The Royal College of Pathologists
Pathology: the science behind the cure

BOWEL CANCER UK

2016 Data Briefing:

Reflex testing for Lynch syndrome in people diagnosed with bowel cancer under the age of 50

Introduction

Lynch syndrome is a genetic condition that can significantly increase the risk of developing bowel cancer by as much as 80%, in some cases. It is caused by a defect in a mismatch repair (MMR) gene, which usually works to prevent cancer. Lynch syndrome is the most common form of hereditary bowel cancer but fewer than 5% of individuals with Lynch syndrome have been diagnosed in the UK[i]. It is estimated to cause over 1,000 cases of bowel cancer in the UK every year[ii].

Tests, such as immunohistochemistry (IHC), which look for problems with these genes, can be carried out on the resected tumour or a biopsy of the tumour to identify which bowel cancer patients are most likely to have Lynch syndrome. Testing at diagnosis is important as we know that a diagnosis of Lynch syndrome can affect treatment options for bowel cancer. If this test is positive, individuals are referred for genetic testing. Performing this provisional screening test will not only help to identify individuals at greater risk of recurrence, but also family members who may have inherited the gene and be at risk of bowel cancer. It is crucial to identify individuals with Lynch syndrome so that they and their families can be offered surveillance programmes to receive regular colonoscopy, which can reduce mortality from bowel cancer by 72%[iii].

A recent National Health Service (NHS) study[iv] found that testing for MMR deficiency in all bowel cancer patients under the age of 70 fulfils cost-effectiveness criteria for approval by the National Institute for Health and Care Excellence (NICE). In 2014 the Royal College of Pathologists (RCPath) published an updated cancer dataset[v] for reporting colorectal cancers. The dataset acknowledged the strong case for testing all colorectal tumours but stated that "given the resource implications of implementing this, it is not considered a core data item for all colorectal cancers currently." As Lynch syndrome is more prevalent in patients under 50 years, the dataset mandated the use of IHC testing of tumour tissue as a reflex test at diagnosis, in all patients under the age of 50 years.

Six months after the publication of the dataset (in 2015) we carried out a Freedom of Information request[vi] (FOI) to all hospitals in the United Kingdom (UK) to determine whether the dataset was being implemented. We discovered that only 49% of hospitals in the UK were testing tumour tissues to identify those patients who may have Lynch syndrome. Many hospitals did so upon referral, at the request of the multidisciplinary team (MDT), rather than as a reflex test at the time that the pathologist makes the diagnosis of cancer.

Since 2015 NICE has begun to develop guidelines to determine whether 'molecular testing for Lynch syndrome in all people with colorectal cancer represents a cost-effective use of NHS resources.' Ahead of the scheduled consultation on the NICE guideline this year, we decided to repeat the FOI request to establish whether the proportion of hospitals in the UK following the RCPath dataset has increased.

Method

In June 2016, we submitted an FOI request to every hospital trust in England, health board in Scotland and Wales, and health and social care trust in Northern Ireland. The FOI requested information on adherence to the RCPath dataset.

The following questions were submitted in June 2016:

1. Do all patients, who are diagnosed with bowel cancer under the age of 50 years in your trust, have a molecular screening test for Lynch syndrome, such as immunohistochemistry or microsatellite instability testing, carried out on tumour tissue?

2. If yes, at what stage does this testing take place? Does it take place:
- Pre treatment i.e. at diagnosis (on a biopsy of the tumour)
- Post treatment i.e. test is carried out on the tumour resection specimen

3. Is this test carried out as a reflex test i.e. automatically or upon referral?
- Reflex
- Referral via MDT
- Referral via Genetics Centre
- Referral via GP
- Other (please explain)

4. Which of the following molecular tests does your trust use to identify people who could have Lynch syndrome?
- Microsatellite Instability (MSI)
- Immunohistochemistry (IHC)
- BRAF and MLH1
- Other

5. Are the results of this reflex test communicated to the patient?

6. If no such reflex test is in place, do you have information on whether there are any plans to introduce molecular testing for Lynch syndrome?

As this was an FOI request, recipients were required to respond within 20 working days.

Findings

In total **185** hospitals were sent the FOI request across the UK and **156** hospitals (84%) responded. 14 other hospital trusts in England deemed this request inapplicable to them. These were specialist hospitals such as; the Royal Orthopaedic Hospital, Moorfields Eye Hospital and Birmingham Women's NHS Trust and they were excluded from the analysis.

