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The impact of multiplex genetic testing on disease risk perceptions

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This study assessed the effects of multiplex genetic testing on disease risk perceptions among 216 healthy adults. Participants, aged 25–40, were recruited through the Multiplex Initiative, which offered a genetic susceptibility test for eight common diseases. Participants completed baseline telephone and web-based surveys prior to making the testing decision. Three months after the receipt of mailed test results, participants completed a follow-up telephone survey. Risk perceptions for the eight diseases were measured at baseline and follow-up, along with beliefs about genetic causation of those diseases. The main results were: (i) mean risk perceptions were considerably stable from baseline to follow-up; (ii) the best predictors of follow-up risk perceptions were the corresponding baseline perceptions and family history; and (iii) within-individuals, most participants increased or decreased their risk perceptions for specific diseases in concordance with the number of risk markers they carry, their family history and their beliefs about genetic causality of diseases. In conclusion, participants presented a vigilant approach to the interpretation of genetic test results, which provides reassurance with regard to a potential inflation of risk perceptions in the population because of multiplex genetic testing.

Conflict of interest

There are no financial or personal relationships that might have biased this work.

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The rapid development and increased availability of genomic technologies is hastening their clinical translation. The clinical application of genomic technologies includes an evolution from traditional genetic testing that evaluates highly penetrant single disease genes to simultaneous testing for multiple common chronic adult-onset conditions, such as cardiovascular disease, diabetes mellitus, and cancer (multiplex tests). Increasing numbers of multiplex tests providing genetic disease risks are available to the public through companies providing direct-to-consumer (DTC) services. Advertising of such tests was reported to cause little anxiety overall, to

increase demand for genetic services, but had little effect on primary care services (1, 2). While a primary assumption underlying the development of genetic tests is that genetic risk information will benefit users (3), there are concerns about the efficacy of information provided to clients within selected DTC models (4, 5), and the actual impact on individuals receiving multiple disease risks from a single test is still largely unknown (6). This report attempts to address the issue by examining a healthy population's perceived risk after receiving personal genetic risk information based on a multiplex test.

Studying individuals' perceptions of disease risk is important mainly because it may influence health-related decisions (7–9), and also because it may relate to psychological distress (10–13). Genetic test results for single diseases have been found to have significant impacts on perceived risk for those diseases (e.g. breast/ovarian cancer, colon cancer, and Alzheimer's disease) (10, 14–16), with carriers of risk mutations presenting higher risk perceptions. However, the impact of multiplex genetic testing on risk perception remains unknown.

Most people hold misconceptions about the nature and limitations of genetic tests (17–19), and misinterpret genetic test results (20, 21). These findings may represent a natural process predicted by fuzzy-trace theory (22), whereby the default mode of encoding numerical risk information is by 'fuzzy', gist representations, capturing the global meaning of risks, which is based, among other factors, on a person's culture, education, and experience (23). Research findings support the theory by showing that genetic risk information is often influenced by personal beliefs/experiences (24–26), pre-conceived expectations about the level of one's risk (27), family history (28, 29), genetic causal beliefs about diseases (30, 31), and coherence – perceived understanding of risk information (32). Emotional reaction to test results may also have an effect on the interpretation of risk information according to the 'risk as feeling' hypothesis (33).

The aims of this study were: (i) to assess changes in risk perceptions from baseline to after receiving genetic test results about lifetime risk for developing multiple diseases; (ii) to examine the effects of several indicators of test results on changes in risk perceptions, including the number of risk markers for specific diseases and across diseases, the number of diseases for which there was at least one risk marker, and the extent of increased risk across diseases; (iii) To examine the effects of factors found associated with perceived genetic risk for single diseases on changes in risk perceptions following a multiplex genetic test. Specifically, we hypothesized that risk perceptions following multiplex genetic testing will increase among participants carrying more genetic risk markers, having a family history of the disease, who attribute disease to genes, whose understanding of test results is poorer, and whose emotional reactions to results are stronger.

Methods

The Multiplex Initiative (MI) was a collaborative transdisciplinary research project of the National Human Genome Research Institute (Bethesda, MD), the Cancer Research Network (http://crn.cancer.gov/) funded by the National Cancer Institute, the Group Health Cooperative (Seattle, WA), and the Henry Ford Health System (Detroit, MI). [The detailed description of methods is described in Appendix S1, Supporting Information (34–37)].

