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ORIGINAL ARTICLE

Predictors of adverse psychological experiences surrounding genome-wide profiling for disease risk

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Abstract This study aimed to identify predictors of adverse psychological experiences among direct-to-consumer (DTC) genomic test consumers. We performed a secondary analysis on data from the Scripps Genomic Health Initiative (SGHI), which studied 2037 individuals tested with commercially available tests yielding personalized risk estimates for 23 common, genetically complex diseases. As part of the original study, the participants completed baseline and follow-up survey measures assessing demographics, personal and family health history, attitudes toward genetic testing, anxiety (State-Trait Anxiety Inventory (STAI)), test-related distress (Impact of Event Scale—Revised (IES-R)), and reactions to receipt of results. To further describe the participants who had an adverse psychological outcome, this secondary analysis defined two different variables ("distress response" and "psychologically sensitive participants") and examined their relationship to various demographic variables and other survey responses. One hundred thirty participants (6.4%) were defined as having a "distress response" to receipt of results based on changes in STAI and/or IES. Four hundred thirty-one participants (21.2%) were defined as being "psychologically sensitive" based on high STAI scores both pre- and post-receipt of results. For psychologically sensitive subjects, younger age emerged as a predictor ($p < 0.0005$). Family history and personal history were only significant predictors for Alzheimer's disease in the psychologically sensitive participants ($p = .03$) and restless leg syndrome in those with a distress response ($p = .03$). Psychologically sensitive participants were more likely to indicate a number of pre-test concerns than were controls, but neither group of participants were any more likely to follow up with their physician or a free genetic counseling service after the return of results.

Keywords Anxiety · Depression · Direct-to-consumer · Genetic testing · Genomic risk assessment · Impact of events · Personalized medicine · Precision medicine · Psychological distress

Introduction

Ever since direct-to-consumer (DTC) genotyping for genomic risk assessment of common, genetically complex conditions first became available in 2007, there has been research, professional statements, and ongoing commentary expressing concerns regarding its provision without the involvement of a healthcare intermediary and the potential psychological effects on consumers (American College of Medical Genetics 2016; McGuire and Burke 2008; Annes et al. 2010; McBride et al. 2010; Stack et al. 2011; Dohany et al. 2012; Gordon et al. 2013; Skirton et al. 2012; Kaufman et al. 2012; Francke et al. 2013; Roberts and Ostergren 2013). Despite these worries, the limited literature shows that a relatively small percentage of consumers exhibit negative psychological effects related to

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such testing (Francke et al. 2013; Roberts and Ostergren 2013; Bloss et al. 2011; Egglestone et al. 2013).

Here we present a novel secondary analysis of the Scripps Genomic Health Initiative (SGHI) (Bloss et al. 2011), which was originally performed by several of this paper's co-authors (ET, NS, CB). The SGHI collected data between 2008 and 2009 on 2037 consumers of DTC genomic risk assessment. As was previously published (Bloss et al. 2011), the original study found that less than 4% of the population had a psychological impact from the testing and return of results process. Specifically, using the Impact of Event Scale—Revised (IES-R), only 2.8% of all subjects reported clinically meaningful test-related distress after receiving personalized genomics results and 3.8% of all subjects experienced a clinically reliable change in anxiety as assessed by the Spielberger State-Trait Anxiety Inventory (STAI). This is similar to that found by (Egglestone et al. 2013), who found that just 2.7% (5/183) of respondents having undergone DTC genomic risk assessment reported an increase in their anxiety. In contrast, a study by 23andMe of 32 individuals having received positive *BRCA1/2* founder mutation results found 12.5% reported having been moderately upset and 28.1% reported transient anxiety after receiving their results (Francke et al. 2013). This suggests that higher penetrance genomic results could pose higher risks of adverse psychological responses, particularly in a DTC context, than an elevated risk for a common, complex condition. While much has been made of the small percentages of individuals who experience adverse psychological outcomes after DTC genomic risk assessment in this and other data sets, little is understood about these individuals.

