Returning a Research Participant's Genomic Results to Relatives: Perspectives from Managers of Two Distinct Research Biobanks

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Introduction

Given the nature of scientific inquiry, biomedical and genomic researchers have forged innumerable ways to advance our understanding of human disease. In many cases, research requires the involvement of human subjects, and in a subset of these studies, the researcher may collect data and biospecimens from many participants, and even serially collect additional materials over time and across a number of geographically dispersed centers. The organized data and biospecimens are collectively known as research biobanks.[1] Researchers have an obligation to disseminate findings from their research through publications and presentations to other professionals, and when possible, to the public. Sharing genomic data is increasingly being mandated; access to data can be obtained through collaborative or state-funded entities. For example, the database of Genotypes and Phenotypes (dbGAP)[2] and the International Cancer Genome Consortium[3] will grant approved research applicants access to de-identified individual level genomic data with accompanying demographic/clinical information.

Surveys of Biobank Managers' Views on Return of Results

For researchers who create and maintain biobanks, there are structural and regulatory frameworks within which biobanks function. In general, biobank managers are trained in and follow best practices as far as operations related to accessioning, processing, and storage. For example, professional organizations[4] and government initiatives[5] are important resources. Nevertheless, there is extensive variation among biobanks with respect to initial motivation to create the biobank, settings of biobanks (e.g., academic, clinical, or commercial), data and biospecimen inventories,[6] data management and security, scope (e.g., single institution samples versus regional or national sample contributions), and sharing policies. As a result of the diverse motivations and goals, context matters. Indeed, a survey about biobank characteristics and

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stewardship practices conducted with 456 biobank managers in the United States reveals extensive variation in acquiring, storing, and sharing biospecimens, and research results, reflecting the diverse origins, processes, and resources used by investigators.[7] At this time, biobanks are not legally obligated to retain identifiers or contact information of participants who contribute samples. In some cases, purposeful de-identification is promoted as a strategy to both protect privacy and avoid consideration of returning results.

Genomic research performed on biobank specimens has additional implications when incidental genomic findings are uncovered. We summarize these in Table 1. It is not a goal or purpose of biobanks to return research results and incidental findings; doing so creates obligations that biobank personnel may not be able to fulfill, including the potential clinical care associated with the information. It is worth noting that many centralized biobanks do not have contact information about patients, nor are biobank personnel involved in consent or future contact with human subjects. Instead, the responsibility for return of research results is typically avoided, when possible. Because their main scientific mission is accessioning and storing biospecimens, the concerns of biobank managers regarding return of results are generally consistent. In the United States (U.S.) survey, Henderson et al. found that although 72% of biobanks have access to identifying information, only 19% offer individual research results to participants, and 38% offer aggregate results.[8] In a survey of attitudes about researchers' duty to communicate research results of 80 researchers in the Netherlands, Meulenkamp et al.[9] found, the majority agreed that participants have to be informed about aggregate research results (79%); participants only have to be informed about variations in their genes when there are implications for treatment or prevention (74%); and if continued research shows results to have clinical implications, the participant concerned has to be contacted (66%). There was mixed response to the statement, "I think it is all right when participants do not get any information about variations in their genes," and nearly complete disagreement (95%) that "Participants have to be informed about all variations in their genes, even when the implications for their health are unclear yet." Similarly, the attitudes among genomics investigators are consistent. In a study of 200 corresponding authors of reports on genome wide association studies (GWAS), Ramoni et al.[10] found that only 4% had returned individual results from GWAS, and 69% believed that return of results to the individual par-

Table 1

Implications for Biobanks When Considering Return of Incidental Findings and Genomic Research Results to Participants and Relatives

Mode of returning results by researcher or designee	Biobanks would need to:	Required resources:
Returning individual results to living participants[a]	• Maintain identifying and follow-up contact information (eliminate de-identification) • Make referrals for clinical care, if needed • Consider CLIA[b] certification or referral for validation testing in a CLIA-approved laboratory • Establish institutional review board approved processes	• Dedicated personnel or time • Clinical skills or expertise not necessarily existing in a biobank (i.e., genetic counseling) • Resources for secure record keeping • Clinical referral contact information • CLIA[b]-approved laboratory referral information
Returning individual results from deceased participants to relatives	• Same as above plus maintain identifying and follow-up contact information on legal next of kin	• Same as above
Returning aggregate results	• Maintain contact information • Enlist cooperation of public relations or communications staff	• Resources for preparing and distributing newsletters or electronic dissemination of aggregate results

a Or parents/guardians if participant is not an adult
b Clinical Laboratory Improvement Amendments

tipant was warranted under at least some circumstances. Klitzman et al.[11] surveyed 241 geneticists in the U.S. and found that 12% had returned incidental findings, but 95% believed that incidental findings for highly penetrant disorders with immediate medical implications should be offered to research participants. In addition, however, these researchers raised concern that the return of incidental findings would impose a significant burden on researchers.