Participants

Selection criteria included adults, 25–40 years old, enrolled in the health plan and not affected with the conditions assayed through the Multiplex test (i.e. type 2 diabetes, heart disease, high cholesterol, high blood pressure, osteoporosis, or lung, colon or skin cancer). The analyses within this manuscript were based upon 216 participants who completed a baseline telephone assessment, agreed to undergo the Multiplex test, received test results, talked with a research educator and completed a 3 month follow-up telephone assessment.

Measures

Risk perception was measured at baseline (in a web-based survey) and in the follow-up using a 7-point scale for each of the eight diseases in the study. Other measured variables were: socio-demographic characteristics, family history, genetic attributions, test results, genetic causal beliefs, perceived understanding of genetic risk (coherence), emotional reactions to test results.

Statistical analyses

Comparisons of average risk perceptions across participants were carried out using paired sample *t*-tests. Regression analyses were used to explain follow-up risk perceptions of each of the diseases (dependent variables) by other study variables. To predict changes in risk perceptions from baseline to follow-up, we applied repeated measures mixed model analyses for each of the eight diseases, using SPSS Version 20 MIXED procedure.

Results

Demographic characteristics of the study population

Eighty two participants (38%) were self-identified as African American, showing success in recruiting populations that are typically underrepresented in genetic testing studies (38). The remaining characteristics of the study population include an average age of 35 years (SD = 4.22), 124 (57%) female, 138 (64%) married or partnered, and 114 (53%) with at least a college degree.

Test results

Distributions of test results are presented in Fig. 1a–c. The average number of risk markers per participant was 9.25 [standard deviation (SD) = 1.58], and the range was

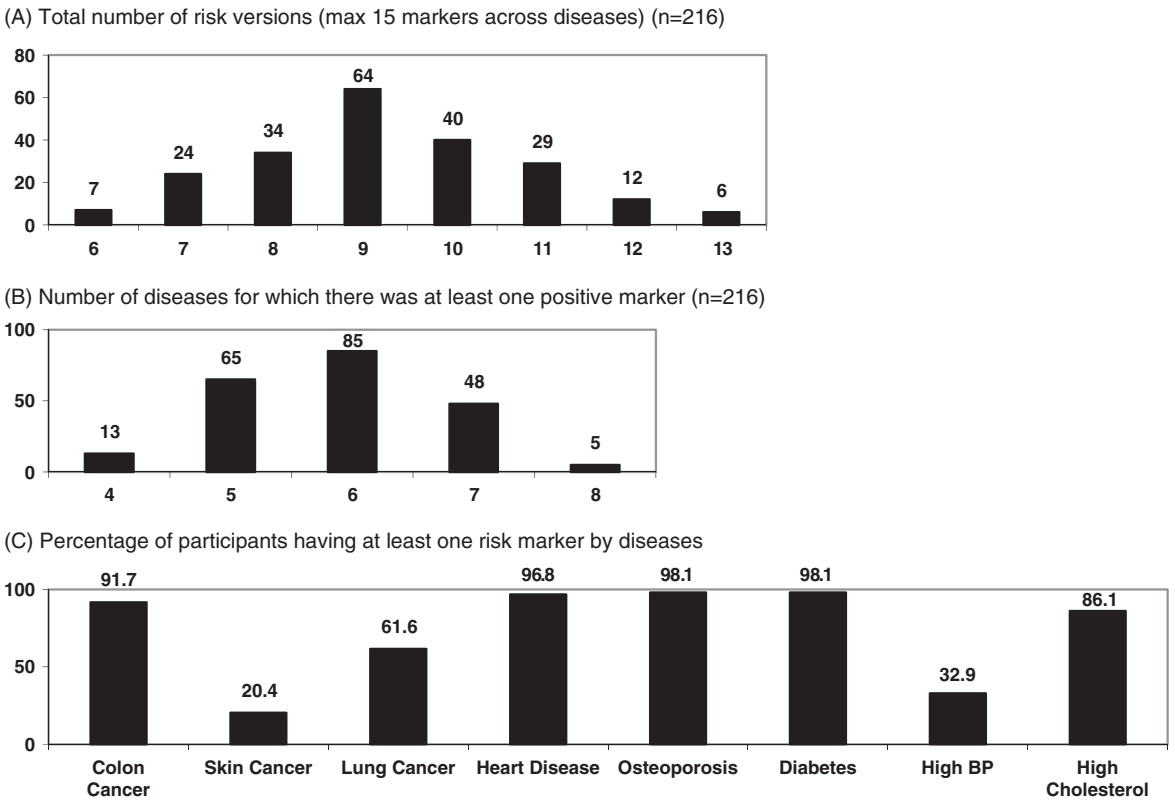

Fig. 1. (**a**) Total number of risk versions (max 15 markers across diseases) ($n = 216$). (**b**) Number of diseases for which there was at least one positive marker ($n = 216$). (**c**) Percentage of participants having at least one risk marker by diseases.

