Oxford University Hospitals NHS
NHS Foundation Trust

Mismatch Repair Testing: MMR/MSI – Who? Why? How?

A guide for the Colorectal MDT (version 1.5 July 2016)

Background

Oncological Benefits: There is increasing recognition of a need to identify patients who are MMR protein deficient. They are a prognostically-priveleged groups who, because of their low baseline risk, may derive reduced absolute benefit from the use of adjuvant therapy. This is certainly true of patients with stage II CRC but is less clear for those with stage III (T3N1) disease. Stage III patients with T4 or N2 disease have much poorer prognosis and it is unlikely that their underlying MMR status will affect their overall prognosis significantly. There are also some data to suggest that these patients are less likely to be MMR deficient.

Family Benefits: The second reason for identifying these patients is that they may have a germline mutation related to Lynch syndrome which represents an increased cancer risk for other family members that requires screening and therefore a referral to the Genetics Service is justified.

There are two ways that potentially dMMR patients and their families are identified.

GROUP1: Pathology Led Referrals.

Professional literature and several internal clinical audits **support** both the cost effectiveness and efficacy of **MMR testing on all cases of primary colorectal cancer diagnosed at any age**. This is supported by guidelines from the Royal College of Pathologists, and this is now **considered standard practice in Oxford.**

ACTION: The mismatch repair genes are MLH1, MSH2, MSH6 and PMS2. When lost (dMMR), this is often in pairs (MLH1 and PMS2, or MSH2 and MSH6).

If **ANY** patient's IHC suggests loss of **ANY** of the MMR proteins (single gene or multiple gene loss), at **ANY** age, then a referral to clinical genetics is recommended. Information regarding this advice should be given to them, either through their CNS or through their oncologist to advise them of this result and this recommendation.

This loss does not mean that a germline (inheritable) MMR mutation is responsible, but a full assessment by the clinical genetic team is the safest way to carry out further genetic testing and fully assess this.

MAKING YOUR REFERRAL:

The referral can be made directly at this stage to the genetics department by any health care professional involved in the individuals' management. Via genetics, with consideration of the careful family history, appropriate gene testing will be performed to delineate familial risk.

If the patient is very unwell / **terminal**, then the minimal action should be to **take and store an EDTA blood sample** for germline DNA analysis. You should request that a blood sample is taken. This **sample should be sent to Molecular Genetics** at the Churchill Hospital stating potential Lynch syndrome for storage pending family referral. Please request that this sample should be extracted two ways.

GROUP 2: Family History led Referrals.

NOTE: Even if the patient doesn't show dMMR, then please also consider a genetics referral if the family history is *extensive* or *unusual*. This means:

- The patient developed CRC under the age of 50 years
- The patient and a close relative(s) were affected by bowel cancer (or other Lynch associated cancers**) at an average age of under 60
- The patient has two close relatives^ that have also been diagnosed with CRC (or other Lynch associated cancers) at any age

These group 2 types of family history referrals should **always** be **accompanied by a completed family history questionnaire**. It is often simpler (in these situations) for the questionnaire to be **completed** by the patient in their own time and then taken to **their GP** who **will carry out the formal genetics referral**.

Appendix 1 ***Patient Information Letter re Lynch Syndrome***

Appendix 2 ***Standard Referral letter to Clinical Genetics***

^ Close relative means mother / father / sister / brother / son / daughter / aunt / uncle / grandmother / grandfather

** Other Lynch associated cancers are stomach, endometrial, ovarian, urological, brain and sebaceous skin cancer

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Lynch Syndrome
Patient information sheet

Why have I been given this information sheet?

As part of the tests that we have done on a sample of your bowel cancer, we have found a result that suggests that you ***may*** have an increased risk of getting bowel cancer. This change in your tumour may have possibly led to your cancer developing. It may demonstrate a genetic predisposition, but these types of changes can also sometimes occur for other reasons. We do not yet know the cause in your case because we do not know enough about your personal and family health history.

Because of these results however, we are recommending further investigations. **To get these investigations done you will need to be referred to the Department of Cancer Genetics at the Churchill Hospital.** The Cancer Genetic team can then review these results, look at your family tree and also look in detail at any other cancers that have occurred in your family members. This allows us to provide more accurate information for you, but also advice about the possible risks for other family members. This advice may include further genetic tests or screening.

What else is in this information sheet?

Attached to this information sheet is a family history questionnaire from the department of Cancer Genetics, along with some information about the cancer genetics service.

What do I need to do now?

If you would like take up the offer of a referral then

- The specialist discussing your cancer treatment who gave you this form can organise a referral directly to the genetics team.
- The appointment can take a few weeks to come through following referral.
- Please complete the family history questionnaire you have been given with as much information as you can get.
- Either post the completed questionnaire directly to the genetics team here in Oxford, or alternatively keep it safe and bring it to the appointment with you.
- We would prefer to get the form in advance of the appointment if possible to help us to prepare and better advise you on that day.

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Details of referrer
XXXXXXX
XXXXXXX

Oxford Cancer Genetics Team
Department of Clinical Genetics
The Churchill Hospital,
Old Rd,
Headington
Oxford OX3 7LJ

Dear Dr

RE:

I would be grateful if you could see and advise this patient who has been recommended for referral to your department for ongoing investigation into their bowel cancer diagnosis.

GROUP1: Tumour testing has suggested that they may be mismatch repair deficient (dMMR). Further genetic investigation of this family is warranted.

I have/ have not enclosed a completed family history questionnaire with this referral.

GROUP 2: This individual's history is suggestive of a familial predisposition to bowel cancer, and further assessment seems warranted: Please indicate if:

- 1) They have a personal diagnosis of CRC under the age of 50 years

  or

- 2) They have TWO close relatives^ affected by bowel cancer (or other Lynch associated cancers**) at an average age of under 60

  or

- 3) They have THREE close relatives^ that are in a first degree kinship (all direct relatives of each other**) diagnosed with CRC (or other Lynch associated cancers) at any age

^ Close relative means mother / father / sister / brother / son / daughter / aunt / uncle / grandmother / grandfather

** Other Lynch associated cancers are stomach, endometrial, ovarian, urological, brain, prostate and sebaceous skin cancer

Many thanks for seeing them and advising further on management.

With best wishes