

UKCGG-National Cancer Genetics MDT meeting: 17.11.2022

Lynch-Like Syndrome - lead by Edinburgh

Meeting contact: **Jennie Murray**

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Thank you to everyone who attended this session. Below is an overview of the presented cases, expert speaker talks, and a general meeting summary.

Presented Cases

Case 1	Young endometrial cancer MMRd in Amsterdam positive family history (unconfirmed). Single MSH2 somatic variant, not present in germline. Screening advice for FDR.	Presented by: Josephine Giblin Bristol josephine.giblin@nhs.net
	Actions/Outcome: Request LoH testing in tumour, seek testing for MMRd in tumours in other family members if possible. Ask lab to double check presence of somatic variant in germline as high VAF (?mosaic). If no LoH, 2yrly colonoscopy for FDR. One suggestion of 5yearly. Question also raised as to whether you would also consider TAH in FDR.	
Case 2	77yr male with pancreatic cancer, loss of PMS2, germline testing negative, somatic testing PMS2 failed. Daughter CRC at 48yrs MMRp no variants in somatic testing, germline DNA stored	Presented by: Jennifer Wiggins Royal Marsden jennifer.wiggins@rmh.nhs.uk
	Actions/Outcome: Consider (If possible) review/repeating IHC on both tumours and MSI on daughters tumour. However PMS2 Lynch is not associated with an increased risk of pancreatic cancer and consensus was low likelihood this is Lynch syndrome. Screening to FDR based on family history of CRC cancer (moderate risk).	
Case 3	Isolated bowel cancer at 41years deceased. Loss of PMS2. Further testing on biopsy identified PMS2 pathogenic variant. Unable to tell if biopsy normal or tumour tissue. Should FDRs be tested for variant.	Presented by: Claire Searle Nottingham claire.searle@nuh.nhs.uk
	Actions/Outcome: Agreement yes, FDR should be tested for the PMS2 variant. If not present in 3 relatives, screen as per family history of CRC (moderate risk).	
Case 4	Endometrial cancer at 55years MMRd MSH2 & MSH6, keratoacanthoma at 57yrs. Germline testing negative, 2 somatic hits in MSH2 at low VAF. Cousin with young onset endometrial and rectal cancer also MMRd MSH2 and MSH6. Amsterdam positive FH. Somatic testing failed. FDR being screened as Lynch-like. Any further testing? PTEN, POLE/D testing negative.	Presented by: Debbie Mackin and Judith Pagan Edinburgh

	Actions/Outcome: Agreed strong suspicion missed germline cause. Comment made that not unusual to get somatic hits in MMR gene in hypermutated MMRd phenotype due to high mutational burden. IHC in keratocanthoma and Test tumour in other relatives was suggested. Agree screen relatives as lynch-like.	
Case 5	Male with colorectal cancer at 65yrs, mother ovarian cancer in 80's. No other FH. Loss of MLH1 and PMS2, one somatic variant identified in MHL1. Germline testing negative.	Presented by: Emma Cowan Aberdeen emma.cowan2@nhs.scot
	Actions/Outcome: LoH testing in tumour. Even if LoH testing uninformative then suggested that a single scope or 5yearly at most would be appropriate screening for FDRs. Also suggestion that as sister would be eligible for national screening then this would be reasonable also.	
Case 6	Male with CRC at 35years. Loss of MLH1 and PMS2. Mother hysterectomy in late 30's. Brother polyps at 41yrs on colonoscopy. Germline testing negative but Lynch genes only.	Presented by: Emma Cowan Aberdeen emma.cowan2@nhs.scot
	Actions/Outcome: Further work up warranted. Expand germline testing and undertake somatic sequencing. High concern for Lynch based on young rectal cancer so relatives should be screened as Lynch-like unless further information obtained. Suggestion that brother's polyps could also have MSI testing in Canada.	