The issue of burden is manifested in the need for an appropriate infrastructure to support return of research results. For example, in a survey of cooperative clinical trials groups, 10 biobank managers[12] largely disagreed that the resource should be responsible for collection of incidental findings and return of incidental results from investigators and disclosure to patients. Furthermore, the managers did not agree that the biobank has funding, or the qualified staff for return of incidental research findings that included clinical action.

Wolf and colleagues[14] have stressed that access to Clinical Laboratory and Improvement Amendments (CLIA)-approved validation testing of returned results should be required. While many results are derived from CLIA-approved diagnostics laboratories, there are many laboratory results that are derived from research laboratories that are not CLIA-approved. If there were an obligation to return results, the added burden and cost of CLIA certification or re-testing in CLIA-certified laboratories presents a cost prohibitive barrier.

Two Biobanks with Different Practices

From our own experience, we have found these concerns to be quite valid. We present two examples of ongoing biobanks at opposite ends of the spectrum of origin and operational processes. One of us (Petersen) directs a pancreatic cancer patient biobank in which the manager is the principal investigator of the discovery research as well as the patient registry approved by the institutional review board (ethics board). In the second example, author Van Ness is the biobank manager of a multiple myeloma patient biobank, but has no contact with the participants who contributed the samples, is not involved in consent, and has no direct access to clinical treatments or outcomes. Both biobanks have a lengthy history, and research with the biobank specimens has generated genomic findings that might be returned to participants or their family members, including incidental findings as well as research that is within the scope of the biobank's explicit purpose.

The pancreatic cancer biobank is a clinic-based research repository at the Mayo Clinic in Rochester, Minnesota, which is supported by the National Cancer Institute funded Specialized Program of Research Excellence (SPORE) in Pancreatic Cancer.[13] The biobank unifies a prospective pancreatic cancer patient registry with the tissue and biospecimen bank resources. In addition to the data and samples, a major and effective means of unifying the resource is through a single research database with web-based portals so that study coordinators and physicians can access it across Mayo Clinic's campuses. The pancreatic cancer biobank developed processes to enable meaningful research into the etiology and treatment of this cancer, including adapting to Mayo Clinic's large patient volume, coordinated multidisciplinary clinical care and treatment programs, searchable electronic schedules, and access to electronic medical records. Specific processes include: ultra-rapid case finding and recruitment (approaching prospective patients prior to confirmed knowledge of diagnosis); inviting participation into research in person, rather than by mail; self-completed risk factor questionnaires, access to all treatment data; and maintaining contact information for follow-up. The importance of ultra-rapid case finding and an in-person approach to informed consent to research is of paramount importance to the utility of the biobank. In the setting of the Mayo Clinic, 61% of patients approached agreed to participate in research (to date, we have approached over 9,000 eligible patients). When approached in person, 80% of patients agree to participate, compared to 27% when approached by mail. More importantly, 65% of 3,461 patients with pancreatic adenocarcinoma were recruited within two days of diagnosis, and an additional 20% were recruited within 30 days of diagnosis. Because of the ultra-rapid method of ascertainment, there is less likelihood of survival bias in research using samples from this biobank, and indeed, samples can be assembled utilizing a variety of demographic, clinical, and tissue criteria. Patients are asked to provide a sample of venous blood for research and for tissue based-studies the biobank has access to thousands of blocks of tissues, both formalin fixed paraffin embedded and frozen, for which annotation has enabled high quality analysis of samples. Results of all assays performed on biobank specimens are retained in the central database, enabling comparisons and cost savings in some cases by avoiding repeated analyses of the same markers on sets of samples.

In the course of performing purposeful genetic research, revelation of individual research results (IRRs) and incidental findings (IFs) is possible. These may be potentially useful to the individual participant or family, following the criteria described by Wolf et al.[14]: analytically valid, reveal an established and sub-

stantial risk of a serious health condition, and that are clinically actionable. In the Mayo Clinic pancreatic cancer biobank, re-identification and re-contact of individual contributors is feasible, although many contributors are deceased due to the lethality of the cancer, and re-contact requires additional resources to identify next-of kin or legal representatives. However, the biobank has limited resources to cover the cost of returning IRRs and IFs.

In contrast to the Mayo Clinic biobank described above, biobanks created by cooperative clinical trials groups recruit and collect samples across multiple sites. Currently, ten U.S.-based groups conduct clinical trials on experimental therapies for cancer, with sample accrual coming from 3,100 sites in the U.S. and abroad. The clinical goals of the groups vary, but typically focus on Phase II and III cancer clinical trials where many participating sites are needed to accrue the numbers of patients necessary to meet study endpoints. Trial completion and data maturity (response, outcomes, survival, etc.) may take several years; and research on samples placed in central banks may be done years after completion of the trial. Typically, the bank has no role in trial study design, consent, or direct access to clinical outcomes. Cooperative group coordinating centers that manage trial data and biospecimen collections are most often located and managed at other sites. Most of the cooperative group biobanks operate under an "honest broker" model, and samples are typically coded and linked to patient identifiers only at the cooperative group operations office where laboratory studies can develop biomarker associations. Such studies are regulated by the operations office and the researcher's own local institutional review boards. Informed consent templates are employed by the cooperative groups, making patients aware of biospecimen banking and potential for research. Notably, the current template contains the single, explicit statement: "Research results will not be returned to you or your doctor." Under this system IRRs and IFs resulting from projects utilizing banked tissue are not currently returned, and participants have the right to deny access to samples under these conditions while still being part of the Phase II or III study. An exception to this policy is if the laboratory results represent clinical trial endpoints or are used in determining eligibility or in stratifying treatment as part of the study design. Recently, cooperative group participation in the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) study[15] requires genetic information about tumor tissue to be returned to the physician with potential implications on drug choices. There has been considerable interest and utility in cancer genomes in clinical practice. However, research to discover inherited germline variants that might carry implications for family members is not specifically performed. Moreover, investigators are often restricted from obtaining patient identifiers, and any burden of returning IRRs or IFs likely falls to other entities, such as the operations offices that hold the clinical outcomes within the cooperative group system, and that operate under the consent statement not to return results.

