Review Series

blood

PRECISION HEMATOLOGY

Ethical considerations in genomic testing for hematologic disorders

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As our technological capacities improve, genomic testing is increasingly integrating into patient care. The field of clinical hematology is no exception. Genomic testing carries great promise, but several ethical issues must be considered whenever such testing is performed. This review addresses these ethical considerations, including issues surrounding informed consent and the uncertainty of the results of genomic testing; the challenge of incidental findings; and possible inequities in access to and benefit from such testing. Genomic testing is likely to transform the practice of both benign and malignant hematology, but clinicians must carefully consider these core ethical issues in order to make the most of this exciting and evolving technology. (*Blood*. 2017;130(4):460-465)

Introduction

Since the groundbreaking work demonstrating inhibition of *BCR-ABL* fusion-positive cells by tyrosine kinase inhibitors in both the laboratory[1,2] and the clinic,[3,4] genomic testing for hematologic disorders has exponentially increased. President Obama's announcement of the Precision Medicine Initiative in 2015 presaged even greater incorporation of genomic testing into practice.[5] As with many emerging technologies, genomic testing raises several important ethical issues that require attention as it integrates into patient care.

In this review, we examine the ethical issues that can arise in the performance of genomic testing for both malignant and benign hematologic disorders. We present 2 clinical cases that illustrate core themes in both somatic and germ line genomic testing in hematology. These issues include (1) challenges related to informed consent and the uncertainty inherent in genomic test results; (2) the prospect of unanticipated (incidental) genomic findings; and (3) the potential for disparate access to and benefit from genomic testing across populations. As the role of genomic testing in hematology expands, clinicians and researchers must be aware of these fundamental considerations.

Case 1

David Jones, a 55-year-old man, enrolls in a clinical trial of genomic screening among healthy adults after learning of it on the local news. As part of the trial, he donates a blood sample for whole-exome sequencing, with a report of the whole-exome sequencing results provided to him and to his physician. David Jones has no significant medical problems, takes no prescription medications, and has a negative review of systems. He has no known family history of hematologic malignancies, thromboses, bleeding diatheses, or early unexplained deaths. His sequencing results reveal a JAK2-V617F mutation, seen in 49% of reads, that is described as "likely pathogenic" and is thought to be somatic in nature.

Prior to undergoing genomic testing, David Jones believed that he was perfectly healthy. He now knows that he carries a mutation seen in a large proportion of patients with myeloproliferative disorders including polycythemia vera, essential thrombocytosis, and primary myelofibrosis.[6,7] However, the mutation is also found in a small percentage of healthy individuals, for whom its clinical significance is less clear.[8-10] Knowledge of this mutation does not in itself change David Jones' health, but it may influence his conception of it.[11] He is left with a great amount of uncertainty: testing may have uncovered a premalignant condition, or it may only have left him with worry and distress, without any countervailing benefits.

Case 2

Martha Davidson is a previously healthy 35-year-old woman of Ashkenazi Jewish ancestry who develops progressive pallor and fatigue over several weeks. A complete blood count shows pancytopenia; a bone marrow biopsy confirms the diagnosis of aplasia. The biopsy specimen is sent for clinical genomic testing to uncover a cause for this aplasia. Results demonstrate a 185delAG mutation in BRCA1 in 47% of reads. Martha Davidson does not have a personal or family history consistent with hereditary breast–ovarian cancer syndrome, although she has few female relatives on her father's side. She has 2 healthy children, an 8-year-old boy and a 5-year-old girl.

This case demonstrates the complexity inherent in genomic testing for hematologic disorders. Martha Davidson underwent genomic testing in attempt to learn about her marrow aplasia, but the 185delAG mutation in the *BRCA1* gene is a well-known founder mutation of high prevalence in Ashkenazi Jews[12,13] that is associated with a substantially increased risk of developing breast and ovarian cancer.[14,15] The BRCA1 protein is also part of the Fanconi anemia/BRCA pathway that,

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when disrupted, can predispose to numerous other tumors, including hematologic malignancies.[16-18] Although additional testing is necessary to determine with certainty whether this variant is somatic or germ line,[19] it is highly likely that in addition to bone marrow failure, Martha Davidson has a previously undiagnosed cancer predisposition syndrome.

