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Beneficence, clinical urgency, and the return of individual research results to relatives

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In “Genomic Inheritances,” Chan et al. describe their experience returning genetic results of deceased ClinSeq participants to interested relatives (Chan et al. 2012). Their research program routinely returns clinically relevant results generated by whole exome and/or whole genome sequencing (WXS/WGS) to living participants, and was therefore well-positioned to respond to an interested family’s request for information. In weighing the ethical considerations relevant to that request, the authors provide a clearly articulated rationale, based in clinical beneficence, for the passive disclosure of a limited range of genetic results to the relatives of deceased participants. Beyond noting the importance of clinical significance, however, the authors do not comment on which types of findings might be most important to return. We believe that the obligation to return research findings should be explicitly limited to well-validated information of high clinical urgency, and – on account of that urgency – that such information should be actively, and directly, disclosed to all at-risk family members.

Research ethics recommendations support the return of clinically actionable individual genetic results to participants (Bredenoord, Onland-Moret, and Van Delden 2011; Fabsitz et al. 2010), and where those results hold tangible health implications for biological relatives, to participants’ family members (Black and McClellan 2011). However, there is ongoing debate about which of the many potentially actionable findings generated from WXS/WGS are most appropriate to offer to participants. Lack of consensus relates both to finite research resources, limiting the practical feasibility of returning large numbers of individual genetic findings, and to the context-specific nature of the “benefit” participants may derive from such disclosure. Prioritization approaches that rank variants by clinical utility and validity have been proposed to expedite decision-making (Berg, Khoury, and Evans 2011). It is not clear, however, whether considerations for return to research participants can or should apply to participants’ relatives, who may have no direct relationship with the original study and whose likelihood of benefit varies probabilistically with the degree of relationship to the study participant and, for highly penetrant conditions, the mode of inheritance.

We suggest that policies for result return should take into account the distinction between results that could be characterized as having clinical urgency – for example, the finding of a RET (ret proto-oncogene) mutation indicating a risk for multiple endocrine neoplasia type 2 – versus results that provide non-urgent information whose clinical relevance is highly context dependent – for example, the finding of a homocystinuria-associated autosomal recessive mutation. Inheritance of a RET mutation is strongly associated with an autosomal dominant form of hereditary thyroid cancer that is highly treatable, but only if detected at an early stage of the disease process (Waguespack et al. 2011). In contrast, carrier status for a disease like homocystinuria will matter most to those who are actively engaged in family planning, and even then would be unlikely to be regarded as urgent in the absence of prior family history of disease. If beneficence is the paramount consideration in decision-making

about return of individual findings, then information that could mitigate imminent and serious harm should be prioritized for return.

To be clear, we are not suggesting that it is inappropriate to offer clinically actionable but otherwise non-urgent information to research participants. Where research resources permit, the offer of a broader class of individual genetic results with the potential to guide screening behavior or other forms of preventive intervention would be a worthwhile way of acknowledging participants' contributions to research. However, it is important to distinguish those findings that are permissible (but optional) to return from those for which a positive "duty to rescue" overrides other contextual considerations (Beskow and Burke 2010).

This approach clarifies the disclosure of genetic research findings to relatives of deceased study participants in at least three important ways. First, it suggests that only information of immediate, significant health relevance should be offered for return. This would limit the number of potentially returnable findings, reducing the scope of researchers' responsibilities to non-study participants. Second, it implies that findings should be offered to those most likely to share the urgent genetic risk identified in the research participant, i.e. first-degree relatives. This too would have the effect of limiting the extent of disclosure, while requiring study staff to work either with the participant (while living) or a surrogate to ensure that all such relatives are contactable. Third, it suggests that great care should be taken with the transmission of research information to relevant relatives. Patterns of familial communication have been shown to be influenced both by individual beliefs about the desirability of communicating genetic risk and by closeness of relationships within the family (Wiseman, Dancyger, and Michie 2010). Relying on a legal intermediary, such as the executor, to convey results could risk leaving the communication of urgent, and potentially complex, information to an unwilling or untrusted designee.

In summary, we agree with Chan et al. that limited disclosure of the results of WXS/WGS to the relatives of deceased research participants is, in certain cases, ethically appropriate. However, if return is to be based in a rationale of clinical beneficence then that reasoning must be used to more deliberately guide choices about which results are returned, to whom, and in what manner. When knowledge of a deceased participants' genetic status could mitigate imminent and serious harm researchers should use all reasonable means to ensure that such information reaches potentially affected relatives in a timely manner, and with sufficient detail to empower those affected to act appropriately.

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