6–13 risk markers. The average number of diseases for which there was at least one positive risk marker per participant was 5.85 (SD = 0.92), and the range was 4–8 diseases. One hundred and ninety five (90%) of the participants had at least one risk marker for type 2 diabetes, osteoporosis, heart disease and colon cancer. One hundred and eighty five (86%) participants had at least one risk marker for high cholesterol, 134 (62%) for lung cancer, 72 (33%) for high blood pressure, and 43 (20%) for skin cancer.

Risk perceptions: from baseline to follow-up

Changes in risk perceptions from baseline to follow-up ranged from 86 (41%) participants increasing their perceived risk for type 2 diabetes to 76 (35%) decreasing their perceived risk for skin cancer and heart disease (Table 1). Comparisons across participants indicated that average risk perceptions remained quite stable from baseline to follow-up. There were only slight average increases of risk perceptions for colon cancer and type 2 diabetes, and a slight average decrease for skin cancer (Table 1). The rank order of mean risk perceptions was highly correlated with population risk (prevalence of the disease in the population) $r_{(\text{Spearman})} = 0.71$ at baseline, and $r_{(\text{Spearman})} = 0.79$ at follow-up.

Regression analyses showed a strong effect of baseline perceptions on follow-up perceptions of risk for each of the diseases, explaining between 29% (high cholesterol) and 48% (skin cancer) of the variance in follow-up risk perceptions. In addition, reported family history of the disease had a significant independent effect on follow-up risk perceptions for colon cancer, lung cancer, heart disease, osteoporosis, and type 2 diabetes. Given the relative stability of mean risk perceptions across participants, the great effect of baseline risk perceptions on follow-up perceptions, and the flux of risk perceptions between baseline and follow-up within participants, our next analyses intended to discover predictors of *within-individuals* changes in risk perceptions from baseline to follow-up.

Prediction of changes in risk perceptions

Time itself had a significant effect only on changes in risk perceptions for *colon cancer*, *skin cancer* and *type 2 diabetes*. However, the interaction between time and test results was significant for *skin cancer*, *lung cancer*, *osteoporosis*, *type 2 diabetes*, and *high cholesterol*. Probing the interactions by using a computational approach (39) indicated that risk perceptions *decreased* over time only among those who had *less* genetic markers for *skin cancer* ($t = -2.69$, $p = 0.01$) and *lung cancer* ($t = -1.81$, $p = 0.07$), compared to those who had more markers (*skin cancer*: $t = 0.06$; *lung cancer*: $p = 0.95$ $t = 0.64$, $p = 0.52$). Risk perceptions *increased* over time only among those who had *more* genetic markers for *osteoporosis* ($t = 2.35$, $p = 0.02$), and *type 2 diabetes* ($t = 2.68$, $p = 0.01$), compared to those who had less

Table 1. Perceived risk (range: 1–7) by diseases at baseline and at 3 months post-receipt of multiplex results ($n = 216$)

	Cumulative lifetime risk (range of risks based upon absence/ presence of risk markers)	Baseline		Follow-up			% within subjects change	
		Mean	SD	Mean	SD	t	Increased	Decreased
Average risk	–	3.25	1.14	3.33	1.07	−1.04	48	43
Colon cancer	5–6%	2.75	1.46	2.93	1.51	−2.01[a]	37	29
Skin cancer	1–5%	2.95	1.78	2.75	1.67	2.14[a]	25	35
Lung cancer	6–8%	2.59	1.58	2.51	1.49	0.80	27	33
Heart disease	29–44%	3.81	1.72	3.90	1.65	−0.82	38	35
Osteoporosis	21–51%	2.81	1.63	2.88	1.58	−0.82	33	29
Diabetes	31–64%	3.34	1.84	3.55	1.66	−1.90[a]	41	31
High blood pressure (51)	86–88%	3.84	1.98	3.95	1.89	−0.99	37	34
High cholesterol	[b]	3.93	1.89	4.12	1.81	−1.58	38	30

SD, standard deviation.
[a]$p < 0.05$.
[b]Cholesterol provided no risk numbers, rather simply higher or lower levels of good cholesterol.

markers (*osteoporosis*: $t = -1.09$, $p = 0.28$; *type 2 diabetes*: $t = 1.15$, $p = 0.88$). Contrary to findings for the other diseases, for *high cholesterol* there were *increases* in risk perceptions among those with *less* risk markers ($t = 2.82$, $p = 0.01$) compared to more risk markers ($t = -0.53$, $p = 0.59$).

