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Return of individual genetic results in a high-risk sample: enthusiasm and positive behavioral change

Sarah M. Hartz, MD, PhD[1], Emily Olfson, BA[1], Robert Culverhouse, PhD[1], Patricia Cavazos-Rehg, PhD[1], Li-Shiun Chen, MD, DsC[1], James DuBois, PhD[1], Sherri Fisher, MS[1], Kimberly Kaphingst, ScD[1], David Kaufman, PhD[2], Andrew Plunk, PhD[1], Shelina Ramnarine, BS[1], Stephanie Solomon, PhD[3], Nancy L. Saccone, PhD[1] and Laura J. Bierut, MD[1]

Purpose: The goal of this study was to examine participant responses to disclosure of genetic results in a minority population at high risk for depression and anxiety.

Methods: Eighty-two subjects in a genetic study of nicotine dependence were offered personalized genetic results. All were nicotine-dependent and 64% self-identified as African American. Pathway Genomics was used to evaluate genetic risks for five complex diseases. Participants returned 4–8 weeks after enrollment for in-person genetic counseling interviews and evaluation of baseline measures. A telephone follow-up was performed 4–8 weeks later to assess responses to results.

Results: Fifty of the 82 subjects (61%) were interested in receiving genetic results. These participants had multiple risk factors, including high baseline measures of depression (66%) and anxiety (32%), as well as low rates of employment (46%), adequate health literacy (46%), and health insurance (45%). Pathway Genomics reported "increased risk" for at least one disease in 77% of subjects. Ninety-five percent of participants reported that they appreciated the genetic results, and receiving these results was not associated with changes in symptoms of depression or anxiety. Furthermore, after return of genetic results, smoking cessation attempts increased ($P = 0.003$).

Conclusion: Even in an underserved population at high risk for adverse psychological reactions, subjects responded positively to personalized genetic results.

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Key Words: genomics; minorities; participants; return of results

INTRODUCTION

Over the past decade, the return of individual genetic research results has emerged as a highly contentious issue.[1–5] Advocates assert that researchers and clinicians have an ethical obligation to offer certain results when possible, based on principles of beneficence and respect of persons.[1,2] Critics emphasize possible harmful effects, including therapeutic misconceptions, financial burdens, and undue anxieties.[1,3,4] Similar concerns regarding potential downstream consequences of individual genetic results have been raised in consumer settings with the increased use of personalized genetic testing, especially for direct-to-consumer companies.[6–10] As genomics research marches forward, a better understanding of how individuals respond to personalized genetic results is critical for informing future policies and decisions regarding appropriate use of this information.

There has been recent controversy over direct-to-consumer genetic testing. Specifically, the US Food and Drug Administration issued concerns that 23andMe was inappropriately offering genetics-based medical recommendations.[11] Because of this, 23andMe stopped offering medical reports with the genetic testing. Rather, 23andMe offers the same genetic testing and ancestry report, but no medical reports.

Despite the controversy concerning 23andMe, studies demonstrate that the public strongly favors opportunities for disclosure of individual genetic results.[12–17] Although African Americans are often underrepresented in genetics research, focus groups indicate that many individuals are interested in receiving their genetic results,[12,14] and offering results may encourage future research participation.[14] In response to the public's interest in individualized genetic information, a growing number of studies over the past 5 years have examined subject responses to actually receiving genetic findings.[18–23] These studies suggest that return of genetic results does not pose substantial psychological or behavioral harms. Because these studies focused primarily on populations that are at relatively low risk for adverse psychological reactions (the majority of subjects studied are college-educated European Americans with health insurance who are employed or retired), the generalizability of these positive findings remains unclear.

An important next step is to investigate participant responses to personalized genetic results in a population at high risk for adverse psychological reactions. In this study, individual research results regarding complex disease risks were returned to participants in a genetic study of nicotine dependence: the

[1]School of Medicine, Washington University in St. Louis, St. Louis, Missouri, USA; [2]Johns Hopkins University, Washington, DC, USA; [3]Saint Louis University, St. Louis, Missouri, USA. Correspondence: Sarah M. Hartz (hartzs@wustl.edu)

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majority of participants were African American, not college educated, unemployed, and uninsured. These data provide critical insight into the psychological and behavioral impact of personalized genetic results in a population that has traditionally been severely underrepresented in genetics research.

