

## Return of results: not that complicated?

James P. Evans, MD, PhD<sup>1,2</sup> and Barbra B. Rothschild, MD<sup>3</sup>

The return of results (ROR) to research subjects in genetic studies has generated tremendous controversy. It is a topic that has caught the attention of a wide range of stakeholders and opinion-makers and resulted in the spilling of voluminous ink. Indeed, this month we feature an issue entirely devoted to the subject. There are many difficult dilemmas to be confronted, which, along with a number of intriguing solutions, are presented in this special issue of *Genetics in Medicine*.

At the risk of oversimplifying an admittedly highly complex set of issues, it may be worthwhile to start from first principles as we attempt to navigate this complicated topic. In this essay, we begin with a few well-accepted ethical principles, a consideration of the central intent of research, and the nature of those results likely to be generated in a genetic study. From that foundation, we attempt to formulate some coherent conclusions that might offer guidance to both researchers and potential subjects as we struggle with this topic.

We start with the following principles that we suspect are relatively uncontroversial:

- Research is a communal endeavor, the overarching purpose of which is to advance a widely shared goal: scientific and medical progress.
- Researchers have an ethical obligation to minimize harm to subjects.
- When possible, subjects should benefit from the research that they enable through their participation. However, individual benefit to the subject is not the *raison d'être* of research.
- Subjects should be given a comprehensive description of the research in which they are asked to participate and should have a free choice of whether to participate or not.
- When information of a medical nature is provided to subjects, it should be reliable, meaningful, and communicated in a responsible manner.
- Transparency in the consent process is essential, including (as precisely as possible) a clear description of what kinds of results will and will not be returned.

So, beginning with these principles, how do we apply them when a subject undergoes whole-genome sequencing? After all, in any such analysis, millions of variants will be generated. How do we determine which of those results should be returned?

We argue that there exists an obligation to return incidentally discovered variants when two conditions are met: (i) when evidence exists demonstrating that a variant is firmly associated with disease or a high risk of disease and (ii) when specific strategies, contingent upon the result in question, have been documented to ameliorate expected morbidity or mortality. A clear example would be the discovery of a mutation in a mismatch repair gene such as *MSH2*, which confers a high risk of colorectal (and other types of) cancer upon an individual and for which there exist well-supported strategies to lower those risks. Such information is life-saving; the offer of its provision not only stands to reduce morbidity and mortality in the unsuspecting research subject if revealed, but a failure to do so will arguably tangibly harm that individual. Researchers have an ethical obligation to share (or at least make a concerted effort to share) such results with their subjects. Because of this ethical obligation, the so-called “opt out” option should not be offered to subjects. By making it clear at the outset of a study that subjects will be approached in this unlikely event, a balance is struck that satisfies both the ethical imperative of the researcher to do no harm and the autonomy of the subject.

There exist only a handful of genes in the human genome in which mutations meet the aforementioned criteria. These genes have been labeled “bin 1” genes in a recently proposed scheme intended to categorize human genes into three broad bins based upon clinical parameters.<sup>1</sup> Bin 1 contains those genes in which the discovery of a mutation would trigger specific medical action and provide definable medical benefit (i.e., possess clinical utility). Bin 2 contains genes known to be associated with human disease or disease risk but for which evidence does not support any specific action (i.e., bin 2 genes demonstrate clinical validity but not clinical utility). Finally, bin 3 contains all other human genes, whose role in, or association with human disease is unknown.

We have estimated that there exist fewer than 100 such “bin 1” genes in the human genome at present. Thus the odds are low that any individual undergoing whole-genome sequencing will be found to have a mutation in a gene necessitating ROR. The vast majority of variants discovered in any individual will, rather, be in one of the two remaining bins. An example of a variant in a bin 2 gene would be discovery of one's *ApoE* status. Although the association between Alzheimer disease and the specific variant an individual carries is clinically valid,

<sup>1</sup>Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; <sup>2</sup>Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; <sup>3</sup>Department of Social Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Correspondence: James P. Evans ([jpevans@med.unc.edu](mailto:jpevans@med.unc.edu))

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there exist no specific interventions to ameliorate the conferred risk. A few thousand genes currently would be categorized in bin 2 and would include, for example, most genes associated with Mendelian diseases for which no clear ameliorative interventions have been documented. It is difficult to envision an *obligation* to inform subjects of their bin 2 variants when incidentally discovered, given the fact that there exist no evidence-based criteria by which to employ this information to improve their health. Finally, the vast majority of variants generated in a whole-genome sequence will be found in genes that have no known association with human health (bin 3). Again, it is difficult to argue that any obligation exists to return that information to a given subject.

The advent of genome-wide association studies has identified a host of variants that subtly affect risk for a variety of diseases. For the most part these “single-nucleotide polymorphism risk” results fall into the (at best) clinically valid (bin 2) category and thus fail to meet any bar necessitating their return to subjects. The vast majority are unconfirmed, carry no demonstrated clinical utility, or both. Indeed, in a recent investigation the same DNA sample was sent to different providers of such testing.<sup>2</sup> The wildly different results obtained (which labeled the same individual as being at high, low, or average risk for a variety of diseases) demonstrate that we have not even achieved clinical validity with such tests, much less, clinical utility. To put it another way, no one really even knows how to interpret genome-wide association study-identified risks; it therefore seems a profound stretch to argue that an obligation to return such information exists.

