Return of Individual Research Results and Incidental Findings: Facing the Challenges of Translational Science

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Abstract
The debate over return of individual research results and incidental findings to study participants is a key frontier in research ethics and practice. This is fundamentally a problem of translational science—a question of when information about an individual that is generated in research should be communicated for clinical attention, particularly as technologies such as whole-genome sequencing and whole-exome sequencing are increasingly used in clinical care. There is growing consensus that investigators should offer participants at least those individual findings of high clinical importance and actionability. Increasing attention to what information biobanks and secondary researchers owe people who provide data and specimens offers an opportunity to treat these source individuals as research partners. Cutting-edge issues include return of results in pediatric populations and return to kin and family, both before and after the death of the proband, as well as how to manage incidental findings in clinical sequencing. Progress will require an understanding of the continuum linking research and clinical care and developing standards and models for return.
INTRODUCTION

The question of whether to return individual research results (IRRs) and incidental findings (IFs) to participants in genetic and genomic research is now recognized as one of the most difficult challenges facing investigators. When our research group based at the University of Minnesota began funded work on this problem in 2005, the debate was in its infancy. Indeed, that project was framed comparatively: Using the more advanced debate at the time over management and return of IFs in neuroimaging research and computed tomography (CT) colonography research (as the latter images most of the torso and frequently reveals extracolonic IFs), our group launched into consideration of how to define, anticipate, manage, and return IFs in genetic and genomic research. In 2008, we published consensus recommendations as part of a symposium offering papers on different pieces of this puzzle (82).

Concern over how to handle IFs in research was preceded by a long history of attention to the question of how to handle them in clinical care. Every clinician has probably had the experience of a patient presenting with a certain complaint and the clinician then discovering an additional and unrelated pathology. Indeed, the term “incidentaloma” is defined in medical dictionaries as an occult adrenal tumor that is accidentally discovered (32, 66). The genetics field has also seen a long-standing debate on how to handle IFs of misattributed paternity revealed by genetic testing (64).

As this concern over clinical incidentalomas moved into the research sphere and edged toward genetics, the National Bioethics Advisory Committee (NBAC) published a report on stored tissue in 1999 (54). That report included a brief section on reporting research results to subjects and offered several recommendations. NBAC urged that institutional review boards (IRBs) develop guidelines and require that protocols address this issue. However, NBAC recommended that disclosure should be “an exceptional circumstance,” and be undertaken only if “the findings are scientifically valid and confirmed,” “the findings have significant implications for subjects’ health concerns,” and “a course of action to ameliorate or treat these concerns is readily available” (54, p. 72). NBAC also suggested that at the time of disclosure, “appropriate medical advice or referral should be provided” (54, p. 72), though later recommendations have instead generally counseled that investigators should offer the IF as a research finding, with referral for clinical follow-up (82). The later recommendations contemplate a handoff of information from the domain of research to that of the clinic, in part to avoid mistaking research for clinical care.

NBAC cited few sources to show earlier attention to the problem of return of research results. The most prescient was a short article by Reilly from 1980 (61). As NBAC recounted, Reilly distinguished three types of findings: “1) ‘findings that are of such potential importance to the subject that they must be disclosed immediately’; 2) ‘data that are of importance to subjects ... but about which [the investigator] should exercise judgment about the decision to disclose... [in effect, these are data that trigger a duty to consider the question of disclosure’; and 3) ‘data that do not require special disclosure’” (54, p. 72, the ellipses and brackets are as shown in the NBAC quotations from Reilly’s article).

By the time NBAC published its report, a significant literature was already emerging on how to manage IFs in imaging research, where they can be visually obvious and hard to overlook. In 1997, for example, Yue et al. (84) published a study of IFs discovered in imaging the brain, as did Katzman et al. in 1999 (42). Over time, the literature on IFs in imaging research became voluminous. In 2005, Illes led a workshop that included investigators and policy makers from the National Institutes of Health (NIH) and focused on IFs in neuroimaging research, yielding progress toward consensus recommendations (35). Consensus recommendations emerged for IFs discovered in CT colonography as well (85). In 2008, our project group published consensus recommendations bridging from imaging research to genetic and genomic research (82).
In the fast-moving fields of genetics and genomics, the 1990s and even the mid-2000s are now a long time ago. With increasing reliance on large-scale genomic research using biobanks and archived data sets, the emergence of whole-genome sequencing (WGS) and whole-exome sequencing (WES), and their growing speed and plummeting cost, as well as developments in informatics allowing increasingly automated analysis of potentially returnable variants and computer-supported communication to clinicians and even participants, the debate over return of IRRs and IFs has intensified. The NIH, and especially the National Human Genome Research Institute (NHGRI) and the National Cancer Institute (NCI), deserves great credit for recognizing the fundamental importance of these issues, committing significant funding to the research needed to build a strong evidence base for solutions, and speeding progress by linking funded investigators through an active consortium (52).

The importance of this issue has now been widely recognized. Both the professional literature (scientific, medical, ethical, and legal) and the popular media now regularly cover this unfolding story. A 2011 news article in *Science* reported that “whether to divulge these results, and how, is arguably the most pressing issue in genetics today” (22, p. 662). In August 2012, the *New York Times* quoted NIH director Francis Collins, calling the issue “one of the thorniest current challenges in clinical research” (49, p. A1). An October 2012 report from the Presidential Commission for the Study of Bioethical Issues, which focused on the privacy challenges posed by the rise of WGS, included recommendations on return of IFs: “Researchers, clinicians, and commercial whole genome sequencing entities must make individuals aware that incidental findings are likely to be discovered in the course of whole genome sequencing. The consent process should convey whether these findings will be communicated…” (59, p. 98). In March 2013, the American College of Medical Genetics and Genomics (ACMG) issued recommendations on how to handle IFs in clinical application of genome and exome sequencing (31), recommendations that were further clarified the following month (1). Those recommendations have led to considerable and prominent debate (51, 80).

I focus here on developments in the context of US policy and regulations, but the debate over return of IRRs and IFs in genetic and genomic research is international, as genetic and genomic research involves projects and data sharing that cross national boundaries (38, 46, 86). Ultimately, international exchange on policy and best practices will be crucial, as a pathway to international harmonization of policies and standards.

