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ARTICLE

The emergence of an ethical duty to disclose genetic research results: international perspectives

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The last decade has witnessed the emergence of international ethics guidelines discussing the importance of disclosing global and also, in certain circumstances, individual genetic research results to participants. This discussion is all the more important considering the advent of pharmacogenomics and the increasing incidence of 'translational' genetic research in the post-genomic era. We surveyed both the literature and the ethical guidelines using selective keywords. We then analyzed our data using a qualitative method approach and singled out countries or policies that were representative of certain positions. From our findings, we conclude that at the international level, there now exists an ethical duty to return individual genetic research results subject to the existence of proof of validity, significance and benefit. Even where these criteria are met, the right of the research participant not to know also has to be taken into consideration. The existence of an ethical duty to return individual genetic research results begs several other questions: Who should have the responsibility of disclosing such results and when? To whom should the results be disclosed? How? Finally, will this ethical 'imperative' become a legally recognized duty as well?

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Introduction

The last decade has witnessed the emergence of international ethics guidelines individual to genetic research involving humans (Table 1). Focusing mainly on these international texts, is there an ethical obligation on researchers to disclose genetic research results to participants or even to provide access to them? Authors of a recent article on the return of research results contend that: 'There are no conditions under which an offer of disclosure of research results should not be made.'[1] This approach is problematic in that whereas on the one hand, the return of clinical trial results (Table 2) relevant to health has long been the norm,[2,3] on the other hand, fundamental research (Table 2) results are by their very nature not individually identifiable, understandable or significant. Early genetic association studies imperfectly predict the development and severity of a condition. Associations with disease are often not validated in more extensive studies and could mislead participants to overestimate the significance of the results.[4,5] Indeed, 'the difficulty in deciding whether to return research results lies in the fact that exploratory genetic factors have not yet reached the point of general clinical acceptance.'[6] Yet, it is self-evident that ongoing communication with participants is important in order to respect their voluntary decision to continue or to withdraw once they have agreed to participate in research as well as to recognize the importance of their altruistic contribution to the progress of research in the field of genetics.

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Table 1 Selected policies and guidelines concerning the duty to return research results

Scope	*Organization*	*Title*	*Date*	*Genetic specific?*[a]
International	Pharmacogenetics Working Group	Returning Genetic Research Results to Individuals: Points-to-Consider	2006	Yes
	UNESCO, International Bioethics Committee	International Declaration on Human Genetic Data	2003	Yes
	World Health Organization	Genetic Databases: Assessing the Benefits and the Impact on Human and Patient Rights	2003	Yes
	Council for International Organization of Medical Sciences	International Ethical Guidelines for Biomedical Research Involving Human Subjects	2002	No
	Pharmacogenetics Working Group	Elements of Informed Consent for Pharmacogenetic Research	2002	Yes
	Human Genome Organization	Statement on DNA Sampling: Control and Access	1998	Yes
	World Health Organization	Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services	1997	Yes
	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	Good Clinical Practices – Consolidated Guidelines	1996	No
	Human Genome Organization	Statement on the Principled Conduct of Genetic Research	1996	Yes
	World Medical Association	Declaration on the Human Genome Project	1992	Yes
	Council for International Organization of Medical Sciences	International Guidelines for Ethical Review of Epidemiological Studies	1991	No
	World Medical Association	Declaration on the Rights of the Patient	1981	No
	World Medical Association	World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects	1964 (2000)	No
Regional (Europe)	European Commission Expert Group on Genetic Testing	25 Recommendations on the Ethical, Legal and Social Implications of Genetic Testing	2004	Yes
	Council of Europe	Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research	2004	No
	European Federation of the International Epidemiology Association	Good Epidemiological Practice (GEP) Proper Conduct in Epidemiologic Research	2002 (2004)	No
	European Parliament — Council of the European Union	Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of laws, regulations and administrative provisions of the Members States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use	2001	No
	Council of Europe	Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine	1997	No
	European Parliament– Council of the European Union	Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data	1995	No
National (United Kingdom)	Nuffield Council on Bioethics	Pharmacogenetics: Ethical Issues	2003	Yes
	Medical Research Council	Human Tissue and Biological Samples for Use in Research- Operational and Ethical Guidelines,	2001	No
National (United States)	NHLBI Working Group on Reporting Genetic Results in Research Studies	Reporting Genetic Results in Research Studies	2006	Yes
	Consortium on Pharmacogenetics	Ethical and Regulatory Issues in Research and Clinical Practice	2002	Yes
	National Bioethics Advisory Commission (NBAC)	Research Involving Human Biological Materials: Ethical Issues and Policy Guidance	1999	Yes
	United States Government	Clinical Laboratory Improvement Amendments Regulations (CLIA)	1988	No

