Informed consent for genetic testing in hematology

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Informed consent is a fundamental component of modern health care. All competent adult patients have the legal and ethical authority to accept (consent) or refuse (dissent) recommended health-related interventions. Various models of informed consent have been described, and herein I introduce a model that divides informed consent into 7 distinct elements: competence, voluntariness, disclosure, recommendation, understanding, decision, and authorization. Genetic testing, which is rapidly becoming a common feature of both clinical care and research in hematology, adds additional layers of complexity to each of these consent elements. Using the example case of Mr. Smith, a man with newly diagnosed acute myeloid leukemia whose clinicians offer him genetic testing of the leukemia through a clinical trial, I highlight the challenges and controversies of informed consent for genetic testing, focusing on each consent element as it pertains to genetic testing in such a setting. Ultimately, given the growing importance of genetic testing for hematologic disorders, clinicians, and researchers in hematology should be facile at participating in all aspects of informed consent for genetic testing.

LEARNING OBJECTIVES

- Identify the fundamental role of informed consent in health care and the different elements that comprise informed consent
- Understand why informed consent for genetic testing is complex and how genetic testing in hematology complicates each consent element

Clinical case

Consider the fictional case of Mr. Smith, a 50-year-old man who has just been diagnosed with CD33$^-$ acute myeloid leukemia (AML) with favorable-risk cytogenetics. Otherwise healthy, he met with his clinical team to discuss treatment options. His clinicians recommend standard induction chemotherapy with cytarabine and daunorubicin ("7+3").[1,2] They also recommend that he participate in a clinical trial that is currently enrolling patients. In this trial, genetic sequencing would be performed on his leukemia cells to see if there are any targetable alterations that could inform further antileukemia therapy. "Sounds good to me," Mr. Smith responds immediately. "That certainly sounds like my best chance for a cure."

Introduction

Genetic testing is rapidly becoming more commonplace throughout medicine, and since the advent of tyrosine kinase inhibitors,[3] its use in hematology has increased similarly.[4] Genetic and genomic testing provide great hope and opportunity to clinicians, patients, families, and scientists, but it also carries with it significant ethical complexity.[5] This article focuses on the unique complexities surrounding informed consent for genetic testing in hematology. I will discuss single tests ("genetic tests"), as well as panel testing and next-generation sequencing ("genomic tests"). For the sake of simplicity, I will refer to these terms together as genetic testing but will specify when particular considerations apply to one type. Genetic testing, even when performed as a clinical (rather than research) test, has numerous unique characteristics in clinical hematology, warranting particular focus on informed consent in this setting. A comprehensive discussion of these unique features is beyond the scope of this article, but they include the possibility of identification of germline variants when performing somatic sequencing, the great uncertainty inherent in genetic testing, and the high rate and potential impact of incidental findings in this type of testing.[5]

Informed consent

Informed consent is a core component of ethical practice of both clinical care and clinical research,[6,7] and many unique features of genetic testing add ethical complexities to informed consent. Importantly, documentation of consent (eg, signature on an informed consent form or vocalization of consent to proceed with an intervention) is only 1 element of informed consent. Various ways of defining informed consent have been proposed, but a widely accepted model divides consent into 7 individual elements, grouped into 3 larger categories: threshold elements, information elements, and consent elements (Table 1).[6] In this article, I will describe these elements and examine the unique complexities inherent in each regarding consent for genetic testing in hematology. Importantly, these elements also apply to informed *refusal*, the autonomous decision to forgo a particular treatment or intervention, although this will not be the main focus of this article. All competent adults have the legal and ethical right to accept or refuse a given medical intervention. The sections that follow describe how to determine whether that acceptance (consent) or refusal (dissent) is legally and ethically sound.

Threshold elements: competence and voluntariness

Competence, the first of 2 threshold elements of informed consent, refers to an individual's ability to understand and appreciate the situation, to weigh the risks and benefits of treatment options (reasoning), and to communicate a choice (Table 2).[8,9] Here, the terms competence and capacity are used interchangeably, though some identify minor distinctions between these concepts. Competence is defined for a given domain and a task within that domain; an individual, for example, may be competent to choose whether to have blood drawn from the left or right arm but may not be competent to decide whether to undergo a surgical procedure. Generally, greater competence is expected for more complex and/or risky health care decisions.[10] In addition, competence can vary over time, as many factors can influence an individual's competence (eg, effect of the underlying disease, medications and treatments, and comorbidities). Importantly, various hematologic disorders could affect an individual's ability to make a competent decision (eg, significant intellectual disability after a stroke due to a hypercoagulable state, postictal state after a seizure from an adverse event during chemotherapy, and age-related dementia unrelated to the underlying hematologic disorder), independent of the decision itself, which will be addressed further later. In this case, Mr. Smith's competence could be affected by several factors related or unrelated to leukemia. The presence of a clinically significant intracranial chloroma, for example, may affect his level of consciousness and ability to make competent decisions. It is also possible that, later in treatment, his competence could be affected by disease progression, treatment toxicities, or other factors, that may predict a change in his competence over time and with changing circumstances.

