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ORIGINAL ARTICLE

How do researchers manage genetic results in practice? The experience of the multinational Colon Cancer Family Registry

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Abstract There is consensus internationally that research participants should be offered the opportunity to receive clinically relevant genetic information identified through research, but there is little empirical peer-reviewed work documenting this process. We report the experience of conducting genetic research with nearly 35,000 participants in the Colon Cancer Family Registry, based in the USA, Canada, Australia, and New Zealand. Investigators from six multinational sites provided information about disclosure protocols, implementation, and uptake of genetic results and made suggestions to inform practice. Across 5 of the 6 registry sites, 1,634 participants in families with mismatch repair or *MutYH* gene mutations have been offered results. Participant uptake ranged from 56 to 86 %. Researchers faced significant challenges in the

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effort to return results. We offer suggestions in five key areas: (1) planning for the disclosure process, (2) participant information, (3) autonomy of participants, (4) monitoring scientific progress, and (5) involvement of stakeholders. Despite increasing discussion of the importance of returning incidental findings from genetic research, this paper highlights the considerable diversity, challenges, and costs faced in practice when returning expected findings with established utility and validity. We argue that more work is needed to ensure that genetic results in research are optimally managed.

Keywords Colorectal neoplasms · Genetic predisposition testing · Hereditary nonpolyposis · Disclosure of research results

Introduction

Genetic and genomic findings from research will create a positive impact on public health when genetic information is translated for disease prevention, early detection, and/or adoption of risk management behaviors. In the 1990s, studies found that the majority of people who pursued genetic testing generally coped well with receipt of their genetic test results if provided with pretest and posttest genetic counseling by a genetic counselor (Hutson 2003; Meiser 2005; Gritz et al. 2005). Since then, genetic counseling has become a significant component in the provision of multidisciplinary cancer risk assessment for clinical practice. Unlike the relatively routine use of genetic testing in medical practice, the management of clinically significant genetic results generated in the course of research has been inconsistent across countries and across different studies (Ravitsky and Wilfond 2006; Dressler 2009; Affleck 2009; Miller et al. 2008; Kollek and Petersen 2011). Institutional Review Boards (IRBs) in the USA previously adopted the stance that only summary outcomes of research results need be provided to participants, rather than individual results (Affleck 2009; Beskow et al. 2001; Partridge and Winer 2002). In Australia, researchers have been ethically obliged to enable participants to decide whether they wish to receive clinically significant genetic information identified in research (National Health and Medical Research Council 2007). In Canada and New Zealand, there is no formal obligation for researchers to return individual participant results, but it has been the practice of cancer genetic researchers to ask participants if they wish to know if clinically significant information becomes available.

More recently, consensus is emerging among US bioethicists and researchers that research participants should be offered the opportunity to receive personal genetic results when there are clinical implications (Dressler 2009), and there is increasing discussion about whether incidental findings as well as expected genetic findings should be returned (Wolf et al. 2012; Green et al. 2012). Survey results show that nearly all research participants expect researchers to return clinically useful information (Meulenkamp et al. 2010; Kaufman et al. 2008; Ceballos et al. 2008).

While there are some agreed upon ethical principles for the return of genetic results in epidemiological research studies (Bookman et al. 2006; Roberts et al. 2010; Dressler 2009), there is little practical information to guide researchers on implementing these principles. Kollek and Petersen (2011) have presented a series of challenges to be addressed in order to return individual research results to participants. They suggest the key questions to be addressed are: What feedback to return? To whom? By whom? How? While such guidelines are useful for individual studies, little is known how these general principles are applied in the context of large-scale multidisciplinary research. The National Health, Lung, and Blood Institute 28-member multidisciplinary working group recently proposed a 5-recommendation guideline on ethical and practical considerations when research genetic test results are provided to study participants (Fabsitz et al. 2010).

Given the rapidly changing environment for disclosing genetic test results to research participants, the four specific aims of this research were (1) to describe the protocols used by a large multinational cancer family registry for returning clinically relevant genetic test results, (2) to report the uptake of these genetic test results, (3) to examine the challenges faced by a cancer registry in its effort to return clinically relevant genetic test results to participants, and (4) to propose recommendations for future practice.

In this paper, we discuss the use of a number of genetic tests in the research setting that have established validity and utility and are widely used in routine clinical practice. For the purposes of this paper, we refer to these genetic test results as "clinically relevant genetic test results."