**DEFINITIONS**

In 2008, our project group offered a definition of an IF as “a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of research but is beyond the aims of the study” (82, p. 219). Since this definition was offered, it has been widely recognized that not only health and reproductive importance but also personal utility to the research participant may suggest possible return of an IF (81). Note that IFs discovered in the course of genetic or genomic research may not be limited to genetic findings: Screening individuals for possible enrollment in research, collecting baseline values on research participants, or gathering phenotypic information (for example, to search for genotype/phenotype associations) may yield a wide range of IFs, such as abnormal blood pressure and other phenotypic findings.

In contrast to an IF, an IRR is a finding concerning an individual research participant that has potential health or reproductive importance or personal utility and is discovered in the course of research on the focal variables under study in meeting the research project’s aims (81). Thus, in genetic or genomic research, IRRs are likely to be genetic or genomic findings.

Of course, distinguishing IRRs from IFs may be more difficult in discovery-driven rather than hypothesis-driven research, as the aims in the former may be broad and the method inductive...
(82). For example, in some genome-wide association studies (GWAS) that search widely across the genome for genotype/phenotype correlations, it may be hard to discern which findings are beyond the aims of the study. For this reason, distinctions in how IRRs and IFs are managed should be carefully justified, especially because research participants may find it difficult to distinguish these two types of findings (81). Indeed, when commentators reference “return of results,” they are often referring to return of both IRRs and IFs, as I will in this review.

Both IRRs and IFs contrast with aggregate research results. These are findings concerning the research population (usually published) that are discovered in the course of research on the focal variables under examination in meeting the research project’s aims. Beskow et al. (9) discuss ethical obligations to offer aggregate research results to research participants and the relationship to return of IRRs. Indeed, return of aggregate results to a research population (as in a newsletter or through a website) can lead individual participants to ask for their own findings.

There are a range of terms for the individuals whose findings are at issue; the literature variously calls them participants (or human subjects), donors, sources, and contributors. Some are indeed participants in research on human subjects as defined by the Common Rule, because they are “living individual[s] about whom an investigator . . . obtains data through intervention or interaction with the individual or identifiable private information” [70, §46.102(f)]. However, much genetic and genomic research is performed on data and specimens that have been collected for clinical rather than research purposes and then deidentified (72). Such research does not qualify as research on human subjects (16). Indeed, the source individuals [the term I use here, though our group has also used “contributors” (81)] may not know their materials are being used in research [though possible changes to the Common Rule have been published for comment, which would require at least rudimentary consent from source individuals (71)]. Thus, “donor” seems the wrong term, as it suggests a past donation.

Finally, a definition of “biobank” is useful. As in much of the literature, I use the term here to refer to a range of structured collections of human biological materials and/or data, archived for ongoing use in research (81). Others have offered similar definitions (56), allowing for discussion of the role of biobanks in the return-of-results debate without getting lost in the welter of terms used for such structured collections, including the terms “biorepositories,” “tissue repositories,” and “DNA data banks.”

WHY HAS THIS ISSUE BECOME IMPORTANT?

Return of results has erupted into a major debate and focus for research. The importance of the issue stems in part from the gap between the preferences in favor of return that many participants and members of the public appear to hold, and past research practice to avoid return. Research is still under way on the preferences of research participants, other individuals who serve as sources of data and specimens used in research, and the public, but the data thus far indicate that most are interested in return (10, 15, 24, 26, 53, 73). Indeed, one survey found that “90% of . . . respondents wanted their genetic or risk information even when there was nothing that currently could be done with that information” (44, p. 836). Although more data and analysis are needed to understand preferences in a range of research contexts, as well as the impact of return on actual participants, the gap between apparent preferences and research practice has led to concern over the ethics of withholding clinically significant IRRs and IFs.

This concern has arisen at a time of broader attention to the problem of how to earn and sustain the trust of individuals recruited for research as well as those source individuals whose data and specimens are used. As Trinidad et al. have noted, “A spate of recent events—including several . . . conflicts over newborn blood samples; the return of biospecimens to the Yanomamô
people; and the best-selling account of the origins of the HeLa human cell line widely used in research—have raised questions about trustworthiness of the research process at a time when new approaches to genomic research place a premium on study participation” (69, p. 287; references omitted). Kohane et al. have argued that withholding data from research participants makes them “passive, disenfranchised purveyors of biomaterials and data” (48, p. 837), not research partners. Illes et al. have similarly maintained that researchers should return IFs based on respect for participant autonomy and interests, as well as a duty of reciprocity toward those who make research possible through their participation (35).

Richardson and Belsky have offered ethical analysis to translate these concerns into investigator duties to return IFs to research participants (62, 63). They argue that participants permit researchers access to their private data, specimens, and bodies, access that researchers otherwise would not have. This grant of access represents an act of partial entrustment (partial because participants are not fully entrusting their medical welfare to the researcher, as they would to a clinician). Richardson and Belsky maintain that the scope of this partial entrustment creates researcher duties of ancillary care. These are not the full duties of care borne by clinicians, but neither are researchers “pure scientists” with no duty of care. Richardson has argued that this duty of ancillary care embraces a duty to return IFs: “Having gotten the participants to waive these privacy rights, the researchers correspondingly come to have duties of care with regard to the pieces of information—and in particular the incidental findings—that fall in their hands by doing the research procedures” (62, p. 266).

Lurking here is a duty to warn or duty to rescue. Beskow & Burke have explicitly embraced the notion of a duty to rescue, which they argue applies “when, in the course of research, an investigator discovers genetic information that clearly indicates a high probability of a serious condition for which an effective intervention is readily available” (8, p. 2). Ossorio has questioned the extent of a duty to warn or rescue, at least for secondary researchers, who are distant from any research interaction with participants (58). Yet even in the case of secondary researchers, she argues that there are cases in which the duty applies and return of results may be obligatory, as well as additional cases in which it may not be obligatory but would still be “morally superior to not doing so” (p. 466).