Better characterizing those with adverse psychological experiences surrounding receipt of genomic risk results, including whether they may be prospectively identified as at risk for these experiences, may guide healthcare and industry providers in provision of clinical services as patients undergo genomic risk assessment and learn their results in both a DTC and primary care setting. Thus, the specific aim of this project was to perform a secondary analysis of the SGHI data to specifically characterize the individuals who have an adverse psychological response to DTC genomic testing. We entered our study with several testable hypotheses: (1) demographic factors could be identified that predicted which participants had an adverse psychosocial impact; (2) family history or personal history of a condition for which one was found to be at increased risk would predict an adverse psychosocial impact, (3) persons who were found to be at a higher risk for more conditions, measured through the total number of conditions for which a subject was at elevated genomic risk, or their average estimated lifetime risk value for each condition, would predict a higher risk of adverse psychosocial impact, and (4) participants with an adverse psychological response may communicate differently or express concerns, both pre and post-results, with healthcare providers.

Methods

Existing data set

The current study is a secondary analysis of data from the SGHI, which is a longitudinal cohort study originally designed to assess psychological and behavioral impacts experienced by consumers of DTC genomic testing. Participants in the SGHI underwent DTC testing between 2008 and 2009 with the Navigenics Health Compass (NHC), which generated risk assessments based on genotyping of approximately 500,000 bases in the individual's DNA. The NHC included personalized risk estimates for 23 common, genetically complex conditions. Details describing the SGHI and NHC have been previously reported (Bloss et al. 2010, 2011). Of relevance to this study, in the personalized risk estimates returned to participants, a condition was flagged as "orange" (implying "elevated risk") if the subject's estimated lifetime risk was more than 20% above average lifetime risk in the general population, or if the overall lifetime risk was more than 25%. Alternatively, a condition was labeled "gray" if it did not meet these criteria.

Participants in the SGHI completed baseline (prior to testing) and follow-up (offered 3 months after testing, with an average completion time of 5.6 months after testing) survey measures assessing variables such as demographics, personal and family health history, attitudes toward genetic testing, "state" (situational) anxiety (measured with the 20-item State Anxiety subscale of the Spielberger State-Trait Anxiety Inventory (STAI)), test-related distress (measured with the Avoidance and Intrusion subscales of the 22-item Impact of Event Scale—Revised (IES-R)), and reactions to receipt of results.

Current study

Within these existing data, we conducted a novel case-control study, comparing individuals who were considered to either have strong negative psychological responses (anxiety and distress) on follow-up survey measures or were considered to be psychologically sensitive with elevated anxiety throughout the process ("cases") to corresponding control groups comprised of individuals who did not show such characteristics. Since there is no single agreed-upon criteria for adverse or negative psychological responses and this was an exploratory study to determine if predictors of anxiety and/or distress could be identified, we defined inclusion criteria for the first set of "cases" in two ways using scores related to the STAI- and IES-R-validated measures. An increase of 12 points or more in STAI state score from baseline to follow-up survey is considered to indicate a reliably and clinically meaningful increase in anxiety (Spielberger et al. 1983; Jacobson and Truax 1991). A score of more than 23 points on

the Avoidance and Intrusion subscales of the IES-R is also considered to indicate clinically significant distress (Bloss et al. 2011; Weiss and Marmar 1997; Creamer et al. 2003). As such, the first case group is termed "distress response" ($N = 130$) and is defined as those with clinically meaningful anxiety and/or distress by meeting one or both of the following criteria: (1) individuals with STAI scores with an increase of 12 points or more between the baseline and follow-up surveys ($N = 77$), and (2) individuals with an IES-R score greater than 23 points ($N = 57$). There were only 4 individuals who met both criteria and their responses were not significantly different from the rest of the cases. The second case group is termed "psychologically sensitive" ($N = 431$) and is defined as those who had a score of ≥ 40 points on *both* the baseline and follow-up STAI measures; based on the definition by (Spielberger et al. 1983), a score of 40 points or higher as indicating clinically relevant state anxiety. This group was thought of as having pre-existing psychological sensitivity (versus an adverse psychological response to the genomic risk results, given that their anxiety was elevated prior to receiving any genomic test results).

Initial statistical analyses were conducted with the use of the statistical software package SPSS 22.0. Pearson's chi-squared, Fisher's exact tests, independent samples *t* tests, and Mann-Whitney *U* tests were used to compare those with and without clinically significant anxiety and/or distress with respect to demographic variables, reported concerns prior to testing, self-report of feelings after receipt of results, and estimated lifetime risk reports from the NHC for the 23 diseases. Analysis of the extent to which demographic characteristics were associated with clinically meaningful anxiety and/or distress was performed via logistic regression. Power analyses of comparison between subjects' reported life changes and estimated lifetime risk reports were conducted with the use of the statistical power analysis tool G*Power (Faul et al. 2009). Because we had limited power, which stemmed from a small number of "cases," we have presented p values < 0.10.