Materials and methods

Setting: Colon Cancer Family Registry

Since 1997, the National Cancer Institute has supported the Colon Cancer Family Registry (CFR), an international consortium for research on colorectal cancer (CRC) etiology (both genetic and environmental) (Newcomb et al. 2007). There are six collaborating registries based at the University of Hawaii (HI), the Mayo Clinic (MA), the Fred Hutchinson Cancer Research Center, Seattle (SE), the University of Southern California consortium of seven sites (USC) in the USA, Ontario (ON) in Canada, and the University of Melbourne for Australia and New Zealand (AU) (see Table 1). Two types of ascertainment were used in Colon CFR sites. Some sites exclusively recruited population-based cases (SE and HI) and some recruited patients from high-risk

clinics as well as population-based cases (MA, USC, ON, and AU). Colon CFR was specifically designed to provide a resource for collaborative interdisciplinary CRC research in genetics, epigenetics, epidemiology, behavioral research, cancer screening, clinical outcomes, and cancer survivorship.

In the past several years, the advancement of genetic technology provided the opportunity to identify families with Lynch syndrome (LS), MutYH-associated polyposis syndrome (MutYH), and Familial Colorectal Cancer Type X. Briefly, LS is a familial cancer syndrome caused by disease-causing mutations in the mismatch repair (MMR) genes and characterized by increased risk and early onset of CRC, endometrial, ovarian, and other cancers. The lifetime CRC risk in individuals with LS is estimated to be up to 82 %, which is substantially higher than the general population CRC risk of 5 %. In 2009, the Evaluation of Genomic Applications in Practice and Prevention working group recommended screening all newly diagnosed CRC patients for LS by genetic testing, so that family members could be similarly tested and, if appropriate, offered early cancer detection interventions in order to decrease morbidity and mortality (Palomaki et al. 2009). Specific cancer screening guidelines are available for early cancer screening and detection in such families (Järvinen et al. 2000). To illustrate, colonoscopy screening is recommended to start at the age of 20 years for those individuals confirmed to have LS. For the general population, colonoscopy screening is recommended to begin at the age of 50 years. Another familial cancer syndrome, MutYH is caused by biallelic disease-causing mutations in the *MutYH* gene, causing >20-fold increased risk in the biallelic carriers (Theodoratou et al. 2010). Cancer screening for MutYH carriers is similar to that currently recommended for individuals diagnosed with attenuated familial adenomatous polyposis, with colonoscopies beginning in the late teens or early twenties (Terdiman 2009). Familial Colorectal Cancer Type X refers to families that conform to the original Amsterdam I Criteria (Vasen et al. 1991) but have proficient DNA MMR in the colorectal tumors, thereby distinguishing them from LS. The increased cancer risks in such families appear to be limited to CRC, and screening recommendations are based upon the family history (Lindor et al. 2005).

Recruitment and research genetic testing

The Colon CFR recruitment of cases and family members occurred in three phases. For phase I (1998–2002), recruitment included population-based and clinic-based enrolment of cases with CRC at any age. Family members were recruited following cases' consent, and the family cancer history was obtained throughout this process. For phase II (2002–2007), population-based recruitment of cases was targeted to those who had a CRC diagnosis under the age of 50 years (clinic recruitment continues to enroll early onset CRC cases and also those with a significant family cancer history). Family members were also recruited following cases' consent (for further details, see Newcomb et al. 2007). For phase III (2007–2012), population-based recruitment continues to target those cases diagnosed with CRC <50 years of age.

As part of the research effort to discover genetic and environmental contributions to CRC, the phase I enrolled cases were asked to sign a consent form allowing tissue block retrieval from institutions where they were treated for CRC. Tumor tissue was tested for the presence of microsatellite instability (MSI) and/or immunohistochemistry (IHC) for protein expression of MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). The results of the initial IHC/MSI tumor testing served as a guide for subsequent MMR gene-specific germline testing. *MutYH* gene germline testing was also conducted for all cases from whom a blood specimen was available. The detection of a germline MMR or *MutYH* disease-predisposing gene mutation in the case resulted in mutation-specific testing for the research-enrolled family member who had also provided a blood sample. As a result, clinically relevant mutations in the MMR genes and biallelic mutations in *MutYH* were detected in the research-collected DNA in a significant number of cases and their family members. However, this testing was not performed in laboratories that were certified by the Clinical Laboratory Improvement Amendments (CLIA) or National Association of Testing Authorities-approved laboratories (http://www.cms.gov/clia/).

Previous research completed by Colon CFR investigators have reported some details of the process of returning genetic research results to participants at individual registry sites. Lindor et al. (2004) found that individuals in the MA registry who had CRC showed a high level of interest in learning their individual MSI/IHC test results. In addition, Ceballos et al. (2008) reported that 95 % of both cases and relatives in the SE registry said they would be willing to receive genetic information.

