COMMENTARY | Genetics inMedicine

The past, present, and future of the debate over return of research results and incidental findings

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In the past year, the debate over return of research results and incidental findings (IFs) has reached new prominence. An article in *Science* declared the debate "arguably the most pressing issue in genetics today."[1] The director of the National Institutes of Health (NIH), testifying before the Presidential Commission for the Study of Bioethical Issues, called the return of results "a hot topic in every conversation about every genetic research protocol that I'm involved in."[2] The National Human Genome Research Institute (NHGRI) at NIH announced significant new funding opportunities and then created a linked community of investigators to tackle this topic, the Return of Results Consortium.

Debate over return of individual research results (IRRs) and IFs is not new. In 1999, the National Bioethics Advisory Commission (NBAC) published a report on research with human biological materials advocating disclosure of research results if "scientifically valid and confirmed," with "significant implications for the subject's health concerns," and "a course of action to ameliorate or treat these concerns is readily available."[3] NBAC cited 1980–1981 work by Veatch for the proposition that subjects had a "right to know what has been learned about them" and by Reilly suggesting that investigators differentiate three categories of findings: those "of such potential importance … that they *must* be disclosed immediately"; those that "are of importance to subjects … but about which … [the investigator] should exercise judgment" on disclosure; and those "that do *not* require special disclosure."[3,4] It is remarkable how prescient Reilly's work was in anticipating a three-category approach that others have further developed since.[5]

Incidental findings are a well-recognized problem in clinical care, where the term "incidentaloma" has been used to refer to serendipitously discovered masses. In imaging research, the question of how to handle unexpected findings of potential clinical significance has been long recognized, leading to consensus systems for grading the urgency of findings and managing notification of research participants and their clinicians. Many credit the development of ever more sensitive imaging technology with generating a growing number of these findings.

In clinical genetics, the unexpected finding of misattributed paternity or chromosomal anomalies has generated a literature on how to manage that information. And in the research domain, unexpected genetic findings have prompted debate about whether these too—similarly to radiological findings of potential clinical importance—should be evaluated and in some cases offered back to the research participant.[4]

It may have been tempting early on to view the question of how to handle IFs as itself incidental, a peripheral concern that occasionally arises and can be handled easily. But that view has now rightly been discarded. Depending on the research modality, the population studied, and the criteria for identifying a finding of concern, these potentially returnable findings may not be rare.[5] And when researchers discover a finding of well-established and urgent clinical significance, silence has become difficult to defend, especially as research ethics has moved from the language of "subjects" to that of "participants" and has more robustly addressed the needs of participants as vulnerable individuals rather than mere means to scientific progress. Social science research on how research participants themselves view return of IFs and IRRs is crucial and now under way.

As the research community has begun to take a hard look at the problem of how to handle IFs and IRRs of health importance to the individual participant, the problem has begun to loom large. At stake is the fundamental question of what investigators owe the individuals who are generous and trusting enough to participate in research. Some commentators say that investigators owe no more than they did before this problem was fully recognized: informed consent to participation in a study that has been found scientifically worthy, with risks acceptable in relation to potential benefits. A concern from the start has been that any responsibility to do any more—to indentify, evaluate, and return a subset of findings—will divert resources and slow the science. But this merely restates the starting point for the debate. It reiterates the traditional deal between researcher and participant: the participant contributes specimens and/or data but receives no "feedback" (as IFs and IRRs are often called outside the United States) even when clinically urgent and actionable information is discovered.

Reiterating the deal struck in the past does not tell us whether we should reconsider it in light of the emergence of technologies that routinely generate findings of established and serious significance to the research participant, attitudinal data suggesting that participants may want IFs and IRRs, and the evolution of research ethics over time toward models of partnership with

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research participants and greater commitment to recognizing their humanity and informational needs. The recent Advance Notice[6] from the Department of Health and Human Services of possible changes to the Common Rule takes that evolution a step further, toward greater respect for not only research participants but also individuals who are sources of specimens and data used in research, even if the research does not qualify as research on human subjects under the Common Rule because the specimens and data were collected originally in clinical care and identifiers were removed before research.

