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Responses to Online *GSTM1* Genetic Test Results among Smokers Related to Patients with Lung Cancer: A Pilot Study

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Abstract

Providing smokers with personal genetic test results indicating increased lung cancer risk may increase uptake of effective smoking cessation services. Using the internet may increase reach and enable real-time assessment of how people process genetic risk information away from the clinic setting. We therefore explored smokers' responses to Web-delivered *GSTM1* genetic test results indicating higher or lower lung cancer risk. Participants were smokers ($n = 44$) biologically related to patients with newly diagnosed lung cancer. Measures were assessed at baseline, before and immediately after receipt of online genetic test results, and at 6-month follow-up. Outcomes included accurate comprehension of results, regret about being tested, cessation-related cognitions (e.g., perceived response efficacy), and uptake of free smoking cessation services (nicotine replacement therapy, printed self-help materials, telephone counseling sessions). Twenty-two "relative smokers" received a *GSTM1*-missing (higher risk) and 22 a *GSTM1*-present (lower risk) result. All relative smokers with *GSTM1*-missing results and 55% of those with *GSTM1*-present results accurately interpreted their results. No relative smokers regretted having taken the test. Relative smokers receiving *GSTM1*-missing results reported lower confidence that quitting could reduce lung cancer risk (perceived response efficacy) than those receiving *GSTM1*-present results. There were no other significant between-group differences. Uptake of smoking cessation services was high (e.g., 91% nicotine replacement therapy uptake). Genetic test results may not influence uptake of free smoking cessation services because of ceiling effects. Further research is needed to determine the risks and benefits of Web-based disclosure of genetic test results.

Introduction

Lung cancer is the leading cause of cancer death worldwide. Each year, >200,000 individuals are diagnosed with the disease in the U.S. alone (1). Cigarette smoking is the leading cause of lung cancer, accounting for 87% of all cases. Although up to 70% of smokers say that they want to quit smoking, only a small proportion successfully do so. A

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number of cessation aids are available to help smokers quit, such as nicotine replacement therapy and telephone counseling, but relatively few smokers avail themselves of these services. Accordingly, increasing the uptake and use of effective smoking cessation services has been identified as a public health priority (2, 3).

The evidence to date suggests that biomarker risk assessments do not directly increase smoking cessation (4). However, in previous studies, the incremental effects of biomarker risk feedback may have been diluted or overwhelmed by the high intensity of the companion quit-smoking interventions [p155] (4). Whether biomarker risk assessments might have intermediate beneficial effects, such as increasing uptake of subsequently offered effective quit-smoking interventions, is still an open question.

One type of biomarker risk assessment that is receiving increasing attention is genetic risk assessment. Genetic risk assessments or genetic test results might have particular beneficial potential when individuals are identified to be at increased risk (5). For example, the gene that encodes for the enzyme glutathione *S*-transferase (*GSTM1*) is deleted in up to 50% of the general population (6). In meta-analyses, this common gene variant (called *GSTM1* null or *GSTM1*-missing) has been associated with increased lung cancer risk with a summary odds ratio for the association of *GSTM1* null with lung cancer of 1.17 (95% confidence interval, 1.07-1.27; ref. 7). Providing individuals with *GSTM1*-missing test results might have beneficial effects related to smoking cessation.

A handful of studies have directly investigated the effects of such genetic susceptibility feedback on smokers' motivation and ability to quit smoking (8-16). In addition, a few studies have used hypothetical genetic testing scenarios to achieve similar goals (17-20). The studies to date have produced mixed results: some have found a modest motivational impact (9, 14-16), but others have found no impact (8, 11, 18). In two randomized controlled trials (11, 16), *GSTM1* genetic risk feedback was offered as part of a complement of smoking cessation modalities of known efficacy, including brief in-person counseling, serialized telephone counseling, and/or nicotine replacement therapy. The trials found modest to no effects of specific genetic test results on cessation-related outcomes. However, smokers in these trials were offered genetic feedback within the context of a smoking cessation intervention: accordingly, those recruited were highly motivated to quit smoking. Under these conditions, genetic risk information may add little value to the efficacy of existing cessation interventions.

An alternative use of genetic risk information may be to engage smokers in intermediate behaviors as an initial step toward quitting, such as learning more about their personal smoking-related disease risk or increasing their interest in trying nicotine replacement therapy or telephone counseling. Conceptual models of information seeking (21) suggest that genetic test results might engage smokers in a deeper processing of information about the health risks for smoking and, in turn, might increase interest in using smoking cessation services. Furthermore, offering genetic susceptibility testing at the time of a family member's diagnosis of cancer, a possible "teachable moment," when the salience of smoking risks might be high, could motivate relatives who smoke to engage deeply with risk information and consider cessation services (22). However, it is also possible that information at this time might not be considered thoroughly because it is too threatening (23). Rather than smoking cessation itself, outcomes indicative of engagement with risk information, such as the rated quality of the information provided, accurate comprehension, and subsequent uptake of offered smoking cessation services, might therefore provide more appropriate indicators of beneficial effects of genetic risk feedback.

