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THE AMERICAN SOCIETY OF HUMAN GENETICS

Public Comment Submitted to the National Academies Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories

Submitted by: The American Society of Human Genetics

November 30, 2017

Dear Dr. Botkin,

The American Society of Human Genetics (ASHG) appreciates the opportunity to provide comments to the National Academies Committee investigating the return of individual-specific research results generated in research laboratories. ASHG, founded in 1948, is the world's largest genetics professional society, with some 7,000 members representing all areas of research and application in human genetics. The Society's membership comprises diverse professionals in medicine, genetic counselling, genetics and genomics, molecular biology, biochemistry, and other areas of experimental science, as well as computational science, statistics, and epidemiology. Our members have been at the forefront of return of results research and practice over the past decade and many have extensive knowledge and experience in the relationship of genomic variation to health and disease and of clinical applications of genomics such as diagnosis and assessment of disease risk.

Executive Summary

ASHG members collaborated to outline areas of consensus as well as issues requiring further discussion regarding the return of individual-specific research results from genetics research studies. ASHG believes that finding consensus regarding returning individual research results is critical, and hopes that the National Academies Committee can use these comments as a starting point for developing its recommendations. ASHG identified four main areas of consensus in the genomics community regarding return of individual research results which include: an obligation for researchers to offer to return valid medically actionable results of high health importance that are related to the primary indication for testing; the need to include research participants in decision-making specifically regarding which results to return; a need for research funding to support the return of research results when expected as part of a research study; and the consideration of the research context and the limitations in research-based assays and variant interpretation methods, which do not meet clinical-grade thresholds. Despite these areas of agreement regarding return of research results, ASHG also highlighted four main areas that require further discussion to reach consensus in the community. These issues include: how to

operationalize the return of results depending on the research context; a need for consensus about which primary research results to return; recommendations for transitioning research participants to clinical care; and the need for a greater understanding of research participants' attitudes towards and use of any returned research results. ASHG urges the Committee to recommend allocating additional resources to further study these areas of disagreement in the research community to facilitate the development of widely accepted guidelines regarding the return of individual research results.

Consensus in the Genomics Community

The issue of returning individual-specific research results is a complicated, multi-layered one, especially in the context of genomics research. There have been discussions amongst researchers, bioethicists, research participants, and clinicians over the past several years, resulting in a number of published consensus statements[1,2,3] on issues related to return of research results. Through this comment, ASHG would like to highlight areas of agreement with these existing statements as well as areas in which a clear consensus has not yet emerged, thereby providing a starting point for the Committee's recommendations at the conclusion of its study.

Recent consensus statements can be divided into a few common themes regarding the return of individual genomics research results, which are detailed below.

The importance of the research environment and the context of different research studies.

ASHG supports the notion that the research environment is *not* the same as that of clinical care, and that existing clinical guidelines should not be assumed to apply to the research setting. It is important to ensure that guidelines developed for the return of individual research results recognize this difference and are formulated with careful review of the legal, ethical and social context. Furthermore, the context of the research environment matters. Unlike in the clinical setting, researchers do *not* generally have a responsibility to provide healthcare for participants, research-based assays and variant interpretation methods are not necessarily equivalent to clinical-grade testing, and research studies have finite funding periods. There are many different considerations that vary among studies that may influence the manner and difficulty with which researchers can return results to participants. The diverse environments in which human genomics research takes place include, among others, basic research laboratories that are not affiliated with clinicians or producing clinical outcomes, biobanks that collaborate with multiple researchers using

[1] Jarvik, G.P. et al. (2014). Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between. The American Journal of Human Genetics *94*, 818-826.
[2] Wolf, S.M. et al. (2012) Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks and Archived Data Sets. Genetics in Medicine *14*. 361- 384.
[3] Wolf, S.M. et al. (2015). Returning a Research Participant's Genomic Results to Relatives: Analysis and Recommendations. Journal of Law, Medicine & Ethics *43*. 440-463.

the same samples, and large population studies without specific hypotheses guiding the initial collection of biospecimens and data, like the *All of Us* research program.

Obligation of researchers to return results.

ASHG and many published consensus statements agree that researchers should offer to return valid medically actionable results of high health importance that are related to the primary indication for testing. Regarding incidental (also called secondary) findings, ASHG believes that researchers do *not* have a general obligation to systematically query for these when they are beyond the scope of the primary research question—i.e. there is no duty to hunt for returnable results, the type of results that are not known to the researchers in the course of their work. However, the specific results that should be returned will vary depending on the context of the research program and research question being studied. While researchers should return medically actionable research findings of high health importance within the context of the research study, we agree with the many consensus statements saying that researchers may decide to offer back a larger set of findings to research participants. All classes of results that might be returned should be addressed during the informed consent process. ASHG also agrees that researchers have no general obligation to recontact participants outside of the study's funding period.

Inclusion of research participants in decision making.

ASHG endorses the concept that research participants may be offered the chance to decline receipt of any research findings. Though many surveys have shown that most research participants expect to receive results that are important for their health, not all research participants want to receive research results. There are a couple of approaches to address this. The first is that the participant can be offered the opportunity to opt in or out of receiving research results. The second approach is that researchers can exclude participants from the study who do not wish to receive results. For example, this can be appropriate in studies where return of results is part of the study design or other situations where researchers have determined that return of results is appropriate.

Research funding should include support for return of results.

To fulfill researchers' duties to address return of results, ASHG suggests that grant funding and other resources should be provided for qualified professionals to return results when that is expected to be a part of a research study. However, researchers should not be obligated to return research results after a particular project is completed or when they are secondary data users.