Table 1 (*Continued*)

Scope	*Organization*	*Title*	*Date*	*Genetic specific?*[a]
National (Canada)	Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada	Tri-Council Policy Statement — Ethical Conduct for Research Involving Humans	1998 (2000, 2002, 2005)	No
	Canadian College of Medical Geneticists	Policy Statement Concerning DNA Banking and Molecular Genetic Diagnosis	1991	Yes
National (France)	National Consultative Bioethics Committee	Opinion and Recommendations on 'Genetics and Medicine: from Prediction to Prevention'	1995	Yes
National (Singapore)	Bioethics Advisory Committee	Genetic Testing and Genetic Research	2005	Yes
Local (Quebec, Canada)	Quebec Network of Applied Genetic Medicine	Statement of principles: Human Genomic Research	2000	Yes

[a]Does the selected policy/guideline broadly apply to all type of research (including genetic) or does it specifically address genetic research?

Table 2 The research continuum

Fundamental research	Although there is no unanimously accepted definition of what constitutes fundamental research, in practice one can identify and distinguish from other types of research those that are carried out with no direct link to a given application and, if not exclusively, in any case and above all with the intent of progressing scientific knowledge (see Commission of the European Communities, *Communication from the Commission. Europe and Basic Research*, Brussels, 2004)
Translational research	This emerging type of research aims to validate new genetic tools, assays and other analytical processes and to assess their clinical validity and utility before their introduction in the clinic.
Clinical trials	Any investigation in human research participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy (see International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *Guidance for Industry E6 Good Clinical Practice Consolidated Guideline*, Geneva, 1996)

Recently, as concerns research involving human participants, authors have begun promoting the return of all peer reviewed results whether negative or positive.[1] More specifically, some maintain the need to return individual genetic research results to participants.[7] Several factors are contributing to the transfer of this approach to the specific field of genetic research. The first is a confusion in the ethics guidelines between fundamental results and clinical trial results (see in particular such 'conflation' in the European Federation of the International Epidemiology Association (IEA)'s *Good Epidemiological Practice (GEP), Proper Conduct in Epidemiologic Research*[8] and in the Canada's three granting councils' *Policy Statement: Ethical Conduct for Research Involving Humans*.[9] The second is the influence of general research ethics guidelines and of personal data access legislation mandating access to results.[10,11] The third is the desire to counter a possible negative public image of genetic research including allegations of 'biopiracy'.[12,13] Finally, the most important factor is the recent marriage of classical clinical trials with genomic research in the field of pharmacogenomics.[14] In the post-genomic era, this new type of 'translational' (Table 2) research is increasingly surfacing in the field of genetics.

Seemingly, returning individual fundamental research results is impossible and nonsensical as the very purpose of this type of research is not the production of individual but generalizable knowledge. Thus, in this context, the concept of individual research results is a scientific misnomer. To avoid confusion, both translational research and the clinical trial context where the individual receives a drug or undergoes some intervention (or even a placebo) need to be distinguished from fundamental research.

Beginning then with a brief contextual snapshot of the international guidelines demonstrating the emergence of an ethical duty to share genetic research results (along with

the existence of the right not to know) (A), the issues of which genetic results and when? (B), by whom? (C) and, to whom? (D), need to be addressed before concluding (E). Guidelines are neither standards nor laws. But, if over time they become professional norms, they may become the legal standard of care for both clinical practice and for research.

Materials and methods

In order to identify and assess international perspectives on the return of research results, we undertook an empirical analysis of both the literature and the ethical guidelines found on major electronic databases using selective keywords. The search profile contained the following keywords: research, study, disclosure, communication, duty to warn, inform, return, reporting, results, right to know, genetics and genomics. The databases searched were Medline, PubMed, Google Scholar, WHO's International Digest of Health Legislation and HumGen (an international database on the ethical, legal and social issues of human genetics; www.humgen.umontreal.ca). Following this preliminary search, the selected items were scrutinized for relevant sources warranting closer reading. Only documents directly relevant to the ethical issues surrounding the communication of research results were kept. The documents were grouped chronologically and by jurisdiction (see Table 1). Then, they were analyzed using a qualitative method approach. The INHERIT BRCAs research program (Interdisciplinary Health Research International Team on Breast Cancer Susceptibility) gave us an appropriate platform to assess the pitfalls, limitations and benefits of our approach.