The present report examines how smokers processed and responded to personal genetic information about a common gene variant, *GSTMI*-missing, in the context of a blood relative's lung cancer diagnosis. Relative smokers were offered genetic testing and test results via Web-based information sessions. The Web-based approach increased reach and meant that “relative smokers” were able to access the information and their genetic test results, regardless of their geographic location. In addition, the Web-based format allowed unobtrusive evaluation of participants' engagement with the information immediately after test results were delivered, enabling examination of behavioral indicators of information processing. If found to be an effective and safe communication tool, this Web-based approach could in the future lend itself to integration with population-based smoking cessation interventions that are self-directed and portable.

In a previous report (24), we compared the characteristics of relative smokers who did versus did not visit the Web site to consider genetic testing. Although the study was not designed to be nor communicated as being a smoking cessation intervention, relative smokers who logged on to the Web site were more motivated to quit smoking than those who did not log on. They also had greater previous awareness of genetic testing for cancer risk and were more frequent internet users (24).

The present analyses focused on comprehension of test results and information processing among the relative smokers who requested genetic testing and received the test results. Based on previous research (23) and stress and coping theories (25), we anticipated that smokers receiving the “higher risk” result (*GSTMI*-missing) might be less likely than those receiving the “lower risk” result (*GSTMI*-present) to fully comprehend the meaning of the test result and more likely to reject their test results (e.g., report lower believability and perceived personal relevance) and to regret having taken the test. We also examined uptake of three types of offered smoking cessation services (e.g., printed and audio self-help materials, nicotine replacement therapy, serialized telephone counseling sessions). Based on information-seeking models (21), we expected that smokers who received higher risk results might be more likely to request cessation services because of increased processing of personal risk results and related information. We also considered an alternative possibility based on stress and coping theory (25) that smokers who received higher risk results might be less likely to take up smoking cessation services because of defensive processing of the personally threatening information. In addition, we explored the impact of test results on motivation to quit smoking and three behavior-related cognitions that have been found in previous research to mediate the relationships between persuasive communications and health behavior or behavior change outcomes: self-efficacy (confidence in ability to quit smoking), response efficacy (confidence that quitting smoking will reduce lung cancer risk), and perceived risk for lung cancer.

Materials and Methods

Recruitment and Procedure

Patients with stage IIIB/IV lung cancer who were receiving care in the Thoracic Oncology Clinic at the H. Lee Moffitt Cancer Center and Research Institute were identified through their providers. The patients were approached by a recruiter during their clinic visit and asked if they would be willing to be contacted for a brief telephone survey about their general well-being and their relatives who smoke. The 482 patients who agreed signed a consent form indicating that they were willing to have their personal health information forwarded to Duke University, the survey center.

Within 1 wk, a trained interviewer called the patient to complete the survey. The survey was completed by 391 patients or their proxies. As part of the survey, patients were asked to give

the names, addresses, and telephone numbers of all the smokers in their family and asked for permission to contact these relative smokers. The 539 relative smokers who were identified were sent a letter informing them of the purpose of the telephone survey, the length of the survey, and types of questions included and were given a toll-free number to call if they did not want to participate. Those who did not call the number ($n = 530$) were called by interviewers from Battelle Survey Research Associates. Those who were successfully contacted ($n = 365$) were asked to complete a 30-min telephone survey. The survey was completed by 304 relative smokers.

Relative smokers were eligible to participate if they were a biological first- or second-degree relative of the patient; ages 18 to 55 years; had smoked at least seven cigarettes in the previous week and at least 100 in their lifetime; had not had cancer themselves; had access to the internet; spoke English; and scored <14 on the Centers for Epidemiologic Survey of Depression. These criteria were set to increase the salience of the test context while minimizing psychological risks for the low intensity communication format.

Eligible relative smokers ($n = 124$) were asked whether they would be willing to participate in a study about the beliefs and attitudes of relatives of patients with lung cancer toward lung cancer risk, genetics, and genetic testing, and how these might influence desire to quit smoking. They were informed that participation would involve reviewing Web-based information and that genetic testing and smoking cessation materials would be offered free of charge. Multiple members of the family could participate; 116 relative smokers from 95 unique families agreed to participate. Within 2 wk, relative smokers who agreed to participate received a packet of information, including a user ID and password, and were invited to log on to Session 1 of the Web site to begin their participation. A total of 58 relative smokers logged on to the Web site.

