

# Returning Results: Let's Be Honest!

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Biobank research has the potential to return results that could have beneficial and even life-saving consequences for participants. This possibility raises some important questions, not only about the ethical duty to return results within a research setting, but also about participants' right to refuse results and researchers' responsibility to respect that choice. This article argues in favor of adopting a return-of-results policy that limits participants' ability to refuse clinically relevant and actionable results. We state that biobanks should allow donors only if they are aware of and agree to this return policy. If they do not agree to this, they retain the option not to participate in the biobank research. The aim of this article is to discuss the practical and ethical reasons in favor of this return-of-result policy and, thus, to underline the importance of "honesty" in biobanking regulations.

**Keywords:** biobanking, return of results, policy, refusal, honesty

## Introduction

RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIAL and data not only holds the promise of increased understanding of interactions between genetic and environmental factors (Olson *et al.*, 2014; Virani and Longstaff, 2015), but it also has the potential to provide to sample donors individual results that could have beneficial and even life-saving consequences (Pullman and Hodgkinson, 2006; Knoppers and Laberge, 2009; Haukkala *et al.*, 2013; Olson *et al.*, 2014). For example, it might be revealed that a donor tests positive for adenomatous polyposis and is at high risk of developing colon cancer. If results are disclosed, the patient can receive early treatment, avoid cancer, and lead a healthy life.

For the past 15 years, the return of results has been a highly controversial issue in the field of biobanking (Knoppers *et al.*, 2006; Halverson and Ross, 2012a; Wolf *et al.*, 2012; Wolf, 2013). Although there is growing consensus about the ethical obligation to return results (Faucett and Davis, 2016)—and guidelines generally recommend communicating research results to participants (Beskow *et al.*, 2012; Richards *et al.*, 2016)—a legal duty in this respect remains questionable (Knoppers *et al.*, 2006). The problem, in fact, is that non-disclosure might expose researchers to legal liability for negligence and in the long run impede research. Furthermore, disagreement continues to exist on the cost-effectiveness and feasibility of returning results.

The idea of an ethical duty to return results finds support in the increasing number of studies that explore donor attitudes

regarding the return of results. A recent study examined the perspective of relatives of deceased patients who had contributed samples to a cancer biobank. Most of them reported altruistic attitudes. They felt obligated to "share their results with blood relatives while alive" and would "want results to be shared with relatives after their death" (Breitkopf *et al.*, 2015). Another study showed that parents of children included in hypothetical biobanks considered biobanks more beneficial if they returned results (Holm *et al.*, 2015). More than 90% of surveyed stakeholders in a third study believed that the return of results is important when considering participation in biobanks (Frye *et al.*, 2015). People's higher satisfaction with biobanks that do disclose findings may explain why returning results, for example, in form of a "personal gene card," has been used to influence the willingness of healthy individuals to participate in a biobank (Tasmuth, 2003). It is also regularly mentioned as a means to implement personalized medicine (Kuriyama *et al.*, 2016).

Although most biobanks are designed as pure research instruments and often lack resources to return results to participants or their families (Petersen, 2015 R11) (Mee *et al.*, 2013), studies assessing participants' preferences for disclosure of results seem to have had some influence on the domain of biobanking. In fact, it has become an emerging practice for many biobanks to integrate technology to return at least some research results to participants (Barazzetti *et al.*, 2017 in this special issue).

For example, the Geisinger Health System in the United States uses MyCode, a "system-wide biobanking program to

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link samples and electronic health record (EHR) data for broad research use". MyCode allows donors to be recontacted and has thus facilitated the return of clinically actionable results to participants since 2013 (Carey *et al.*, 2016). Also, the Partners HealthCare Biobank in Boston and the Mayo Clinic Biobank in Rochester (Minnesota) have chosen to return research results (Olson *et al.*, 2013). The former biobank informs research participants that they will receive a letter whenever a potentially meaningful research result is found and that "an appropriate practitioner"—a physician, a nurse, or genetic counselor—will contact them to explain the results. As only certified clinical laboratories can deliver clinically recognized results in the United States, the practitioner will propose to redo the testing to confirm the research results. The biobank respects participants' right not to know: they have the right to decline disclosure of results (Olson *et al.*, 2013; Karlson *et al.*, 2016).

