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

highly useful. Second, the act of looking must not be unduly burdensome to those same actors.[23] It seems unlikely that there is an expansive duty to look at the present moment, given that genomic medicine is still in its infancy and that comprehensively analyzing genomic data remains an intensive endeavor. But as our understanding of genomic medicine improves, and as bioinformatic tools become more sophisticated, a duty to search for incidental findings will gradually emerge. The validated lists of clinically significant variants that professional societies and expert bodies have begun to produce[7] will remove much of the burden associated with looking for GIFs. This, in turn, will make the obligation to use these tools to search for GIFs more compelling, particularly as the lists become more refined over time.

A Right Not to Know?

Informed consent, a foundational concept in both research and clinical ethics, is perhaps the one area of consensus that has emerged from the extensive debates about GIFs: There generally has been agreement that GIFs should be disclosed only when they are desired by research participants who have explicitly consented to receive the information. Most of the proposed frameworks for managing GIFs discuss whether there is an obligation to offer certain categories of individual findings to research subjects, which suggests that subjects should have the power to control the information that is disclosed to them, and that they can decline an offer.[14,15] Even more explicitly, some have argued that there is a right not to know that should be highlighted in the consent process[24] and that incidental findings should not be disclosed if the subject expresses a desire not to know—or at least that they should only be disclosed if subjects have actively expressed their desire to know.[13,16] This position reflects the prevailing standard of care in clinical genetics, where only desired information is returned because of the potential harms to patients and their families.[19]

Despite the apparent consensus, the underlying justification for and scope of an individual's interest in not knowing important genetic information deserves a more in-depth examination. A robust right not to know genetic information may not be as straightforward as it seems, particularly in this new genomic era. Are there any (albeit limited) circumstances where it might be ethically appropriate to override an individual's expressed wish not to know genetic information about himself or herself? The standard ethical view is that autonomous individual choices should be respected. But one can anticipate situations in which a clinical team will be faced with a dilemma about whether to disclose the discovery of a medically important GIF, such as a genetic variant associated with a serious disease that is amenable to intervention, or instead to honor a patient's expressed preference not to learn this kind of information.

Some have argued that for a defined subset of extremely important variants, subjects and patients should not be given an option to refuse; if they agree to have their genomes sequenced, they must also agree to learn about these important variants.[7] This is in contrast to the early history of genetic research and testing, which focused on conditions that were not treatable, potentially stigmatizing, or might influence a decision about whether to continue a pregnancy—contexts in which it is considered reasonable for a person not to want to know the results of genetic tests. The kinds of conditions being debated for mandatory disclosure policies are serious and treatable, however, and such that it is not clear why a reasonable person would not want to know about them and calls into question the notion of an absolute right not to know. Even in such cases, it is generally believed that patients should be informed up front that certain kinds of information will automatically be disclosed to them if they consent to have their genome sequenced as part of research or clinical care.[7]

Disclosure to Children of Variants Related to Adult-Onset Conditions

Genomic sequencing has also called into question long-standing views on the kinds of genetic information that are appropriate to test for and disclose to pediatric patients.[25] Until now, clinical practice guidance has recommended that only information that is clearly actionable in childhood be disclosed and that the decision to learn about adult-onset conditions should be delayed until the age of majority out of respect for the child's developing autonomy.[26,27] This so-called right to an open future constrains parents' otherwise wide discretion to obtain information in the interest of making decisions about their child's health care.

The proliferation of genomic sequencing calls this default into question.[26] The recent ACMG guidelines propose that when a child's genome is sequenced, the parents should be told about adult-onset conditions, arguing that it is inappropriate for the "child's right not to know [to supersede] the parent's opportunity to discover a life-threatening risk factor."[7] Predictably, this deviation from long-standing norms has proven to be controversial, and a number of commentators have vigorously pushed back on that precise issue.[19,20,28]

Even if one accepts the arguments for safeguarding a child's future autonomy, difficult ethical and logistical problems will remain. First, it is unclear how best to obtain a child's assent. Young children

obviously have limited decision-making ability, but that capacity increases as they approach the age of majority. How much weight should be given to assent as children mature? Second, if future autonomy requires that one must safeguard a child's genetic status until he or she is an adult, what is a researcher or clinician's responsibility toward that information once the child has come of age? One can reasonably argue that there is an obligation to set up systems for recontacting children when they turn 18 years of age to offer them a chance to learn more about their genomic health information. But this raises difficult questions about the burden associated with such follow-up, particularly when the clinical relationship existed years earlier.

Disclosure of Variants to Relatives of Patients

If there is an emerging obligation to disclose certain categories of incidental genomic information to patients, is there also a corresponding obligation to disclose information that may be relevant to a patient's relatives? Although patients should ideally be communicating with their relatives about their shared family health history,[29] what if a patient has died before doing so? When should clinicians be expected to disclose important GIFs to relatives of deceased patients, and what is the best mechanism for family disclosure, taking into account issues of confidentiality and burden to the provider?

These are obviously complicated questions that will depend on the specific context of a given case (eg, how much clinical benefit the information provides, the relationship between the decedent and his or her family, and whether the decedent expressed any preferences for or against sharing the information with family.) In the end, it will be very difficult to predetermine situations where disclosure to surviving family members is required by the principle of beneficence, as compared with situations where disclosure is merely supererogatory. A case can be made, however, for many researchers and most clinicians to consider at least a passive return policy, which would pose minimal burden while maintaining the possibility of providing significant clinical benefit to relatives of the decedent.[30]

Implications for Clinical Care

We have learned a remarkable amount in the past few decades about genomics and its potential contributions to human health and medical practice. However, this is just the beginning; significant additional research will be required before genomics can fully transition "from base pairs to bedside."[3] The adoption of any new technology often proceeds in fits and starts; some have characterized the sink or swim nature of reckoning with complex GIFs at the dawn of clinical genomic sequencing.[31] The successful introduction of genomics into health care will require the involvement and education of a broad range of health-care professionals, including pulmonologists and other subspecialists who may not have genetics training. With calls to redefine lung disease at the molecular level and to use genomic approaches to understand lung pathophysiology, there is likely to be significant progress in the translation of genomics into clinical pulmonology in the coming decades.[32] Genomics is ultimately going to play an important role in the practice of pulmonary medicine, and it will be important for pulmonologists and other subspecialists to be well informed about what to expect.

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