Relative smokers who visited the Web site were guided through a series of structured steps, including an overview of study procedures and additional consenting information. As part of this Session 1, they completed a brief survey and were then guided through a series of information pages about the roles of smoking and genetics in the development of lung cancer. The development and structure of the Web content was guided by theoretical models (25-29), clinical models of genetic services delivery, and the notion that the relative smokers may be experiencing a teachable moment given their relatives' diagnosis of lung cancer (22). Topics covered included the following: how does lung cancer develop, what is harmful about cigarette smoke, pros to consider in deciding about genetic testing ("strengths" of the *GSTM1* test), cons to consider in deciding about genetic testing ("weaknesses" of the *GSTM1* test), and how can you lower your risk for lung cancer? The strengths list included the following: the result gives you information about one of the ways your body may handle the chemicals in cigarette smoke that cause lung cancer; the results could motivate you to quit smoking; and the test is simple and painless. The weaknesses listed included the following: if you are found to be at higher genetic risk, the news could be distressing; the result may not motivate you to quit smoking; the result can only tell you whether your risk is higher or lower than average, not whether or not you will get lung cancer; and the result will not tell you about your genetic risk for other diseases of smoking. The information pages also included the information that smokers who have the *GSTM1* enzyme "may be at slightly lower risk of getting lung cancer" and that smokers who do not have the *GSTM1* enzyme "may be at slightly higher risk of getting lung cancer."

Relative smokers could move backward and forward within the presentation of the information. After reviewing the information, the relative smokers began a survey section and were not able to move back into the information section. At this point, they were offered free genetic testing for the *GSTM1* genotype. They were given the options to accept,

decline, or delay the decision to take the test. Those who agreed to be tested for *GSTM1* were sent a buccal swab kit, instructions for collecting the sample, a consent form, and a postage-paid return mailing.

About 3 wk later, participants were sent e-mails and asked to return to the Web site for Session 2 and to receive their results or to review smoking cessation materials. Of the 58 relative smokers who logged on to Session 1, 44 took the genetic test and returned to the Web site for Session 2. These 44 relative smokers comprise the participants in this report. All participants who returned to the Web site were shown graphical images and descriptions of six smoking cessation services they were being offered at no cost: a generic quit smoking booklet; relaxation tapes; a personalized booklet describing the benefits of smoking cessation that was tailored to individual responses to the baseline survey; up to six counseling calls from a smoking cessation specialist; transdermal nicotine patches (nicotine replacement therapy); and a “quit kit” that included nonpharmacologic items to help handle immediate withdrawal symptoms. After reviewing this information, they were offered another opportunity to view the information pages about smoking and genetics in lung cancer from Session 1. An internal tracking system recorded which of the information pages each participant viewed. They were then asked to complete the final online survey. After completing the Session 2 survey, participants were asked if they would like to receive any of the free smoking cessation services they had just viewed. Requests for smoking cessation services were responded to promptly, and when requested, telephone counseling was provided by trained smoking cessation specialists at Duke University Comprehensive Cancer Center. All relative smokers offered genetic testing were contacted for a 6-mo telephone follow-up survey.

At the 6-mo follow-up, relative smokers who had not visited the Web site were notified that they were still able to participate in the online sessions if they were interested, and those who requested to be tested at this point received free testing. They received \$50 each for completing measures at Sessions 1 and 2, regardless of whether they were tested. A study team at the National Human Genome Research Institute's Social and Behavioral Research Branch monitored the Web-based data collection and provided, as needed, genetic counseling services to the relative smokers. Procedures were approved by the National Human Genome Research Institute and the Moffitt and Duke institutional review boards.

Measures

Most of the primary information-processing outcomes were assessed online in Session 2 immediately after test results were provided. Decisional regret was assessed in the 6-mo follow-up telephone survey. The cessation-related cognitive variables were assessed at two or more time points (baseline, Session 1, Session 2, and/or 6-mo follow-up). In that the Web-based assessments were self-administered surveys and the baseline and 6-mo follow-up surveys were interviewer-administered surveys conducted over the phone, there were slight wording differences in some of the survey items.

Demographic Characteristics—Participants provided demographic information at baseline, including gender, age, education, employment status, and race/ethnicity. They also provided information about how many cigarettes they smoked in a typical day, commonly used as an indicator of nicotine addiction (30).

Comprehension of Test Results and Information Processing

Accurate Recall and Interpretation of Test Result—This was assessed with two items in the online Session 2 and the 6-mo telephone follow-up survey. The first assessed accurate recall: “Did your result show that you are missing the *GSTM1* enzyme or have the

GSTM1 enzyme? (1 = missing the GSTM1 enzyme; 2 = have the GSTM1 enzyme).” *GSTM1*-missing smokers were coded as accurately recalling their results if they responded 1 (missing the GSTM1 enzyme), and *GSTM1*-present smokers were coded as accurately recalling their results if their response was 2 (have the GSTM1 enzyme). The second item assessed accurate interpretation: “Your test result shows that your risk of getting lung cancer in your lifetime is? Check which applies. 1 = higher risk; 2 = average risk; 3 = lower risk.” *GSTM1*-missing smokers were recorded as accurately interpreting their results if their response was 1 (higher risk), and *GSTM1* present smokers as accurately interpreting their results if they response was 3 (lower risk).