Colon CFR Translational Working Group

The Colon CFR Translational Working Group (TrWG) was formed in 2009 to assist with the translation of clinically relevant research findings to registry participants. The 23 members of the Colon CFR TrWG include principal investigators (clinicians or genetic epidemiologists), program managers, genetic counselors, consumer representatives, and social and behavioral researchers. The Colon CFR TrWG coordinated the effort to document the experience of the six collaborating registry sites on the return of results to their respective participants.

Participants

In this study, six individuals served as key informants and represented their respective Colon CFR. These individuals

Table 1 Summary of Colon CFR

Site	Hawaii Family Registry of Colon Cancer, USA	Ontario Familial Colorectal Cancer Registry, Canada	Mayo Colorectal Cancer Family Registry, USA	Australasian Colorectal Cancer Family Registry, Australia, NZ	Seattle Familial Colorectal Cancer Registry, USA	University of Southern California Consortium, USA
Abbreviation	HI	ON	MA	AU	SE	USC
Number of sites	1	1	1	1	1	7
Number of cancer cases[a]	517	2,405	1,247	1,463	2,357	2,030
Genetic counselor originally involved in the study as an investigator	N	Y	N	Y	N	Y

[a] For each cancer case, relatives were also recruited

were nominated by the principal investigator of each Colon CFR site. All data were collected from this key informant (e.g., a study coordinator, genetic counselor, or study researcher) who, when necessary, consulted other relevant registry staff to complete data collection.

Data collection

Data were collected on the disclosure process at each registry site in order to answer several questions, including: Have research-generated genetic results been returned? If so, which results? To whom? By whom? What protocols were followed? Data were gathered using a combination of fixed-response and free-response questions. Copies of consent forms, protocols, and letters used by the registries were also obtained.

Examples of fixed-response questions include: *Do you have IRB approval to offer genetic test results? (Y/N) Do you offer genetic counseling to cases who are MMR+? (Y/N) Do you offer CLIA confirmation testing? (Y/N/NA).* Free-response questions included: *When was your site in the CFR first able to offer DNA results? What process was used to make this decision?* Questions covered the decision-making process, protocol development, IRB approval, and implementation of the process for returning genetic test findings to study participants, with particular attention paid to problems or barriers faced during the process for those sites that had not begun to return results.

Registries that had begun disclosing results provided information on the number of participants who could be contacted and deemed eligible for genetic counseling based on research results, as well as the number of participants who received their genetic test results. From these two figures, uptake of genetic testing at each registry site was calculated.

Data analysis

Data from fixed-response questions were summarized. Qualitative analysis was performed on free-response questions and protocols, consent forms, and letters used in the disclosure process by LK and DF to identify the range of ways that genetic results had been managed by registries and to identify barriers and key points of variation and similarities across registries. Both free-response and fixed-response answers were summarized in a written report, and key informants were asked to review the written report to confirm that the data presented and analysis conducted were accurate.

Recommendation development

On completion of data collection and analysis and verification from each key informant on the accurate representation of the experience at their respective registry site, a group discussion was held with key informants and members of the TrWG. The aim of the discussion was to reach consensus on the key principles that the group would apply in future research involving disclosure of individual genetic information. The agreed list of recommendations was then further refined through email discussion. All registries have institutional ethics approval for conduct of Colon CFR activities.

Results

The Colon CFR has recruited 10,019 cases and 24,708 family members from the USA, Canada, Australia, and New Zealand. Registry-wide molecular testing has identified deleterious germline mutations in MMR genes in at least 1 member of 424 families (153 *MLH1*, 206 *MSH2*, 39 *MSH6*, and 26 *PMS2*). In addition, 48 biallelic *MutYH* gene carriers have been identified. To date, disclosure to approximately 1,600 participants in families with MMR or *MutYH* gene mutations has been undertaken by 4 of the registries (ON, AU, MA, and HI). Disclosure has commenced in one other registry (SE) and is planned for the sixth (USC).

The disclosure process: informed consent

The original informed consent varied across the six registries. In AU, ON, and MA, the information given to participants at enrolment indicated that individual results might become available; however, only ON asked participants whether they wanted to be informed. The USC consortium, SE, and HI all indicated during the informed consent process that no individual results would be made available to research participants (for quotes from each form, see Table 2).

The disclosure process: which research findings are disclosed?

