



# Mismatch Repair Screening of Gastrointestinal Cancers: The Impact on Lynch Syndrome Detection and Immunotherapy

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## Abstract

**Introduction** Mismatch repair immunohistochemistry (MMR IHC) or microsatellite instability (MSI) testing is now routinely performed in patients with colorectal cancer (CRC) to select those requiring Lynch syndrome testing. MMR IHC is also carried out on CRC and upper gastrointestinal (GI) cancers to select patients for immunotherapy. We review the Royal Marsden Hospital's pathway of molecular to germline testing for Lynch syndrome in the context of NICE guidance and the National Test Directory.

**Methods** We conducted (i) a retrospective audit of adherence to NICE guidance DG27 for patients diagnosed with CRC March 2017–August 2018 and (ii) a retrospective service evaluation of MMR IHC/Lynch syndrome testing in patients diagnosed with upper GI cancers January 2019–2020.

**Results** Of 394 patients with CRC, 346 (87.8%) had MMR IHC testing. Thirty-eight of 346 (10.9%) were MMR deficient (MMR-D) and 5 (1.4%) were found to have pathogenic germline variants causing Lynch syndrome. Of 405 patients with upper GI cancers, 221 (54.6%) had MMR IHC testing. Ten of 221 (4.5%) were MMR-D and 1 (0.5%) had a pathogenic germline variant causing Lynch syndrome.

**Discussion** This study highlights the small but significant number of patients, with CRC or upper GI cancers, which were caused by Lynch syndrome. It also highlights weaknesses in our testing pathway that limit access to germline testing. As MMR testing increases, it is important that clinicians are aware that patients with MMR-D tumours require reflex somatic testing or referral for germline testing. We have incorporated the guidelines into a pathway for use in clinics and multidisciplinary teams.

**Keywords** Lynch syndrome · Mismatch repair · Microsatellite instability · Colorectal cancer · Immunotherapy · Gastrointestinal cancer

## Introduction

The mismatch repair (MMR) pathway plays an important role in DNA repair, identifying mismatched bases. It is critical to replication fidelity and genome stability and may be defective

in a number of different cancer types [1, 2]. Absence of immunohistochemical (IHC) staining for MMR-related proteins is used to detect defects in the MMR pathway. Such MMR-deficient (MMR-D) tumours have a defective MMR pathway which results in microsatellite instability (MSI) and leads to accumulation of large numbers of mutations in both cancer and non-cancer-related genes, and the generation of neoantigens [1, 2]. These neoantigens stimulate an anti-tumour immune response, and as such MMR-D tumours have been shown to have an elevated response to immunotherapy using checkpoint inhibitors [3, 4].

MMR IHC or MSI testing has traditionally been performed for patients with colorectal cancer (CRC). However, recent immunotherapy trials now support testing in all advanced solid tumours [3]. MMR-D/MSI-high (MSI-H) tumours frequently occur due to somatic alterations in MMR proteins, most

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frequently hypermethylation of *MLH-1*. However, MMR-D/MSI-H tumours can also indicate the presence of a germline pathogenic variant in one of five genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) causing Lynch syndrome. Recent results have shown that the presence of MMR-D/MSI-H tumours is predictive of Lynch syndrome across a range of cancers including urothelial, prostate, pancreas, adrenocortical, small bowel, gastric and germ cell tumours, sarcomas, and mesotheliomas [5].

Historically, patients with CRC were highlighted for germline genetic testing for Lynch syndrome using family history and age of onset-based guidelines, such as the Amsterdam criteria. The emergence of a molecular understanding of the disease prompted testing strategies to evolve and include pathological assessment of the tumour as detailed in the Bethesda criteria [6]. In addition to MMR IHC/MSI, the absence of a somatic *BRAF* V600E missense variant and/or tumour *MLH1* promoter hypermethylation now provide further indication of who should proceed to germline testing [7].

