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Outcomes of a randomized controlled trial of genomic counseling for patients receiving personalized and actionable complex disease reports

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Abstract

There has been very limited study of patients with chronic disease receiving potentially actionable genomic based results or the utilization of genetic counselors in the online result delivery process. We conducted a randomized controlled trial on 199 patients with chronic disease each receiving eight personalized and actionable complex disease reports online. Primary study aims were to assess the impact of in-person genomic counseling on 1) causal attribution of disease risk, 2) personal awareness of disease risk, and 3) perceived risk of developing a particular disease. Of 98

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Compliance with Ethical Standards

Conflict of Interest: EG is currently a paid employee of Genome Medical. She worked for the Coriell Institute for Medical Research at the time that this study was developed and the majority of the data collection period. The authors have no additional conflicts of interest to disclose.

Informed Consent: All procedures followed were in accordance with the ethical standards of the local medical ethical boards of the Ohio State University Wexner Medical Center and the Coriell Institute for Medical Research and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Animal Studies: This article does not contain any studies with animals performed by any of the authors.

intervention arm participants (mean age = 57.8; 39% female) randomized for in-person genomic counseling, 76 (78%) were seen. In contrast, control arm participants (n=101; mean age = 58.5; 54% female) were initially not offered genomic counseling as part of the study protocol but were able to access in-person genomic counseling, if they requested it, 3-months post viewing of at least one test report and post-completion of the study-specific follow-up survey. A total of 64 intervention arm and 59 control arm participants completed follow-up survey measures. We found that participants receiving in-person genomic counseling had enhanced objective understanding of the genetic variant risk contribution for multiple complex diseases. Genomic counseling was associated with lowered participant causal beliefs in genetic influence across all eight diseases, compared to control participants. Our findings also illustrate that for the majority of diseases under study, intervention arm participants believed they knew their genetic risk status better than control arm subjects. Disease risk was modified for the majority during genomic counseling, due to the assessment of more comprehensive family history. In conclusion, for patients receiving personalized and actionable genomic results through a web portal, genomic counseling enhanced their objective understanding of the genetic variant risk contribution to multiple common diseases. These results support the development of additional genomic counseling interventions to ensure a high level of patient comprehension and improve patient-centered health outcomes.

INTRODUCTION

The ability to simultaneously analyze multiple genomic risk variants for common adult-onset disease, and apply this information in a meaningful way to patients remains a formidable challenge. Given the complexity of common health conditions like diabetes, coronary artery disease and cancer, the application of genome-based analyses can provide insight into risk but is only part of the risk equation (Eichler et al., 2010). Family health history, medical history and health behavior attributes (e.g. causal beliefs, lifestyle) must also be factored into how disease risk is presented to and perceived by the individual (Dewey et al., 2011; Inglis, Koehn, McGillivray, Stewart, & Austin, 2015; Ormond, 2013). Influences such as level of education, genetic and genomic knowledge, numeracy and literacy, and health status may affect an individual's ability to understand, process, and incorporate genomic risk information for common adult-onset disease (Haga, 2014; Haga et al., 2013; Lautenbach, Christensen, Sparks, & Green, 2013; McBride et al., 2009; O'Neill, McBride, Alford, & Kaphingst, 2010; Roberts, Dolinoy, & Tarini, 2014).

Effective genetic counseling should make disease risk information understandable and personally relevant. To achieve these goals in the era of genomics, genetic counseling has incrementally evolved into "genomic counseling", which takes the traditional diagnosis-focused approach for a single or few diseases, expands it to a greater number of conditions, and includes a more prevention oriented approach (Middleton, Hall, & Patch, 2015; O'Daniel, 2010; Ormond, 2013). Presenting genomic risk influences in the context of non-genetic risk variables through genomic counseling may help individuals recognize that for some diseases, the genetic contribution is more significant (e.g. age related macular degeneration), while for other diseases, lifestyle attributes, such as body mass index (e.g. type 2 diabetes) are paramount. As more genome based tests become available, it will be important to develop genomic counseling strategies for providing risk information for

diseases with multiple levels of risk and complexity (Cameron, Marteau, Brown, Klein, & Sherman, 2012; Marteau & Weinman, 2006; Shelton & Whitcomb, 2015). The study of disease risk perceptions and the impact of genomic counseling on this process may increase understanding of how genomic risk information could facilitate informed decisions, aid adaptation to personal risk, and influence actions to improve health outcomes (Cameron et al., 2012; Heshka, Palleschi, Howley, Wilson, & Wells, 2008). Although studies have shown that genetic counseling can positively affect risk perception for hereditary cancer (Julian-Reynier et al., 2011; McInerney-Leo et al., 2006) and for Alzheimer disease (Ashida et al., 2010), research is needed to assess whether genetic/genomic counseling modifies risk perception for other diseases (Smerecnik, Mesters, Verweij, de Vries, & de Vries, 2009). The study of the impact of multiplex genomic testing on healthy individuals has shown perceptions of disease risk were mostly influenced by prior beliefs about genetic causality of diseases, and by family history (Shiloh et al., 2015). Little is known about how participants offered genomic counseling for multiple potentially actionable diseases perceive its potential benefit. Prior studies show that 10% or fewer individuals offered genetic/genomic counseling for genome based results received through online delivery have used this service (Bloss, Wineinger, Darst, Schork, & Topol, 2013; Kaufman, Bollinger, Dvoskin, & Scott, 2012; Schmidlen et al., 2014).

Patients with chronic disease may have different motivations for predictive testing and represent more varied socio-economic status (SES) than “healthy” individuals seeking predictive genomic risk information. Individuals with a chronic disease may also vary in their understanding and response to multiple actionable genomic risk reports, and may treat risk information related to their diagnosis differently than risk information for other diseases. The Ohio State University-Coriell Personalized Medicine Collaborative (OSU-CPMC) was designed as a randomized cohort study to measure the effects of in-person post-test genomic counseling on patients with chronic disease (heart failure; hypertension) receiving multiple personalized and potentially actionable complex disease reports through a web-based portal (Sweet et al., 2014). The primary aims of the randomized trial were to explore the following hypotheses: 1) Is genomic counseling associated with changes in causal attribution of disease risk and personal awareness of disease risk among participants with chronic disease following receipt of multiple genomic results online? 2) Does perceived risk of developing a particular disease increase among participants who receive genomic counseling? We also sought to examine the extent to which genomic counseling was associated with changes in: disease risk due to updated/expanded family history collection following assessment by the genetic counselor, genetic/genomic knowledge, and overall satisfaction.

METHODS

Background

Participants in the Coriell Personalized Medicine Collaborative (CPMC) receive multiple potentially actionable complex disease and pharmacogenomics risk reports through a secure web portal as described by Keller et al (Keller M, 2010). All CPMC participants are administered online surveys that collect demographic, medical and family histories, lifestyle,

and medication information to produce personalized risk reports that are based on genetic risk factors, family history, and non-genetic risk influences (e.g. BMI). All CPMC participants also have the option to complete an online genetic education and genetic knowledge survey. The CPMC web portal also offers text and multimedia format educational materials and tools that enable study participants to learn more about basic genetics concepts, complex disease genetics, pharmacogenetics, family history risk, relative risk and health condition specific summaries detailing disease etiology, risk factors, treatment and available preventative or risk reducing actions. Results from primary outcomes of various trials related to the CPMC have been previously reported (Gordon et al., 2012; Schmidlen et al, 2016; Schmidlen et al., 2014; Sweet et al., 2016).