Expert Speaker Talk

Andrew George and Dr Terri McVeigh

The slides can be accessed in the resources section of: <https://www.cangene-canvaruk.org/cancer-genetics-mdt>

Talk Summary:

Andrew George (Presentation Title: The potential benefit of MMR, MSI and TMB as SoC in the RMH Diagnostic pathway considering the introduction of the NHS National Genomic Test Directory) gave an overview of a somatic testing pathway in development at the Royal Marsden which incorporates a large NGS (RMH200) somatic panel, NGS MSI and MMR IHC compared to current standard of care testing in colorectal cancer. They demonstrated that their NGS pathway is as effective at identifying Lynch syndrome as current techniques and more efficient.

Dr Terri McVeigh (Royal Marsden) then described the increasing workload for Clinical Genetics as a result of escalating somatic testing and the challenges in advising screening for FDRs of patients with unexplained MMR deficient tumours.

Meeting Summary

This meeting provided an opportunity to conduct a scoping exercise to see how centres are currently managing families with MMR deficient tumours where germline testing has been negative and somatic testing has not confirmed a likely sporadic cause.

Following the above talks, the attendees were asked to vote on five questions. The questions and results of the poll are as follows plus additional comments made at the time of the poll:

1. In patients with MMR deficient tumours where constitutional and somatic testing has been uninformative, this should be referred to as 'unexplained MMR deficiency' rather than 'Lynch-like syndrome'

Strongly Agree 14%, Agree 64%, Neither Agree or Disagree 18%, Disagree 4%, Strongly Disagree 0%

2. In isolated cases with an MMR deficient tumour, which is not endometrial or colorectal, somatic testing in addition to constitutional testing is not required.

Strongly Agree 5%, Agree 32%, Neither Agree or Disagree 37%, Disagree 22%, Strongly Disagree 5%

3. For patients with an MMR deficient tumour AND modified Amsterdam positive family history but constitutional and somatic testing inconclusive, FDR should be offered screening in line with Lynch syndrome.

Strongly Agree 14%, Agree 71%, Neither Agree or Disagree 10%, Disagree 4%, Strongly Disagree 1%

4. For patients with an MMR deficient tumour WITHOUT a modified Amsterdam positive family history, where constitutional and somatic testing have been inconclusive, screening should be offered to FDR based on the family history of colorectal cancer.

Strongly Agree 6%, Agree 69%, Neither Agree or Disagree 15%, Disagree 9%, Strongly Disagree 1%

5. For patients where there is clinical uncertainty, then referral for discussion at a clinical MDT is recommended

Strongly Agree 37%, Agree 56%, Neither Agree or Disagree 6%, Disagree 1%, Strongly Disagree 0%

It was commented on that responses to the above questions would likely vary depending on age of diagnosis and tumour type. There was some confusion over interpretation of question 2 with some individuals commenting that, on reflection, they voted the opposite from what they meant. It was also commented that first line somatic testing would be preferential to germline testing in relation to question 2.

Six cases were then presented and discussed. A consensus was reached on screening advice for FDR in each case. Most centres appear to take a similar pragmatic approach to screening in FDR in dMMR tumours considering the tumour type, family history and age of diagnosis. It was raised that lack of access to LoH testing in the UK is a deficiency

impacting on the ability to complete somatic testing and therefore assess risk to relatives. It was also suggested that perhaps there should be an age cut off for somatic testing in isolated late onset cases. It was also raised that the cumulative amount of clinician/MDT time spent deciding on screening in families is unlikely to be cost effective with respect to number of cancer deaths prevented. This was agreed with by several attendees. There was also acknowledgment that organising somatic testing is currently very time consuming for clinicians. Finally, a suggestion was made that clear criteria for screening could be applied based on age, tumour type and family history but cases not covered by this should be discussed in an MDT.

A formal UKCGG consensus meeting to establish guidelines for the management of such cases is now planned (aim April 2023).

Next meeting details

Date	19 th January 2023
Time	12:30 pm-1:45 pm
Theme	Mixed Cases
Leading centre	Wales
Contact for cases	Sarah.Pryde3@wales.nhs.uk

**Please send any questions or ideas for future meetings to Helen Hanson
(helen.hanson@stgeorges.nhs.uk)**