

Disclosure of individual genetic data to research participants: the debate reconsidered

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Despite extensive debate, there is no consensus on whether individual genetic data should be disclosed to research participants. The emergence of whole-genome sequencing methods is increasingly generating unequalled amounts of genetic data, making the need for a clear feedback policy even more urgent. In this debate two positions can be broadly discerned: a restrictive disclosure policy ('no feedback except life-saving data') and an intermediate policy of qualified disclosure ('feedback if the results meet certain conditions'). We explain both positions and present the principal underlying arguments. We suggest that the debate should no longer address whether genetic research results should be returned, but instead how best to make an appropriate selection and how to strike a balance between the possible benefits of disclosure and the harms of unduly hindering biomedical research.

Feedback of genetic research results: an evolving debate

As a result of rapid developments in next-generation sequencing technology, the question of whether individual genetic data should be disclosed to research participants – and if so, which data are to be disclosed and by whom – has increasingly become a topic of debate. This debate, however, has become highly complex and theoretical. It covers a wide variety of genetics and genomics research, from biobank and archived tissue research to genome-wide association studies (GWAS; Glossary) and from family-based single-gene studies to whole-genome sequencing (WGS) studies. It includes several types of research participants, including healthy volunteers and patients. It concerns a broad category of genetic information, including validated and non-validated, highly and poorly predictive, and more or less probabilistic genetic data [1]. In addition, it includes both intended research results and unexpected (incidental) findings beyond the scope of the research [2,3].

Despite extensive debate, there is no consensus regarding when and how to disclose individual genetic data to

research participants in studies with a genetic component. As a consequence, researchers and research ethics committees continue to struggle with the question of whether research protocols should adopt provisions about the return of genetic data and, if so, how this should take shape. Clarity on this subject is increasingly important, particularly in view of the changing (genetic) landscape, such as the advance of WGS studies, the emergence of biobanks, the growth of commercial activities in this field, and the shift from bench to bedside wherein genetic results are increasingly translated to the clinic [4,5]. Both the quantity and the significance of the data generated by WGS methods generate an urgent need for a clear disclosure policy [5]. As the spotlight in genomic studies is turned on increasingly larger parts of the genome, the chance of generating genetic findings increases [6]. The currently

Glossary

Ancillary care: ancillary care is that which is not required to make a study scientifically valid, to ensure the safety of a trial, or to redress research injuries.

Analytic validity: a result is analytically valid when it accurately and reliably identifies a particular genetic characteristic.

Archived tissue research: retrospective research using stored tissue left-over after a clinical treatment or tissue taken purposefully for a specific research project.

Biobank: a 'library' or collection of human biological samples matched with phenotypic data.

Clinical utility: a result is clinically useful when it leads to an improved health outcome.

Clinical validity: a result is clinically valid when a genotype accurately and reliably identifies or predicts a phenotype. Clinical validity thus refers to the quality and quantity of empirical evidence regarding the association between a genotype and a particular clinical outcome.

Genome-wide association studies (GWAS): GWAS are aimed at finding genetic variations that contribute to common, complex diseases. By comparing DNA characteristics of people with a disease and a matching control group, genomic loci that are associated with health and disease can be identified.

Personal utility: a result is personally useful when the outcome has value to the individual.

Pharmacogenetics: the study and clinical testing of genetic variation in different metabolic pathways that affect individual responses to drugs.

Pleiotropy: the ability of a single gene to influence multiple traits or conditions.

Therapeutic misconception: the mistaken belief that a research project's primary aim is therapeutic, whereas research is often primarily aimed at yielding scientifically accurate and generalizable knowledge.

Whole-genome sequencing (WGS): sequencing the entire DNA of an individual to generate a personal genome sequence database.

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Table 1. Arguments supporting a restrictive or qualified disclosure policy

Restrictive disclosure policy ('no, unless'):	Qualified disclosure policy ('yes, if'):
Genetic research results should not be returned to individual research participants with the exception of life-saving results	Genetic research results should be returned to individual research participants if the results meet certain conditions
1. Disclosure promotes the therapeutic misconception	1. Beneficence requires disclosure
2. Disclosure rests on a mistaken interpretation of autonomy	2. Autonomy requires disclosure
3. Disclosure would pose an untenable burden on research infrastructure	3. Reciprocity requires disclosure
4. Disclosure is not feasible	4. The blurring of the distinction between research and clinical care is not necessarily negative
5. Disclosure has harmful consequences	5. Disclosure improves public understanding of genetics

available guidance for feedback has not been elaborated with the current genomic research and WGS studies in mind [4]. In order to contribute to the debate on this topic, and eventually to the development of appropriate guidance, this article reviews the substantial but fragmented literature in the field. After having identified and explained the central positions and underlying arguments as they appear in the literature, we suggest how to move the debate forward.