Voluntariness, the second threshold element, refers to an individual's ability to make a choice independent of outside influence.[6,11] The standard for voluntariness typically is high: a decision is only *involuntary* if it is coerced or made under a credible and intended threat.[11] In health care, such an occurrence is rare. More common, however, are subtle forms of influence that do not reach the level of coercion, such as persuasion or manipulation. There is a great debate about how much influence is too much, but it depends significantly on the level of vulnerability of a patient.[11] When considering compensation for participation in a clinical trial, for example, a large monetary payment for participation may be differentially influential, depending on an individual's financial means. In this way, even though such a large payment may not be coercive, it could be seen to take advantage of an individual's vulnerability.

Given the potential vulnerability of patients undergoing genomic sequencing, this is a significant concern for patients

Table 1. Elements of informed consent

Consent category	Consent element	Case example
Threshold elements (preconditions)	Competence/ capacity	In this case, Mr. Smith is assumed to be competent to make a decision about treatment of his leukemia, including the genetic testing that has been recommended. It is possible, however, that if he had a large intracranial chloroma or large burden of CNS disease (or unrelated neurologic dysfunction) that he may not be able to competently make these decisions and provide informed consent for his treatment plans.
	Voluntariness	Mr. Smith must be given the opportunity to make a voluntary decision about how to proceed in treating his acute myeloid leukemia, free of coercion.
Information elements	Disclosure	The clinician-investigators must disclose risks and benefits of the proposed interventions, including risks and benefits of leukemia sequencing, to Mr. Smith, as well as other disclosures relevant to Mr. Smith's decision (including that the sequencing is part of a research study, not standard clinical care).
	Recommendation	To help Mr. Smith make an informed choice about whether to enroll on the sequencing trial, his clinician-investigators should recommend to him the intervention they feel best aligns with his values and beliefs, given his present clinical condition and circumstances.
	Understanding	In order to proceed, Mr. Smith should be able to demonstrate to his team that he understands the information about the clinical trial (including the sequencing that is part of it) that has been disclosed to him and the plan that his team has recommended.
Consent elements	Decision	Mr. Smith should be able to clearly state which available option he has chosen and why that is his choice.
	Authorization	Prior to initiation of therapy (and enrollment on the trial, if he opts to enroll), Mr. Smith should confirm that he authorizes his team to proceed and to carry out his stated decision.

Adapted from Beauchamp and Childress.[6]

Table 2. Required elements of decisional capacity and competence

Decisional element	Definition	Case example
Understanding	The patient's ability to grasp the meaning of information communicated by the physician and other caregivers.	Ms. Haverford has just been diagnosed with an advanced hematologic malignancy, but she has been completely silent while her physician explains her the diagnosis and recommended treatment. Further inquiry is necessary to ensure that she understands the information that has been communicated to her.
Appreciation	The patient's ability to appreciate the consequences of their situation (medical condition, need for treatment [when applicable], and likely benefits and harms of each possible treatment).	Ms. Haverford is a highly educated patient who has clearly understood the information conveyed, but she seems to question how certain it is that she really has cancer and thus whether any treatment is actually needed. Exploration of her appreciation of his condition is clearly needed.
Reasoning	Patient can weigh risks and benefits within/across treatment options and arrive at a decision that is consistent with their starting premise(s).	Ms. Haverford has been clear that she places great value on comfort but elects a treatment approach that is likely to cause substantial distress. This discordance deserves a careful inquiry into the reasoning underlying that decision.
Communicating a choice	Patient can clearly indicate the preferred treatment option and maintain that choice for a sufficient period of time for it to be implemented.	Ms. Haverford demonstrates great ambivalence about a treatment choice, not clearly embracing any option but shifting among them. The basis for that ambivalence should be explored and, if possible, resolved.

