Published in final edited form as:

J Empir Res Hum Res Ethics. 2010 September ; 5(3): 17–30. doi:10.1525/jer.2010.5.3.17.

Returning Individual Research Results: Development of a Cancer Genetics Education and Risk Communication Protocol

J. Scott Roberts, David I. Shalowitz, Kurt D. Christensen, Jessica N. Everett, Scott Y. H. Kim, Leon Raskin, and Stephen B. Gruber

University of Michigan

Abstract

The obligations of researchers to disclose clinically and/or personally significant individual research results are highly debated, but few empirical studies have addressed this topic. We describe the development of a protocol for returning research results to participants at one site of a multicenter study of the genetic epidemiology of melanoma. Protocol development involved numerous challenges: (1) deciding whether genotype results merited disclosure; (2) achieving an appropriate format for communicating results; (3) developing education materials; (4) deciding whether to retest samples for additional laboratory validation; (5) identifying and notifying selected participants; and (6) assessing the impact of disclosure. Our experience suggests potential obstacles depending on researcher resources and the design of the parent study, but offers a process by which researchers can responsibly return individual study results and evaluate the impact of disclosure.

Keywords

genetic testing; cancer; *CDKN2A*; risk communication; return of research results; protocol development

The extent of investigators' responsibility to communicate the results of their research to study participants has been extensively debated over the last decade, prompting several national and international organizations to issue guidelines on the topic (Beskow et al., 2001; National Research Council, 2005; Bookman et al., 2006; National Bioethics Advisory Commission, 1999; National Heart, Lung and Blood Institute, 2004; National Human Genome Research Institute, 2010; World Health Organization Human Genetics Programme, 1998). In general, the results of clinical research are typically classified as either aggregate study results, representing synthesized data and conclusions drawn from groups of research participants, or individual results, representing distinct data relevant to individual participants (Fernandez et al., 2007; Partridge et al., 2003; Partridge et al., 2005). Both categories should be considered separately and ethically distinct from so-called "incidental findings" which constitute information discovered about participants during the course of research, but not related to the study's specific aims (Miller, Mello, & Joffe, 2008). There is broad consensus on at least two points. First, participants should have access to the general conclusions of studies in which they participated, after the study has finished. Surveys on this topic have established participants' desire to have access to these data (Fernandez et al., 2007; Partridge et al., 2003; Partridge et al., 2005); commentators tend to ground

participants' right to access aggregate results by appealing to considerations of reciprocity and respect (Partridge & Winer, 2009; Ravitsky & Wilfond, 2006; Shalowitz & Miller, 2008). Second, it is widely (though not unanimously) agreed that investigators have at least some responsibility to proactively notify participants of information discovered during the course of research that has the potential to substantially affect participants' health or prevent significant harm. Still debated, however, is the extent to which research results must be verified before disclosure, the level and type of impact necessary to warrant disclosure, and the specific responsibilities of investigators when communicating individual research results to participants (Dressler, 2009). For example, some guidelines mention a need to confirm biological research results (i.e., by retesting samples) before disclosing results (National Research Council, 2005; National Bioethics Advisory Commission, 1999), while others do not (Bookman et al., 2006; National Heart, Lung and Blood Institute, 2004). The National Heart, Lung and Blood Institute (2004) suggests that results must imply a relative risk of disease of 2.0 or higher before disclosure is considered, but most guidelines refer to the significance of findings in more general terms.

Existing commentaries and guidelines also often do not take into account relevant data on the process and impact of returning individual research results, or acknowledge the lack thereof. Arguments related to the disclosure of individual research results often depend on unverified empirical assumptions regarding, for example, the desire of participants to receive research results, the challenges of communicating results, and the effects on participants of receiving research information. Participants' attitudes and intentions have been assessed in responses to hypothetical scenarios (e.g., Fernandez et al., 2007), but there remains a need for data from "real-life" studies. Furthermore, the literature suffers from a lack of knowledge of the financial costs of implementing disclosure protocols, as well as appropriate measures to evaluate all aspects of the disclosure process. It is therefore important both to collect empirical data where there exist gaps in our knowledge, and to provide investigators with the tools necessary to pilot and assess strategies for returning of results. With such resources, investigators should be better able to craft disclosure policies that are appropriately respectful of research participants and inclusive of empirical data relevant to their recommendations.

Here, we present our experience in developing a protocol for returning individual genetic test results to interested research participants at one site of a large, international, population-based study of the genetic epidemiology of melanoma. Communication of results from this study was of particular interest for three reasons. First, much of the attention regarding disclosure of research results has centered on genetic information (S. M. Wolf et al., 2008). This is likely because of the rapid increase in large-scale genomic studies that has sparked public and media interest in genetic risk information for a variety of diseases. Second, cancer genetics is one of the most active domains of clinical genetics research. Third, the individual research result in question, *CDKN2A* genotype, provides an excellent example of information of potential clinical significance that is not yet incorporated into standard clinical care (Kefford et al., 1999). Consequently, our experiences in developing a protocol for communicating individual research results in this context should be of broad interest to the research ethics community. In this paper, we focus on the process and rationale involved in developing study procedures and outcome measures. Given the lack of empirical studies in this area, a detailed accounting of our methods and decision-making seemed appropriate. Main study results (i.e., the psychological and behavioral impact of results disclosure on participants, and its costs for investigators) will be reported in a separate paper.

Protocol Development: Methods and Preliminary Results

Development of the study protocol necessitated numerous procedural decisions regarding return of results to participants. Over the course of several months, our multidisciplinary team of investigators met to consider various options for disclosure and to craft a protocol that would offer genetic test results and assess their impact on participants. In this section, we provide a detailed review of the process we underwent in developing and implementing the study protocol. Figure 1 presents the study flowchart.

We provide an overview of the parent study from which results were derived, describe our justification for the decision to offer results to participants, and discuss the various challenges and decisions faced when designing and enacting study procedures. Although a detailed description of study results will appear in a separate and forthcoming paper, we provide some preliminary results as they pertain to topics addressed in our protocol.

Overview of Parent Study

Participants were originally enrolled as part of the Genes, Environment and Melanoma (GEM) Study, an international population-based study to improve the understanding of genetic susceptibility to melanoma, a type of skin cancer. Methodological details of the GEM Study are extensively described elsewhere (Begg et al., 2005). In brief, the GEM Study utilized a case-control design to identify rare but highly penetrant disease-causing variants by defining controls as individuals with a first invasive primary melanoma and cases as those diagnosed with a second or higher order invasive or *in situ* melanoma (Begg et al., 2006). A main study aim was to estimate the relative risk of *CDKN2A* mutations in the general population (Berwick et al., 2006). Coordinated at the Memorial Sloan-Kettering Cancer Center (MSKCC), the GEM Study population consisted of incident cases of melanoma identified through cancer registries in New South Wales (Australia); Tasmania (Australia); British Columbia (Canada); Ontario (Canada); Turin (Italy); California (USA); New Jersey (USA); and North Carolina (USA). It also included incident cases of melanoma identified at the University of Michigan Comprehensive Cancer Center (UMCCC), which evaluates approximately 50% of the melanomas diagnosed in the state of Michigan. This Michigan population provided participants for our study.

