Group A and Group B or within each group. Intolerance for uncertainty declined more steeply in Group B at both time points and resulted in a significant difference in change between groups at both time periods. There was a significant decrease in genetics knowledge at 1 and 6 months relative to baseline in Group A but no significant change in Group B (Appendix S3). The DRS results indicated that both groups

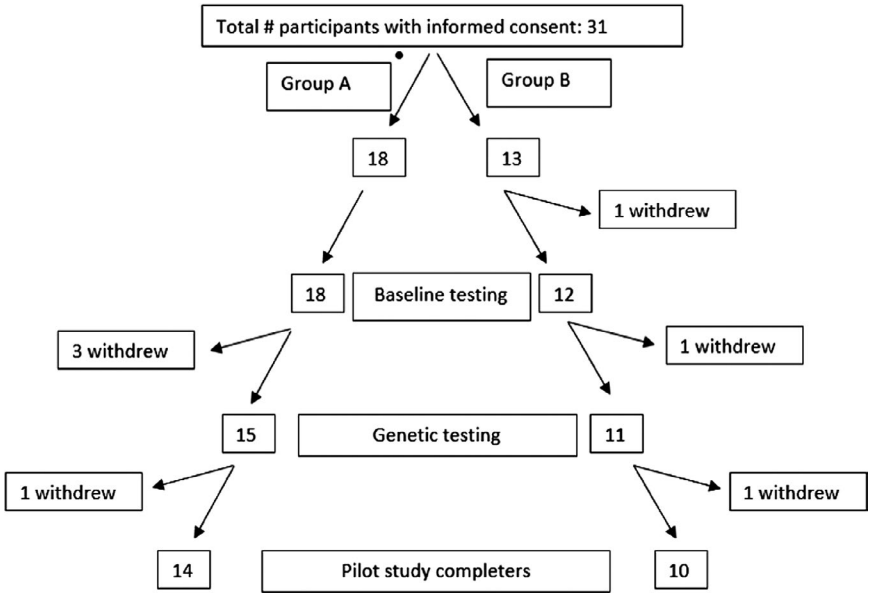

FIGURE 1 Number of participants recruited and withdrawals from study (Group A = known mutation; Group B = unknown mutation)

TABLE 1 Demographics of all participants completing the study

Metric	Group A ($N = 14$)	Group B ($N = 10$)	p-value
Sex (% male/%female)	28.57/71.43	40/60	0.558
% Age			
18–29	14.29	10	0.985
30–39	57.14	50	
40–49	7.14	10	
50–59	14.29	20	
60–69	7.14	10	
% Single/married (%)	35.71/64.29	30/70	0.77
Highest education			
%High school	0	0	0.478
% 2-year college	0	10	
% 4-year college	35.71	30	
%Advanced degree	64.29	60	
% Ethnicity			
Non-Hispanic/ Hispanic	85.71/14.29	100/0	0.235
Race			
%Asian	0	0	0.459
%Black or African/ American	7.14	0	
%White	85.71	100	
%Multi-racial	7.14	0	
Religion			
%Catholic	14.29	20	0.441
%Jewish	42.86	20	
%Muslim	0	10	
%Protestant	7.14	20	
% Other	14.29	0	
%None	21.43	30	
How religious?			
%Not at all	28.57	25	0.444
%Moderately	57.14	37.5	
% Very	14.29	37.5	

Note: Group A: individuals at risk for a clinically or genetically confirmed monogenetic disease (e.g., HD) or at risk for a specific known family mutation for frontotemporal dementia (FTD), Alzheimer's disease (AD), or Creutzfeldt–Jacob disease (CJD); Group B: individuals at risk for an autosomal dominant neurodegenerative disease without a known family mutation.

TABLE 2 Genetic results

Result	Group A ($N = 14$)	Group B ($N = 10$)
Positive: *N* (%)	9 (69.23% of Group A)	1 (10% of Group B)
HTT	5 (55.56% of positives)	0
C9orf72	3 (33.33% of positives)	0
PRNP	1 (1.11% of positives)	0
MAPT	0	0
PSEN1	0	1 (10.0% of positives)
VUS (*PSEN1*)		1 (10.0% of Group B)
APOE4		1 (10.0% of Group B)
Negative: *N* (%)	5 (38.46% of Group A)	7 (70.0% of Group B

