A Clinical Audit of a Lynch Syndrome Referral Protocol

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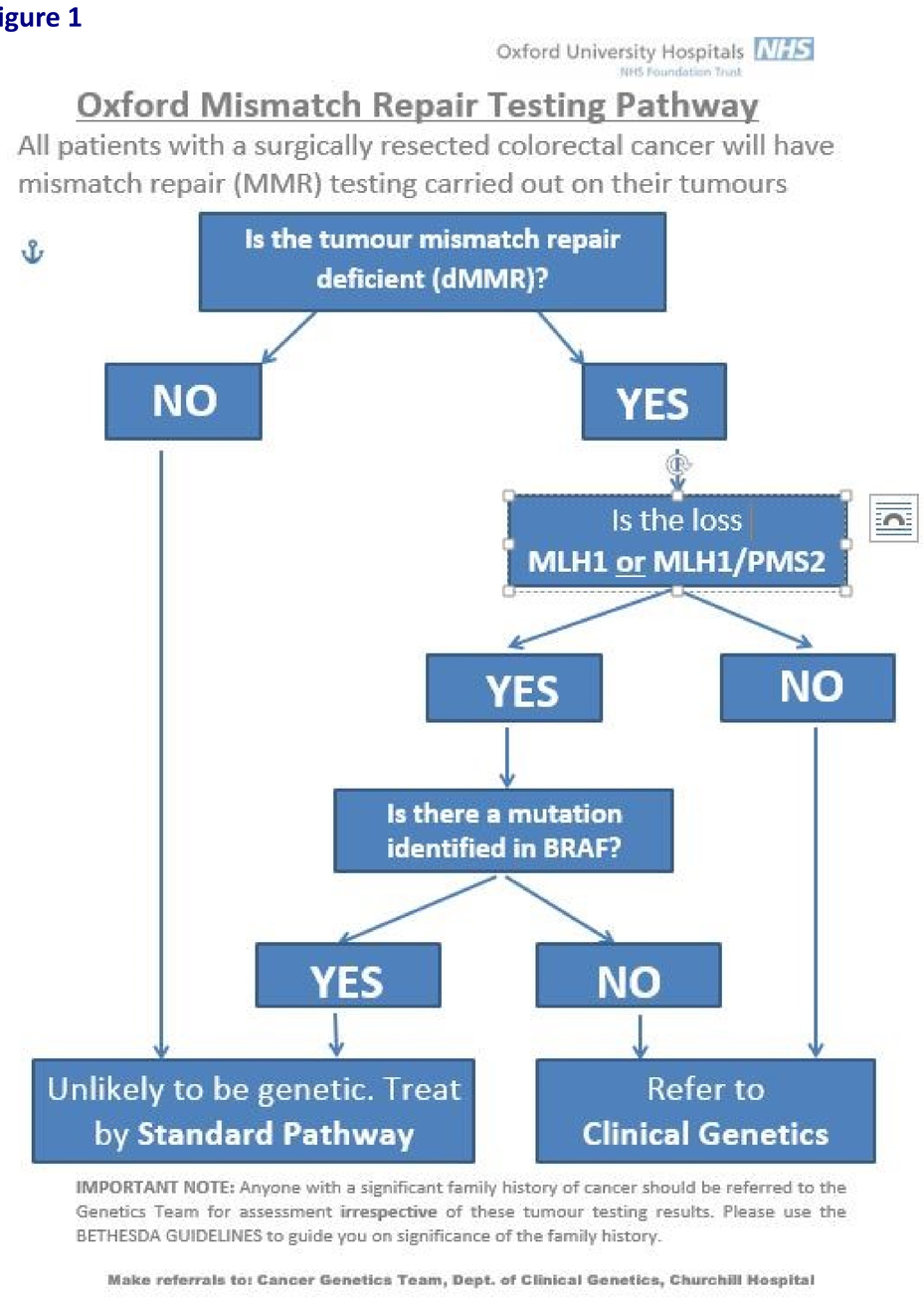
Background

Approximately 14% of patients with colorectal cancer have tumours that exhibit a deficiency in mismatch repair (MMR) genes, of which 3% have Lynch syndrome where the mutations have germline origin. Lynch syndrome is associated with significant lifetime cancer risks, so early diagnosis is required to optimise outcomes (Vasen et al 2015). Previously family history assessment was used to identify individuals with Lynch syndrome, but a significant proportion were not identified due to familial heterogeneity.; therefore routine MMR immunohistochemistry testing of resected tumours (from patients with primary colorectal cancer aged 18 to 70 years old) has been practiced at a local NHS Trust since 2012. The primary aim of this testing was to inform treatment decision making, since the use of adjuvant chemotherapy is not beneficial in treating MMR deficient tumours. As a result of this testing, individuals with Lynch syndrome have been identified. Previous data suggests that only a small proportion of these individuals have been referred to clinical genetics for counselling on the risks associated with this finding (Adelson et al 2013).

Figure 1



Aim

A clinical audit of the referral process was conducted on data from between 01.01.2014 and 31.12.2014 to identify compliance with the Lynch syndrome referral protocol developed by the local NHS Trust MMR Group (Figure 1).

