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PERSPECTIVE

Five Principles: Returning Genetic Testing Results to Research Participants

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In recent years, genomic testing has become increasingly common in both research and clinical trials, sparking a debate over whether and how genomic testing results should be returned to research participants. In the past, many institutional review boards required that the consent form research participants sign must stipulate that they would not have their genetic results returned to them. However, with the increased availability of these results, the question as to whether genomic testing results should be returned to research participants and under what circumstances has become important. A meeting in October 2013 with the Clinical Sequencing Exploratory Research Consortium and the Electronic Medical Records and Genomics Network addressed this issue (Jarvik *et al.*, 2014). With the idea in mind that research studies should ''be as noncoercive and respectful to participant choice as possible,'' those attending the meeting agreed on five basic principles that should be followed upon returning genomic testing results to research participants.

Principle 1 states that there is a difference between clinical care and research, resulting in a difference in the nature and amount of information returned to the patient between the two situations. Principle 2 states that researchers performing genomic testing would not have to examine areas of the genome that are not already being examined during their study. Principle 3 states that if the results are returned to the participant, this should be done in a way such that the results can be understood well. Principle 4 states that information of an ''important and actionable'' medical nature discovered about the participant during the research process should be returned to the participant. Principle 5 states that if the participant does not give his or her consent for return of results, then the results should not be returned to the participant.

Difference Between Clinical Care and Research

Principle 1 discusses the differences between research and clinical care, reflected in the differences in the relationship between the researcher and participant and between the physician and patient. While a clinician's main focus is the patient, this is not the case for the researcher. The researchers' main objective is their study, although they still have an ethical obligation to respect the research participant and have a duty to avoid harming the participant (Terry, 2012).

Limited to the Area of the Genome Under Study

The main goal of principle 2 is to establish that returning important genomic results to participants should not put an unreasonable burden on the researcher. Researchers should not have to go outside the boundaries of their study to discover genomic testing results that are viable and qualified to be returned to the participants. While the American College of Medical Genetics and Genomics (ACMG) recommended returning ''incidental'' findings, it is believed that not many genomic findings from research studies are truly incidental. Identifying viable genomic results to be retuned to a patient requires a great deal of analysis by the researcher and is not likely to be done in a majority of genomic studies. The second principle also states that while returning results to a participant may have an additional financial cost, if researchers believe that there is a possibility these results could arise, they should estimate the cost and include it in the budget. This principle further states that the obligation to return genomic results to participants ends at the conclusion of the funding period.

A Floor and Ceiling for the Level of Detail of a Result

Principle 3 discusses the level of detail in the genomic testing results returned. The point of principle 3 is to create a ''floor'' and ''ceiling'' for that detail. The minimal results, or floor, would consist of only returning important genomic findings within the boundaries of the research to the individual; the maximum amount, or ceiling, of results returned would be the individual's entire genome sequence with interpretation. We suggest that a higher ceiling is the entire genome and interpretation.

Actionable Results Should Be Returned

Principle 4 aims to establish that any valid results of an important and actionable nature should be returned to the participant, although what is ''actionable'' is a matter of judgment. A starting point for what is considered actionable

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could be the 56 disease–gene pairs offered by the ACMG. However, this principle raises the question of the age at which it is appropriate to return results and whether and when adult-onset conditions should be disclosed. According to meeting attendees, if parents have consented to receiving genomic results for their child, the family is known to carry an adult-onset condition, and this condition would not change the child's upbringing, testing the child for the variant causing the condition has little to no benefit. However, if the variation would cause a significant change in the child's upbringing, such as screening or diet, then the family would benefit from learning about the condition. In addition, there may also be a benefit to the family if a child is tested and a variant is found (one not known to be carried in the family), alerting other family members that they should be tested for the same variant.

Consenting to Receive Research Results

The point of the principle 5 is to clearly establish that the participant must consent to, but also has the right to refuse consent to, receiving genomic testing results. If return of genomic testing results to the patient is possible, this should be established in the original consent form signed by the participant and should be clearly explained to and understood by the participant. In addition, if returning genomic findings is a main portion of and necessary to the study, then participants should be allowed to decline enrollment entirely. Parents should also have the right to refuse the return of genomic results of their children, unless there is a large health significance to returning the results to the minor in childhood. It was also suggested that participants be reminded of their right to refuse results before receiving them. This brings up the suggested phrasing conversations between researchers and participants: ''If we find … do you want'' rather than ''we have … do you want.''

At the conclusion of the meeting, the attendees agreed that results be returned to participants only with compelling reasons and careful explanation, although two areas of controversy remain that require further discussion. The first is the role of Clinical Laboratory Improvement Amendment (CLIA) compliance, and the second is the optimal methods for return. There is controversy as to whether non–CLIA-compliant results should be returned to participants or exclusively results produced in CLIA-compliant labs. One analysis concluded that people have a ''First Amendment right for a researcher to share non-CLIA results with a willing participant'' (Evans, 2014). There are also questions revolving around how the results should be returned to participants. Some advocate that methods be returned only in person during a face-to-face meeting, through a genetic counselor or clinical provider, while others argue that a computer-aided and Web-based return could be possible. Although areas of dispute remain, the attendees agreed that research differs from clinical settings, researchers do not have to go out of their way to find genomic results important enough to return to the participant, results should be returned to the participant in a way that they can be understood, information of an important and actionable medical nature discovered during a study should be returned to the participant, and the participant has the right to refuse to consent to the return of results.

It would be good to now vet these principles with participants, the individuals who would be most affected by decisions predicated on them. Few mechanisms are available to engage the public in these issues, but community and participant engagement must be increased if we are to build an effective learning healthcare system. The lines between research and clinical care continue to blur as we advance toward iterative systems that incrementally improve on the basis of established feedback systems. It is time for the voice of the participants to be heard and for principles such as these to reflect their preferences.

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