The debate surrounding the right to refuse clinically relevant results received particular attention in 2013 when the American College of Medical Genetics and Genomics (ACMG) released a practice statement urging analysis of 56 genes whenever clinical sequencing was undertaken, with no opportunity for patients to decline the extra analysis (Green *et al.*, 2013). Although the ACMG has in the meantime changed its guidance on clinical sequencing by permitting patients to opt out (ACMG, 2015), it has highlighted a tension between participants' rights, preferences, and well-being.

This dilemma had been identified already many years ago in a study on arrhythmogenic right ventricular cardiomyopathy—a lethal autosomal dominant cause of sudden cardiac death in young people—which was carried out in Newfoundland and Labrador, two areas where this disease has a high prevalence (genetic subtype ARVD5) (Pullman and Hodgkinson, 2006). Two study participants who had refused to receive results were found to be carriers of the mutation. One of them was informed against his will because he was working in a public transport position and thus could place the general public at risk in case of a cardiac event while driving (Pullman and Hodgkinson, 2006). The second participant was not informed out of respect for his initial refusal. Although his death could have been prevented, he died at a very young age (Pullman and Hodgkinson, 2006).

This study raises some important questions, not only about the ethical duty to return results within a research setting (Samuels *et al.*, 2008; Hodgkinson *et al.*, 2009) but also about participants' right to refuse results and researchers' responsibility to respect or override that choice. The researchers in Pullman's and Hodgkinson's study discussed the need for policies that do not offer the option of refusing disclosure of life-saving results.

Unfortunately, the beneficial consequences of returning results to biobank participants are still not well studied and randomized studies are scarce (Kullo *et al.*, 2015). Benefits heavily depend on the type and penetrance of a particular disease. In the case of a monogenetic disease with high penetrance, for example, the disclosure of results will have important implications as it will enable the donor to start potentially life-saving treatment immediately. In other situations, the benefits might be less direct. The discussion is further complicated by the distinction between research results and incidental findings (Olson *et al.*, 2014) or so-called unexpected results that are not related to the original research purpose. This distinction is difficult to maintain in biobank

research as future research projects are yet unknown and, therefore, research results cannot yet be fully anticipated.

The aim of this article is to underline the importance of *honesty* in biobanking regulations. Striving for honesty is crucial to build public trust and support for research (Resnik, 2015). To be operationally and financially sustainable, biobanking depends on public goodwill and trust. Trust, in fact, is essential for the recruitment of research participants and for receiving funding from granting agencies. Still, the trust that society places in science is fragile and needs to be nurtured and protected (Yarborough, 2014). Of course, the public is not uniform and might have different expectations of research (Resnik, 2015): although there seems to be a general expectation that results will be disclosed, some donors invoke the right not to know. Given the impossibility to honor these divergent expectations, policies should clearly explain which expectations will be fulfilled (Resnik, 2011) and which expectations (e.g., respect for autonomy) will be overruled in the name of other ethical principles, such as beneficence.

Despite it posing many difficulties, we argue in favor of adopting a return-of-results policy that limits participants' ability to refuse clinically relevant and actionable results. We state that biobanks should allow donors only if they are aware of and agree to this return policy. If they do not agree to this, they retain the option not to participate in the biobank research. The aim of this article is to discuss the practical and ethical reasons in favor of this return-of-result policy. We start by providing an overview of the practical and ethical barriers to returning individual biobank results.

### Practical Issues Related to the Return of Results

A number of practical issues interfere with or even prohibit biobank policies to return results. One of the most persistent is financial feasibility (Black *et al.*, 2013; Bledsoe *et al.*, 2013). However, the cost argument is also an ethical issue given that limited resources raise questions of ethically justified distribution.