Distinguishing between the different types of disclosure

First, it is important to distinguish between the different types of disclosure. Although several types of disclosure have been proposed, the debate has centred on the question whether researchers should actively offer individual genetic research results [7].

Aggregate or individual disclosure

Research results can be returned to participants on an aggregate level and on an individual level. In the first case, participants are collectively informed about the central findings and conclusions of the research project. Generally speaking, it is uncontroversial to offer research participants the opportunity to receive a mailing with the principal findings of the research project in which they participated – although the suitability of disclosure on an aggregate level is not undisputed for all types of studies, and not all participants are interested in receiving results [8]. Less consensual is the question of whether participants should receive feedback on their individual genetic data. Because the debate has centred on this question, the focus of our review will be on individual disclosure. Obviously, a necessary condition for individual disclosure is that the data can be linked to a specific research participant. Fully anonymous data cannot be returned – although debate is possible whether complete anonymity is still feasible and desirable, as even unidentified genetic data may be linkable to individuals [9,10].

Passive or active disclosure

Furthermore, research results can be disclosed passively or actively. Passive disclosure refers to disclosure on explicit request by a research participant. The right to have access to one's personal, genetic and medical data is recognized in many international and national legal guidelines [11–13]. The central discussion in this respect therefore is not whether participants can access their data, but whether researchers should actively offer genetic results to individual research participants [14].

Scope of disclosure

A second issue concerns the scope of disclosure of genetic research results. At one end of the spectrum it is argued that no individual genetic research results should be disclosed whatsoever. This, however, is an exceptional position, because only one publication adhered strictly to a 'no disclosure at all' policy, even of life-saving information – and this article was restricted to biobank research [15]. At the other end of the spectrum it is argued that all individual genetic data should be returned to research participants if the participants so request [16,17]. However, as with the other extreme position (no disclosure whatsoever), full disclosure is rarely defended.

The overwhelming majority of commentators defend either a very restrictive disclosure policy or an intermediate position of qualified disclosure. Given this, we offer an outline of these positions – as they appear in the literature – and examine the arguments that have been put forward to support each position (Table 1).

Arguments in favour of a (very) restrictive disclosure policy

A restrictive disclosure policy would mean that genetic research results should not be returned to individual research participants with the exception of life-saving data [18]. Five different arguments have been put forward to support this restrictive disclosure policy.

Disclosure promotes the therapeutic misconception

The most prominent argument supporting a restrictive disclosure policy contends that blurring the distinction between research and clinical care has the potential to lead to the therapeutic misconception – which arises when a research participant mistakenly believes that the primary aim of the research project is therapeutic [19]. Whereas clinical practice indeed aims at advancing the best interests of each individual patient, the primary aim of research is to yield scientifically-accurate and generalizable knowledge. Disclosing individual results, so the argument goes, conflates clinical care and research. As a consequence, participants could suffer from the therapeutic misconception and researchers might be inclined to overstate the benefits of enrolment [15,18,20–23]. Whereas recognition of the personal meaning of genetic information and a conception of clinical utility that exceeds direct medical benefit are appropriate to the goals and norms of clinical genetics, so it is argued, they are inadequate as a basis for disclosure in the research context [24,25]. Whereas it is incumbent upon clinicians to act in the best interests of their patients, researchers are required to conduct good

science with the potential to benefit populations of people. Conducting good science includes protecting research participants, including efforts to minimize the therapeutic misconception [20].

Some refine this argument by differentiating according to the type of genetic research study. In 'classic' family-based single-gene studies, research results can have immediate clinical implications. It is suggested that researchers might therefore have more reason to disclose results in such a context than in relation to biobank research, genetic databases and pharmacogenetic studies where multiple conditions are examined, frequently with multifactorial interactions, and that tend to generate less clinically-relevant results [26,27].

