NHLBI TOPMed Program
Ethical, Legal, and Social Issues (ELSI) Committee (DRAFT) Report

January 5, 2016

The Trans-Omics for Precision Medicine (TOPMed) Program is an NHLBI sponsored research initiative to use whole genome sequencing (WGS) and other 'omics technologies with deep phenotyping in contributing cohorts to define genetic contribution to disease and risk factors. The charge to the TOPMed ELSI Committee is to provide guidance to the TOPMed Steering Committee regarding the generation and use of WGS data in the ethnically and culturally diverse collections of participants in the project. While TOPMed is a research project focused on identification of genes and variants, these data may provide powerful prediction for a selected number of heritable conditions. Because WGS data can identify Mendelian conditions, they can also have implications to family members of the participant in TOPMed. As such, there are significant considerations about return of results, including decisions about which results are suitable to return, the process used in transmitting the information, and appropriate recognition of personal and cultural expectations. In addressing these issues, the heritable nature of these data and impact on the participant and their relatives need to be considered. Over the past three months, the TOPMed ELSI Committee has considered the following regarding the issue of **Return of Genetic Results**.

Main findings

1. Issues arising in return of research results are influenced by study context, including the information provided in the consent process, the relationship of the investigator with the cohort participants, the status of the study, the composition of the cohort, the results likely to emerge from the study and, potentially, other factors. Therefore, specific policies regarding return of results will need to vary by study.
2. There is a growing consensus in the genomics research community that "actionable" genetic results are the most relevant to consider for return. Typically "actionability" is construed as being clinically actionable, *i.e*., there is some action that can be taken as part of the individual's health care, thereby excluding non-medical, or "personal", utility. By this definition, an example of an actionable result would be a gene variant indicating an increased risk of colorectal cancer, which could inform screening recommendations, while an example of a non-actionable result would be an apoE genotype indicating an increased risk of Alzheimer Disease. We note that determination of actionability may be difficult for many variants and may change over time for a particular gene variant as new scientific evidence clarifies gene disease associations and the benefits of medical intervention. The value of the return of results also depends on the ability of the participant and the participant's community to act on those findings, making actionability further dependent on context.
3. These and other issues related to return of results will benefit from further discussion and consensus development.

Recommendations

1. We recommend that each study develop a provisional policy for return of results, taking into account its consent process, its participant population, the actionability of the results

to be generated by the study, and the practical tasks to be undertaken to support the process of returning results. This provisional policy should define criteria for the return of research results for that study and, for any results to be returned, the responsible parties and the task(s) for which they are responsible. We anticipate that each study will need to develop an evaluative process (for example, a committee to review study results for potential return).

2. We recommend an ongoing dialog within TOPMed regarding the issues arising in return of research results, rather than creation of a static set of rules or guidelines. We anticipate that this discussion will allow the TOPMed consortium to identify broadly shared *principles* to guide return of results and will allow each study to refine its policies.

Should obligations of researchers be time-limited?

- Discussion is needed regarding whether researchers have any obligation to consider return of results beyond the time period of support for TOPMed or for studies that are no longer active (with samples that were collected many years ago). Under what time frame should return of results occur?
- Over time, new scientific evidence is generated. While the definition of "actionability" is unlikely to change, the classification of gene variants as "actionable" may change due to new scientific information. Should variants be periodically reassessed for actionability? If so, who shares responsibility for that task?

Family members

- Return of results policies will need to consider the "benefit" that participant genomic knowledge could provide to family members. We anticipate that this will need to be considered in the context of the study (*e.g.*, unrelated participants with family members; family studies in which not all family members have WGS data, yet were consented to participate; family studies in which other members were not participating in the core study)
- We note that it is defensible to limit researcher's responsibility to cohort participants whose samples are selected for WGS.

Informed consent and notification of potential to return results

- Most TOPMed studies collected informed consent and subsequent data prior to the era of sequencing. At that time. informed consent was consistent with data sharing policies in dbGaP (under controlled access). Most consent forms did not include information specific to "whole genome" (or exome) sequencing and thus likely did not cover the potential for the return of "actionable" findings unrelated to main study outcomes. Further discussion is needed on approaches investigators could or should take to inform participants about the potential for return of results. There may be limitations of what can be done, especially for those TOPMed studies no longer having contact with cohort participants, with pre-existing consent forms. This issue should be examined for each study.

Participants' rights to access

- There is a predominant societal trend for participants and individuals to want control of their own data (*i.e.*, a "right to know" and, possibly, a "right to own"). It is unclear whether

individual TOPMed studies would be in a position to respond if a participant asked for his/her "sequencing data".
- Although return of information to participants upon request may not be covered in existing informed consent forms, the TOPMed consortium should discuss potential responses to this possibility.
- Under the HIPAA Privacy Rule, individuals have a right to access their protected health information contained within a designated record set. It is unclear whether WGS data generated in a research context would fall under a "designated record set" and thus be subject to this legal access right. For more, see:
    - http://www.hhs.gov/ohrp/sachrp/commsec/attachmentc:letter9/28/15.html, and
    - B. Evans et al., Regulatory changes raise troubling question for genomic testing, *Genetics in Medicine* 2014:16:799-803.

Precision Medicine Initiative (PMI) and the NHLBI TOPMed Program
- The TOPMed Program is part of the NHLBI support for the Precision Medicine Initiative. As such, TOPMed investigators should determine how their policies and recommendations are aligned with the PMI.
- The recent PMI report asserts that there cannot be a "one size fits all" model for return of results. Participants need a way to express their personal preferences. This will also vary by population and the characteristics of the participants and their experiences.
- The PMI report recommends that PMI participants should have access to aggregate results. This includes creating a mechanism for reporting aggregate results in lay language and in accessible forms (*e.g.*, on a publicly available website).
- The TOPMed ELSI Committee recommends several options as being responsive to the PMI report, including the reporting of aggregate results to participants through newsletters (SAFHS and MESA) and creating interfaces and resources for individuals to access their own genetic results, consistent with return policies generated for each study.

Logistics
- Should a participating TOPMed study wish to return results, there will need to be a defined, documented approach. This will likely require participant re-contact, confirm interest in receiving results, independent blood sampling, testing the repeat sample in a CLIA-certified laboratory, evaluation by an ACMG-certified medical geneticist, and consultation with a genetic counselor to receive and interpret the result. The cost for returning a result was estimated at ca. $1,000-$1,500 per participant.
- One size does not fit all situations, as the nature of the return process might differ by populations as well as the types of results (*e.g.*, pharmacogenetics versus a *BRCA1/BRCA2* variant).
- The committee recognizes that this is a new and rapidly evolving field needing additional research. It is recommended that this issue is trans-NIH, and that support for research and application in the TOPMed Program should include additional social science research to generate empiric evidence to inform best practices and inclusion of this cost in individual budgets

Fundamentally, the TOPMed ELSI Committee felt that the TOPMed researchers have an obligation to be transparent to their participants. The informed consent process and research participation more broadly are opportunities to educate participants, to let them know in advance that return of a genetic result is a possibility. A challenge for some TOPMed studies is that they have already collected their samples, so there weren't opportunities for proactive discussions with participants regarding return of results. The challenge for other TOPMed studies is that they need to develop procedures and implement them to conduct these discussions.

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