Published in final edited form as:
JAMA. 2013 July 24; 310(4): 369–370. doi:10.1001/jama.2013.41709.

Return of Secondary Genomic Findings vs Patient Autonomy:

Implications for Medical Care

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In April 2013, the American College of Medical Genetics (ACMG) recommended that clinical laboratories conducting whole genome sequencing (WGS) and whole exome sequencing (WES) for specific clinical indications should also analyze and report any mutations identified from a list of 57 genes considered medically actionable, regardless of whether patients wish to receive the results.[1] These recommendations have sparked a heated debate with profound implications for countless physicians and their patients.

The use of exome sequencing is rapidly increasing in clinical care. Pediatricians are using this tool to assist in diagnosing rare conditions. Oncologists are performing genomic analysis on an increasing number of patients, comparing tumor and normal cells to identify somatic cell mutations that can guide selection of therapy. In the not-too-distant future, such sequencing may be incorporated even more commonly into patient care.

Yet, in interrogating the genome for mutations causing patients' disease, laboratories generate data on other genes unrelated to the indication for testing. With some additional effort, laboratories can evaluate genes that confer increased risk for conditions like breast cancer, colon cancer, aortic rupture, and cardiac conditions that can cause sudden death, for which preventive interventions are available. The ACMG argues that laboratories have a fiduciary duty to seek and return such results for the 57 genes on its list. The guidelines suggest that the laboratory should report these results to the physician, who can then determine whether to convey the results to the patient. However, once such information is in the medical record, to believe that a physician would or could withhold such information from a patient appears unrealistic.

Identification of mutations in these genes[2] is not trivial, given the multitude of errors in the scientific literature about the pathogenicity of many genetic variants, the inexact science of predicting pathogenicity computationally, and the inability to perform the necessary functional experiments to test for pathogenicity. Until well-curated human mutation databases are available, patients may be told about many mutations that, because of

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

incomplete penetrance and misclassification of benign variants as mutations, are likely neither to cause disease nor confer substantial risk when ascertained in the general population. It is possible that patients with exome sequencing would be identified as having mutations at a frequency that is much higher than the prevalence of these diseases in the general population. Such erroneous misclassifications could cause anxiety and lead patients to inappropriately seek expensive medical screening (eg, magnetic resonance imaging and echocardiograms) or unwarranted procedures such as prophylactic mastectomies.

Moreover, profound disagreements have arisen over whether mutations in these 57 genes should be reported to all patients, regardless of patient preferences or age. Critics have argued[3] that patient autonomy should be respected by allowing patients to choose whether to receive these secondary findings. Whereas proponents claim that the ACMG recommendations still give patients the choice to undergo exome sequencing or not, opponents counter that patients may need testing for diagnosis and treatment of their conditions, but simply not wish to be tested for these other conditions. Currently, many well-informed individuals with known family histories of cancer syndromes, such as hereditary breast and ovarian cancer (*BRCA1* and *BRCA2*) and Li-Fraumeni syndrome (*TP53*), choose to forgo or defer genetic testing, given that disease manifestations and timing cannot be predicted. Additionally, identification of some mutations (eg, hereditary breast and ovarian cancer) has led to difficulty obtaining life insurance.[4] Furthermore, in some communities such as certain Orthodox Jewish groups, identification of a mutation can severely stigmatize patients and their families.

Additional considerations emerge when the patients are children. For most of the conditions on the list of 57 genes, the mutations are incompletely penetrant and many will not manifest until adulthood. Harm may ensue from identifying children as at-risk during formative critical periods of childhood development when identity is significantly shaped by parental perceptions and attitudes. The new ACMG guidelines contradict the organization's prior guidelines for genetic testing in children formulated with the American Academy of Pediatrics, which recommended against predictive genetic testing in minors for adult-onset conditions that are not medically actionable before adulthood.[5,6] The earlier guidelines suggested that children should be allowed to decide for themselves, when they reach adulthood, whether to undergo these tests. Although some have argued that identification of a child with a mutation will allow cascade genetic testing to identify adult family members immediately at risk of disease, it may only be a few years until genomic screening is readily available, allowing these other family members to pursue testing if they desire.

In response to these criticisms, proponents of the recommendations[7] have argued that physicians routinely seek incidental findings in other areas of medicine (eg, finding a cardiac abnormality on a chest x-ray ordered to examine possible rib fractures). Opponents have responded that radiographic analogies are not wholly applicable, because actively interrogating additional genes is more analogous to adding an x-ray of the abdomen when a chest x-ray was originally ordered.

At stake are fundamental differences in ethical views and interpretations—concerning the ethical responsibilities of clinicians and laboratories, and of paternalism in the name of beneficence vs autonomy. A balance between beneficence and autonomy would seem to be optimal, but striking such a fine balance may prove difficult. Several laboratories have already decided not to follow the ACMG recommendations and instead allow patients to opt-in or opt-out of the interrogation of the 57 genes.

Given the controversy, it is critical to consider what should be done next. Several steps appear vital. First, this debate has been occurring without sufficient data. The pathogenicity

of rare variants and the prevalence and general population penetrance of true mutations in these 57 genes should be determined. Patients' preferences for and responses to this information are currently unknown, but they are actively being sought by researchers and will probably be elucidated in the next 2 to 3 years. Input from all stake-holders should be sought, including patients, patient advocacy groups, and professional organizations such as the American Society of Clinical Oncology. The ACMG policy has sparked a valuable discussion, but careful consideration and debate, continued data collection, and curation and refinement of the classification of genetic variants are all necessary to arrive at the best policy for this important medical tool. Rather than rushing to implement a policy, it seems more prudent to continue discussion, research, and analysis and ensure that all the ramifications of the policy are considered before laboratories adopt the ACMG recommendations. While proponents may argue that policy is urgently needed, such short-term benefits are outweighed by the long-range advantages of developing as optimal a policy as possible.

Acknowledgments

Funding/Support: This research was funded by grants R01 HG006600, R21 HG006596, and P20 HG005535-02 from the National Human Genome Research Institute.

Role of the Sponsor: The National Human Genome Research Institute had no role in the preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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