Disclosure rests on a mistaken interpretation of autonomy

Although those supporting a restrictive disclosure policy do not deny the importance of showing respect for the autonomy of the participants, they disagree that this necessarily requires disclosure. Respect for participants means recognizing that human beings are capable of self-determination as autonomous agents. It also requires researchers to provide full information about the trial and to allow people to enrol and withdraw. According to this argument, however, it does not require them to actively disclose individual research results to the participants [18]. According to some, even if there is a right to information about oneself, a person can waive that right under certain circumstances. Individuals who understand the information-nondisclosure policies of a research protocol, and who nonetheless choose to participate, are not violated in their autonomy [22,28]. This means that it is ethical to carry out research which does not feed results back providing that the participant's consent for it is valid. Others in turn argue that notifying participants from the outset that genetic information will not be disclosed to them does not resolve the underlying moral question regarding the responsibilities of researchers towards participants [29].

Disclosure would impose an untenable burden on research infrastructure

Another argument put forward to support a restrictive disclosure policy contends that the practicalities of returning results could impose untenable burdens on the existing research infrastructure. Proponents of this argument assert that providing individual research results would require trained personnel with appropriate expertise. Genetic counselling measures are not anticipated in the research context [30]. Moreover, if results are obtained in a research laboratory, feedback could also imply re-testing of the genetic data in an accredited clinical laboratory [termed a 'Clinical Laboratory Improvement Amendments (CLIA)-certified lab' in the USA]. If the costs for re-testing are paid by the research team, resources that could be used for research are used for disclosure. If the costs, however, are met by the individual participant, this could create possible inequities between those who can and those who cannot afford this service [31]. Disclosure can be resource-intensive, and some argue that it would be unethical to use those resources for feedback when they could have been

used for research [32]. Moreover, it is argued, the distinction between research and clinical care provides a justification for why resources that could be used for returning results should be used solely for research [15]. Research participants could also be concerned that using resources for informing participants might detract from the actual research itself [33]. Fairness requires balancing the preferences of the participants against prioritization of resource utilization to maximize the benefits of research to society [34]. The current trend towards increasingly larger scale studies and WGS studies only reinforces the argument – feedback on all useful results would be extraordinarily costly in time and money [22].

Disclosure is not feasible

The fourth argument underlying a restrictive disclosure policy questions the feasibility of returning genetic research results. Feasibility is questioned for two reasons.

First, it is questioned whether research participants are capable of understanding the wide array of possible findings. A disclosure policy requires that research participants are educated beforehand about the range of possible findings [35]. Critics argue that it is not feasible to select these findings beforehand: it would require a fairly lengthy list of possible types of conditions to which the genetic findings might be relevant in a variety of ways. Meaningful selection of which results one would want to receive from WGS studies seems not feasible. In addition, most genetic data are probabilistic or pleiotropic. Pleiotropy regards the possibility that the acquisition of genetic information about one condition, either at the same time or in the future, can provide information about a different condition [25,36]. In addition, research participants frequently lack full comprehension regarding the study they participate in [37], and there is evidence that people are not very good at understanding complicated statistics and can differ widely in their preference for receiving genetic information – and this can change during their lives [38].

Second, it is questioned whether researchers (should) have the ability to communicate adequately the results to participants [39]. Often the researcher is not a clinician-researcher but a bench scientist. Although it could be the responsibility of the researcher to seek advice, many argue it is not the responsibility of researchers to communicate the results themselves [40]. Many genetic and/or epidemiologic researchers are not ready to think of their relationship with participants as a reciprocal one in which they are under an obligation to return genetic research results [41]. Moreover, if researchers indeed have a duty to return results to participants this could create an unreasonable and unmanageable precedent. What will be the limits of the fiduciary obligations of researchers to research participants [18,42]? What should the researcher do when genetic data are also relevant for family members [43]?

Disclosure has harmful consequences

A final argument supporting a restrictive disclosure policy is based on the principle of nonmaleficence. The information disclosed to research participants could be harmful in several ways. In the context of genetic information such harm could affect not only the research participant but also

his/her family members [44]. First, it could have adverse psychological consequences. Knowledge of being at increased risk of developing a certain condition could leave people in distress and cause anxiety. The preferences and circumstances of a research participant can also change during his/her life and relationships [38,42]. Second, the information could have adverse social and financial consequences, such as affecting someone's opportunity to obtain or maintain health insurance [43,45], and could potentially be stigmatizing. In the case of research with ethnic groups, the results could be inconsistent with their own histories and myths [46]. In view of these potential harmful consequences, so this argument goes, any disclosure policy should be extremely cautious.

Arguments in favour of a qualified disclosure policy

An intermediate position of 'qualified disclosure' holds that genetic findings should be disclosed if they meet particular conditions. Although the majority of commentators and guidelines adopt a variant of a qualified disclosure, the conditions for disclosure and the underlying argumentation vary widely. Below we set out the five arguments deployed in the literature to defend a qualified disclosure policy.

