

Guidelines for the assessment of mismatch repair (MMR) status in Colorectal Cancer

March 2017

Background

Mismatch repair (MMR) deficiency is seen in approximately 15% of colorectal cancers and can be a feature associated with sporadic colorectal cancer, or be caused by Lynch Syndrome. The publication in 2014 of a revised dataset for reporting Colorectal Cancers by The Royal College of Pathologists (April 2014) and an NIHR Health Technology Assessment (HTA) on strategies for testing for Lynch Syndrome (September 2014) requires the development of standardised IHC MMR testing in pre-specified groups of patients with colorectal cancer. The RCPATH dataset recommends MMR immunohistochemical (IHC) testing is considered a core item for patients under the age of 50 and in those adenocarcinomas, where assessment of prognosis is important, with morphological features of MMR deficiency.

MMR deficiency in Lynch Syndrome and sporadic colorectal cancers

Lynch Syndrome (LS) is an autosomal dominant hereditary condition which causes approximately 4% of all cases of colorectal cancer. Lynch syndrome is caused by mutations in a group of genes responsible for MMR e.g. MLH1, MSH2, etc. Loss of function of one of these genes can be demonstrated by assessment of protein expression by IHC, or by assessment of microsatellite instability (MSI). If loss of expression of an MMR protein is seen on IHC assessment the patients' germline DNA can then be subjected to analysis to identify a specific mutation. LS related colorectal cancer occurs in patients at a median age of 46 years with a preponderance of right sided, mucinous, poorly differentiated tumours. Primary tumours of other organs are also a feature of LS but occur less commonly than colorectal cancers. Screening to identify LS in patients with high risk features who have developed colorectal cancer is currently undertaken but the NIHR HTA provides further impetus to develop and expand this service.

It is important to recognize that loss of expression of MMR is seen in approximately 15% of patients with colorectal cancer and that most of these patients do not have LS. Histological features of MMR deficiency include mucinous phenotype, an expansile rather than infiltrative margin, tumour infiltrating/associated lymphocytes, a Crohn's like inflammatory reaction, two or more tumour subclones and poor differentiation. The majority of sporadic MMR deficient tumours occur in the right side of the colon. Loss of MMR expression in tumours by gene mutation and/ or promotor hypermethylation is a well described pathway for the development of colorectal cancer and is associated with a number of other abnormalities including the presence of BRAF mutations.

More recently, NICE has published guidance (<https://www.nice.org.uk/guidance/dg27>) which indicates that all new diagnoses of colorectal carcinoma, regardless of age, should be investigated either by IHC or MSI testing, with IHC being the preferred first-line method in the Manchester area.

Any guidelines developed for the assessment of MMR status need to clearly delineate the pathways for patients with LS and non-LS colorectal cancers.

MMR, prognosis and adjuvant chemotherapy

MMR deficiency has been demonstrated to confer an improved prognosis compared to MMR proficient tumours. Pre-clinical data suggests that MMR deficient tumours may be resistant to 5FU chemotherapy. Clinical data suggests the benefit of adjuvant 5FU chemotherapy following colorectal cancer resection is reduced but it is uncertain whether this relates to the already good prognosis of these tumours or to resistance to 5FU chemotherapy. Selected use of MMR testing may therefore be useful to identify patients who have a good prognosis in whom 5FU adjuvant chemotherapy may not be beneficial.

Service development

The only regional histopathology laboratory currently performing MMR IHC testing is based at Central Manchester Foundation Trust with the majority of requests from Consultants in Clinical Genetics. The proposed expansion of MMR IHC testing proposed would require a significant increase in the number of tests performed annually. Discussions at Colorectal Pathway Board meetings and in a separate work group agreed that a centralized regional centre, based in histopathology at Manchester Royal Infirmary, for MMR IHC testing would be the optimal service model.

Groups to be assessed for MMR status

The following hierarchy will be used for the assessment of MMR by IHC:

1. All cases of colorectal cancer occurring in patients aged under 50 years old
2. Cases by case following discussion at local Colorectal Cancer MDT meetings:
 - a. Additional cases aged between 50 and 60 years old with histopathological and clinical features suspicious of Lynch Syndrome and a family history of LS related cancers.
 - i. Features suspicious of LS in the patient may include:
 1. Synchronous colorectal cancers
 2. Metachronous colorectal cancers
 3. High grade/ poor differentiation
 4. Signet ring cancers
 5. Mucinous tumours
 6. Previous or current adenomas
 7. Previous or current LS tumours (endometrial, ovarian, biliary tree, stomach, upper urinary tract, pancreas).
 - ii. Features in family history
 1. First degree relative with colorectal, small bowel, endometrial, ovarian, biliary tree, stomach, upper urinary tract, pancreas diagnosed <60 years of age.
 2. Two close relatives (first/second degree) with any of above <70 years of age.
 - b. At Oncologists request – in cases where prognostic information will aid decision making re chemotherapy e.g. TNM stage 2 cancers aged 50-70 years.