Acceptability of Test Result Information—This was assessed with five semantic differential items, each assessed on a seven-point scale: “To what extent do you consider the information you just read about your result to be? (1) Believable–Unbelievable; (2) Trustworthy–Not trustworthy; (3) Easy to understand–Hard to understand; (4) Relevant to you–Not relevant to you; (5) Important to you–Not important to you.” Each participant gave a score of between 1 and 7 for each of the five items separately. Lower scores indicated more positive, higher acceptability responses (e.g., 1 = believable), and higher scores indicated more negative, lower acceptability responses (e.g., 7 = unbelievable).

Processing of Genetic Test–Related Information—This was assessed based on viewing patterns of the information pages in Session 2. This was not new information to the participants (having been required to view these information pages in Session 1). Participants were presented with a menu of the eight information pages and given the option to review any or none of the pages. One of these pages had the heading, “Weaknesses of the GSTM1 test,” and another had the heading “Strengths of the GSTM1 test.” For each page, participants were assigned a dichotomous score of 1 if they did not view the information page and a score of 2 if they viewed the information page. We also examined the total number of information pages (out of the possible eight) viewed by each participant.

Decision Regret/Satisfaction—Participants were asked to report their level of agreement (1 = strongly disagree, 7 = strongly agree) with two statements (I regret the decision I made, I am satisfied with my decision) at 6-mo follow-up.

Uptake of Smoking Cessation Interventions

Uptake of Offered Smoking Cessation Services—This was assessed in Session 2, as follows: “Free Quit Smoking Services. If you are interested in trying to quit smoking, please click on the box below to request any or all of the services listed below: (1) American Lung Association Freedom from Smoking Booklet; (2) American Lung Association Relaxation Tapes; (3) Family Ties Customized Booklet; (4) Quit Kit with Journal; (5) Coaching Sessions; (6) Nicotine Replacement Therapy.” Items 1 to 4 were combined to create a single “uptake of self-help materials” variable; item 5 was labeled “uptake of telephone counseling,” and item 6 was labeled “uptake of NRT” (nicotine replacement therapy).

Self-Reported Use of Smoking Cessation Medications—This was assessed at 6-mo follow-up with the item: “Have you used medications, such as nicotine gum, nicotine patch or Zyban, to help you try to quit smoking since we last spoke on [date of the last interview was specified]? (1 = yes, 2 = no).”

Cessation-Related Cognitions. Motivation to Quit Smoking—Motivation (desire) to quit smoking was assessed at baseline and 6-mo follow-up with a single item. Response options ranged from 1 (not at all) to 7 (very much).

Perceived Risk for Lung Cancer—Participants' perception of lung cancer risk conditional upon their continuing to smoke at their current level was assessed at baseline, Session 2, and at the 6-mo telephone follow-up, on a scale from 1 to 7, wherein 1 was “certain not happen” and 7 was “certain to happen.”

Perceived Self-Efficacy—Participants were asked to rate their confidence in their ability to quit smoking in the next 6 mo at baseline, Session 2, and at the 6-mo telephone follow-up, on a scale from 1 “not at all confident” to 7 “very confident.”

Perceived Response Efficacy—Participants were asked to rate their confidence that quitting smoking would lower their risk for getting lung cancer at Session 1 and at Session 2, wherein 1 = not at all confident and 7 = very confident.

Statistical Analyses

Relationships among each outcome variable, the primary predictor variable (genetic test result), and control variables (including the outcome variable at baseline where appropriate) were analyzed using linear mixed models to account for familial clustering (that is, whether two or more participants were drawn from the same family). Before running the models, five potential control variables (gender, education, age, motivation to quit, and nicotine addiction) were tested for inclusion in each of the models. For each model, only those controls that had statistically significant associations with the outcome ($P < 0.20$ criterion), after controlling for other statistically significant control variables and the predictor variable, were included. For example, gender was included in the model if it was found to have an independent association with the outcome being tested in that particular model. This was accomplished using backward elimination with forward checking. Significance levels were reported at the $P < 0.05$ level and also the $P < 0.10$ level because of the exploratory nature of the study.

