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The Ethics of Genetic Testing for Inherited Cancer-Predisposing Genes

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Abstract

Once an individual has been identified as a carrier of an inherited cancer-predisposing gene or pathogenic germline variant (PGV), there are measures that have been proven to prevent and diagnose the associated cancers at an earlier, more curable stage. Consequently, patients who are offered and undergo testing are afforded opportunities and health-care information that profoundly affect their lives and the lives of their family members who choose to be tested as well. For years, the debate over the controversial topic of whether all patients should be offered germline testing for cancer-predisposing PGVs centered around questions of the analytical sensitivity of the assays (i.e., the ability of the test to correctly identify those who carry a PGV), legal implications for those identified as PGV carriers, cost to the health-care system, and the uncertain management implications of test results. Currently, the standard of care is to offer testing to individuals where the anticipated benefits of testing outweigh the harms. Here, the ethical question of whether all patients have the right to testing for PGVs is considered.

The National Comprehensive Cancer Network (NCCN) Hereditary Cancer panel publishes the standard-of-care guidelines in the United States that identify criteria for which individuals should be offered genetic testing for cancer-predisposing pathogenic germline variants (PGVs; NCCN, 2023). Genetic exceptionalists and the NCCN panelists have suggested that the primary rationale for limiting testing is that, unless there is a high pretest probability of uncovering a PGV, the harms of testing outweigh the benefits (NCCN, 2023; Burke et al., 2022; Green & Botkin, 2003). Over the years, the harms of concern associated with genetic testing have included the unanticipated anxiety associated with discovering a PGV, the burden of informing family members of recommended testing should the patient be found to carry a PGV, the availability of resources that allow the patient who is found to carry a PGV to undergo recommended screening for associated cancers, and the anxiety associated with a negative test result because those patients may still carry cancer-associated inherited genes that are not included in the panel ordered. The possibility of uncovering

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a variant of uncertain significance (VUS) is now seen as the key particular harm associated with genetic testing (NCCN, 2023).

Variants of uncertain significance are uncovered in roughly 25% of individuals. Although over 90% of VUS are eventually reclassified as benign, rather than PGVs, there is anecdotal evidence that patients might experience significant anxiety if informed that they carry a VUS (Burke et al., 2022). Also, genetic exceptionalists contend that genetic testing is fundamentally different from other laboratory tests that imply risk, not because these tests are less accurate in their estimate of risks, but rather because of the profound implications for both the patient and their relatives associated with a test result. Although the guidelines recommend that before testing patients should be thoroughly counselled and shared-decision making is mandatory, even well-trained providers with expertise in genetics might not be capable of assessing the likelihood of emotional and psychological consequences caused by a particular test result for a particular patient (Burke et al., 2022; Green & Botkin, 2003).

In general, the NCCN Guidelines suggest that only those individuals estimated to have a high pretest probability of carrying a PGV or those where an uncovered PGV would be "actionable" should be offered testing or when there is clinical utility from discovering a PGV. Actionable is defined as meaning there are recommended measures to diagnose earlier cancers associated with a PGV or better treat patients with an uncovered PGV. However, neither clinical utility nor actionability allow for the possibility that the information gleaned from the test may be desired by the patient, even when there are no measures proven to mitigate the risks associated with that result. Recommended measures include tests or procedures included in the NCCN Guidelines as well as participation in clinical trials where identification of the PGV results in the patient being eligible for a clinical trial. Although the NCCN panelists only include measures that are "evidence based," naturally there are considerable differences in opinions among providers or patients as to what constitutes an evidence-based measure. Practically speaking, payers typically will not cover testing or measures not endorsed in the NCCN Guidelines, regardless of whether a particular patient views a test as actionable despite the NCCN considering that same test result not actionable.

On the other hand, oncology providers and other proponents of universal testing have argued and provided evidence that far more individuals and their relatives could benefit from measures proven to diagnose PGV-associated cancers earlier and take advantage of targeted therapies than would be tested, even if providers offered everyone testing who meets NCCN criteria (Subbiah & Kurzrock, 2023). Also, it has been suggested that patients are entitled to the information itself, even if not clinically useful by current definitions. For example, a definition of clinical utility used by the Secretary's Advisory Committee on Genetics, Health, and Society is: "Clinical utility refers to... the value of information to the person being tested...Even if no interventions are available to treat or prevent disease, there may be benefits associated with knowledge of a result" (US Department of Health and Human Services, 2006). Thus, endorsing universal testing might be considered the morally correct action, regardless of whether there is clinical utility or actionability related to the result.