Notes:

- The approach taken is to ensure referral for MMR testing is embedded within histopathology departments for cases occurring in the age of 50 years.
- Additional referrals can be discussed and made from an MDT meeting with the commonest examples listed above.

Pathway for MMR testing

1. Referral

- a. The reporting histopathologist identifies a patient fulfilling group 1 criteria, or is requested to refer by the MDT based on individual factors.
- b. The referrer should be listed as the Consultant Surgeon or Consultant Oncologist responsible for the patients care.
- c. When patients are referred directly for MMR testing the histopathology report should include a clear statement that referral has been made. If histopathological factors concerning for LS are present a recommendation for discussion at the MDT should be made within the report.

2. Histopathological material

- a. Please provide a tumour block, preferably in continuity with normal tissue, as well as a separate block of normal tissue. Please provide sufficient demographic data, including a copy of the original histopathology report.

3. Analysis of material

- a. Tumour material will be assessed for loss by IHC of MLH1, PMS2, MSH2 and MSH6.
- b. Samples from tumours demonstrating MLH1 loss and/ or PMS2 loss by IHC will be sent to the regional genetics laboratory at St.Mary's Hospital for analysis of MLH1 promotor methylation and BRAF mutation status.

4. Dissemination of results

- a. A report of MMR IHC results and any additional molecular analysis will be produced and sent to the referring histopathology department and referrer. The report must include a clear statement regarding the recommended treatment plan.
- b. It is desirable to document the results as an addendum to the original histopathology report.

5. Referral to Clinical Genetics by the Clinical team (Surgical/ Oncology)

- a. Patients with loss of MSH2 and/or MSH6 or with loss of PMS2 alone are at high-risk of LS and should be referred.
- b. Patients with loss of MLH1 alone or with PMS2 loss who on additional analysis do not have a BRAF mutation and/ or do not have MLH1 promotor methylation should be referred.

Funding arrangements

The referring laboratory will be invoiced £135 per case for the IHC testing.

All referring laboratories will be required to set up a purchase order in order for the request to be invoiced. Once a report has been issued an invoice for £135 per sample will be sent to the laboratory manager of the referring laboratory.

If genetic testing is required, further tissue sections will be prepared by the MRI Immunohistochemistry laboratory staff and sent to the genetics laboratory at St. Mary's Hospital who will issue a separate invoice for their work.

