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RETURN OF RESULTS: ETHICAL AND LEGAL DISTINCTIONS BETWEEN RESEARCH AND CLINICAL CARE

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Abstract

The return of individual results to research participants has been vigorously debated. Consensus statements indicate that researchers and bioethicists consider the return of research results most appropriate when the findings are clinically relevant. Even when clinical utility is the motivator, however, the return of individual research results is not equivalent to clinical care. There are important differences in the domains of research and medical care, both from a legal standpoint and in terms of the ethical responsibilities of clinicians and researchers. As a corollary, researchers risk promoting a therapeutic misconception if they create quasi-clinical settings for return of clinically relevant research results. Rather, efforts should be focused on clarity in the provision of research results, appropriate caveats and, most important, appropriate referrals when the results may be helpful to consider in medical care.

Keywords

Genetic research results; medical practice; CLIA; HIPAA

INTRODUCTION

The return of individual results to research participants has been vigorously debated. A prominent argument in favor of returning results is that participants may benefit from clinically actionable information they might not otherwise obtain (Ravitsky & Wilfond, 2006; Greely, 2007; Dressler, 2009; Ramoni et al, 2013). Some also argue that participants have a right to research information about themselves whether or not it is actionable, and that providing results to participants is both a matter of respect and a way to engage participants in the research process (Fernandez et al, 2004; Shalowitz & Miller, 2005;

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Dressler, 2009; Angrist, 2011). However, others argue against the return of individual results, at least as a routine or expected process, on the basis that research is intended to provide generalizable knowledge rather than individual benefit (Parker, 2006a; Parker, 2006b; Dressler, 2009; Clayton & McGuire, 2012); that research results are provisional by nature and could therefore be confusing or harmful (Parker, 2006a; Miller et al, 2008; Dressler, 2009; Clayton & McGuire, 2012); and that diverting research resources to the task of providing individual results is inappropriate (Miller et al, 2008; Dressler, 2009; Clayton & McGuire, 2012).

The issue is not new for genetic researchers. Working with families afflicted with rare genetic diseases, they have often sought to share research information with their participants, particularly when family members might benefit. In a compelling case reported in 1993, Biesecker and colleagues describe a research team confronted with genetic research results of value to participants, in the context of a protocol that ruled out return of results (Biesecker et al 1993). The research was part of a collaborative effort that ultimately led to the identification of the breast cancer gene *BRCA1*. A participant from a large family segregating a genetic predisposition to breast and ovarian cancer contacted the study team to report her plan to proceed with a prophylactic mastectomy. However, the team's linkage data indicated that she had not inherited the family predisposition. The researchers felt they should provide this information to the participant, to allow her to avoid an unnecessary surgery. The paper reports on the team's careful analysis of the implications of their findings, consultation with the Institutional Review Board (IRB), and development of a study protocol to offer results to all study participants (Biesecker et al, 1993).

The example offers a persuasive argument for returning research results in some circumstances. It also raises an important question: If clinical relevance is the motivation for returning research results, how does this process differ from returning test results in clinical care? Two trends make this question increasingly important for human genetic research: wider use of whole genome/whole exome analysis in research is likely to generate results of potential interest for the majority of participants; and genomic information has increasing clinical utility. Media attention to genomic research and its health implications may also increase participant interest in obtaining results.

CLINICAL RELEVANCE AS A CRITERION FOR RETURNING INDIVIDUAL RESEARCH RESULTS

Surveys of researchers and clinicians (Edwards et al, 2012; Lemke et al, 2013; Klitzman et al, 2013; Ramoni et al, 2013), as well as the example described by Biesecker et al (1993), indicate that offering clinically useful information is an important rationale for returning individual research results. Several expert consensus groups have considered the question (National Bioethics Advisory Commission; 1999; Bookman et al, 2006; Knoppers et al, 2006; Wolf et al, 2008; Fabsitz et al, 2010). All have identified medical actionability as a central consideration in determining whether or not a researcher should return results.

Empiric studies of participant views are less clear. Focus groups and surveys both document high participant interest in receiving individual results from research participation

(Fernandez et al, 2004; Murphy et al, 2008; O'Daniel & Haga, 2011; Bollinger et al, 2012; Lemke et al, 2012). Some studies suggest a greater interest in results that are medically actionable, but participants also express interest in nonactionable results (Bollinger et al, 2012; Lemke et al, 2013). These views offer a justification for liberal return of individual research results, and some genomic studies have been crafted to do so (Ball et al, 2012; Kohane and Taylor, 2010).

Nevertheless, the consensus among researchers and other professionals emphasizes the return medically actionable findings (Wolf, 2013; Knoppers et al, 2006; Fabsitz et al, 2010). As a result, participants are most likely to be offered results when they have clinical relevance. In this context, the differences between research and clinical settings must be considered.

