

## The Ever-Evolving Concept of Clinical Significance and the Potential for Sins of Omission in Genetic Research

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Chan and colleagues (2012) illustrate an approach to a difficult ethical scenario concerning whether or not to return a subset of a deceased individual's genetic research results to his family. Their case arose in the course of ClinSeq, a pilot project intended to investigate the use of new genome sequencing technologies in clinical research as well as the process of returning individual genetic findings. Although at first blush a circumscribed scenario, their case is representative of the ambiguity at the interface of genetic research and clinical practice, and of the ever-expanding expectations imposed on genetic researchers. We agree that it is sometimes warranted to offer the return of selected postmortem genetic findings to the family; Tassé (2011) recently expounded on this topic. However, Chan and colleagues have chosen to disclose only variants deemed clinically significant, where "there is evidence that the variant is linked to a significant harm *and* there are measures that one can take to prevent or treat the potential harm" (Chan et al. 2012). We suggest that the first of these conditions is an ever-evolving concept, and that the second is sufficient but not always necessary.

The assignment of "significant harm" is complicated by the clinical uncertainty associated with nearly all genetic findings in regard to common complex diseases. Reduced penetrance (i.e., where the proportion of individuals with the variant who are destined to develop the associated disease is not 100%, and often much lower) and variable expression of even variants known to be highly pathogenic are the norm in genetics. These issues present major challenges in interpretation and for genetic counseling, especially with respect to the predictive power of the individually rare variants prioritized by the ClinSeq group (Carvajal-Carmona 2010). Such findings are truly "moving targets"; our appreciation of the role of most variants will almost certainly change over time as more data accrue. To insist upon a near-complete level of certainty would preclude the return of almost all variants. Indeed, the mutation underlying Huntington disease is oft discussed precisely because it is a singular mutation that both is well characterized and demonstrates complete, though age-related, penetrance. Many have benefitted from forewarning about this mutation by, for example, using this information to inform reproductive decision making and future planning (Williams et al. 2010), yet this rare variant was singled out as one that would *not* be offered

to be communicated to participating families in the ClinSeq study (Chan et al. 2012). This is because Chan and colleagues predicate disclosure on the existence (today) of preventive or early treatment measures relating to the associated disease.

As an illustration, suppose that Participant 1 (Chan et al. 2012) had a novel, likely deleterious, mutation in the low-density lipoprotein receptor (LDLR) gene and the researchers believed this variant to have a bearing on his elevated cholesterol. They argue that because the adult offspring of Participant 1 may have inherited this variant, and because the putatively associated disease is treatable, such information should be returned. However, an increased risk to these offspring was already known on the basis of their positive family history, and existing general preventive measures were therefore already indicated for them. It would be virtually impossible at this time to quantitatively modify this prior risk to an offspring on the basis of whether they did or did not inherit the LDLR variant in question. One could reasonably ask, what new medical information, beyond lending further confirmatory support, could this variant thus provide at this time? Contrast this “actionable” genetic variant with the mutation underlying Huntington disease, where there may or may not have been any previous indication that the offspring might be at risk, where the mutation is extremely well characterized, and where knowledge of the mutation in the family could present new-found opportunities for benefit. Restricting disclosure to situations in which options to ameliorate the early course of the associated disease are readily available may be somewhat arbitrary if interpreted narrowly, and could lead to an unintended infringement on personal autonomy—that is, a potential sin of omission.

To allow greater acknowledgment of individual autonomy, reportable findings could include select pathogenic variants where there is potential personal utility that is not tied to specific preventive measures. This would be counterbalanced by an increased emphasis on the uncertainty associated with almost all genetic variants. Such an approach would be consistent with recent consensus statements (e.g., National Cancer Institute 2010) and empirical reports (e.g., Bollinger et al. 2012) that downplay the importance of “actionability.” Nor would all reportable variants need to be as certain, or associated with a condition as severe, as the mutation causing Huntington disease. We do not believe that researchers necessarily have an obligation to return such results, but instead suggest that they may, motivated by a desire for reciprocity, even go so far as to choose to offer to return selected, clinically validated genetic results that might have personal meaning to the individual participant or, postmortem, the family. When surveyed, individuals and their families have largely supported the concept that genetic research results are of potential value to report when perceived to explain to some extent the cause(s) of a preexisting condition (Costain et al. 2012). In our study of adults diagnosed later in life with a genetic syndrome and their caregivers, perceived psychological benefits (e.g., knowing more) were greater than perceived direct physiological benefits (e.g., improvements in treatment and management) (Costain et al. 2012). For many rare genetic variants at the moment, such psychological benefits may be more common than direct treatment benefits.