All GEM participants at the Michigan site had a melanoma identified between January 1, 2000 and August 31, 2003. Participants provided either blood samples or buccal swabs for DNA analysis. GEM participants also completed a comprehensive phone interview and written questionnaire on melanoma risk factors. The individual research results of interest were genotypes of the cyclin-dependent kinase inhibitor type 2A (*CDKN2A*), in which mutations were hypothesized to be risk factors for melanoma, as well as pancreatic cancer in some cohorts. The senior author of this paper (SBG) served as the Principal Investigator of the study site for the entirety of the GEM project.

Decision to Disclose *CDKN2A* Genotype Status

Communicating requested individual research results is typically appropriate as long as (a) the significance of results (or lack thereof) is communicated accurately and understandably, and (b) disclosure poses no significant known harms, including the compromising of a participant's or third party's safety, or the study's scientific validity (Shalowitz & Miller, 2005). We considered our results analytically valid; that is, we believed the GEM Study's genetic testing procedures were sufficiently rigorous such that research results could be trusted as the participant's actual genotype. Furthermore, we considered our results to be clinically valid, in that the association of *CDKN2A* with increased incidence of melanoma is supported by a substantial body of literature published since the completion of the GEM

Study (Udayakumar & Tsao, 2009), and the relative risk for a subsequent melanoma among GEM Study participants has been calculated at approximately 4.3 (95% CI: 2.3–7.7) (Berwick et al., 2006).

Many commentators also recommend that communicated individual research results have clinical utility for participants. The scope of this utility is much debated, however, with some referring only to medically actionable information, and others incorporating a broader range of meaningful information, including any data relevant to reproductive decision-making or career or financial plans, as in the case of late-onset disease (National Bioethics Advisory Commission, 1999; Ravitsky & Wilfond, 2006). For the GEM population, individual and aggregate results were of uncertain clinical significance. All participants had already been advised by their physician to undergo periodic skin surveillance and avoid sun exposure as part of their melanoma follow-up. Although the presence of a *CDKN2A* mutation is associated with increased risk of a new primary or recurrent melanoma, recommended prevention and surveillance strategies would not change for this group. Nevertheless, knowledge of increased risk could conceivably affect risk behaviors (e.g., avoidance of sun exposure) or individualized screening strategies to be determined by participants and their primary physicians. Knowledge of genetic status could also potentially affect participants' life decisions beyond medical care and prompt the notification of blood relatives who might also be at risk. We could not prospectively assess the extent to which *CDKN2A* results would have personal meaning to GEM participants; however, *offering* individual results allowed participants to make their own judgments.

The GEM Study informed consent document indicated that participants would not receive individual test results, although they could obtain a summary of aggregate study results upon request. Some investigators may believe they are bound to the disclosure policy stipulated in the parent study's informed consent document. However, the presence of such a statement does not necessarily preclude investigators from offering individual results if it becomes clear that access to such information is ethically justifiable (Banks, 2000; Emanuel, Wendler, & Grady, 2000). While recognizing that there were some reasons *not* to disclose *CDKN2A* results, our approach was to offer access to these results via participation in a separate research protocol to which participants affirmatively consented. We therefore provided individual *CDKN2A* genotype results to a subsample of GEM Study participants as part of a research protocol approved by the Institutional Review Board of the University of Michigan Medical School.

Format for Disclosing Results

The standard of care in clinical practice for disclosure of genetic test results is an in-person session with a certified genetic counselor or other clinical genetics specialist. However, it is unclear whether disclosure of genetic research results would necessarily have to be communicated per usual clinical protocol. Given that traditional genetic counseling procedures for adult-onset disorders (e.g., Huntington disease) are time-intensive and that there are limited numbers of genetic counselors, there has been a move in clinical research to develop more feasible models of genetic education and counseling (Schwartz et al., 2005). For example, ancillary education tools (e.g., CD-ROM) have been shown to reduce face-to-face time with clinicians in genetic counseling for hereditary breast and ovarian cancer (Wang et al., 2005), and telephone disclosure protocols have also shown comparable safety and efficacy in this context (Baumanis et al., 2009; Klemp et al., 2005).

Furthermore, there is evidence that many research participants would prefer to receive research results via written communication rather than in person (Shalowitz & Miller, 2008). However, there are very few data specifically addressing the preferences of participants to receive individual *genetic* results. One study found that participants in this situation are

“relatively open with regard to how they would prefer to be recontacted” (Ormond et al., 2004). Another study suggested that people considering genetic testing are more likely to decline the service if offered in only one format (e.g., telephone vs. in person) rather than having a choice (Sangha, Dircks, & Langlois, 2003). We allowed interested participants to choose whether they would receive their results by telephone or via an in-person session at the Cancer Genetics Clinic of the University of Michigan. Providing this option was reinforced by the large catchment area of the study, as 36% of identified recruits lived 75 miles or more from our site. In either format, a certified genetic counselor with cancer genetics experience would deliver the information and related counseling and education. Ultimately, all participants in our study opted for results disclosure by telephone.

Decision on Retesting of Research Samples

U.S. investigators and research administrators may be concerned that the Clinical Laboratory Improvement Amendments of 1988 (CLIA) prevents disclosure of research results if the data were obtained in a research laboratory that is not CLIA certified. Whether retesting of research samples in a CLIA-certified laboratory is required before *any* type of disclosure is an unsettled question of law. We contend that such retesting, while often preferable and required, is not necessarily mandated in all situations. CLIA delineates quality control standards for laboratories performing tests for the purpose of “providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings,” thereby enhancing the analytic validity of clinical laboratory results (Centers for Medicare and Medicaid Services, 2003). If the decision to communicate research results is because of their potential clinical significance, retesting should occur in a CLIA-certified laboratory (if the original research laboratory was not CLIA certified). If, however, results are communicated because of non-clinical value, such as personal meaning (or, in our case, because response to research results was what was being assessed in our study), CLIA certification is not necessarily required. Investigators should consider their potential responsibilities in communicating clinically significant individual results in developing study protocols and ensure appropriate laboratory quality standards are in place.