Informed consent and the uncertainty of genomic testing

These cases highlight the importance of informed consent for genomic testing. Informed consent requires delivery of information to the patient, adequate comprehension of that information, and an informed and voluntary decision to proceed.[20] Implicit in this definition is an understanding of each of the different potential outcomes of the intervention. Genomic testing broadens the possibility of such outcomes, including discovery of incidental or secondary findings with implications for both the patient and his or her biological relatives.[21] To optimize truly *informed* consent, a growing number of professional medical associations recommend comprehensive counseling prior to pursuing such testing.[22-24] Counseling is time intensive and expensive but has been shown to be effective at increasing knowledge about both the benefits and the limitations of genomic testing.[25,26] Counseling is particularly important before genomic testing, which differs from many other medical tests in the wide range and frequently unanticipated nature of the results that might be returned. In case 1, David Jones has received an unexpected incidental somatic finding, but genomic testing might also have uncovered a pathogenic germ line variant (as it likely did for Martha Davidson) or a variant of uncertain significance (VUS). Sequencing might also have uncovered no germ line variant known or suspected to be associated with inherited risk, an outcome that should not be interpreted as "negative" but one that for many can paradoxically be disappointing.[27,28] Comprehensive pretest counseling can help prepare patients for such a wide range of possible results.

Despite the importance of pretest genomic counseling, the question of who should provide it is unsettled. Many physicians express low confidence in their genetic/genomic knowledge[29]; many institutions do not employ full-time genetic counselors,[30] and even geneticists and genetic counselors may be less familiar with genetic predisposition to marrow-derived disorders than they are with predisposition to solid tumors, given that the latter has been recognized for far longer.[31] Despite this, pretest counseling is increasingly important because genomic testing further integrates into the clinical care of hematology patients. It ensures that patients are alerted to the wide range of possible findings from such testing and are given the option to abstain ("informed refusal") from testing when doing so is consistent with their values and priorities. Many individuals do not desire information about their genetic risks, particularly those for which they cannot intervene.[32] Although not without limits, this wish is generally respected under the so-called "right not to know,"[33] a right that is only meaningful if the decision to decline is an informed one.

Given the complexities of genomic testing, it is also important that clinicians explore their patients' hopes and expectations as part of pretest counseling. It is not surprising that patients have high and sometimes unrealistic hopes for genomic testing,[27,28,34,35] but the same can also be true of physicians.[28,29,35] Unfortunately, most experiences with genomic testing have not been as successful as those associated with the use of tyrosine kinase inhibitors, but it is these successes that patients and research subjects often hear about and hope for. As a healthy volunteer, David Jones likely did not have significant expectations for the testing, but he also did not likely expect the results that he received. Martha Davidson may have hoped that genomic testing would provide clues about her diagnosis that would inform her treatment, but she likely did not expect to learn that she could have a cancer predisposition syndrome. It is imperative that all those undergoing genomic testing receive adequate counseling prior to testing to ensure that their expectations are in line with its realities and possible outcomes. In addition, little is currently known about how germ line and somatic genomic testing for hematologic disorders affect patients psychologically, with most data extrapolated from the solid tumor predisposition literature.[27] Studies addressing this deficiency in the literature would be invaluable.

Once testing has occurred, additional challenges remain because of the complexity inherent in interpreting the results, which includes result curation, interpretation, and communication of information to the patient.[36] Germ line genomic variants typically are classified according to their pathogenicity (pathogenic, likely pathogenic, uncertain significance, likely benign, benign). Although guidelines have been developed for categorizing genomic variants,[37] laboratories regularly disagree about how variants should be classified,[38,39] and efforts to standardize classification of somatic variants are ongoing.[40,41] Even at a single institution, interrater agreement about the pathogenicity of a given variant may only be moderate.[42] Furthermore, once the pathogenicity of a variant is determined, its clinical significance and how it should be reported to the ordering provider and patient must be determined. These judgments may vary based on a variety of factors, including the scientific evidence available at the time of the report and the context in which the testing was performed.[43] When genomic testing is performed on nucleated peripheral blood cells, for example, it can be difficult to determine whether variants are germ line or somatic and the significance of these variants. This difficulty is demonstrated by somatic mutations that have been reported to appear and disappear in such disorders as Wiskott-Aldrich syndrome and Fanconi anemia.[44-46]

Variants of uncertain significance warrant particular attention, because reporting practices for such findings are quite variable,[47,48] and the likelihood of relevance of a VUS is generally thought to be dependent on whether it was discovered incidentally or as part of diagnostic testing for an associated phenotype or family history. When the finding is incidental to the purpose of the test, some have argued for reporting back only pathogenic and likely pathogenic findings.[49] We address this topic in greater detail below.