Benevolence requires disclosure

The first argument put forward to support a qualified disclosure policy holds that the principle of benevolence (i.e. doing good for the sake of others) requires that researchers disclose results that are likely to be valuable to the physical or psychological well-being of the participant, or to their reproductive decision-making and life-planning. The argument proceeds as follows – based on respect for research participants, researchers have a duty to maximize benefit and minimize harm. If results are clearly clinically useful, then they should be returned, even if resources are limited or capabilities have not been developed. After all, there are a number of possibilities for making the feedback of results financially and practically feasible, for example by including a budget for disclosure in the initial grant application [47]. If data are analytically valid but have less clinical utility, then the guiding principle should be whether the results could be of personal meaning for the participants [26,34,48].

Autonomy requires disclosure

This argument holds that if participants assign personal value to results they should, out of respect for the participant's autonomy, be disclosed. Even if there are risks or potential harmful consequences, participants should decide themselves if they want to run those risks by requesting results [32]. Some add that offering the possibility of disclosure becomes even more important when the research setting is the only venue in which testing is available [26]. Whether the availability of a genetic test outside the research context (i.e. in a clinical or commercial context) should influence the disclosure policy is a topic of debate. On the one hand, if a genetic test or analysis is widely available through a clinical laboratory, then this implies significant clinical validity and utility, and could thus indicate a duty to disclose. On the other hand, wide

availability outside the research lab lessens the obligation of the researchers to provide the information (especially if the lab is not CLIA-certified) and creates the possibility of referring participants to CLIA-certified labs [24].

Reciprocity requires disclosure

Reciprocity is used as an argument supporting disclosure in two ways. First, some argue that people tend to expect an element of reciprocity when contributing to research, particularly in the context of biobank research. They emphasize that we cannot assume research participants to be pure altruists who expect nothing in return for their willingness to contribute [49]. They, so it is said, expect care in return, and this can be materialized by returning clinical useful results [50]. Also, researchers sometimes view access to genetic results as a form of compensation, with the favourable side-effect that it could increase participation rates [39]. For example, one of the main motivations for people to participate in the Estonian Biobank Project was reported to be the opportunity to receive personal genetic data [51]. In addition, studies suggest that participants would not wish researchers to be in possession of individual genetic information about them that they themselves do not possess [52].

Second, some commentators perceive reciprocity as an ancillary care justification for disclosure [41]. 'Ancillary care' [53] is used in this context to support the view that participation in research involves at least a partial, even if tacit, entrustment of health to the researchers. The view that individual results should not be offered because the goal of research is to produce generalizable knowledge does not preclude other responsibilities towards participants [54]. Reciprocity requires that the nature of the relationship between researchers and participants is taken into consideration because the extent of the duty to offer results could be influenced by the duration and the intensity of this relationship [24,34,55,56]. In large cohort studies and pedigree studies, for example, researchers often have a very well-established and long-term relationship with the participants. Offering results could help to foster a productive partnership between researchers and participants [57].

However, critics question the fairness of relying on the duration and intensity of the relationship in deciding whether or not to disclose. For example, when samples or data are used by another research group for secondary analysis, the researchers have no contact with the participants [55]. Would it not be fair, it is asked, to give equal treatment and equal consideration to strangers? To treat differently participants who might have the same preferences and interests is to discriminate against participants who, by chance, find themselves in a less intense research relationship [41].

The blurring of the distinction between research and clinical care is not necessarily negative

This argument, in fact a response to the therapeutic misconception argument, contends that the blurring of research and clinical care already takes place or that it is not necessarily negative if appropriately recognized. The possible negative consequences of such blurring could for

example be mitigated by letting team members – other than the principal researcher providing the results or asking permission – provide the results to another medical professional, such as the general practitioner or clinical geneticist [47]. However, although clinicians are increasingly involved in studies with a genetic component, the amount of genetics experience they have is likely to be small. Some argue that clinical genetics training should therefore be included in the design and implementation of such studies [26]. In addition, if researchers truly believe that little or no information relevant to health promotion and disease prevention is likely to accrue from the research, how could they expose participants to the risks of participation, or request public funding for the project [54]?