Issues Requiring Further Discussion

Despite the above points of consensus, there are still areas of disagreement in the genetics and genomics community regarding the details of which research results to return and how to return

them. These areas of disagreement are described in the above references as well as in others that are focused on returning incidental and secondary research findings.[4,5] These areas of disagreement reflect interests of the research community and the public in developing a consensus on how best to return research results. It is ASHG's hope that the Academies report will encourage continued research and discussion to resolve these areas of disagreement.

Determining the research context and operationalizing the return of results.

There is no one-size-fits all model for a research framework. There are many variables that influence the research results that are obtained and how they should and can be returned to participants. These factors include characteristics of the participants themselves (e.g., newborns vs. cancer patients), the genetic anomalies being investigated (e.g., somatic cancer genomes vs. rare disease), and the clinical background of the research team members (e.g., oncologists vs. medical geneticists). A significant area of concern is how to customize return of results for different research contexts in human genetic and genomic research. Guidelines offer general direction, but putting them into effect in a specific project requires careful engagement with the details of the research design.[4,6]

What primary results should be returned?

Within the consensus that researchers should return medically actionable research findings, there is disagreement on whether and how to validate results before their return. In the United States, officials from the Centers for Medicare & Medicaid Services (CMS) have taken the position that results returned to patients or research participants needs to be generated or confirmed in a CLIA-compliant lab. On the other hand, a detailed legal analysis of the CLIA law does not provide support for this CMS interpretation and concludes that return of non-CLIA results to desiring research participants is likely legal.[7] This has never been tested in court. There is debate in the genetics research community on whether the burden of obtaining CLIA laboratory accreditation is necessary, and if the CLIA designation improves the quality of the result.[8] There is also concern that researchers could use non-CLIA methods to avoid return of results. Researchers also continue to discuss whether guidelines for return of adult-onset medically actionable results should be the

[4] Darnell, A.J. et al. (2016). A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research. The American Journal of Human Genetics *98*. 435-441.
[5] Opportunities and Implications for Research Stemming from the ACMG Recommendations for the Return of Incidental Findings in Clinical Genome Sequencing. Workshop Summary. (2014). https://www.genome.gov/pages/policyethics/healthissues/nhgri_incidental_findings_workshop_summary.pdf Accessed November 13, 2017.
[6] Ravitsky, V. and Wilfond, B.S. (2006). Disclosing Individual Genetic Results to Research Participants. The American Journal of Bioethics *6*. 8-17.
[7] Evans, B. (2014). The First Amendment Right to Speak about the Human Genome. University of Pennsylvania Journal of Constitutional Law *16*. 549–636.
[8] Burke, W., Evans, B.J., and Jarvik, G.P. (2014). Return of Results: Ethical and Legal Distinctions Between Research and Clinical Care. The American Journal of Human Genetics *166*, 105-11.

same for pediatric and adult research participants[1], and what is the minimal gene or variant set that should be returned based on high health importance and actionability.

How should the transition be handled from research ascertainment of a finding to clinical care?

While the genetics research community agrees that medically actionable results should be returned if a research participant agrees to receive the results, an important question is how best to return research results in order to support an appropriate transition to clinical care. There is general consensus that researchers returning a result should recommend that the research participant consult with a qualified healthcare provider when necessary, but the appropriate way to accomplish this clinical "hand-off" depends on the context of the research study. Some researchers recommend that participants list a healthcare provider or detail their health insurance coverage when they enroll in a study. However, not all research participants may have an established healthcare provider and insurance coverage, which introduces issues of health inequity. Though guidelines on return of results have urged researchers to plan for these problems by creating feasible referral pathways for these participants, the details of how to do this needs more work.

Understanding participants' attitudes towards and use of research results.

Finally, more research is needed into participant and family attitudes towards returned research results, as well as on the impacts of returning results on researchers, health care utilization and other outcomes. In addition, there is debate concerning how best to handle research participant "requests for" their results, including uninterpreted sequencing data files (e.g. BAM files). The *All of Us* research program has promised to return all individual data to participants, and ASHG believes there is much research to be done into how participants value and might use these raw data, as well as best practices in doing so. Altogether, further work needs to be done to understand the range of outcomes for participants who receive data or interpreted results from research studies.

As we have indicated, there is considerable consensus on many aspects of return of individual results, even though there are dissenting opinions on what limits should exist for returning research results. Most importantly for the Committee's work, there is agreement that attaining consensus on a set of guidelines for returning results is badly needed. The way to generate the necessary consensus is through a better understanding of participant, researcher, and other societal perspectives; analysis of clinical and social outcomes based on what results a participant chooses and receives; how research results are returned to participants and followed up; how the process of returning results is supported; and how to approach the return of results when participants lack an established healthcare provider or insurance coverage.

Recommendations

Moving forward, we encourage the National Academies Committee to consider these comments as a starting point for building a consensus in the community and in society as whole, and also to encourage the allocation of research funds to studying topics involved in the return of research results that would benefit from further investigation. ASHG also encourages that genetics and genomics studies, including the *All of Us* research program, play a role in studying the contentious issues outlined above. ASHG sees such studies as an opportunity to learn more about researcher, participant, clinical impact, and other social perspectives in a way that will help to establish best practices that can be followed by researchers in many research contexts.

We at ASHG thank you for your consideration of our comments and suggestions. We would welcome the opportunity to serve as a resource to your Committee as it moves forward with its important work.

Sincerely,

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