Study Design and Participants

To assess the effects of in-person genomic counseling on patients with chronic disease, a separate sub-study [The Ohio State University-Coriell Personalized Medicine Collaborative (OSU-CPMC)] was conducted on a group of participants enrolled in the larger Coriell Personalized Medicine Collaborative (CPMC). The present sample is comprised of 199 out-patients with either hypertension or congestive heart failure. In addition to completing CPMC required questionnaires, OSU-CPMC participants completed baseline (76 question) and follow-up (90 question) surveys designed to measure perceived risk, causal attribution and personal awareness of disease risk; general and relative risk numeracy; genetics/genomics knowledge; confidence in use of test results, and genomic counseling satisfaction (if applicable) (Study Schema, Figure 1; Survey Questions, Table I). Additional questions (e.g. measurement of health behaviors) were also part of the OSU-CPMC study surveys and will be published separately. The study was approved by the institutional review boards at Ohio State and the Coriell Medical Institute. Informed consent was obtained from all study subjects.

Procedures

The OSU-CPMC study procedures have been described in detail previously (Sweet et al., 2014). In brief, adult patients diagnosed with either congestive heart failure or hypertension after 06/2008, and under the care of an OSU physician, were eligible for study participation. Eligible patient participants were enrolled in the clinical setting by a study recruiter who collected a saliva sample and administered a one-hour educational presentation including access to the CPMC web portal, the randomization component, background information on DNA, genes, and single nucleotide polymorphisms, CPMC test report composition, relative risk (RR), and the availability of free in-person genomic counseling. Two hundred forty-eight patients were enrolled after being identified as study eligible by OSU physicians over a two year period; 4 additional OSU patient participants were recruited via Research Match, an online NIH research registry which advertised the study Saliva samples and consent forms were sent to Coriell, and unique CPMC web portal accounts were created. Of the 252 patients enrolled, 42 were removed from the study because they failed to complete the required baseline questionnaires (Figure 2). Genotyping was unsuccessful on two patients, while an additional nine with heart failure died after completion of baseline measures but before completion of follow-up measures. Thus, of the original 252 study participants, 199

patient participants (99 heart failure, 100 hypertension) completed all required baseline evaluations.

Block randomization was implemented by a computer generated random number list (Microsoft SQL, Microsoft Corporation, Redmond, WA, USA) prepared by an investigator with no involvement in the trial. Participants were stratified by diagnosis (hypertension or heart failure) and enrolling physician (n=20). All 199 individuals were block randomized to either the intervention arm (98 participants) or control arm (101 participants), with each arm receiving eight CPMC personalized disease reports [age related macular degeneration (AMD), coronary artery disease (CAD), type 1 diabetes (DM1), type 2 diabetes (DM2), hemochromatosis (HH), melanoma (MEL), prostate cancer (PRO), systemic lupus erythematosus (LUP)] (Sweet et al., 2014). These eight conditions were chosen given the relative high frequency of the genetic variant used to assess risk, varied effect size of each genetic variant on risk (RR 0.08 – >6.0), and because each condition is potentially actionable via lifestyle modification and/or medical intervention. The reports present personalized risk information as relative risk for each of the 8 conditions, based on genetic variant, family history and health behavior risk factors individually, in both graphical and numeric format (Figure 3).

Participants received an email notice directly from the CPMC web portal of the availability for online viewing of their test reports, and that they could choose whether or not to view each report. If a participant did not view at least one test report, study personnel contacted them by phone or email a maximum of five times over a 3-month period. When viewing a CPMC test report, participants are initially directed to a webpage containing written and video-based educational material describing the specific condition, the role of each risk factor, and approaches to prevention and treatment. Participants may choose not to view these educational materials and to proceed directly to their individual test report.

At the time of test result release, participants also received separate email notification from the Ohio State genetic counseling team reminding them of the randomization component, their assignment into either the intervention or control arm, and the availability of genomic counseling. Intervention arm participants were told they would be contacted for an in-person genomic counseling session within one month of viewing at least one of the eight CPMC reports. In contrast, control arm participants were not initially offered in-person genomic counseling as part of the study protocol but were reminded that they were able to access in-person genomic counseling, if they requested it, 3-months post viewing of at least one test report and post-completion of the follow-up survey (Figure 1). They were also reminded that they could access a CPMC genomic counselor by phone if necessary for urgent questions. The study was closed for data analysis on August 22, 2014.

Genomic Counseling Session

Genetic counseling protocols for Mendelian disorders as well as those available in the context of multiplex genomic studies were reviewed and content areas catalogued to develop the design of a structured in-person genomic counseling session (Bloss, Darst, Topol, & Schork, 2011; DeMarco, Peshkin, Mars, & Tercyak, 2004; Gollust et al., 2012; Gordon et al., 2012; Kasparian, Wakefield, & Meiser, 2007; Payne et al., 2008; Sanderson et al., 2009;

Schmidlen, Gordon & Christman, 2009; Smerecnik et al., 2009; Vassy et al., 2012). The Reciprocal-Engagement Model of genetic counseling practice, built on the tenets of patient-centered education, relationship, autonomy, support provision and facilitative decision-making was used to guide the counseling process (Veach, Bartels, & Leroy, 2007). In-person genomic counseling was provided from one of two licensed genetic counselors. The genomic counseling session, which was scheduled for one hour but sometimes extended to 1.5 hours, included a review of results for all eight test reports, assessment of medical history, and, in accordance with the recommendations of the National Society of Genetic Counselors Task Force, construction of at least a 3-generation pedigree in order to provide a context in which the counselee could understand the test report risk information and risk assessment (National Society of Genetic Counselors' Definition Task et al., 2006; Smerecnik et al., 2009). Given that participants have the potential for multiple "increased" risk variables (genetic variant, family history and health behaviors; Table SI), "decreased" risk variant(s) for DM1, and differing ranges of relative risk for each disease (0.08 – >6.0), we developed a tabular visual display for use in the genomic counseling intervention which synthesized each of the risk factors into a one-page document to provide an overall quick reference summary (Sweet et al., 2014). All individual increased risk variables were highlighted, and risk was also compared to the general population risk for each disease. The participant was asked which reports they wanted to review with the counselor, and based on this preference at least one CPMC report was accessed live via the web portal during the counseling session to associate with the quick reference summary. Genomic counseling focused on the risk factors each participant had for a given disease, to include additional disease risks identified through comprehensive review of the medical and family histories, and other health behaviors not included in the CPMC report. Specific actions to prevent and/or lower disease risk were also provided. A risk summary letter providing a focused interpretation of the eight personalized CPMC health condition study reports, the medical and family histories, recommended screening and prevention measures, and, if indicated, referral to another medical provider was then mailed to any participant that received in-person genomic counseling. The summary letter was also made available to the OSU health care team through the EPIC® electronic medical record.

Survey Measures

Baseline and follow-up measures included new items developed from a review of the literature, after review with the respective study authors, and modified items from existing CPMC surveys (Jenkins et al., 2007; Keller M, 2010; Sweet et al., 2014). Table I provides a list of questions for each of the survey measures discussed below. All survey questions included in the baseline and follow up were identical with the exception of, the follow up survey also included one question on *personal awareness of disease risk* based on the receipt of genetic results for each disease; one question on *perceived risk* of developing a particular disease; and for intervention arm participants only, 4 questions on *satisfaction with the genomic counseling process*.

Risk Perception

Causal Attributions of Disease Risk—A participant's *causal attribution of risk* for each disease was assessed for each risk factor at baseline and follow-up (e.g. "How much do

you think having a genetic risk variant determines whether or not a person will develop each of the following conditions?") (O'Neill et al., 2010). Five point Likert scales were used for these items, and ratings were combined across diseases to generate composite scores of the overall importance a participant placed on genetic variants, family history, and environment for disease risk. Cronbach's alphas were 0.88, 0.88, and 0.85, respectively, for these composite items.

Personal Awareness of Risk—We assessed each participant's *personal awareness of risk* due to family history and environmental factors at baseline and at follow-up for each disease using original matrix format measures ("Do you have an increased risk for any of the following conditions due to your family history?"). Personal awareness of risk based on the addition of a genetic variant for each disease was then also assessed at follow-up ("Do you have an increased risk for any of the following conditions due to a CPMC genetic risk variant?"). Response options for these questions included: yes, no, not applicable, don't know, do not want to answer.