MATERIALS AND METHODS

Setting and participants

This return of results study builds on an ongoing genetic study of nicotine dependence, the Collaborative Genetic Study of Nicotine Dependence (COGEND).[24,25] In 2013, COGEND was recruiting nicotine-dependent smokers from the St. Louis metropolitan area. All nicotine-dependent COGEND subjects were eligible for this return of results study until 50 subjects were recruited. After completion of the COGEND interview, eligible subjects interested in participating in this return of results study were read basic explanations of the genetic testing procedures and the interpretation of genetic results. Those who expressed continued interest were given a complete description of the study design, including example genetic results (**Supplementary Material** online). Individuals who chose to be study participants then signed an informed consent form. This study protocol was approved by the institutional review board at Washington University School of Medicine.

Study design

Participants were assessed three times: at the time of consent, before receiving genetic results (4–8 weeks after consent), and during a telephone follow-up (4–8 weeks after return of genetic results and genetic counseling). At the time of consent, participants were assessed for anxiety using the Beck Anxiety Inventory[26] and for depressive symptoms using the Center for Epidemiological Studies Depression Scale.[27] Participants donated saliva samples, which were sent to Pathway Genomics (San Diego, CA) for microarray-based genetic analysis of risk for five complex diseases: lung cancer, breast or prostate cancer, colorectal cancer, heart attack, and type II diabetes (example results are given in the **Supplementary Material** online). Pathway Genomics genotyped the saliva samples for known genetic variants related to these diseases and used a proprietary algorithm to define individuals as being at "increased risk," "above-average risk," and "average risk."

Pathway Genomics was chosen for this return of results study because it is accredited in accordance with the US Health and Human Services Clinical Laboratory Improvement Amendments of 1988 and therefore meets basic standards for return of results. Genotyping from the original parent study of nicotine dependence was not performed in a Clinical Laboratory Improvement Amendments–certified laboratory. We chose to return genetic results of five complex diseases for which smoking cessation is critical for reducing overall risk. Of note, the strongest genetic risk factor for lung cancer is the same as the strongest genetic risk for smoking behavior. Pathway Genomics does not offer reports on nicotine addiction.

Participants returned 4–8 weeks after donating samples to receive their genetic results. At the beginning of this meeting, each participant was assessed for health literacy using the REALM-R.[28] Current health-care accessibility, smoking behavior, cessation attempts, diet, and exercise were also assessed.

Subsequently, the results were given to the participant in the context of a genetic counseling session. Although genetic counselors were given up to 1 hour to meet with each subject, the average counseling session lasted ~10 min. The genetic counselor gave personalized results to each participant and emphasized the importance of smoking cessation. The counselor then offered to answer any questions the subjects had about their results. Before leaving, subjects were given a folder containing individual genetic results (without identifying information) and smoking cessation tips.

Each participant was called on the telephone 4–8 weeks after receiving the genetic results and asked about his or her response

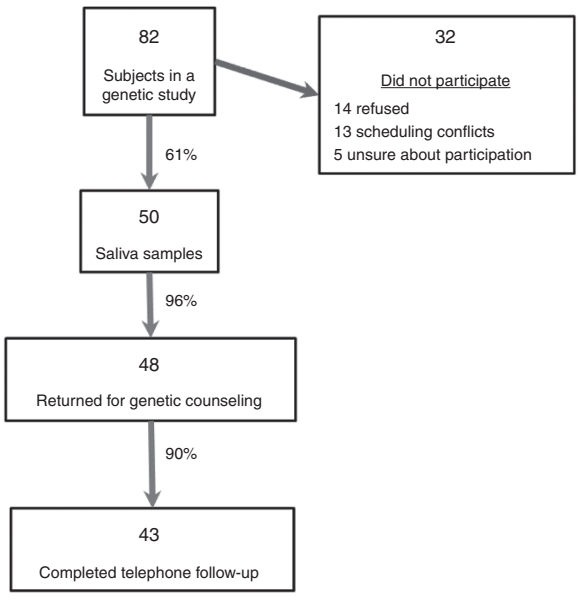

Figure 1 Flowchart of subject participation.