One may counter with the objection that “some subjects may want such information”. Great! That is precisely the business model upon which a host of direct-to-consumer genetic testing companies have been founded. Individuals are free to obtain such information through that route or through consultation with a medical provider. But it undermines the central intent of the research endeavor to attempt to turn it into a mechanism for satisfying the curiosity of potential subjects by providing tantalizing—but essentially meaningless—information. Research is a broad endeavor with the goal of communal benefit in which subjects agree to place themselves at some inconvenience (and some risk) in order to advance scientific knowledge. Subjects may legitimately expect that they could, under certain circumstances, personally benefit from participating. For example, the participant may occasionally greatly benefit from whole-genome sequencing when they learn the unexpected news that they have a mismatch repair mutation that predisposes them to preventable cancer. Given the confirmed benefit that such knowledge conveys, a strong argument exists that there is an obligation to return those results. But it is not part of the research compact—and we do subjects no favors—to return results of questionable (or no) demonstrable meaning or significance. By doing so we simply perpetuate the “therapeutic misconception” that is already too pervasive.<sup>3</sup> The research compact is a voluntary arrangement and if subjects are unsatisfied with what they stand to receive in return for their participation, they simply need not participate.

An overly broad imperative to return information to subjects not only threatens to undermine the central goal of research, diverting it from the common good and turning it into a pseudocommercial or pseudomedical arrangement, it also threatens to pile tremendous new costs on an already strained system. Any clinically relevant results that are to be returned to subjects must be confirmed in a Clinical Laboratory Improvement Amendments–certified laboratory, a nontrivial issue in terms of money and time. Moreover, the actual return of that information must be done by someone with some degree of clinical training. If ROR fails to meet the twin requirements of reliability and responsible context of return, we simply spew unreliable information to research subjects and create a false aura of reliability around results that we actually do not understand.

The argument is sometimes made that offering to return a wider array of results to subjects will increase participation in research. Although this may be true, such arguments are irrelevant and not a little cynical. We might improve enrollment in research studies by offering free horoscopes to potential participants. Does that mean we should do so?

The participation of both researchers and subjects in a research study is voluntary. If subjects do not find the terms of a study agreeable, they are free to decline participation. Indeed, some may well feel that without access to all of the information generated from their sample they will not agree to be a subject in a given study. The principle of subject autonomy requires that they have that right. Likewise, a researcher designing a study is free to offer a wide range of returned results. As long as those results are analytically valid and delivered responsibly, this seems acceptable. However, the researcher is, in our opinion, under an overt obligation to return only those results that would result in documentable harm to a subject were they withheld.

We argue that ROR (or at least an obligatory discussion with subjects reporting that such results have been uncovered) is mandatory when a deleterious mutation is discovered in a bin 1 gene. Thus, the categorization of those genes that fall within bin 1 is a critical task. We suggest that a centralized process that involves experts and stakeholders be established to determine those genes for which sufficient evidence exists to warrant inclusion in bin 1 and therefore ROR in the event of an incidental discovery. Obvious candidates for bin 1 are the Lynch-associated mismatch repair genes, such as *MSH2* discussed earlier, since withholding such information would result in harm. Other likely candidates would be *RET* mutations associated with multiple endocrine neoplasia type 2 and deleterious mutations in the *FBNI* gene given strong evidence that aneurysm rupture is both likely and preventable. Such deliberations will not always be clear-cut. But by centralizing the process, researchers and subjects will be able to refer to a transparent set of guidelines to inform this complex issue and know where they stand with regard to their obligations to return results. Such a (necessarily iterative) process could be similar to how diseases are currently considered for inclusion in newborn

screening panels by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children.<sup>4</sup> All will not agree into which bin every gene in the human genome should be assigned. However, by establishing a centralized and transparent process for categorization, both researcher and subject will be free to make decisions about study design and participation with full knowledge of what is expected of them and what they can expect in return. Subjects' expectations (and researchers' obligations) will also need to have some time limits placed upon them, because today's bin 3 gene may well be tomorrow's bin 1 gene. Therefore, it will be critical for informed consent to include a time limit during which an individual may expect that bin 1 results would be communicated to them, including results newly categorized as bin 1 during the study.

ROR is a fraught topic that raises complex questions of responsibility, obligation, and the limits of paternalism. Many approaches can be envisioned that are tailored to the needs of both researchers and subjects. But the key question is how to establish the minimum obligation to which researchers should

be subject. We feel that the approach outlined here preserves the central intent of the research endeavor—the advancement of communal knowledge—while also respecting the rights of individual subjects and ensuring that they are not harmed.

## DISCLOSURE

The authors declare no conflict of interest.

## REFERENCES

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