The Study Risks section of our informed consent document—mailed in the Announcement Mailing and reviewed with study personnel during the Recruitment Call—therefore read as follows: “There is an unknown risk regarding the accuracy of your test results. Because genetic testing in the GEM Study was performed for research purposes, your blood sample in that study was not examined at a laboratory regulated by the federal government through the Clinical Laboratory Improvement Amendments (CLIA). CLIA sets standards for laboratories performing clinical testing and ensures laboratories are achieving those standards. While we have no reason to believe your test results are incorrect, they were not obtained from a CLIA-approved lab, a process that would have been followed had the test been conducted as part of your health care. After the study is complete, you have the option of re-testing your sample at a CLIA-approved lab. This confirmation testing is optional, and you are under no obligation to have it performed. The cost of such testing would not be covered by the study but is covered by some insurance companies.” The letter to participants accompanying results disclosure read, “It is important to note that this testing was not completed in a lab certified for clinical use. You have the option of having *CDKN2A* testing repeated in a clinical laboratory; this would cost about \$350¹ and may or may not be covered by your health insurance.” Specific CLIA-approved laboratories were not recommended to participants, but the genetic counselor was available to provide options for

¹\$350 was the estimated cost to confirm a point mutation among presumed mutation carriers. A cost estimate of \$600–700 was provided to non-carriers because full-gene sequencing would be necessary to confirm the absence of a mutation.

those interested. Participants who were found to be mutation carriers were subsequently notified that the costs of their resting could be lower given that retesting to confirm a mutation is typically less expensive than other types. Ultimately, none of our participants pursued retesting during the course of our three-month follow-up period, although one mutation carrier stated an intention to have retesting performed eventually.

Some experts have suggested higher rates of test errors (e.g., sample mix-ups) in research laboratories versus CLIA-approved ones, although we have not seen any published data documenting this discrepancy. Such concerns, while perhaps speculative in nature, are related both to potential false positive and negative results. We would not want participants to make subsequent decisions based on incorrect information, nor would we want them to be erroneously reassured by false negative results. In addition, retesting would enhance our genetic counselors' confidence in the information we were providing. To address these concerns, we retested samples in a second research laboratory (not CLIA-certified) to gain an appreciation for the likelihood of discordant results in our sample. Three samples were not properly archived and could not be retested. Of the 36 samples retested, we did find one discordant result (3% rate of discordance), although this participant opted not to participate in our recontact protocol. This underscores the need for investigators to be mindful of the potential harms of discordant or otherwise inaccurate results.

Development of Education and Risk Communication Materials

Our planning discussions focused on: (1) the risk information to be disclosed; (2) how to communicate this information; and (3) recommendations, if any, regarding clinical follow-up. Unfortunately, the quantitative risk for melanoma conferred by a *CDKN2A* mutation is unclear. Published penetrance estimates through age 80 for *CDKN2A* mutations range as high as 67% (95% CI = 31% to 96%) (Bishop et al., 2002). Researchers in the GEM Study estimated the risk for melanoma among *CDKN2A* mutation carriers to be 28% through age 80 (95% CI: 18–40%) (Begg et al., 2005). Further complicating matters was that these estimates describe risk for a first primary melanoma, whereas the relevant risk for GEM participants would be a recurrence of cancer or the development of a second or higher-order primary melanoma. We decided to combine the point estimates referenced above and counsel participants that *CDKN2A* mutations confer a 30–65% risk for melanoma by age 80 and may also increase risk of a new primary melanoma. Although the large range of this estimate was unsatisfying, we believe it reflects the state of current knowledge and addresses the fact that mutations may confer varying levels of melanoma risk. Furthermore, we believed that skilled genetic counselors could help explain this estimate and its caveats. In addition, the cancer genetics literature suggests that test recipients often do not retain specific quantitative estimates but rather a qualitative understanding (i.e., “the gist”) of their risk (Julian-Reynier et al., 2003).

A number of studies have also suggested an association between *CDKN2A* mutations and pancreatic cancer, but this finding has not been consistently demonstrated among families with no family history of pancreatic cancer (Goldstein, 2004). Our educational materials thus stated, “Some families with *CDKN2A* mutations may also be at increased risk for other cancers, particularly pancreatic cancer. People who have a family history of melanoma and pancreatic cancer should talk with their doctors about whether or not additional screening tests are necessary.” To avoid prompting participants to seek invasive procedures for pancreatic cancer screening given weak evidence, our study clinician proactively discussed *CDKN2A* and pancreatic cancer risk in the genetic counseling sessions only if participants had a family history of the condition. However, other participants who were concerned about pancreatic cancer risk were free to raise this issue with the genetic counselor.

We next turned our attention to conveying the information effectively. An educational brochure was developed based on protocols developed by Peshkin et al. (2008) for telephone genetic counseling of women considering *BRCA1/2* testing. The study's genetic counselor (JNE) took the lead in developing brochure content, organized by: (1) risk factors for melanoma; (2) melanoma genes; (3) pros and cons of receiving genetic test results; (4) implications of *CDKN2A* testing for cancer risk; (5) methods of reducing melanoma risk, and (6) resources for more information (the full brochure is provided as an online Appendix at <http://caliber.ucpress.net/doi/suppl/10.1525/jer.2010.5.3.17>). Risks were presented using words and numbers, supplemented by pictographic visual aids, which have proven efficacy in enhancing risk comprehension (see Figure 2) (Fagerlin et al., 2007). A study genetic counselor reviewed these materials with participants in the genetic counseling session.

Lastly, we felt it important not merely to provide risk information, but also to provide resources for reducing and coping with potential health threats. Because all participants were already melanoma survivors, we asked counselors to reinforce the importance of adhering to indicated melanoma screening and health behaviors. To enhance comprehension of the information provided, we also decided to mail each participant a summary of the main points of the education session. Finally, we provided genotype details to those participants who tested positive for a *CDKN2A* mutation, to facilitate subsequent confirmatory testing, or sharing with a medical professional or family member.

Identification and Notification of Potential Participants

Our eligible study population consisted of 663 GEM Study participants at its University of Michigan site, seven of whom had identified *CDKN2A* mutations. We selectively recruited all participants with known *CDKN2A* mutations due to the potential clinical and personal utility of knowing their carrier status. However, we did not have the resources to enroll all mutation-negative participants into our study. *CDKN2A* mutation carriers were first identified and matched per GEM Study records by sex, ethnicity, and age (± 4 years) with non-carriers. We attempted to enroll three non-carriers to each carrier through sampling with replacement. GEM participants who had indicated they were not interested in taking part in follow-up studies were excluded from consideration. Given time and budget limitations, we ultimately attempted to enroll 32 mutation-free individuals.

As mentioned earlier, the original GEM Study protocol was not designed to offer participants the individual results of their genotyping. As a result, there were several obstacles to enrolling GEM participants in our protocol. First, while some contact had been maintained between participants and investigators through clinical visits and a study newsletter, most participants had not been seen or contacted in years. In many cases, this required updating contact information through review of existing clinical records. In addition, the clinical course of melanoma is severe enough that we felt obligated to screen the medical records of potential participants to identify any who had died since their GEM Study participation; we thereby avoided the potential distress involved in contacting family members of the deceased. Ultimately, we attempted to reach 39 participants overall, but we could not establish contact with ten of these.