(A) Emergence of an ethical duty to share genetic research results

Global research results The usual avenue for communication of research results is through scientific publication. According to the revised Declaration of Helsinki (2000), at a minimum, 'negative as well as positive (global) research results should be published or otherwise publicly available.'[15] This is certainly becoming the norm in clinical research where failure to publish results is now viewed as a form of scientific misconduct. Unpublished data can lead to additional, redundant trials being performed, useless or even harmful interventions remaining in use and, ultimately, do not contribute to the growth of society's collective knowledge.[16]

However, publishing clinical research results in a scientific journal or in a regulatory database is no longer ethically sufficient. The ethical principles of respect for the person, beneficence and justice obligate the researcher to offer results in a manner that is clear and understandable to the research participants.[1,17]

The recent draft guidelines of the European Federation of the IEA) state that,

> Research results should be published without undue delay, and disseminated critically and in good faith, supported by proper documentation. Findings that contradict the main results should always be presented in the text. It is advisable to publish the main results in a form that reaches the participants of the study and other interested members of the community where the study took place (eg a newsletter, local newspapers etc.) (emphasis added).[8]

Communication can take the form of a personal letter, a news bulletin, a newspaper article, website or a similar forum. In the actual context, the chosen media should be specified at the beginning of the consent process. Such transparency in the communication of global results (often the only benefit from research) is not the same, however, as giving back individual results.

Individual research results To illustrate the evolution of the concept of returning individual research results, the 1991 Council for International Organizations of Medical Sciences (CIOMS) *International Guidelines for Ethical Review of Epidemiological Studies* maintained that being informed of findings 'that pertain to their health' is one of the 'reasonable' benefits of participation for 'communities, groups and individuals' in research.[18] A decade later, this position was underscored by CIOMS by not only suggesting informing participants of the findings of the research in general but also by clarifying that 'individual subjects will be informed of any finding that relates to their particular health status' (emphasis added).[10] A similar position was also expressed by the Council of Europe[19] and, in the specific context of genetic research, by UNESCO[20] and the WHO (World Health Organization).[21] All these international guidelines also recognize the logical *a contrario* position, that of the 'right not to know'.

The emergence of this nebulous 'right not to know' further confounds the determination of whether an ethical duty to return genetic research results exists. Indeed, this right depends on the informed consent process and therefore needs to be discussed before the research even begins. At that time, the participant can exercise a choice concerning possible future communication of research results.

The right not to know was legally consecrated in the 1997 Council of Europe's *Convention on Human Rights and Biomedicine*.[22] The *Convention* is a legally binding instrument in the European countries that have ratified it[23] (ie before ratification, each State has to bring its laws in comformity with the Convention. Such legislation must include legal sanctions and require compensation for individuals who have suffered undue harm following

medical treatment or research). Article 10 on the right to privacy and to information states: 'everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed.'[22] Whereas the *Convention* was on biomedicine generally, UNESCO's 2003 *International Declaration on Human Genetic Data*[20] conferred this right not to be informed 'where appropriate (to) identified relatives who may be affected by the results' (art. 10) (emphasis added).

It should be noted that earlier statements on the right not to be informed contained provisions that the interests of others could override this right of the individual not to receive information. In 1981, the World Medical Association (WMA), as concerns patients' rights generally, would not respect the refusal by an individual to receive results if 'required for the protection of another person's life' (7.d).[24] Likewise, in 1997, WHO's *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services* would override the wish of an individual not to know clinical test results in the situation of the 'testing of newborns or children for treatable conditions.'[25]

(B) Which genetic research results and when?

International guidelines generally address neither the specific issue of which results nor the timing of their communication, except the obvious obligation to 'inform a subject when medical care is needed'(4.3.2).[3] We have already noted the position of CIOMS on the return of any finding that relates to particular health status.[8] Thus, can we presume a duty to return global results to all participants as well as the need to return individual results if reliable and clinically significant? Nowhere is this more problematic than in the specific context of genetic research. This is because, 'human genetic research is not conducted with the aim of providing research participants with specific information about their genetic status or health. Generally, genetic information derived from research is of unknown or uncertain predictive value. Therefore, special care must be taken to prevent inadvertent release of immature data' (emphasis added).[26]

The 2002 Consortium on Pharmacogenetics maintains that 'researchers are obligated to offer the research participant the option of disclosure of research information when its reliability has been established and when the disclosure is of potential benefit to the subject' (emphasis added).[27] The Consortium, however, did not attempt to define what would constitute 'potentially beneficial' or 'reliable' results, presumably preferring to leave a margin of professional interpretation to the research team. According to the Pharmacogenetics Working Group, the issue of whether to disclose also depends on other criteria such as the standard operating procedure of the research sponsor, the scientific validity, the clinical relevance, quality assurance, the measures to maintain confidentiality, the ability of researchers or sponsors to provide the appropriate counselling, the legal and ethical framework, etc.[6,28]

