Offering Individual Genetic Research Results: Context Matters

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The disclosure of individual genetic research results to study participants continues to be the subject of vigorous debate, centered primarily on the nature of the results. We suggest that research context, which is foreseeable when a study is designed, is a vital consideration that has not been sufficiently incorporated into the discussion. Adapting an ancillary care framework to explore what different contexts might call for with regard to offering individual genetic research results, our analysis suggests that, beyond exceptionally rare circumstances that give rise to a duty to rescue, a one-size-fits-all threshold cannot be developed for decisions about returning individual results. Instead, researchers and institutional review boards must consider the scope of entrustment involved in the research, as well as the intensity and duration of interactions with participants and the vulnerability and dependence of the study population.

INTRODUCTION

Whether to reveal individual results to participants in genetic research continues to be vigorously debated. This debate has centered primarily on the nature of the results: What are the criteria for the kinds of information that should, could, or should not be offered to participants? Perhaps not surprisingly, there are widely diverging views about how to define these categories. Although many agree that results should be offered only when they have utility, opinions vary as to whether the line should be drawn at clinical utility (that is, a proven therapeutic or preventive intervention is available), at personal utility (such as for reproductive decision-making or life planning), or in recognition that some individuals will find the information useful in and of itself (for example, through an enhanced sense of personal identity).

Adding to the policy debate is a growing body of evidence documenting participants’ interest in receiving results (1, 2). Being responsive to participant preferences—within the parameters of the responsible use of research resources—may be consistent with the general ethical principles of respect for persons and beneficence (3) and may promote participation and public support of the research enterprise (4). There are good reasons, however, to be cautious in interpreting these data. First, survey responses may not reflect what participants’ nuanced preferences would be if they were given a more complete picture of the limited validity and utility of most individual findings (5). Second, the perceived worth of the information varies at an individual level. Any particular result could be viewed as helpful or harmful, depending on one’s circumstances and values (6). Some have therefore recommended that each participant be given the opportunity at the time of initial consent to choose whether and what kind of results to receive (7–9). However, even if these choices were periodically updated, it is difficult to imagine how participants could be given enough information to make a fully informed decision, except at the time when a specific result is available. Finally, focusing on fulfilling participants’ individual preferences, values, and goals inappropriately conflates research and medical care.

In this Commentary, we suggest that researchers may choose to offer certain kinds of results based on their knowledge of participants’ preferences, but such preferences should not define researchers’ fundamental obligations. Rather, we suggest that research context is a key consideration that has been little discussed but bears explicit analysis. We adapt an ancillary care framework to explore what different contexts might call for with regard to offering individual genetic research results. Assessments of the nature and value of the information may still be required to decide whether to offer a particular result but perhaps will be facilitated by a more grounded understanding of researchers’ obligations in different contexts.

RESEARCHERS’ OBLIGATIONS AND THE IMPORTANCE OF CONTEXT

The goal of biomedical research is to produce generalizable knowledge that will eventually contribute to improved human health. In pursuing this goal, researchers must use sound methodology and uphold scientific integrity, minimize risks and burdens to participants, and exhibit respect for persons by obtaining participants’ voluntary informed consent, protecting their privacy and confidentiality, and ensuring their right to withdraw (10). As distinct from medical care, which requires that physicians optimize risk/benefit ratios and health outcomes for each patient, research does not require such proportionality. Within appropriate limits, it is ethically permissible to expose participants to risks that are justified by the value of the knowledge to be gained (10). In clinical research, for example, participants may be exposed to new therapies whose efficacy and side effects are not fully known. Genetic research typically involves informational risk, including the potential for psychosocial harm and for the loss of privacy or confidentiality.

Within the research context, some studies are designed to examine participants’ understanding and use of genetic information. This is an important area of inquiry to inform the responsible translation of such information into clinical and public health practice, as well as to inform the debate about disclosure of individual research results. However, this aim is not intrinsic to most genetic research, nor should it be. If researchers do plan to routinely offer certain kinds of results, a systematic assessment of participants’ reactions would be desirable, because we currently have limited knowledge about how individuals respond to health-related genetic information. But designing research with disclosure of individual genetic results as an integral component is a morally optional choice, not an obligation of all researchers.

Duty to rescue: A fundamental obligation. A duty to rescue is based on the premise that, when confronted with a clear and immediate need, an individual who is in a position to help must take action to try to prevent serious harm when the cost or risk to self is minimal (11, 12). This condition...
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is met when, in the course of research, an investigator discovers genetic information that clearly indicates a high probability of a serious condition for which an effective intervention is readily available.

These criteria closely resemble the high threshold for the return of results recommended by the National Bioethics Advisory Commission (13) and are perhaps what Greely (14) had in mind when he suggested that the failure to return clinically meaningful research results to individuals “seems, at least in extreme situations, immoral, possibly illegal, and certainly unwise.” His example of such an extreme situation is the finding of a mutation conferring a high risk of early-onset colorectal cancer. Knowledge of the mutation could allow a person to pursue life-saving screening; without a dramatic family history of the disease, the participant might be unaware of the risk. Given the relative novelty of genetic testing in general clinical practice, it is predictable that researchers who uncover this information will be among the few in a position to help, and they can provide this help at little cost to themselves or their studies.

