

## Unrecognized Familial Cancer Syndromes in Hospice Patients—A Precious, but Fleeting Opportunity for Recognition and Testing

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### Opinion

Hospice physicians may not be aware that a significant number of their cancer patients may have an unrecognized familial cancer syndrome, and that identification of these patients is critical in providing them and their families with potentially lifesaving information. Ideally, such patients would be identified and tested by their gynecologist, primary care physician or oncologist, but this is sadly often not the case. This issue deserves more discussion as to why this matters and the predicament it poses to the medical directors of hospice programs.

Hereditary cancers are uncommon, but identifying them is critical for offering potentially affected relatives and an opportunity for testing and cancer prevention. These cancers are caused by deleterious mutations in normal genes that repair faulty DNA segments. Some are mismatch repair genes, whereas others act as to suppress cancer. Mutations in these genes are passed on through families, putting carriers at very high risk of disease. There are clear guidelines from the National Comprehensive Cancer Network as to which patients should be offered screening [1]. However, these criteria may miss a significant portion of cases [2]. Most insurance companies will cover testing of affected patients, but are more restrictive in covering unaffected relatives unless there is a family history of a known harmful mutation.

Hereditary cancer syndromes should be suspected in patients with uterine cancer occurring before age 50, Gleason 7 or higher prostate cancer (at any age; with a family history of colon or uterine cancer), bilateral breast cancers, breast cancer before age 50, being of Ashkenazi Jewish descent, high grade ovarian cancer (any age), breast cancer in a male, colon cancer before age 50, “triple-negative” breast cancer, multiple cancers in a family and unusual types of cancer, such as adrenal carcinoma [3-6].

Unfortunately, patients who meet criteria for genetic testing for familial cancer syndromes are sometimes referred to hospice without being offered screening. Some of these cases were not recognized by the oncologist, while some patients don't take advantage of the opportunity, given the press of other issues. It seems that the attention has been focused on treating the cancer, rather than considering what caused the cancer or the implications for the surviving relatives. By the time these patients are referred to hospice, they have a very limited life expectancy and limited time in which to perform the testing.

Genetic testing services differ on their resources and reliability in categorizing some of these variants of undetermined significance. Genetic counseling is required before testing, and again post-test counseling is required to review the meaning of the results with the patient/family. This can be done by the ordering physician, but

consultation with genetic counselors by phone or in person is also available [7]. Some insurance companies have recently required a licensed genetic consultation before approving coverage of testing. However, the real issue is who pays for the test? Patients receiving palliative care while undergoing disease-modified therapies still have expenses partially or completely covered by their health insurance. When patients elect hospice care, however, the hospice assumes responsibility for all costs of services related to the terminal disease state.

Hospices run on a limited budget. Genetic testing can be expensive, with the cost varying markedly between different laboratories. Testing, however, is fairly simple, and can be done through either a blood or saliva sample. The results are reported as positive for a known deleterious mutation, negative for a (harmful or any) mutation, or ‘variant of undetermined significance’—meaning that there is not yet enough data to be sure whether the mutation is harmless or not. Deleterious mutations are called ‘actionable’—there is evidence that individuals carrying such a mutation can undertake defined steps to reduce their cancer risk.

One imperfect option is to see if testing for features of hereditary cancer syndromes can now be performed on the cancer tissue blocks (in those cases in which a biopsy was done and/or tissue still available). In Lynch syndrome (formerly called hereditary non-polyposis colorectal cancer syndrome) hallmarks of mismatch repair gene mutations can be identified by immunohistochemistry (IHC) (83% sensitivity; 89% specificity) or microsatellite instability (high degrees of MSI have 77%-89% sensitivity and 90% specificity) [8]. But often tissue isn't available for such testing. This tissue testing is considered part of the pathological examination and doesn't require separate patient consent. However, some familial colon cancer syndromes are missed by both MSI and IHC analysis, as these tumors are related to mutations in tumor suppressor genes. Blood samples from the patient can also be ‘banked,’ for later testing, but again this requires an initial processing payment and delays testing even further.

Genetic testing using Next-Gen sequencing can rapidly identify deleterious mutations in genes that put patients and their relatives at risk for specific cancer types. In fact, the number of potentially heritable and deleterious genes that are recognized has grown considerably [9-12].

Screening of unaffected family members based on their relationship to the affected individual may not be covered without proof of the presence of a pathogenic mutation. Moreover, there may not be accurate details of family history to meet criteria for testing family members. Testing the affected patient is urgent because if a pathogenic mutation is found, the family members can be offered the less costly

testing for the specific gene mutation, and insurance coverage is more likely.

What good does this information offer? For patients who are getting palliative care but are not yet on hospice, there are certain regimens that include a poly (ADP-ribose) polymerase (PARP) inhibitor that take advantage of the mutation's presence to allow more effective treatment [13,14]. For unaffected relatives who are found to carry a deleterious mutation there are a variety of options available for detecting or even preventing cancer. For example, BRCA 1/2 carriers can consider regular breast cancer screening with MRI in addition to mammography, early childbearing with prophylactic oophorectomy (especially the Fallopian tubes) and consideration of prophylactic mastectomy [7,15]. A shorter interval between colonoscopies is recommended for Lynch mutation carriers and hysterectomy may be useful after childbearing is no longer desired [8,16].

Thus the hospice physician should: 1) Identify patients who are candidates for screening for familial cancer syndromes, using established criteria. 2) Consider if such information would offer benefit to the patient's relatives, or if the information would just be of academic interest. 3) Consider if knowing such information might offer the patient targeted therapies that might extend survival. Since even targeted therapies have toxicities and hospice patients have advanced disease, close collaboration with the patient's oncologist would be essential. 4) Work out details of testing to see if the patient's insurance prior to electing the hospice benefit would cover the expense of testing. Family members, after being informed of the possibility of a familial cancer syndrome risk (with the patient's consent) may elect to contribute to the cost of testing, if the hospice is unable or unwilling to. 5) The ordering physician, or a genetic counselor, should provide pre-test counseling, discussion of the results and recommendations for what should be considered next. Some family members may meet criteria for testing, just based on their relationship to the hospice patient (example: a sister of a woman diagnosed with ovarian cancer), or by having a relevant cancer but not yet be enrolled in hospice—in which case the hospice can suggest testing through their own primary care providers.

Thus palliative/hospice physicians are faced with difficult choices. We want to provide comfortable end-of-life care for our patients. Our patients are generally beyond the point where the benefit of further cancer-directed treatment is nil. On the other hand, we do not want to miss the opportunity for providing potentially life-saving information for the patients' families. For now, we should keep our ears open for cases that raise a flag for potential hereditary syndromes, and when

appropriate check with the referring physician to see if this has already been done. If not, we need to look at offering genetic counseling and testing before the patient expires. Ideally, when offered, such testing should not be considered the financial responsibility of hospice. However, until there is better awareness of the importance of case-finding and referral for testing in the general medical community, it is certain that those of us in the palliative care community will see many such cases and will face this challenging situation.

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