A distinction must be made between pharmacogenetic drug trials where it could be considered a requirement to disclose individual results of direct interest and benefit to the participant and hypothesis testing studies of no direct medical relevance which would not need to be shared with the participant.[27] This latter position reflects the current trend as concerns fundamental genetic and pharmacogenetic research. In Europe, see for example the Medical Research Council's *Human Tissue and Biological Samples for Use in Research- Operational and Ethical Guidelines*.[29]

Indeed, in 2003, this position was affirmed at the international level by WHO in its report on *Genetic Databases: Assessing the Benefits and the Impact on Human and Patient Rights*. Although WHO states that in most situations, genetic research data will remain of abstract significance, it maintains that there may be situations where data might be of value in a clinical setting. Even so, the following conditions should be met before disclosure:

(a) 'the data have been instrumental in identifying a clear clinical benefit to identifiable individuals;
(b) the disclosure of the data to the relevant individuals will avert or minimize significant harm to those individuals;
(c) there is no indication that the individuals in question would prefer not to know.'[21]

In short, if individual genetic research results are to be returned at all, at a minimum, they should meet the requirements of scientific validity, clinical significance, benefit (ie existence of prevention or treatment) and the absence of an explicit refusal to know. However, it could well be that a result that has no clear clinical benefit at the time of the research will turn out to be very important to the participant at a later time. This raises the question of how long can the ethical duty to return results last? Members from the Pharmacogenetics Working Group have recently suggested that 'some pragmatic limitations on the research endeavor should be put in place so that responsibilities of investigators, sponsors, participants, and ethics committees are not left open ended.'[6] More specifically, the American National, Heart, Lung, and Blood Institute (NHLBI) Working Group on Reporting Genetic Results in Research Studies stipulates that 'responsibilities of the investigators cannot extend beyond the period of funding.'[4]

The requirements of validity, significance, and benefit could be assessed by answering the following questions:

(1) 'Does the genetic test that generated the results accurately identify the genetic variant of interest?

(2) Does the identification of the variant permit an accurate prediction of the presence (or risk) of a clinical condition?
(3) Can the identification of the clinical condition (either disease or risk for developing a disease) improve the patient's health outcome?'[30]

To be truly effective, evaluation methods to assess the clinical significance of genetic tests will need to be as complete and unbiased as possible.[30]

In the past, when the above three criteria were met, the researcher retained discretion over the decision to communicate research results or not. Recent international norms now suggest an ethical obligation to disclose all research results meeting these criteria. This is illustrated by the 2004 *Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research* recently issued by the Council of Europe; 'If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them' (emphasis added).[19] But how can one determine what is relevant for each research participant? For example, an argument could be made that an information about a genetic predisposition can be relevant to the participant even though it is unlikely to affect immediate health outcomes (eg lifestyle). One solution, advanced by the Pharmacogenetics Working Party, would be to subject research findings to both peer review and ethics review before disclosure.[31] The NHLBI Working Group on Reporting Genetic Results in Research Studies also maintains that decisions regarding reporting of research results should only be made with IRB approval.[4] It remains to be seen what will be the effect of this extensive duty on genetic research results.

An important precaution that genetic researchers would be wise to take is to validate their research results via a licensed or accredited clinical laboratory. This is in fact a legal obligation in the United States.[32,33] However, this solution might be difficult to implement in some countries as the qualities, accessibility and availability of tests vary greatly and validating research results in a clinical laboratory is not always economically feasible for researchers.

(C) By whom?

While this obligation to disclose both individual and global genetic results is developing, few guidelines at the international level specify with whom this duty lies. Generally, no person is named specifically to carry out this task. The 1998 WHO *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services* mentions 'professionals.'[25] Concerning results in clinical trials generally, the International Conference on Harmonization speaks of the investigator or institution (4.3.2).[3] The Pharmacogenetics Working Group also makes a specific suggestion: according to them, 'the subject's physician may be in the best position thoughtfully to communicate these results as part of follow-up healthcare contacts'.[28] Neither UNESCO nor WHO address this topic in their recent norms governing genetic data.[20,21]