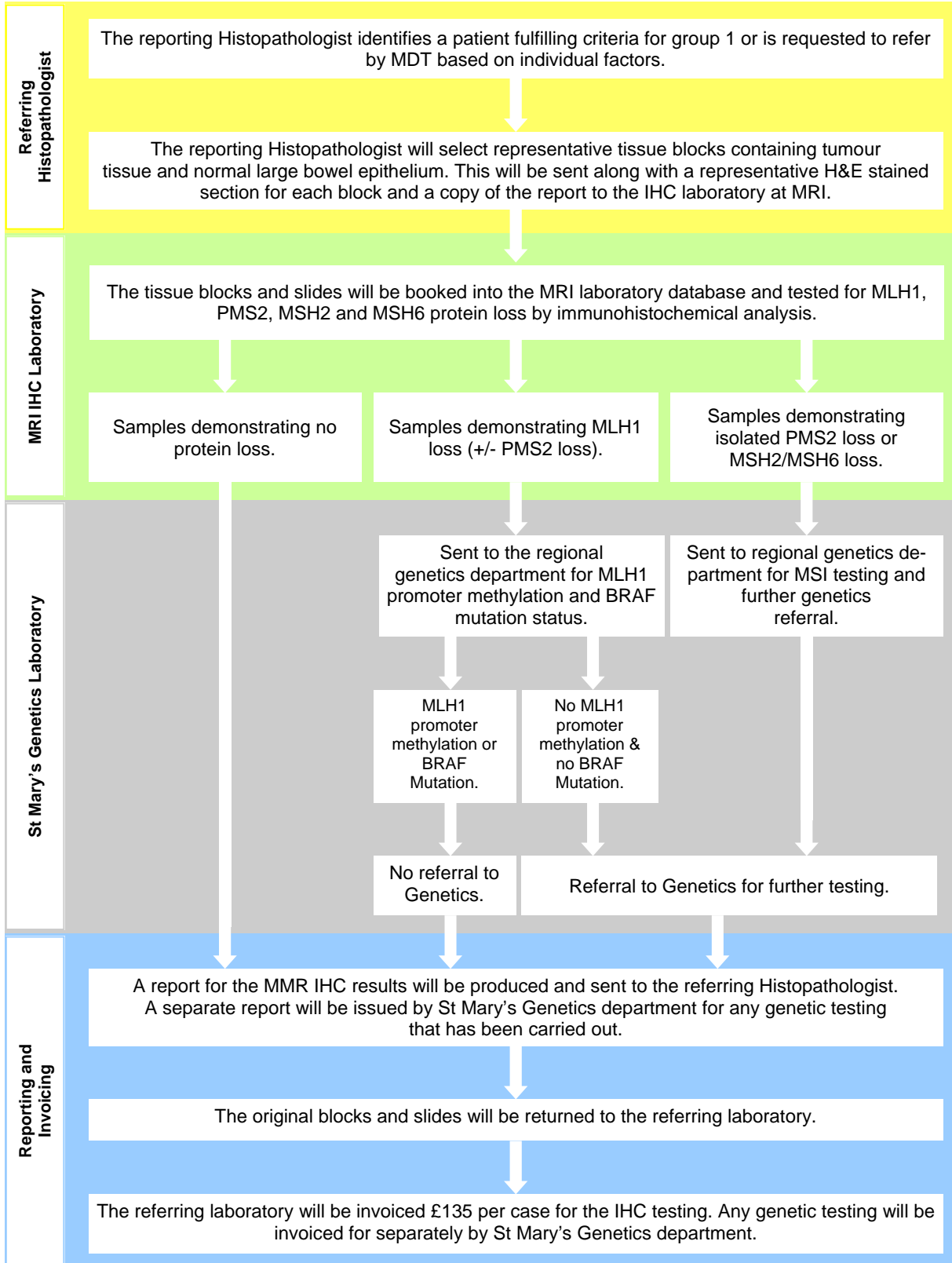
Appendix

Diagnostic MMR Flow Diagram

Diagnostic MMR Request Form



MRI MISMATCH REPAIR TESTING PATHWAY





Diagnostic MMR Testing
Immunohistochemistry Laboratory
Dept. of Adult Histopathology
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL

Tel: 0161 276 8786
Fax: 0161 276 6348

REQUEST FOR MISMATCH REPAIR IMMUNOHISTOCHEMISTRY TESTING

<p>PATIENT DETAILS</p> <p>Surname:</p> <p>Forename(s):</p> <p>DoB: Sex: M/F</p> <p>NHS No:</p> <p>Hospital No:</p> <p>Address:</p> <p>Postcode:</p>	<p>REFERRER DETAILS</p> <p>Consultant Surgeon/Oncologist:</p> <p>Consultant Histopathologist:</p> <p>Date of Request:</p> <p>Address for Reporting:</p> <p>Tel:</p> <p>Fax:</p> <p>Email:</p> <p>Reported by:</p> <p><input type="checkbox"/> Email (an 'nhs.net' email account is required)</p> <p><input type="checkbox"/> Fax (a 'safe Haven' fax no is required)</p>
<p>REFERRED MATERIAL DETAILS</p> <p>Please send one tumour and one normal tissue block with a representative H&E slide from each. Also ensure that a copy of the report is also included.</p> <p>Referring Laboratory:</p> <p>Normal Tissue Block No:</p> <p>Tumour Tissue Block No:</p>	<p>INVOICING DETAILS</p> <p>Laboratory Manager Name:</p> <p>Contact Email:</p> <p>Purchase Order Number: <i>Please note this is required to process your payment</i></p> <p>Invoicing Address:</p> <p>Postcode:</p>
<p>CRITERIA FOR TESTING (Please tick)</p> <p><input type="checkbox"/> Direct Request from Histopathology. Patient <50 years old at time of diagnosis with colorectal adenocarcinoma.</p> <p>The patient has been discussed at an MDT and;</p> <p><input type="checkbox"/> Is 50-60 years old and has a tumour with histological features suggestive of Lynch syndrome and a family history of Lynch syndrome related malignancies.</p> <p><input type="checkbox"/> MMR status will aid decision making regarding chemotherapy treatment (oncologist request).</p>	