Implications for Biobanks

In the survey of ten cooperative group biobank directors, significant concern was raised over the complexities of implementing return of results to participants,[16] and that complexity is magnified when considering return to family members. It was clear from the survey that cooperative biobank management does not have independent jurisdiction on policies governing return of results. Because these biobanks receive samples from widely distributed sites and distribute samples to multiple secondary researchers, governance is central to the cooperative group operations office. Moreover, most researchers have no role in the participant's clinical care, within the trial or any clinical treatments outside the trial.

The lack of relationship between cooperative clinical trial biobanks and participants is an important feature of the research context which affects decisions about return of IFs or IRRs. Indeed, the bank has no information as to whether genetic conditions have manifested, or testing might have been done at other sites. Addressing this would require dissemination of health care information that is not within the purview of the bank. Clinical trials have an endpoint, and as a result, the participant may not be under the care of any cooperative group physician, nor even at the last recorded residence. Again, the complexity of informing family members is significantly magnified: information about a participant is typically housed at sites located at a distance from the biobank. Alternative approaches of re-identification and policies to inform participants or their family members would require a significant revamping of the structure and governance of cooperative biobanks.

Black et al. recognized the implications of imposing new obligations to return IFs on biobanks: "The creation of a new ethical responsibility without a consideration of how (and whether) it should be funded creates uncertainty for researchers throughout the course of their research…."[17] Bledsoe et al. argued that the recommendations of Wolf et al.[18] "…would require significant financial investment and could place an unsustainable burden on many biobanks and researchers using biobank specimens and health

information. The recommendations could have a negative impact on research by creating a disincentive for the establishment of biobanks, the distribution of samples and data, and subsequent research on those specimens and data." Wolf responded by emphasizing that lack of recommendations reduce efficiency and increases costs, and called for better collaboration and criteria for evaluating findings among biobankers and primary/secondary researchers, including the option of a "trusted intermediary."[19] The need for improving stewardship of biobanks,[20] combined with recommendations that include potential use of intermediaries, raises the very real issue of burden, including identifying the resources to satisfy ethical concerns.

A proposed change discussed in Ferriere and Van Ness[21] would be to offer invitations to participants to initiate their own re-contact to learn meaningful results. This is consistent with the recommendations of Wolf et al.[22] A study-specific, but neutral, re-contact web-based portal might allow such a process, but would require oversight and recognition that only well-defined results, developed and curated by individuals with appropriate expertise, should be disseminated. Based on the surveys discussed above, most biobank managers do not feel they have that expertise to return relevant findings. It is clear that the majority of biobanks follow the myeloma biobank model (national cooperative accrual of de-identified biospecimens and no contact with participants) rather than the pancreatic cancer biobank (clinic-based accrual of biospecimens from a patient cohort with identifiers and capacity to recontact participants). Until the debate over the stewardship responsibilities of biobanks to research participants is resolved by policy or by changes in human research protection practices, both models offer lessons relevant to the design of future biobanks, with respect to recognizing and accommodating obligations on return of IRRs and IFs.

Summary

Although there are strong professional and regulatory guidelines governing biobanks, these research resources are quite heterogeneous in origin, operations, and practice. Biobanks currently do not have a responsibility to return incidental findings, including aggregate reports or reports to individual research participants. Furthermore, the majority of biobank managers are wary of taking on this responsibility, which in many instances carries structural barriers and considerable cost. In limited cases, clinic-based biobanks with linked identifiers to participants might consider returning IRRs and IFs. Managing return of research results to individual participants or families will require resources and novel processes so that participants realize the potential benefits without impairing the primary scientific purpose of biobanks.

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Acknowledgments

This work was supported in part by National Institutes of Health (NIH), National Human Genome Research Institute (NHGRI) R21HG006594 and National Cancer Institute (NCI) and NHGRI R01 CA154517 (Petersen, Koenig, Wolf, PIs); P50 CA102701; and R01 CA97075. All views expressed are those of the authors and do not necessarily reflect the views of NIH, NCI, or NHGRI. In addition, partial support was provided by the Mayo Clinic Center for Individualized Medicine.

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