Results

Demographics

A total of 2037 participants in the SGHI completed the follow-up survey measure and were thus included in this analysis. As has been previously published (Bloss et al. 2011), the SGHI population is a largely Caucasian (84%), well-educated population with high socio-economic status; approximately 25% of the participant population were Scripps employees, assumedly with a higher scientific and/or medical literacy and interest (Boeldt et al. 2015).

Two case/control groups, "distress response" and "psychologically sensitive," were established for analysis based upon STAI and IES-R scores. The "distress response" group consists of 130 individuals while the corresponding control group consists of 1907 individuals. The "psychologically sensitive" group consists of 431 individuals while the corresponding control group consists of 1606 individuals.

Descriptive statistics for demographics and selected outcome variables are presented for the two study populations in Table 1. Individuals in the psychosocially sensitive group were more likely to be younger ($p < 0.0005$, $t = -7.17$, df = 749) and not have children ($p < 0.0005$, $\chi^2 = 13.33$, df = 1). Both case groups had statistically significant differences in income distribution ("distress response": $p = 0.001$, $Z = -3.22$, "psychologically sensitive": $p = 0.010$, $Z = -2.58$); however, both groups had a median income range of $100,000–$149,999 for both cases and controls.

In both analyses, logistic regression analysis of demographic characteristics (gender, age, having biological children, ethnicity (Caucasian or not), income category, highest level of education achieved) was not found to yield an effective predictive model. For psychologically sensitive subjects, however, younger age emerged as a predictor ($p < 0.0005$).

Pre-test concerns about participating in study

In the baseline survey, subjects were asked whether they had any concerns about participating in the study. Specifically, they could select tickboxes for concerns related to learning about their disease risk, to not knowing how they would feel about their results, to the quality and reliability of the testing lab and results, and to potential privacy issues about their data. A prior publication reported (Bloss et al. 2010) that approximately half of all overall participants indicated the statement that they had no concerns related to participation. In the current study, we found that the psychologically sensitive cases were significantly more likely to indicate concerns related to learning about their disease risk ($p < 0.0005$, $\chi^2 = 21.62$, df = 1), not knowing how they would feel about their results ($p < 0.0005$, $\chi^2 = 16.32$, df = 1), the quality and reliability of the testing lab and results ($p = 0.063$, $\chi^2 = 3.46$, df = 1), and potential privacy issues about their data ($p = 0.003$, $\chi^2 = 8.55$, df = 1) (Table 2). The subjects who demonstrated a distress response to receipt of their results were not significantly more likely to indicate any of the listed pre-test concerns.

Genomic risk results

There were no significant differences detected in either the total number of conditions for which each subject was found to be at "orange" elevated genomic risk or the total or average estimated lifetime risk value given for each of the conditions between cases and controls for either comparison group. The "distress response" case group trended towards a slightly

Table 1 Demographic and outcome variable comparisons between subjects in "distress response" and "psychologically sensitive" groups*