Since 2017, the UK National Institute of Health and Care Excellence (NICE) guidelines have recommended that all patients with CRC should be offered tumour MMR/MSI testing, to guide sequential testing for Lynch syndrome [8]. More recently, NHS England has published a National Genomic Test Directory indicating “which genomic tests are commissioned by the NHS in England, the technology by which they are available and the patients who will be eligible to access the tests”. The rare and inherited disease criteria define which living, deceased, and unaffected individuals with a personal and/or family history of Lynch-related cancers can access testing [9]. Furthermore, delivering comprehensive services for the detection of Lynch syndrome is a priority transformation project for the seven Genomic Medicine Service Alliances which have recently been established across England, with the aim of embedding genomics into routine clinical care.

At the Royal Marsden Hospital (RMH), universal tumour MMR IHC testing was already in place for CRC when the NICE guidance was published. Since January 2019, MMR testing for upper gastrointestinal (GI) cancers has also been performed to define patients suitable for immunotherapy trials.

Here, we review our pathway of molecular to germline testing for Lynch syndrome, in the context of the NICE guidance, the National Test Directory, and therapeutic decision making.

## Methods

### Study Population

The Royal Marsden Hospital is a tertiary referral cancer hospital treating patients from local hospitals and further

afield. We sought to review our pathway for the detection of Lynch syndrome to ensure comprehensive assessment of all patients and to implement improvements to the pathway where necessary.

Our review comprised a retrospective audit of adherence to NICE guidance DG27 of molecular testing for Lynch syndrome for all newly diagnosed CRC patients between 1st March 2017 and 31st August 2018. This included 394 patients.

In addition, we performed a retrospective service evaluation of MMR IHC/Lynch syndrome testing of all patients diagnosed with upper GI cancers between 1st January 2019 and 1st January 2020. This included patients with a diagnosis of adenocarcinoma of the small bowel (hereon referred to as small bowel cancer), pancreatic ductal adenocarcinoma (hereon referred to as pancreatic cancer), cholangiocarcinoma and gallbladder cancer (hereon referred to as biliary cancer), and gastroesophageal adenocarcinoma (GOA). In total, 405 patients were identified.

Patients were identified using the appropriate ICD10 diagnostic codes between the dates specified. Pathology reports were reviewed for all patients to confirm appropriate diagnosis within the specified dates, and to determine if tumour MMR IHC testing had been undertaken. Patients with MMR-D tumours were reviewed in more detail to obtain information regarding referral to cancer genetics, and anti-cancer therapies received.

## Assessment Standards

### Cohort A: CRC

Our primary objective was to audit our performance against the national standards defined in the NICE guidance DG27 [8]. Standard targets are given in brackets:

1. Tumour MMR IHC testing on eligible patients (100%)
2. Somatic *BRAF* V600E testing performed on *MLH1*/*PMS2* deficient tumours (100%)
3. Patients with MMR-D attend Clinical Genetics (100%)

Our secondary objective was to determine the number of patients proceeding to immunotherapy:

1. Proportion of patients with metastatic MMR-D tumours that received immunotherapy

### Cohort B: Upper Gastrointestinal Cancers

There are no national standards for detecting Lynch syndrome in patients with upper GI cancers. Therefore, a service evaluation was designed with the primary objective of determining:

1. The number of patients with newly diagnosed small bowel cancer, pancreatic cancer, biliary cancer, or GOA for whom tumour MMR IHC testing was performed
2. The number of patients with MMR-D tumours who attended Clinical Genetics

Our secondary objective was to determine the number of patients proceeding to immunotherapy.

1. Proportion of patient with metastatic MMR-D tumours that received immunotherapy

Approval for this work was granted by the RMH Clinical Audit Committee and Committee for Clinical Research. Audit ID: CG11 for CRC and Service Evaluation ID: 908 for upper GI cancers.