The question of whether researchers bear duties to return IRRs and IFs has provoked this outpouring of research and analysis in large part because it straddles the worlds of research and clinical care, with their different norms and objectives. The core question is whether information discovered in the course of research should be conveyed to individual participants in order to trigger clinical evaluation and follow-up. In that sense, return of results is a “bridge” problem, because it bridges the world of research and the world of clinical care. On the research side of the bridge, investigators debate whether information acquired in the course of research should be communicated across that bridge to the domain of clinical care.

The problem of whether to return IRRs and IFs thus challenges the dichotomy between research and clinical care that ethics (and law, for that matter) has long embraced (77). On the clinical side, copious work on medical ethics, as well as court decisions and legislation, has established that the physician owes the patient a robust duty of clinical care. The physician’s goal is to serve the patient’s interests. A great deal follows from this, including informational obligations to disclose to the patient the diagnosis, treatment options, and other information material to treatment decisions. However, on the research side, the researcher’s core goal is to seek generalizable knowledge for the benefit of the many. The researcher owes a much thinner duty of clinical care, focused on averting and addressing research-caused harm. Researchers are obliged to seek research participants’ informed consent to be part of the research, but they currently have had no duty to seek consent from individuals whose clinically derived data and specimens are used
without identifiers. And what information the researcher should report back to the participant or individual source of data and specimens is the precise question posed by the return-of-results debate.

This dichotomous vision of the contrasting worlds of research and clinical care is rooted in the history of human subjects research. Traditionally, research asked narrow, circumscribed questions in time-limited investigation, aimed at advancing aggregate knowledge and welfare. In contrast, medical care addressed the patient’s full panoply of health issues, extended over the patient’s lifetime, and was provided by clinicians committed to advancing the patient’s individual welfare. However, newer research realities challenge this stark contrast. Genetic and genomic research may now ask broad, uncircumscribed questions in discovery research and analysis of the full genome or exome, including as part of GWAS. Research may no longer be time-limited, now that data sets and specimens are archived and reanalyzed indefinitely. Research technologies are so powerful that they routinely generate findings of potential clinical significance for individual welfare.

The return-of-results problem is thus one of many signs that the old, dichotomous vision of research and clinical care as widely separated will need to evolve into a new, more translational vision of connected realms. The rise of genomic medicine and pharmacogenomics is interdigitating research and clinical care as well. Rather than relying on the old, dichotomous vision, we may need to reconceptualize research and clinical care along a translational continuum. The problem of returning IRRs and IFs has become a catalyst to forging this new vision.

Unlike some commentators, I am not urging the erasure of the boundary between research and clinical care. Kass et al. (40) have recently argued that because health care delivery systems should routinely analyze the data they generate in order to learn and improve, and because of the long-recognized difficulty of distinguishing some clinical trials from clinical care (for example, when a cancer patient enrolls in a clinical trial in a last-ditch effort to fight his or her disease), we should abandon the research-treatment distinction. However, this new proposal, which requires more work and specification (25, 29), actually addresses a different problem than the one discussed here. Much of the genetic and genomic research generating the debate over IRRs and IFs is basic human subjects research rather than clinical trials. Moreover, it is precisely the research context that generates some of the most difficult questions surrounding return of IRRs or IFs; because of the research context, the findings at issue may not be fully validated and understood and may not have been generated by a diagnostic laboratory. Thus, I am calling not for erasure of the distinction between research and clinical care, but rather for recognition that the return-of-results problem calls for ethical (and legal) work on how to handle the bridge between the two domains. As IRRs and IFs generated in research are considered for return owing to potential significance in the clinical domain, and as genomic technology developed in research itself moves into clinical application, we need ethical work to address the bridge between research and clinical care.

**HOW IRRs AND IFs ARISE**

Both IRRs and IFs can arise throughout the course of research. This is true in the context of an individual study, starting at the beginning with recruitment and ascertaining eligibility. It is also true as data and specimens from multiple studies or those left over from clinical care are collected and aggregated, stored in biobanks or archived data sets, and used in secondary research. In 2012, our group published the results of a project on managing IRRs and IFs in genomic research involving biobanks and archived data sets (81). Addressing this issue forced us to conceptu
Figure 1
A biobank research system. Adapted from Reference 81. Used with permission from the Nature Publishing Group, copyright 2012.

how IRRs and IFs arise as data and specimens flow through what we called a biobank research system. Figure 1 depicts such a system, comprised of three types of entities:

- **Stage 1**: Data and/or specimens from contributors are gathered by primary research and collection sites. The initial collection may take place in research or in clinical care. Research may itself occur at the stage 1 sites.

- **Stage 2**: The data and/or specimens are fed into a biobank for curation, annotation, and storage, making them available for subsequent research. (Note that some biobanks collect their own data/specimens, without involving any stage 1 sites.) The subsequent research on banked data and/or specimens may take place at the biobank itself, at multiple secondary research sites (stage 3 sites), or at both.

- **Stage 3**: Those secondary research sites comprise stage 3 of the biobank research system.

IRRs and IFs can arise at all three stages of this system. At stage 1 primary research and collection sites, IFRs may arise when ascertaining an individual’s eligibility to participate and collecting baseline information, as noted above. In addition, IRRs and IFs may arise in any subsequent research conducted at these sites.

At stage 2 biobank sites, where data and specimens are archived and processed to be made available for further research, IFs may arise during the processing of data and/or specimens. For example, a biobank that processes tumor specimens by reconfirming the reported pathology may discover an erroneous diagnosis (sometimes called a “discrepant diagnosis”). Biobank quality control is another potential source of IFs. For example, a biobank conducting routine quality control by chromosomal confirmation that a contributor reported as female is indeed XX may discover sex chromosome abnormalities and wonder whether these should be offered to the source individual or her physician. In addition, any research conducted at the biobank may yield IRRs or IFs. These may be discovered in the genetic data or in the phenotypic data about an individual, including in his or her electronic medical record, if that is used in the research.

At stage 3 sites, secondary researchers using data and/or specimens obtained through the biobank may discover IRRs or IFs in the course of performing their research. These are particularly
challenging to handle, as secondary research may be far removed from data and specimen collection both in time and geographically, secondary researchers may have no relationship with the source individuals, and the data and specimens are likely to have been deidentified before being conveyed to the secondary researchers.