Table 1 Characteristics of subjects offered genetic results

	Participants (n = 50)	Nonparticipants (n = 32)
Average age (SD)[a]	34.9 (5.8)	33.3 (5.5)
Male[a]	46%	47%
African-American[a]	62%	44%
Bachelor's or associate's degree[a]	30%	23%
Employed[a]	46%	50%
Has health insurance	45%	—
Limited health literacy	54%	—
Baseline depression (CES-D ≥16)	66%	—
Baseline anxiety (BAI ≥16)	32%	—

BAI, Beck Anxiety Inventory; CES-D, Center for Epidemiological Studies Depression Scale.

[a]No statistical difference between participants and nonparticipants ($P > 0.05$).

to the results, as well as current health-care accessibility, smoking behavior, diet, exercise, symptoms of depression (Center for Epidemiological Studies Depression Scale),[27] and symptoms of anxiety (Beck Anxiety Inventory).[26]

Statistical analysis

All statistical analyses were performed using Statistical Analysis System (SAS 9.3; SAS Institute, Cary, NC). Changes in dichotomous variables over time (depression, anxiety, and smoking cessation attempts in the past month) were evaluated using McNemar's test, and changes in continuous variables (change in depression and anxiety scales) were modeled using linear regression. Power calculations (SAS PROC POWER) were also used.

RESULTS

Participant characteristics

Eighty-two subjects were offered return of genetic results; 61% (50/82) of these subjects accepted the invitation to participate (**Figure 1**). Of the 32 subjects who declined participation, 41% (13/32) reported scheduling conflicts. No statistical differences between the participants (n = 50) and nonparticipants (n = 32) ($P > 0.05$) for sex, race, educational attainment, employment status, or age (details of demographics in **Table 1**) were observed.

The participants themselves were at very high risk for psychiatric events (**Table 1**). Specifically, their baseline symptoms of depression and anxiety (strong predictors of future major depression disorder and anxiety)[29] were very high. In addition, many subjects had limited health literacy, had low education levels, were unemployed, or were uninsured (**Table 1**). These factors increase the chance of confusion or distress, which may in turn increase the risk for depression or anxiety.

Genetic results

The participants reported an overwhelmingly positive reaction to the results: 95% of the subjects said they found the results worthwhile. All but one subject discussed the results with someone outside the study, including their doctors (17%) and family or friends (95%).

Most of the subjects (77%; 33/43) received a genetic report with "increased risk" for at least one of the five tested diseases. The most common disease with increased risk was colorectal cancer (16/43). None of the women received a report stating they had an increased risk for breast cancer (*BRCA1* and *BRCA2* variants were not genotyped; **Supplementary Material** online).

Two subjects reported being upset by the results. Both of these subjects had "above average" risk for lung cancer; one also had "above average" risk for heart disease. Both found the results worthwhile, both told their friends about the results, and neither had a clinically significant increase in anxiety.

Changes in depression and anxiety

Receiving genetic results did not lead to changes in the proportion of subjects meeting criteria for depression as defined by a Center for Epidemiological Studies Depression Scale score ≥16, or anxiety as defined by a Beck Anxiety Inventory score ≥16 (**Table 2**). In addition, even for individuals who received reports indicating increased risk of any disease or each specific disease, we observed no significant increase in the overall proportion of subjects with depression or anxiety (**Table 2**).

To further investigate the impact of receiving genetic results on symptoms of depression and anxiety, we evaluated whether increased risk of disease was related to change in depression or anxiety scores (**Table 3**). No associations were seen between changes in depression or anxiety scores and reported genetic risk of disease (**Table 3**).