## Results

### Cohort A: CRC

In total, 394 patients with CRC were reviewed, with a median age of 67 years (range 17–95 years) (Table 1). Of the 346 (87.8% (target 100%)) patients who had MMR IHC tumour analysis, 38 (10.9%) were MMR-D. Of these, 7 patients had MSH2/MSH6-deficient tumours of whom 6 (85.7%) were seen by clinical genetics, and one died before review (Fig. 1).

Tumours deficient in MLH1 and/or PMS2 were identified in 31 patients. Twenty-two had *BRAF* V600E testing prior to review by clinical genetics. Eight were found to be *BRAF* V600E wild type and were referred to genetics. Of the 9 patients who did not undergo *BRAF* V600E testing, 4 were referred to genetics and 2 attended. Overall, 77.4% (24/31) of patients with MLH1 and/or PMS2-deficient tumours had *BRAF* V600E testing (target 100%).

Eight patients whose tumours were MLH1 and/or PMS2-deficient and *BRAF* V600E wild type, and 6 with MSH2 and/

or MSH6 deficient tumours, underwent germline testing out of a total of 15 patients eligible for germline testing (93.3%, target 100%, Fig. 1). Pathogenic variants causing Lynch syndrome were identified in 5 patients, which comprised 1.4% (5/346) of those patients with CRC that underwent IHC testing. In 9 of the 14 patients (64.3%) who underwent germline testing, a cause for MMR-D was not identified.

Sixteen patients with metastatic disease had MMR-D tumours of whom 6 (37.5%) received immunotherapy through clinical trials or access to private medical care.

### Cohort B: Upper Gastrointestinal Cohort

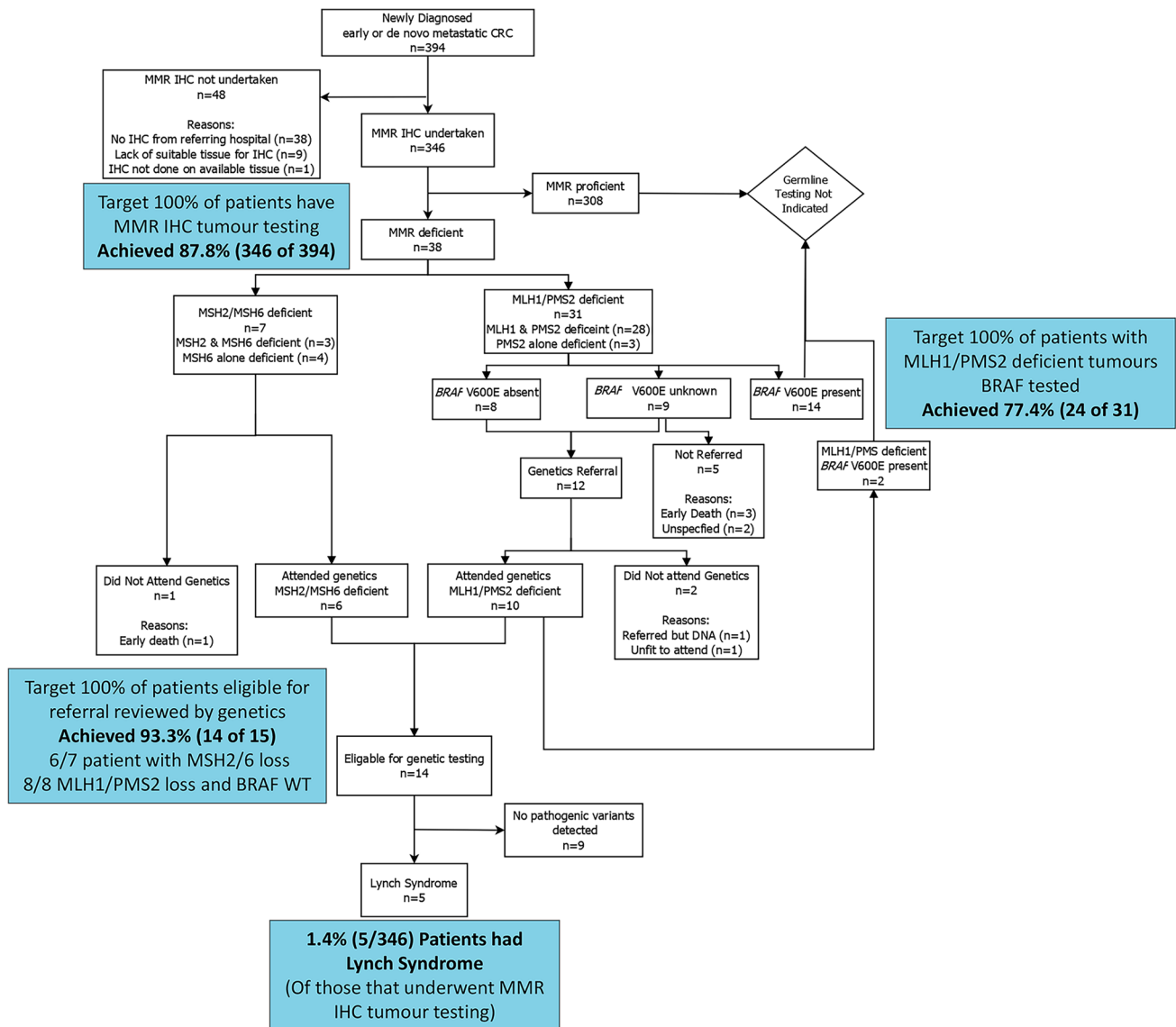
In total, 405 patients with an upper GI malignancy were reviewed, with a median age of 69 years (range 37–93 years) (Fig. 2). This was further split into 220 patients with GOA, 152 patients with pancreatic cancer, 24 patients with a biliary cancer, and 9 patients with small bowel cancer. Just over half of patients (221/405, 54.6%) had MMR IHC tumour analysis of which 4.5% (10/221) were MMR-D, including 4.5% (6/134) of GOAs, 1.4% (1/72) of pancreatic cancers, 0% (0/8) of biliary cancers, and 42.9% (3/7) of small bowel cancers.