Perceived Risk—To assess each participant's *perceived risk* of developing a particular disease we used a single 5 point Likert scale validated question at follow-up only ["What do you think is your chance of developing each of the following diseases in your lifetime?" (McBride et al., 2009)]. We compared their responses to the actual risk for each disease based on the CPMC results.

Genomic Counseling Modification of Disease Risk—To examine the extent to which the genomic counseling intervention (versus control group) was associated with changes in individual actual disease risk compared to risk conveyed through the CPMC report, we recorded (1) the number of CPMC study reports for which family history or lifestyle risk was modified, (2) the number of new disease risks identified through additional medical and family history assessment, and (3) the number of specialty referrals.

Numeracy and Genetic/Genomic Knowledge—As numeracy is associated with an individual's perceptions of risk, we adapted four numeracy scales from a previous study to assess our patient sample (Lipkus, Samsa, & Rimer, 2001). Two original multiple choice questions were included to evaluate numeracy regarding relative risk based on family history (CAD) and genetic variant (DM2), because relative risk is used in the CPMC test reports (e.g. "if a person has a genetic variant that gives a relative risk for developing type 2 diabetes of 1.3, how likely are they to develop type 2 diabetes compared to someone with no copies of that genetic variant?") (Table I). All six numeracy questions were short answer questions scored as correct or incorrect. Personal perceptions of genetic knowledge were assessed using a single multiple-choice, original item ("Compared to most people, how would you rate your knowledge of genetics?". Response options: better than most people; about average; less than most people).

A genetic/genomic knowledge and genetic education history survey (Table I) was used to assess knowledge of basic genetics, inheritance, influence of gene/environment interactions on complex diseases, disease susceptibility and genetic variation. The twenty questions were either from previously published studies (Christianson et al., 2010; Furr & Kelly, 1999;

Jallinoja, 1999; Keller M, 2010; O'Neill et al., 2010) or formulated for the CPMC parent study to assess participant baseline genetic/genomic knowledge. Information relating to the genetic knowledge questions was covered in the participant informed consent process either as part of the explanation of the personalized medicine study provided during the consent presentation or within the text of the informed consent document. Specifically, this included an explanation of the human genome, genes, chromosomes, SNPs, complex disease genetics, and drug response. Information on the following topics was available for all participants to view on the CPMC web portal throughout the course of study: basic genetics concepts, complex disease genetics, pharmacogenetics, family history risk, and relative risk. Information relating to complex disease genetics, relative risk, lifestyle and family history risk was also provided during the in-person genomic counseling session. Knowledge was assessed using true/false questions scored as correct or incorrect. Percent correct was calculated across the sets of these questions and used as the dependent variable (follow-up) and covariate (baseline).

Individual Questions/Evaluations—Satisfaction with the content and process of the in-person genomic counseling session for intervention arm participants was assessed with 4 items from the 6 item Genetic Counseling Satisfaction Scale (GCSS)(DeMarco et al., 2004). Items included "I feel better about my health after meeting with my genetic counselor"; "The genetic counseling session was valuable to me" and "The genetic counseling session was about the right length of time I needed". We modified one original GCSS item "My genetic counselor helped me to identify what I needed to know to make decisions about what would happen to me) to read "The genetic counselor gave me information I needed". We replaced two original GCSS items with statements more relevant for our study (i.e. "I know what to do with my results"; "All individuals should meet with a genetic counselor when receiving this type of disease risk information"). Modifications of items from the GCSS were not validated prior to inclusion in this study. The response scale for these items was: Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree, and Did Not Want to Answer.

Statistical Analyses

We used two approaches to analysis: "Per-Protocol" (PP) and "Intention to treat" (ITT) (Abraha & Montedori, 2010; Gupta, 2011). PP analysis is a comparison of the two treatment groups, and includes only those participants who completed the treatment (e.g. genomic counseling) as originally allocated. ITT analysis means that all study participants who were enrolled and randomly allocated to receive genomic counseling were included in the analysis, and are analyzed in the groups to which they were randomized. Per Protocol results are presented as the primary analyses in the main text, and ITT analyses results are included in the supplemental results for comparison. More specifically, the analyses in the main body include only individuals who completed their "treatment" (in-person genomic counseling or no in-person genomic counseling) according to the group in which they were randomized. This resulted in the removal from analyses of five participants from the randomized control group that had in-person genomic counseling prior to completing the follow-up survey. One additional individual from the control group was also removed as they received phone genomic counseling from a CPMC genetic counselor. Therefore, we had 76/98 (77.6%) of

intervention arm participants receiving in-person genomic counseling; and no control arm participants (n=95) receiving in-person genomic counseling in the per protocol analysis (n=171). For socio-demographic associations (n participants=199), Student's t-test, Fisher's exact tests, or Wilcoxon Rank Sums tests were used as deemed appropriate.

Survey Analyses

In general, survey variables were of one of three types: 1) composite, where multiple questions are combined to get an overall score (Likert type and percent correct), 2) binary responses (yes/no, correct/incorrect), and 3) single item Likert-like questions (ordinal response 1–5), which determined the corresponding models used for their analyses. 1) For composite measurements that were summaries across multiple questions, such as percent correct across genetic knowledge questions or combined Likert scale questions, linear models were employed with a covariate for baseline scores (to adjust for baseline differences between groups) and with additional covariates for gender, age, disease group, and education level. 2) For dichotomous follow-up measurements (such as correct/incorrect assessment of self-risk), logistic models were used with covariates for baseline response, gender, age, disease group, and education level. To determine whether intervention participants had different knowledge of their personal risk compared to non-intervention participants, Fisher's exact tests were employed. 3) For questions of certainty of personal disease occurrence (Likert type, but not Likert scale; that is, analyses of single question responses with a Likert type response), ordinal logistic models were employed with covariates for baseline response, gender, age, disease group, and education level within disease. Cronbach's alpha (Cronbach & Warrington, 1951) was calculated for Likert type questions that together addressed a particular general theme as an indication that the combination of these questions was reliable as a Likert scale item (Clason, 1994). Missing values were assumed to be at random regarding follow-up responses. False discovery rate (Benjamini Y, 1995) adjustment was used to correct for multiple testing across main effects tests (n=86), and a false discovery rate threshold of 20% was used to declare significance.

RESULTS

Participant Socio-demographic and Clinical Characteristics

Table II and Figure 2 depict enrollment numbers and socio-demographic information for intervention and control group participants. There were no significant ($p < 0.05$) differences in ethnicity, gender, income or education between intervention and control group participants, or in separate analyses (PP/ITT). Sixty-nine percent (n=137) of participants had an associate's degree or higher. There were more male participants, 107 (53.8%) than female; and 25 (12.5%) worked in a health care-related occupation (e.g. nursing). Mean age was 58.1 years (range from 24 to 94). Of the eight diseases under study, 95 participants had a personal diagnosis of at least one disease (Table SII). There were 40 subjects with 1 elevated genetic variant risk variable; 68 subjects with 2 elevated genetic risk variables; and 87 subjects with 3+ elevated genetic risk variables (Table SIII). There were no significant differences between study groups on these variables.

The number of reports viewed by intervention arm participants is provided in Table III. Of 183 (91.4%) study participants who viewed at least one CPMC test report, and thus were administered the follow-up survey, 129 (64 intervention arm; 59 control arm) completed the follow-up survey. Across the entire sample, completion was greater than 90% for all follow up survey questions, with the exception of the last four questions on the survey regarding genomic counseling satisfaction. Only 29 (of 76) intervention arm participants completed these last 4 questions.

Of 98 intervention arm participants, 76 (77.6%) were seen for in-person genomic counseling. Four individuals did not show up for their appointment. Of the remaining 18 eligible intervention arm participants, eight never viewed a CPMC report; six never scheduled an appointment; and four declined genomic counseling. The mean number of days from participant completion of the baseline survey to genomic counseling was 224; from release of test results to genomic counseling (90); from viewing test results to genomic counseling (52), and from genomic counseling to completion of follow-up survey (168) (Table SIV). The mean number of days from report viewing to completion of follow-up surveys was comparable between groups (intervention, 222; control, 175).