The table describes the fictional case of Ms. Haverford, who was recently diagnosed with an advanced hematologic malignancy. Whereas Mr. Smith's team appeared to have no concerns about his capacity and competence, this table describes the fundamental elements of decisional capacity and competence, and how these might apply in a case such as that of Ms. Haverford.
 Adapted from Marron et al, 2020.[9]

with hematologic disorders. Even though Mr. Smith's clinical team did not intend to mislead or manipulate him, it is possible that, given the gravity of his diagnosis, he felt compelled to participate in the clinical trial, as exemplified by his remark that the trial sounds like his best chance of a cure. Although this scenario would be unlikely to meet the standard of coercion, it could nonetheless raise concerns about whether Mr. Smith's decision was influenced by his vulnerable status. It also speaks to the possibility of therapeutic misconception,[12] which will be discussed in greater detail later.

When examining voluntariness regarding genomic sequencing, it is also important to consider the possible discovery of information about those other than the individual who provides consent for testing. Were Mr. Smith to undergo sequencing and learn that he had a germline alteration that predisposed him to leukemia, it could have implications for his relatives as well (assuming the mutation was not de novo). Some have argued that individuals have a duty to warn others upon learning of possible risks to them, such as a germline risk similar to this one.[13] It remains controversial, however, whether and how relatives should provide consent (or at least be alerted) before testing, counseling, and disclosure. This is of particular importance given the growing role of cascade testing in identifying those at risk of genetic disorders who have an affected relative.[14] An added complexity is that related donor hematopoietic stem cell transplantation is often considered for those with hematologic malignancies (particularly those resulting from a germline predisposition). Before transplantation, however, it is important to be sure that the potential donor does not have the same germline alteration as the index patient, although best practices in this setting remain controversial.[15] Assuming that Mr. Smith provides consent for sequencing, is there an expectation that he will confirm that his first-degree relatives also provide consent? And if he learns that he indeed has a predisposition for germline cancer, how should this subject be broached with his relatives, who may involuntarily (or at least unwittingly) receive medical information about themselves, without their explicit consent? And if he has such a predisposition, how should family members be approached to serve as a potential related stem cell donor, understanding that they also would be likely to have to undergo sequencing to ensure that they do not have the same predisposition? Further work is necessary to answer these complex, challenging questions.

Information elements: disclosure, recommendation, and understanding

Disclosure, the first of 3 information elements of consent, refers to the ethical obligation of complete and comprehensive disclosure of the risks and benefits of a given intervention and disclosure of any potential conflicts of the clinician.[6] The former is generally more salient regarding genetic testing, but conflicts of interest and commitment also warrant consideration, particularly given that many clinicians and researchers have a financial stake in testing that they may order or recommend (either at their own institution or via private testing facilities). Returning to the former, clinicians disclose risks and benefits as a matter of daily practice with regard to new treatments, surgeries, and other interventions, and similar disclosure is important with regard to genetic testing. Unlike invasive procedures, the physical risk of such testing typically is minimal, but there are unique risks related to genetic testing. A growing body of literature highlights the potential psychological implications of genetic testing, including increased stress and anxiety and effects on overall psychological well-being.[16,17] Furthermore, although the Genetic Information Nondiscrimination Act and Affordable Care Act protect against genetic discrimination on the part of some types of insurance and in a subset of other areas, despite these protections, there remains a risk of discrimination based on genetic and genomic findings.[18]