Seventy percent (7/10) of patients with upper GI MMR-D tumours were referred to clinical genetics. Four of the 7 underwent germline testing (1 small bowel, 1 pancreatic cancer, 2 GOA) and 3 died before review (Fig. 2). A pathogenic variant causing Lynch syndrome was identified in 1 patient with small bowel cancer, which comprised 0.5% (1/221) of patients with an upper GI malignancy that underwent IHC testing and 25.0% (1/4) of patients that underwent germline testing.

None of the 10 MMR-D patients had metastatic disease; however, one patient was enrolled in a trial involving immunotherapy based on the MMR-D status.

**Table 1** Clinicopathological data of enrolled patients. Collected data included age at diagnosis, tumour stage, and site

	No. of patients	Age		Tumour stage (TMN)				
		Median	Range	I	II	III	IV	Unknown
<b>Colorectal</b>	<b>394</b>	<b>67</b>	<b>17–95</b>	<b>17</b>	<b>89</b>	<b>179</b>	<b>119</b>	<b>0</b>
Rectal	165	65	17–95	12	36	88	29	0
Sigmoid	58	68	24–88	2	15	21	20	0
Colon	171	68	20–94	3	38	63	67	0
<b>Upper GI</b>	<b>405</b>	<b>69</b>	<b>37–93</b>	<b>29</b>	<b>46</b>	<b>77</b>	<b>215</b>	<b>38</b>
Small bowel	9	71	40–86	0	2	4	1	2
Biliary	24	69	40–81	0	3	2	11	8
Pancreas	152	70	36–88	7	14	19	87	25
GOA	220	69	37–93	22	27	52	116	3



**Fig. 1** Consort diagram showing MMR IHC testing for CRC. Including subsequent investigation and referral to clinical genetics, and evaluation of audit standards

## Discussion

This retrospective study of 799 patients with a colorectal or upper GI cancer, at a single tertiary referral centre identified 48 patients (6.0%) with MMR-D tumours, including 38 patients with CRC, identified over an 18 month period and 10 upper GI cancer patients over a 12-month period. Of these patients, 6 were found to have Lynch syndrome, 5 with CRC, and 1 with a small bowel cancer. Of the 346 patients who had MMR IHC tumour analysis, 1.4% (5/346) had Lynch syndrome, consistent with national figures [8].