Risk Perception

Causal Attributions of Disease Risk—We examined to what extent intervention arm participants who had genomic counseling believe that different risk influences (genetic variant, family history, health behavior) contribute to a person's risk for developing each of the eight diseases, and if receiving genomic counseling was associated with changes, from baseline in their causal attributes. At baseline, there was no evidence supporting differences in causal beliefs between the two groups. In follow-up, genomic counseling was associated with decreased genetic causal beliefs across all eight diseases, compared to control participants (estimate=0.4, raw p=0.019; FDR p=0.142, 95% C.I. 0.06–0.7); Table IV; SV ITT). Here and throughout the results, estimate refers to the estimate of the coefficient for the variable of interest in the statistical models. Additional analyses were then performed for each disease to determine if only a subset of the diseases might be driving the association. As seen in Table IV (SV, ITT), genomic counseling was positively associated with lowering participants' causal beliefs in the degree of genetic variant influence for three diseases (LUP, raw p=0.0008, DM1, raw p=0.010; PRO, raw p=0.005; estimates = 1.3, 0.92, 1.0, respectively).

Personal Awareness of Risk—Baseline personal awareness of risk, based on two factors, family history and health behavior, was in general accurate and highly predictive of follow up awareness of risk for each disease in each group. Upon examining whether genomic counseling affected personal awareness of risk (whether subjects correctly reported that they were at increased risk based on family history and health behavior risk influences), there was no significant effect of genomic counseling (FDR $p > 0.25$) Table SVI). However, we also asked participants in their follow-up questionnaire whether they knew they had an increase in disease risk due to a genetic risk variant, and found that intervention arm participants who had genomic counseling answered "don't know" at a lower rate than control subjects, for six of the eight diseases (FDR $p < 0.2$; Table V; SVII ITT). We then

compared the accuracy of participants' personal awareness of disease risk to their actual genetic variant results; significant associations with genomic counseling were seen for DM1 and DM2 (FDR p=0.2 and 0.12, respectively) with more individuals in the genomic counseling arm accurately describing the risk for DM1 and DM2 than in the control arm.

Perceived Risk—Lastly, at follow-up, we asked participants to report their perceived risk for developing each of the eight diseases in their lifetime, and compared those results to their actual risk results. Although we found no main effect due to genomic counseling, participants who had elevated BMI as a risk factor for DM2 (FDR=0.04), genetic variant risk for DM2 (FDR p=0.12; estimate=2.0; raw p=0.001), family history risk for MEL (FDR p=0.05, estimate=1.9; raw p=0.003) or genetic variant risk for MEL (FDR p=0.01, estimate=2.3, raw p=0.0002) had an elevated perceived risk for developing these diseases compared to those without these risk factors (Table VI; SVIII ITT).

Genomic Counseling Modification of Disease Risk—To examine whether genomic counseling was associated with changes in individual actual disease risk, we compared the number of CPMC study reports for which family history risk was modified based on the collection of a three generation pedigree, as well as the number of new disease risks identified through additional family history assessment. We also recorded the number of specialty referrals that were made by this additional risk assessment. Among all study participants (intervention and control arm) who had genomic counseling (n=81), family history disease risk was modified for 61 (75.3%; 95% CI 65.9%–84.7%). There were 104 instances of specific modification of participant disease risk, which accounted for 6% of all risk variables for which individuals had a risk determined separately at genomic counseling (Table VII). Genomic counseling also identified 31 individuals who were referred for additional genetics evaluation (n=22) or increased screening (n=9) (Table VIII).

Numeracy and Genetic/Genomic Knowledge—We used a number of questions to assess participant's simple genetic knowledge, complex genomic knowledge, and levels of numeracy. At baseline, the mean percentage of correct answers on the 14 simple genetic knowledge questions was relatively high (77%), as well as for the six complex disease questions (75%). Basic genetic knowledge (at baseline) was associated in the multivariable model with higher levels of education (raw p <0.0001; estimate= 0.04; 95% CI 0.02–0.05). Furthermore, there was strong evidence that baseline performance was highly predictive of follow-up performance on the numeracy (Tables SIX, SX) and genetic/genomic knowledge questions (numeracy raw p< 0.0001, estimate=0.53, 95% CI 0.40–0.66; simple genetic knowledge raw p< 0.0001, estimate=0.54, 95% CI 0.34–0.74; complex genetic knowledge raw p<0.0001, estimate=0.45, 95% CI= 0.26–0.65) suggesting that in a generally highly educated group, genomic counseling did not provide an added knowledge benefit (FDR p > 0.39) (Tables SXI-SXIII), at least at the difficulty level of the questions included in the current study.

Individual Questions/Evaluations—Of intervention arm participants who had in-person genomic counseling, 83.1% (95% CI 70.5–91.2%) expressed confidence in knowing what to do with test results, as compared to control arm participants (61.8%; 95% CI

47.7%–74.3%). Likewise more intervention arm participants who received genomic counseling (73%; 95% CI 59.5%–83.3%) felt that individuals should meet with a genetic counselor when receiving these types of test results, than control arm participants (54.4%; 95% CI 40.6%–67.8%). Only 29 participants who had in-person genomic counseling completed the 4-question survey section on satisfaction; of these, 24 (82.7%; 95% CI 63.5–93.4%) reported feeling better about their health following genomic counseling. Twenty-seven participants (93%; 95% CI 75.8–98.8%) felt the genomic counseling session was the appropriate length of time. A similar percentage of counselees (93%; 95% CI 75.8–98.8%) felt the genomic counseling session was valuable, and that the counselor provided needed information (Table SXIV).

DISCUSSION

In a population of patients affected with chronic disease receiving multiple, actionable and personalized complex disease risk reports through an online portal, we sought to determine if in-person genomic counseling had an impact on 1) causal attribution of disease risk, 2) personal awareness of disease risk, and 3) perceived risk of developing a particular disease. We found that those receiving genomic counseling had enhanced objective understanding of the genetic variant risk contribution for multiple actionable complex disease reports. Indeed, participants receiving genomic counseling were significantly more likely to understand the relative and limited predictive contribution of common genetic risk factors for complex disease compared to control subjects. Participants receiving genomic counseling also were more confident and accurate in knowing their genetic risk status than control subjects, which is consistent with broader literature on the benefits of genetic counseling (Armstrong et al., 2015). Furthermore, the more comprehensive assessment of family history through genomic counseling allowed for disease risk to be modified in a significant percentage of cases. Our study participants demonstrated similarly high levels of genetic knowledge to that reported in the larger CPMC cohort (Schmidlen et al., 2016) as well as that found by Haga et al., who also studied genetic knowledge in the context of common, complex diseases (Haga et al., 2013). In a highly educated population of patients provided with genetics/genomics education during recruitment and with access to online genetics/genomics educational material prior to genomic counseling, we did not find significant improvement in genetics/genomics knowledge or numeracy following genomic counseling. Given that the information assessed by the genetic knowledge questionnaire was covered at multiple points during the study recruiting session, discussed in the informed consent document, and included in the educational web pages on the CPMC web portal, in addition to the highly educated population, these findings are not surprising. While some of the topics covered in the genetic knowledge questionnaire (complex disease genetics, family history risk) were also reinforced in the genomic counseling session, the focus of the genomic counseling sessions was on personal risk assessment and not on a review of the specific genetic/genomic knowledge items queried.