Once a registry decided to return genetic results to participants, they then decided which of the genetic test results (e.g., MSI, IHC, deleterious germline mutations and/or variants of uncertain significance (VUS), or Familial Colorectal Cancer Type X; Lindor et al. 2005) would be returned and to which research participants (i.e., cases and/or relatives). These considerations were guided by the principle that genetic test results must have clinical utility and validity prior to disclosure in the research setting. However, registries arrived at different conclusions about the genetic results that were considered to have clinical significance. Table 3 illustrates which results were offered, and to whom, for each registry site. The five registries currently returning genetic test results all chose to return information about deleterious MMR and biallelic *MutYH* mutations to both cases and their relatives. However, the assessment of the utility of other research findings varied, with some registries choosing to return information about VUS findings and if a family met the criteria for Familial Colorectal Cancer Type X (Lindor et al. 2005), while others decided not to offer this information to participants.

The disclosure process: registry-specific protocols for returning results

Protocol information for each registry is included in Table 3. Details of the protocols used to return genetic test results depended, in part, on the health care system in the country. Canadian and Australasian investigators were able to utilize government-funded genetic testing and counseling services. In ON, all cases were offered genetic counseling to discuss participation in the registry and explain tumor analysis done on their CRC. When relevant, they were offered clinical germline testing through the Ontario Ministry of Health and Long-Term Care, which integrates genetic counseling. In Australia, participants who were informed that there were genetic results, and those who wished to avail themselves of this information, were referred to the state government-funded Family Cancer Genetic Services, where genetic counseling was provided, a new blood sample taken, and clinical testing was performed (Keogh et al. 2009). In New Zealand, participants were informed that there was clinically relevant information available and offered referral to their local government-funded genetic service for counseling and testing through an accredited diagnostic laboratory. In the USA, recommendations for changes in health care management are made based on genetic testing results conducted in a CLIA-approved laboratory (Fabsitz et al. 2010). For this reason, research participants from MA, HI, and SE received genetic counseling through the research study, but the research results were considered preliminary, and no change in their medical care was recommended until they were verified on a fresh blood specimen in a CLIA-approved testing laboratory. Costs for repeat testing were assumed either by the registry or by the participants' personal medical plan. The USC consortium will follow a similar protocol in disclosing genetic test results to their participants.

For all registries who have returned genetic results, two sessions (predisclosure of the test result and when providing genetic information) were required with participants. A summary letter was also provided to the participant following the genetic counseling sessions. A combination of in-person and telephone counseling was offered, by either a genetic counselor or physician employed by the registries or government-funded genetic counseling services.

Uptake of genetic testing

Participant uptake of genetic information on MMR and biallelic *MutYH* results ranged from 56 to 86 % (see Table 4). The reasons some participants declined the opportunity to know their genetic test result were not systematically obtained, although research on the reasons participants decline genetic information is underway at several sites.

Barriers to the disclosure process

Researchers were asked about the challenges they faced in the process of returning genetic results to participants. The most commonly cited were (1) lack of existing protocols or consensus guidelines to inform the process on how and when to return genetic test results; (2) logistics and costs that could accrue to reconsent research participants if they would like to know their genetic test results; (3) limited involvement of genetic counselors at some registries; (4) in the USA, the requirement to have genetic testing performed in a CLIA-approved laboratory; (5) IRB/ethics boards initially declined to approve reconsent of participants for the purpose of providing genetic information to registry participants; and (6) budget constraints due to unplanned cost of returning results and the required CLIA-approved testing.

Table 2 Excerpts from the original informed consent information provided to participants at each site

Quote from original ON informed consent

"You may be given the opportunity to be informed of research results that may affect your personal risk of colon polyps/cancer …. If individual results are available, the Ontario Familial Colorectal Cancer Registry, consisting of a group of health-care professionals will review the quality of research results and decide when, and if, they should be available to the study participants. If you do not want to know the results from research, please let us know."

Quote from original AU informed consent

"It is becoming possible to test for specific colorectal cancer genes and we are undertaking some work in this area, on a research basis. Should we find information relevant to you and your family, we will offer to give this information to you through the Victorian Clinical Genetic Service."

Quote from original MA informed consent

"No results will be given to you unless researchers at Mayo Clinic find something important that could be useful for you to know. If this occurs, you will be notified in writing of the option of learning of this research result and would be given an opportunity to learn more about the risks and benefits of learning about a test result before actually getting a result."

Quote from original HI informed consent

"If I want to know how these research findings (from the FR) would make a difference for me personally, especially about genetic factors, I can have counseling and possible testing outside this research study. These services would have to be at my own cost. The Registry staff can give me a list of names and addresses of certified cancer genetic specialists."

Quote from original USC informed consent

"Results of gene studies will not be made available to you or any other individual participants. We hope that the knowledge gained from this and future research studies will be of benefit to you, your relatives, and future generations by improving screening, prevention and treatment of colorectal cancer."

Quote from original SE informed consent

"Test results will not be available on an individual basis since the tests are for research purposes only. That is, they have no verified clinical relevance at this time."

