Navigating the Intersection between Genomic Research and Clinical Practice

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ABSTRACT

The Risk Assessment Program (RAP) at Fox Chase Cancer Center (Philadelphia, PA) is a multi-generational prospective cohort, enhanced for personal and family history of cancer, consisting of over 10,000 individuals for whom data on personal and family history of cancer, risk factors, genetic and genomic data, health behaviors, and biospecimens are available. The RAP has a broad research agenda including the characterization of genes with known or potential relevance to cancer, gene–gene and gene–environment interactions, and their contribution to clinically useful risk assessment and risk reduction strategies. Increasingly, this body of research is identifying genetic changes which may have clinical significance for RAP research participants, leading us to confront the issue of whether to return genetic results emerging from research laboratories. This review will describe some of the important fundamental points that must be debated as we develop a paradigm for return of research results. The key issues to address as the scientific community moves toward adopting a policy of return of research results include the best criteria for determining which results to offer, the consent document components necessary to ensure that the participant makes a truly informed decision about receiving their results, and associated logistical and cost challenges.

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Introduction

The last 25 years have seen an explosion of information about the contribution of genetics to health and disease. This has been brought about by a wave of family studies and by rapid progress in the technology to identify and sequence genes. This genetic revolution is having an impact not only on our understanding of the etiology of disease, but also on the prevention, early diagnosis, and treatment of many medical conditions. Nowhere is this more pronounced than in the field of oncology where genetic discoveries are increasingly being translated into clinical applications. The progress being made in genetics has stimulated the creation of large cohorts and biobanks to facilitate future genetic research.

The Risk Assessment Program (RAP) at Fox Chase Cancer Center (Philadelphia, PA) is a multi-generational prospective cohort, enhanced for personal and family history of cancer, consisting of over 10,000 individuals for whom data on personal and family history of cancer, host risk factors, environmental exposures, genetic and genomic data, health behaviors, and biospecimens are available. The RAP has a research agenda which is broad and includes the characterization of genes with known or potential relevance to cancer, the interaction of these genes with other genetic variants, host, and environmental factors, and their contribution to clinically useful risk assessment and risk reduction strategies. Increasingly, this body of research is identifying genetic changes which may have clinical significance for RAP research participants, leading us to confront the issue of whether to return genetic results emerging from research laboratories. Already several international laws and policies encourage or require that research participants be informed about potential research results as part of the consent process (1). This review will describe some of the fundamental points that must be debated as we develop a paradigm for return of research results.

Historically it has not been the practice to share results from research laboratories with research participants. The primary goal of scientific research has been to advance science, not to provide a direct benefit to an individual research participant. Reasons for this long standing policy include differences in laboratory procedures, which may lessen the accuracy of the results, a lack of certainty about the clinical utility of the findings, fears about loss of privacy and discrimination, and feasibility and cost considerations. The massive amount of genetic and genomic data that can now be generated in real time, however, has given the scientific community pause to reconsider this practice from a clinical, ethical, and regulatory view. Data generated by a research laboratory may benefit research participants in terms of cancer prevention, early detection, treatment, or reproductive choices, and furthermore may benefit other family members (2). Several studies among research participants have found considerable interest in knowing results of research studies using their data and/or biospecimens, especially if there are health benefits to knowing

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the findings (3, 4). This has led to an emerging consensus to recommend that some research results with clinical utility be made available to participants (5, 6). There is however considerable debate among scientists as well as patient advocates about which results to share, how and by whom they will be communicated, and how to address challenging practical issues, including quality assurance of the research samples, validity of the findings, infrastructure requirements, costs, and clinical follow-up (7). Regulatory bodies who oversee human research have been largely silent on this issue.

Materials and Methods

The ultimate goal of the RAP registry is that of achieving the best science possible within the context of acceptable ethical and legal constructs. The RAP team has identified a number of questions to address as we move toward adopting a policy of return of research results to our participants.

What criteria should be used to determine which research results to offer to research participants?

The National Bioethics Advisory Commission recommends the return of genetic or genomic research results which meet the following criteria: (i) "the findings are scientifically valid," (ii) "the findings have significant implications for the subjects' health concerns," and (iii) "a course of action to ameliorate or treat these concerns is readily available" (8). There is general consensus that priority be given to health conditions which pose a serious threat to the individual and for which there are established therapeutic or preventive interventions (9–11). The challenges are defining what constitutes a serious threat, what degree of benefit should be available, and determining which genetic data meet these requirements. An approach adopted by several research groups is to form an oversight committee composed of individuals with clinical genetics expertise to monitor the research results on an ongoing basis and advice the research team on which findings meet the *a priori* guidelines for return. Another consideration is whether to limit return of only those results related to the purpose of the initial research, or to include findings which were not anticipated (incidental findings) but which may have the potential to confer clinical benefit (12). While there is considerable agreement on the return of research results, which are clinically valid and can be acted upon, there is also debate about the return of variants for which there is currently no known therapeutic or preventive action, but which may be of interest to the research participant (2).

What are the potential risks and benefits of sharing research results?