For example, in recent articles published in the American Society of Clinical Oncology journals, the authors have contended that all patients with cancer "deserve" testing and that universal testing is "inevitable" because the guidelines deny many patients testing who would be discovered to have "actionable" abnormalities (Subbiah & Kurzrock, 2023; Esplin et al., 2022; Hampel & Yurgelun, 2022). Although not explicitly stated, the authors appear to use the word "deserve" because, without testing, the best management cannot be determined, and they contend that all patients are worthy, entitled to, or deserve the best management available. Also, there is a huge disparity between socioeconomic groups in testing because among those not meeting the NCCN Guidelines criteria, only those who can afford to pay out of pocket are tested (Sorscher, 2023). Presumably, many patients currently not eligible for germline testing would be tested if universal testing is offered and this will be costly. However, the cost of germline testing has decreased substantially in the last few years and is now roughly $250 dollars. In addition, the test need be done only once in each individual,

the disparity between socioeconomic groups in who undergoes testing will be mitigated, and one long-standing criticism of our health-care system related to cancer—the emphasis on treating disease after it is established rather than focusing on prevention and earlier detection—might also be lessened by endorsing universal testing (Burke et al., 2022; Esplin et al., 2022; Sorscher, 2023).

Last year, in the *Annals of Internal Medicine*, Lehmann and colleagues published a position paper on behalf of the American College of Physicians (ACP) that was largely concerned with the ethical considerations for which individuals should be offered genetic testing for inherited genes that predispose to developing cancer (Lehmann et al., 2022).

The authors contended that patients with low pretest probabilities of testing positive for a PGV should be denied testing. On behalf of the Ethics, Professionalism and Human Rights Committee of the ACP, the authors wrote "Bayesian reasoning applies—the pretest likelihood of a genetic disorder may be so low, for example, that testing should not be offered" and "In the face of uncertainty, physicians must weigh the benefits and harms of testing and make decisions based on probabilities" (Lehmann et al., 2022). The authors do not explain why, by applying Bayesian reasoning (which is the application of probability reasoning based on observations and logical inference), there is an ethical argument for denying patients with low pretest probabilities of carrying a PGV testing for that PGV. In fact, invoking the use of Bayesian reasoning has been considered for another common decision patients make with the aid of their health-care provider: enrollment on clinical trials. Although physicians and advanced practitioners might use inductive or abductive reasoning to estimate the probability of outcome or benefit from enrollment and make recommendations according to that estimate, "the value that the patient places on those events (which only the patient can know)" is also a key aspect of shared decision-making (Lilford, 2003).

In other words, their reasoning seems to be at odds with the accepted notions of patient autonomy and shared decision-making. Assuming that the patient is thoroughly and accurately informed of the harms and benefits associated with a test, the idea that a provider knows better than their patient whether the harms outweigh the benefits of a test for a particular patient is paternalistic. In oncology, patients routinely elect to receive highly toxic therapies with very little likelihood of benefiting but do so after giving their informed consent. Presumably, their decisions are consistent with their own values and goals, not necessarily those of their provider.

Those who believe that every patient has the right to decide, for themselves, whether they wish the knowledge provided by germline testing or not are heartened by the American Cancer Society policy statement that "Everyone has a right to a fair and just opportunity to prevent, find, treat and survive cancer" (American Cancer Society, 2023). Germline testing for PGVs affords opportunities for patients and family members. Although not explicitly stated, it seems reasonable to infer that those opportunities should only be afforded patients if the test has been proven to have few false positive and false negative results and patients can be thoroughly informed of the ramifications known to be associated with the potential results. There are now evidence-based recommendations that either prevent cancer from ever occurring or diagnosing the cancers associated with particular PGVs at an earlier stage (NCCN, 2023).

The conundrum over whether every individual is entitled to genetic testing remains unsettled for a variety of reasons as described. However, the current policy that physicians, advanced practitioners, and other stakeholders, not patients, decide for which patients the harms outweigh the benefits is essentially not contributory to the ethical considerations related to endorsing universal testing. Provided they understand the uncertainties, harms, and benefits related to germline testing, patients should be afforded the opportunity to pursue germline testing. In part due to the accepted notions of patient autonomy and the practice of shared decision-making, it is an anachronism to suggest that decisions regarding who is entitled to undergo these highly accurate tests should not be made by each patient themselves.

Hippocrates said, "It is much more important to know what sort of a person has a disease than what sort of a disease a person has." "What sort of a person has a disease" can now be uncovered with

germline genetic testing. This further expands the concept of truly personalized medicine. It is time to consider that everyone, according to their own values and goals, should be allowed to decide for themselves whether they wish to be tested for cancer-predisposing PGVs.

Disclosure

Dr. Sorscher is currently employed by Biotheranostics, Inc./A Hologic Company. He was formerly and briefly employed by Invitae Corp. Ms. DeTroye has no conflicts of interest to disclose.

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