Disclosing Individual Genetic Results to Research Participants

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Disclosing Individual Genetic Results to Research Participants

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Investigators and institutional review boards should integrate plans about the appropriate disclosure of individual genetic results when designing research studies. The ethical principles of beneficence, respect, reciprocity, and justice provide justification for routinely offering certain results to research participants. We propose a result-evaluation approach that assesses the expected information and the context of the study in order to decide whether results should be offered. According to this approach, the analytic validity and the clinical utility of a specific result determine whether it should be offered routinely. Different results may therefore require different decisions even within the same study. We argue that the threshold of clinical utility for disclosing a result in a research study should be lower than the threshold used for clinical use of the same result. The personal meaning of a result provides additional criteria for evaluation. Finally, the context of the study allows for a more nuanced analysis by addressing the investigators’ capabilities for appropriate disclosure, participants’ alternative access to the result, and their relationship with the investigators. This analysis shows that the same result may require different decisions in different contexts.

Disclosure of individual results to participants in clinical and epidemiologic research has emerged as a complex and contentious issue. The approaches and practices of investigators, institutional review boards (IRBs) (Hull et al. 2004), and funding agencies (Bookman et al. 2006) are quite diverse. Some argue that disclosure should be the routine practice in research, based on the principle of respect for participants (Partridge and Winer 2002; Fernandez, Kodish, and Weijer 2003; Shalowitz and Miller 2005), while others emphasize the balance of benefits and harms and argue that disclosure should be limited to certain situations (Fuller et al. 1999; National Bioethics Advisory Commission 1999; Beskow et al. 2001; Clayton and Ross 2006). Furthermore, the federal regulations regarding the conduct of clinical research do not provide clear guidance in this matter (Code of Federal Regulations 1991). While there is an emerging consensus in the literature regarding the disclosure of aggregate study findings (Beskow et al. 2001; Partridge and Winer 2002; Fernandez, Kodish, and Weijer 2003), individual genetic results raise challenging issues that require further analysis and policy recommendations.

The development of ethically justified policies regarding the disclosure of individual genetic research results is important for several reasons. First, genetic research is increasingly prevalent as the focus is shifting from studying rare diseases in isolated families to determining the contribution of genetics to common disorders such as cancer and heart disease (Collins et al. 2003). Second, the probabilistic character of genetic information and the pleiotropic nature of genes make accurate interpretation and communication particularly challenging. Third, the potential impact of genetic information on family relationships, reproduction, and personal identity highlights the subjective value of genetic results and may further complicate their communication.

Challenging situations can be anticipated to arise more frequently in both clinical trials and epidemiologic studies. Should investigators offer participants results regarding the apolipoprotein (Apo)
c.4 allele in a clinical trial for the prevention of Alzheimer’s disease (Petersen et al. 2005)? Should they offer participants individual results of BRCA1 mutations in epidemiologic studies (Malone et al. 1998)? These examples show the importance of choosing an approach to disclosure of individual genetic results when planning the research, in order to minimize ad hoc solutions to issues that may emerge. Including a plan about disclosure in the study design also allows IRBs to assess the appropriateness of the plan and could improve the ability of investigators to communicate their intentions to participants during the consent process.

We delineate a framework that will assist investigators and IRBs in deciding whether to offer individual genetic results and, when needed, in choosing an appropriate plan for their communication.

TWO POTENTIAL APPROACHES

When considering the appropriate approach to the disclosure of individual genetic research results, two opposite ends of a spectrum can be described. Both polarized approaches are inadequate, because they focus either solely on the perspective of an investigator or that of a participant, but fail to offer a comprehensive balanced view.

The research-focused approach suggests that results should generally not be offered because the primary goal of research is not to provide individuals with information about themselves but rather to produce generalizable knowledge (National Bioethics Advisory Commission 1999). This approach is inadequate because even when the primary goal of research is acknowledged, investigators still have other responsibilities towards research participants (Richardson and Belsky 2004). For example, beneficence justifies offering participants information that is of direct clinical utility and respect requires that their preferences be taken into account.

The autonomy-focused approach suggests that all results should be offered because participants have a right to access information about themselves (Shalowitz and Miller 2005). The recent legal climate created by the Health Insurance Portability and Accountability Act (HIPPA) Privacy Rule (Neale and Schwartz 2004), which reinforces individuals’ control over much of their health-related information, is consistent with this approach. However, this approach does not distinguish appropriately between research and clinical practice. In addition, even if a right to receive research results is acknowledged, it is still unclear which raw data count as “results.” It is not reasonable to require that all data collected in the process of research be accessible to participants, such as preliminary data from a laboratory notebook.