Results

Characteristics of Relative Smokers

Overall, 57% of the 44 relative smokers were female, the mean age was 40 years (range, 23-55 years), 23% were college graduates, and most (96%) were White. Twenty-four (55%) reported that they had previously used some form of smoking cessation service or product. Twenty-two (50%) of the relative smokers received a *GSTM1*-missing (higher risk) test result, and 22 (50%) received a *GSTM1*-present (lower risk) test result. As Table 1 shows, a greater proportion of *GSTM1*-missing than *GSTM1*-present smokers were male ($P = 0.001$), and almost twice as many *GSTM1*-missing smokers as *GSTM1*-present smokers were college educated ($P = 0.29$). Most of those who tested (16 *GSTM1*-missing and 18 *GSTM1*-present) completed the 6-month telephone follow-up survey.

Comprehension of Test Results and Information Processing

Accurate Recall and Interpretation of Test Result—As Table 2 shows, immediately after receiving their genetic test results online in Session 2, all *GSTM1*-missing relative smokers accurately recalled that they had the *GSTM1* enzyme missing, and all those with *GSTM1* present accurately recalled that they had the *GSTM1* enzyme present. All relative smokers maintained accurate recall of the test result at 6-month follow-up.

All relative smokers with the *GSTM1*-missing result accurately interpreted the result to indicate higher risk for lung cancer. However, accurate interpretation was lower among those with the *GSTM1*-present result, with 12 (55%) accurately interpreting their test result as indicating lower risk. Nine (41%) relative smokers with the lower risk result interpreted

their result as “average risk,” and one (5%) skipped the question. Patterns of accurate interpretation were similar at 6-month follow up: 15 (94%) relative smokers with the *GSTM1*-missing result accurately interpreted their results as higher risk; 1 (6%) interpreted it as average risk. Among those with the *GSTM1*-present result, eight (44%) interpreted their results as average risk and 10 (56%) interpreted it as lower risk (see Table 2).

Acceptability of Test Result Information—Table 2 shows that there were no significant differences between the two genetic test result groups in their perceptions of the acceptability of genetic test results (1 = high acceptability, 7 = low acceptability). The mean acceptability scores indicated high acceptability overall: believable, 1.39 (SD, 0.58); trustworthy, 1.39 (SD, 0.58); easy to understand, 1.39 (SD, 0.62); relevant, 1.39 (SD, 0.62); and important, 1.32 (SD, 0.56)

Processing of Genetic Test–Related Information—Those with the *GSTM1*-present result were more likely (albeit nonsignificantly) to view the information pages about the weaknesses and about the strengths of the genetic test (see Table 2). Overall, 18 (41%) participants viewed the weaknesses of the *GSTM1* test information page, and 18 (41%) viewed the strengths of the *GSTM1* test information page. We also compared the total mean numbers of information pages (out of the possible eight) viewed by *GSTM1*-present versus *GSTM1*-missing participants, which were 3.1 (SD, 2.64) and 2.6 (SD, 2.66), respectively. The difference was insignificant ($P = 0.54$).

Decision Regret/Satisfaction—At 6-month follow-up, no participants in either group regretted, and all but one were satisfied with the decision to have taken the test (see Table 2).

Uptake of Smoking Cessation Interventions

Uptake of Offered Smoking Cessation Services—There were no significant differences in uptake of the smoking cessation services between those who received the *GSTM1*-present and *GSTM1*-missing test results: 91% versus 100%, respectively, selected the self-help materials, 91% versus 91% selected the nicotine replacement therapy, and 41% versus 50% selected the serialized telephone counseling.

Self-Reported Use of Smoking Cessation Medications—At the 6-month follow-up, the proportion of smokers in each group who reported medication use did not differ significantly (44% versus 41%, respectively).

This observational study was not sufficiently powered for nor was it a study aim to assess smoking cessation as an outcome. However, participants were asked about their smoking status at 6-month follow-up. Six (17%) of the 35 smokers reported having quit smoking between baseline and the 6-month follow-up (one of the smokers in the *GSTM1*-present group and five of the smokers in the *GSTM1*-missing group reported that they had quit smoking).

Cessation-Related Cognitions

Motivation to Quit Smoking—Mean motivation scores reported by the *GSTM1*-present relative smokers were 6.44 (SD, 0.98) and 6.56 (SD, 0.70) at baseline and 6-month follow-up, respectively. The equivalent scores reported by the *GSTM1*-missing relative smokers were 6.35 (SD, 1.11) and 6.12 (SD, 0.78). Mean change scores were +0.11 and –0.24 for the *GSTM1*-present and *GSTM1*-missing relative smokers, respectively ($P = 0.087$), indicating a medium effect size ($d = 0.40$).

Perceived Risk for Lung Cancer—In the *GSTM1*-present relative smokers, mean perceived risk scores were 5.67 (SD, 1.03), 5.40 (SD, 0.99), and 5.50 (SD, 1.34) at baseline, online Session 2, and 6-month follow-up, respectively. The equivalent scores in the *GSTM1*-missing relative smokers were 5.44 (SD, 1.20), 5.73 (SD, 1.22), and 5.47 (SD, 1.51), respectively. None of the differences between the two groups were significant.