Another frequently discussed barrier is operational feasibility. Questions concern issues such as who should be responsible for keeping contact addresses up to date, who should contact participants (physicians or other healthcare providers) (Elger *et al.*, 2008; Elger, 2010), and which means of contact should be used (Coors *et al.*, 2015) given that research participants have various preferences and expectations? For example, in a recent study including young patients undergoing treatment for substance and conduct problems (SCPs) and members of a control group, a majority (close to 70% in both groups) reported phone recontact as the "best" option, whereas a substantial majority in the range of one-fifth to one-third considered recontact by e-mail or social networking websites as viable options (Coors *et al.*, 2015). The feasibility of recontacting is negatively affected by the way in which many current biobanks are organized. An example is the Biobank Ireland Trust that has decided to adopt an organization where results will not be returned (Mee *et al.*, 2013). Special problems exist concerning pediatric biobanks, as most of them do not recontact children at the age of maturity to ask for their choices and address updates (Salvaterra *et al.*, 2012).

Another difficulty concerns the question of which results need to be returned. Many published recommendations require that results that are returned need to be accurate (or

valid) and actionable (Knoppers and Laberge, 2009; Wolf *et al.*, 2012). However, the definition of what constitutes an accurate and actionable result is not clear-cut and often varies in practice. This is shown by the recent controversy surrounding the policy statement of the ACMG (Wolf *et al.*, 2013), which calls for clinical genetic testing laboratories to always obtain and return results of a defined list of “pathogenic and likely pathogenic variants” in 57 specified genes without patient consent (Green *et al.*, 2013). The ACMG has been widely criticized not only because of the lack of patient consent but also because of scientific reasons as to the choice of the 57 genes (May, 2015; Richards *et al.*, 2015).

Another practical difficulty when returning results, particularly in the United States, is that patient care requires validation of results in a Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratory (Olson *et al.*, 2014). However, research results are generally obtained from laboratories that are not CLIA approved.

Finally, a practical as well as legal issue follows from the unresolved question of who is responsible for organizing and granting the return of results (Hawkins, 2010). Researchers fear liability if they promise to return results. The existing legal uncertainty “may lead to unmanaged variation in practice and poor quality care” (McGuire *et al.*, 2014). Indeed, return of results blurs the line between research and healthcare obligations. Delivering individual results to patients falls within the obligation of healthcare providers and has traditionally not been an obligation of researchers. In practice, this creates organizational and practical difficulties as to whether and how researchers should collaborate or team up with clinicians and divide or share the responsibilities related to the return-of-research results.

### Ethical Issues Related to the Return of Results

Research participants’ and patients’ right to know as well as the right not to know their results has been widely established in international conventions and ethical guidelines (President’s Commission, 1983; Europe, 1997; Domaradzki, 2015; Sheehan, 2015). The right not to know is supported by reference to the ethical principle of respect for autonomy (President’s Commission, 1983). Although the knowledge of a genetic predisposition may help to treat the disease early or prevent it altogether, there is also the risk that participants might be harmed by discrimination and stigmatization, especially in the case of a serious future disease or a mental disorder. Although respect for autonomy is a widely agreed-upon principle, the question remains of exactly how much choice participants should have to grant respect for autonomy.

Results from public consultations and patient and professional surveys show various attitudes regarding the return of results (Hens *et al.*, 2009; Caulfield *et al.*, 2012; Halverson and Ross, 2012a; Lemke *et al.*, 2012).

Researchers feel that they have variable duties: in a recent study, most researchers (74%) indicated that participants have to be informed when results have implications for treatment or prevention (Meulenkamp *et al.*, 2012). Within the context of pediatric biobanks, scholars regularly refer to children’s right to an open future to restrict the return of results (Hens *et al.*, 2011). The idea is that children should have the greatest possible scope to exercise their personal life choices and that parents should not make decisions that might compromise this right.