Conceptualizing the flow of data and specimens through the entire research system is important. It allows consideration of the proper stage for stripping identifiers and which entity (if any) should hold the codes to allow reidentification. It also allows consideration of how the documents that structure the relationships between the stage 1 sites and stage 2 biobank and then between the stage 2 biobank and stage 3 secondary researchers (including material transfer agreements and data access agreements) should address responsibilities for return of IRRs and IFs.

Most of the literature to date on IRRs and IFs in genetic and genomic research either focuses on those that arise in stage 1 primary research or does not specify the context in which the findings arise and must be addressed. However, much genomic research now occurs in biobank research systems and has to be addressed in this context. That was the focus of our 2012 consensus paper (81) and associated symposium. Addressing the more complex reality of genomic research conducted on a large scale through a biobank research system requires first examining the analysis that has emerged thus far on how to handle IRRs and IFs in primary research.

**RECOMMENDATIONS FOR PRIMARY RESEARCH**

The key questions that have structured the debate over return of IRRs and IFs in primary research have included the following:

- **What findings are we talking about?** What criteria should define returnable IRRs and IFs? Do returnable findings include only those of clinical significance? What about findings of reproductive significance (such as carrier status)? And what about findings of personal utility (such as a variant predicting serious illness and early death, which might prompt an individual to put his or her affairs in order and alter life decisions)? If a finding must be “actionable” to warrant return, how should “actionability” be defined? Should “actionability” refer only to a clinician’s ability to alter the patient’s clinical course, or should findings that a patient may find personally useful be considered “actionable” as well?

- **How are these findings ascertained?** Do investigators have a duty to actively search for these findings, or should return of IRRs and IFs be limited to those that investigators and others discover without an active search?

- **What should investigators do once they spot a suspected IRR or IF?** What personnel and procedures are needed to set up a responsible process for evaluating these findings? Should the research team include (or arrange access to) a clinician with relevant expertise to examine the research findings of concern and confirm whether they warrant communication to participants for potential clinical evaluation and follow-up?

- **What further steps are needed to raise confidence in the finding to the level necessary for return?** Given that false positives occur even in clinical testing, what level of confidence in a research finding is required for return, given that return itself may then trigger clinical evaluation? Does return require confirmation of genetic IRRs or IFs in a lab certified to return findings for diagnosis or treatment use under the Clinical Laboratory Improvement Amendments (CLIA) (23, 81)? If so, how is this best accomplished?

- **To whom should return be offered?** Should return be offered only to research participants themselves? Are there circumstances under which return should be offered to the participant’s clinician in addition to or instead of the participant? Should return be offered only to participants who consent? Are there findings of such gravity and actionability that they should
be returned even if the participant has not consented? How should participant consent for return be sought?

- What systems and processes should be set up to support ethical handling of IRRs and IFs? What should research protocols and consent forms say in advance about the likelihood of finding IRRs and IFs and how they will be handled? What should IRBs require? What should funders themselves require, and what funding is needed to support sound management of IRRs and IFs?

In our 2008 consensus recommendations for how to handle IFs, our project group concluded that investigators do shoulder duties to anticipate and manage IFs in their research (82). We urged that they create a pathway for handling these findings and offered a flowchart as well as a description of that pathway. We suggested that researchers should address their plan for managing IFs in their proposed protocol and in the consent process, and should obtain IRB approval. IRBs and funders should oversee fulfillment of these duties, ensure the necessary budget, and provide guidance.

In developing criteria for return, we distinguished three categories: findings that should be returned, findings that may be returned, and findings that should not be returned (82). This three-way division has proven durable, and a number of subsequent recommendations similarly distinguish should return, may return, and (often) do not return (including recommendations from Fabsitz et al. (23) and Berg et al. (7)). In our 2008 paper, we sorted findings into these categories based on whether return potentially offered strong net benefit to the participant (should return), possible net benefit (may return), or unlikely net benefit (do not return). Thus, we made the ethical judgment that returnability should hinge on the importance of return from the perspective of the research participant. In the “should return” category, we included both findings of high clinical significance and those of high reproductive significance, as long as the research participant consented to their return.

Although the three-way division has endured, as has the inclusion of findings of high clinical significance in the “should return” category, other features of our proposal have sparked more debate. A subsequent consensus paper by Fabsitz et al. (23) stripped findings of reproductive significance out of “should return.” That paper restricted “should return” to findings with important health implications, revealing established and substantial risks, when the findings were actionable (defined as having the potential to change the disease course). In addition, findings in this category had to be analytically valid, their disclosure had to comport with law (such as any applicable CLIA requirements), and the participant had to consent to receipt of the findings.

This was a more clinician-centered delineation of the “should return” category. The actionability requirement and definition meant that investigators had to conclude that clinicians could potentially use the returned finding to make a positive difference in the individual’s clinical course—a different ethical perspective than we took in our 2008 paper (82), which was instead guided by what information participants themselves would likely find valuable. This debate over whether to tether return to what clinicians can use as opposed to what participants can use remains unresolved. It echoes a long-standing debate [the subject of seminal court cases such as Canterbury v. Spence (17) as well as legislation] over whether informed consent in clinical care calls for disclosure of the information deemed relevant by professional custom, or instead the information that patients are likely to find material.

Both our 2008 recommendations (82) and the recommendations from Fabsitz et al. (23) address return of IFs in the context of research. Consequently, both have drawn objections from those who argue for maintaining a wall between research and clinical care. Three key objections have been that (a) returning IRRs and IFs requires time and resources, diverting personnel and funds from research (14); (b) offering IRRs and IFs to participants may cause them to confuse research
for clinical care; and (c) guidelines recommending return of some IRRs and IFs may invite liability for failure to return (21).

As to the first of these objections, there have been few studies as yet analyzing the costs of return. Those costs are likely to vary considerably depending on study design, the types and frequency of IRRs and IFs identified, the size of the sample population, and the determination of what IRRs and IFs to actually return. A common recommendation, which our own consensus papers include (81, 82), is that funders need to increase research budgets in order to support addressing IRRs and IFs. The reality is that ethics—including the basic requirement of informed consent—takes time and costs money (79).