Note: HTT for HD; *C9orf72* for frontotemporal dementia/amyotrophic lateral sclerosis; *PRNP* for Creutzfeldt–Jakob disease (CJD), *MAPT* for frontotemporal dementia; *PSEN1* for Alzheimer's disease; Group A: individuals at risk for a clinically or genetically confirmed monogenetic disease (e.g., HD) or at risk for a specific known family mutation for frontotemporal dementia (FTD), Alzheimer's disease (AD), or Creutzfeldt–Jacob disease (CJD); Group B: individuals at risk for an autosomal dominant neurodegenerative disease without a known family mutation.

had little regret at either 1 month (Group A: mean = 7.2, $SD = 3.3$; Group B: mean = 5.6, $SD = 1.8$; $p = 0.355$) or 6 months (Group A: mean = 7.75, $SD = 3.72$; Group B: mean = 5.875, $SD = 1.458$; $p = 0.239$) after learning their test results, and there was no significant difference between the groups (Appendix S3). An additional analysis was performed to determine whether any of the change scores were driven by the genetic testing results. No statistical difference was found on any of the measures between participants with positive versus negative results; however, with only one positive result in Group B, this analysis may not be meaningful.

Using the linear mixed-effects model where change score was treated as a continuous outcome and genetic results, gender, age, education, and race (White vs. non-White) were adjusting for baseline score, GAD ($p < .001$), PHQ ($p < .0001$), PPC ($p < .0001$), and IUS ($p = 0.001$) baseline scores had a significant correlation with the change scores. Additionally, genetic results were significantly associated with change scores of GAD ($p = 0.01$), PHQ ($p = 0.02$), and IUS ($p = 0.004$); age was significantly associated with GAD ($p = 0.001$) and IUS ($p = 0.03$) change scores, and race was significantly associated with PHQ ($p = 0.034$) and genetic knowledge ($p = 0.008$) change scores.

3.1 | Interview

When interviewed, the great majority of the participants were happy with their decision to test and felt supported and prepared by each testing protocol. A few people at risk for HD commented that the protocol was too long and paternalistic or objected to specific parts that raised anxiety such as the neuropsychiatric evaluation. However, most participants said that if they were starting over, they would want to follow the same procedure. This response is also reflected in the DRS results where both groups' scores reflected little

TABLE 3 Change scores in measures between baseline and 1 month after test results and baseline and 6 months after test results (with a 95% confidence level)

	Group A ($N = 14$)		Group B ($N = 8$)		Baseline difference between groups A and B	Difference in change between groups A and B
Covariate	**Change**	***p*-value**	**Change**	***p*-value**	***p*-value**	***p*-value**
GAD: 1 month	2.046 (0.317, 3.775)	**0.023**	−1.675 (−4.071, 0.721)	0.160	0.157	**0.003**
6 months	1.403 (−0.326, 3.132)	0.106	−2.300 (−4.696, 0.0958)	0.059		**0.003**
PHQ: 1 month	−0.069 (−1.310, 1.172)	0.909	−1.967 (−3.672, −0.262)	**0.026**	0.110	**0.047**
6 months	0.217 (−1.025, 1.458)	0.720	−2.092 (−3.797, −0.387)	**0.019**		**0.018**
PPC: 1 month	2.892 (0.216, 5.567)	**0.036**	1.697 (−1.266, 4.660)	0.245	**0.006**	0.469
6 months	3.345 (0.603, 6.087)	**0.019**	0.950 (−2.013, 3.913)	0.510		0.163
mRRQ: 1 month	−1.594 (−8.324, 5.136)	0.627	−3.582 (−12.097, 4.932)	0.391	0.781	0.631
6 months	−6.380 (−13.110, 0.350)	0.062	−5.832 (−14.347, 2.682)	0.169		0.894
IUS: 1 month	−1.352 (−11.756, 9.051)	0.788	−21.162 (−36.225, −6.100)	**0.009**	0.302	**0.005**
6 months	−2.860 (−13.381, 7.661)	0.575	−22.662 (−37.724, −7.600)	**0.005**		**0.005**
Knowledge: 1 month	−2.394 (−4.426, −0.362)	**0.023**	−0.946 (−3.499, 1.607)	0.449	0.586	0.255
6 months	−3.108 (−5.141, −1.076)	**0.005**	−2.321 (−4874, 0.232)	0.072		0.531