With passage of time and the acquisition of new knowledge, the classification of a given variant, and, as a result, its clinical significance, may change. The possibility that the interpretation of a variant might evolve, for example, that a VUS might be reclassified as likely pathogenic, or a likely pathogenic variant might be reclassified as likely benign, creates challenges for patients, clinicians, and clinical genomics laboratories. At present, there is no established standard for periodic reinterpretation by genomics laboratories of previously reported variants.[37] In the absence of an explicit statement to the contrary from the laboratory, clinicians and patients should not expect to receive unsolicited notice of revised interpretations.[50,51] Rather, if they have questions about whether the interpretation of a variant has changed over time, they should proactively contact the original laboratory.

The circumstances are even murkier in direct-to-consumer genomic testing, in which there is no clinician to discuss the results and their significance with the patient who underwent testing, raising the possibility of misleading or inaccurate interpretation and communication of results.[52] A leading argument in favor of direct-to-consumer genomic testing is the possibility of instituting health changes based

on test results,[53] but evidence is mounting that such changes are uncommon.[54] This lack of action only adds to the uncertainty inherent in genomic testing, an uncertainty that informed consent discussions must address.

Although an adult patient's genomic results are typically reported to the patient, if she dies or becomes incapacitated before results are returned, questions arise as to who should receive the results.[55] When caring for patients who are at risk of dying before results are available, clinicians or genetic counselors ordering genomic testing should ask patients to identify, and should document, a designee who should receive results if the patient is unable to receive them herself.

Incidental findings

Many of the ethical challenges in genomic testing result from the possibility of incidental findings (ie, results that are outside of the original purpose of the testing) and secondary findings (ie, results that are sought by the investigator or clinical laboratory but that are not the primary purpose of the testing).[21] Although most patients and research participants wish to receive all their genomic results,[35,56] many do not adequately understand the implications of these results. Health literacy is a major challenge in medical practice,[57] and understanding of genomics is no exception. A sizeable minority of patients who have undergone genomic testing of their cancer, for example, is unaware that such testing can uncover cancer risk.[56] In case 2, Ms. Davidson may not have understood that the testing could provide such incidental data about her risk of future cancers, and she might not have requested that information if given the choice.

Incidental findings are not only relevant in the setting of cancer predisposition syndromes. Depending on the scope of and analytic approach to sequencing, Martha Davidson might also have unexpectedly learned that she carries a pathogenic mutation in *MYBPC3*, imparting an increased risk of hypertrophic cardiomyopathy, or in *HTT*, the mutation responsible for Huntington disease. The American College of Medical Genetics and Genomics recently published guidelines supporting return of certain incidental genomic findings, including mutations that impart risk of a cancer predisposition syndrome, certain cardiovascular disorders, and a handful of other conditions, when exome or genome sequencing is performed in the clinical setting.[49] Although the American College of Medical Genetics and Genomics initially recommended mandatory return of selected incidental findings, it subsequently endorsed an opt-out option in response to criticism from geneticists, bioethicists, and others.[58,59]

Implications of genomic testing do not apply only to the individual who consented to testing. If a genomic variant is in the germ line, that individual's children, siblings, and other genetic relatives may also be at risk. Although personal health information is confidential and protected in the United States by both the Health Information Portability and Accountability Act[60] and by codes of modern medical ethics,[23] exceptions exist when confidentiality puts the health and/or safety of another at risk. These exceptions form the foundation for laws requiring report of imminent harm to another individual to legal authorities,[61] a duty that is extrapolated to the mandated reporting to the health department of certain transmissible infections.[62] These tenets have been applied to genetic/genomic data in the form of the "duty to warn," which states that there may be an obligation to provide such risk information to susceptible individuals when it is discovered.[63] Clinicians generally satisfy this duty by disclosing genetic risk information to their patients and encouraging them to inform relatives of their risk so that they can pursue testing.

Genomic testing in minors raises particularly complex questions related to the possibility of incidental or secondary findings.[49] Some have argued that incidental findings in genes associated with adult-onset conditions should not be tested or reported for pediatric patients unless interventions are available in childhood to modify risk.[58,64] The core argument in this debate is whether the benefit to the child and her parents of knowing the genetic risk outweighs the fact that there is no action that the child can take at the present time based on this genetic information that will affect morbidity or mortality.[65] Those who argue against return of such findings to pediatric patients point to the child's right to an open future, that she be able to choose for herself whether to undergo such predictive genetic/genomic testing once she reaches adulthood. In contrast, those who advocate for return of these results cite the potential for the knowledge to benefit both the patient, by prompting actions she might take in the future, and the patient's adult relatives by alerting them to their potential risk.[49,65-67] A growing literature addresses additional ethical issues that warrant consideration in the genomic testing of minors,[64,65,68,69] but a detailed discussion of these is beyond the scope of this review.