Method

The audit standard used was "that all patients aged between 18 and 70 and treated with surgical resection for primary colorectal cancer should have MMR testing, and cases found to be mismatch repair deficient (dMMR) should be referred to the clinical genetics service for counselling and potential investigation of germline mutations". Sequential audit objectives were developed using the referral protocol. De-identified binomial data were summarised using descriptive statistics to analyse the proportion of patients who were treated according to the Lynch syndrome referral protocol. Sub-group analysis by age stratification was also conducted.

Results

Table 1. Number of individuals with primary colorectal cancer who had their tumour tested for MMR in 2014

Age Group	Total	MMR Untested	MMR Tested
All Cases	256	41 (16 %)	215 (84 %)
Under 50	18	3 (17 %)	15 (83 %)
Aged 50-70	112	14 (12.5 %)	98 (87.5 %)
Aged over 70*	126	24 (19 %)	102 (81 %)

Table 2. Number of primary colorectal tumours tested found to be deficient in MMR in 2014

Age Group	Total Tested	MMR Stable	MMR Deficient
All Cases	215	180 (84 %)	35 (16 %)
Under 50	15	12 (80 %)	3 (20 %)
Aged 50-70	98	89 (91 %)	9 (9 %)
Aged over 70*	102	79 (77.5 %)	23 (22.5 %)

Table 3. Management of individuals aged 18—70 with dMMR primary colorectal tumours in 2014 (12 cases)

Audit ID	Loss identified	BRAF requested	BRAF Result	Genetics referral recommended?	Genetics referral made?
A002	MLH1/PMS2	Yes	Negative	Yes	Yes
A025	MLH1/PMS2	Yes	Negative	Yes	Yes
A218	MSH2/MSH6	N/A	-	Yes	No
A028	MLH1/PMS2	Yes	Positive	No	No
A130	MLH1/PMS2	Yes	Positive	No	No
A126	MLH1/PMS2	No	-	Yes	No
A159	MLH1/PMS2	No	-	Yes	No
A072	PMS2	N/A	-	Yes	No
A023	MSH2/MSH6	N/A	-	Yes	No
A077	MSH2/MSH6	N/A	-	Yes	No
A209	MSH6	N/A	-	Yes	Yes
A171	MSH6	N/A	-	Yes	No

Conclusions and Recommendations

Although cases over 70 years old were not included in the audit standard, we found tumours from most patients over 70 years had been tested for MMR deficiency (at the clinician's request to inform treatment decision making), which revealed some important findings. The majority of, but not all, tumours from patients who met the Lynch syndrome referral protocol inclusion criteria (based on age, diagnosis and treatment) underwent MMR testing; however only 30% of the dMMR cases were referred. Although the proportion of patients with MMR (sporadic and germline) mutations is relatively low, the results have major clinical significance, informing decision making about both adjuvant treatments and familial screening (where germline mutations have been detected). Recommendations have been made to ensure patients whose tumours are MMR deficient are referred to the clinical genetics service for counselling, and testing for germline mutations. Reflexive B-RAF testing is not always carried out to confirm the potential significance of the MMR loss. It is important that reflexive BRAF testing is carried out whenever loss of MLH1/PMS2 is identified. High rates of MMR testing were requested for cases over the age of 70. Whilst analysis of this data was outside the scope of the audit standard set, these cases represent the highest proportion of tumours deficient in MMR; the majority of which have loss of MLH1/PMS2. Thus, there is an increased need for reflexive BRAF testing. Based on findings from this and previous clinical audits (including Colling *et al*., 2015), the following actions are recommended for managing patients with primary colorectal carcinoma in 2016:

1. **All cases of primary colorectal adenocarcinoma should have reflexive MMR testing performed at the time of resection.**
2. **Cases identified to be dMMR with loss of MLH1 or MLH1/PMS2 should have reflexive BRAF testing.**
3. **All cases identified as dMMR (defined as loss of MSH2, MSH2/MSH6, PMS2 as well as MLH1/PMS2 with no BRAF) should be referred to the local clinical genetics team for counselling.**

These recommended changes will be prospectively audited throughout 2016.

References

Adelson, M., Pannick, S., East, J., Risby, P., Dawson, P. and Monahan, K. (2013) UK colorectal cancer patients are inadequately assessed for Lynch syndrome. *Frontline Gastroenterology.* 5 p31-35

Colling, R., Church, D., Carmichael, J., Murphy, L., East, J., Risby, P., Kerr, R., Chetty, R. and Wang L.M. (2015a) Screening for Lynch syndrome and referral to clinical genetics by selective mismatch repair protein immunohistochemistry testing: an audit and cost analysis. *Journal of Clinical Pathology.* 0 p1-4.

Loughrey, M.B., Quirke, P. and Shepherd, N.A. (2014) *Standards and datasets for reporting cancers. Dataset for colorectal cancer histopathology reports.* Available at http://www.rcpath.org /publications-media/publications/datasets/colorectal-cancer.htm

Snowsill, T., Huxley, N., Hoyle, M., Jones-Hughes, T., Coelho, H., Cooper, C. Frayling, I. and Hyde, C. (2014) A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. *Health Technology Assessment.* 18 (58).

Vasen H.F.A., Tomlinson, I. and Castells, A. (2015) Clinical management of hereditary colorectal cancer syndromes. *Nature Reviews Gastroenterology & Hepatology*. 12 p88-97.