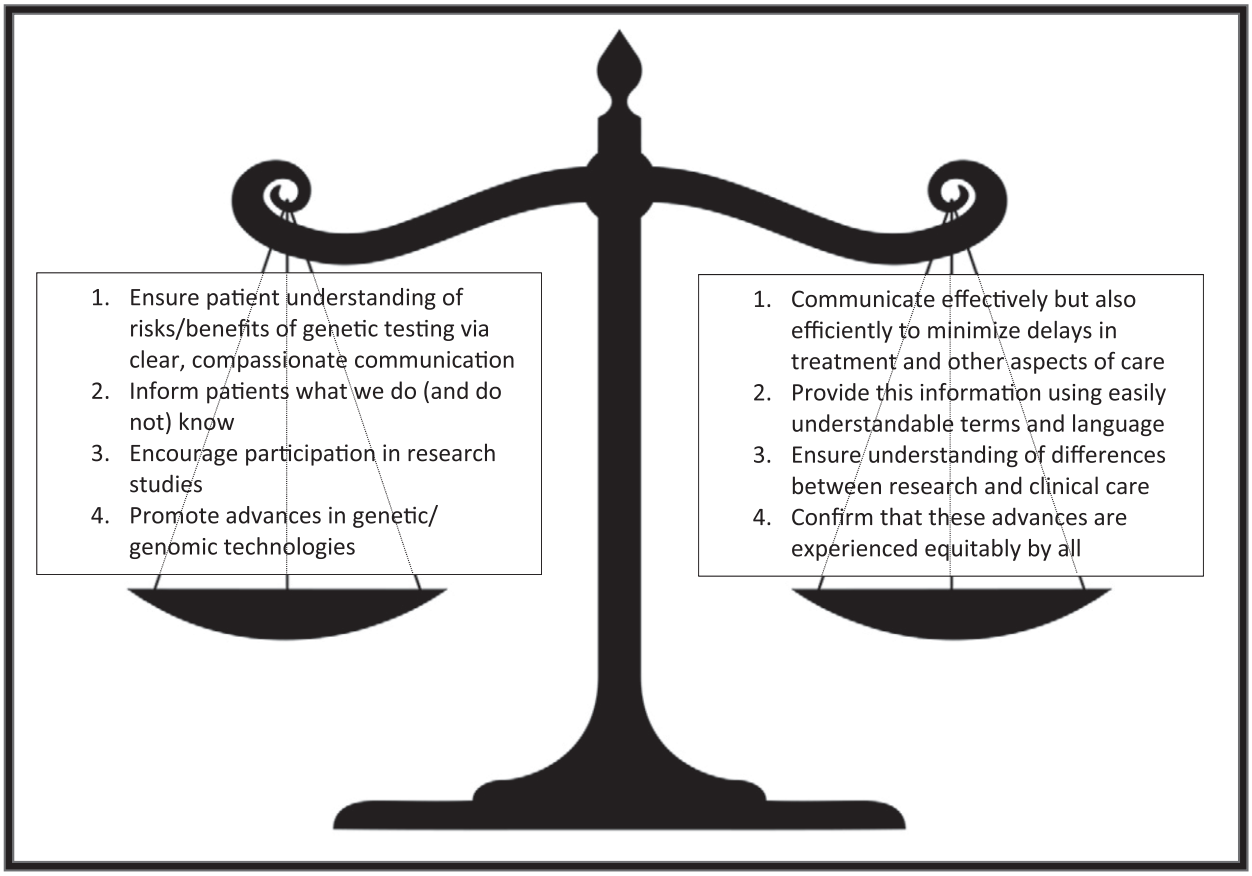

Figure 1. The balancing act of informed consent for genetic testing in hematology.

An additional important consideration regarding disclosure in genetic testing is that of whether the testing is part of clinical care or research. Typically, this distinction is clear, and until relatively recently, testing (particularly next generation sequencing) was performed only as part of a research study. Today, however, as genetic testing rapidly moves from the laboratory to the clinic, this distinction can become less clear. Classically, therapeutic misconception has described the conflation of understanding of the goals of research (generalizable knowledge) and clinical care (individualized patient-level benefit) and is seen in ~60% of research participants.[12] Mr. Smith's response speaks to why this distinction is important; his belief that genetic testing represents his best chance of a cure seems to imply that he thinks the testing is intended, first and foremost, to improve his clinical care. Further details of the research study are necessary to be certain, but because his sequencing would be part of a clinical trial, the truth may not be so straightforward. Not surprisingly, many participants in research on pediatric and adult genetic testing express similar misunderstanding regarding whether the testing is intended primarily to help them (clinical) or develop generalizable knowledge (research) and may overestimate the expected impact of genetic testing on their care and clinical outcome.[16,19,20] This speaks to the importance of pretest counseling about genetic testing. Unfortunately, however, many clinicians express low confidence in their ability to provide adequate counseling about genetic results,[21,22] and many institutions lack sufficient genetic counselors for this purpose.[23] This insufficiency is further complicated by variability in the role played by genetic counselors across institutions[24] and the need for greater education of genetic counselors about germline predisposition syndromes,[25] with the latter likely to be even more prevalent regarding predisposition to hematologic and hematopoietic disorders.

The final 2 information elements of informed consent, recommendation and understanding, will be discussed together, as they are inextricably linked.[6] Clinicians' recommendations carry great weight with many individuals; as a result, a clinician's recommendation is likely to significantly influence a patient's choice about a given intervention. The patient's choice also relies on having an understanding of that choice, which may be the most challenging aspect of informed consent for genetic testing. The public's health literacy and numeracy are known to be poor,[26] and given the probabilistic nature of genetics, it is not surprising that low levels of genetic knowledge are prevalent.[27] Unfortunately, disparities in knowledge about genetics have been reported according to race, education, and age,[16,27] which has troubling implications for both consent for genetic testing and for the use of genetic results.