Potential participants were informed of a new study regarding communication of research results via a mailing sent from the Michigan site PI of the GEM Study (SBG). The mailing stated that much had been learned about melanoma genetics since their initial enrollment, and that a new study was being conducted to learn whether participants were interested in learning more about melanoma genetic information, including the possibility of learning their individual genetic information. Potential participants were provided the opportunity to decline participation in the study. Those who did not opt out were telephoned by the study coordinator for enrollment after review of the study's goals and a consent document

included in the initial mailing. A second packet of materials was then mailed to interested participants including information about *CDKN2A* genotype and its implications for cancer risks. Participants were contacted via telephone by genetic counselors to schedule an in-person or telephone genetic counseling session, to review the mailed information, and to discuss any concerns they may have had about the implications of *CDKN2A* genotyping. Participants were then given a choice as to whether or not to receive their genotype and corresponding risk information, thus satisfying the participant's right not to know information that they might deem burdensome or otherwise unwelcome. The genetic research result was disclosed either during the same call or a subsequent session, according to the participants' preferences.

Assessing the Impact of Disclosure

Little is currently known about the impact of communicating the results of genetic testing for melanoma risk. Available studies suggest that (1) uptake of an offer of testing is high, (2) communication of genetic testing results does not change behaviors related to surveillance, and (3) receipt of results does not cause significant emotional distress (Bergenmar, Hansson, & Brandberg, 2009; de Snoo et al., 2008). Although consistent with the broader literature on communication of research results (Shalowitz & Miller, 2008), these studies are extremely small and methodologically limited.

We therefore sought to compile measures that would be useful to other researchers interested in assessing the impact and costs of returning individual genetic research results. We were aided in this process by one of the authors' (JSR) experience with assessing the psychological and behavioral effects of genetic susceptibility testing (Green et al., 2009; Roberts et al., 2005). Based on existing literature on communication of research results, we were most interested in assessing: (1) psychological impact, (2) recall and comprehension of risk information, (3) perceptions of personal utility and attitudes towards being recontacted, and (4) cost to investigators of implementing disclosure protocols (see Table 1 for a summary of measures). We plan to publish results from these measures in a forthcoming paper.

One concern about disclosing genetic research results for a serious condition such as cancer is that the information may induce psychological harms. We therefore assessed the psychological impact of receiving individual research results using three validated measures. First, we used a brief 5-item tool to measure general depression and anxiety symptoms (D. M. Berwick et al., 1991); while more comprehensive measures are available, we chose this instrument both to reduce respondent burden and because prior related work on the impact of genetic testing had not suggested significant adverse psychological effects in response to risk information (Butow et al., 2003; Douma et al., 2008). Second, to differentiate the emotional effects of results disclosure in particular from more general distress or worry, we used a measure of event-related distress (Horowitz, Wilner, & Alvarez, 1979), as well as a validated measure that assesses the emotional impact of cancer risk assessment in particular (Cella et al., 2002).

Another concern about disclosure of research results is that participants may not fully understand their meaning, with misconceptions potentially leading to undue concerns, false reassurance about risk status, or regrettable decisions. Recall and comprehension of results disclosed were therefore assessed using measures developed as part of the aforementioned REVEAL Study (Roberts et al., 2005). Recall was assessed by asking participants to report both their genetic test results and the numerical melanoma risk estimate provided. Comprehension was assessed by asking participants to (1) rate their risk of developing another melanoma compared to the general population and persons with a family history of melanoma, and (2) list possible options for risk reduction and screening.

We also assessed potential benefits of receiving research information. For example, we assessed perceptions of personal utility and attitudes towards being recontacted. For example, participants were asked to indicate agreement with statements such as “genetic testing for melanoma risk should be offered to everyone” and rate the usefulness of the information, explanation, and consultation provided in the study. We additionally asked participants to report changes, if any, in screening and protective behaviors (e.g., skin self-exams; use of sunblock) and to indicate whether they had shared their results with family members or health professionals.

Finally, investigators may not have the capacities in terms of personnel, resources, or finances to implement disclosure protocols even if they are inclined to do so. We therefore assessed the costs associated with returning results by tracking the monetary costs to develop each component of the intervention, including creation and printing of educational and mailing materials, costs of retesting samples, and the fees associated with utilized clinical space. Opportunity costs were also tracked by recording the time needed to complete each component of the protocol, including notification, informed consent, education, and results disclosure.

We recognize that our approach to assessment is not without limitations and that our follow-up period (three months) may not allow us to capture all meaningful responses to research results, such as health behavior changes. Nevertheless, we believe that a systematic approach to assessing the impact of returning individual research results will help answer key questions regarding benefits, harms, and feasibility.

Discussion

Our experience with protocol development demonstrates the complexity and challenges that face investigators who disclose individual research results. Although a substantive body of literature establishes a link between various *CDKN2A* mutations and risk of melanoma, the magnitude of these risks is difficult to pinpoint, and genetic testing is of uncertain clinical utility in our population. *CDKN2A* genotyping also has uncertain personal and reproductive meaning for participants. Given the rapid pace of research on genomic risk factors and biomarkers for disease, it is likely that many other projects will yield research results of unclear import. It would be helpful to have more specific guidance in this process than exists in current policies. Thresholds for relative and absolute risk conferred by identified risk factors might be more firmly established, and guidelines could more explicitly address the level to which a finding needs to be replicated across studies to be reported. Finally, the concept of personal (e.g., reproductive) utility might receive greater consideration such that all research results do not have to be medically actionable to warrant disclosure.

Another ethical issue faced was whether results could be returned without being confirmed via retesting. Some experts maintain that retesting of research results in a CLIA-certified laboratory should be mandatory before disclosure (Ravitsky & Wilfond, 2006), while others contend that such retesting is not required so long as test findings are labeled as research results with their inherent limitations explained (Quaid, Jessup, & Meslin, 2004). We concluded that the latter approach was justified in our case. Future practice in this area would be facilitated by research on the likelihood of test errors in research versus CLIA-approved clinical laboratories. It is understandable why commentators would presume that the latter setting would be less prone to test errors, but we are unaware of any published data addressing the existence or extent of this presumed discrepancy. In our own experience, retesting of samples originally analyzed in a research laboratory was able to identify one test error (out of 36 retested samples), but it is not known whether similar testing in a CLIA-approved laboratory would have resulted in a different error rate. Although investigators

should consider carefully the balance between respect for research participants and concern over the potential harms of potentially discordant results, we contend that mandating retesting in a CLIA-approved laboratory prior to disclosure in *all* situations is an overly rigid policy.

We faced several practical challenges in our recontact process. Despite the excellent data management of the parent study (e.g., detailed and well-maintained databases, storage of biological samples), we encountered numerous barriers to returning research results. First, many participants were difficult to reach given the long time that had elapsed since study participation, and we were not aware of their a priori preferences whether or not to receive individual research results. This difficulty reinforces recommendations to proactively determine participant preferences and to establish reliable and inexpensive post-study means of communication between participants and investigators (Fernandez, Skedgel, & Weijer, 2004). For example, preferences regarding disclosure of significant individual research results are often now addressed in the initial study informed consent process, and study websites can allow participants to maintain contact with research personnel well after the study has concluded, at low cost and burden to both parties. Another challenging issue was how to convey risk information given the still-evolving scientific literature on the association between *CDKN2A* genotype and risk of melanoma. Our team included experts in cancer genetics, genetic counseling, health education, and risk communication; we were therefore able to craft education materials that provided accurate and potentially useful information while acknowledging scientific uncertainties and the limits of current knowledge. We advise investigators to expect that translation of research findings into health communications may require expertise in the aforementioned disciplines, as well as a willingness to acknowledge that what is divulged may be imprecise and subject to revision over time.