Table 3 Genetic test results offered and protocols for returning genetic results

	HI	ON	MA	AU	SE
Which genetic results were offered, and to whom?					
MMR mutations					
To cases	Y	Y	Y	Y	Y
To their relatives	Y	Y	Y	Y	Y
Biallelic *MutYH* mutations					
To cases	Y	Y	Starting	Y	Y
To their relatives	Y	Y	Starting	Y	Y
VUS					
To cases	Y	Y	N	N	Y
To their relatives	N	N	N	N	N
Familial Colorectal Cancer Type X					
To cases	Y	Y	N	N	Y
To their relatives	N	Y	N	N	N
Protocols for returning genetic results					
Who provides counseling? (genetic counselor [GC])	Study GC	GC shared by study and hospital	Study MD or GC	Government-funded GC service	Study GC
Mode of delivery of genetic counseling	In-person/telephone	In-person/telephone	Telephone	In-person	In-person/telephone
Participant encouraged to seek CLIA-approved testing	Yes	NA[a]	Yes	NA[a]	Yes

CLIA Clinical Laboratory Improvement Amendments

[a] Testing offered through clinical services

Table 4 Uptake of research-generated genetic information by individuals in familial with pathogenic MMR or *MutYH* mutations identified

	HI (2008–2010)	ON (1998–2010)	MA[a] (2008–2010)	AU (1999–2009)	SE[b] (2011–present)
Eligible for genetic counseling based on research results and contactable	25	460	185	862	102
Had first genetic counseling session	18	412	145	542	24
Received genetic test results at second counseling session	18	394	144	480	21
Decision pending	0	22	12	80	NA
Uptake (received results/eligible) (%)	72	86	78	56	NA

[a] MMR results only

[b] SE is yet to complete approaching all eligible participants

Recommendations

During the recommendation development group discussion, key informants and TrWG members described a number of issues to address if they were to initiate a new process involving genetic information. These issues are summarized in Table 5.

A key factor contributing to the ease or difficulty of the disclosure process in the registries was the set of decisions that were made at the outset of the study. We suggest that researchers should develop a plan for disclosing (or justify withholding) genetic information that has an impact on medical management at the outset of research and that this plan should be reflected in the IRB (or ethics) application, the informed consent form, and the funding application. The plan should include how the issue of accredited diagnostic laboratory confirmation will be managed.

We suggest that participants should be informed about return of genetic findings in more detail while obtaining informed consent, including the difference between research results and clinic results, the difference between the role of a researcher and a clinician, the meaning and clinical implications of not receiving any genetic results, a clear outline of the process involved for offering results, and both the advantages and disadvantages of receiving results. It may be necessary to ask participants at the outset of research more detailed questions about their preferences for the return of genetic information. It is also important to take into consideration that preferences should not necessarily be binding, as the knowledge about and utility of genetic findings will no doubt continue to change with time, as it has over the last few decades. In particular, the clinical relevance of VUS will become better appreciated as they are reclassified over time.

Finally, we have suggested that key stakeholders are invited to contribute their expertise at all stages of research. For example, genetic counselors (Zierhut and Austin 2011), consumer representatives, and government agencies are all likely to contribute expertise and guidance in both the design and implementation of the process of ethical disclosure of genetic results.

Discussion

While the findings reported here involve the experience of only one multinational cancer registry, the fact that the registries comprising the Colon CFR are spread across four countries has allowed us to report how the disclosure process varies depending on the setting. We have been also able to report what happens when guidelines and principles designed to inform the process of disclosure are applied in practice and the practical barriers faced by researchers, and we have used data from these experiences to make recommendations for future practice.

Five of the six registries had instituted processes that enable the return of clinically relevant genetic test results to their research participants, and the sixth has approval to do so. Analysis of the original informed consent forms and subsequent changes made to the consent process at each registry revealed the key steps needed to be taken to return results to participants: (1) inform the participants that individual clinically relevant results could become available and (2) ask participants whether they wish to receive results if such results become available. Registries that did not initially include these two steps had to modify their protocols in order to do so. This added step delayed the process of disclosing results and created additional work for the researchers and IRBs, as new approvals were required. By 2013, all six registries had informed consent procedures that both inform participants that results may become available and ask participants either at the time of initial informed consent or when results become available whether they want to receive results.