Perceived Response Efficacy—Mean perceived response- efficacy scores in the *GSTM1*-present relative smokers were 5.91 (SD, 1.85) and 5.77 (SD, 1.60) in online Session 1 and online Session 2, respectively. The equivalent scores in the *GSTM1*-missing relative smokers were 6.00 (SD, 1.77) and 4.91 (SD, 1.54). The difference in Session 2 was significant ($P = 0.015$) and indicated a medium effect size ($d = 0.71$; see Fig. 1).

Perceived Self-Efficacy—There were no significant differences over time in confidence in ability to quit smoking between the *GSTM1*-present and *GSTM1*-missing relative smokers.

Discussion

In this pilot study, genetic test results for lung cancer risk delivered online seemed to be reasonably well accepted: all smokers in this population reported that they found the information they received to be personally relevant and important, all correctly recalled their test results, and none regretted having taken the test. These preliminary findings tentatively suggest that delivering genetic test results for smoking-related disease risk online might be acceptable to some individuals, perhaps at least to those who opt for or self-select themselves into online genetic testing, although further research on the acceptability of online delivery of genetic test results is clearly needed.

The relative smokers in the higher risk *GSTM1*-missing group were no more likely than those in the lower risk *GSTM1*-present group to view the online information page about the weaknesses of the genetic test. They were also as likely as the lower risk *GSTM1*-present group to report that they found the information they had received to be believable and trustworthy. Thus, we did not find any evidence of the higher risk *GSTM1*-missing group displaying patterns of engagement with the Web site to suggest that they were looking for loopholes in the information. In addition, our expectation that these higher risk relative smokers would be less likely to fully comprehend their test results than those receiving the lower risk results was not confirmed. Instead, feedback of test results seemed to be confusing to participants who received the lower risk *GSTM1*-present genetic test results, only half of whom accurately interpreted their result as indicative of lower risk for lung cancer. The finding differs from the results of one previous study (23) in which smokers who received high-risk genetic test results for lung cancer risk were significantly more likely to misinterpret their test results, which had suggested that smokers might downplay or defensively process personally threatening risk information. Relative smokers who were told they were at lower risk for lung cancer in the present study may have had difficulty in interpreting these test results because the results seemed counterintuitive, given that they were smokers who had blood relatives diagnosed with lung cancer. When they responded that they personally interpreted their result as average risk, they might cognitively and emotionally have been combining their lower-risk test result with their higher-risk family history status. This raises the complexity of assessing what is actually accurate versus inaccurate interpretation of genetic test results for common disease risks. Further research is needed to evaluate how best to effectively communicate and ensure comprehension of personal risk information that amalgamates family history and genetic and behavioral risk factors to be true to the multifactorial nature of common disease risk.

We found no differences by test result in perceptions of absolute risk for lung cancer. This is consistent with the findings in the two previous studies that have given smokers *GSTM1* genetic test results. Neither study reported significant between-group differences in perceived risk (11, 16). Given that the *GSTM1*-missing (or null/null) genotype genuinely conveys only a slight increase in disease risk, these results might suggest that smokers are capable of incorporating this new information into their perceptions of disease risk without overreacting to the genetic-based information. As more gene variants are discovered and complex risk algorithms are built, it will increasingly be possible to give smokers risk information of greater magnitude, at which point we can evaluate whether higher-risk probabilities incrementally increase perceived disease risk.

We also found no difference in uptake of smoking cessation services between smokers who received the higher- versus lower-risk genetic test results. This may be explained by ceiling effects because we saw very high levels of uptake of the services across the board. The high uptake was likely influenced by these smokers being highly motivated to quit smoking (24) and that the services were offered free of charge. It has previously been shown that offering pharmacologic interventions, especially nicotine replacement therapy, to smokers free of charge increases quit rates (31, 32) and increases calls to other services such as Quitline (33).

The offer of information about genetic susceptibility to lung cancer in the context of a family member's diagnosis attracted a highly motivated group of smokers. Thus, this approach did not succeed in engaging the harder to reach smokers who were not motivated to quit smoking. It also meant that the smokers in the study sample were highly self-selected. In addition, as we have previously reported and discussed (24), only 44 of the 124 eligible relative smokers took the genetic test, further underscoring that those who took the test were likely to be a select group of interested smokers. One option to consider in the future is to target young adults who have optimistic biases about the health effects of smoking but who might be particularly inquisitive about new technologies and discoveries.

