What the doctor didn't order: Exploring incidental findings in clinical genome sequencing

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With whole-genome and whole-exome sequencing declining in price and improving in accuracy, these technologies are rapidly being integrated into clinical medicine. However, one of the most difficult obstacles to this integration is the uncertainty about searching for and reporting genetic results that are "incidental" or unrelated to the reasons the test was initially ordered.

A group of specialists led by Robert C. Green, MD, MPH of Brigham and Women's Hospital and Harvard Medical School and Howard J. Jacob, PhD of Medical College of Wisconsin, has published a paper that explores the options clinicians and laboratories will face as genetic sequencing becomes more and more common. The paper, "Exploring Concordance and Discordance for Return of Incidental Findings from Clinical Sequencing," publishes online in the journal *Genetics in Medicine* on March 15.

"This is the first study to ask specialists in genetics and laboratory medicine about the conditions they would like to see returned to clinicians who order genome sequencing," said Dr. Green. "While there was not perfect agreement between them, it was heartening that the majority of specialists agreed that many incidental genetic findings should be returned."

The investigators asked 16 specialists to independently evaluate 99

commonly ordered genetic conditions and select which ones they would recommend reporting to the ordering physician if discovered incidentally through whole exome or whole genome sequencing. Respondents provided separate recommendations for disclosing each condition based on whether the patient was an adult or a child and on the strength of evidence that the particular genetic variant was pathogenic. The central question was this: Would well-meaning specialists agree on which findings to disclose?

Specialists did agree on many counts, unanimously favoring disclosure of 21 conditions to adult patients. Concordance was generally high for adult patients when the genetic variant was known to be pathogenic, with at least 80% of the specialists recommending return of results for 64 different conditions, and particularly for conditions with potential for medical intervention (such as cancer predisposition syndromes).

The specialists differed more when the patient was a child, when the variant was only "presumed" or "predicted pathogenic," and for conditions without potential for medical intervention (for example, neurodegenerative disorders such as Alzheimer's disease).

"Whole-exome and whole-genome sequencing are valuable pieces of information, but they are just a piece of the clinical picture," said Dr. Jacob. "As a lab value, this data is important, but we also need to be cautious and judicious when we return information to patients. This study provides us valuable insight; the next logical step is learning what patients would want to know about their genome."

"One of the toughest issues facing the rollout of clinical sequencing is whether there is a responsibility on the part of clinicians and laboratories to seek and return incidental genomic findings," said Dr. Green. "This paper should inform ongoing efforts to seek consensus in this difficult area."

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