Schrader and colleagues provide four compelling examples of the power of genetic testing to impact medical management for probands and their family members.

Genetic testing may not detect a deleterious mutation

In each of the four cases presented, a deleterious mutation was identified. However, in clinical practice, the majority of germline genetic testing results are “uninformative negative,” even among individuals who have personal and/or family histories that are highly suggestive of a cancer predisposition syndrome.[1,2] In other words, comprehensive testing (eg, full-sequence and large rearrangement analysis of a specific gene or genes) is not 100% sensitive and does not detect every possible mutation. Thus, the absence of a deleterious mutation in a proband (ie, the first individual in a family to be tested) may occur because a mutation was missed by the testing method(s), because a highly penetrant mutation exists in another gene, or because the individual does not have a mutation that is present in the family but not yet identified. There may also be combinations of genetic factors (eg, due to several single nucleotide polymorphisms) that are acting in concert to contribute to elevated cancer risks within a family. Determining which of these possible explanations is most likely to account for the absence of a deleterious mutation in a proband is extremely difficult, if not impossible.

The history or presentation may not clearly suggest a hereditary cancer syndrome

When a patient's personal and/or family history does not point to a specific cancer susceptibility syndrome, the list of differential diagnoses and associated genetic tests may be lengthy. After mutations in major genes are ruled out, pursuing additional genetic testing can be expensive, and may not be covered by insurance. The vague interpretation of uninformative results, coupled with the potential dilemma of whether to obtain additional genetic testing can be frustrating to patients. Moreover, uninformative genetic test results in newly diagnosed patients may not provide any additional guidance regarding immediate surgical and/or medical management decisions, and these patients may not have the luxury of time to wait for the results of further genetic testing. These issues are discussed at length during an ongoing genetic counseling process.

The first three cases described by the authors depict relatively straightforward presentations of cancer predisposition syndromes associated with highly penetrant gene mutations. But many individuals with an inherited susceptibility to cancer have more subtle manifestations. Furthermore, family history as the basis for cancer risk assessment is an imperfect tool. It is not uncommon for the family structure to (1) be small, thus hampering the ability to discern hereditary patterns (eg, autosomal dominant inheritance); (2) contain too few people of the gender at risk (eg, a family of mostly males when assessing for hereditary breast/ovarian cancer); (3) exhibit too few individuals who are alive or who survived to an age at which they would have most likely manifested the phenotype(s) of interest; or (4) be incomplete, because information about family health history is not known.

It may not be possible to initiate testing in the most appropriate family member

To maximize the utility of genetic testing, it is often ideal to initiate testing in a family of an individual with cancer. In the case of Miss Y, if she had tested negative for the CDH1 mutation found in her paternal aunt, this apparently asymptomatic young woman would have undergone an unnecessary endoscopic procedure. Thus, a better approach would have been for Miss Y's affected
aunt to have had genetic testing before Miss Y underwent gastroscopy. Miss Y was able to ask her aunt to undergo genetic testing, and fortunately the aunt agreed. Sometimes, however, unaffected patients are estranged from their affected relative or, if the relative is dealing with advanced disease, the patient may feel uncomfortable broaching the topic of genetic testing.

When very ill patients are interested in genetic testing, as in the case of Mr. X, who had metastatic pancreatic cancer and an undoubtedly poor prognosis, genetic counseling should be tailored to their needs while still ensuring that pertinent implications for them and their relatives are addressed. For seriously ill individuals, the cost of genetic testing may not be covered by insurance if medical necessity cannot be established. However, patients may still be willing to pay out-of-pocket for what could be lifesaving information for their at-risk relatives.

In the case of Mrs. V, tumor testing with immunohistochemistry indicated the likely presence of a germline MSH2 mutation, which was confirmed. The authors state that her tumor was assessed because the history was consistent with Lynch syndrome. However, several institutions in the United States now offer universal testing of tumors from all newly diagnosed patients with colon cancer,[3] and less commonly, from patients with endometrial cancer. Such testing will identify some patients with Lynch syndrome who have otherwise unremarkable family histories.[4] This information may impact not only the patient's surgical and adjuvant treatment, but it may also enable at-risk relatives to obtain genetic testing.

The growing importance of genetic counseling

Many patients are not required to provide informed consent prior to tumor screening for mismatch repair defects. Patient fact sheets and computer-based education may be feasible ways of providing initial information and preparing patients for what to expect if an abnormality is identified, including a possible recommendation for follow-up germline testing. However, because of the complexity of the issues involved in genetic testing, test result interpretation, and familial implications, we strongly recommend that physicians and other health care providers partner with genetic counseling professionals to deliver timely, high-quality pre- and post-test information to patients.

The future of genetic testing: new hope, new challenges

Finally, as the authors observe, “clinical genetics is changing.” It is hoped that the eventuality of affordable whole-genome testing will obviate the need to perform pricey, often stepwise, analysis of single genes. In the wake of this broad testing, some individuals will be identified who have highly penetrant mutations in cancer susceptibility genes, and their cancer risks can be clearly delineated. However, many individuals will have lower- to moderate-penetrance mutations for which risk levels and management options will be uncertain, and all patients will have genetic variations of unknown significance. As testing becomes more pervasive, we are already identifying patients at increased risk for cancers for which proven screening strategies do not yet exist. Thus, for the clinical utility of genomic testing to be fully realized, improved cancer screening and risk-reduction options will need to be developed. Accessible and comprehensive genetic counseling can help patients through this medical maze, and further facilitate ongoing research into these critical and timely issues.

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