Smokers receiving the higher-risk result reported a very slight decrease in motivation to quit smoking, although baseline levels in both groups were high and remained high in absolute terms at follow-up. This relatively small change from high baseline rates did not negatively influence uptake of smoking cessation services. However, the finding does highlight that personal genetic information about common gene variants of low penetrance must be communicated in such a way to avoid inadvertently reducing motivation to change behavior. On the other hand, we also found that, of the 6 relative smokers who reported having quit smoking at 6-month follow-up, five of these were in the *GSTM1*-missing group. Although this finding must be interpreted with caution because of the small sample size, it is in line with previous research that has suggested that providing smokers with genetic test results indicating increased disease risk might enhance quitting under some circumstances (14-16). These apparently contradictory findings in the present study require further exploration in future research.

We found some evidence that smokers who received higher-risk test results were slightly discouraged about whether quitting smoking could now reduce their risk for lung cancer (that is, perceived response efficacy) immediately after they received their test results. We do not know whether this effect dissipated over time because perceived response efficacy was not measured at follow-up. In previous studies (8), negative affect reported immediately following receipt of test results had dissipated by the 6-month follow-up. If Web-based approaches are pursued, these possibly mild and short-term adverse effects might be offset by carefully developed additional Web site content, pointing out more strongly, for example, the benefits that all smokers get from quitting in terms of reducing multiple disease risks,

regardless of genotype. Research is urgently needed to more fully determine the risks and benefits of Web-based disclosure of genetic test results. For example, research comparing the cognitive, emotional and behavioral effects of Web-based approaches to genetic testing for common diseases with in-person and telephone approaches would be very useful. Further research is also needed to evaluate whether telephone or in-person support lessens any observed iatrogenic effects of the Web-based approach.

Limitations of the present study include that there was no control or comparison group, so we cannot know how the rates of uptake of smoking cessation services and the cognitive changes we observed would have compared with relative smokers not offered online genetic testing. Our rate of participation among racial or ethnic minority groups was low because of the demographics of those receiving care at our recruitment site, and we cannot generalize to more diverse samples. The number of patients with lung cancer who were initially approached but who declined to participate was not recorded. Given the exploratory nature of this pilot study, we were under-powered to detect some differences, so these findings should be viewed as preliminary and replicated in larger samples. Finally, the ranges of outcomes possible were potentially truncated by two factors: first, by our stringent exclusion criteria and, second, by the fact that smokers who opt for genetic testing self-select themselves into the genetic testing process because they are motivated to quit smoking (24, 34).

However, these limitations need to be balanced against the strengths, which include this study being the first, to our knowledge, to offer genetic testing for a common gene variant online. This is an important line of investigation given the importance of maximizing intervention reach. Indeed, numerous commercial companies are already doing exactly this. Empirical data such as that presented here can inform policy and regulatory decisions about these Web-based approaches to genetic testing. Further research is urgently needed that investigates the psychological and behavioral effects of genetic testing for common complex conditions using different approaches to delivering genetic test results.

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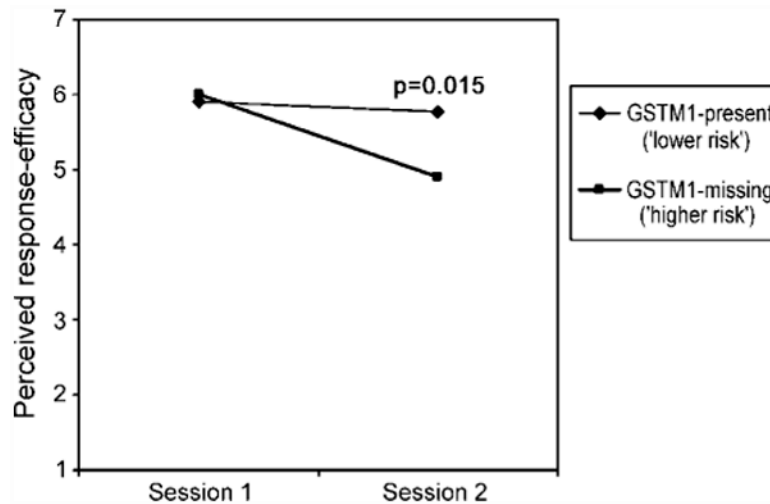


Figure 1. Perceived response efficacy (confidence that quitting smoking will reduce lung cancer risk) among smokers related to patients with lung cancer before and immediately after receiving genetic test results online.

