IN BRIEF A Summary of the Evidence

DNA Mismatch Repair Deficiency Tumour Testing for Patients With Colorectal Cancer: A Review

Key Messages

- Test all cancerous tumours of the colon or rectum for mismatch repair deficiency (dMMR).
- If dMMR is found, and if MLH1 protein expression is absent, the tumour tissue should automatically be tested for MLH1 promoter hypermethylation.

Considerations for Implementation

- If dMMR is found, and if subsequently the tumour tissue is found to not have MLH1 promoter hypermethylation (and MLH1 protein expression is absent), it is possible that the patient has Lynch syndrome and should be considered for further testing (i.e., germline sequencing) to determine the diagnosis of Lynch syndrome.
- The result of the dMMR test can inform decisions about chemotherapy, regardless if the diagnosis is Lynch syndrome.
- All of these tests require a clear consent process, including an option for patients to decline testing. Education about the tumour tests should be available. Genetic counselling should be available for all patients considering germline testing so that they can understand their results and have support in making decisions about disclosing results to family members, and about future colorectal cancer screening.

Context

Cancers of the large intestine (colon) and of the rectum (the last section of the colon) are referred to as colorectal cancer. In many patients, there is no obvious cause for why they developed colorectal cancer, but sometimes it's an inherited condition that's passed along genetically within a family. Lynch syndrome is the most common inherited condition that puts people at increased risk of developing colorectal cancer and other types of cancers. Knowing if a patient has Lynch syndrome can help guide decisions about treatment and can also have implications for family members.

Technology

Germline genetic sequencing is the gold standard for confirming Lynch syndrome, but the test is time-consuming and expensive. Before performing this test, it's possible to pre-screen patients to identify those most likely to have Lynch syndrome. Pre-screening can be done using criteria (such as age and family history) or by doing other preliminary tests. One preliminary test is to look for mismatch repair deficiency (dMMR) in the tumour tissue, which is something that occurs in Lynch syndrome (but can also occur for reasons unrelated to an inherited cancer predisposition). With dMMR, cells lack the proteins that correct mistakes in DNA replication. When mistakes go uncorrected, they can lead to tumour development.

Two tumour tests exist for dMMR: one using the polymerase chain reaction (PCR) to look for abnormal repeated DNA sequences (a sign that the mismatch repair proteins did not perform their job and might be missing), and one using immunohistochemistry (IHC) to see if the mismatch repair proteins are present (expressed) in the tumour tissue. These tests can provide insight into the function of the four key proteins involved in the DNA mismatch repair process — if all four of them are present or working, the condition is not Lynch syndrome. If one or more is missing or not working, there is a chance the patient has Lynch syndrome. If it is the MLH1 protein that is missing, a follow-up test can help shed more light on the likelihood of Lynch syndrome being the cause of the tumour. A lack of the MLH1 protein is usually caused by a non-inherited (non-Lynch syndrome) defect called MLH1 promoter hypermethylation, so testing for this defect can help rule out Lynch syndrome.

Issue

Testing tumours for dMMR has been identified as a practice that is potentially overused. There is uncertainty about who should have dMMR tumour testing, how well dMMR testing works, and its cost-effectiveness.

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Methods

CADTH conducted a health technology assessment on the clinical and cost-effectiveness of dMMR tumour testing for patients with colorectal cancer, including a review of published literature on patient preferences and experiences. A review of ethical considerations was also conducted. Based on the results, a panel of experts developed recommendations for the adoption of dMMR testing.

Results

PCR-based and IHC-based tumour tests have similar sensitivity and specificity for detecting dMMR, but IHC-based testing is less expensive and has the advantage of identifying which mismatch repair protein is affected, which can guide follow-up testing.

Universal testing of colorectal tumours for dMMR followed by reflex testing for MLH1 promoter hypermethylation can identify patients for germline sequencing and inform chemotherapy decisions, and it was one of the cost-effective strategies. This testing strategy has the advantage of identifying more cases of Lynch syndrome and decreasing the potential for missed diagnoses of Lynch syndrome. Universal testing (rather than using criteria such as age or family history) also improves equity.

The review of patient experience literature suggests that most patients value knowing if their colorectal cancer is hereditary, and the implications for their family members. The review also highlighted generally low levels of knowledge about genetic testing and a need for support throughout the testing process.

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