A cause for MMR-D was not identified in 64.3% of patients who underwent germline testing; however, the most frequent cause of MMR-D is somatic *MLH1* promoter

hypermethylation [10] which was not routinely tested for at this centre at the time of study. NICE guidance DG27 recommends tumour *MLH1* promoter hypermethylation testing on all *MLH1*-deficient, *BRAF* wild-type CRC prior to germline testing [8]. Had this testing been available, the number of patients with an unidentified cause for MMR-D would have been significantly lower, as 50–60% of cases of MMR-D tumours are caused by *MLH1* hypermethylation [10]. This testing would also result in fewer patients requiring genetic testing.

Our review indicates that one-third of CRC patients eligible for review in clinical genetics were not seen (8 of 24, either due to lack of referral or early death). These are missed opportunities for testing patients and potentially

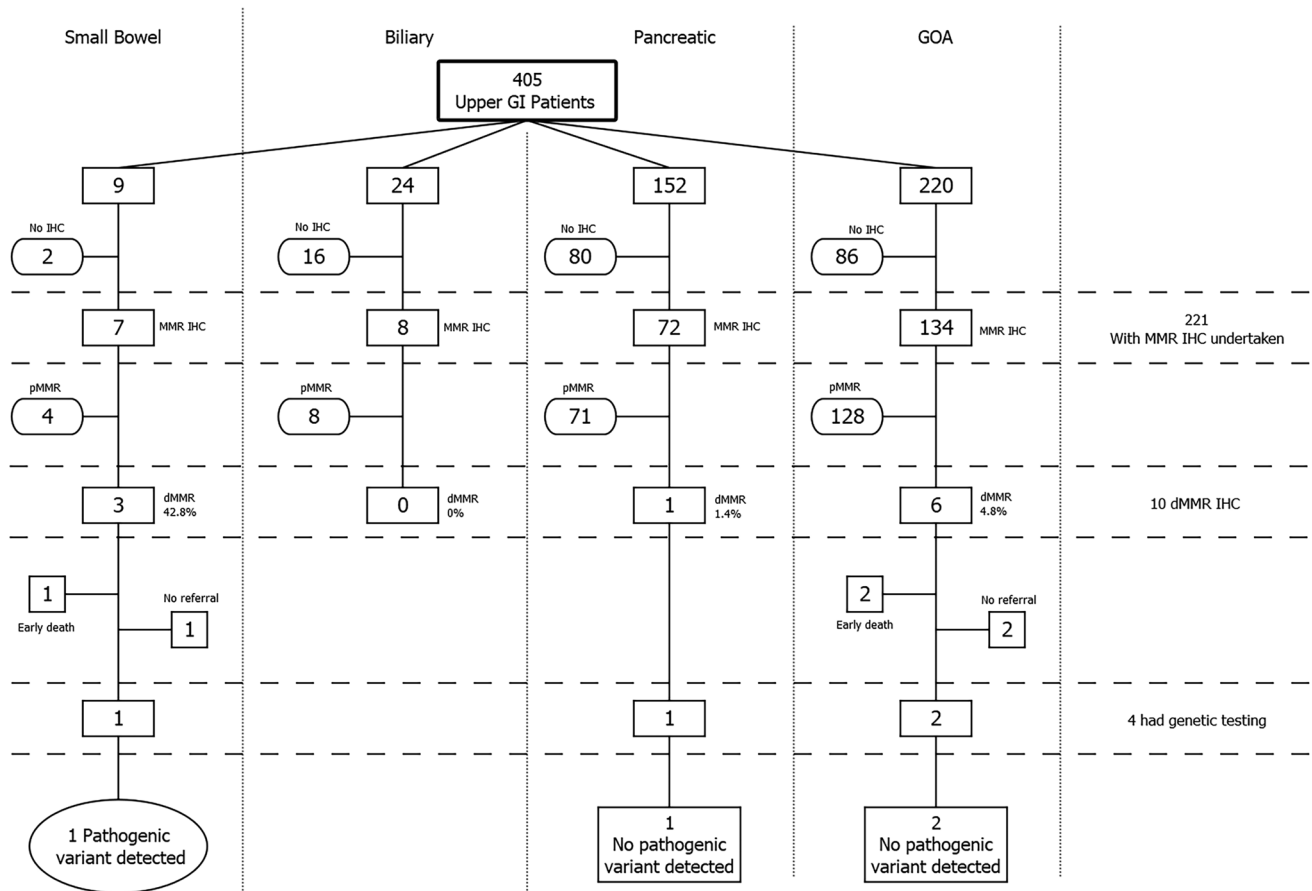


Fig. 2 Summary of MMR IHC and genetic testing of patients with upper GI cancers

identifying Lynch syndrome, with the subsequent implications for patient and family. A key limitation in our pathway was failure to identify when tumour MMR IHC testing had not been performed by referring centres. Centres should therefore remain vigilant that referred patients have had MMR IHC testing, and as the NICE standards are implemented more widely, so testing rates are likely to improve over time.

Another weakness, in some instances, was lack of reflex *BRAF* V600E testing and/or the availability of *MLH1* hypermethylation testing. As targeted treatments become more widely available for *BRAF* V600E mutated CRC, so *BRAF* testing will increasingly be requested by non-genetic clinicians, as part of routine care [11, 12]. Similarly, *MLH1* hypermethylation testing availability is improving. Enhanced access to *BRAF* and *MLH1* hypermethylation testing for non-genetic clinicians and raising awareness that patients with *MLH1*-deficient, *BRAF* mutant/*MLH1* hypermethylated CRC do not require onward referral to genetics, should reduce referrals and so save patients unnecessary appointments and anxiety.