The second objection, that research participants may mistake research for clinical care, is a long-recognized problem that significantly predates the return-of-results debate. Researchers and IRBs now routinely address the “therapeutic misconception” and take steps to minimize this confusion. Explicitly addressing possible return of IRRs and IFs with research participants might actually be an opportunity to emphasize the distinction between research and clinical care. Investigators will need to explain to participants the option of receiving findings generated in research that will then need to be pursued and clarified through clinical workup.

Finally, concern over potential liability seems at least premature, if not misplaced (78). There have been no court cases as yet over return of results. However, guidelines that help move the research community toward a shared sense of what is owed to research participants may actually help avert potential liability by articulating flexible standards. Without those, a research participant who is not offered a particular IRR or IF and arguably suffers harm as a consequence will be freer to argue that lack of return was a breach of the researcher’s duty causing compensable harm. With flexible guidelines in place, investigators can instead point to their reasonable use of those guidelines. None of the guidelines published to date state that investigators should return all possible IRRs and IFs; instead, the guidelines customarily restrict “should return” to a small subset of findings.

Despite the concerns articulated over return of IRRs and IFs, it is now difficult to find commentators who argue that absolutely no IRRs and IFs should be returned. The reality that some IRRs and IFs are clinically urgent is widely recognized. Indeed, consensus approaches to IFs in imaging research clearly recognize that some IFs are clinically urgent and categorize them this way (45).

The progress that has been made on return of results in primary research is the necessary backdrop for the more complex debate over return of IRRs and IFs in research that involves biobanks. I turn next to that debate.

**RECOMMENDATIONS FOR BIOBANKS AND SECONDARY RESEARCH**

Because biobanks are increasingly the engines of large-scale genomic research, determining how to handle return of IRRs and IFs in the simpler model of primary research is not enough. It is essential to grapple with how to manage IRRs and IFs as data and specimens move through all three stages of a biobank research system.

However, the conventional view has been that once data and specimens move beyond primary research and collection sites to biobanks and then to secondary researchers (that is, to stages 2 and 3 in the biobank research system), either no IRRs and IFs should be returned at all, or the biobanks and secondary researchers should convey any IRRs and IFs to the relevant primary site to determine whether any return should be undertaken (54, 81). This view minimizes or eliminates biobank and secondary researcher responsibilities to manage IRRs and IFs.

There is a growing recognition, however, that this conventional view presents several problems (81, 45). First, some findings are so clinically urgent that failing to return them poses serious ethical
challenges. An example is biobank discovery when processing newly acquired tumor specimens that the pathology and diagnosis noted at the primary collection site (stage 1) appear to be incorrect. This problem of discrepant diagnosis has led to a literature on how to manage and return what may be an IF of urgent clinical importance (50).

A second problem is that primary research and collection sites may lack the capacity to address the finding. In some scenarios, the primary site has merely supplied data and specimens that were collected in clinical care, and it may lack the expertise to analyze the returnability of the genetic or genomic findings generated by the biobank or secondary researchers. Even if the primary site collected the data and specimens in research, the relevant investigator may now be gone and the investigator’s research project concluded.

More fundamentally, there is a strong argument for a systemic approach to managing IRRs and IFs that arise as data and specimens flow through a biobank research system. This flow is controlled by policies and documents such as material transfer agreements and data access agreements (81). Those policies and agreements should address the responsibilities of primary research and collection sites, biobanks, and secondary researchers to manage IRRs and IFs. Only this kind of systemic approach will lead to harmonized expectations and clear notice to all of the actors regarding their responsibilities.

Our 2012 consensus paper was the first to offer this kind of systemic analysis of how to approach the return-of-results problem in a biobank research system (81). We readily acknowledged that biobanks are varied. Some are population-based, whereas others are disease-based. They vary by source population, size, age of collection, and range of data and specimens collected. They may aggregate data and specimens that were collected for clinical purposes and are now deidentified, so that research on that material falls beyond the scope of “research on human subjects” under the Common Rule (16, 72). In contrast, data and specimens may have been collected for research or carry identifiers, in which case the Common Rule’s regulation of human subjects research applies.

Despite this variety, all biobanks and biobank research systems have the potential to discover IRRs and IFs. There is a need for guidance, especially guidance that offers the flexibility to tailor approaches to the realities of a given biobank research system. Although some commentators have suggested that the sheer variety of biobanks counsels against general guidelines (28, 45), the virtue of offering guidance to biobanks has already been recognized by publication of the influential Best Practices for Biorepositories issued by the NCI Office of Biospecimen and Biorepository Research (55). A substantial literature has also emerged on the ethical responsibilities of biobanks, including duties of responsible custodianship (10, 19, 36, 76). Leaving each biobank to grapple alone with the return-of-results problem, without even general guidelines, invites inefficiency, unnecessary costs, and unwarranted inconsistencies.

Biobanks are already beginning to address return-of-results issues, so the time is ripe to offer guidance and to invite debate over proposed policy. The Electronic Medical Records and Genomics (eMERGE) Network of biobank research sites has a network-level Return of Results Oversight Committee to offer general guidance, which individual sites can then tailor to their circumstances and needs (27). The Coriell Personalized Medicine Collaborative has an Informed Cohort Oversight Board (ICOB), a model suggested by Holm & Taylor (34). The NIH Gene-Environment Association (GENEVA) Studies use a Committee on Incidental Findings (28). Not all biobank research systems can return results; Vanderbilt’s BioVU is an example of a biobank that irretrievably strips identifiers, so that reidentification, and thus return, cannot be accomplished (60). However, this remains an unusual practice. More common is to retain a key code that allows reidentification. Indeed, in some research designs, participants are fully identified and followed prospectively.
Our project group offered consensus recommendations for return of results from biobank research systems (81). The most fundamental recommendation was to approach the issue of return of results systemically, by considering how IRRs and IFs can arise as data and specimens move through the entire system and by allocating among the key players within that system the responsibilities for dealing with return issues. We recognized that the biobank itself sits at the center of the three-stage system, with relationships (including written agreements) extending both to primary research and collection sites and (in the other direction) to secondary researchers. This puts biobanks in an important position to help ensure that the biobank research system as a whole addresses return-of-results issues.