Previous studies have shown that 1) individuals see distinct causal roles for genetic variant and health behavior risk influences for common disease; and 2) these separate causal beliefs are not incompatible (Kaphingst et al., 2012; McBride et al., 2009; McBride, Birmingham, & Kinney, 2015; Sanderson et al., 2009; Shiloh et al., 2015). In fact, for common disease

risk, although individuals may view separate influences on distinct tracks, large segments of the population also appear to have disparate views of the relationship between genes and health behavior attributes on perceived risk (Ashida et al., 2011; Condit & Shen, 2011; Haukkala et al., 2015). O'Neill et al. (2010) found that healthy individuals, when provided complex disease results, had a tendency to favor genetic causation over health behaviors when the number of personal risk factors increased, which corresponds with our own findings. Our sample of patients appeared to embrace stronger causal belief in the genetic influence on common disease risk, possibly due to having personal experience in dealing with a chronic disease. The genomic counseling intervention, in addition to providing more insight into the interrelationship between genetics and health behaviors as contributors of risk, may also have countered existing causal genetic deterministic beliefs and emotions predicated by personal disease experience. This may allow, in turn, greater understanding of the multifactorial nature of complex disease and an opportunity for additional interventions to improve patient-centered health outcomes (Austin, 2015; Lewis et al., 2015; McBride et al., 2015; Ormond, 2013). As all study participants received pre-test education during the informed consent session, and had access to online educational resources, genomic counseling may also have served to reinforce the test report message, and increase confidence in use of multi-page, detailed results. These findings are consistent with previous work showing that incorporation of evidence-based communication strategies in the result delivery process result in more accurate interpretation (Birch, 2015; Haga et al., 2014).

As compared to online family history collection and risk assessment, a three or four generation, more comprehensive family history was obtained and assessed through genomic counseling. In this targeted disease population, the assessment of comprehensive family history resulted in a significant number of modifications of participant disease risk, to include identification of individuals for which more targeted testing or screening was appropriate. For example, the family history relative risk value chosen by the CPMC for use in the CAD risk report came from a publication that provided family history risk assessment for CAD based only on parental history of CAD (Myers, Kiely, Cupples, & Kannel, 1990). This points to a limitation of online familial risk assessments in general, which are based on what the participant provides, but also what algorithm(s) the online tool includes, which can often be limited, incomplete or incorrect. Via genomic counseling, participants with possible Mendelian conditions were also identified. The CPMC family history risks were not designed with Mendelian disease risk detection in mind, but were designed very specifically to the complex diseases included, and usually based on first-degree relative information. While web tools can be invaluable for the purposes of triage (Sweet, Sturm, Rettig, McElroy, & Agnese, 2015), they can also miss the intricacies of a 3–4 generation pedigree assessment collected and assessed during genomic counseling. Comprehensive risk assessment by a genetic counselor, whether by interpreting medical and family histories or by incorporating genetic variant and health behavior attributes into the analysis, remains an integral part of the result delivery process in genetic/genomic counseling (National Society of Genetic Counselors' Definition Task et al., 2006; Smerecnik et al., 2009).

Study Limitations

Unlike use of multiplex testing by “healthy” adults, our participants were all included due to their diagnosis of a chronic disease (heart failure or hypertension). We had a number of individuals who never completed baseline measures, did not view a single test report, or complete follow-up surveys. The randomized groups did not fully capture the magnitude of the genomic counseling vs. no-genomic counseling effects because some intervention group individuals did not receive genomic counseling, and some control arm subjects received genomic counseling. Our recruitment efforts may have bias, especially for the heart failure cohort, as almost 40% of eligible participants approached did not have access to a computer and thus declined participation. We had a higher than expected patient SES, and the sample was highly educated and predominantly Caucasian. There were self-reported data (e.g. family history) for the web portal, potentially introducing reporting bias. We had no control over which CPMC reports participants selected to view on their own via the web portal, with the exception of reports reviewed during the genomic counseling session. During the genomic counseling session, all eight health condition reports were reviewed with the participant. Some participants may have gotten more information than they wanted or had an interest in learning. We had no ability to track which educational topics were viewed by participants on the CPMC web portal during the course of study. While using only two genetic counselors for the in-person genomic counseling sessions helped to standardize the intervention, this limits generalizability of study findings. We utilized portions of published measures, with modification of some items, and creation of new survey measures. The low response rate for items evaluating genomic counseling received raise caution about the generalizability of these results. Given the modest sample size, which was not representative of any particular disease population, and which may have been underpowered to detect real differences, these should be considered preliminary results and further investigation is needed.

Research Recommendations and Practice Implications

Based on the limitations of this study, further research on the effects of genetic/genomic counseling on patients receiving multiple, actionable complex disease results in an online format is necessary. Given the steady increase in the availability of genomic based results, including those available through online formats, there remains appreciable need for additional research on the effectiveness and extension of genetic/genomic counseling service delivery beyond traditional referral reasons (i.e. Mendelian disease risk) and service delivery approaches (Haga et al., 2014; Lewis et al., 2015; Ormond, 2013; Shiloh et al., 2015; Trepanier & Allain, 2014). These include phone (telemedicine) as well as use of e-learning approaches (both static and interactive) either alone or to supplement counseling (Birch, 2015; Haga et al., 2014). Use of adjunct e-learning approaches and automated family history risk assessment tools may be an avenue to impact patient knowledge and improve patient-centered health outcomes while increasing the efficiency of genomic counseling interventions. The degree of genomic counseling needed will vary per patient, and per indication. In fact, counseling for common risk variants may not always require advanced or specialized counseling from a genetic counselor, but rather other health care professionals, with supplemental training in genetics/genomics (e.g. nurses) could help in this manner (Mills & Haga, 2014; O’Daniel, 2010; Ormond, 2013; Shelton & Whitcomb, 2015).

CONCLUSION

In conclusion, our findings show that genomic counseling significantly affected comprehension of the genetic variant risk contribution when patients were presented with multiple potentially actionable complex disease reports through an online portal. Our study demonstrates that genetic counselors can work in many ways to affect patient's understanding of risk including: 1) providing appropriate breakdown of the various components of disease risk (genetic variant(s), family history, non-genetic influences) when presenting risk for multiple diseases at the same time, 2) adding additional context to this risk based on personal and family history, to include comprehensive assessment through development of a 3–4 generation pedigree, and 3) increasing patient understanding by providing side-by-side comparison of risks factors found in online test reports, to that provided in a visual one-page summary that was used in the counseling session. Our findings also suggest that genomic counseling for common disease risks, especially in the setting of patients with chronic disease receiving test results with actionable components, may allow opportunity for additional patient-centered interventions. Providing insight on the varied effect of genetic variants on risk, to include the limited predictive contribution of many of these variants, and as relative to other risk factors, may allow patients to develop more accurate perceptions of risk and what risks they can modify. Given that most common diseases are multifactorial in nature, with potentially actionable components via lifestyle modification and/or medical intervention, improving patients risk perceptions may impact personal utility and efficacy, especially if supplemented with effective health behavior recommendations and interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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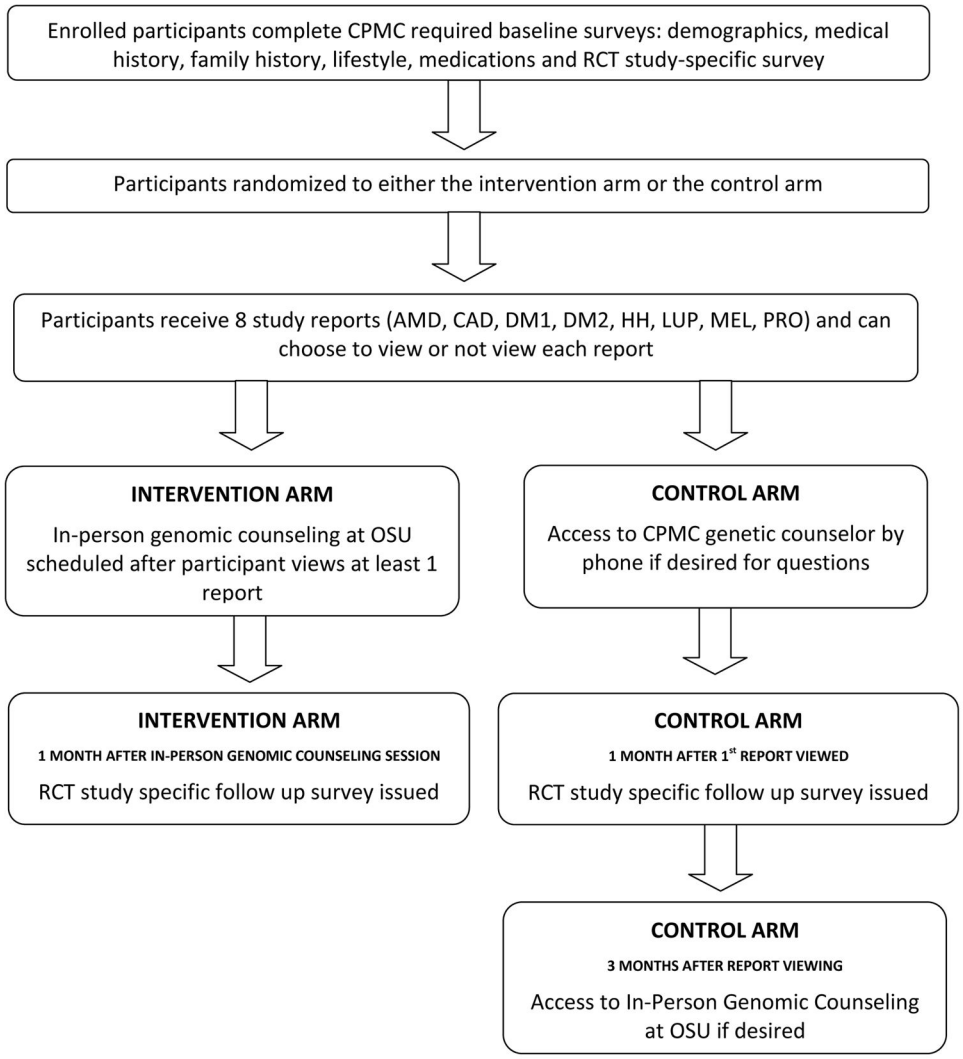

