Returning Pleiotropic Results From Genetic Testing to Patients and Research Participants

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Multiple recent guidelines and recommendations, in both the clinical and research realms, call for reporting of genetic information (including incidental information) that is clinically useful to patients and research participants and suggest it is appropriate to withhold information that is inaccurate, not actionable, or could potentially lead to harm. Although based on 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. Variants in some genes have related pleiotropic effects (eg, \(BRCA1\) and \(BRCA2\) mutations increasing susceptibility for multiple cancer types), and variants in other genes affect multiple phenotypes that are less similar (eg, mutations in \(PAH\) leading to phenylketonuria, eczema, light pigmentation, and mental retardation). Insofar as current recommendations do not account for pleiotropy, 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 reportable genetic variants are likely to be generated from whole-genome sequencing and related approaches. Most current guidelines attempt to assign these variants to 1 of 3 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 (ie, the validity and strength of the genotype-phenotype association) and clinical utility (ie, 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 it is appropriate to return a particular genetic result.

One well-known example involves the \(APOE\) gene, for which applying current criteria to different phenotypic associations with the same genetic variant (\(\varepsilon4\)) 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 not be returned (due to its associations with a nonmodifiable risk of developing Alzheimer disease). In the face of such conflicting recommendations, an investigator or clinician must decide whether it is more appropriate to not return any information (avoiding potential harm), return only the clinically useful association...
Although pleiotropy has been documented by geneticists for more than 100 years, its effect on the clinical utility is still uncertain. Pleiotropy, the phenomenon where a genetic variant is associated with multiple phenotypes, can have significant implications for the return of genetic test results. Although pleiotropic effects are recognized by clinicians and researchers, the return of pleiotropic results requires further policy discussion about how best to weigh the evidence of pleiotropic associations—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.

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. Using the publicly-accessible Online Mendelian Inheritance in Man resource (http://omim.org), we counted the number of phenotypes (Mendelian Inheritance in Man [MIM] disorders) listed as having a gene-phenotype relationship with each MIM gene listed in the ACMG policy statement. 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 in the Supplement). Thus, while reporting variants in these genes provides information about the 55 actionable phenotypes described in the recommendations, these variants also provide information for an additional 116 phenotypic relationships (up to 10 per gene) that are not otherwise mentioned or acknowledged. 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 criteria for reporting to patients or research participants.

The broad pervasiveness of pleiotropy, and evident complications it poses for return decision-making, demands proactive consideration by clinicians, researchers, and policy makers 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 health care 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 the 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 clinician, researcher, patient, and participant 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.
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 address this increasing class of genetic testing results.

**ARTICLE INFORMATION**

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**REFERENCES**