Thus, we submit that uncovering individual results of this kind constitutes a duty to rescue. Endorsement of this duty can be found even among those voicing opposition to the routine return of individual results. Parker (15), for example, affirms that the goal of research is to provide societal benefit in the form of generalizable knowledge, not to address participant preferences for information, but allows that if a result meets “Tarasoff-informed criteria of a duty to warn or disclose, then arguably concern to protect the subject’s welfare would warrant the offer (perhaps even the imposition) of such highly valuable (read: reliable lifesaving or severe-morbidity-preventing) information.” The legal precedent for the criteria to which Parker referred came from a 1976 case (Tarasoff v. Regents of the University of California), in which the California Supreme Court held that a mental health professional had a duty to warn a person in imminent danger from a client, even though the warning breached the client’s confidentiality.

Although the duty to rescue is a legal concept, our intent is to propose an ethical underpinning for what participants have called basic “human decency” when discussing researchers’ obligations concerning genetic information (4). Participants should be informed during the consent process that these kinds of results, which can be expected to be exceptionally rare, will be disclosed. Making this statement, without regard to the choices that participants might be given about what other results they do or do not want to receive, ameliorates the possibility of having to override their stated wishes.

Researchers’ potential obligations. When offering results is not necessary to complete the aims of the study and is not required by the duty to rescue, the concept of ancillary care provides a useful framework for examining researchers’ obligations in different contexts. According to Richardson and Belsky (12, 16), ancillary care obligations are based on (i) the scope of what participants have entrusted to researchers and (ii) the strength of the claims concerning researchers’ responsibilities.

Participants entrust certain aspects of their health to researchers when they enroll in a study, and the scope of this entrustment is set by the specific set of permissions that researchers obtain during the informed consent process to carry out the study validly and safely (12). Thus, the scope of entrustment is partial and depends on the nature of the study.

In genomic research, the permissions obtained are often broad. For example, researchers may seek biospecimens for detailed genomic analysis and request ongoing access to participants’ medical records for studies of “how genes affect health, or how genes affect response to treatment” (17). Even when the initial study addresses a particular condition, consent is often requested to store materials for use in unspecified future research. [This is why separating research results from incidental findings, based on whether the information is related to the study aims (7), is problematic for much genomic research, and we do not make that distinction here.]

Thus, a statement of the scope of entrustment for much genomic research might be “The role of genes in human health and disease.” Despite its breadth, this scope is not unlimited. First, participants in most genomic research entrust their information

Fig. 1. Framework for evaluating researcher obligations. Adapted from (16).
to researchers—not aspects of their health care, as may be the case with the clinical research initially contemplated under ancillary care frameworks. Second, the scope does not cover the entirety of participants’ well-being or matters of personal meaning that have been argued as reasons to offer individual results (18).

In addition, researchers are not automatically responsible for all aspects of health that fall within the scope of entrustment (12, 16). Several contextual factors influence the strength of the rationale for ascribing ancillary responsibilities (Fig. 1), as follows:

Degree of vulnerability. During the informed consent process, participants grant researchers certain permissions—for example, to collect biospecimens and confidential medical information. Participants thus become vulnerable to researchers’ discretion-ary power (16), in that researchers’ decisions about how to respond to the information they collect or generate may affect participants’ well-being (12). This vulnerability may be compounded when participants are ill or experiencing oppression or poverty (16).

Thus, the nature of the study population is an important contextual consideration. As Joffe and Miller note (10), the principle of respect for persons takes on additional dimensions when research is focused on sick individuals because of their status as patient subjects, not just research subjects. They further suggest that investigators must debrief patient subjects at the conclusion of research, provide medically relevant information that has emerged during the course of research, and make appropriate referrals for or provide ongoing treatment.

With regard to genetic research, investigators who plan to recruit participants who have been diagnosed with a particular condition may decide to offer certain kinds of individual results beyond those required by the duty to rescue. For example, they may decide to offer results that inform participants’ understanding of their illness, even when clinical utility is not established. Such decisions can be made during the study design stage, as could plans to involve participants’ physicians in communication about results. The ancillary care framework suggests that the offer of such information may represent an obligation, rather than a choice, when the depth of the relationship and the degree of dependence between participant and researcher are sufficiently strong.

Depth of relationship. The depth of researcher/participant relationships will vary from study to study, because different protocols demand interactions of varying intensity, duration, and longevity. Relationships may also be influenced by institutional commitments; for example, research undertaken within a health maintenance organization may be influenced by the institution’s commitment to its members’ health care. When considering ancillary obligations, researchers have a stronger moral responsibility to engage with a fuller range of participants’ needs when the relationship is deeper (12).