Figure 1. Study Schematic

Legend:

AMD: Age Related Macular Degeneration

CAD: Coronary Artery Disease

CPMC: Coriell Personalized Medicine Collaborative

DM1: Type 1 Diabetes

DM2: Type 2 Diabetes

HH: Hemochromatosis

LUP: Systemic Lupus Erythematosus

MEL: Melanoma

PRO: Prostate cancer

RCT: Randomized Controlled Trial

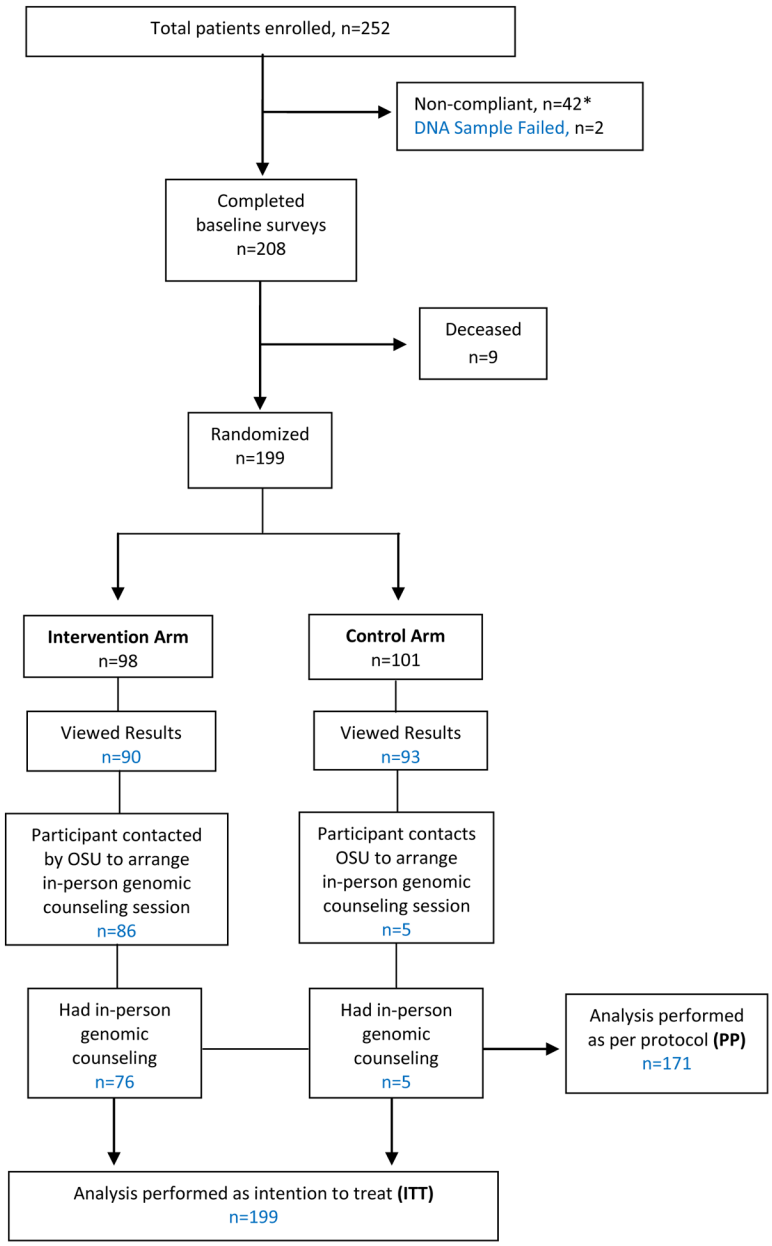

Figure 2.

Enrollment, Study Groups, Outcomes

*Non-compliance was when an individual had not completed the baseline surveys within a 45 day time limit