Investigators who prefer not to disclose results tend to rely on the research-focused approach. Other investigators who prefer to disclose results tend to rely on the autonomy-focused approach. This current state of affairs is problematic because an approach should be adopted based on ethically appropriate criteria, not to satisfy a prior preference. It is therefore important to develop an alternative substantive approach to address disclosure, which is the main goal of this article. In addition, it is important to involve independent evaluators, such as IRBs or data monitoring committees, to review and comment on the investigators’ chosen approach and to provide advice when unanticipated results or new interpretations of results must be considered.

AN ETHICAL FRAMEWORK FOR A RESULT-EVALUATION APPROACH

We propose a result-evaluation approach according to which the appropriate plan depends on the nature of the information generated by the study and on the context of the study. This approach is comprehensive because it allows investigators and IRBs to consider multiple relevant values. We argue for an ethical framework that is based on the principles of beneficence, respect, reciprocity, and justice, which are fundamental ethical principles of research (Emanuel, Wendler, and Grady 2000; Richardson and Belsky 2004; Pelias 2005).

Beneficence requires that investigators offer results that are clinically useful, which means results are expected to be valuable to participants’ physical or psychological well being, to their reproductive decision making or to their life planning. Respect for participants requires that investigators provide results that may be of interest to participants and that have been acquired based on their participation. Respect also requires that investigators respond to participants’ preferences to receive, or not receive, a certain result. Results should therefore be offered, allowing participants to express their preferences, so that even within one study individual participants may be handled differently. Reciprocity requires considering the nature of the relationship between investigators and participants because the extent of the obligation to offer results is influenced by the duration and the intensity of this relationship. Finally, justice requires balancing participants’ preferences against considerations of prioritizing resource
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utilization to maximize the benefits of research to society.

CONSIDERING THE NATURE OF THE INFORMATION

Determinative Considerations: Analytic Validity and Clinical Utility

In order to develop an appropriate disclosure plan for a particular study, investigators and IRBs should first evaluate the nature of the information that the study is likely to generate. Different informational considerations determine the approach to offering results (Figure 1).

Analytic Validity

A result is analytically valid when it accurately and reliably identifies a particular genetic characteristic, such as a nucleotide sequence or a gene expression profile. Accuracy and reliability must be achieved both at the research stage of assay development and at the clinical application stage in which laboratory proficiency and quality control are required. Results should not be offered when they are not analytically valid because such information is not reliable (Schulte 1991; Fuller et al. 1999). Incorrect information may lead to harmful outcomes such as unnecessary interventions, emotional distress, or a false sense of security.

In the United States, analytic validity in clinical laboratories is ensured by the Clinical Laboratory Improvement Amendments (CLIA) of 1988 (Ehrmeyer and Laessig 2004). Research laboratories are required to be CLIA certified when they offer results to individual participants for the purpose of assessing the health of the individual. In cases where a research laboratory is not CLIA certified and investigators intend to offer clinically relevant results, they should plan to send samples to a second, certified laboratory.

Clinical Utility

A result is clinically useful when it is analytically valid and can be used to improve a participant's well-being. A judgment of clinical utility depends on empirical data about the balance of clinical benefits and risks related to the knowledge of a particular genetic result. Clinically useful results should be offered to research participants. Furthermore, as evidence for clinical utility becomes stronger, a test may be appropriately considered for use in clinical practice (Burke and Zimmern 2004). The assessment of clinical utility is based on three considerations: the association between the result and the clinical condition (clinical validity), the likelihood

Figure 1. Informational considerations.
of a clinically effective outcome, and the value of the outcome to the individual. These three considerations should be considered as benchmarks to be evaluated in decisions about disclosure. Together they provide an assessment of clinical utility.

Clinical validity. Clinical validity refers to the quality and quantity of empirical evidence regarding the association between a genotype and a particular clinical outcome, such as increased or reduced risk of a given condition (Holtzman and Watson 1999). Clinical validity begins to emerge with a suspected association between genotype and clinical condition and is strengthened when the association is supported by a single publication and then many publications. However, many reported associations are not robust: a comprehensive review showed that of 166 putative associations that have been studied three or more times, only six have been consistently replicated (Hirschhorn et al. 2002). Clinical validity is strengthened further when investigators gain an understanding of the functional or causal relationship between genotype and clinical condition. An appropriate threshold of clinical validity is necessary to establish clinical utility because disclosure of results that have very uncertain meaning has little justification. Limited clinical validity can also result in unnecessary procedures or anxiety. Different investigators and IRBs may hold differing views regarding the appropriate threshold for clinical validity.