Variable		"Distress response"			"Psychologically sensitive"		
		Case ($N = 130$)	Control ($N = 1907$)	p value	Case ($N = 431$)	Control ($N = 1606$)	p value
Gender (% female)		63.1	54.8	0.066 ($\chi^2 = 3.38$, df = 1)	58.7	54.4	0.113 ($\chi^2 = 2.52$, df = 1)
Age (year)	Mean Range	46.3 ± 11.3 23–72	47.7 ± 12.1 19–85	0.727 ($t = -0.35$, df = 2035)	43.3 ± 10.8 20–75	47.6 ± 12.2 19–85	< 0.0005 ($t = -7.17$, df = 749)
Have children (% yes)		55.4	62.6	0.103 ($\chi^2 = 2.66$, df = 1)	54.5	64.1	< 0.0005 ($\chi^2 = 13.33$, df = 1)
Subject of prior GT (% yes)		6.2	5.8	0.875 ($\chi^2 = 0.03$, df = 1)	6.7	5.6	0.377 ($\chi^2 = 0.78$, df = 1)
STAI score at baseline	Mean Range	36.5 ± 9.7 21–64	35.1 ± 9.6 20–72	0.114 ($\chi^2 = 1.58$, df = 2035)	48.4 ± 6.0 40–72	31.7 ± 7.0 20–60	< 0.0005 ($\chi^2 = 49.25$, df = 767)
STAI score at follow-up	Mean Range	45.0 ± 11.2 21–79	34.0 ± 9.5 20–73	< 0.0005 ($t = 11.01$, df = 142)	48.6 ± 6.5 40–79	31.0 ± 6.9 20–64	< 0.0005 ($t = 49.19$, df = 710)
IES-R score	Mean Range	17.0 ± 17.9 0–60	2.3 ± 4.2 0–23	< 0.0005 ($t = 9.32$, df = 130)	5.0 ± 8.4 0–45	2.8 ± 6.6 0–60	< 0.0005 ($t = 5.0$; df = 580)
Income ($)	Mean Modal	100,000–149,999 50,000–99,999	100,000–149,999 100,000–149,999	0.001 (Z=−3.22)	100,000–149,999 100,000–149,999	100,000–149,999 100,000–149,999	0.010 ($Z = -2.58$)
Graduation from 4-year college (%)		74.6	80.5	0.101 ($\chi^2 = 2.69$, df = 1)	80.6	78.7	0.377 ($\chi^2 = 0.79$, df = 1)
Ethnicity (% white)†		83.8	84.2	0.911 ($\chi^2 = 0.01$, df = 1)	82.4	84.7	0.242 ($\chi^2 = 1.37$, df=1)
Recommend to (% yes)Δ	Family	77.1	82.1	0.191 ($\chi^2 = 1.71$, df = 1)	81.7	82	0.901 ($\chi^2 = 0.02$, df = 1)
	Others	79.8	83.7	0.294 ($\chi^2 = 1.10$, df = 1)	84.2	83.2	0.651 ($\chi^2 = 0.21$, df = 1)
Discuss results with (% yes)‡	PCP	27.7	26.4	0.752 ($\chi^2 = 0.10$, df = 1)	23.7	27.3	0.132 ($\chi^2 = 2.27$, df = 1)
	GC	13.8	10.1	0.177 ($\chi^2 = 1.82$, df = 1)	7.9	11	0.058 ($\chi^2 = 3.60$, df = 1)
Mean follow-up interval (months)		5.7	5.6	0.742 ($t = 0.33$, df = 2035)	5.8	5.6	0.198 ($t = 1.29$, df = 639)

*Plus-minus values are means ± SD. p values for comparisons of gender, have children, subject of prior GT, education, ethnicity, recommend to family/others, and discuss results with PCP/GC were calculated by means of Pearson chi-square; those for age, scores on STAI and IES, and mean follow-up interval by means of independent samples t test; and those for income and education by means of the Mann-Whitney U test

†Ethnicity was self-reported

Δ Based on survey question: would you recommend that (your family members/other people you know) undergo genetic risk assessment?

‡Based upon survey questions: Did you share the results of your genetic test with your physician or healthcare provider? Did you speak with a Navigenics certified genetic counselor about your genetic test results?

Table 2 Concerns about participating in study reported at baseline*†

Variable	"Distress response"			"Psychologically sensitive"		
	Case ($N = 130$)	Control ($N = 1907$)	p value	Case ($N = 431$)	Control ($N = 1606$)	p value
I do not have concerns	45.4	49.7	0.365 ($\chi^2 = 0.89$, df = 1)	39.4	52.1	< 0.0005 ($\chi^2 = 21.62$, df = 1)
Concerns related to learning about disease risk	13.1	12.4	0.828 ($\chi^2 = 0.05$, df = 1)	19.7	10.5	< 0.0005 ($\chi^2 = 26.34$, df = 1)
Concerns related to not knowing how I will feel about my results	15.4	16.4	0.759 ($\chi^2 = 0.09$, df = 1)	22.7	14.6	< 0.0005 ($\chi^2 = 16.32$, df = 1)
Concerns related to the quality and reliability of the testing lab and results	14.6	15	0.893 ($\chi^2 = 0.02$, df = 1)	17.9	14.3	0.063 ($\chi^2 = 3.46$, df = 1)
Concerns related to potential privacy issues about my data	40.8	36.9	0.373 ($\chi^2 = 0.80$, df = 1)	43.2	35.5	0.003 ($\chi^2 = 8.55$, df = 1)

*p values were calculated by means of Pearson chi-square

†Based on survey question: Do you have concerns about participating in this initiative? Please check all that apply

higher total ($p = 0.061$, $t = 1.88$, df = 2035) and average ($p = 0.123$, $t = 1.54$, df = 2035) estimated lifetime risk values, though there was limited power in these analyses (0.456 and 0.414, respectively; Table 3).