Given these complexities, it is not surprising that commentators have suggested that investigators consult with their Institutional Review Board (IRB) or Research Ethics Board (REB) to craft plans and policies regarding return of research results (Quaid et al., 2004; Ravitsky & Wilfond, 2006; L. E. Wolf, Bouley, & McCulloch, 2010). Though sparse, available data indicate that IRB/REBs do not often have policies governing the return of aggregate or individual research results, nor do most investigators include plans regarding communication of results (Shalowitz & Miller, 2008). Additional data regarding practices in this area would be helpful, as well as collaboration to establish standards and shared resources relevant to results disclosure (L. E. Wolf et al., 2010). Caulfield and colleagues, in a consensus statement on research ethics in whole genome research, have gone so far to suggest that new independent governance entities may need to be established to regulate data sharing across teams of investigators in large-scale projects (Caulfield et al., 2008). For example, it is not clear whose duty it is to recontact participants if clinical significance of results is established by secondary data analyses conducted by investigators far removed from initial data collection. The rapid expansion of multi-site, international projects will only complicate the ethical and logistical issues surrounding return of research results. Of note, ours was the only site out of nine in the parent study that elected to offer access to *CDKN2A* information, underscoring the possibility that different sites within the same overall study may pursue distinct strategies regarding return of results.

It should be noted that lessons drawn from our experience may not necessarily apply to all situations where return of research results is being contemplated. For example, our research results were of *possible* (not definite) net benefit to participants, and our team of investigators had relatively well-developed technical and counseling capabilities and a long-standing relationship with some of the participants. These parameters may vary significantly in other research contexts, possibly necessitating different decisions or approaches. Our

project represents an initial and hopefully instructive example of a process by which a protocol to return individual research results to participants is detailed and systematically evaluated. Related future studies will be valuable in determining conditions under which return of results may be advisable, and in assisting researchers in developing methods and capabilities for results disclosure.

Best Practices

Our experience provides a model for investigators and oversight bodies to consider when implementing disclosure protocols and includes a number of components that are not standard in clinical care. In particular, we offered telephone genetic counseling and disclosure as an alternative to in-person appointments. This method—opted for by all participants in our study—greatly expanded the reach of our disclosure protocol and allowed subjects who had permanently or seasonally moved to other parts of the United States to participate.

Our experience also highlights a number of issues researchers need to keep in mind if they are to disclose research results to individuals. First and foremost, our experience emphasizes the need to prepare for possible future disclosure while developing protocols for initial studies. Recontacting study participants is only possible if data are linked to individual identifiers, and confirmation of results—should investigators deem it necessary—is only possible if information or samples are archived carefully. Furthermore, participant preferences about whether and how they should receive results should be incorporated into intake or consent procedures. Second, the effectiveness of disclosure protocols will be limited by out-of-date contact information. Despite having access to updated contact information through medical records, we were unable to establish contact with ten of the 39 GEM Study participants we targeted. Procedures for tracking participants beyond study participation (e.g., provision of a study website URL for participants to maintain contact) should be implemented at study's completion if results might ultimately be returned. Finally, our experience demonstrates the benefits of a multidisciplinary approach. Key steps such as selecting who should be offered disclosure, deciding what information should be shared and how to share it, developing educational materials, and communicating information to subjects were facilitated by having a team with expertise in each of those areas.

Research Agenda

Given the lack of research in this area, there are numerous needs for data to inform practice and policy regarding return of research results. First, more extensive understanding of the perspectives of various stakeholders involved in this debate could provide guidance and justification for institutional policies. Such work should not be confined to research investigators and participants but should also include representatives from regulatory bodies, funding agencies, and appropriate community and advocacy groups. Both qualitative (e.g., interviews, focus groups) and quantitative (e.g., surveys with large, representative populations) approaches would be helpful here. The deliberative jury approach is a methodology that holds particular promise for thoughtful consideration of complex issues involved, identification of areas in need of further conflict resolution, and generation of points of consensus (Graham & Corinne, 2000). As mentioned earlier, IRBs might also be systematically surveyed to gain a fuller sense of current policies in this area.

Another broad goal would be to generate information about the likelihood and extent of harms and benefits resulting from research results disclosure. Potential harms include psychological distress from information about risk or presence of severe and/or incurable conditions, misunderstanding of research results (which could result in misinformed decisions regarding health care and advance planning), and social discrimination based on

disease risk information. Research could not only provide information about the probability of such harms but could also suggest mitigating factors, such as individual differences predictive of response to results and communication strategies that enhance understanding of information disclosed. Although the existing clinical research literature may also provide guidance in these areas, disclosure of research results may differ in important respects from standard clinical practices. For example, some results may be returned years after they were obtained, and disclosure may not always occur according to typical clinical procedures (i.e., in person and with a trained clinician). Such distinctions suggest that findings from clinical research may not always generalize to this context.

With regard to potential benefits from results disclosure, future studies could examine the likelihood and extent of improved health behaviors (e.g., to prevent or reduce risk of disease) and informed health decision-making. Another dimension exploring further is the perceived personal (vs. clinical) utility of research results. That is, participants may find research information useful even if it does not directly inform medical care. For example, disclosure of *APOE* genotype (a practice discouraged in current medical practice) has been shown to be of interest to individuals at risk for Alzheimer's disease for numerous reasons, such as to inform advance financial and life planning and to share with family members given *APOE*'s potential as an inherited risk factor (Roberts et al., 2003). It has also been suggested that access to research results may enhance study participation, but this has not been well studied. Whether sharing of individual results affects study recruitment or retention could be assessed in future research.

Finally, further research could shed light on the feasibility of different practices for returning research results. Investigators may only be willing and able to entertain the possibility of returning results if they are reassured that the process will not entail extensive resources. It would be therefore of interest to delineate typical financial and time costs of various aspects of the recontact process, including (but not limited to) identification and notification of participants, development of health education materials, verification of research results, and personnel. It would also be helpful to know more about the potential cost savings of proactive measures such as identification of participant preferences regarding results disclosure during the informed consent process and use of web-based approaches for tracking and communicating with participants following study completion. It is recognized that the answers to the research questions above may depend greatly on the context of the parent study in question, including the health issue addressed and the type of research result under consideration. Nevertheless, this proposed agenda addresses key issues that presumably cut across various domains of medical and public health research.