The threshold of evidence for clinical validity should be lower for offering an individual research result than for general recommendations for routine clinical practice. A result may have enough clinical validity to be reliably integrated into an individual’s decision-making, even before it is established enough in the literature to be integrated into routine clinical practice and particularly when the other two considerations for establishing clinical utility are satisfied. A lower threshold of clinical validity is justified also because of participants’ contribution to the collection of data and to the cumulative understanding of the information. Finally, the ability to monitor any adverse effects of misunderstood information is greater in the research setting.

Likelihood of safety and effectiveness. The second consideration is the likelihood that the clinical outcome will be safe and effective. To assess the likelihood, one should compare the safety and effectiveness of interventions that might follow the disclosure with a situation in which no intervention occurs. For example, a result regarding the presence of the BRCA1 mutation may lead to increased surveillance, which is likely to have the effective outcome of early diagnosis. Assessment of likelihood should be based on review of the evidence, as is now more routinely employed in making broad recommendations for population-based health care services.

Value of the outcome. The third consideration is a normative assessment of the value of the outcome. Information that reduces the risk of sudden death is more valuable than, for example, information about the genetic capacity for athletic endurance. While clinical utility is generally framed as related to medical intervention or prevention (Holtzman and Watson 1999), results can be clinically useful for reasons other than medical benefit. Provision of genetic results may also reduce participants’ anxiety, inform their reproductive decisions, or inform their life plans in the case of late-onset conditions such as Huntington’s disease. Such an expanded conception of utility is consistent with current clinical testing practices that are justified based on psychological well being and life-planning benefits. It is also consistent with the ethical principle of beneficence that includes benefits outside of a narrow medical context.

The assessment of clinical utility of a research result should include such broader personal benefits. One example of this issue is whether to disclose individual results of the Apo e4 allele, which is associated with increased risk for coronary artery disease (Tiret et al. 1994; Stengard et al. 1996) and for Alzheimer’s disease (Rubinsztein and Easton 1999). To date, the clinical utility of this result for medical intervention or prevention remains uncertain. However, knowing in advance that one is at a higher risk of developing Alzheimer’s disease or heart disease may have clinical utility if this information is useful for decision making about future living conditions.

Threshold of clinical utility. There are several reasons why the threshold of clinical utility for justifying disclosure of results should be lower for individual decision making between patient and clinician in a research context (or a participant and investigator) than for general recommendations for routine clinical practice.

First, individual decision making, provides an opportunity for nuanced decision making by examining the evidence and considering individual goals and values. However, a policy recommendation for routine use may be interpreted as an endorsement of the evidence and may lead to less
deliberative decision-making by a particular patient or clinician. Second, general policy recommendation must go beyond evidence of individual benefits/harms and consider other factors such as budget constraints, and other service delivery issues such as clinician capacity and service quality. For example, although gene expression profiling has not yet been recommended by policy makers for routine use in clinical oncology as a prognostic tool, such profiling can still be useful to inform individual decision making, such as a treatment decision regarding adjuvant chemotherapy (van de Vijver et al. 2002). Finally, adverse outcomes resulting from individual decisions will be limited to a few specific individuals, whereas the impact will be magnified when a policy recommendation is followed by the general population.

Clinical utility and informed consent. The clinical utility of a result is such an important consideration that, even when it has not been anticipated in advance, once it passes the appropriate threshold it should still determine the course of action that should be taken. For example, in a study that examined gene expression in breast biopsy specimens (Hedenfalk et al. 2001), clinically meaningful results were not anticipated and therefore the IRBs waived the requirement to obtain participants’ consent to use their specimens, provided that investigators would not contact them with any results. However, the result from one participant was unexpectedly suggestive of a BRCA mutation. Our analysis suggests that because of the clinical utility of a BRCA result, the investigators should make an effort to facilitate communication with the affected individual and offer this result, even in the absence of an ongoing relationship, expectation of receiving such results, and informed consent. A similar question was raised in a different study regarding whether to disclose the result of a mutation in the cardiac myosin-binding protein C gene, which is associated with increased risk of hypertrophic cardiomyopathy (Verweij and Hamel 2002). Investigators arrived at a similar conclusion and offered the result to the participant even in the absence of prior consent.