To allocate responsibilities across the system, we identified four general steps involved in dealing with return of results: (a) clarifying general criteria for what should be returned, may be returned, and should not be returned; (b) analyzing a particular finding in light of these criteria; (c) reidentifying the source individual; and (d) recontacting the individual to offer the finding. We summarized these four steps using the acronym CARR (clarifying, analyzing, reidentifying, recontacting). We then offered specific recommendations for each step.

For the first CARR step—clarifying general criteria for return—we recommended that biobanks have a multidisciplinary committee such as an ICOB to work with an IRB on these return issues. As Fabsitz et al. (23) also recommended, a nationwide or central advisory committee would be helpful, to offer recommendations on the criteria for return and a periodically updated list of returnable variants. A given biobank research system might decide to deviate from those central recommendations, but would at least have a place to start.

To aid in formulating criteria for return of IRRs and IFs, we offered a set of criteria similar to those for return in primary research, but with key caveats. Thus, we suggested that biobank research systems should return IRRs and IFs that reveal an established and substantial risk of a serious health condition, that are actionable (offering a significant potential to alter the onset, course, or treatment of disease), that are analytically valid, and whose return complies with legal requirements (such as applicable CLIA requirements), but only if the source individual has consented to return. We went on to suggest that a biobank research system may return additional IRRs and IFs with participant consent, if they reveal an established and substantial risk of likely health or reproductive importance, or if they have personal utility to the source and return is likely to provide net benefit from that person’s perspective.

However, among the caveats we offered was that “[t]he greater difficulty and cost of biobank return, the lower likelihood of benefit with lapse of time, and the reality that some contributors will not have consented to research, justify more restrictive criteria for return in biobank research than primary research” (81, p. 373). Thus, although our 2008 consensus paper (82) included some findings of reproductive importance in the “should return” category, our 2012 paper (81) focusing on biobanks did not. We also noted that biobanks may hold data and specimens for so long that relocating and contacting the source individual may be challenging, and the utility of return for that individual may be diminished. We further addressed the special challenges facing preexisting biobanks (as opposed to new biobanks that can consider return-of-results issues in their design). Older biobanks may hold data and specimens collected with consent forms that failed to address and seek consent for return or that stated there would be no return. We addressed options for recontacting source individuals for consent to return, but also the need otherwise to respect the prior explicit agreement that there would be no return.

For the second CARR step—analyzing a particular finding for potential return—we made a distinction. We urged that when IRRs or IFs arise in primary research, the primary researcher and institution should be responsible for handling them, working with their IRB. However, when IRRs and IFs arise later in the flow of data and specimens through the biobank research system,
the biobank itself has a crucial role to play. Thus, when IRRs and IFs arise in the biobank’s own collection of data or specimens (that is, when these are collected by the biobank directly rather than through separate primary research and collection sites); when they arise in biobank quality control, processing, or research; or when they arise in secondary research on data and specimens supplied by the biobank, we urged that the biobank bear primary responsibility for analyzing whether a particular IRR or IF should be offered back to the source individual.

For the third CARR step—reidentifying the source individual—a distinction is again necessary. When only the primary researcher holds the key code to reidentify individuals, reidentification must occur at the primary research site. However, we urged that biobanks consider holding the key code or using a trusted intermediary to hold the code (36, 83). This avoids relying entirely on the primary research site to maintain the capacity for reidentification over the extended period of time during which biobank and secondary research is continuing. Planning for how to handle the return-of-results issue within a biobank research system thus requires planning how deidentification (if undertaken) will occur, how the key code allowing reidentification will be held, and thus what entity has the capacity to reidentify individuals as needed over time.

Finally, for the fourth CARR step—recontacting the individual to offer the finding—we suggested considering that in many cases the primary research or collection site may be best situated to perform recontact. This site may be the only one in the biobank research system that has had direct contact with the source individual (although in some biobank research systems, the biobank itself may collect data and specimens directly from these individuals and thus have direct contact), which may mean that it is also the site with which the source individual is most familiar. Thus, even if the biobank or a “trusted intermediary” performs reidentification, the primary research or collection site may instead perform recontact.

This allocation of CARR responsibilities to different entities within the biobank research system demonstrates the importance of analyzing return of results systemically in genetic and genomic research involving biobanks. Our recommendations are sometimes misunderstood as thrusting all CARR responsibilities on biobanks themselves (14). But that overlooks the systemic thrust of our analysis, distributing duties across the biobank research system, of which biobanks themselves are only one part.

Since we offered these recommendations, debate and research have continued. Bledsoe et al. (14) have argued that the cost of return can potentially be excessive. Yet there has been little work to date determining these costs (79). Rigorously evaluating the costs will be challenging, as cost will depend on the number of variants to be analyzed for potential return and the number to be returned, the method of sorting those variants to be returned, the size of the research population, the method of return, and other variables. Indeed, the first of these—the number of variants to be analyzed for potential return and then returned—itself remains a subject of research and debate (18, 39, 47, 74). However, the fact that return of results requires expenditure of effort and funds is not itself an argument to avoid the practice. The reality is that ethics—including informed consent, IRB review, and the like—costs money (79). If ethics calls for return, the key question will be how to scale that return and develop procedures that make it feasible and compatible with achieving research objectives (5, 6, 47).

Normative guidance on return of results will and should evolve as research contributes further to the evidence base. We recommended a middle course. There are some commentators and researchers who would be much more restrictive, offering little or even no return (14, 21). There are others who would be far more generous, offering considerably more than our criteria suggest, including the possibility of offering a source individual his or her full data set (48, 68). Thus, commentators from both sides can debate our proposals.
Research continues on what findings source individuals wish to receive, what means of return are effective, and what consequences return has for those individuals in terms of their subsequent utilization of medical care and their health outcomes. Further research will need to consider what genetics professionals consider to be returnable results and why (30). A good deal of effort is going into identifying a roster of returnable results, with underlying criteria to justify the list. And researchers continue to debate how best to minimize false positives and create a process to restrict return to those findings whose meaning is adequately established. Of course, work is still required to reach consensus on what constitutes “adequately established” and how best to reconcile the effort to protect source individuals from false positives and data whose meaning is currently uncertain with the reality that some of these individuals want their data with accompanying indications of what is known and not, so that they can await further research to improve interpretation.