A power analysis was used to determine whether lack of a statistical association suggests lack of a clinical association. A clinically significant increase in symptoms of depression was defined as an increase of 6 on the Center for Epidemiological Studies Depression Scale score, which corresponds to two symptoms of depression increasing from "rarely" to "most or all of the time." Similarly, a clinically significant increase in symptoms of anxiety was defined as an increase of 6 on the Beck Anxiety Inventory score, which corresponds to anxiety increasing from "no anxiety" to "mild anxiety," or "mild anxiety" increasing to "moderate anxiety." Using the observed sample size and SE, we calculated that there was 89% power

Table 2 Return of genetic results does not increase the proportion of subjects with depression or anxiety

		Depression (CES-D ≥16)			Anxiety (BAI ≥16)		
	n	Baseline	Follow-up	*P* value	Baseline	Follow-up	*P* value
Full sample	43	66%	73%	0.55	32%	27%	0.69
Subjects at increased genetic risk for:							
Any diagnosis	33	63%	76%	0.21	30%	27%	0.65
Lung cancer	7	71%	71%	1.0	29%	29%	1.0
Heart attack	9	67%	67%	1.0	33%	22%	0.32
Type II diabetes	6	67%	83%	0.32	17%	17%	1.0
Colorectal cancer	16	56%	75%	0.26	25%	31%	0.32
Prostate cancer	8	87%	75%	0.32	38%	38%	1.0
Breast cancer	0	—	—	—	—	—	—

BAI, Beck Anxiety Inventory; CES-D, Center for Epidemiological Studies Depression Scale.

Table 3 Anxiety and depression scores are not clinically increased by return of genetic results, even when there is increased risk for disease

		Depression scale (CES-D)		Anxiety scale (BAI)	
	n	Average change in score	*P* value	Average change in score	*P* value
Full sample[a]	43	0.5	0.75	2.9	0.10
Average change in score based on increased genetic risk for:					
Any diagnosis	33	1.7	0.15	3.9	0.24
Lung cancer	7	–4.0	0.35	6.3	0.58
Heart attack	9	3.1	0.25	3.1	0.94
Type II diabetes	6	2.3	0.74	7.2	0.55
Colorectal cancer	16	2.3	0.40	5.2	0.27
Prostate cancer	8	–0.5	0.72	1.1	0.64
Breast cancer	0	—	—	—	—

Clinically significant change for both scales (BAI and CES-D) is 6. BAI, Beck Anxiety Inventory; CES-D, Center for Epidemiological Studies Depression Scale.

[a]With current sample size and SE, there is 89% power to detect an overall increase of 6 in CES-D score and 97% power to detect an overall increase of 6 in BAI score for $P < 0.05$.

Table 4 Smoking cessation attempts increased following the return of personalized genetic results

		Attempted smoking cessation in the past month		
	n	Baseline	Follow-up	*P* value
Full sample	43	21%	53%	0.0005
Subjects at increased genetic risk for:				
Any diagnosis	33	24%	52%	0.003
Lung cancer	7	14%	57%	0.08
Heart attack	9	22%	33%	0.32
Type II diabetes	6	33%	67%	0.15
Colorectal cancer	16	25%	50%	0.05
Prostate cancer	8	38%	63%	0.15
Breast cancer	0	—	—	—

to detect a clinically significant change in depression and 97% power to detect a clinically significant change in anxiety. This suggests that we had adequate power to detect clinically significant effects in the overall sample.

Behavioral response

Our secondary analyses examined whether return of genetic results changed behavior. Attempts at smoking cessation were measured at two time points: baseline of 4–8 weeks after the parent genetic study of nicotine dependence (at the time of genetic counseling) and follow-up of 4–8 weeks after genetic counseling for the return of results study (Table 4). Subjects were more likely to attempt smoking cessation after receiving genetic results relative to a similar duration of time after participation in the study of nicotine dependence alone ($P = 0.003$). A strong increase in attempts to quit occurred among individuals who received reports with increased genetic risk for lung cancer (quit attempts increased from 14% to 57%), but this difference was not statistically significant ($P = 0.08$).

DISCUSSION

After receiving personalized genetic results, participants from a genetic study of nicotine dependence reported that the results were useful and they did not experience an increase in symptoms of depression or anxiety. This overall positive response to return of genetic results is particularly noteworthy because the sample is comprised of underserved individuals at high risk for adverse psychological events, as evidenced by high rates of baseline symptoms of depression and anxiety, as well as low rates of employment, health insurance, and health literacy.