Disclosure improves public understanding of genetics

The final argument underlying qualified disclosure is that disclosure could have the beneficial effect of improving the general public understanding of the essential role of research in healthcare. It could help to educate the public about the complexity, ambiguity and occasional meaninglessness of many genetic findings [58,59]. Moreover, this argument contends that more active involvement of potential research participants in decisions about when to offer to provide individual genetic results could give people a greater say in biomedical research and encourage people to think about ethical issues in biomedical research [59].

Concluding remarks

Having identified the main positions and arguments it is now time to develop a research ethics policy for the disclosure and communication of genetic research results. In developing concrete guidelines the following ingredients warrant consideration.

First, it is interesting that the two extreme positions of ‘no disclosure whatsoever’ and ‘full disclosure’ are seldom defended. A duty to inform when this could save the life of a research participant appears to be widely recognized. The imperative to rescue identifiable individuals when facing avoidable death is also known as the rule of rescue – the duty to provide reasonable emergency assistance to persons in serious and immediate peril [60]. Similarly, if researchers have life-saving genetic information about a research participant then a strong case can be made for disclosing these results. Further discussion should therefore no longer address whether genetic research results should be returned, but instead should address which results and who decides upon the appropriate procedures for identifying and subsequently disclosing results.

Second, one of the most salient and still unsettled issues concerns the determination of the appropriate criteria for disclosure. Which data should be returned? What (quality) requirements should the data meet to be eligible for disclosure? Four criteria have been put forward: analytic validity, clinical validity, clinical utility and personal utility [61,62]. All these criteria are still under discussion and require refinement.

A point of discussion, for example, is how the thresholds for analytic and clinical validity should be determined: what would count as sufficient evidence? Most genetic tests

are only moved to clinical laboratories once their value in diagnosis, prognosis, or treatment has been established. Whereas some argue that it is sufficient to assess analytic validity by peer review [16,58], others contend that a genetic result should not be considered proven until it has been independently replicated and peer-reviewed [2,45,63–65]. As with analytic validity, there are no consistent criteria for determining when the threshold for clinical validity has been achieved because clinical validity can be a moving target and ‘time-sensitive’, with (unclassified) variants being reclassified based on scientific evidence over time [2,66,67].

The concept of clinical utility is also debated, because the clinical utility of testing varies widely, depending on the magnitude of the risk, the accuracy of the risk prediction, the potential for risk reduction, the efficacy of available interventions, and the implications for the capacity of the individuals concerned to obtain health insurance. Moreover, the assessment of clinical utility does not, for some, sufficiently consider the importance of individual preference [17,58,68]. They introduce the concept of personal utility as the evaluation of whether something has utility is a normative assessment to be made by the participant, and not by the researcher [68]. It has been proposed that research participants should be given a range of options for disclosure of research results, including for example reproductive significance, the length of time for which they would seek disclosure, and whether family members are to be informed after death [62,69–71]. To formulate concrete guidelines it is necessary that these four criteria are further elaborated.

Third, whereas a research team should not be unreasonably hindered in fulfilling their primary duty, which is to conduct research, the success of genetic/genomic research also depends on the participation of a sufficient number of research participants and the maintenance of public trust in the research enterprise. This implies that it might be desirable and useful to search for (innovative) ways of actively involving participants in research in general and in the disclosure policy specifically, and particularly if the participants are enrolled by novel forms of informed consent (e.g. broad consent in the context of biobank research). Empirical studies confirm that participants prefer to have genetic results returned to them, at least when the results are actionable and accurate [31,52,72–75].

Fourth, the diversity of genetic/genomic research can yield different types of research results. GWAS and genetic epidemiology studies, for example, are more likely to result in genetic variations associated with a particular phenotype, and this often means there is a high prevalence but low or modest risk. By contrast, in WGS studies the likelihood of uncovering causal monogenic mutations could be much higher, reflecting low prevalence but significant risk to the individual concerned. In biobank research the type of results obtained depends on the nature of the studies performed with the archived tissue. When developing concrete guidelines it could therefore be worthwhile to distinguish between the different types of genetic study (results) instead of seeking a uniform policy for all such studies [56,76,77]. No disclosure is unethical because it

fails to adhere to the rule of rescue, whereas full disclosure is nonsensical (at best) because it could imply disclosure of all raw sequencing data – and any policy in between will oblige us to consider how best to select the results which are eligible for disclosure. In addition, any disclosure policy should search for an appropriate balance between the possible benefits of disclosure and the harms of unduly hindering biomedical research. Further interdisciplinary debate is therefore necessary to discuss how and by whom an appropriate selection can justifiably be made.

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