We assessed various combinations of personal and/or family history for conditions as they may relate to psychological experience and significant trends emerged for two conditions. For Alzheimer's disease, "psychologically sensitive" cases were significantly more likely to have a positive personal or family history than controls (28.1% of cases, 23% of controls; $p = 0.029$, $\chi^2 = 4.78$, df = 1) (Table 4). Additionally, "psychologically sensitive" cases were significantly more likely to have a positive family history plus personal "orange" elevated risk than controls (28.1% of cases, 23.1% of controls; $p = 0.032$, $\chi^2 = 4.59$, df = 1) (Table 5). For restless leg syndrome, both the "distress response" and "psychologically sensitive" case groups were more likely to have a personal or family history of the syndrome ("distress response": 17.7% of cases, 11.4% of controls; $p = 0.033$, $\chi^2 = 4.55$, df = 1; "psychologically sensitive": 14.4% of cases, 11.2% of controls; $p = 0.063$, $\chi^2 = 3.47$, df = 1) (Tables 4 and 5).

Reactions to receipt of genomic risk results

There were no differences with regard to communicating about results with healthcare providers (26.5% of the total population shared results with a primary healthcare provider and 10.4% spoke with a Navigenics certified genetic counselor) between case and control groups for either the distress response or psychologically sensitive group (Table 1). Table 6 shows how subjects in each group responded to the question of whether they experienced any changes in their lives as a result of receiving their genomic risk results. Subjects with a psychological distress response reported significant changes in the way they thought of themselves as a result of receiving their risk assessment compared to controls ($p = 0.032$), and both subjects with a psychological distress response and those who were psychologically sensitive reported significant changes in their emotions ($p < 0.0005$ and $p = 0.049$, respectively). Of specific relevance, both case groups reported being significantly more concerned about their health at follow-up than their respective control groups ($p = 0.011$, $Z = -2.59$ and $p = 0.001$, $Z = -3.46$, respectively) (Table 7).

Discussion

This study performed a secondary analysis to characterize individuals with adverse psychological experiences surrounding genomic risk assessment for a set of 23 common, complex conditions and identify predictors of such reactions by a secondary analysis of data from the Scripps Genomic Health Initiative (SGHI). Of the 2037 individuals studied, 130 (6.4%) experienced adverse psychological reactions to receipt of their test results using one of two definitions. This relatively small percentage of subjects with adverse psychosocial response is consistent with other similar reports in the literature around the receipt of low-penetrance genomic data (Francke et al. 2013; Egglestone et al. 2013). Our study was unable to find any demographic factors that predicted who would have an adverse psychological response aside from those participants who self-indicated pre-participation concerns. Further, the only medical conditions that were predictive of clinically significant psychological distress or psychological sensitivity were having a personal or family history of Alzheimer's disease or restless leg syndrome, and it remains unclear if this is a clinically meaningful discovery.

Table 3 Comparisons of mean (± standard deviation, minimum-maximum) values for numbers of "orange" conditions, total estimated lifetime risks (ELTR), and average estimated lifetime risks (ALTR) for the set of conditions*

Variable	"Distress response"			"Psychologically sensitive"		
	Case (N = 130)	Control (N = 1907)	p value	Case (N = 431)	Control (N = 1606)	p value
Orange	7.4 ± 2.3 (3–17)	7.4 ± 2.3 (0–16)	0.823 (t = −0.22, df = 2035)	7.4 ± 2.1 (0–16)	7.4 ± 2.3 (2–17)	0.858 (t = 0.18, df = 2035)
Total ELTR†	229.7 ± 28.7 (100–308)	225.0 ± 27.7 (3–346)	0.061 (t = 1.88, df = 2035)	225.5 ± 25.8 (3–346)	225.3 ± 28.3 (113–341)	0.882 (t = 0.15, df = 2035)
Average ELTR‡	10.6 ± 1.2 (8–14)	10.3 ± 1.6 (3–53)	0.123 (t = 1.54, df = 2035)	10.4 ± 1.1 (3–53)	10.4 ± 1.6 (113–341)	0.857 (t = −0.18, df = 2035)

*p values were calculated by means of independent samples t test

†The total estimated lifetime risk (ELTR) is a total of the risk estimates (percentage) for all of the conditions

‡The average estimated lifetime risk (ELTR) is an average of the risk estimates (percentage) for all of the conditions

Though we were unable to identify many significant predictors of either clinically meaningful anxiety and/or distress responses to receipt of results or heightened anxiety both before and after receipt of results indicating psychological sensitivity, our analyses have provided some insights into our study population. First, we were able to differentiate two types of patients who experience distress after genomic testing—one population who experiences a change in distress and one that experiences distress both before and after testing, who we refer to as the psychologically sensitive patients. These psychologically sensitive patients indicated a significantly higher frequency of pre-test concerns about participating in the SGHI than their corresponding control group in all but concerns related to quality and reliability. In contrast, individuals with a distress response indicated fewer pre-test concerns. It is possible that the distress response individuals may have been less effective at pre-test identification of which aspects of the SGHI may have ultimately lead them to experience a distress response.