As mentioned earlier, another important component of understanding is whether a genetic test is performed for clinical or research purposes. In our case, Mr. Smith demonstrates some confusion about this distinction, sometimes referenced as therapeutic misconception.[12] Although some individuals' decisions may not change if they are testing for clinical vs research purposes, the distinction is an important one for many and warrants

clarification. Further, a patient who provides truly informed consent for genetic testing must understand both what the test is likely to offer and what it will not, which may differ in clinical vs research settings. Full disclosure of risks and benefits of testing helps delineate what testing offers, but the nature of genetic testing makes such disclosure (and resultant understanding based on it) difficult. We do not know how Mr. Smith's team described the testing to him, but clinicians and researchers often use ill-defined (or at least variably defined) terms such as "actionable results." Discussions about potential outcomes of testing are challenging as well; to support informed decision making, the patient should know how likely testing is to find an actionable result (and what that means), to lead to a change in treatment, and to improve a patient's chance of survival and cure. Research demonstrates that patients and families commonly misunderstand these and other features of genetic testing.[16,19]

The potential for misunderstanding of these complex concepts speaks to the importance of ensuring that patients understand all aspects of the genetic testing being proposed, for them to make informed decisions. Explanations can take time, but it is time well spent. Clear communication alone does not always impart improved understanding, however, as has been seen regarding communication about such concepts as prognosis.[28,29] Recent work examining specific strategies for improving a patient's understanding regarding genetic testing shows promise,[30,31] but more work is needed in this area.

Consent elements: decision and authorization

These final 2 elements of informed consent, decision and authorization, refer to an individual's decision among proposed treatment options and authorizing (or refusing) one of them.[6] Unfortunately, many think of consent as a signature on a form that documents consent; importantly, this form serves only as legal proof that a person has opted to move forward with a given intervention and authorizes the clinician to proceed. This consent document is an important legal record, but the entire consent process (including all elements described to this point) remains ethically required. Consent is much more than a signature on a form, but the signature (literal in some cases, figurative in others), representing an individual's decision and authorization to proceed, is a necessary element of valid informed consent.

Importantly, many aspects of medical care are thought not to require explicit consent. A clinician does not ask for consent to listen to a patient's heart, for example, or for sending off a particular laboratory test. Genetic testing, however, is far more complex and nuanced than such standard aspects of medical care,[5] leading most to argue that a more formal consent process (including some form of documentation of the patient's decision and authorization) is recommended for such assessments. There is a robust body of literature regarding what aspects of medical care require explicit consent,[6,32,33] but a full analysis of the subject is beyond the scope of this article.

Consent disparities and conclusions

Informed consent is a core component of modern medical practice, and its importance is particularly noteworthy, and particularly complex, in genetic testing.[5] Consent has 7 elements, each of which demonstrates added complexity when the consent is for genetic testing. The case of Mr. Smith, although rather straightforward medically, highlights some of these complexities, ranging from difficulty defining and communicating the potential risks and benefits (and uncertainties) of genetic testing, to the difficulty in verifying the understanding of these. Without question, however, as genetic testing becomes more common in both research and clinical practice in hematology, ensuring that patients provide informed consent for testing will become all the more important.

As the global community becomes more aware of unfortunate disparities in health care access and outcomes, disparities related to genetic testing warrant mentioning. Work with genomic repositories such as The Cancer Genome Atlas demonstrates that much more is known about genetic and genomic diversity (in both healthy and disease states) among Whites than among those of racial and ethnic minorities.[34] This disparity imparts the possibility that genomic knowledge will disproportionately benefit those about whom we know more, which has been confirmed in several recent analyses.[35,36] These inequities are only beginning to be understood, but recent work identifies that this may translate into disparate outcomes from genetic and genomic advances. The use of tyrosine kinase inhibitors in chronic myeloid leukemia, for example, appears to disproportionately benefit those of European background over African Americans.[37,38] Compounded by decreased availability of genomic testing for those with lower income,[39] lower rates of enrollment by those of minority background in genetic and genomic research studies,[40,41] and reports of less knowledge about genetics among those of minority background and with less education,[16,27] we are at a crossroads to ensure that future advances in genetic testing and genetic technologies are equitably accessible to all.[42]

Ultimately, informed consent is a complex balancing act (Figure 1) that serves to support and demonstrate respect for an individual's autonomous choices. The importance of supporting and respecting this choice is readily apparent when considering consent for genetic testing in hematology in both research and clinical settings. As the role of genetic testing in hematology grows further, to provide optimal and equitable care to their patients, all hematologists must exhibit practical knowledge of the elements of informed consent as they relate to genetic testing in hematology.

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