The depth of relationships in genomic research can range from a single interaction to collect a biospecimen and snapshot of health information, to extensive ongoing interactions in community-based participatory research with disadvantaged populations (19). With the advent of large-scale repositories that facilitate unprecedented sharing, a rapidly increasing amount of genomic research can occur with no interaction at all between researchers and the individuals who contributed the specimens and/or data under study.

Depth of relationship is therefore a critical contextual factor in analyzing researchers’ obligations concerning genetic results. We suggest that it be assessed at the level of the investigator (or entity) who originally collects and stores the biospecimens and data for research, with the obligations extending to sharing that occurs under the control of that investigator. If these assessments indicate that the original collector has a responsibility to offer certain kinds of results, secondary users of the stored materials should be required (for example, through material transfer agreements) to notify the original collector of such results.

When data are submitted to centralized repositories, such as the National Institutes of Health’s database of Genotypes and Phenotypes (20), subsequent sharing is no longer under the control of the original collector and may take place long after the original collector’s relationship with participants has ended. Informing participants during the original consent process that they will not receive individual results from this specific kind of sharing places a reasonable limit on researchers’ obligations.

Degree of gratitude. Researchers may owe a debt of gratitude to participants who have accepted uncompensated risks and burdens or offered researchers a hard-to-come-by scientific opportunity (16). Although gratitude is an important consideration in determining ancillary care obligations in clinical research, there are several reasons why it is less applicable for genetic research results.

Framing the offer of individual results as an expression of gratitude implies that participants will receive something of worth in exchange for taking part. In most cases, this would be an erroneous characterization of such results. Further, gratitude should not depend on researchers’ success in answering the study question (such as identifying a genetic trait associated with a health outcome), nor on a participant’s relationship to the findings (such as possession of the genetic trait) (21, 22); out of fairness, expressions of gratitude should be of established and relatively uniform value to all (15). Finally, the offer of genetic information that is unlikely to have much certainty or clinical value may create an inappropriate incentive for people to participate in research that they otherwise would not take part in (15, 23).

For these reasons, we believe that gratitude is best expressed by the provision of aggregate results. Participants volunteer to help generate the data needed to address the study’s research questions—the aggregate results—and informing them of these results expresses respect for them as persons as well as acknowledges their contribution to the study (15).

A special situation arises where advocacy organizations for rare disorders collaborate closely with researchers, providing an otherwise hard-to-come-by scientific opportunity. As part of such endeavors, researchers and families can reach agreement during the study design phase about how results will be handled. However, many of the drawbacks of “gratitude” still apply; the more powerful rationale for providing results in this situation is degree of vulnerability (due to illness) and depth of relationship.

Degree of dependence. Participants may become dependent on researchers because they are impoverished, lack insurance, or join a trial because it is their last hope (16). Thus, researchers may be in a unique position to help participants.

Translating from the ancillary care framework (12), a key question for assessing dependence in genomic research is “How much difference would provision of individual genetic research results make to participants’ health?” In many cases, not revealing individual results would have no affect on participants’ well-being because little is known about the clinical validity or utility of the results.
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In some cases, however, researchers may be in a unique position to help because the genetic information is beneficial and other sources for obtaining it are limited. Health care providers’ preparedness to order and interpret genetic tests and to recommend appropriate followup care, as well as third-party reimbursement for these services, remain substantial challenges (24). These issues of availability and access are features of the larger environment in which genomic research occurs, not of a study itself. However, researchers should monitor this evolving landscape and be aware of the extent to which it affects their study population’s ability to obtain needed genetic services. When results will be offered, participants must still understand that research analyses cannot be guaranteed to occur with the same timeliness as clinical testing.

These three factors—vulnerability, relationships, and dependence—influence the strength of the rationale for researchers’ obligations within the scope of entrustment. Because each of these factors can vary independently, obligations to offer individual results must be assessed for each study (Table 1). In evaluating researchers’ potential obligations (Fig. 1), strength-of-claim factors must be weighed against the importance of reasons for not providing ancillary care (12). In some contexts, the rationale for providing individual results is insufficient to justify spending scarce research resources to do so.

CONCLUSION

Debate over the disclosure of individual genetic research results has stalled, in part because there is ample room for reasonable people to disagree about the value of various kinds of information. Research context is a vital element that has not been sufficiently incorporated into the discussion, and the concept of ancillary care provides a useful framework for assessing the relationship between context and researchers’ potential obligations.

Our analysis suggests that, beyond the fundamental duty to rescue, a one-size-fits-all threshold cannot be developed for decisions about the return of individual results (Table 2). Instead, researchers and institutional review boards (IRBs) must consider the scope of entrustment involved in the research, the intensity and duration of interactions with participants, and the vulnerability and dependence of the study population. The strength of this approach is that the research context is foreseeable at the time when a study is designed. Thus, the possibility of return of results can be planned and, importantly, included with more specificity in research budgets and informed consent processes.

As part of such planning, researchers and IRBs should try to anticipate the results that are likely to emerge, but—perhaps more so for current genetic research than for other types of research—many results cannot be foreseen. Professional judgment will always be required in determining whether to offer particular individual results. However, those decisions should be informed by the obligations that follow from different research contexts.

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