Published in final edited form as:
JAMA. 2014 February 26; 311(8): 795–796. doi:10.1001/jama.2014.369.

Returning pleiotropic results from genetic testing to patients and research participants

Jonathan M. Kocarnik, PhD, MPH[1,2] and **Stephanie M. Fullerton, DPhil**[1,3]

[1]Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA.

[2]Epidemiology, University of Washington, Seattle, WA.

[3]Bioethics and Humanities, University of Washington, Seattle, WA.

Multiple recent guidelines and recommendations, in both the clinical and research realms, call for the return of genetic information (including incidental information) that is clinically useful, and suggest it is appropriate to withhold information that is inaccurate, not actionable, or could potentially lead to harm (1). While based in sound ethical principles, including beneficence and respect for persons, these guidelines have largely ignored an important biological phenomenon long-recognized in genetics: pleiotropy, the concept of a single gene or genetic variant affecting multiple phenotypes (2). Variants in some genes have related pleiotropic effects (e.g. *BRCA1* and *BRCA2* mutations increasing susceptibility for multiple cancer types), while variants in other genes impact multiple phenotypes that are less similar (e.g. mutations in *PAH* leading to phenylketonuria, eczema, light pigmentation, and mental retardation). Insofar as current recommendations do not take pleiotropy into account, such guidelines are incomplete—and in some cases, contradictory. This could pose important practical problems for clinicians and investigators who may be trying to decide which, if any, genetic results to return to patients or to study participants.

Large numbers of potentially returnable genetic variants are likely to be generated from whole genome sequencing and related approaches. Most current guidelines attempt to assign these variants to one of three categories: those that *should* be returned (results given), those that *may* be returned (results offered), and those that *should not* be returned (results withheld). Variants are typically assigned to these categories according to their clinical validity (i.e. the validity and strength of the genotype-phenotype association) and clinical utility (i.e. whether information about a specific genotype is useful for treatment or prevention of disease). Other criteria can include personal utility or analytic validity. However, all current guidelines appear to apply these criteria with reference to a single genotype-phenotype association, without considering such associations in the context of additional pleiotropic relationships. In some instances, this can lead to conflicting conclusions regarding whether or not it is appropriate to return a particular genetic result.

One well-known example involves the *APOE* gene, where applying current criteria to different phenotypic associations with the same genetic variant (epsilon4) may lead to recommendations that this information *may* be returned (due to its implications for cardiovascular disease risk, a potentially actionable phenotype) and, simultaneously, *should*

Correspondence to: Jonathan M. Kocarnik, 1100 Fairview Ave N, M4-B402, PO Box 19024, Seattle, WA 98109, Phone: (206) 667-5257, Fax: (206) 667-7850, jkocarni@fhcrc.org.

The authors declare no conflicts of interest.

Both authors contributed to this manuscript in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Author JMK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

not be returned (due to its associations with a non-modifiable risk of developing Alzheimer's disease). In the face of such conflicting recommendations, an investigator/clinician must decide whether it is more appropriate to not return any information (avoiding potential harm), return only the clinically useful association (promoting potential benefit), or opt instead for full disclosure of all relevant associations, on the assumption that benefits outweigh the potential disadvantages of receiving unwanted or unhelpful information. However, returning only one of several pleiotropic associations will not always be feasible, because a simple web search of the genotype may readily reveal the others. In an era of increasing information availability, media attention, personal health information accessibility, and medical self-management, there is potential for inadvertent psychosocial or physical harm to result from a participant/patient discovering pleiotropic genetic information. This may particularly be the case when ancillary information involves risks for a disease that is more severe, life-threatening, stigmatizing, or less treatable than the initial indication. Importantly, such independent discovery of additional pleiotropic associations may occur long after any initial contact with a clinician, researcher, or genetic counselor.

While this problem of pleiotropy for the return of *APOE* results has been previously acknowledged (3), increasing evidence of the pervasiveness of pleiotropy suggests that this will not be an isolated example (4). A recent study found that 233 of the genes in the NHGRI GWAS catalog (17%) had pleiotropic effects (5). Another study found that 16 of 42 pharmacogenetic genes (38%) gave risk information for diseases other than the pharmacogenetic indication (6). Additionally, several genes appear to be highly pleiotropic: variants in the *TERT* locus, for example, have been associated with at least 24 different tumor types. Moreover, as the identification of pleiotropy requires at least one association to be previously reported, both the number of genes that demonstrate pleiotropic effects, as well as the number of pleiotropic associations for a given gene, can be expected to expand as genetic knowledge improves. Indeed, several studies are actively searching for new pleiotropic relationships with known genetic variants (7). Additionally, efforts to quantify the degree of pleiotropy in animal models suggest that pleiotropy is common in the genome, and that some genes have a large number of pleiotropic effects (2).