Note: GAD = Generalized Anxiety Disorder 7-item Scale (higher scores indicate greater anxiety), PHQ = Patient Health Questionnaire-9 (higher scores indicate greater depression); PPC = Perceived Personal Control Questionnaire (higher scores indicate greater perceived personal control); mRRQ = Modified Rumination-Reflection Questionnaire (higher scores indicate more rumination); IUS = Intolerance of Uncertainty Scale (higher scores indicate more intolerance); Group A: individuals at risk for a clinically or genetically confirmed monogenetic disease (e.g., HD) or at risk for a specific known family mutation for frontotemporal dementia (FTD), Alzheimer's disease (AD), or Creutzfeldt–Jacob disease (CJD); Group B: individuals at risk for an autosomal dominant neurodegenerative disease without a known family mutation.

regret (Appendix S3). Interview statements included, 'I'm sorry that I didn't do it earlier'; 'Would do it a million times over'; 'I wanted to know even if it was uncertain'. '(A VUS) did not make a difference because I did not know what I was testing for to begin with'; '(A VUS) was concerning but did not change my decision…I was thinking that with time, there would be more literature to define these results'; 'I always thought there would be a reasonable degree of uncertainty regardless of testing'.

Baseline measures of IUS varied within each group but were generally at low levels. After receipt of results, the IUS stayed relatively constant for Group A while declining significantly for Group B, including for the one individual who received a VUS.

Participants reported that their initial reactions to the genetic test result included shock, relief, surprise, happiness for their children, and survivor's guilt. Some Group B participants wondered about false-negative results. As reflected on the GAD and PHQ, most participants were coping well at 6 months, with 77% of participants having GAD and PHQ scores below 5 (the cutoff for mild anxiety or depression). Some said they had an initial rise in anxiety which subsided over time. The person who received a VUS in Group B was disappointed to not receive a definitive answer and reported some initial anxiety that dissipated over time. When asked about a hypothetical VUS, some participants said that they would think of a VUS as a pathogenic variant, while others said that they would feel the same uncertainty they felt prior to testing. None would change their decision to test based on the possibility of a VUS, including the individual who received the VUS.

The reported changes in lifestyle were highly variable. Many participants, both carriers and non-carriers, made no changes while a few reported working out more, eating more healthfully, taking supplements, and starting in vitro fertilization with pre-implantation genetic testing. Many of the participants who tested positive reframed their results and commented that 'they will live life to the fullest' and 'spend more time with their families'.

4 | DISCUSSION

In this project, we aimed to study the psychological outcomes of people undergoing predictive NGS panel testing for autosomal dominant neurodegenerative diseases without a known family mutation as compared to targeted genetic testing for a known family mutation. Results from both the validated measures and interviews indicate that within the framework of a modified HD protocol (as explained in the Methods section), NGS testing appears to be safe and useful to those people requesting testing through this study. We suggest that any differences in changes in the psychological measures at 1 and 6 months post-result between the groups can be attributed to baseline PPC, to the act of initiating genetic testing, and to genetic results.

We hypothesized that no change score differences would be found between Groups A and B. However, our results revealed significant post-result change differences in anxiety, depression, and intolerance to uncertainty between the groups. These differences are not explained by demographic factors because the two groups were well matched on demographics and baseline psychological measures except for perceived personal control. A possible explanation for the higher baseline PPC in Group A was the knowledge that they would receive a definitive answer regarding the presence or absence of the known family mutation and, therefore, felt more in control of their decision to test.

We propose that undertaking genetic testing removes the stress of inertia which can add to the stress of uncertainty. This hypothesis is corroborated by interview statements indicating satisfaction with the choice to test. These results, as well as the DRS results, suggest that using NGS panels on individuals without a known family mutation can be beneficial for people and cause no significant adverse outcomes.

Although only one VUS was revealed, in interviews Group B participants reported not worrying about the potential of receiving a VUS. Interviews and the IUS change scores for this group indicated that the act of genetic testing was more important than a VUS and genetic results did not increase intolerance of uncertainty. Biesecker, et al. (2014) found that tolerance of uncertainty is influenced by pre-existing beliefs about uncertainty, not by test results. Hence, the baseline IUS scores are a better predictor of the ability to deal with uncertainty than the result. We hypothesize that the participants in this study were a self-selected group who could tolerate both the possibility of positive results and the uncertainty generated by a VUS.