Educational Implications

Important concepts involved in returning of research results should be conveyed to key stakeholders including investigators, ethics committees, students in relevant fields, and research participants. The former three groups should be made aware of existing consensus statements on the topic from leading organizations and experts in the field, as well as emerging empirical research on the topic. Special sections on returning of research results could be integrated into existing means of research ethics education, including both courses and web-based modules now in use at the national (e.g., NIH) and local levels. Here, a case-based approach would provide a useful means of stimulating consideration of the various options and challenges that might arise in a given situation, and a casebook of both positive examples and cautionary tales might be amassed. Investigators should be educated on how to articulate a reasonably detailed plan to address the returning of research results in their proposed studies, and in some cases they might even be encouraged to include resources for results disclosure in their grant application budgets. Ethics committees that have established

successful policies in this area should be encouraged to disseminate these widely: for example, via websites and list-servs of relevant professional organizations, as well as conference symposia and workshops. Research participants should be explicitly educated in the informed consent process about their future access to individual research results, including the rights and responsibilities of the involved parties. If research results are not to be shared, participants should be provided a well-justified explanation. Participants should be kept abreast of aggregate study results via study newsletter or website, which might also serve as a means of notifying them when significant individual research results are available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the University of Michigan Comprehensive Cancer Center's Clinical/Translational Resource Allocation Committee and the University of Michigan Office of the Vice President for Research (Ethics in Public Life Initiative) for financial support. This research was supported by the National Institutes of Health through the University of Michigan's Cancer Center Support Grant (5 P30 CA46592). We thank Jill Cooper for her assistance in creating materials and the study database, and we thank Monica Marvin for her assistance on protocol development and results disclosure.

Biographies

J. Scott Roberts is Assistant Professor of Health Behavior and Health Education at the University of Michigan School of Public Health. His research focuses on the process and impact of genetic risk assessment for adult-onset disorders, and he has served since 2001 as co-PI on the NIH-funded REVEAL Study, a series of randomized clinical trials examining the impact of a genetic susceptibility testing program for Alzheimer's disease. Dr. Roberts also serves as a core member of the University of Michigan's Bioethics Program. Dr. Roberts served as principal investigator of this study and oversaw all aspects.

David I. Shalowitz is a recent graduate of the University of Michigan's School of Medicine and a current resident in obstetrics and gynecology at Brigham and Women's Hospital. He trained in bioethics at the National Institutes of Health and has published a number of articles about disclosing individual results to research participants, including first-author works in the *Journal of the American Medical Association* and *PLoS Medicine*. Dr. Shalowitz assisted on protocol development and manuscript preparation.

Kurt D. Christensen is a doctoral candidate in Health Behavior and Health Education at the University of Michigan. His experiences include ongoing work with the Genetic Alliance on genetics education and former work with the Michigan Center for Genomics and Public Health on the dissemination of genetic policies. His current research focuses on the perceived utility of genetic susceptibility testing for common, chronic diseases. Mr. Christensen coordinated all aspects of the study except education, counseling, and results disclosure.

Jessica N. Everett is a genetic counselor with over ten years of experience and currently works with the University of Michigan's Cancer Genetics Clinic. In addition to her clinical work, Ms. Everett is an author on multiple articles about the practice of genetic counseling. Ms. Everett oversaw development of study education materials and disclosed genetic information to participants.

Scott Y. H. Kim is Associate Professor of Psychiatry at the University of Michigan. His research focuses on a variety of ethical issues around the topic of informed consent. Dr. Kim is a core faculty member of the University of Michigan's Bioethics Program and an investigator in the University of Michigan Center for Behavioral and Decision Sciences in Medicine. Prior to joining the University of Michigan faculty, he directed the Program in Clinical Ethics at the University of Rochester Medical Center and served as an IRB chair there. Dr. Kim provided guidance on protocol development.

Leon Raskin is a research investigator at the University of Michigan. His research includes a focus on integrated genetic approaches to drug discovery for melanoma. Dr. Raskin confirmed genotype data and provided test reports.

Stephen B. Gruber is Professor of Internal Medicine, Epidemiology, and Human Genetics at the University of Michigan Medical School and School of Public Health. He also directs the Cancer Genetics Clinic and serves as the Associate Director for Cancer Prevention and Control for the University of Michigan Comprehensive Cancer Center. His research focuses on genetic and environmental contributions to cancer. Dr. Gruber directed the University of Michigan site of the GEM Study and served as co-PI of this project, leading the development of educational materials and clinical recommendations regarding melanoma and genetics.

References

- Ashida S, Koehly LM, Roberts JS, Chen CA, Hiraki S, Green RC. Disclosing the disclosure: Factors associated with communicating the results of genetic susceptibility testing for Alzheimer's disease. *Journal of Health Communication: International Perspectives*. 2009; 14(8):768–784.
- Banks TM. Misusing informed consent: A critique of limitations on research subjects' access to genetic research results. *Saskatchewan Law Review*. 2000; 63(2):539–580. [PubMed: 12666671]
- Baumanis L, Evans JP, Callanan N, Susswein LR. Telephoned BRCA1/2 genetic test results: Prevalence, practice, and patient satisfaction. *Journal of Genetic Counseling*. 2009; 18(5):447–463. [PubMed: 19462222]
- Begg CB, Hummer AJ, Mujumdar U, Armstrong BK, Kricker A, Marrett LD, Millikan RC, Gruber SB, Culver HA, Zanetti R, et al. A design for cancer case-control studies using only incident cases: Experience with the GEM study of melanoma. *International Journal of Epidemiology*. 2006; 35(3):756–764. [PubMed: 16556646]
- Begg CB, Orlow I, Hummer AJ, Armstrong BK, Kricker A, Marrett LD, Millikan RC, Gruber SB, Anton-Culver H, Zanetti R, et al. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. *Journal of the National Cancer Institute*. 2005; 97(20):1507–1515. [PubMed: 16234564]
- Bergenmar M, Hansson J, Brandberg Y. Family members' perceptions of genetic testing for malignant melanoma: A prospective interview study. *European Journal of Oncology Nursing*. 2009; 13(2):74–80. [PubMed: 19179113]
- Berwick DM, Murphy JM, Goldman PA, Ware JE Jr, Barsky AJ, Weinstein MC. Performance of a five-item mental health screening test. *Medical Care*. 1991; 29(2):169–176. [PubMed: 1994148]
- Berwick M, Orlow I, Hummer AJ, Armstrong BK, Kricker A, Marrett LD, Millikan RC, Gruber SB, Anton-Culver H, Zanetti R, et al. The prevalence of *CDKN2A* germ-line mutations and relative risk for cutaneous malignant melanoma: An international population-based study. *Cancer Epidemiology, Biomarkers & Prevention*. 2006; 15(8):1520–1525.
- Beskow LM, Burke W, Merz JF, Barr PA, Terry S, Penchaszadeh VB, Gostin LO, Gwinn M, Khoury MJ. Informed consent for population-based research involving genetics. *Journal of the American Medical Association*. 2001; 286(18):2315–2321. [PubMed: 11710898]
- Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac-de Paillerets B, Chompret A, Ghiorzo P, Gruis N, Hansson J, et al. Geographical variation in the penetrance of *CDKN2A*