One especially interesting aspect of these data is the fact that only 15% (306/2037) of the total study population indicated concerns related to quality and reliability of the DTC lab and their results. This is in contrast to the concerns that have been documented in the literature (Ng et al. 2009; Mathews et al. 2012; Annas and Elias 2014). Given that the study population had a high level of education and may have greater-than-average scientific acumen compared to the general population (Roberts and Ostergren 2013), the general population may be less able to understand potential limitations of this type of data and potentially more likely to overestimate the meaning this information has to their lives. This may be one point in support of the argument that discussion of these types of results with a genetics specialist who is equipped to provide context for interpretation could serve to increase the likelihood of appropriate understanding of results. Overall, there are limited data on how people incorporate this type of moderate and low predictive genomic information into their lives and whether or not it is likely to present clinically relevant psychological risks to them in the long term.

Limitations

This study is limited by the use of an existing sample for the study population. These participants are largely Caucasian, highly-educated, and of high socioeconomic status, with likely high medical and/or scientific literacy and comfort. Thus, caution should be taken in generalizing this analysis to the broader population of those who may undergo genomic testing for common, complex conditions in the future. These features may both explain the relatively low rate of adverse psychosocial outcomes in the original SGHI study and our

Table 4 Percentage of subjects with a positive personal *or* family history of the listed condition*

Variable	"Distress response"			"Psychologically sensitive"		
	Case ($N = 130$)	Control ($N = 1907$)	p value	Case ($N = 431$)	Control ($N = 1606$)	p value
Heart attack	53.8	58.8	0.264 ($\chi^2 = 1.25$, df = 1)	57.8	58.7	0.724 ($\chi^2 = 0.13$, df = 1)
Abnormal heart rhythm	30.8	31.2	0.918 ($\chi^2 = 0.01$, df = 1)	30.2	31.4	0.610 ($\chi^2 = 0.26$, df = 1)
Aortic aneurysm	6.2	6.8	0.771 ($\chi^2 = 0.09$, df = 1)	7.4	6.6	0.545 ($\chi^2 = 0.37$, df = 1)
Prostate cancer	23.4	18.9	0.209 ($\chi^2 = 1.58$, df = 1)	17.9	19.6	0.427 ($\chi^2 = 0.63$, df = 1)
Breast cancer	27.9	29.1	0.769 ($\chi^2 = 0.09$, df = 1)	27	29.6	0.288 ($\chi^2 = 1.13$, df = 1)
Lung cancer	19.2	24	0.219 ($\chi^2 = 1.51$, df = 1)	21.6	24.2	0.251 ($\chi^2 = 1.32$, df = 1)
Colon cancer	25.4	20.2	0.155 ($\chi^2 = 2.02$, df = 1)	19.5	20.8	0.554 ($\chi^2 = 0.35$, df = 1)
Melanoma	12.3	15.6	0.312 ($\chi^2 = 1.02$, df = 1)	15.7	15.3	0.873 ($\chi^2 = 0.03$, df = 1)
Alzheimer's disease	20.8	24.3	0.362 ($\chi^2 = 0.83$, df = 1)	28.1	23	0.029 ($\chi^2 = 4.78$, df = 1)
Restless leg syndrome	17.7	11.4	0.033 ($\chi^2 = 4.55$, df = 1)	14.4	11.2	0.063 ($\chi^2 = 3.47$, df = 1)
Multiple sclerosis	6.2	3.6	0.140 ($\chi^2 = 2.18$, df = 1)	3.7	4.2	0.626 ($\chi^2 = 0.24$, df = 1)
Crohn's disease	3.8	2.9	0.530 ($\chi^2 = 0.39$, df = 1)	3.5	2.8	0.460 ($\chi^2 = 0.55$, df = 1)
Lupus	3.1	3.6	0.770 ($\chi^2 = 0.09$, df = 1)	2.6	3.8	0.214 ($\chi^2 = 1.55$, df = 1)
Thyroid disease	23.8	27.4	0.382 ($\chi^2 = 0.77$, df = 1)	29.9	26.4	0.143 ($\chi^2 = 2.14$, df = 1)
Glaucoma	23.8	22	0.628 ($\chi^2 = 0.23$, df = 1)	23.4	21.8	0.466 ($\chi^2 = 0.53$, df = 1)
Diabetes, type 2	43.8	49.6	0.208 ($\chi^2 = 1.59$, df = 1)	51.7	48.5	0.233 ($\chi^2 = 1.42$, df = 1)