Registries are acting on their perceived ethical responsibility to inform research participants of the availability of clinically important genetic information arising in their research studies. Determining the clinical significance of

Table 5 Lessons learned by the Colon CFR

If we were to start a new genetic family study, we would try to ensure that…

1. Researchers develop a plan for disclosing (or justify withholding) genetic information that impacts on medical management at the outset of the study, including
   (a) In the IRB (or ethics) application
   (b) In the informed consent form
   (c) The cost in the funding application
   (d) Resolving the issue of diagnostic accredited laboratory confirmation
   (e) Develop a plan to monitor scientific progress
2. Respect the individual autonomy of each family member. Inform participants in more detail, including
   (a) the difference between research results and clinic results
   (b) the difference between a researcher and a clinician
   (c) the meaning of not receiving any genetic results
   (d) an outline of the process for offering results
3. Involve key stakeholders at all stages of research, for example
   (a) Potential participants
   (b) Health care providers (i.e., physicians, genetic counselors, nurses)
   (c) consumer representatives
   (d) government agencies

genetic information is a complex and evolving process, and as we reported, even within the Colon CFR, there were differences among registries about which results were deemed clinically relevant. Botkin et al. (2010) have provided a framework for evaluating genetic tests and list a number of factors that could be considered in making decisions about clinical relevance including clinical validity, clinical utility, and ethical, legal, and social implications. We argue, as suggested by Rothstein (2006), that decisions on how to manage clinically relevant genetic results should be considered and planned at the outset of the research. Variability across registries in protocols for the return of findings from genetic tests suggests that, while guidelines in the research setting are useful, they need to be targeted to the type of genetic research being conducted, varied health care systems, local cultures and customs, and legal requirements in the country in which the research is conducted. Guidelines developed by Fabsitz et al. (2010) suggest that results not confirmed by a clinically approved laboratory should not be returned to participants. This guideline places researchers who accept them in the untenable ethical position of having important clinical information about participants and withholding it from them. Our study reports that, in practice, such results are being returned to some individuals in the USA, but along with the information that the results are preliminary and that they should be verified before medical management is altered.

There was some variation in the uptake of genetic results by participants across the four registries able to report on uptake, with Australia reporting lower uptake rates than the North American registries. For participants who decided not to receive their results in Australia, it is likely that the implications of genetic test results for life insurance eligibility plays a role (Keogh et al. 2009). The passage in 2008 of the federal Genetic Information Nondiscrimination Act (GINA) may diminish this concern among US research participants. Although the legislation does not apply to life and long-term care disability insurance, GINA currently protects individuals pursuing genetic testing from discrimination in acquiring health insurance and employment. Studies of predictors for participant uptake and the impact of genetic counseling interventions are complete or underway at MA, SE, AU, and Canada (Esplen et al. 2003, 2004).

Devising universally applicable guidelines for the return of clinically relevant genetic test results in research settings is challenging, particularly within a multinational and multisite context with varied genetic counseling models. We have compiled a set of suggestions for future researchers based on our own experience of returning results to research participants. Our consensus suggestions are designed to be used to supplement guidelines that are currently available (Botkin et al. 2010; Fabsitz et al. 2010; Bookman et al. 2006; Dressler 2009). We have also described the disclosure protocols used by registries in order to increase the information available to research consortia managing clinically relevant genetic results on participants.

Limitations

This study was not conducted prospectively to study the return of results but has instead been conducted retrospectively in order to describe how clinically relevant genetic

results were handled in a large multinational registry. The findings apply largely to the specific case of MMR and MutYH testing, and the findings will not apply to all genetic tests conducted in the course of research. In addition, we did not set out to describe the predictors of the uptake of genetic testing by participants and have made no attempt to determine the predictors in this study, although other studies in the Colon CFR have been specifically designed to do this and will be published separately. We were also not able to compare the different protocols used, as we do not have outcome measures on which these different disclosure protocols could be compared. Despite this, we have provided recommendations based upon a systematic analysis of real-world experience in research genetic disclosure.

Future issues

The issue of return of research-generated genetic results will become more important and complex as rapid technologic developments increase the pace of discovery of the genetic basis of human disease. The ability to genotype large numbers of people rapidly and inexpensively for research purposes is fueling the need to develop consensus about the role of the researcher in providing clinically relevant research results to study participants (Knoppers et al. 2006; Ravitsky and Wilfond 2006; Wolf et al. 2008). In addition to the expected genetic results, whole genome and exome sequencing studies reveal unanticipated findings (e.g., abnormal sex chromosome complement XXY, XYY, 45X, XXX, hemochromatosis, Factor V Leiden, or the cystic fibrosis gene mutation). Despite recent papers suggesting that these unanticipated findings should also be returned to participants (Wolf et al. 2012; Green et al. 2012), this paper has illustrated the need to fully fund and plan for the return of genetic results at the outset of research, a task that is even harder for findings that are not anticipated at the outset. Schully et al. (2011) have demonstrated the need for more research on the translation of findings from gene discoveries into clinical practice and public health in order to fully realize the benefits for disease prevention and health promotion.