A growing number of commentators and consensus groups have now concluded that the tradition of silence should yield in some instances to an offer of return. Indeed, it is increasingly hard to find commentators who argue for zero return even when findings are clinically urgent, well-established, and highly actionable. Our research group first examined the issue of return of IFs in an NHGRI-funded project that yielded a 2008 consensus recommendations paper,[5] as part of a larger symposium collecting 17 articles. Further NHGRI funding then allowed us to take the next step and undertake the project that has produced this symposium, widening our focus to IRRs as well as IFs, and progressing to consider large-scale genetic and genomic research involving biobanks and archived data sets.[4] As in the first project, we convened an outstanding and multidisciplinary group of project members, and then reached out to a wider community of researchers to present their work and collaborate with us at project meetings. Our May 2011 public conference in Bethesda, MD, is now archived online (http://www.lifesci.consortium.umn.edu/conferences/2011_ifbb/agenda).

This symposium issue presents the consensus article that emerged from this group process,[7] as well as a large and rich set of articles by project members and others. This 2-year project has taken us from the relative simplicity of an individual research project facing the question of whether to return IFs—the focus of our earlier project—to the modern-day reality of research conducted in what our consensus paper calls a "biobank research system," with primary research and collection sites feeding samples and data into a central repository that, in turn, is supplying secondary researchers with samples and data for further research. As we explain and analyze in the consensus paper, IFs and IRRs can arise at each step in this biobank research system. Figuring out how to plan for and handle such findings is a complicated task that requires grappling with the entire research system and its interconnections. We offer detailed analysis as well as 10 action-oriented recommendations. At the center of our recommendations is the biobank itself (defined broadly to include entities holding collections of specimens as well as those holding collections of data). While recognizing the heterogeneity of biobanks, we offer recommendations that would recognize core responsibilities that would generally rest with the biobank itself.

The debate over how to manage IFs and IRRs is far from over. We hope that our consensus article and the other articles in this symposium make a contribution to progress. But most important may be that we as a research community are having this debate at all. Facing the question of what IFs and research results are owed back to research participants is a crucial next step toward recognizing these participants and contributors as vital partners in the research enterprise. The challenges here are enormous. The prospect of returning IFs and IRRs forces us to rethink the long-accepted division between research and clinical care. And the difficulty of agreeing on what findings are appropriate for return, the challenge of funding and organizing return in a way that avoids overwhelming the research effort, and the task of ensuring responsible interpretation of findings and clinical follow-up are daunting. The debate will probably heat up and the obstacles loom larger before the pathway to best practices and evidence-based solutions becomes clear.

Indeed, concepts on which many commentators currently rely in this debate will need more work. Right now, many recommendations place only findings of health importance in the "should return" category, even though individuals may assign high importance to findings with major reproductive implications. After all, genetics is about families, and many research participants may see information that would allow them to avoid passing on devastating conditions to their children as even more important than information about their own health. And even though most recommendations to date have conditioned "should return" on the "actionability" of findings, it remains unclear precisely what that means. It is debatable whether the utility of findings should be viewed from the standpoint of clinicians, the standpoint of individual participants, or some combination.

Where is this debate over return of IFs and IRRs headed? The answer lies in the history itself, a history of progress toward recognizing the humanity and informational needs of research participants. Increasingly, participants will be offered individual information. Limits will be set, to preserve the capacity to perform research and to protect participants from faulty information. And not all studies and biobanks will undertake individual return. It will take years of research and work to tailor return to serve participants' needs and research realities.

Meanwhile, our work in this symposium and that of our many collaborators and commentators attempts the next big step—bringing the debate over return of results and IFs into the complex world of large-scale genetic and genomic research using biobanks. The pages that follow represent a shift to grappling more fully with the real world of genomic research, to offering a more developed dialogue over IFs and IRRs with new insights and new reservations, and to progressing toward even greater appreciation of the needs of the individuals who participate in research. Debating return of IFs and IRRs in genetic and genomic research involving biobanks is the next step toward recognizing research participants, as well as those who contribute specimens and data, as genuine and essential partners in the research process.

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DISCLOSURE

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