

Position Statement

Subject: **Consent for performing MSI or IHC screening for Lynch syndrome (HNPCC)**
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Lynch syndrome (or hereditary non-polyposis colon cancer, HNPCC) is a heritable disorder caused by a germline mutation in any one of four DNA mismatch repair (MMR) genes. Tumours arising in this condition typically demonstrate microsatellite instability (MSI) and loss of expression of one or more MMR genes (detected by immunohistochemistry [IHC]). MSI is also a feature of a proportion of tumours with somatic (non-heritable) epigenetic inactivation of one of the MMR genes, MLH1. Hence these investigations have limited specificity for Lynch syndrome.

It has become standard clinical practice to perform MSI and IHC for Lynch syndrome by performing MSI or IHC testing (or both) of tumours in patients with clinical or pathological features suggestive of the syndrome. Loss of expression of one or more of the MMR genes, MSH2, MSH6 or PMS2, is strongly suggestive of a diagnosis of Lynch syndrome. Loss of expression of the MLH1 gene is a weaker indication of an underlying heritable mutation as a somatic non-heritable epimutation is more likely, particularly in older patients without a family history of colorectal cancer. Those cancers with a non-heritable epimutation of the MLH1 gene may have a specific concurrent mutation in another gene (BRAF V600E) which is not a feature of cancers due to a heritable mutation in MLH1, thereby differentiating loss of MLH1 expression due to sporadic versus heritable mutations. Furthermore, MSI and MMR IHC provide prognostic and predictive information that is particularly relevant in the adjuvant setting in which such studies may be used to guide treatment decisions.

Regional differences have emerged throughout Australasia with respect to whether these tests represent *de facto* tests for a familial disorder and hence should be subject to the same consent and counselling requirements as other tests for germline mutations. Regarding MSI and MMR IHC tests as genetic tests may prevent a clinician or pathologist from directly initiating requests for these tests, thereby precluding their use as screening tests and as prognostic and predictive biomarkers.

The RCPA considers that MSI and MMR IHC are tests that assist in characterising a patient's tumour. In view of the limited specificity of these tests for HNPCC, these investigations do not constitute genetic testing for a familial disorder. Patients with MSI tumours should be screened for MMR deficiency by IHC. Patients of any age with tumours shown to be deficient by IHC for MSH2, MSH6 or PMS2 and younger patients with CRC showing MLH1-deficiency and lacking a BRAF V600E mutation should be referred for possible genetic testing to identify a familial mutation.

The College recommends that there be no requirement for additional consent or genetic counselling prior to performing MSI or IHC for mismatch proteins, and considers it appropriate for the relevant clinician or reporting pathologist to initiate such tests. This is currently standard practice in several states.