Further research will also need to address how to implement return of results, including the protocols, systems, informatics, consent processes, and costs involved. Analyzing and resolving these specifics and different models for return will be crucial to making progress.

Frontier issues prompting further research include how to approach return of results in pediatric populations (37, 43, 75). Issues include how to address return of results in pediatric assent and parent or guardian permission, to whom to offer pediatric IRRs and IFs, whether some findings (such as an IF of adolescent pregnancy) should be offered only to the adolescent, and how to handle disagreement between the pediatric proband and the parents or guardians on return of results. As WGS and WES are used in research on children and even newborns, the question arises of whether to refrain from offering even to parents or guardians those findings that lack clinical utility in childhood (33). This would be in keeping with long-established guidelines urging that children be tested only for genetic variants with established clinical utility in childhood, preserving the option to choose or refuse testing for other variants once they reach the age of majority (4).

Another pressing issue is determining under what circumstances (if any) IRRs and IFs should be offered to a participant’s or source individual’s genetic kin or broader family (including nongenetic partners and relatives). Kin or family members may already receive a proband’s IRRs and IFs if the proband is a child or an adult without decision-making capacity. In these cases, the kin or family member receives results in his or her capacity as a source of permission for the child to participate in the research or as a source of consent for the adult without capacity. The further issue, however, is whether IRRs or IFs should ever be offered to kin or family members because of the potential implications for their own health or reproductive decision-making. Our research group is examining this issue collaboratively with investigators at the Mayo Clinic in the context of research based in a pancreatic cancer biobank (Disclosing Genomic Incidental Findings in a Cancer Biobank: An ELSI Experiment; NIH, NCI, and NHGRI grant 1-R01-CA154517). Because median life expectancy for probands diagnosed with pancreatic cancer remains short, the questions arise of whether to offer IRRs and IFs of significance to kin or family before or after death of the proband, whether proband consent is needed in order to share these findings, and what the utility and impact of sharing these findings are (57). Recent debate on returning results to kin and family after the proband’s death has focused on whether the shared familial nature of genetics makes a proband’s genetic findings a resource that should be available to kin and family (13, 20) and how this comports with the ethics and law that have traditionally protected individual privacy and confidentiality, including after death (65, 67).

MOVING INTO CLINICAL CARE

The debate over return of IRRs and IFs that I have analyzed so far is a debate over the proper conduct of research. However, with the development of WGS and WES and their increasing
integration into clinical care, concern has surfaced over what to report to patients from the resulting flood of findings. This has led to the emergence of a literature that resembles the literature on return of research results and is often mistaken for guidance on return of results in research, but that actually addresses the question of what to return in a clinical context.

Thus, Berg et al. (7) offer a schema for sorting WGS results into three “bins” that correspond with a requirement to report; an option to report, depending on shared decision-making involving both patient and provider; and an imperative not to report. However, this is all in the context of clinical deployment of WGS. Their bin 1 ("should report") covers results that are “known to cause disease or strongly predicted to disrupt function,” are “medically actionable,” and have “direct clinical utility based on the current literature” (7, p. 501). Their bin 2 ("may report") covers results that are “clinically valid but not directly actionable” (p. 502) in light of the recognition that some patients may want this information. They further subdivide bin 2 into results of low risk and doubtful current utility (bin 2A), results of medium risk and doubtful current utility that may cause distress (bin 2B), and results that may cause high distress (bin 2C). Their bin 3 (“should not report”) covers variants of no or unknown significance.

Although this proposal addresses return of results in the context of clinical use of WGS, there has been debate over where WGS sits in the translational pipeline, whether WGS is ready for clinical use, and, if it is ready, what indications it should be used for. In a 2012 policy statement, the ACMG “recognize[d] that genomic sequencing approaches can be of great value in the clinical evaluation of individuals with suspected germ-line genetic disorders. Although this is an area that will continue to evolve with further research and technological development, there are already instances in which genomic sequencing approaches can and should contribute to clinical care” (2, p. 2). Yet, in that same year, a committee of the American College of Obstetricians and Gynecologists cautioned that, when personalized genomic tests are used to assess predictive risk, they “should be viewed as investigational at this time;” as there is need to assess their validity and utility (3, p. 1318). However, the ACMG in early 2013 issued recommendations on IFs in genome and exome sequencing already being used in clinical care (31). Clearly, WGS is in transition into clinical use and for broadening indications (11).

The ACMG 2012 policy statement on clinical use of genome sequencing directly addresses IFs in WGS and WES (2). The statement acknowledges that when WGS or WES is used for any purpose, IFs “are highly likely, if not inevitable” (p. 2). It goes on to say that labs and clinics need policies on disclosure of IFs and should share those policies with patients. Before testing, individuals should be counseled on what “will or will not be disclosed” (p. 3). The standards for disclosure should be sensitive to whether asymptomatic or affected individuals are undergoing testing. When screening asymptomatic individuals, standards for return should be high to avoid reporting multiple false positives. However, when considering “diagnostic results that are clearly related to a patient’s phenotype or clinical condition . . . a lower threshold for reporting is appropriate” (p. 2). Patients should be allowed to opt out of receiving some IFs, although “exceptional” cases may arise (p. 3).