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References

Affleck P (2009) Is it ethical to deny genetic research participants individualised results? J Med Ethics 35(4):209–213. doi:10.1136/jme.2007.024034

Beskow LM, Burke W, Merz JF, Barr PA, Terry S, Penchaszadeh VB, Gostin LO, Gwinn M, Khoury MJ (2001) Informed consent for population-based research involving genetics. JAMA Am Med Assoc 286(18):2315–2321. doi:10.1001/jama.286.18.2315

Bookman E, Langehorne A, Eckfeldt J, Glass K, Jarvik G, Klag M, Koski G, Motulsky A, Wilfond B, Manolio T, Fabsitz R, Luepker R (2006) Reporting genetic results in research studies: summary and recommendations of an NHLBI working group. Am J Med Genet A 140A:1033–1040

Botkin JR, Teutsch SM, Kaye CI, Hayes M, Haddow JE, Bradley LA, Szegda K, Dotson WD, on behalf of the EWG (2010) Outcomes of interest in evidence-based evaluations of genetic tests. Genet Med 12(4):228–235

Ceballos R, Newcomb P, Beasley J, Petersen S, Templeton A, Hunt J (2008) Willingness to disclose genetic status to family members: a comparison of colon cancer cases and relatives. Genet Test Mol Biomark 12(3):415–420

Dressler LG (2009) Disclosure of research results from cancer genomic studies: state of the science. Clin Cancer Res 15(13):4270–4276. doi:10.1158/1078-0432.ccr-08-3067

Esplen M, Aronson M, Rothenmund H, Butler K, Gallinger S, Laceby J, Bapat B, Toner B, Wong J (2003) Motivation, anticipated distress and knowledge level of colorectal cancer patients undergoing genetic testing. Familial Cancer 1(70)

Esplen M, Aronson M, Rothenmund H, Butler K, Gallinger S (2004) Relatives of colorectal cancer patients participating in a population-based familial colorectal cancer registry. Psycho-Oncology 13(8)

Fabsitz R, McGuire A, Sharp R, Puggal M, Beskow L, Biesecker L, Bookman E, Burke W, Burchard E, Church G, Clayton E, Eckfeldt J, Fernandez C, Fisher R, Fullerton S, Gabriel S, Gachupin F, James C, Jarvik G, Kittles R, Leib J, O'Donnell C, O'Rourke P, Rodriguez L, Schully S, Shuldiner A, Sze R, Thakuria J, Wolf S, Burke G (2010) Ethical and practical guidelines for reporting genetic research results to study participants. Updated guidelines from a National Heart, Lung, and Blood Institute Working Group. Circ Cardiovasc Genet 3:574–580

Green RC, Berg JS, Berry GT, Biesecker LG, Dimmock DP, Evans JP, Grody WW, Hegde MR, Kalia S, Korf BR, Krantz I, McGuire AL, Miller DT, Murray MF, Nussbaum RL, Plon SE, Rehm HL, Jacob HJ (2012) Exploring concordance and discordance for return of incidental findings from clinical sequencing. Genet Med 14(4):405–410

Gritz E, Peterson S, Vernon S, Marani S, Baile W, Watts B, Amos C, Frazier M, Lynch P (2005) Psychological impact of genetic testing for hereditary nonpolyposis colorectal cancer. J Clin Oncol 23(9):1902–1910

Hutson S (2003) Attitudes and psychological impact of genetic testing, genetic counseling, and breast cancer risk assessment among women at increased risk. Oncol Nurs Forum 30(2):241–246

Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomaki P, De La Chapelle A, Mecklin JP (2000) Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 118(5):829–834

Kaufman D, Murphy J, Scott J, Hudson K (2008) Subjects matter: a survey of public opinions about a large genetic cohort study. Genet Med 10(11):813–839

Keogh L, van Vliet C, Studdert D, Maskiell J, McCrae F, John DS, Gaff C, Young M, Southey M, Giles G, Rosenthal D, Hopper J, Jenkins M (2009) Is uptake of genetic testing for colorectal cancer influenced by implications for insurance? Med J Aust 191(5):255–258

Knoppers B, Joly Y, Simard J, Durocher F (2006) The emergence of an ethical duty to disclose genetic research results: international perspectives. Eur J Med Genet 14(12):1322

Kollek R, Petersen I (2011) Disclosure of individual research results in clinico-genomic trials: challenges, classification and criteria for decision-making. J Med Ethics 37:271–275