Incidental and secondary findings present further challenges related to the need for additional testing, insurance coverage for testing, and the possibility of genetic discrimination. First, it is likely that the unexpected results for David Jones and Martha Davidson will require confirmatory testing and possibly other tests and/or interventions. Although often seen as an end to the "diagnostic odyssey,"[70,71] genomic testing has the potential to begin a new such odyssey, sometimes leading to the conclusion that the initial result was a false positive. Second, health insurers' policies differ greatly with regard to what types of genomic testing they cover and in what situations.[72] In David Jones' case, his insurance company might not pay for confirmatory testing given that he is asymptomatic and the initial testing was performed as part of a research trial (the results of which typically are not used for clinical decision making). Finally, although the Genetic Information Nondiscrimination Act of 2008 provides individuals in the United States protection against genetic discrimination in health insurance and employment,[73] and the Affordable Care Act, if it survives, protects against discrimination in the individual health insurance market due to preexisting conditions,[74] these protections do not apply to other forms of insurance (including life, disability, and long-term care). Fortunately, documented cases of discrimination based upon genetic predisposition are rare.[75,76]

Access and equity

Disparities in health and health care are among the greatest problems facing medicine.[77] Although technological advances might reduce these disparities,[78] improvements will only occur if access to and benefits from advances are equally available to all. At present, the potential benefits of genomic testing are unequally distributed. In genomic sequencing repositories such as The Cancer Genome Atlas, sequencing data for racial and ethnic minorities are underrepresented compared with those for non-Hispanic whites.[79] Without robust normal and pathogenic genomic datasets derived from members of racial and ethnic minorities, interpreting genomic findings among members of these groups is challenging. Recent work comparing the rates of known pathogenic variants among participants in the Framingham and Jackson Heart Studies (cohorts of primarily European and African Americans, respectively) found much higher variant frequencies in the Framingham than in the Jackson cohort.[80] The National Heart, Lung, and Blood Institute's Exome Sequencing Project revealed similar patterns

of discrepancy by national origin.[38] It is improbable that individuals of non-European ancestry harbor fewer pathogenic genomic variants than do individuals of European descent; rather, we likely lack sufficient genomic data from minority groups to confidently identify pathogenic or likely pathogenic findings. In addition to potentially underdiagnosing pathogenic genomic findings, an inadequate understanding of the normal genomic landscape for minority groups can also lead to a disproportionate number of false-positive misdiagnoses.[81,82] As a result, individuals from racial and ethnic minority groups are at increased risk of both false-positive and false-negative genomic testing results as compared with individuals from majority groups.

This inequity does not exist only in the realm of genomic data repositories. Rates of enrollment in genomic sequencing research trials and genome-wide association studies among members of racial and ethnic minorities are often disproportionately low compared with their representation in the population.[83,84] In addition, new data suggest that the greatest success story in genomic testing in hematologic malignancies, the use of tyrosine kinase inhibitors for chronic myeloid leukemia, appears to impart greater survival benefits to individuals from European backgrounds than to African Americans.[85,86] Whether this outcome disparity is related to biologic differences or to some other factor, it highlights the need for improved strategies to ensure that genomic testing and its benefits are equally accessible to all populations. Finally, just as access to expensive therapeutics is limited in some less wealthy countries, the same holds true for access to advanced genomic testing.[87,88] Clinicians and policymakers must prioritize equitable access to clinically essential genomic testing on a global level.

Conclusions

Since completion of the Human Genome Project in 2001, the time and costs required for genomic testing have fallen exponentially, whereas the storage and computing power needed to handle the massive volumes of data that sequencing generates have grown dramatically.[89] Over this interval, genomic technologies have been increasingly integrated into clinical research and patient care. As with any new technology, however, genomic testing for hematologic disorders is not without its pitfalls. Great care must be taken to ensure that core ethical considerations, including informed consent and the prospect of unanticipated/incidental findings, are considered prior to the performance of genomic testing. At the same time, efforts are needed to reduce the likelihood of inequities in access to and benefit from genomic testing. As the development of tyrosine kinase inhibitors in the 1990s demonstrated, genomic testing opens exciting new doors for the diagnosis and treatment of hematologic disorders, but clinicians and researchers must take care to consider these important ethical considerations as the field of hematology enters the age of precision medicine.[90]

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