Table 1
Characteristics of smokers related to patients with lung cancer who took the *GSTM1* genetic test and received their results

Variables	Whole sample (n= 44)		<i>GSTM1</i> present(lower risk; n = 22)		<i>GSTM1</i> missing (higher risk; n = 22)		Difference	
	n	%	n	%	n	%		
Gender	19	43.2	4	18.2	15	68.2	$\chi^2 = 11.21$; <i>df</i> = 1; <i>P</i> = 0.001	
	Male							
	Female	25	56.8	18	81.8	7	31.8	
Age, y	Mean (SD; range, 23-53 y)	40.0 (8.2)		40.8 (8.5)		39.2 (8.0)	<i>F</i> = 0.41; <i>df</i> = 1; <i>P</i> = 0.53	
Education	High school	11	25.0	7	31.8	4	18.2	$\chi^2 = 2.46$; <i>df</i> = 2; <i>P</i> = 0.29
	Technical/some college	23	52.3	12	54.5	11	50.0	
	College graduate	10	22.7	3	13.6	7	31.8	
Employed full-time	Yes	33	75.0	16	72.7	17	77.3	$\chi^2 = 0.12$; <i>df</i> = 1; <i>P</i> = 0.73
	No	11	25.0	6	27.3	5	22.7	
Race/ethnicity	White	42	95.5	22	100	20	90.9	$\chi^2 = 2.10$; <i>df</i> = 2; <i>P</i> = 0.35
	Other (Asian/Irish)	2	4.5	0	0	2	9.1	
Relationship to patient	Offspring	28	63.6	15	68.2	13	59.1	$\chi^2 = 4.23$; <i>df</i> = 3; <i>P</i> = 0.24
	Sibling	7	15.9	2	9.1	5	22.7	
	Aunt/uncle/niece/nephew	5	11.4	4	18.2	1	4.5	
	Grandchild	4	9.1	1	4.5	3	13.6	
Primary caregiver to patient	Yes	7	16.3	5	23.8	2	9.1	$\chi^2 = 1.71$; <i>df</i> = 1; <i>P</i> = 0.19
	No	36	83.7	16	76.2	20	90.9	
Frequency of seeing patient	Daily	2	4.5	1	4.5	1	4.5	$\chi^2 = 1.27$; <i>df</i> = 4; <i>P</i> = 0.87
	Weekly	6	13.6	3	13.6	3	13.6	
	Monthly	9	20.5	4	22.7	4	18.2	
	Lives with patient	1	2.3	1	4.5	0	0	
	Other	26	59.1	12	54.5	14	63.6	
No. of cigarettes smoked per day	Mean (SD; range, 1-30)	16.3 (7.2)		16.2 (7.5)		16.3 (7.0)	<i>F</i> = 0.00; <i>df</i> = 1; <i>P</i> = 0.95	
Previous use of smoking cessation services/products	Yes	24	54.5	11	50.0	13	59.1	$\chi^2 = 0.37$; <i>df</i> = 1; <i>P</i> = 0.54
	No	20	45.5	11	50.0	9	40.9	

Table 2
Comprehension and information processing of *GSTM1* genetic test results delivered online among smokers related to patients with lung cancer

Outcomes	Test result			Difference
	<i>GSTM1</i> -present (lower risk)	<i>GSTM1</i> -missing (higher risk)		
<i>Immediately after receiving genetic test results (online Session 2)</i>				
<i>Accurate comprehension, n (%)</i>				
Accurate recall of test result	22 (100)	22 (100)		NS
Accurate interpretation of test result	12 (55)	22 (100)		$\chi^2 = 12.94; df = 1; P < 0.001$
<i>Acceptability of test information*</i>				
Believable	1.23 (0.52)	1.55 (0.60)		NS
Trustworthy	1.27 (0.55)	1.50 (0.60)		NS
Easy to understand	1.32 (0.65)	1.45 (0.60)		NS
Relevant	1.32 (0.65)	1.45 (0.60)		NS
Important	1.23 (0.53)	1.41 (0.59)		NS
<i>Processing of genetic test – related information</i>				
Viewed strengths information page, n (%)	11 (50)	7 (32)		NS
Viewed weaknesses information page, n (%)	10 (45)	8 (37)		NS
Total no. of information pages viewed	3.1 (2.6)	2.6 (2.7)		NS
6-mo Follow-up				
<i>Accurate comprehension, n (%)</i>				
Accurate recall of test result	18 (100)	16 (100)		NS
Accurate interpretation of test result	10 (56)	15 (94)		$\chi^2 = 6.35; df = 1; P = 0.011$
<i>Decisional outcomes</i>				
Regret decision to take genetic test [†]	0 (0%)	0 (0%)		NS
Satisfied with decision to take genetic test [†]	17 (100%)	16 (94%)		NS

NOTE: Values represent means (SDs) unless otherwise indicated.

Abbreviation: NS, not significant.

* Possible scores range from 1 to 7; lower scores indicate more positive and higher acceptability responses (e.g., 1 = believable), and higher scores indicate more negative responses or lower acceptability (e.g., 7 = unbelievable).

[†]Measured using a seven-point scale (1 = strongly disagree, 7 = strongly agree); values shown are proportions who gave responses of 4 to 7, that is, who somewhat to strongly agreed with statement.