At the national level, several groups have come up with suggestions. According to the Consortium on Pharmacogenetics, the consent form should state who will make the determination of reliability and who will have the responsibility of informing the participants.[27] A consensus seems to be that a researcher would not be the appropriate person to disclose the results. For instance, both the American Society of Human Genetics and the Canadian College of Medical Geneticists hold that 'the results of DNA analyses should be reported to the appropriate health care professional, who in turn has the responsibility of informing individuals or family of the results and their meaning.'[34,35] The Quebec Network of Applied Genetic Medicine (RMGA) suggests communication by the 'treating physician' in the case of specific, individual genetic research results.[36] In France, the National Consultative Ethics Committee for Health and Life Sciences recommends that 'the results of the tests must be communicated in person by a physician whose competence permits a full explanation of the significance of the results.'[37]

Canada's three granting councils, in their *Policy Statement,* seem to recommend that the genetic researcher be the one to report results back to the individuals: 'The genetic researcher shall seek free and informed consent from the individual and report results to that individual if the individual so desires.'[9] However, even they recognize that 'considerations should be given to combining clinical expertise with that of the research geneticist.'[9]

Thus, it could be posited that the participant's treating physician or at the very least a clinician involved with the research team would be an appropriate person to report the research results rather than the researcher. However, this implies that from that point on, the research findings will be entered in the medical record of the research participants. They then will be afforded the same level of confidentiality protection as any other kind of medical information.

Another important person to involve in the process is the genetic counselor. In recent applications, concerning research projects on predictive testing, pre- and post-test genetic counseling is seen as integral to the research. Both researchers and the institutional review board now have to ensure the availability of such counseling when appropriate,[9] that is when genetic tests become available. On that topic, UNESCO takes the position that

> It is ethically imperative that when genetic testing that may have significant implications for a person's

> health is being considered, genetic counselling should be made available in an appropriate manner.[20]

(D) To whom?

First in 1996[38] and later in 1998,[39] the Ethics Committee of the Human Genome Organisation (HUGO) affirmed the longstanding ethical tenet of no communication to the person tested or to others without consent. Nevertheless,

> [S]pecial considerations should be made for access by immediate relatives. Where there is a high risk of having or transmitting a serious disorder and prevention or treatment is available, immediate relatives should have access to stored DNA for the purpose of learning their own status. These exceptional circumstances should be made generally known at both the institutional level and in the research relationship.[39]

Thus, while not supporting the notion of an obligation to communicate genetic results to relatives, it supports the position of access to such information by immediate relatives. HUGO avoided defining what is meant by 'immediate relatives'. Generally, these exceptional circumstances should be made known during the process of obtaining consent. The WMA in its 1992 *Declaration on the Human Genome Project* mentioned the 'at risk family members' of the patient (emphasis added).[40]

UNESCO distinguishes between identified relatives and those who cannot be found owing to anonymization of data. It goes further, however, by adding the right of such identified relatives not to be informed. Indeed, we have seen that according to article 10 of UNESCO's 2003 *International Declaration on Human Genetic Data*, 'Where appropriate, the right not to be informed should be extended to identified relatives who may be affected by the results.'[20]

Recommendation 8 of WHO's 2003 report on *Genetic Databases* speaks of 'relevant individuals' without further qualification, thus seemingly including others not just the research participant or the family. It is interesting to note that WHO maintains its long-held position on the possibility of overriding the objection of participants to the release of clinically relevant data to third parties:

> Disclosure in these circumstances is permissible even in the face of objection from the person who originally contributed data to the database. The onus is on those who would seek to disclose to justify this action. Ethical approval for such disclosures should be sought.[21]

Acknowledging that 'an individual's privacy interest in his genetic information might not be absolute' yet fully realizing the complexity of the issues involved, the Pharmacogenetics Working Group recommended that any decision regarding familial disclosure be made on a case-by-case basis.[6]

Conclusion

Resolution of the question of whether there is a duty to return global or individual genetic research results depends on the type of study, the clinical significance and reliability of the information, and whether the study involves patients, genetically 'at-risk' families for a tested predisposition or healthy volunteers. Further confounding the emerging duty to return genetic research results is the situation in which the researcher is also a clinician and the participant is also a patient.

However handled, the issue of notifying (or not) participants of results should be disclosed and agreed to in advance (ie on the consent form). As stated by the European Commission in 2004: lie on the consent form

> Public trust in research surrounding genetic testing is largely dependent on how the use of samples and data in and from biobanks is undertaken and communicated. This applies in particular to [t]he communication of study results and, where appropriate, of individual test results.[17]

Finally, although at the international level there may be an emerging ethical 'imperative' to return results in genetic research, this begs the further question of whether this duty should be legally recognized. It is hoped that fear of potential legal liability will not give rise to protectionist approaches mandating such a duty under law. Like research 'results', an ethical 'imperative' is also a misnomer, for the ethics of decision-making in the research context depends on dialogue and agreement between participants and researchers.

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