THE BRITISH ASSOCIATION OF GYNAECOLOGICAL PATHOLOGISTS

Recommended Terminology for Reporting Mismatch Repair Protein Immunohistochemistry with or without MLH1 Promoter Methylation Results

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Background

- There are currently no universally accepted guidelines for testing for a mismatch repair (MMR) defect in newly diagnosed gynaecological malignancies.
- A recent survey carried out within the British Association of Gynaecological Pathologists (BAGP) and the International Society of Gynecological Pathologists (ISGyP) demonstrated wide variation in current practice, ranging from no testing, testing in selected cases according to variety of criteria, and universal testing.
- Despite the wide variation in current coverage, there was almost unanimous agreement amongst respondents that there should be uniform terminology for reporting MMR immunohistochemistry (IHC).
- An international, multidisciplinary consensus meeting was hosted at the University of Manchester in April 2017 with the aim of developing gynecological-specific guidance for the diagnosis, prevention and surveillance of Lynch syndrome-associated gynecological malignancies.
- In response to the BAGP and ISGyP survey, and as one outcome of the consensus meeting, the authors above were tasked with developing reporting terminology for MMR IHC.
- The BAGP endorses and recommends the use of this terminology.

Recommended Terminology for Reporting Mismatch Repair Protein Immunohistochemistry (MMR IHC) +/- *MLH1* promoter methylation results

- Recommended terminology is tabulated below.

Table: Recommended Terminology for Reporting Mismatch Repair Protein Immunohistochemistry (MMR IHC) +/- *MLH1* promoter methylation results[a,b,c,d]

MMR result	Recommended report
Normal, MLH1, PMS2, MSH2 and MSH6 tested	**MMR IHC Normal:** The tumour cells show normal nuclear staining for MLH1, PMS2, MSH2 and MSH6. Conclusion: There is no immunohistochemical evidence of a mismatch repair deficiency*.
Normal, only MSH6 and PMS2 tested	**MMR IHC Normal:** The tumour cells show normal nuclear staining for PMS2 and MSH6. Conclusion: There is no immunohistochemical evidence of a mismatch repair deficiency*.
Abnormal, MSH6 loss	**MMR IHC Abnormal, MSH6 loss:** The tumour cells show loss of expression of the mismatch repair protein MSH6 (with normal nuclear staining for MLH1, MSH2 and PMS2). Conclusion: This mismatch repair deficiency is associated with Lynch and related syndromes. **This patient should be referred to Clinical Genetics services.**
Abnormal, PMS2 loss	**MMR IHC Abnormal, PMS2 loss:** The tumour cells show loss of expression of the mismatch repair protein PMS2 (with normal nuclear staining for MLH1, MSH2 and MSH6). Conclusion: This mismatch repair deficiency is associated with Lynch and related syndromes. **This patient should be referred to Clinical Genetics services.**
Abnormal, MSH2 and MSH6 loss	**MMR IHC Abnormal, MSH2 loss:** The tumour cells show loss of expression of the mismatch repair proteins MSH2 and MSH6 (with normal nuclear staining for MLH1 and PMS2).

	Conclusion: This mismatch repair deficiency is associated with Lynch and related syndromes. **This patient should be referred to Clinical Genetics services.**
Abnormal, MLH1 and PMS2 loss, *MLH1* promoter hypermethylation absent	**MMR abnormality, MLH1 loss and *MLH1* Promoter hypermethylation absent:** The tumour cells show loss of expression of the mismatch repair proteins MLH1 and PMS2 (with normal nuclear staining for MSH2 and MSH6). *MLH1* promoter hypermethylation is not present. Conclusion: While this mismatch repair deficiency could be sporadic, it is probable that this mismatch repair deficiency is due to Lynch or related syndromes. **This patient should be referred to Clinical Genetics services.**
Abnormal, MLH1 and PMS2 loss, *MLH1* promoter hypermethylation present	**MMR abnormality, MLH1 loss and *MLH1* Promoter Hypermethylation present:** The tumour cells show loss of expression of the mismatch repair proteins MLH1 and PMS2 (with normal nuclear staining for MSH2 and MSH6). The *MLH1* promoter shows hypermethylation is present in the tumour. Conclusion: This combination indicates that this mismatch repair deficiency is almost certainly sporadic rather than due to Lynch Syndrome**.** **This patient does not require referral to Clinical Genetics services*.**
Abnormal, MLH1 and PMS2 loss, *MLH1* promoter hypermethylation not tested	**MMR abnormality, MLH1 loss and *MLH1* Promoter hypermethylation not tested:** The tumour cells show loss of expression of the mismatch repair proteins MLH1 and PMS2 (with normal nuclear staining for MSH2 and MSH6). *MLH1* promoter hypermethylation has not been tested. Conclusion: This pattern is likely to be sporadic, although it is possible that this mismatch repair deficiency is due to Lynch or related syndromes. **Testing for *MLH1* Promoter hypermethylation is recommended OR this patient may be referred to Clinical Genetics services.**
Abnormal, MLH1 and PMS2 loss, *MLH1* promoter hypermethylation	**MMR abnormality, MLH1 loss and *MLH1* Promoter Hypermethylation testing results pending:** The tumour cells show loss of expression of the mismatch

pending	repair proteins MLH1 and PMS2 (with normal nuclear staining for MSH2 and MSH6). *MLH1* promoter hypermethylation testing in the tumour has been requested. Conclusion: This pattern of mismatch repair deficiency may be either sporadic or due to Lynch or related syndromes – the result of testing for *MLH1* promoter hypermethylation will provide further information. A supplementary report will be issued when these results become available.
***Referral to Clinical Genetics services should be considered despite this result in the presence of a strong family/clinical history.**	

[a]For referral laboratories only reporting mismatch repair status the report should include:
Specimen type:
Site of sample:
Diagnosis:
Overall cellularity (biopsy samples only): High/average/low
Percentage neoplastic nuclei in test area for DNA extraction:

[b]Good fixation is important for obtaining reliable and reproducible patterns of MMR expression by IHC and can be evaluated by assessing MMR expression by internal control cells. Pre-operative biopsies are often better fixed than hysterectomy specimens and may be considered as a better sample for MMR IHC testing, depending on availability. MMR IHC should be reported only in the presence of positive internal control cells, such as stromal cells or lymphoid cells, that are immediately adjacent to the tumour cells under analysis; it must be stated if there is no internal control for comparison.

[c]Rare abnormalities of mismatch repair protein expression are not included in this table and these may be reported as free text where present; examples include weak/patchy/cytoplasmic/punctate or dot-like nuclear patterns of abnormal MMR expression, subclonal/heterogeneous patterns of MMR staining abnormality, and loss of expression of different combinations of MMR proteins (other than the expected MLH1 & PMS2 – or – MSH2 & MSH6 combinations).

[d]The molecular mechanism for the strong association of BRAF mutation with CRC harbouring somatic MLH1 hypermethylation is incompletely understood but appears to be tissue/tumour-specific; unlike algorithms in use for CRC, BRAF immunohistochemistry or sequencing cannot be used as a proxy for somatic *MLH1* hypermethylation in gynecological cancers, as oncogenic *BRAF* mutations occur so rarely in these.