A Guiding Consideration: Personal Meaning

Although results that have clear analytic validity and clinical utility should be offered to participants, results that are analytically valid but have less clinical utility are more contentious. For such results, consideration of personal meaning should guide investigators in determining the appropriate approach. (Figure 1). Genetic results have the potential to affect participants’ relationships or personal identity. Issues related to lineage can arise in family studies, issues related to ethnic or cultural identity can arise in ancestry studies (Behar et al. 2003) and issues related to personal identity can arise in studies about genetic associations of behavioral traits that are potentially modifiable, such as obesity or addiction (Shields, Lerman and Sullivan 2004).

In some circumstances, results that have personal meaning may also have clinical utility. For example, a misattributed paternity result may mean that a child is not at risk because she should not have a mutation that has been suspected based on a certain pedigree. In many other circumstances, however, the benefits and risks of learning such information may be difficult to assess or predict, because its meaning and value vary among individuals and their families or communities (Davis 2000). Whereas some individuals may prefer to learn information of this nature, others may not want to know because of the possible harms of disclosure. For example, information about misattributed paternity can have an adverse impact on a family, and information about the genetic basis of tribal affiliation may lead to exclusion of certain members and thus have an adverse impact on the excluded individuals and on the community as a whole.

Potential harms of this kind can justify a plan not to routinely offer results. Investigators should carefully evaluate the benefits and risks of offering such results and exercise caution in planning their approach. They can also assess participants’ preferences empirically by using preliminary conversations with potential participants, focus groups, or community meetings (Fernandez, Skedgel, and Weijer 2004). When participants express interest in results that have personal meaning, these results should be offered, depending on the study context as described later in the text. There is a need for more empirical research to help guide decisions regarding whether to offer results that have complex implications.

CONSIDERING THE STUDY CONTEXT

Genetic research includes studies that investigate a range of patterns of inheritance in a range of populations. These different contexts affect the appropriateness of offering results because they influence investigators’ capabilities for appropriate disclosure, participants’ alternatives for accessing the information, and the relationship between investigators and participants. When clinical utility is high,
contextual considerations help determine the appropriate strategy for making results available (Figure 2). When clinical utility is not as high, contextual considerations help determine the extent of the obligation to offer results (Figure 3).

**Investigators’ Capabilities**

The capabilities of investigators to appropriately communicate results should be considered. Capabilities primarily include maintaining a satisfactory level of quality control in the laboratory and ensuring effective communication by providing genetic counseling when needed.

When the result in question has sufficient clinical utility, there is greater justification for ensuring that results are offered within the framework of the study, and the study budget should be designed appropriately to include such elements as testing in a CLIA-certified laboratory (Figure 2). Moreover, although a clinician-investigator may feel fully capable of communicating the information, a basic scientist-investigator may not be as able to communicate results appropriately. In these cases, a genetic counselor should then be available as a part of the research team.

In some cases, results are clinically useful but resources are limited. For example, an investigator whose laboratory is not CLIA-certified may find that the budget cannot include testing in a CLIA-certified laboratory because the cost will be too high and then the study cannot be performed (Fuller et al. 1999; Fernandez, Skedgel, and Weijer 2004). In such a case, the ethical responsibility to offer results can be met by providing participants with appropriate referral information regarding clinical services for testing and counseling. However, if clinically useful results are not otherwise available outside the context of the study, then the investigators have an obligation to develop their capabilities. Although developing these capabilities will divert resources from other research objectives, the fact that participants have no other access to this useful information can justify this reallocation of resources.

In other cases, results may not have a clearly established clinical utility. In such cases, routinely offering results may not be justified. For example, in a population study of a large cohort, the cost of routinely offering all the results can be so high that planning to do so may impede or hinder the research. Such a plan would strain already limited resources for research that should be invested in a way
that creates generalizable knowledge and benefits the public.

The issue of resource allocation is complex because it is relevant both at the level of the researcher, who is managing a fixed research budget and must prioritize between different research aims, and at the level of the research sponsor or funding agency, who has a fixed (but larger) budget and must prioritize between a number of research projects and their scope. In both cases, different approaches to disclosure will affect the research budget and therefore will affect other research activities. There is a tension between obligations to provide results to participants and obligations to achieve other research objectives. Because neither obligation trumps the other, at both levels a decision has to be made after careful ethical deliberation regarding the balance between these two obligations.