A recent study on the preference models that parents have for their children (who participate to biobank research) (Bacon *et al.*, 2015) shows that parents’ choices on disclosure of results were influenced by the gravity of the disease and by possible preventive measures. Parents, however, were also concerned that research results may have negative psychological effects on the child. Overall, the study findings indicate that parents need support to make such choices and the authors propose the creation of educational tools.

Like researchers, the general public seems to have a strong desire to obtain access to individual research results (Murphy *et al.*, 2008) but tends to focus on clinically actionable results.

Biobank participants, in contrast, are often interested in receiving as much information as possible (Husedzinovic *et al.*, 2015). Haukkala *et al.* studied the attitudes of participants enrolled in a population biobank study who received information concerning an unexpected genetic result. The participants indicated that they perceived this information process as mainly positive. They “considered that delivering genetic information about a life-threatening, but actionable condition has more beneficial than adverse consequences” (Haukkala *et al.*, 2013). Even patients suffering from stigmatizing diseases seem to follow this trend. Indeed, in a recent study, 78% of young participants suffering from SCPs and 73% of control group participants without SCP would like to receive results about their health, including those that have behavioral implications (Coors *et al.*, 2015). The authors conclude that even vulnerable populations want to know individual research results. “Data from this special and vulnerable population, which includes youth involved in the criminal justice system and substantial minority participation, bring an essential and missing perspective to the discussion of RIR [return of individual results]” (Coors *et al.*, 2015).

What follows from the desire of most, but not all, stakeholders to know? If the return of research results causes additional costs, how then should we balance patient autonomy with interests of biobanks and researchers? Research might proceed more quickly and efficiently if resources are invested mainly in the biobank and not for return-of-results technologies and practices. Some stakeholders think that returning results is ethically unjustified as biobanks should serve public rather than individual health interests (Forsberg *et al.*, 2009). So the question arises: does respect for autonomy imply that biobank participants have the right to a maximum of options, that is, to choose which results are returned and when (Hens *et al.*, 2011)?

In the following section we will address this question and propose a solution that takes into account and responds to the practical and ethical concerns.

### In Favor of a Pragmatic and Honest Solution

From a practical and ethical point of view, a variety of justifiable solutions exist concerning the return of results. Valid arguments can be made that resources for return of results should be minimized to maximize resources for further research and advancement of knowledge that profits public health. However, honesty imposes limits on this kind of governance of biobanks. The principle of respect for autonomy implies that research participants should receive truthful information to enable them to make informed decisions about participating in biobank research. Honesty is the foundation needed to create trust between physicians,

researchers and research participants, patients, or the public. Trust is critical for any biobank project (Halverson and Ross, 2012b; McWhirter *et al.*, 2014; Ma *et al.*, 2015) to encourage participation, that is, transparent and truthful communication is not only ethically and legally required to ensure valid consent but it is also important to render biobank research possible, which depends on the willingness of a great number of participants to make their samples and data available.

Pragmatic solutions exist to promote honesty and grant feasibility. The first and most important step is to accept that respect for the right not to know has ethical and legal limits and biobank participants should not be promised something that cannot be granted. As biobank research is evolving constantly, at the time of enrollment, full information about future uses and future types of results is impossible. It cannot be excluded that research findings will emerge that might save the life of participants and others involved (Pullman and Hodgkinson, 2006).

Even if a research participant is not a bus or train driver, many people drive cars and might endanger the lives of others if they are affected by a disease that causes sudden death. Even if they are the only passenger in the car, the accident will often involve other vehicles or pedestrians. Practically all countries have laws that permit overriding patient wishes in circumstances in which the lives of others are at stake.