Against this background, the ACMG’s 2013 recommendations on how to handle IFs in clinical use of genome and exome sequencing are puzzling (31). The recommendations call for deliberate analysis of 56 extra genes whenever clinical sequencing is ordered for a primary indication (such as searching for a treatment target in a patient with advanced cancer). This is an unusual use of the term “incidental findings” to refer to results of a predetermined extra analysis in a patient who will most likely be asymptomatic for the conditions associated with those 56 extra genes. The rationale for this added analysis is that pathogenic variants in those genes may be highly actionable and offer an opportunity for clinical benefit unrelated to the reason for the sequencing. However, the ACMG’s 2013 recommendations depart from other recommendations and even their own
2012 policy by sharply limiting the role of patient choice. If patients want clinical sequencing for their primary indication (such as cancer care), they are compelled to accept the additional, unrelated analysis of the 56 extra genes. The laboratory must then report the analysis of those genes to the patient’s clinician. As the ACMG states, “We recognize that this may be seen to violate existing ethical norms regarding the patient’s autonomy and ‘right not to know’ genetic risk information” (31, p. 568). Indeed, the ACMG’s subsequent clarification statement asserts that failure to report the IFs on its list would be “unethical” (1, p. 1). The ACMG urges the same approach regardless of patient age, rejecting the long-standing consensus to limit pediatric testing to variants of clinical utility in childhood, to preserve the child’s autonomous right to decide on further testing at adulthood (4).

The ACMG 2013 recommendations on IFs have engendered considerable debate (e.g., 51, 80). Those recommendations strip patients of their autonomous right to decide on whether to allow analysis of those extra genes and whether to receive the findings (80). The irony is that when the return-of-results debate began in the research sphere almost a decade ago, one of the strongest arguments for offering IFs to research participants was respect for their individual preferences when they wished to receive this information. Now that sequencing is moving into clinical care, respect for patient autonomy and decisional rights should be heightened, not diminished. Patients’ decisional rights are long-established in the clinic, including the ethical and legal right to refuse even life-saving interventions (80). To impose analysis of extra genes and reject the patient’s “right not to know” threatens to undermine patient confidence that genomic medicine will respect their decisional rights.

THE TRANSLATIONAL FUTURE OF RETURN OF IRRs AND IFs

The fact that recommendations emerging for return of IFs in clinical WGS and WES are so close to recommendations for return of IRRs and IFs in research suggests a way forward for the translational future of genetics and genomics. Recognizing that genetic and genomic analytic tools (including WGS and WES) move over time from research use into clinical care, we may be able to identify a core set of IRRs and IFs that should be offered to the consenting participant. Moving then into clinical sequencing, offering this type of information should be necessary but not sufficient, as treating clinicians have even greater duties to offer information to patients about their health than researchers have to participants.

In refining criteria for return of IRRs and IFs in research, we will need to identify how established and substantial the risk should be, how useful the return is, and whether that usefulness is best judged from the standpoint of what interventions clinicians can offer (clinical actionability) or from the standpoint of what the source individuals find useful (which is likely to be a broader set of findings, including some with reproductive and even personal utility). Although work on returnability now customarily embraces actionability as a core criterion, it remains unclear exactly how actionability should be defined. Nor is it clear why actionability should be limited to findings with health implications, omitting findings with high and established reproductive importance. From the standpoint of source individuals, such reproductive findings may be highly actionable.

In confronting the challenge of return of IRRs and IFs, we are facing the translational nature of genetics and genomics. What is in the domain of research today is quickly moving into the clinic. And it is unavoidable that, in the course of conducting research, we will discover information about source individuals of clinical significance and even urgency. Imaging researchers have already confronted this reality.

The return-of-results debate thus forces us to rethink the traditional dichotomy in ethics (as well as in law) between the domain of research and the domain of clinical care. This old, static
dichotomy was built on premises that are increasingly outmoded. Research on human genetics and genomics is translational science, yielding insights that can rapidly move into clinical care. And in a host of scenarios, researchers seek genetic and genomic insight into burdensome diseases and disabilities while helping individuals and families end their diagnostic odysseys or while shedding light on any remaining interventional options for otherwise terminal disease. Research and clinical care are connecting along a translational continuum. Instead of a wall between the two, we now have a permeable membrane. The return-of-results debate is about how to structure the flow of information through that membrane.

CONCLUSION

The debate on return of IRRs and IFs is ultimately about people. It is about the research participant who does not know that she has a variant associated with malignant hyperthermia or Lynch syndrome, or that she has a BrCA2 variant associated with increased risk of breast cancer. It is about the family enrolling a child with a puzzling and devastating developmental disorder in genomic research, hoping that research to aid others will also yield some clue to the puzzle.

The debate is also about the investigator chafing at the custom of offering no information to participants, no matter how significant and actionable—the researcher troubled by the tradition of silence (12). Nearly 30 years ago, Katz published his classic study of the tradition of silence in the doctor-patient relationship (41). His most famous example was that of a physician who finds himself disturbed shortly before performing a mastectomy on a young woman, troubled by information he had withheld from her. He goes to her bedside to reveal what he had withheld, and it changes her choice of treatment. Katz was tracing the roots of a sea change in clinical care, a change that yielded a duty to share information with patients, to treat them as individual decision-makers entitled to material information about their conditions.

We stand now at the brink of a similarly profound change in research. Research is not the same as clinical care: It seeks generalizable knowledge in order to later yield diagnostics and treatments to benefit the many. But the only way to generate that knowledge is to earn and keep the trust of those people generous enough to participate in research. Even when research is conducted on data and specimens left over from clinical care, the trend is increasingly to recognize that these crucial materials derive from real people, who may continue to incur a privacy risk even if the materials are deidentified, who retain a stake in the responsible use of their materials, and who may benefit greatly in some cases from return of results.

Return of results is the next frontier in the challenge of treating those people whose data and specimens make research possible as partners. Much work remains to be done to develop appropriate criteria for return, efficient and sustainable processes, the evidence base to shape model protocols, and approaches that make sense for individual research projects and biobank research systems. But the silence is broken. The effort has begun to treat research participants and source individuals as indispensable partners in the research enterprise and people with a real stake in learning individual findings of significance.

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LITERATURE CITED

42. Katzman GJ, Dagher AP, Patronas NJ. 1999. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. JAMA 282:36–39
68. Thakuria J. 2010. Managing IFs and IRRs in genomic biobanks and archives. Presented at working group meeting, Managing Incidental Findings and Research Results in Genomic Biobanks and Archives, Washington, DC, June 28–29


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Errata

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