RESEARCH VERSUS CLINICAL CARE

Much has been written about the difference between research, which is a process focused on the production of generalizable knowledge, and clinical practice, which is a process focused on the optimal health care of individuals (e.g., Karlawish & Lantos, 1997; Zlotnik-Shaul & McKneally, 2003; Miller & Weijer, 2006; Appelbaum & Lidz, 2008; Clayton & McGuire, 2012). A key distinction involves the differing obligations of researchers and clinicians. Researchers have a responsibility to protect participants from harm, but they are not tasked with optimizing or even taking responsibility for a participants' health care. Rather, a researcher is tasked with preserving the integrity of the research process. Indeed, the therapeutic misconception, occurring when a participant erroneously assumes that a research study will provide clinical benefit, is a major concern in bioethics (Henderson et al., 2007; Appelbaum & Lidz, 2008; Halverson & Ross, 2012). A clinician, by contrast, is committed to providing care directed to the best interests of the patient (Crawshaw et al, 1995; Pellegino, 2001).

Another crucial distinction between research and clinical care relates to the right of individuals to receive information about themselves. In the clinical setting, respect for autonomy demands a high level of patient access to the patient's own health data. This point is reflected as a core principle in the Health Insurance Portability and Accountability Act Privacy Rule (HIPAA Privacy Rule). HIPAA grants patients a legal right to inspect and receive copies of their own health information. No Institutional Review Board (IRB) or other ethical oversight is required; if patients want to receive their own clinical information, providers are obligated to supply it.

In the research setting, there is no similar consensus or legal requirement that research subjects should have access to the information investigators know about them. To the contrary, the weight of bioethical and researcher opinion argues against granting research subjects an unrestricted right to demand return of individual research results (e.g., Knoppers et al, 2006; Fabsitz et al, 2010). For example, Knoppers and colleagues note the emergence of an international consensus on the return of individual research results; however, the results to be returned must meet the criteria of scientific validity, accuracy in identifying or predicting risk, and potential to lead to improved health outcomes (Knoppers et al, 2006).

Further, disclosures to research participants receive careful IRB oversight. An IRB's authority to intervene in this context derives not from HIPAA but from research regulations such as the Federal Policy for the Protection of Human Subjects (Common Rule) that have the purpose of assuring that risks to human participants are minimized. The impact of this distinction is profound and not widely appreciated. An IRB has the authority to restrict individuals' access to information about themselves if the communication is construed as research, but does not have this same authority to restrict access to information incident to clinical care. In research, an IRB may in fact refuse to allow release of information that the investigators believe should be released and that participants want to receive, if it deems the communication to involve unacceptable risk or other participant harms (Common Rule).

Determining the dividing line between research and medical practice is therefore particularly important when research results are being returned due to their clinical relevance. It may be intuitively appealing, but it is legally inaccurate, to view return of results as medical practice merely because it transmits information that may have potential medical significance (Evans, 2013). Law recognizes a distinction between informing a person of the need to seek medical care and actually rendering medical care. Were this not true, many mothers who admonish their children to see a doctor could be liable for practicing medicine without a license. From a legal standpoint, informing a person of the need to consult with a physician is not the same thing as practicing medicine (Gore et al, 2013).

Legally, a communication amounts to medical practice only if it takes place in the context of a physician-patient relationship (PPR) and is part of the process of rendering clinical care (Blake, 2006; Kohlman, 2013). A crucial question is whether the act of returning a medically significant research finding transforms an investigator/research subject relationship into a PPR. How PPRs are formed is a question of state law in the United States, and there is a large body of case law that treats PPRs as contractual in nature: in other words, a PPR can come into being only if the physician and patient both agree (expressly or impliedly) to enter such a relationship (Gore et al, 2013). To establish a PPR, physicians must take some affirmative action with regard to treatment of a patient and, importantly, simply advising an individual to contact another clinician is not by itself sufficient to establish a clinical care relationship (Gore et al, 2013).

Return of research results lacks the treatment step that is necessary to create a PPR and transform research into medical practice. In keeping with this distinction, in *Ande v. Rock* (2002), the only published American court opinion addressing failure to return a research finding (Gordon, 2009), the court treated return of results as distinct from the practice of medicine. Moreover, many researchers are non-clinicians with neither the expertise nor the legal authority to provide clinical care.

Whether return of results is research or clinical care also matters in the context of laboratory regulations. Regulations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) define requirements for clinical laboratories. The CLIA regulations were intended to ensure that laboratory tests used in clinical care meet acceptable quality standards. Laboratories that supply test results for use in clinical care must be CLIA-certified or CLIA-exempt (together, CLIA-compliant). Research laboratories, on the other hand, have a choice.