Although it remains important to “be respectful of the public” and thus to make sure that biobank guiding principles and operations are “responsive to and inclusive of the values and beliefs of their participants” (Lemke *et al.*, 2012), respect for autonomy does not include unlimited rights. It surely entails the right to refuse participation in research, but not the right to have all theoretically possible choices. Indeed, autonomy rights of participants to request particular options might be limited by those of researchers. Those autonomy rights provide the latter with the possibility to limit participation to persons who accept that researchers have a moral duty to inform participants about results that might save their lives or those of others. If biobank participants are informed honestly, they will know that their right not to be informed is limited, because of legal obligations to protect others and because of moral obligations recognized by many researchers and biobankers as part of the ethical principle to avoid harm.

A practical and medical problem remains as to the definition of the thresholds of what is to be considered a sufficiently serious harm to health and what kind of research results are sufficiently valid and actionable. As medical knowledge evolves over time and new medical facts are expected to be available in the future, an ethical return-of-results policy must remain open to those future changes.

Procedural solutions to enact this flexibility involve the implementation of an expert commission that will make decisions about which types of future results fall into these categories. This type of expert commission could be part of each biobank, or could even be an international medical body that makes recommendations to biobanks worldwide.

The honest statement in the patient information and informed consent documents would, therefore, contain a sentence similar to the following: if research results have a serious and potentially beneficial impact on the health or life of a participant or disclosure is needed to prevent serious harm to others, the biobank will return results to the participants’ treating physicians. Indeed, as it is difficult for indi-

vidual biobank participants to assess the clinical significance of a research finding, biobank policies should not only define a procedure on how decisions on clinical significance are made, but also avoid unrealistic burdening of participants with information that is too complex for them to understand adequately (Vermeulen *et al.*, 2014). Therefore, according to the great majority of published studies, individual research results need to be provided and explained to participants by a physician or genetic counselor.

This solution is feasible and costs are limited. First, “financial and logistical complications” (Samuel *et al.*, 2012) can be minimized, thanks to scientific advances. Technical solutions exist, for example, tools to compare and manage results and the process of returning them to participants’ treating physicians (Bemmels *et al.*, 2012).

Second, the main costs of research will fall into the realm of health insurance if a serious disease requires follow-up and/or genetic counseling (Virani and Longstaff, 2015) or—further testing, for example, in a CLIA-certified laboratory in the United States. The treating physician can also find a way to protect participants efficiently against avoidable harm that might result from the received genetic knowledge. With regard to the principle of the child’s right to an open future, it is important to emphasize that it can also be used in support of the argument to return results. Indeed, in case of a preventable serious disease, the child’s future will be significantly compromised if the information is not transmitted and irreversible health changes take place that cause the child to suffer, remain impaired, or even die (Hens *et al.*, 2011).

Honest communication policies should also prevent false expectations and inform participants on the probabilities of benefiting from individual return of results. The honest solution for returning results should thus avoid any therapeutic misconceptions that could follow from expectations of regular clinically useful return of results. A study has shown that therapeutic misconceptions are frequent and are a bidirectional phenomenon, for example, researchers and biobankers might encourage exaggerated expectations to recruit participants (Halverson and Ross, 2012c).

## Conclusions

In the controversy about the returning of research results (including incidental findings) to research participants, one main aspect is not sufficiently recognized and considered: the moral—and in the case of significant harm to others in many jurisdictions also legal—obligation to override a biobank participant’s right not to know.

It is important to communicate these limitations honestly to those who provide samples and data to a biobank. Given technological advances and the existence of simple, pragmatic solutions, it is no longer credible to refer to financial and operational feasibility as unsurmountable barriers to return results. Insisting that participants have the right to have a maximum of options—wrongly used as a barrier to show that returning results is unrealistic—is also devoid of thorough ethical justification.

Biobanks should accept the increasing ethical consensus about returning results that are life saving and prevent serious harms. A pragmatic and ethical solution is to set up a default policy that informs participants about how serious diseases and clinically valid and actionable results are defined and

transmitted to their treating physicians while maintaining the choice to abstain from participation in the biobank.

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