Lindor N, Sloan J, Goldberg R, Bowen D, Nigon S, Roche A, Petersen G, Thibodeau S, Burgart L, Leontovich O, Morlan B (2004) Colorectal tumour microsatellite instability test results: perspectives from patients. Hereditary Cancer Clin Pract 2(2):69–75

Lindor N, Robe K, Petersen G, Haile R, Casey G, Baron J, Bapat B, Aranson M, Hopper J, Jass J, Le Marchand L, Grove J, Potter J, Newcomb P, Terdiman J, Conrad P, Moslein G, Goldberg R, Ziogas A, Anton-Culver H, de Andrade M, Siegmund K, Thibodeau S, Boardman L, Seminara D (2005) Lower cancer incidence in Amsterdam-I Criteria families without mismatch repair deficiency. Familial Colorectal Cancer Type X. J Am Med Assoc 293(16):1979–1985

Meiser B (2005) Psychological impact of genetic testing for cancer susceptibility: an update of the literature. Psychoonology 14(12):1060–1064

Meulenkamp T, Gevers S, Bovenberg J, Koppelman G, van Hylckama VA, Smets E (2010) Communication of biobanks' research results: what do (potential) participants want? Am J Med Genet 152A(10):2482–2492

Miller FA, Christensen R, Giacomini M, Robert JS (2008) Duty to disclose what? Querying the putative obligation to return research results to participants. J Med Ethics 34(3):210–213. doi:10.1136/jme.2006.020289

National Health and Medical Research Council (2007) National statement on ethical conduct in human research. Available at http://www.nhmrc.gov.au/publications/synopses/e72syn.htm

Newcomb P, Baron J, Cotterchio M, Gallinger S, Grove J, Haile R, Hall D, Hopper J, Jass J, Le Marchand L, Limburg P, Lindor N, Potter J, Templeton A, Thibodeau A, Seminara D (2007) Colon Cancer Family Registry: an international resource for studies of the genetic epidemiology of colon cancer. Cancer Epidemiol Biomark Prev 16(11):2331–2343

Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN (2009) EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 11(1):42–65

Partridge AH, Winer EP (2002) Informing clinical trial participants about study results. JAMA J Am Med Assoc 288(3):363–365. doi:10.1001/jama.288.3.363

Ravitsky V, Wilfond B (2006) Disclosing individual genetic results to research participants. Am J Bioeth 6(6):8–17

Roberts J, Shalowitz D, Christnesen K, Everett J, Kim S, Raskin L, Gruber S (2010) Returning individual results: development of a cancer genetics education and risk communication protocol. J Empir Res Hum Res Ethics 15(3):17–30

Rothstein M (2006) Tiered disclosure options promote the autonomy and well-being of research subjects. Am J Bioeth 6(6):20–21

Schully SD, Benedicto CB, Gillanders EM, Wang SS, Khoury MJ (2011) Translational research in cancer genetics: the road less traveled. Public Health Genomics 14(1):1–8

Terdiman JP (2009) MYH-associated disease: attenuated adenomatous polyposis of the colon is only part of the story. Gastroenterology 137(6):1883–1886

Theodoratou E, Campbell H, Tenesa A, Houlston R, Webb E, Lubbe S, Broderick P, Gallinger S, Croitoru EM, Jenkins MA, Win AK, Cleary SP, Koessler T, Pharoah PD, Kury S, Bezieau S, Buecher B, Ellis NA, Peterlongo P, Offit K, Aaltonen LA, Enholm S, Lindblom A, Zhou XL, Tomlinson IP, Moreno V, Blanco I, Capella G, Barnetson R, Porteous ME, Dunlop MG, Farrington SM (2010) A large-scale meta-analysis to refine colorectal cancer risk estimates associated with MUTYH variants. Br J Cancer 103(12):1875–1884

Vasen HFA, Mecklin JP, Meera Khan P, Lynch HT (1991) The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 34(5):424–425

Wolf S, Paradise J, Caga-anan C (2008) The law of incidental findings in human subjects research: establishing researcher's duties. J Law Med Ethics 36(2):361–383, 214

Wolf SM, Crock BN, Van Ness B, Lawrenz F, Kahn JP, Beskow LM, Cho MK, Christman MF, Green RC, Hall R, Illes J, Keane M, Knoppers BM, Koenig BA, Kohane IS, LeRoy B, Maschke KJ, McGeveran W, Ossorio P, Parker LS, Petersen GM, Richardson HS, Scott JA, Terry SF, Wilfond BS, Wolf WA (2012) Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genet Med 14(4):361–384

Zierhut H, Austin J (2011) How inclusion of genetic counselors on the research team can benefit translational science. Sci Transl Med 3(74):1–3. doi:10.1126/scitranslmed.3001898