VIEWPOINT

Reporting Genomic Sequencing Results to Ordering Clinicians

Incidental, but Not Exceptional

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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)?—**Yes**.

The use of genomic sequencing in medicine is increasing substantially as this technology becomes less expensive and of demonstrated diagnostic utility.[1,2] Potentially clinically relevant incidental findings from clinical exome or genome sequencing (hereafter referred to as genomic sequencing) will arise whenever an individual undergoes genomic sequencing. There is a great deal of controversy regarding how such findings should be addressed by clinical sequencing laboratories because many possible findings are of medical interest and processes for genomic testing and interpretation are not yet standardized. To date, the traditions of genetic testing and reporting have exceptionalized all genetic risk information as potentially dangerous to the well-being of patients. This tradition, in the era of genome sequencing, must be reconsidered.

Recently, the American College of Medical Genetics and Genomics (ACMG) issued recommendations[3,4] that addressed how incidental test results should be handled by clinical testing laboratories. The recommendations include a list of medically important conditions and genes to be evaluated in every case of clinical genomic sequencing, suggest standards for the laboratory in interpreting and communicating variants, and recommend the routine return of these findings to the ordering clinician whenever genomic sequencing is performed, regardless of the age of the patient. In this way, ambiguity in laboratory reporting can be minimized and a common foundation established for moving forward with the reporting of clinical sequencing in the practice of medicine.

The recommendations deliberately diverge in some ways from prior practice standards related to locus-specific testing in clinical genetics. Ethical justifications for these recommendations are addressed elsewhere.[5] The return of incidental findings for a small subset of disorders and genes in genomic sequencing is guided by well-established principles underlying the practice of medicine and is in the best interest of the patient. Incidental findings in clinical medicine are often mischaracterized as unintentional observations.

However, a better characterization would be that such findings are potentially important observations noted during systematic examination by those with appropriate training. For example, a dermatologist consulted for a rash should not miss or fail to report a nearby mole suggestive of melanoma because he or she is instructed and trained to perform a systematic examination of the skin.[6] Similarly, when a radiologist reviews a chest x-ray for the evaluation of a possible rib fracture, he or she has been trained to perform a systematic review of the film, reporting any abnormalities that rise to an established professional standard, regardless of the indication for the study.[7] Importantly, radiologists are specifically trained neither to report every conceivable finding, nor to stop after "satisfaction of search"[8] reveals an indicated finding. Rather radiologists use professional standards to assess and report a subset of unexpected findings that are likely to be medically important. Even though such findings are not always clinically useful, depriving clinicians and patients of these additional findings would not be in the best interest of patient care. In medicine, the search for, and discovery of low-probability, incidental findings by trained health care professionals is not a specified test to which a patient can consent or refuse, but is a process inherent to the performance of good medical care.

The ACMG recommendations have been criticized for ignoring the preferences of patients who might not wish to learn such information. This criticism stems largely from the history of single gene testing in which patients are given a discrete choice about undergoing testing for a specific gene mutation, and are counseled before and after testing because of the emotional repercussions and reproductive implications of positive findings. This practice for single gene testing should not change. But genomic sequencing is a single assay of more than 20 000 genes through which a large amount of unexpected, medically relevant information might be generated. Even though empirical data about the risk of many such variants in the general population (as opposed to a family manifesting the disease) are limited, the ACMG recommendations have proposed a consensus view that for selected variants in selected genes, surveillance and intervention could be lifesaving and such results should be routinely reported. Over time, this list of reportable variants will evolve, expanding and contracting as evidence is amassed regarding the utility of findings or lack thereof.

