VIEWPOINT

Mandatory Extended Searches in All Genome Sequencing

"Incidental Findings," Patient Autonomy, and Shared Decision Making

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Viewpoints
pages 365 and 369

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Should incidental findings discovered with whole-genome sequencing or testing be sought and reported to ordering clinicians and to patients (or their surrogates)? **—No.**

An incidental finding occurs when a medical test or procedure directed at one condition unexpectedly reveals a separate finding. An example would be when a radiologist notices a chest mass on abdominal computed tomography. By contrast, the American College of Medical Genetics and Genomics (ACMG) statement proposes that whenever genome sequencing is ordered in the clinical setting, laboratories have a mandatory duty to analyze 57 genes (revised to 56 genes) and to report the results to the clinicians and patients, regardless of the patient's age or medical condition.[1] Any positive findings from these additional analyses are hardly incidental; they are the results of a new recommendation for mandatory testing beyond the scope of the original request that will require a significant amount of time, effort, and resources.[2] This approach is similar to requiring a laboratory to test every blood sample for human immunodeficiency virus, hemoglobin A_{1c} level, and 54 other tests for which early treatment can reduce morbidity or mortality, even if the physician had only ordered, and the patient had only consented to, a cholesterol measurement.

Clinically, implementing mandatory testing for conditions beyond the scope of the original request is unsound. Although the 56 mutations have been found to be highly pathogenic in high-risk patients, their meaning is less clear in low-risk groups. In a clarification to its original recommendations, the ACMG indicated that the testing is to be restricted to "explicitly focus only on unequivocally pathogenic mutations in genes where pathogenic variants lead to disease with very high probability and where evidence strongly supports the benefits of early intervention,"[3] but the studies on which they rely almost exclusively involve high-risk patients and families. As the ACMG stated in a 2012 report on clinical genomic sequencing: "The threshold for determining which results should be returned to individuals seeking screening should be set significantly higher than that set for diagnostic testing due to the much lower a priori chance of disease in such individuals."[4]

Experience with *BRCA* is illuminating. As *BRCA* testing expanded to low-risk women, its positive and negative predictive values decreased significantly.[5] High-risk *BRCA*-positive women are advised to undergo frequent mammograms and to consider prophylactic chemotherapy (eg, tamoxifen) or surgery to reduce their risk of developing cancer. All of these recommendations have health risks of their own: radiation exposure from mammograms, increased risk of thrombophlebitis from the medication, and operative and postoperative complications from surgery as well as the psychosocial costs of perceiving oneself as high risk. As the US Preventive Services Task Force reaffirmed in its 2013 draft update on "Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer," these interventions may cause more harm than good when offered and used by women who are less likely to develop disease.[5]

In some ways, mandatory testing in genomic testing/sequencing beyond the scope of the original request more closely resembles the experience with mandatory expanded newborn screening (NBS) than targeted testing for genes for breast cancer. When parents are informed about a positive result on NBS, they are usually unprepared because consent for testing was not sought and many parents were not aware that screening was being performed. Although NBS was initially developed to screen for conditions for which early diagnosis and treatment were critical to prevent morbidity and mortality, it has now expanded beyond the public health emergency to more of a public health service, with some conditions not requiring immediate action, some not having effective treatments, and other conditions not being clearly pathogenic.[6]

For example, NBS for lysosomal storage diseases such as Krabbe disease was implemented in New York in 2006 and illustrates some of the challenges raised by screening. When this testing was implemented, it was expected that 90% of the variants identified would have infantile onset and that these children would benefit from early identification and treatment. Five years later, the available data show that 90% of the variants are adult-onset and that early treatment—bone marrow transplant—has been much less successful than hoped for.[7] As a result, NBS for Krabbe disease has created a group of children who are now "patients in waiting,"[8] and no one can give their families clear information about when, if ever, symptoms will develop. These "at-risk" children receive frequent follow-up with invasive diagnostic tests with their attendant risks, and their parents can experience distress from the uncertainty. As is so often true, stopping a practice once started is difficult. Expanding testing of these 56 genes to low-risk populations may have the same effect.

Some concerns with the ACMG approach are not solely focused on the current mandatory list of 56 genes but also on the inevitable future lists containing many more genes. In developing these recommendations, key stakeholders, including primary care physicians and members of the public at large, were absent. Other concerns include lack of detailed inclusion and exclusion criteria, lack of piloting in the general population to understand the likely penetrance and expressivity of these genes beyond high-risk families, and absence of consideration about reimbursement or the costs that unwanted testing and disclosure will entail.

Implementing mandatory testing for conditions beyond the scope of the original request is in conflict with key ethical principles of patient autonomy and shared decision making. Autonomy means the authority to make decisions for oneself. To make an informed decision, patients need to know the risks and benefits, the alternatives, and the possible implications of refusal. Mandating that laboratories seek out unrequested information violates patient autonomy because patients who are offered testing using genomic sequencing methodologies must agree to an analysis of their genome more expansive than the clinical question and leaves patients with only an all-or-none decision: agree to more expansive analysis or refuse the sequencing. This position contrasts with the 2012 ACMG statement on clinical genomic sequencing that stated "patients should be given the option of not receiving… secondary findings."[3] Mandating analysis and reporting beyond that recommended by the ordering clinician may lead to harm if patients and clinicians decide to avoid testing in order to avoid unwanted information.

The concept of shared decision making refers to the practice of involving patients and clinicians in an active consent process in which the final decision is based on bidirectional communication of medical facts and patient values. While physicians have technical clinical knowledge, patients make medical decisions based on the medical recommendation as well as cost and their own experiences and values, incorporating their own interests as well as the interests of their families. As such, patients need to have ultimate authority and responsibility for deciding what health care they will receive and what they will refuse. Mandatory testing removes the decision about what tests will be done and reported from the patient-physician relationship. Patient choice about the scope of testing is particularly important because physicians will have strong incentives to disclose all results they receive, knowing that the risk of legal liability from nondisclosure typically exceeds that from disclosing results that patients did not desire.

As expressed in this Viewpoint, these objections to the ACMG recommendations are focused on the mandatory duty to test and to report results. This is not a debate about whether truly incidental findings discovered in the course of a clinical evaluation of the genome should be discussed with patients, but whether a sample collected for the diagnostic purpose of evaluating a particular clinical question must be evaluated for a list of additional health risks even if against the wishes of the patient, the clinician, or both. Our response is a resounding no because this approach violates good clinical practice and the ethical foundations of medicine.

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