CHEST

Commentary

AHEAD OF THE CURVE

Grappling With Genomic Incidental Findings in the Clinical Realm

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We have learned a remarkable amount in recent decades about genomics and its potential contributions to human health and medical practice. However, genomic sequencing technology, which is starting to become incorporated into clinical care, also raises ethical challenges. In particular, there has been significant debate about the appropriate management of genomic incidental findings (GIFs), which we define as pathogenic or likely pathogenic test results that are not apparently relevant to the diagnostic indications for which the tests were ordered. Although there is an emerging consensus that clinicians will have at least some obligation to disclose GIFs to patients, the scope of that obligation is unclear. This commentary identifies nuanced issues that clinicians will likely face in the foreseeable future regarding their emerging obligations to disclose clinically actionable GIFs. Will clinicians be expected to look actively for GIFs? Should GIFs for adult-onset disorders be disclosed to children? What obligations will clinicians have to disclose GIFs to family members of deceased patients? What role should informed consent play? There is value to exploring the range of views on these questions at this time, before genomic sequencing has fully matured as a technology, so that clinicians can anticipate how they will respond to the discovery of GIFs once sequencing becomes a more routine part of clinical care. Genomics is ultimately going to play an important role in the practice of pulmonary medicine, and it is important for pulmonologists and other subspecialists to be well informed about what to expect.

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Abbreviations: ACMG = American College of Medical Genetics; GIF = genomic incidental finding

Genomic sequencing technology, which has become more efficient and less expensive in recent years, is starting to become incorporated into clinical care.[1,2] Although additional research is needed to realize its full medical potential, genomic sequencing is emerging as an important tool for understanding and diagnosing a broad range of rare disorders and complex genetic phenotypes, for pharmacogenomics, and for screening for disease risk.[3-5] The massive quantity, scope, and complexity of data that are generated by genomic sequencing pose important ethical challenges. In particular, there has been significant debate about the management of incidental findings and the extent to which researchers and clinicians are obliged to seek and disclose an ever-expanding list of genetic results of varying significance.[6]

Although there is no single agreed-upon definition of incidental finding, we have adapted the following definition for this commentary: a pathogenic or likely pathogenic test result that is not apparently relevant to the diagnostic indication for which the test was ordered.[7] Incidental findings are not unique to genomic sequencing.[8-10] The use of chest CT scans to diagnose pulmonary embolism, for example, can generate incidental findings that outnumber the intended diagnostic findings by more than 2:1.[11] This creates significant decision-making challenges for researchers and clinicians who must decide whether and how to act on these incidental findings, and there have been calls to

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develop systematic approaches for contending with the processing, interpreting, reporting, and acting on incidental findings across various clinical settings.[12]

Debates about genomic incidental findings (GIFs) emerged around the early uses of genomic sequencing in research protocols, with significant disagreements about the scope of researchers' obligations to disclose GIFs to research participants.[13] Although there is no widely accepted consensus at this time, the trend in the literature points to growing acceptance of at least a limited duty to disclose GIFs that is grounded in a variety of justifications, including beneficence, respecting a participant's right to know, reciprocity, professional role responsibilities, and a duty to warn. Many proposals have focused on the utility of the information to an individual research participant and recommend that GIFs be disclosed when they are actionable and point to a serious medical condition for which an effective clinical intervention is readily available.[14-16] Additional conditions for disclosure of GIFs have been suggested, such as genetic counseling, consent, and assurances that results are analytically valid. Each of these measures imposes additional burdens on researchers and clinicians. For example, ensuring that genetic test results that will be disclosed have been validated in a laboratory that has been certified under the Clinical Laboratory Improvement Amendments of 1988 (42 USC 263a) adds additional logistical steps and financial considerations to genomic sequencing. The benefits of these measures to research participants need to be balanced with the burdens on researchers and clinicians, and there are a number of relevant research projects underway to explore the nuanced dimensions of GIFs and how best to manage and disclose them in various settings.[17]

Disagreements have persisted as the conversation about GIFs has shifted from the research to the clinical setting, although the arguments in favor of disclosure have become more forceful.[7,18] A working group of the American College of Medical Genetics (ACMG), for example, has recently taken the position that not only must highly penetrant and clinically actionable GIFs be disclosed to patients, but that a list of 56 specific genes should actively be assessed by laboratories any time that genomic sequencing is used in the clinical setting, irrespective of the patient's age.[7] The ACMG group also recommended that although patients should be able to make an informed decision about whether to have their genome sequenced, they should not be given a choice about receiving the results of the specified GIFs if they go forward with sequencing. These recommendations have had a polarizing effect on the field, generating a flurry of position statements both against[19-21] and in favor of[22] the ACMG working group position, with arguments that pit the autonomy of patients against a perceived duty to prevent severe adverse health outcomes.

The debates about GIFs exist, at least in part, because of the immature state of the science. At present, the ability to interpret genomic variants is limited, given the state of knowledge about the full spectrum of genotype-phenotype correlations.[18,19] As we learn more about these correlations and develop increasingly refined tools to assess genetic variants, it will be more straightforward to identify, interpret, and act upon GIFs. Our goal in this commentary, therefore, is not to take a position on whether the disclosure of a specified list of GIFs in the clinical setting is obligatory or premature at this moment in time. Instead, we endeavor to identify some of the nuanced issues that clinicians will likely face in the foreseeable future, given an emerging obligation to disclose clinically actionable GIFs that we assume will become more compelling to act upon as our knowledge of genomics expands. These issues include whether clinicians will be expected to look actively for GIFs, the role of patients' informed consent, whether GIFs for adult-onset disorders should be disclosed to children, and obligations to disclose GIFs to family members of deceased patients. There is value to exploring the range of views on these questions at this time, before genomic sequencing has fully matured as a technology, so that clinicians can begin to anticipate how they will respond to the discovery of GIFs once sequencing becomes a more routine part of clinical care.

Challenging the "Stumble Strategy"

Assuming that there is an obligation to disclose at least some kinds of GIFs, there is a more fundamental, yet relatively unexamined question about whether there should also be a positive obligation to interrogate sequence data to look intentionally for GIFs. The standard view has been that one does not need to look actively and deliberately for incidental findings; there is only an obligation to return those that are stumbled upon unintentionally.[13] This so-called stumble strategy was premised on the assumption that incidental findings will be relatively uncommon and rarely uncovered in the course of research or clinical care.[23] Although this premise was true in an era of more targeted use of genetic testing, it is at odds with the realities of the current genomic era: Given the massive amounts of data being sequenced, it will be more common to identify GIFs that reveal important medical information.[6]

While a number of factors are relevant to the existence of a duty to look, it is helpful to focus on two in particular. First, if researchers, clinicians, and laboratories are going to be tasked with looking for incidental information, the information to be sought must be