*p values calculated by means of Pearson chi-square. Sixteen (as opposed to 24) conditions were assessed here because personal and family history of all of the NHC conditions were not assessed

difficulty in identifying predictors towards it. Additionally, 44% of subjects who completed the baseline survey and underwent genomic testing did not complete the follow-up survey and thus were not analyzed. As a result, it is possible a segment of individuals with a distress response or high anxiety surrounding the time of testing dropped out of follow-up, which would lead to an underestimate of the individuals with distress responses.

Critical to interpretation of DTC testing data is that these studies most likely include a biased population of

Table 5 Percentage of subjects with a positive family history *and* "orange" (elevated) estimated lifetime risk of the listed condition*

Variable	"Distress response"			"Psychologically sensitive"		
	Case ($N = 130$)	Control ($N = 1907$)	p value	Case ($N = 431$)	Control ($N = 1606$)	p value
Heart attack	34.6	40.8	0.165 ($\chi^2 = 1.93$, df = 1)	39.4	40.7	0.648 ($\chi^2 = 0.21$, df = 1)
Abnormal heart rhythm	25.4	26	0.885 ($\chi^2 = 0.02$, df = 1)	23.9	26.5	0.281 ($\chi^2 = 1.17$, df = 1)
Aortic aneurysm	5.4	6.8	0.528 ($\chi^2 = 0.40$, df = 1)	7.2	6.6	0.663 ($\chi^2 = 0.19$, df = 1)
Prostate cancer	22.3	18.6	0.290 ($\chi^2 = 1.12$, df = 1)	17.9	19.1	0.575 ($\chi^2 = 0.31$, df = 1)
Breast cancer	26.9	28.1	0.771 ($\chi^2 = 0.09$, df = 1)	26.2	28.5	0.345 ($\chi^2 = 0.90$, df = 1)
Lung cancer	19.2	23.9	0.229 ($\chi^2 = 1.45$, df = 1)	21.6	24.1	0.274 ($\chi^2 = 1.20$, df = 1)
Colon cancer	25.4	19.9	0.134 ($\chi^2 = 2.24$, df = 1)	19.5	20.5	0.648 ($\chi^2 = 0.21$, df = 1)
Alzheimer's disease	20.8	24.4	0.352 ($\chi^2 = 0.87$, df = 1)	28.1	23.1	0.032 ($\chi^2 = 4.59$, df = 1)
Restless leg syndrome	9.2	8.1	0.641 ($\chi^2 = 0.22$, df = 1)	9	7.9	0.442 ($\chi^2 = 0.59$, df = 1)
Multiple sclerosis	4.6	3.4	0.446 ($\chi^2 = 0.58$, df = 1)	3.7	3.4	0.723 ($\chi^2 = 0.13$, df = 1)
Crohn's disease	2.3	2.7	0.801 ($\chi^2 = 0.06$, df = 1)	3.5	2.4	0.227 ($\chi^2 = 1.46$, df = 1)
Lupus	3.1	3.2	0.939 ($\chi^2 = 0.01$, df = 1)	2.1	3.1	0.142 ($\chi^2 = 2.15$, df = 1)
Glaucoma	22.3	21.3	0.795 ($\chi^2 = 0.07$, df = 1)	23.2	20.9	0.305 ($\chi^2 = 1.05$, df = 1)
Diabetes, type 2	43.8	49	0.257 ($\chi^2 = 1.28$, df = 1)	51.3	47.9	0.219 ($\chi^2 = 1.51$, df = 1)

*p values calculated by means of Pearson chi-square

Table 6 Percent of subjects' who reported life changes since receipt of test results*†