Responses from the leading laboratories performing clinical sequencing in the United States have been encouraging. For instance, the molecular laboratory at Baylor College of Medicine currently does not offer an opt-out for incidental findings considered medically actionable, but requires opt-in for an extended report of additional incidental findings. Some other laboratories are not yet fully following the ACMG recommendations and are maintaining a global opt-in or opt-out for incidental findings, whereas several are including incidental findings without any provision for opt out (oral com-

munication, Heidi Rehm, PhD, June 11, 2013). Even though the ACMG recommendations have only been available for a few months, nearly all of these laboratories are reporting on, or preparing to report on, at least the genes and variants listed in the ACMG recommendations. The Baylor approach was based on extensive experience with structural variant detection using chromosomal microarray analysis (CMA), which can also generate incidental findings, albeit at a lower frequency than does genome sequencing. For example, parental CMA performed as part of a prenatal or pediatric evaluation occasionally identifies a structural variant within a well-established cancer susceptibility gene. Reporting this finding could alert the ordering physician and be lifesaving for the parent in question.[9] The Baylor laboratory has found that clinicians and patients, if properly prepared and oriented to this approach to incidental findings, generally react positively to such findings and are willing and able to address the consequences in both CMA and genomic sequencing (written communication, Christine Eng, MD, June 20, 2013).

Some critics have suggested that patient autonomy is threatened by this approach to incidental findings. However, this position ironically overvalues the incidental genetic finding as an end in itself, rather than as a clue to be contextualized through education, consultation, and joint decision making by the ordering clinician or consultant and patient. The issue is autonomy, but the salient concern is when in the process of testing should patients exercise their autonomy. Patient autonomy is, of course, available when patients are asked to agree to or decline genome sequencing and are provided an explanation that clinically important incidental findings will occasionally be discovered. But patient autonomy is not necessarily enhanced by the ability to refuse one or all complicated, hypothetical, and low-probability genetic risk variants that may or may not be relevant to that particular patient and family. Informed choice is best exercised when a previously unsuspected risk factor is discovered and can be appropriately contextualized by the clinician working with the patient. Together, they can review the family history, repeat a focused physical examination, or perform additional diagnostic studies.

It would be unrealistic to propose to every patient undergoing a physical examination, laboratory testing, or radiological procedure that they consent in advance to the panoply of low-probability findings that might be discovered, or that the clinician, radiologist, or laboratory be required to mask or delete such findings from the report because a patient might be fearful of their discovery. Offering patients a complete opt-out for incidental findings offers only the illusion of autonomy because it does not respect the choices of patients who might wish to hear about some results, but not others. Similarly, categorical statements of preference such as "tell me about treatable conditions, but not untreatable conditions" will never be adequate to guide the management of incidental findings in genomic sequencing because the value of the incidental finding to the health of the individual patient, like any other laboratory value, cannot be accurately assessed until it is clinically contextualized for that patient.

The ACMG recommendations stressed that empirical evidence on the penetrance of selected genes and variants in patients without family history is incomplete and data on the benefits and costs of uncovering unexpected genetic risk information are desperately needed. Such evidence should trigger regular reevaluation and modification of the initial list proposed by the ACMG. Medical genomics has arrived, and sequencing a patient's genome for any purpose provides an opportunity to discover unexpected but medically important information. Incidental findings in genomics should not be handled differently from other incidental findings in medicine. Rather than exceptionalize the return of incidental genomic findings, clinicians and patients should embrace them as adjuvant information of potential utility and as a welcome component of modern medical practice.

ARTICLE INFORMATION

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Green reported having grants pending with the National Institutes of Health; and receiving travel reimbursement from several institutions and companies for conferences. Dr Lupski reported board membership with Ion Torrent Systems Inc; having several grants pending with the National Institutes of Health; receiving payment for lectures from Athena Diagnostics; having ownership in several patents; owning stock in Ion Torrent Systems Inc; and receiving travel reimbursement from several institutions and companies for conferences. Dr Biesecker reported journal editing for Wiley-Blackwell; receiving royalties from Genentech for cell lines; and receiving travel reimbursement from several institutions and companies for conferences.

Funding/Support: Dr Green is supported by grants HG02213, HG005092, CA154517, HG006615, and HG003178 from the National Institutes of Health. Dr Lupski is supported by grants NS058529 and HG006542 from the National Institutes of Health. Dr Biesecker is supported by the Intramural Research Program of the National Human Genome Research Institute.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Drs Green and Biesecker were 2 of the authors of the American College of Medical Genetics and Genomics (ACMG) recommendations but the views expressed in this article are those of the authors and do not necessarily represent the views of the ACMG, the National Institutes of Health, the National Human Genome Research Institute, or other institutions to which they are affiliated.

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