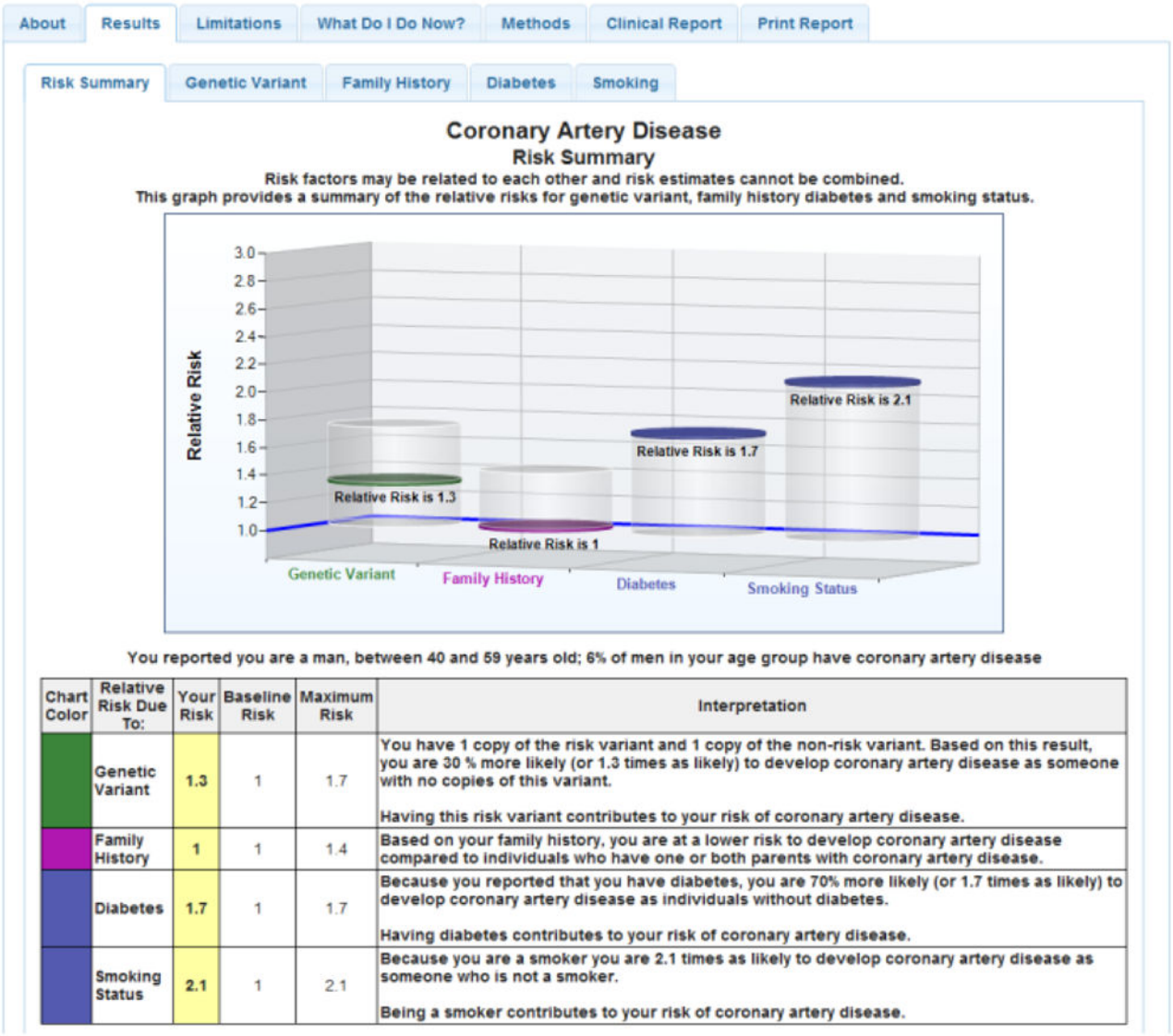

Chart Color	Relative Risk Due To:	Your Risk	Baseline Risk	Maximum Risk	Interpretation
	Genetic Variant	1.3	1	1.7	You have 1 copy of the risk variant and 1 copy of the non-risk variant. Based on this result, you are 30 % more likely (or 1.3 times as likely) to develop coronary artery disease as someone with no copies of this variant. Having this risk variant contributes to your risk of coronary artery disease.
	Family History	1	1	1.4	Based on your family history, you are at a lower risk to develop coronary artery disease compared to individuals who have one or both parents with coronary artery disease.
	Diabetes	1.7	1	1.7	Because you reported that you have diabetes, you are 70% more likely (or 1.7 times as likely) to develop coronary artery disease as individuals without diabetes. Having diabetes contributes to your risk of coronary artery disease.
	Smoking Status	2.1	1	2.1	Because you are a smoker you are 2.1 times as likely to develop coronary artery disease as someone who is not a smoker. Being a smoker contributes to your risk of coronary artery disease.

Figure 3.

Sample CPMC Coronary Artery Disease Report

Solid discs represent the participant's relative risk, and vertical cylinders depict the range of relative risk (RR) values possible for the risk variable. On-line risk reports are organized using a tabbed approach, with separate tabs for disease condition information, risk results, limitations, methods or review educational material. To ensure readability, the CPMC test report design was informed by multiple rounds of pilot testing conducted by allowing individuals with no scientific background to review report drafts and provide feedback.

Table I

Study-Specific Survey Questions

Causal Attributes of Disease Risk	**Baseline and Follow up** How much do you think having a genetic risk variant determines whether or not a person will develop each of the following conditions? How much do you think family history determines whether or not a person will develop each of the following conditions? How much do you think environmental risk factors (for example, smoking, poor diet, high Body Mass Index (BMI)) determine whether or not a person will develop each of the following conditions?
Personal Awareness of Risk	**Baseline** Do you have an increased risk for any of the following conditions due to your family history? Do you have an increased risk for any of the following conditions due to your environmental risk (for example, smoking, poor diet, high Body Mass Index (BMI))? **Follow up** Do you have an increased risk for any of the following conditions due to your family history? Do you have an increased risk for any of the following conditions due to your environmental risk (for example, smoking, poor diet, high Body Mass Index (BMI))? Do you have an increased risk for any of the following conditions due to a CPMC genetic risk variant?
Perceived Risk	**Follow up** What do you think is your chance of developing each of the following diseases in your lifetime?
Numeracy and Genetic/Genomic Knowledge	*Expanded and General numeracy scale items*[1] If the chance of getting a disease is 10%, how many people out of 100 would be expected to get the disease If the chance of getting a disease is 10%, how many people out of 1000 would be expected to get the disease? Imagine that we rolled a fair, six-sided die 1,000 times. Out of 1,000 rolls, how many times do you think the die would come up even (2, 4, or 6)? In the ACME PUBLISHING SWEEPSTAKES, the chance of winning a car is 1 in 1,000. What percent of tickets to ACME PUBLISHING SWEEPSTAKES win a car? *Relative Risk Numeracy - Investigator Generated Questions* People without a family history of coronary artery disease have a 20% risk to develop coronary artery disease. People with a family history have a relative risk of 2.0 (they are 2 times as likely to develop coronary artery disease as those without a family history). What is the risk for someone with a family history? If a person has a genetic variant that gives a relative risk for developing type 2 diabetes of 1.3, how likely are they to develop type 2 diabetes compared to someone with no copies of that genetic variant? *CPMC: Personal perception of genetic knowledge* Compared to most people, how would you rate your knowledge of genetics? a. Better than most people b. About average c. Less than most people *CPMC: Genetic/Genomic Knowledge*[2,3] It is possible to see a gene with the naked eye Healthy parents can have a child with a hereditary disease The carrier of a disease gene may be completely healthy All serious diseases are hereditary Genes are inside cells The child of a disease gene carrier is always also a carrier of the same disease A gene is a piece of DNA A gene is a part of a chromosome All body parts have all of the same genes It has been estimated that a person has about 20,000 genes A person's race and ethnicity can affect how likely they are disease Once a genetic marker for a disorder is found in a person the disorder can be prevented or cured Only mothers can pass on genetic disorders The onset of certain diseases is due to genes, environment and lifestyle [2] Each of us has variations in our genes that make it more likely that we will get certain diseases [3] A "complex disease" is a health condition brought on by many genes and lifestyle and environment [4] A single nucleotide polymorphism or "SNiP" is a variation present in some individuals that stretches across in a large section of DNA[4] *OSU-CPMC Study Specific: Genetic/Genomic Knowledge* If a person has a genetic marker for a disorder, the person will always get the disorder [5] People who have a genetic marker for a disease are unhealthy[5] A person's health habits can influence whether or not their genes cause disease[6]

Individual Questions/Evaluations	*Satisfaction/Confidence in Use of Results*[7] The genetic counseling session was about the right length of time I needed The genetic counseling session was valuable to me The genetic counselor gave me information I needed I felt better about my health after meeting with my genetic counselor I know what to do with my results

[1] Source: Lipkus (2001)

[2] Source: Jallinoja (1999)

[3] Source: Christianson (2010)

[4] Source: Keller (2010)

[5] Source: Furr (1999)

[6] Source: O'Neill (2010)

[7] Source: DeMarco (2004)

Table II

Socio-demographic and Clinical Characteristics of Intervention versus Control Group Participants

Demographic Category	Subject Category	Intervention Arm (n=76)	Control Arm (n=95)	*p* value	Test
Age (mean)		57.8	58.5	0.86	Welch's t-test
Number of reports viewed (mean)		6.73	0.79	0.61	Wilcoxon Rank Sums
Race (Caucasian)	Yes	68	88	0.59	Fisher's Exact Test
	No	8	7		
Gender	Female	33	49	0.356	Fisher's Exact Test
	Male	43	46		
Education	<HS	3	0	0.13	Ordinal Logistic
	HS Grad/GED	2	10		
	Vocational/Trade	1	0		
	Some College	13	23		
	Associate Degree	12	12		
	Bachelor Degree	20	24		
	Graduate Degree	25	26		
Received GC	Yes	76	0	<0.0001	Fisher's Exact Test
	No	0	95		
Follow Up	Yes	64	59	0.002	Fisher's Exact Test
	No	12	36		
Income	<$25k	5	10	0.24	Wilcoxon Rank Sums
	$25–50k	12	19		
	$50–75k	19	14		
	$$75–100k	19	17		
	>$100k	19	34		
	Did not want to answer	2	1		
Diagnosis	HTN	43	44	0.22	Fisher's Exact Test
	HF	33	51		
Health Care Occupation	Yes	9	13	0.82	Fisher's Exact Test
	No	67	82		