Variable	"Distress response"			"Psychologically sensitive"		
	Case ($N = 130$)	Control ($N = 1907$)	p value	Case ($N = 431$)	Control ($N = 1606$)	p value
Body image	4.6	8.3	0.181	10.2	7.5	0.074
Childbearing decisions	0.8	0.6	0.577	0.9	0.6	0.492
Emotions	11.5	3.4	< 0.0005	5.6	3.4	0.049
The way I think of myself	22.3	14.9	0.032	18.1	14.7	0.084
Relationship with partner	5.4	2.6	0.086	3.9	2.4	0.097
Relationship with children	2.3	1.7	0.486	1.9	1.7	0.835
Relationship with other relatives	3.1	1.8	0.301	2.6	1.7	0.232
Employment	2.3	0.7	0.077	1.6	0.6	0.057
Insurance	3.8	1.5	0.055	2.8	1.3	0.049
Other	10.8	9.1	0.529	10	9	0.512
None	58.5	69	0.015	61.7	79	0.001

*p values were calculated by means of Fisher's exact test

†Based on survey question: What changes, if any, have occurred in your life as a result of receiving your genetic test results? Each variable listed was represented as an independent box to check or leave unchecked. Unfortunately due to the limitation of existing survey data, qualitative data elaborating on what specific changes (or direction of changes) occurred is not available

early-adopter individuals who are self-selecting to receive such data. As has been noted in predictive testing for Huntington disease (Codori et al. 1994) and other Mendelian highly penetrant conditions, early adopters are likely self-selected individuals who may be better prepared to both understand and emotionally incorporate such results into their self-concept, and thus, these studies may potentially underestimate the psychosocial impact that may be noted if such genomic testing becomes more widespread in the future.

Finally, as noted in the methods and results section, the sample size, particularly for the "distress response" group, was too small to have enough statistical power to detect the ideal effect sizes at the recommended 0.80 level (Cohen 1992). Thus, it is possible that a larger sample size would demonstrate statistically significant differences and thus, further study of larger samples would be useful.

Conclusions

DTC genomic risk assessment has been a subject of much discussion and study over the past several years, and it is still to be determined how much of personalized genomics will primarily utilize the DTC format (for example through "apps") as compared to a healthcare system delivery model as the primary manner in which genomic information is provided to patients and consumers in the future (Annas and Elias 2014; Allison 2012). There are also changing trends with regard to the role of pre-test genetic counseling, with ClinGen's Consent and Disclosure of Results (CADRe) workgroup developing a rubric to assess which genomic tests warrant a more traditional genetic counseling pre-test approach as compared to a targeted discussion or even static educational materials (personal communication). Although we identified

Table 7 Comparisons between subjects reported concern about their health after receipt of test results*

Variable	"Distress response"			"Psychologically sensitive"		
	Case ($N = 130$)	Control ($N = 1907$)	p value	Case ($N = 431$)	Control ($N = 1606$)	p value
Significantly or somewhat less concerned about my health (%)	18.9	20.8	0.011 ($Z = -2.59$)	16.5	21.8	0.001 ($Z = -3.46$)
As concerned about my health (%)	38.5	50.8		47.9	50.6	
Significantly or somewhat more concerned about my health (%)	42.6	28.4		35.6	27.5	

*p values were calculated by means of Mann-Whitney U test. Those who selected the answer "Less concerned about my general health, but more concerned about one disease" were omitted from this analysis as this response did not clearly fit into a category

only a small number of individuals with a psychological distress response, our inability to identify meaningful predictors of such adverse psychological experiences surrounding genomic risk assessment serves to emphasize the difficulty in easily assessing who may have a post-test distress response (Dohany et al. 2012; Matloff and Caplan 2008). Our study's key finding suggests that a subset of patients receiving genomic risk information can be described as psychologically sensitive and may be at risk for adverse psychological outcomes after results disclosure. As such, it is important to identify ways to best serve these patients before they receive genetic testing results. It should be acknowledged that there are likely both patient-specific and result-specific risk factors that may help predict psychological distress and be used to identify candidate patients who stand to benefit from special attention. At a minimum, we encourage both healthcare providers and DTC companies developing future approaches to find ways to assess psychological distress and sensitivity before testing and to encourage more extensive consideration and pre-test discussion in those patients identified as being psychologically sensitive (Shiloh et al. 2013; Boeldt et al. 2015). Genetic counselors, psychologists, social workers, and other mental health professionals may be useful in providing such services.

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Compliance with ethical standards

Conflict of interest Kelly Ormond was a paid consultant for Navigenics in 2007–2009, during which time the original SGHI data was obtained, but she was not involved in the creation or oversight of the original Bloss et al. (2011) study or its data in any way.

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