For *type 2 diabetes* and *high blood pressure* another significant interaction was found, between time and reported family history. Risk perceptions *increased* over time only among those who reported a family history of the disease (*type 2 diabetes*: $t = 2.66$, $p = 0.01$; *high blood pressure*: $t = 2.29$, $p = 0.02$), compared to those who did not report a family history (*type 2 diabetes*: $t = 0.13$, $p = 0.89$; *high blood pressure*: $t = -0.91$, $p = 0.36$). Perceptions for *heart disease and high cholesterol* were also found affected by the interaction between time and genetic determinism. Risk perceptions *increased* significantly among participants with *stronger* genetic deterministic beliefs (*heart disease*: $t = 1.94$, $p = 0.05$; *high cholesterol*: $t = 2.63$, $p = 0.01$), compared to weaker beliefs (*heart disease*: $t = -0.65$, $p = 0.51$; *high cholesterol*: $t = -0.33$, $p = 0.74$). Only for *lung cancer*, the interaction between time and attributing the disease to genes was significant. Risk perceptions *decreased* among those who attributed lung cancer to genes ($t = -2.03$, $p = 0.04$), compared to those who had lower genetic attributions for the disease ($t = 0.88$, $p = 0.38$).

Discussion

Our study provides evidence that the receipt of multiplex genetic test results had minimal effects on average disease risk perceptions. This finding is quite surprising considering that *all* participants received test results indicating that they carry at least six risk markers, for at least four diseases (although the attributable risk associated with each marker was low). The small average group changes in risk perceptions, observed among a few diseases, were distributed almost evenly between increases and decreases, consistent with random fluctuations. These findings concur with reports about the relatively resistant nature of risk perceptions following receipt of information from a web-based family history tool that assesses familial risk for six diseases (40).

Notwithstanding the stability of *average* risk perceptions, the majority of participants changed their risk perceptions from baseline to follow-up, showing both increases and decreases. These intra-individual changes were largely consistent with the number of risk markers carried by participants. Risk perceptions of skin and lung cancers decreased only among those with less risk markers, and risk perceptions of osteoporosis, type 2 diabetes and high blood pressure increased only among those with more risk markers. The direction of changes in risk perceptions indicates that participants may have considered the information about population risks as references, i.e.: test results induced decreases in risk perceptions for cancers, for which population risks are relatively low, and induced increases in risk perceptions for the other diseases, for which population risks are relatively high (especially high blood pressure). Surprisingly, risk perceptions of high cholesterol were increased among those with *less* risk markers. We can only speculate about the reasons for this finding. First, unlike other diseases, test results for high cholesterol were provided without risk numbers, rather simply higher or lower levels of good cholesterol, which may have confused participants. Secondly, because people tend to see diet as the most usual cause of raised cholesterol (41), it is possible that finding out that one does *not* have a genetic risk for high cholesterol had diverted attention to dietary attributions and the elevated risk associated with them. Correspondingly, 'contradictions in talk about diet' have been recently described as a major theme among individuals who have undergone genetic testing for familial hypercholesterolaemia (FH) where no genetic mutation has been identified (42). Nonetheless, it is noteworthy that only disease-specific results, rather than general aggregations of test results, affected risk perceptions.

Regarding predictions of the fuzzy-trace theory (22, 23), it seems that gist-based impressions of being at-risk for common-diseases were not based on aggregated test results, but rather, on baseline risk perceptions,

family history and deterministic genetic beliefs. Because health-related information that is concordant with existing beliefs evokes less intensive information processing and is considered more trustworthy and accurate (43), *a priori* beliefs about personal susceptibility to diseases may be seen as anchors for gist-based impressions of genetic risk information (44). Likewise, because risk perception is affected by lay models of inheritance in the family (45), a family history of diseases may have considerable impacts on the formation of 'fuzzy', gist representations of risk. These notions are consistent with previous research showing the importance of baseline perceptions, family history and genetic attributions on genetic risk perceptions (27–29, 31).