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Table III

Number of Risk Reports Viewed Per Disease By Intervention Arm Participants (n=76)

Disease	Pre-Genomic Counseling	Post-Genomic Counseling
AMD	71	2
CAD	64	4
DM1	54	5
DM2	55	5
HH	59	6
LUP	54	8
MEL	53	10
PRO	45	10

Legend:
AMD: Age Related Macular Degeneration
CAD: Coronary Artery Disease
DM1: Type 1 Diabetes
DM2: Type 2 Diabetes
HH: Hemochromatosis
LUP: Systemic Lupus Erythematosus
MEL: Melanoma
PRO: Prostate cancer

Table IV

Causal Attributes of Genetic Variant, Family History, and Environmental Disease Risk: General Composite Score Across All Eight Diseases Under Study

	Estimate	CI (lower)	CI (upper)	Std. Error	*p* value	FDR *p* value
Genetic Variant	0.378	0.06	0.69	0.158	0.019	0.142
Family History	0.089	−0.181	0.358	0.136	0.515	0.744
Environmental	0.096	−0.18	0.37	0.139	0.494	0.744

Additional Analyses: Causal Attributes of Genetic Variant Disease Risk				
Disease	**Risk Factor**	**Estimate**	**Std. Error**	***p* Value**
AMD	Genetic Variant	0.297	0.349	0.395
CAD	Genetic Variant	0.369	0.352	0.295
DM1	Genetic Variant	0.923	0.358	0.010
DM2	Genetic Variant	0.108	0.344	0.752
HH	Genetic Variant	1.101	0.373	0.003
LUP	Genetic Variant	1.274	0.379	0.0008
MEL	Genetic Variant	0.574	0.350	0.101
PRO	Genetic Variant	1.03	0.365	0.005

Legend:
Survey Question: How much do you think having a genetic risk variant determines whether or not a person will develop each of the following conditions?
Null Hypothesis: Genomic counseling does not influence the importance that participants place on a given factor (genetic variant, family history, environment) on determining disease risk
Estimate: The estimated coefficient in the model for Intervention Arm participants. The range of possible values is −infinity to +infinity
AMD: Age Related Macular Degeneration
CAD: Coronary Artery Disease
DM1: Type 1 Diabetes
DM2: Type 2 Diabetes
FDR: False discovery rate
HH: Hemochromatosis
LUP: Systemic Lupus Erythematosus
MEL: Melanoma
PRO: Prostate cancer

Table V

Participant Awareness of an Increase in Disease Risk Due to a Genetic Variant

	Yes *n*	No *n*	FET *p* value	FDR *p* value
AMD				
GC intervention	34	23	0.049	0.241
Control	9	35		
CAD				
GC intervention	36	24	0.02	0.142
Control	27	18		
DM1				
GC intervention	12	48	0.003	0.050
Control	10	33		
DM2				
GC intervention	34	26	0.006	0.082
Control	14	30		
HH				
GC intervention	9	45	0.17	0.453
Control	4	39		
LUP				
GC intervention	17	40	0.017	0.142
Control	6	36		
MEL				
GC intervention	19	41	0.002	0.04
Control	6	36		
PRO				
GC intervention	5	47	0.037	0.197
Control	2	33		

Legend:
Survey Question: Do you have an increased risk for any of the following conditions due to a CPMC genetic risk variant?
AMD: Age Related Macular Degeneration
CAD: Coronary Artery Disease
DM1: Type 1 Diabetes
DM2: Type 2 Diabetes
FDR: False Discovery Rate
FET: Fisher's Exact Test
GC: Genomic Counseling
HH: Hemochromatosis
LUP: Systemic Lupus Erythematosus
MEL: Melanoma
PRO: Prostate cancer

Table VI

Perceived Risk

Disease	Risk Factor	Genomic Counseling *p* Value	Actual Risk *p* Value	Genomic Counseling FDR *p* Value	Actual Risk FDR *p* Value
AMD	Family	0.127	0.270	0.372	0.574
	Smoking	0.195	0.968	0.503	1.00
	Variant	0.082	0.814	0.307	0.891
CAD	Diabetes	0.576	0.506	0.744	0.744
	Family	0.234	0.565	0.569	0.744
	Smoking	0.296	0.564	0.600	0.744
	Variant	0.649	0.071	0.811	0.300
DM1	Family	0.101	0.747	0.334	0.882
	Variant	0.043	0.492	0.228	0.744
DM2	BMI	0.467	0.001	0.744	0.043
	Family	0.715	0.067	0.868	0.300
	Variant	0.813	0.010	0.891	0.119
LUP	Family	0.067	0.032	0.300	0.196
	Variant	0.109	0.102	0.346	0.333
MEL	Family	0.249	0.003	0.572	0.051
	Variant	0.077	0.0001	0.307	0.010

Legend:
Survey Question: What do you think is your chance of developing each of the following diseases in your lifetime?
Null hypothesis: genomic counseling and actual risk do not have an influence on a participant's belief that they will/will not develop the disease
Hemochromatosis (HH) was not included because there were no participants with *HFE* mutation (the only reported risk factor) that completed follow up.
Prostate cancer (PRO) was not included because the number of participants with a risk factor was too small to estimate using modeling
AMD: Age Related Macular Degeneration
CAD: Coronary Artery Disease
DM1: Type 1 Diabetes
DM2: Type 2 Diabetes
FDR: False Discovery Rate
HH: Hemochromatosis
LUP: Systemic Lupus Erythematosus
MEL: Melanoma
PRO: Prostate cancer

Table VII

Genomic Counseling Modification of Disease Risk Due to Additional Family History Assessment

Disease Variable	Test Report Risk	Post Genomic Counseling Risk	Number of Changes to Risk	Change Due to Additional Family History Obtained	Change Due To Modification of Family History Risk
AMD	No Risk	Increased	5	5	
AMD	Increased	No Risk	2		2
Subtotal			7	5	2
CAD	No Risk	Increased	11	11	
CAD	Increased	Moderate*	18	18	
CAD	Increased	High**	7	7	
Subtotal			36	36	-
DM1	No Risk	Increased	1	1	
DM1	Increased	No Risk	20		20
Subtotal			21	1	20
DM2	No Risk	Increased	13	13	
Subtotal			13	13	-
LUP	Increased	No Risk	23		23
Subtotal			23	-	23
MEL	No Risk	Increased	2	2	
MEL	Increased	No Risk	2		2
Subtotal			4	2	2
TOTAL			104	57	47

Legend:

*Moderate: personal or family history of coronary heart disease conferring relative risk of 2.0[1]

**High: personal or family history suggestive of familial coronary heart disease generally associated with an increased risk (2–5 fold) with risk increasing based on the number of affected relatives, and early age of diagnosis[2]

*1*Source: Scheuner (2003)

*2*Source: Scheuner (2010)

AMD: Age Related Macular Degeneration

CAD: Coronary Artery Disease
DM1: Type 1 Diabetes
DM2: Type 2 Diabetes
HH: Hemochromatosis
LUP: Systemic Lupus Erythematosus
MEL: Melanoma
PRO: Prostate cancer

Table VIII

Indication for Specialty Referral

Specialty Area	Indication	Number of Cases
Cardiovascular Genetics		
	Cardiomyopathy	9
	Familial Hypercholesterolemia	3
	Aortic Aneurysm	1
Cancer Genetics		
	Hereditary breast-ovarian cancer	5
	Hereditary colorectal cancer	1
	Other hereditary cancer	2
Medical Genetics		
	Muscular Dystrophy	1
Subtotal		**22**
High Risk Cardiovascular Screening clinic		6
Inherited Arrhythmia Clinic		2
Nutritional Services		1
Subtotal		**9**
Total		**31**