- mutations for melanoma. *Journal of the National Cancer Institute*. 2002; 94(12):894–903. [PubMed: 12072543]
- Bookman EB, Langehorne AA, Eckfeldt JH, Glass KC, Jarvik GP, Klag M, Koski G, Motulsky A, Wilfond B, Manolio TA, et al. Reporting genetic results in research studies: Summary and recommendations of an NHLBI working group. *American Journal of Medical Genetics Part A*. 2006; 140(10):1033–1040. [PubMed: 16575896]
- Butow PN, Lobb EA, Meiser B, Barratt A, Tucker KM. Psychological outcomes and risk perception after genetic testing and counselling in breast cancer: A systematic review. *Medical Journal of Australia*. 2003; 178(2):77–81. [PubMed: 12526728]
- Caulfield T, McGuire AL, Cho M, Buchanan JA, Burgess MM, Danilczyk U, Diaz CM, Fryer-Edwards K, Green SK, Hodosh MA, et al. Research ethics recommendations for whole-genome research: consensus statement. *PLoS Biology*. 2008; 6(3):e73. [PubMed: 18366258]
- Cella D, Hughes C, Peterman A, Chang CH, Peshkin BN, Schwartz MD, Wenzel L, Lemke A, Marcus AC, Lerman C. A brief assessment of concerns associated with genetic testing for cancer: The Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychology*. 2002; 21(6):564–572. [PubMed: 12433008]
- Centers for Disease Control and Prevention (CDC). Behavioral Risk Factor Surveillance System Survey Questionnaire. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 1999.
- Centers for Disease Control and Prevention (CDC). Behavioral Risk Factor Surveillance System Survey Questionnaire. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2000.
- Centers for Medicare and Medicaid Services. Laboratory Requirements. *Federal Register*. 2003. Retrieved April 10, 2010 from http://www.access.gpo.gov/nara/cfr/waisidx_04/42cfr493_04.html
- de Snoo FA, Riedijk SR, van Mil AM, Bergman W, ter Huurne JAC, Timman R, Bertina W, Gruis NA, Vasen HFA, et al. Genetic testing in familial melanoma: Uptake and implications. *Psycho-Oncology*. 2008; 17(8):790–796. [PubMed: 18613292]
- Douma KFL, Aaronson NK, Vasen HFA, Bleiker EMA. Psychosocial issues in genetic testing for familial adenomatous polyposis: A review of the literature. *Psycho-Oncology*. 2008; 17(8):737–745. [PubMed: 18613296]
- Dressler LG. Disclosure of research results from cancer genomic studies: State of the science. *Clinical Cancer Research*. 2009; 15(13):4270–4276. [PubMed: 19549775]
- Eckert SL, Katzen H, Roberts JS, Barber M, Ravdin LD, Relkin NR, Whitehouse PJ, Green RC. Recall of disclosed Apolipoprotein E genotype and lifetime risk estimate for Alzheimer's disease: The REVEAL Study. *Genetics in Medicine*. 2006; 8(12):746–751. [PubMed: 17172937]
- Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *Journal of the American Medical Association*. 2000; 283(20):2701–2711. [PubMed: 10819955]
- Fagerlin A, Ubel PA, Smith DM, Zikmund-Fisher BJ. Making numbers matter: Present and future research in risk communication. *American Journal of Health Behavior*. 2007; 31(Suppl 1):S47–S56. [PubMed: 17931136]
- Fernandez CV, Santor D, Weijer C, Strahlendorf C, Moghrabi A, Pentz R, Gao J, Kodish E. The return of research results to participants: Pilot questionnaire of adolescents and parents of children with cancer. *Pediatric Blood & Cancer*. 2007; 48(4):441–446. [PubMed: 16425279]
- Fernandez CV, Skedgel C, Weijer C. Considerations and costs of disclosing study findings to research participants. *Canadian Medical Association Journal*. 2004; 170(9):1417–1419. [PubMed: 15111476]
- Goldstein AM. Familial melanoma, pancreatic cancer and germline CDKN2A mutations. *Human Mutation*. 2004; 23(6):630. [PubMed: 15146471]
- Green RC, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T, Eckert SL, Butson M, Sadovnick AD, Quaid KA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease: The REVEAL Study. *New England Journal of Medicine*. 2009; 361(3):245–254. [PubMed: 19605829]

- Griffin CA, Axilbund JE, Codori AM, Deise G, May B, Pendergrass C, Tillery M, Trimbath JD, Giardiello FM. Patient preferences regarding recontact by cancer genetics clinicians. *Familial Cancer*. 2007; 6(3):265–273. [PubMed: 17308889]
- Hall MA, Camacho F, Lawlor JS, Depuy V, Sugarman J, Weinfurt K. Measuring trust in medical researchers. *Medical Care*. 2006; 44(11):1048–1053. [PubMed: 17063137]
- Horowitz M, Wilner N, Alvarez W. Impact of event scale: A measure of subjective stress. *Psychosomatic Medicine*. 1979; 41(3):209–218. [PubMed: 472086]
- Julian-Reynier C, Welkenhuysen M, Hagoel L, Decruyenaere M, Hopwood P. CRISCOM Working Group. Risk communication strategies: State of the art and effectiveness in the context of cancer genetic services. *European Journal of Human Genetics*. 2003; 11(10):725–736. [PubMed: 14512961]
- Kefford RF, Bishop JAN, Bergman W, Tucker MA. Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: A consensus statement of the Melanoma Genetics Consortium. *Journal of Clinical Oncology*. 1999; 17(10):3245–3251. [PubMed: 10506626]
- Klemp JR, O'Dea A, Chamberlain C, Fabian CJ. Patient satisfaction of BRCA1/2 genetic testing by women at high risk for breast cancer participating in a prevention trial. *Familial Cancer*. 2005; 4(4):279–284. [PubMed: 16341803]
- Michie S, Axworthy D, Weinman J, Marteau T. Genetic counselling: Predicting patient outcomes. *Psychology and Health*. 1996; 11(6):797–809.
- Miller FG, Mello MM, Joffe S. Incidental findings in human subjects research: What do investigators owe research participants? *The Journal of Law, Medicine & Ethics*. 2008; 36(2):271–279.
- National Bioethics Advisory Commission. *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. Vol. 1. Rockville, MD: NBAC; 1999.
- National Heart, Lung and Blood Institute. NHLBI Working Group on Reporting Genetic Results in Research Studies Meeting Summary. Bethesda, MD: National Institutes of Health; 2004.
- National Human Genome Research Institute. *Federal Policy Recommendations Including HIPAA*. 2010. Retrieved April 20, 2010 from <http://www.genome.gov/11510216>
- National Research Council. *Guidelines for Human Embryonic Stem Cell Research*. Washington, DC: National Academies Press; 2005. Available online at <http://www.nap.edu/catalog/11278.html>
- Ormond, KE.; Smith, ME.; Cirino, AL.; Chisholm, RL.; Wolf, WA. “Duty” to recontact participants in a population-based genetic database: The NUGene experience. Paper presented at the American College of Medical Genetics Annual Conference; Kissimmee, FL. March 6; 2004.
- Partridge AH, Burstein HJ, Gelman RS, Marcom PK, Winer EP. Do patients participating in clinical trials want to know study results? *Journal of the National Cancer Institute*. 2003; 95(6):491–492. [PubMed: 12644548]
- Partridge AH, Winer EP. Sharing study results with trial participants: Time for action. *Journal of Clinical Oncology*. 2009; 27(6):838–839. [PubMed: 19164202]
- Partridge AH, Wong JS, Knudsen K, Gelman R, Sampson E, Gadd M, Bishop KL, Harris JR, Winer EP. Offering participants results of a clinical trial: Sharing results of a negative study. *Lancet*. 2005; 365(9463):963–964. [PubMed: 15766998]
- Peshkin BN, DeMarco TA, Graves KD, Brown K, Nusbaum RH, Moglia D, Forman A, Valdimarsdottir H, Schwartz MD. Telephone genetic counseling for high-risk women undergoing BRCA1 and BRCA2 testing: Rationale and development of a randomized controlled trial. *Genetic Testing*. 2008; 12(1):37–52. [PubMed: 18373403]
- Quaid KA, Jessup NM, Meslin EM. Disclosure of genetic information obtained through research. *Genetic Testing*. 2004; 8(3):347–355. [PubMed: 15727261]
- Ravitsky V, Wilfond BS. Disclosing individual genetic results to research participants. *American Journal of Bioethics*. 2006; 6(6):8–17. [PubMed: 17085395]
- Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Green RC. Reveal Study Group. Genetic risk assessment for adult children of people with Alzheimer's disease: The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study. *Journal of Geriatric Psychiatry & Neurology*. 2005; 18(4):250–255. [PubMed: 16306249]