Overall, this study had a high participation rate (61%) and almost all of the participants indicated that receiving genetic results was worthwhile (95%), suggesting that individuals from minority high-risk populations appreciate personalized genetic findings. This extends results from focus groups that found that the majority of African Americans were interested in receiving genetic results.[12,14]

Participants did not have increased scores on depression or anxiety measures in response to receiving genetic risk information on complex diseases, results similar to those of studies of other populations at relatively lower risk for adverse events.[18,22] Bloss et al.[18] offered subsidized personalized genetic testing of complex diseases to individuals working in health and technology, and responses from more than 2,000 participants showed no measurable changes in anxiety 3 months after receiving genetic information. In addition, preliminary findings from a survey of 1,800 customers of two genomics companies suggest there is no elevation in anxiety or distress during the year after receiving genetic results.[22] Our findings build on these studies by demonstrating that even in a high-risk population defined by low health-care literacy, high levels of unemployment, and lack of insurance, symptoms of depression and anxiety were not increased after disclosure of genetic complex disease information.

Beyond not causing a substantial increase in symptoms of depression or anxiety, after disclosure of genetic risks for complex diseases there was an increase in smoking cessation attempts. This raises the question of whether return of genetics results may motivate smoking cessation attempts in a nicotine-dependent population, contributing to the debate over whether genetic information can motivate risk-reducing health

behaviors.[30] Specifically, subjects were significantly more likely to make quit attempts 4–8 weeks after return of results in the genetic counseling session as compared with a baseline measured 4–8 weeks after the original interview for the parent study of nicotine dependence. This finding suggests that the smoking behavioral change was driven by the process of receiving personalized genetic results and not simply by interviewer contact or discussion about smoking cessation. However, further studies that include a control group are necessary to determine whether increased quit attempts are attributable to receiving personalized genetic results rather than confounding factors such as increased study engagement.

Even though we observed an increase in attempts to quit smoking, cessation is difficult, and often numerous attempts are made before smokers are able to successfully quit. A recent meta-analysis found that communication of DNA-based risk estimates was not associated with smoking cessation.[31] However, we can speculate that increased motivation to quit during the period after return of genetic results may be an opportune time for intensive smoking cessation therapies.

This study has several limitations. First, we used a convenience sample recruited through a parent study of nicotine dependence, and our study did not include a control group. Second, the sample size of 50 participants is modest; therefore, the observed results may be driven by a limited number of individuals. Nonetheless, the study was appropriately powered to detect clinically significant changes in symptoms of depression and anxiety (89 and 97%, respectively). Third, we returned genetic risk results of five complex diseases and did not include highly penetrant genetic variants, such as *BRCA1* or *BRCA2* mutations. It is possible that results associated with a greater increased risk of disease may prompt additional distress. Studies that returned pathogenic variants in *APOE* for Alzheimer disease,[20] *BRCA1* and *BRCA2* for hereditary breast and ovarian cancer,[19] and *CDKN2A* for melanoma[23] found that these potentially alarming disclosures caused only modest distress. Additional studies are necessary to extend these analyses to underserved and high-risk populations. Fourth, our findings are based on a single follow-up assessment at 1–2 months and cannot be used to assess the long-term effects of the genetic results. In addition, it would be useful to expand the qualitative component of this study. Future qualitative and quantitative studies that follow research participants after receiving genetic results are needed to better understand their perceptions of genetic risk and how it shapes health outcomes over the long term.

Conclusion

This study lays the foundation for understanding how high-risk underserved populations respond to personalized genetic results, informing the debate surrounding the consequences of returning these results. Specifically, we demonstrate that, similar to other populations, high-risk minority participants appreciate return of results, do not have increased symptoms of depression or anxiety, and may benefit from receiving individual genetic information. Technical and scientific barriers regarding the disclosure of genetic results in research, clinical, and consumer settings still exist, and overcoming them will require continued progress in several areas, such as definitive identification and characterization of genetic risk factors, validation of algorithms to estimate risk, and development of standardized policies and procedures to prioritize and communicate genetic information. The empirical evidence presented in this study suggests that once these barriers are crossed, personalized genetic results may be positively received in underserved populations.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

L.B. is listed as an inventor on Issued U.S. Patent 8,080,371, "Markers for Addiction," covering the use of certain SNPs in determining the diagnosis, prognosis, and treatment of addiction. D.K. is an unpaid consultant for an ongoing academic study of customers of 23andMe and Pathway Genomics. The other authors declare no conflict of interest.

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