Depression levels showed no significant change in Group A while declining more in Group B at both time points. Previous studies have shown that any distress typically is most severe soon after testing and returns to baseline both in carriers and in non-carriers of HD pathogenic variant until approaching the age of onset (Almqvist et al., 2003; Hayden & Bombard, 2005). An explanation for this finding may be that reducing uncertainty is enough to reduce distress and that uncertainty was greater for Group B than Group A such that greater change was found in Group B. Group B also became more tolerant of uncertainty after receiving definitive results, even when the cause of the disease in the family was undetermined. Studies suggest that the people at greatest risk for post-test distress are those who demonstrate high levels of anxiety or depression at baseline (Decruyenaere et al., 1999; Gargiulo et al., 2009; Paulsen et al., 2013). In our study, those individuals were asked to stop the testing process after psychiatric assessment according to the HD protocol, leaving a self-selected group who were potentially more able to cope with any result. Of note, a study using different types of clinical settings found that some level of anxiety after the receipt of positive results is appropriate and probably helpful to propel individuals into planning (Robinson et al., 2019).

Interviews echoed the findings of the questionnaires, showing that most participants were satisfied with the experience and able to come to terms with their results. Most studies on the outcome of predictive testing for HD have reported similar findings of benefit from testing and no significant impact on people's lives other than reproductive decisions (Cohn-Hokke et al., 2018).

4.1 | Study limitations

The most significant limitations of this study were the small sample size and the single VUS found in Group B. Additionally, our study population was principally well-educated and White, and results may not generalize to a broader population. We can only interpret results for this self-referred group. However, in our experience, the great majority of individuals coming for predictive testing are self-referred rather than being referred from physicians. Additionally, those individuals who were at higher risk for adverse outcomes because of pre-existing depression or anxiety were withdrawn from the study and additional individuals elected to withdraw, perhaps because they felt they could not cope with potential results.

Lastly, individuals may have volunteered for this study because testing was free and clinical testing using NGS panels is not generally available for asymptomatic individuals. This incentive may have encouraged some individuals to proceed. However, most stated that they would have paid for testing if it had been available. Several people withdrew from the study without giving reasons. These people may have enrolled into the study in order to obtain free testing or for other reasons.

4.2 | Practice implications

The results of this study suggest that individuals with an autosomal dominant history of a neurodegenerative disease can be offered NGS testing panels appropriate for the family disease even without a known family mutation. However, our study was conducted within a modified HD protocol and excluded people with significant anxiety or depression. Our recommendations, thus, can only apply within this framework.

4.3 | Research recommendations

We suggest that this study be extended to a larger, more diverse population.

5 | CONCLUSIONS

In this study, the use of NGS panels for predictive testing for neurodegenerative disease appeared to be safe and beneficial to people wanting to end uncertainty about their genetic status when performed within a modified HD protocol. Though significant differences in psychological outcomes were found between the group of people having single-gene testing for a known family mutation and those being tested through an NGS panel for an unknown autosomal dominant neurodegenerative disease, these differences were probably partly driven by group differences in percentage of participants receiving positive genetic results. Participants did not demonstrate decision regret and were largely pleased with the testing protocol. As demonstrated by the analysis of the covariates: genetic results, gender, age, education, and race, baseline personal characteristics of those being tested and test results appear to be more important for the psychological impact of genetic testing than the type of testing and the act of taking the genetic test is beneficial in most cases regardless of the result.

AUTHOR CONTRIBUTIONS

Jill Goldman contributed substantially to study conception and design; collection, analysis, and interpretation of data; draft and revision of the manuscript. Shanghong Xie was responsible for all quantitative data analysis and interpretation and contributed to the drafting and revision of the manuscript. Dina Green contributed to the interview design, conducted and analyzed interviews, entered data into the database, and contributed to the drafting and revision of the submitted manuscript. Ali Naini was primarily responsible for analysis and interpretation of genetic data and contributed to the draft and revision of the manuscript. Mahesh Mansukhani was responsible for design, analysis, and interpretation of genetic data and contributed to the draft of the manuscript. Karen Marder contributed substantially to study conception and design and interpretation of data and to the drafting and revision of the manuscript and examination of all participants. All authors approved the submitted document and agree to be accountable for all aspects of the work.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

Jill Goldman, Shanghong Xie, Dina Green, Ali Naini, Mahesh Manusukjani, and Karen Marder declare that they have no conflict of interest.

Human studies and informed consent

All procedures performed in studies involved human participants were in accordance with the ethical standards of the Columbia University Medical Center Institutional Review Board and with the 1964 Helsinki and its later amendments or comparable ethical standards. All participants gave informed consent prior to their inclusion in this study.

Animal studies

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

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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