A potential risk to the return of research results is the possibility of false-positive findings, which can lead to incorrect and misleading information and unnecessary screening and prophylactic surgeries. Errors can occur in the coding, transport, storage, and processing of data and biospecimens. Most research laboratories do not have the same standards of accuracy as clinical laboratories. On the other hand, false-negative test results can lead to an unfounded sense of reassurance. Participants, without the benefit of genetic counseling, may lack comprehension of the genetic results shared with them and their potential implications for medical and reproductive decisions. Learning of unanticipated genetic risks may threaten personal identities and family relationships, and may cause psychosocial distress. Genetic information may lead to loss of privacy, stigmatization, labeling healthy people as sick, and discrimination in the workplace (13, 14). Without a network of family and social support, the psychologic and social risks of genetic information may outweigh the clinical benefits (15). Potential benefits include increased knowledge of genetic susceptibilities which can translate into primary and secondary prevention, avoidance of unnecessary screening and/or treatment, access to novel treatments, and the ability to make informed reproductive decisions. There may be relief from uncertainty, an enhanced sense of control over one's health, and perceived benefits to family members who may share the genetic risk (3).

What are appropriate methods of contacting research participants to offer return of research results?

Typically a process of deidentification of the individual research participant's data is performed to protect their privacy and confidentiality. A secure method for restoring identifying information is a necessary first step for contacting research participants for return of results. In the case of large cohorts and biobanks, investigators may not have a means to identify participants and will have to rely on sites from which the participants were recruited to create the link. This can be labor intensive and is especially problematic for participants who are deceased or lost to follow-up. Establishing this expectation when research participants are first enrolled will facilitate this process. Methods of contact can include mail, phone, or secure text. There is debate about whether to provide specific information about the research finding in the initial contact, or to simply indicate that a finding of interest has been reported.

What role should some form of genetic counseling have in preparing participants to receive research results?

Research participants who learn that they carry genetic variants that may impact their health outside of a clinical context are likely to be unprepared to understand the true meaning of the results and may experience confusion and psychologic distress. Internationally, many institutional review boards require the availability of genetic counselors or other health care providers with expertise in clinical genetics to be part of the process of explaining the potential impact of the research results, determining the participant's preferences regarding receipt of the results, and of confirming those results in a clinically certified laboratory (6). While the availability of a counseling team will facilitate a truly informed decision on the part of the research participant as to whether they want to pursue learning of their research results, and a greater

understanding of the significance of the findings, it has the potential to overwhelm the clinical resources at recruitment sites and to add unanticipated costs to the research budget. Ideally this problem is best addressed by including these costs in the research budget.

Does the research team have a responsibility to inform family members of the research findings?

One of the benefits of the decision to offer research participants the return of certain research results is the extension of this information and its potential benefits to family members. The current policy in the clinical setting is to consider the proband as the gatekeeper of genetic information for the rest of the family. Studies have shown however, that while there is a significant rate of sharing of clinical genetic information among family members, the complexities of intrafamilial relationships can compromise the selectivity and quality of the information shared. Both emotional forces within the family, as well as social and cultural beliefs about health and disease can affect communication patterns (16). The ethical and social responsibilities involved in communicating genetic results to the family members of research participants mirror these complexities (17). Often the research team will have no relationship with a participant's relatives (18). One option to consider is to allow the research participant to list those family members with whom their test results can be shared in the consent process. Alternatively, the research team can prepare materials explaining the nature of the test result and its implications for family members for the research participant to use in approaching their family. As we move into an era when return of research results is increasingly practiced, we must also involve research participants in creating a plan for disclosure of their information to other family members in the case of death, and provide support and resources to the family members involved (19).

How should cost issues be handled?

The return of research results will often pose a significant burden on the research team. It will require considerable financial commitments for staff to recontact the participants, for the involvement of medical professionals including when possible genetic counselors, for obtaining an additional blood sample for confirmation of the findings in a clinically certified laboratory, and for the cost of the clinical confirmation studies. Most research grants have not included these personnel and infrastructure costs. Each research team will have to address this issue given their access to clinical personnel and their institutional resources.

Discussion

As our understanding of the molecular basis of cancer progresses, and the technologies that support that progress advance, the translation of genetic information from the research laboratory to the clinic will expand, with the goal of improving health outcomes. The field of oncology, with its strong history of clinical trials, has always demonstrated its willingness to use new knowledge and new technologies to expand its therapeutic options. The advent of genomic medicine paves a way to broaden this success to the field of cancer prevention.

Traditionally, the informed consent process has served as the foundation for ethical scientific research, and it continues to be relevant to the setting of genetic research. Having recognized some of the unique and challenging issues associated with genetic research, it is incumbent upon investigators in this field to pay particular attention to the content of the informed consent process as they plan their research design, in their funding application, and in their allocation of resources. Key elements to address include a plan for determining which research results will be offered; clarity on the choices available to research participants; a description of the anticipated risks, benefits and costs of receiving research results; a discussion of the counseling process and support available to participants and family members; the need to confirm research results in a certified clinical laboratory; measures taken to protect privacy and confidentiality; and implications of research results for family members and plans for cascade testing within the family when appropriate. Because genetic information can be interpreted differently among different cultural groups based on their values and historical experiences, language for the consent document should be socially and culturally appropriate for the population being studied.

Creation of a model for return of genetic research results will require an ongoing dialogue with scientists, clinicians, regulatory bodies, commercial genetics laboratories, insurers, research participants, and the public at large to increase society's knowledge about genetic and genomic technologies, to ensure that all stakeholders are capable of making well informed decisions (13). Our experience with research emanating from the RAP Registry provides us with an opportunity to create a roadmap for future research about the return of research results and offers guidance for the educational needs that are emerging. There is a lack of knowledge among both providers and the public about genetic syndromes, genetic testing, ethical and legal aspects of informed consent, the psychologic impact of genetic risk, and responsibilities to family members (20). The issues discussed in this review have been recognized by the scientific community and new models are emerging to support the return of research results. As we explore the challenges associated with this new opportunity for our RAP participants, we have a unique opportunity to widen the research agenda on how best to make the promises of genomic medicine a reality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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