Chan and colleagues and others (National Cancer Institute 2010; Scherer and Dawson 2011) have noted potential disadvantages of disclosure. Counseling and clinical testing of additional family members can be both costly and time-consuming, and can present a

disincentive to consider the return of any substantial number of variants. On the other hand, understanding the family context is a key research imperative. Distinguishing private family mutations from disease-associated variants, and determining penetrance and variable expression, in the course of family studies will lead to greater understanding of variants and thus enhanced clinical significance (Carvajal-Carmona 2010). There are currently inadequate numbers of health care providers who are specially trained to interpret and communicate this information (Scherer and Dawson 2011). The move to return selected research results could help spur further genetics training and education. The potential for psychological harm of disclosure is often cited (Scherer and Dawson 2011), but empirical support is limited. The few existing studies (see, e.g., Ashida et al. 2010; Bloss, Schork, and Topol 2011) suggest that such risks may be minimal, provided the uncertainty about the clinical expression of any variant is clearly communicated in the course of appropriate genetic counseling. More data, including evidence derived from the pioneering ClinSeq study itself, will be informative in this regard. We further emphasize that even if an individual's postmortem genetic finding is disclosed to a family member, that family member retains personal choice about whether or not to be tested for the variant him- or herself at that time or in the future.

We urge genetic researchers and bioethicists to consider adopting an interpretation of clinical relevance that takes into account the natural uncertainty of such relevance and the frequent absence of preventive or other tailored treatment options. The scenario encountered by Chan and colleagues presents a new twist on the long-standing debate regarding the return of individual research results, which may now be giving undue weight to unverified paternalistic concerns about inducing harm and less weight to autonomy and the potential sin of omission. Embracing an evolving and individualized definition of clinical relevance, ever mindful of the limits of our knowledge and the need to effectively communicate these uncertainties, may allow more researchers to give back to those individuals and their families who make their genetic research possible.

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## References

- Ashida S, Koehly LM, Roberts JS, Chen CA, Hiraki S, Green RC. The role of disease perceptions and results sharing in psychological adaptation after genetic susceptibility testing: The REVEAL study. *European Journal of Human Genetics*. 2010; 18(12):1296–1301. [PubMed: 20664629]
- Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. *New England Journal of Medicine*. 2011; 364(6):524–534. [PubMed: 21226570]
- Bollinger JM, Scott J, Dvoskin R, Kaufman D. Public preferences regarding the return of individual genetic research results: Findings from a qualitative focus group study. *Genetics in Medicine*. 2012; 14(4):451–457. [PubMed: 22402755]
- Carvajal-Carmona LG. Challenges in the identification and use of rare disease-associated predisposition variants. *Current Opinion in Genetics & Development*. 2010; 20(3):277–281. [PubMed: 20564784]

- Chan B, Facio FM, Eidem H, Hull SC, Biesecker LG, Berkman BE. Genomic inheritances: Disclosing individual research results from whole-exome sequencing to deceased participants' relatives. *American Journal of Bioethics*. 2012; 12(10):1–8.
- Costain G, Chow EW, Ray PN, Bassett AS. Caregiver and adult patient perspectives on the importance of a diagnosis of 22q11.2 deletion syndrome. *Journal of Intellectual Disability Research*. 2012; 56(6):641–651. [PubMed: 22142442]
- National Cancer Institute. Bethesda, MD: 2010. Workshop on Release of Research Results to Participants in Biospecimen Studies. Available at: <http://biospecimens.cancer.gov/resources/publications/workshop/rrra.asp> [accessed May 21, 2012]
- Scherer SW, Dawson G. Risk factors for autism: Translating genomic discoveries into diagnostics. *Human Genetics*. 2011; 130(1):123–148. [PubMed: 21701786]
- Tassé AM. The return of results of deceased research participants. *Journal of Law, Medicine & Ethics*. 2011; 39(4):621–630.
- Williams JK, Erwin C, Juhl A, Mills J, Brossman B, Paulsen JS. Personal factors associated with reported benefits of Huntington disease family history or genetic testing. *Genetic Testing and Molecular Biomarkers*. 2010; 14(5):629–636. [PubMed: 20722493]