Many do choose to comply with CLIA, but CLIA's research exception at 42 C.F.R. section 493.3(b)(2) provides that CLIA compliance is not required if research laboratories "test human specimens but do not return patient specific results for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of individual patients."

This language in section 493.3(b)(2) stratifies the need for CLIA compliance, depending on the *purpose* for which a laboratory reports results. It is not at all uncommon for compliance obligations to vary depending on the regulated entity's purpose: for example, individuals need a driver's license if they plan to use a car for driving, but not if they only plan to use it for riding. Unfortunately, the CLIA regulations do not clarify how to assess whether a test report is for "diagnosis, prevention, and treatment" as opposed to being for some other purpose. Returning an ancestry or recreational genetic test result clearly would not meet this criterion. However, when a result has potential clinical relevance, does it follow that any communication about that result is for "diagnosis, prevention, or treatment? If the investigator intends the report for one purpose, but it is later misused for another purpose, which purpose governs? The CLIA regulation is defective in its failure to clarify these matters.

With respect to clinically relevant results, some sources suggest that the CLIA regulations "prohibit the return of results to patients unless the laboratory is CLIA certified" (SACGHS, 2008) and that CLIA "[i]ncludes research when results are returned and specimens have unique ID" (Yost, 2003). These interpretations construe section 493.3(b)(2) as requiring CLIA compliance if clinically relevant individualized results are returned for any purpose or under any circumstances. This, in effect, treats the return of clinically relevant research results as equivalent to provision of medical care. Clearly, if return of results amounts to medical care, CLIA compliance seemingly would be inescapable. Yet, as described earlier, law strongly supports the conclusion that return of research results is *not* in itself medical care. Signaling the need to seek further diagnosis and treatment serves a purely informational purpose and does not, itself, amount to diagnosis and treatment. According to this analysis, a research laboratory that returns individual results could take advantage of CLIA's research exception and elect not to comply with CLIA, if return of research results is kept within the boundaries of informational communication and avoids crossing the line into clinical care.

CASE EXAMPLE

The importance of these distinctions for researchers can be illustrated by a hypothetical example:

Example: Tumor tissue is submitted as part of a research protocol evaluating an innovative gene expression profile for prognosis and treatment guidance in a specific type of lymphoma; research procedures are performed in a laboratory that is not CLIA compliant. Inconsistent results lead to further evaluation of the tissue sample, which suggests that the participant's lymphoma diagnosis is incorrect. These results have implications for the participant's care. Confirmation of these

findings will require evaluation of a new sample with diagnostic probes not available in the research laboratory.

Because the results would be valuable to the participant and the participant's health care providers, many researchers would perceive an ethical obligation to return such findings. Before returning the results to the participant or referring physician, however, the researcher would require IRB approval.

In considering the issue, we argue that an IRB should take into account the following points: (1) Failure to return the results could result in significant harm to the participant due to failure to achieve the correct diagnosis and treatment; (2) According to the legal definition of medical practice, returning these results does not constitute the provision of health care, because the research team is not assuming responsibility either for confirmation of the research findings or for health care decisions based on the confirmed results. Importantly, the research results in themselves do not constitute a clinical diagnosis. Rather, the researcher is offering information that may be useful to others (the participant and his/her health care providers) in undertaking examination, testing or other medical care aimed at diagnosis or treatment; (3) The lack of laboratory CLIA compliance should not therefore be a bar to returning the results; (4) A responsible plan for return of results should include adequate documentation that the sample has been accurately identified; clear explanation of the research finding, with appropriate caveats regarding the need for follow-up testing and cautions against direct use of the result in medical care; and a clear recommendation for medical follow-up.

We note that this interpretation differs from commonly held views about the CLIA research exception (e.g., Hudson, 2011). However, we believe that the CLIA regulation, like other legal texts, is best interpreted in light of the established canons of legal construction that courts apply when interpreting the wording of statutes and regulations (Scalia and Garner, 2012). Terms like "treatment" that appear in CLIA's research exception need to be interpreted with reference to state law sources that define the scope of medical practice and, therefore, inform the distinction between medical practice and research. These sources of law, as discussed earlier in this article, strongly support an interpretation that the return of results does not, by itself, amount to medical treatment (Gore et al, 2013; Kohlman, 2013, Blake, 2006; *Ande v. Rock* (2002)).

This case example, like the case reported by Biesecker et al (1993), points to the importance of returning clinically relevant research findings in some instances. We argue that there is no legal bar to returning such results, and a strong ethical justification to do so. However, there is also justification for limiting the individual research results that are returned. Relatively few results will have the time urgency and clinical significance of those described in these examples. In addition, research laboratories may not always have procedures in place that are sufficient to ensure adequate identification of the sample.