Contrary to predictions based on the 'risk as feeling' hypothesis (33), emotional reactions did not moderate changes in risk perceptions. This may have resulted from the fact that emotional reactions were generally mild (a mean of 3 on a scale of 1–7). It could also result from the fact that risk perceptions were measured in this study by using a perceived likelihood scale, directing respondents' attention to the cognitive component of risk rather than to 'feeling at risk' (46). Given the concurrent measurement of both constructs, we also cannot rule out the possibility that the mild emotional reactions actually reflected the relatively small changes in risk perceptions. The coherence hypothesis (32), whereby individuals who feel they understand the link between genes and disease risk would perceive their risk as lower, was also not supported with regard to changes in risk perceptions in the context of multiplex testing.

The above findings show that results of a multiplex genetic test changed individuals' risk perceptions congruently with findings reported in studies of genetic testing for *single* diseases (10, 13, 15, 16, 30). This is not trivial. Unlike testing for a single disease, within a multiplex setting, participants get much more information, and may select the type and amount of information they focus on. In addition, compared to single-disease studies where participants often are seeking out risk information because of interest/concern about a particular condition, many of the diseases included in a multiplex test may not have been of interest to the respondents (47). Finally, while test results for a single disease can be either favorable or unfavorable, eliciting the interpretation of increased risk as opposite to 'normal', in multiplex genetic testing every individual discovers that he/she has numerous risk markers distributed along several diseases, so that the feedback becomes relatively undifferentiated. This may result in a 'dilution effect', creating an 'ordinary' interpretation of carrying a few risk markers, and perceiving them as less significant. These suppositions about differences between single and multiplex genetic tests were not examined in this study. They require further research that will compare, by standard measures, the effects of single genetic test results to *the same* results included in a multiplex test.

Finally, while some findings can be generalized across diseases, such as the prediction of post-test risk perceptions by baseline risk perceptions, other findings were disease specific. This is in line with the observation that responses to genetic test information may vary across diseases (20), and points to the need to be more sensitive to variability among diseases (48).

Limitations

Our study design has limitations that must be mentioned. The results are limited by sampling biases, with certain social groups underrepresented despite the robust population-based recruitment strategies (38). Follow-up measurements some 3 months after disclosure of test results can also be problematic in view of the evidence that risk perceptions evolve over time lapsed from testing (11), sometimes depending on decisions about preventive interventions more than simply on the outcomes of mutation tests (14). Future studies may be advised to add a measuring point closer to obtaining test results, and re-contact participants at more distant time points post-receipt of results, e.g. 1 year, 3 years, etc., to re-assess risk perceptions. Other limitations of the study include the number and identity of diseases examined, requiring replications of our study with tests for other common health conditions. It is also worth noting that assessments of risk perceptions relied solely on a 7-point scale anchored by extreme judgments between 'certain not to happen' and 'certain to happen'. These may have affected the results, given that different measures of risk perception such as comparative scales or judgments contingent on one's behavior are not interchangeable (46, 49, 50). We also note that the questions eliciting the presence or absence of a family history for the disease studied did not identify the degree of relationship with the affected relative or the number of affected family members. It is possible that effects for family history might have been stronger if this assessment had been more specific. Finally, it is important to emphasize that this study was undertaken within a rigorous web-based educational setting, limiting the generalizability of our conclusions to DTC multiplex testing that offer little professional assistance in interpreting results.

Conclusions

All participants in multiplex genetic testing have been found as carriers of several risk markers for various common diseases. Despite this, their interpretations of their risks were quite relaxed. There was no indication of an average increase in subjective risk perceptions for the diseases examined. Risk perceptions after receiving test results were mostly predicted by prior risk perceptions and by family history of the relevant diseases. However, at an individual level, most participants have increased or decreased their risk perceptions for specific diseases in concurrence with the number of risk markers they carried, their family history and their beliefs about genetic causality of diseases. These findings indicate that participants applied a vigilant approach to the interpretation of genetic test results and provide reassurance with regard to a potential inflation of risk perceptions in the population because of multiplex genetic testing. It is important to note that these results were obtained within a

program providing extensive educational material both before and after testing and receiving test results. More research is required to examine the effects on risk perceptions of other programs, including more genetic tests and among different populations. In addition, direct comparisons between genetic test results received through multiplex tests *vs* single disease genetic tests are needed in order to better understand information processing of genetic test results.

Supporting Information

The following Supporting information is available for this article:

Appendix S1. Methods in detail.

Additional Supporting information may be found in the online version of this article.

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