- Roberts JS, LaRusse SA, Katzen H, Whitehouse PJ, Barber M, Post SG, Relkin N, Quaid K, Pietrzak RH, Cupples LA, et al. Reasons for seeking genetic susceptibility testing among first-degree relatives of people with Alzheimer disease. *Alzheimer Disease and Associated Disorders*. 2003; 17(2):86–93. [PubMed: 12794385]
- Sainfort F, Booske BC. Measuring post-decision satisfaction. *Medical Decision Making*. 2000; 20(1): 51–61. [PubMed: 10638537]
- Sangha KK, Dircks A, Langlois S. Assessment of the effectiveness of genetic counseling by telephone compared to a clinic visit. *Journal of Genetic Counseling*. 2003; 12(2):171–184.
- Schwartz MD, Peshkin BN, Valdimarsdottir H, Tercyak KP, Taylor KL. Decision making and decision support for hereditary breast-ovarian cancer susceptibility. *Health Psychology*. 2005; 24(4):S78–S84. [PubMed: 16045423]
- Shalowitz DI, Miller FG. Disclosing individual results of clinical research: Implications of respect for participants. *Journal of the American Medical Association*. 2005; 294(6):737–740. [PubMed: 16091577]
- Shalowitz DI, Miller FG. Communicating the results of clinical research to participants: Attitudes, practices, and future directions. *PLoS Medicine*. 2008; 5(5):e91. [PubMed: 18479180]
- Smith G, Wales C. Citizens' juries and deliberative democracy. *Political Studies*. 2000; 48(1):51–65.
- Udayakumar D, Tsao H. Melanoma genetics: An update on risk-associated genes. *Hematology/Oncology Clinics of North America*. 2009; 23(3):415–429. [PubMed: 19464594]
- Vickberg SMJ. The Concerns about Recurrence Scale (CARS): A systematic measure of women's fears about breast cancer recurrence. *Annals of Behavioral Medicine*. 2003; 25(1):16–24. [PubMed: 12581932]
- Wang C, Gonzalez R, Milliron KJ, Strecher VJ, Merajver SD. Genetic counseling for BRCA1/2: A randomized controlled trial of two strategies to facilitate the education and counseling process. *American Journal of Medical Genetics, Part A*. 2005; 134A(1):66–73. [PubMed: 15690408]
- Weinstock MA, Risica PM, Martin RA, Rakowski W, Smith KJ, Berwick M, Goldstein MG, Upegui D, Lasater T. Reliability of assessment and circumstances of performance of thorough skin self-examination for the early detection of melanoma in the Check-It-Out Project. *Preventive Medicine*. 2004; 38(6):761–765. [PubMed: 15193896]
- Wolf LE, Bouley TA, McCulloch CE. Genetic research with stored biological materials: Ethics & practice. *IRB: Ethics & Human Research*. 2010; 32(2):7–18. [PubMed: 20373733]
- Wolf SM, Lawrenz FP, Nelson CA, Kahn JP, Cho MK, Clayton EW, Fletcher JG, Georgieff MK, Hammerschmidt D, et al. Managing incidental findings in human subjects research: Analysis and recommendations. *Journal of Law, Medicine & Ethics*. 2008; 36(2):219–248.
- World Health Organization Human Genetics Programme. Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services (No. WHO/HGN/GL/ETH/98.1). Geneva: WHO; 1998.
- Zick CD, Mathews CJ, Roberts JS, Cook-Deegan R, Pokorski RJ, Green RC. Genetic testing for Alzheimer's disease and its impact on insurance purchasing behavior. *Health Affairs*. 2005; 24(2): 483–490. [PubMed: 15757934]

Fig. 1.
Study Flowchart.

Fig. 2.
Sample Risk Communication Tool Used in Educational Materials.

TABLE 1

Summary of Study Measures.

Variables assessed	Scale reference	# of Items
<i>Recall and comprehension of risk information</i>		
Risk/relative risk perceptions	Roberts et al., 2005	13
Information recall	Eckert et al., 2006	10
<i>Health-related behaviors</i>		
Preventive health behaviors	CDC, 1999, 2000; Weinstock et al., 2004	7
Communication of test results	Ashida et al., 2009	2
Changes in insurance	Zick et al., 2005	4
<i>Psychological impact</i>		
Depression and anxiety symptoms	D. M. Berwick et al., 1991	5
Test-specific distress	Horowitz, Wilner, & Alvarez, 1979	7
Impact of disclosure	Cella et al., 2002	25
Subjective impact of testing	Green et al., 2009	4
Concern about future melanomas	Vickberg, 2003	25
<i>Personal utility and attitudes toward recontact</i>		
Study expectations and satisfaction	Sainfort & Booske, 2000; Michie, Axworthy, Weinman, & Marteau, 1996	3
Preferred method of administration	Fernandez et al., 2007	2
Obligations of researchers	Griffin et al., 2007	1
Trust of researchers	Hall et al., 2006	1
Willingness to participate in future studies	Klemp et al., 2005	1