A stringent default expectation for return of individual research results is also consistent with responsible use of research resources. Some research studies may of be designed to return a broad array of results, or to focus on return of results as an area of study. But for research studies that do not have such an emphasis, results arguably should be returned only

when there is a compelling reason to do so, such as the provision of clinically relevant information that the participant might otherwise not be able to obtain. This approach avoids deflecting resources intended for research goals to the process of returning results. This issue is potentially of concern to participants as well as researchers and funders. For example, a recent study of biobank participants affirmed participants' interest in receiving personal results, but also found that participants would prefer that resources allocated to return of aggregate results be directed to additional research instead (Bane et al, 2013).

Finally, determining how to return individual research results without triggering a therapeutic misconception is an important research question in its own right. In some cases, as in our hypothetical example, the hand-off between research and clinical care can be accomplished through contact with a referring clinician. In other cases, methods will be needed to ensure that participants are given accurate information and recommendations, while helping them to understand the difference between a research finding and clinical care.

WHEN RESEARCH IS INTEGRATED WITH CLINICAL CARE

Although research in general is distinguishable from clinical care, and is subject to different ethical expectations and legal requirements, some research projects blur this distinction. Clinical trials that occur in the health care setting are an example. In these studies, participants may agree to be randomized to experimental or usual care arms but the experimental treatment is provided as part of the participant's health care. An example of integrating genomic research into clinical care is provided by the National Human Genome Research Institute's CSER consortium (CSER); each study in this consortium is providing genomic testing in a clinical setting, in order to investigate questions related to clinical implementation of whole genome and whole exome testing. As a measure of the clinical integration of these studies, genomic results obtained as part of the research studies are reported to the participant's medical record.

In some research, particularly clinical studies of rare diseases, the researcher may also be a member of the clinical care team for the participants. This research setting imposes obligations on the researcher to ensure a careful informed consent process aimed at ensuring not only voluntariness of research participation but also that the research will not detract from the patient's clinical care. Safeguards may be needed to separate clinical from research procedures in this context.

Even when research is undertaken as part of clinical care, the research and clinical care activities are theoretically and legally distinguishable, but these distinctions may be so fine as to create a risk of patient confusion or inadvertent regulatory violations. In such situations, the prudent course often is for investigators simply to presume that the regulatory requirements of clinical care apply. Thus, results reported to participants in the CSER studies are derived or confirmed in a CLIA-compliant laboratory. Participants in these studies receive care from licensed clinicians who can assume responsibility for the appropriate clinical use of the genomic results.

Most genomic studies, however, are not conducted in clinical settings or integrated with clinical care. While there are unresolved questions about the best approach to returning research results for these studies, the starting point should be an acknowledgment of the substantial practical, legal and ethical differences between research and medical practice.

CONCLUSIONS

Research is distinct and separable from medical care, both legally and ethically. This difference has important implications for the return of clinically relevant research results. There is no legal duty on the part of researchers to direct their efforts toward medical well-being of research participants, nor to disclose individual research findings. Conversely, there are strong ethical justifications for returning research findings that provide participants with clinically relevant information, particularly if the information would be difficult or impossible to obtain by other means. Returning a broad array of individual research findings to participants is possible, but the merits of doing so need to be balanced against the costs of applying research resources to this purpose. The procedures used in either case cannot be considered equivalent to the provision of clinical care.

From a regulatory standpoint, the applicability of CLIA regulations to this process is questionable, unless the research is being conducted as part of the participant's health care. In some instances, using lack of CLIA certification as a rationale for blocking return of results is ethically problematic. If, as in our hypothetical case example, the results are of high clinical relevance, time urgent and impossible to replicate in a CLIA-certified laboratory, withholding results would arguably result in unacceptable harm to the participant.

Defining what research results should be returned, even among those that are clinically relevant, remains a matter of debate and may vary with research context (Beskow & Burke, 2010; Lakes et al, 2013). Nevertheless, when a researcher and IRB agree that a result should be returned, the distinction between research and clinical care remains important. Appropriate methods for returning results in a research context are not defined and would benefit from further investigation. Because returning an individual research results is not equivalent to clinical care, however, researchers who provide results should avoid acting as clinicians (even if they are, in fact, clinicians).

Thus, while return must be competently handled, our analysis suggests that the call by some experts to require the return of genetic research results by genetic counselors is ill conceived (e.g., Dressler, 2009). Researchers should not assume responsibilities of care, nor does it benefit the participant if they appear to do so. They risk promoting a therapeutic misconception if they create quasi-clinical settings for return of clinically relevant results. Rather, efforts should be focused on clarity, appropriate caveats and, most important, appropriate referrals when the results may be helpful to consider in clinical care.

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Biography

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