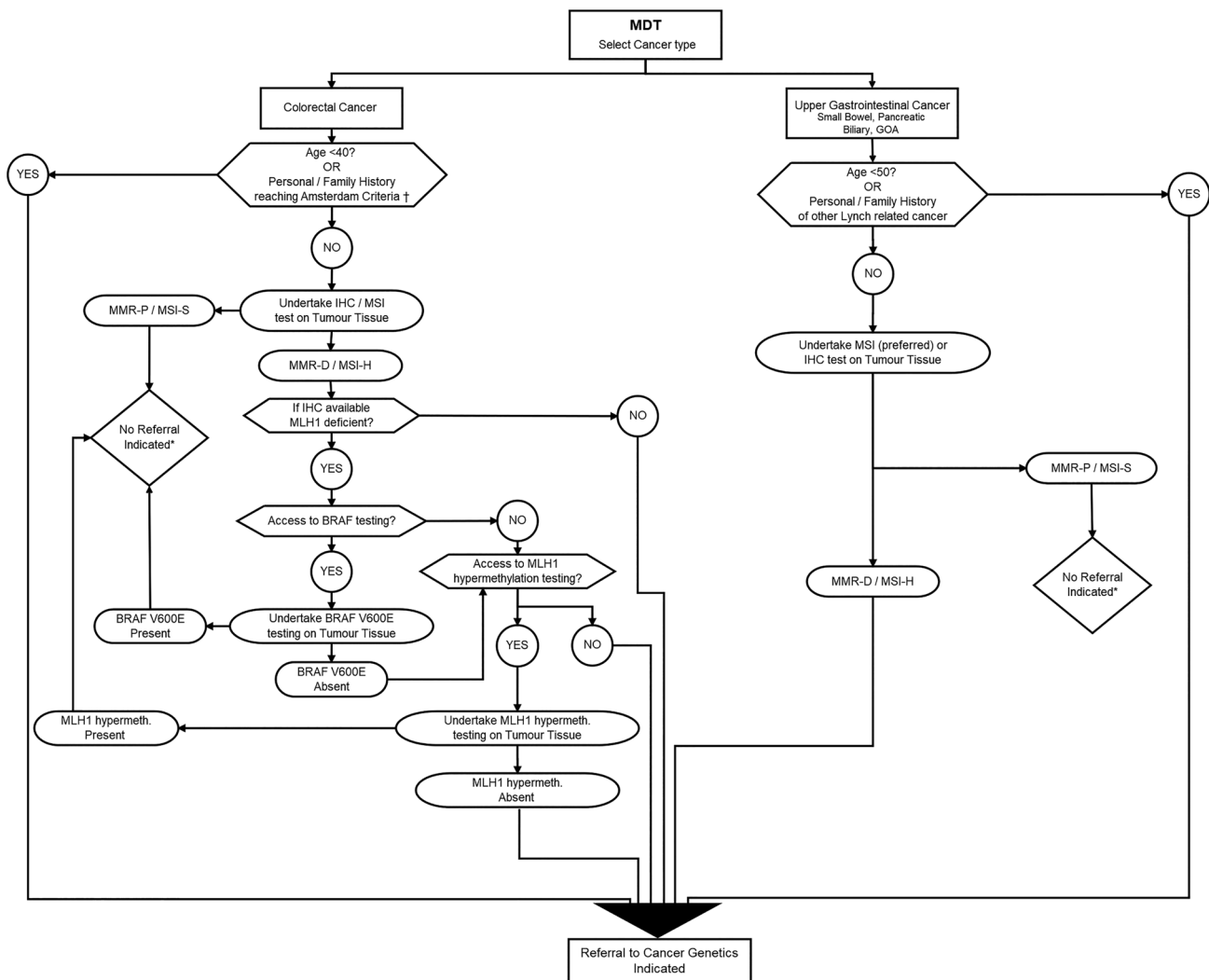
Our work demonstrates that patients who have MMR-D tumours were being selected for immunotherapy treatments, whether through clinical trials or private care. The small number of metastatic patients reflects the finding that MMR-D patients appear to have a generally favourable prognosis [13]. There is now phase 3 evidence that patients with MMR-D upper GI cancers have enhanced and enduring responses to immunotherapy [3, 13]. It is therefore likely that tumour MMR IHC/MSI testing, which is already universal for CRC, will be extended to upper GI malignancies. Indeed during the COVID-19 pandemic, nivolumab was approved in the UK for first-line treatment of MMR-deficient/MSI-H upper GI malignancies due to the remarkable response to immunotherapy [14]. Tumour MMR IHC/MSI testing rates for upper GI cancers are therefore likely to be greater than the advised rates based on the incumbent National Test Directory [9], and in time, such testing may become universal. As stated, the main purpose of MMR testing in upper GI cancers is to identify patients with MSI-H tumours for the provision of immunotherapy. As this study demonstrates, the pickup rate for Lynch syndrome, based

upon IHC testing in this group, is much lower than amongst CRC patients (Fig. 2) and is therefore of less importance than for CRC. Furthermore, in the absence of definitive guidance for screening for Lynch syndrome in upper GI cancers, MSI testing may be the preferred over MMR IHC testing.

Our data highlights the need for greater multidisciplinary team (MDT) working to optimise genomics, both somatic and germline, for patient benefit. We have incorporated the relevant guidelines into a testing/referral pathway and summarised it in a flowchart (Fig. 3), for use in appropriate clinics and MDT meetings.