**Participants’ Alternative Access**

Another contextual consideration is whether participants have other alternatives to obtain the specific results in question. In some cases, tests are commercially available even if there are no policy recommendations for routine clinical use. In other cases, alternative access is not possible if no other laboratory has the expertise to perform the test.

Whereas investigators’ responsibility to offer results diminishes when tests are available in other settings, they still have an obligation to inform participants about the clinical availability of testing (Figure 2). This responsibility is particularly important if participants are unaware of the existence of results that may be meaningful to them, which could occur in epidemiologic studies in which associations are confirmed long after initial enrollment. In such cases, sending participants newsletters that update them about aggregate study findings is an appropriate and cost-effective way of fulfilling this obligation. However, when access to results is not otherwise available, and clinical utility has been established (as may happen with a rare condition), investigators are obligated to offer the results and, if necessary, to develop the necessary capabilities (Figure 2).

Information about clinical availability is only sufficient when participants have the ability to pay for testing and counseling elsewhere. However, when a test is clinically useful and participants cannot afford testing, investigators should refer participants to available social support services that may provide funding.

**Relationship Between Investigator and Participant**

The obligation to offer results increases when the interaction with a research participant is more extensive because a more intense relationship creates
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a stronger requirement for reciprocity (Figure 3). The nature of the relationship is defined by the level of involvement (e.g. does the investigator have personal contact with the participant?), the duration of the interaction (e.g. does the reaction extend over many years?), and the nature of the contribution of a participant to the research (e.g. does participation entail discomfort or a time commitment?).

For example, an epidemiologic study of samples that entails no personal contact with participants attenuates justifications to directly communicate results that do not exceed a high threshold of utility. In such a case, it is adequate to send participants a newsletter informing them of the aggregate findings and, when relevant, of the existence of alternative access to testing. In contrast, in a longitudinal study of families with multiple affected members that involves an ongoing engaged relationship with participants, the ethical duty to offer results is amplified because participants who are actively involved in the research process deserve to be offered even more preliminary results whose interpretation is less clear. In addition, the frequent contact can facilitate the communication of the result.

CONCLUSION AND RECOMMENDATIONS

Informational and contextual considerations should guide investigators and IRBs regarding the choice of an appropriate plan for offering or not offering a specific result. Cases of clear analytic validity and substantial clinical utility are relatively easy to resolve. In the research context, however, most results are likely to have less clinical utility and the decision about disclosure requires further evaluation involving personal meaning and contextual considerations. The same result can therefore be handled differently in different studies. Table 1 shows that these considerations may point in the direction of disclosure in study A and in the direction of non-disclosure in study B for Apo e 4 results.

No matter which approach is chosen, it is important to inform participants about the plan during the consent process. Consent forms should explicitly articulate the plan regarding aggregate findings, regarding specific results that have probable implications for participants, and regarding other results that are preliminary and have less meaning. Moreover, the offering of individual results should involve effective communication and address issues such as study limitations, interpretation of data, and the place of the study in the general scientific framework.

In some contexts disclosure is controversial. It is important therefore to conduct trans-disciplinary research on people’s interest in receiving results and on their responses to them. Conducting more studies such as the Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) study (Roberts et al. 2004), which offers Apo e 4 testing, can be useful in providing opportunities to learn more about participants’ actual preferences and evaluate the benefits and harms of offering specific results. When results are offered in a research context, feedback from the IRB may enhance subject protection.

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Table 1. Contextual Considerations in Deciding Whether to Offer Apolipoprotein e4 Test Results.

<table>
<thead>
<tr>
<th>Study Feature</th>
<th>Study A</th>
<th>Study B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Family-based, longitudinal, epidemiologic</td>
<td>Population-based, cross-sectional, epidemiologic</td>
</tr>
<tr>
<td>At-risk population</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Participants Preference of prefer to know</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Investigators–participant relationship</td>
<td>Prolonged and intense</td>
<td>One-time</td>
</tr>
<tr>
<td>Investigators have capabilities for appropriate disclosure (eg, laboratory and counseling)?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

In These Two Hypothetical Studies of a Result (Apolipoprotein e4) with Moderate Clinical Utility (Moderate Clinical Validity and Moderate Likelihood of an Outcome of Moderate Value), the Context of Study A Points Towards Offering Disclosure of Results and the Context of Study B Points Towards Non-Disclosure.
and Elaine Ostrander for helpful discussions on this topic.

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