To demonstrate the relevance of pleiotropy for result return policy, consider the American College of Medical Genetics and Genomics (ACMG) recommended list of 56 genes for which incidental findings should be sought and reported in clinical exome and genome sequencing (8). Using the publically-accessible Online Mendelian Inheritance of Man resource (omim.org), we counted the number of phenotypes (MIM disorders) listed as having a gene-phenotype relationship with each MIM gene listed in the ACMG policy statement (8). Phenotypes without an assigned MIM number were not counted, and multiple phenotypes with the same MIM number were only counted once per gene.

Of the 56 ACMG genes, 43 (77%) had multiple associated phenotypes listed, with an average of 3.5 phenotypes per gene (range 1–11, eFigure 1). Thus while reporting variants in these genes provides information about the 55 actionable phenotypes described in the recommendations (8), they also provide information for an additional 116 phenotypic relationships (up to 10 per gene) which are not otherwise mentioned or acknowledged. The distribution of pleiotropy observed in the ACMG subset of genes is somewhat similar to the L-shaped distribution of pleiotropy seen in some animal models (2) (eFigure 1). Together, this example suggests that even stringent attempts to limit disclosure of incidental findings to only a highly scrutinized list are still likely to provide additional pleiotropic information that may not meet the same return criteria.

The broad pervasiveness of pleiotropy, and evident complications it poses for return decision-making, demands proactive consideration by clinicians, researchers, and

policymakers with an interest in ensuring responsible communication of genetic information. Pleiotropy poses important implications for return of result decision-making, as well as research oversight and healthcare management. Specifically, more complete classification schemes that consider pleiotropic associations will be needed to determine which results are appropriate to return to patients and research participants, and under what circumstances. The development of such schemes will likely require further policy discussion about how best to weigh evidence of pleiotropic associations—including the type and degree of ancillary information implicated—against other criteria such as clinical utility. Ideally, procedures for evidence review and criteria governing return decisions in the presence of pleiotropy would be widely disseminated and discussed. Resources will also need to be devoted to exploring the responsible return of pleiotropic information, including the investigation of researcher/clinician and participant/patient understandings of the salience of such information. In addition, informed consent practices may need to be developed that specifically acknowledge pleiotropy, and explain the likely conveyance of additional information of unknown significance with potentially any returned genetic result.

While pleiotropy has been documented by geneticists for over 100 years, its effect on the return of results from genomic analysis is yet to be recognized. Clinicians and researchers should be aware that additional phenotypes may be associated with any given genetic result returned, and that this information is easily accessible. For pleiotropic variants, current guidelines provide incomplete and potentially conflicting guidance on what information should be returned to patients and research participants. These guidelines will likely need to be revised to appropriately handle this increasing class of genetic testing results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants R25CA94880 and T32CA09168 from NCI, and grants U01HG006507, P50HG003374, and U01HG004790 from NHGRI. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or the authors' affiliated institutions.

The authors also thank Drs. Ulrike Peters, Carolyn M. Hutter, and Holly Tabor for their mentorship contributions to this project.

References

1. Christenhusz GM, Devriendt K, Dierickx K. To tell or not to tell? A systematic review of ethical reflections on incidental findings arising in genetics contexts. Eur J Hum Genet. 2013; 21(3):248–255. [PubMed: 22739341]
2. Wagner GP, Zhang J. The pleiotropic structure of the genotype-phenotype map: the evolvability of complex organisms. Nat Rev Genet. 2011; 12(3):204–213. [PubMed: 21331091]
3. Wachbroit R. The question not asked: the challenge of pleiotropic genetic tests. Kennedy Inst Ethics J. 1998; 8(2):131–144. [PubMed: 11657425]
4. Solovieff N, Cotsapas C, Lee PH, Purcell SM, Smoller JW. Pleiotropy in complex traits: challenges and strategies. Nat Rev Genet. 2013; 14(7):483–495. [PubMed: 23752797]
5. Sivakumaran S, Agakov F, Theodoratou E, et al. Abundant pleiotropy in human complex diseases and traits. Am J Hum Genet. 2011; 89(5):607–618. [PubMed: 22077970]
6. Henrikson NB, Burke W, Veenstra DL. Ancillary risk information and pharmacogenetic tests: social and policy implications. Pharmacogenomics J. 2008; 8(2):85–89. [PubMed: 17486108]
7. Pendergrass SA, Brown-Gentry K, Dudek SM, et al. The use of phenome-wide association studies (PheWAS) for exploration of novel genotype-phenotype relationships and pleiotropy discovery. Genet Epidemiol. 2011; 35(5):410–422. [PubMed: 21594894]

8. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013; 15(7):565–574. [PubMed: 23788249]