The pathway includes the importance of family history. Currently, the test directory guidelines for CRC indicate that patients aged less than 40 or patients whose family history fulfils

the Amsterdam criteria ( $\geq 3$  cases over  $\geq 2$  generations with  $\geq 1$  case affected at  $< 50$  years) should be referred directly to clinical genetics [9] regardless of tumour MMR/MSI status. There are two reasons for this. Firstly, it is possible for patients to have IHC-proficient tumours and still have inherited genetic defects in the MMR genes. This may occur due to presence of missense mutations in MMR genes which result in retained MMR protein expression but where the proteins are dysfunctional, such that IHC is normal, but tumours are MSI-H [15]. In patients at very high risk of a genetic cause for their cancer as defined by family history, these patients should therefore proceed to genetic testing irrespective of IHC findings. Secondly, Lynch syndrome is not the only inherited genetic cause of CRC and patients at high risk of having an inherited genetic cause for their cancer, based upon their personal and/or family history, should also be offered



**Fig. 3** Proposed management workflow for referral to clinical genetics for Lynch syndrome testing. Including separate assessment of CRC and upper GI malignancies. \*No referral indicated for Lynch syndrome testing; however, pancreatic cancer age  $< 60$ ; personal/

family history of cancers; or personal history of bowel polyps may still warrant clinical genetics referral. † Amsterdam criteria:  $\geq 3$  cases over  $\geq 2$  generations with  $\geq 1$  case affected at  $< 50$  years

polyposis and DNA polymerase gene testing [16]. Similar reasons support the recommendation that upper GI patients aged < 50 and/or with a family history of Lynch syndrome-related cancers, be referred directly to cancer genetics services.

Our pathway (Fig. 3) provides a structure for tumour analysis and genetic referrals, but there will be a subset of patients who have MMR-D tumours that do not harbour somatic *BRAF* mutations or *MLH1* promoter hypermethylation, in whom no abnormalities in the MMR genes are identified on germline testing. Although for some such patients, somatic MMR gene testing will reveal a cause for their MMR-D status of their cancer; there will remain a small cohort in whom no somatic or germline cause can be determined. Such patients are currently classified as having “Lynch-like Syndrome”. It is likely that this group incorporates both patients with sporadic disease as well as individuals with a hereditary cause for their cancer, which remains unidentified. “Lynch-like” patients therefore present a difficulty in terms of determination of their risk and the risk for their families [17]. Current British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG) guidance recommends that patients with “Lynch-like Syndrome” and their first-degree relatives are managed similarly to those with Lynch syndrome, with 2 yearly colonoscopy screening [18].

The proposed streamlined pathway (Fig. 3) could facilitate reflex testing and appropriate and timely referral. This is particularly important for patients with advanced disease, to allow germline DNA sampling to take place as required. In addition, emerging data suggests that *MLH1*/*PMS2*-deficient CRC that are *BRAF* wild type are a useful subset for the detection of rare, actionable oncogenic kinase fusions [19, 20]. Going forward, this pathway can evolve, incorporating such discoveries once confirmed, allowing further utility to be derived from tumour testing.

The foundation to multidisciplinary working needs to be education. A nationwide survey of UK gastroenterology trainees demonstrated that there is a clear appetite for genomics teaching and development of clinical guidelines [21]. Such provision will promote confidence and engagement and facilitate mainstreaming approaches, so providing streamlined, timely care for patients.

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**Author Contribution** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Mark Openshaw, Zoe Kemp, Tiffany Foo, Catherine Moss, and Jennet Williams. The first draft of the manuscript was written by Mark Openshaw and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Data Availability** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics Approval** This is an observational study. Approval for this work was granted by the Royal Marsden Hospital Clinical Audit Committee and Committee for Clinical Research (Service Evaluation 908 & Audit ID CG11).

**Informed Consent** No identifying information was collected/published for this observational study. Therefore, informed consent was not required.

**Conflict of Interest** Financial interests: ZK has received honoraria for educational talks from AstraZeneca and Lilly. Non-financial interests: none.

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