Country	Contacted	Responded**	Did not respond
England	159	130	15
Scotland	14	14	0
Wales	7	7	0
Northern Ireland	5	5	0
Total	185	156	15

** 14 specialist hospitals are excluded from this table as the FOI request was not applicable

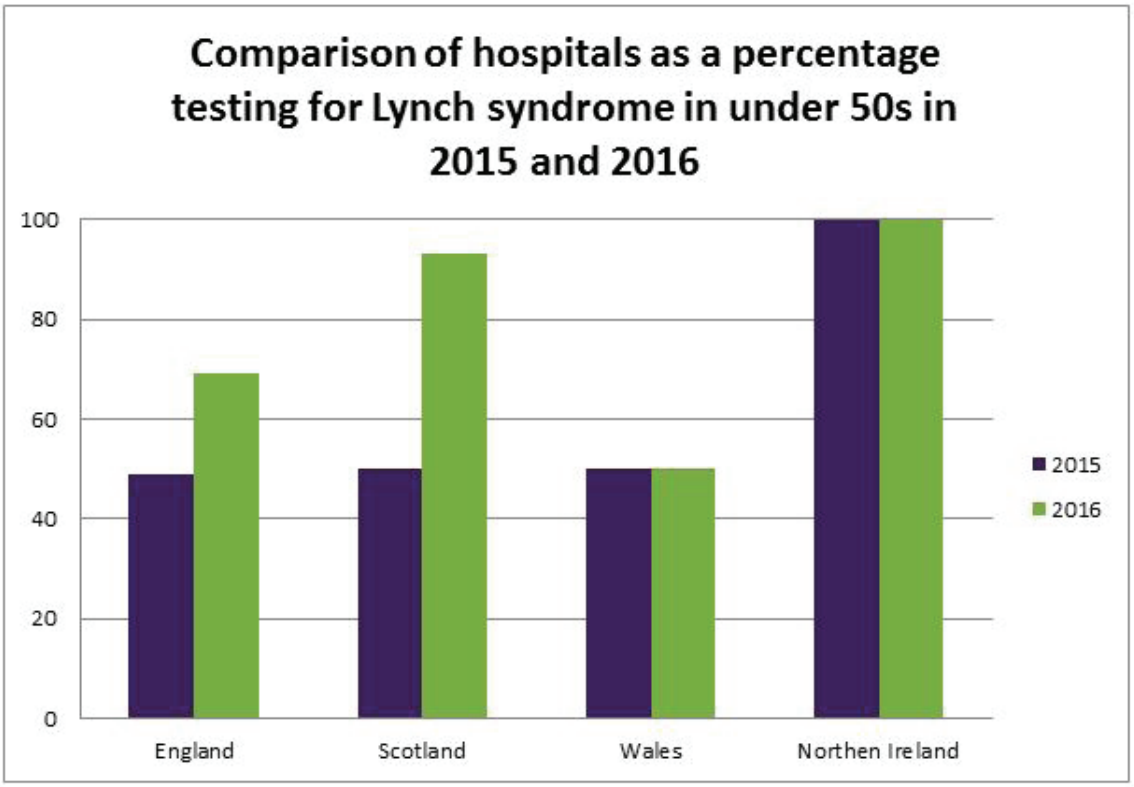
In England an **83%** response rate was achieved based on **130** responses – an increase of **5%** from 2015. A 100% response rate was achieved in Scotland, Wales and Northern Ireland.

Numbers of hospitals testing in patients under the age of 50

1. Do all patients, who are diagnosed with bowel cancer under the age of 50 years in your Trust, have a molecular screening test for Lynch syndrome, such as immunohistochemistry or microsatellite instability testing, carried out on tumour tissue?

Number of hospitals that stated all patients diagniosed with bowel cancer under the age of 50 are tested for Lynch syndrome	**Yes**	**No**
England	90 (69%)	40 (31%)
Scotland	13 (93%)	1 (7%)
Wales	2 (29%)	5 (71%)
Northern Ireland	5 (100%)	0
Total	110 (71%)	46 (29%)

Across the UK 110 hospitals (71%) now report testing for Lynch syndrome in all patients under the age of 50 diagnosed with bowel cancer This is an increase from 49% in 2015.



In England 90 hospitals **(69%)** now test all bowel cancer patients under the age of 50 compared to 61 **(49%)** in 2015.

In Scotland, 13 out of the 14 health boards now test, compared to 7 in 2015. However there has been no improvement in Wales, with still only two health boards testing bowel cancer patients under the age of 50.

All Health and Social Care Trusts (HSCTs) in Northern Ireland perform molecular testing for Lynch syndrome in patients under the age of 50.

Testing pathways

2. Is this test carried out as a reflex test i.e. automatically or upon referral?

Country	Reflex	Referral via Genetics Centre	Referral via MDT	Combination	Referral via GP
England	49	6	30	5	0
Scotland	7	0	4	2	0
Wales	0	1	1	0	0
Northern Ireland	5	0	0	0	0
Total **(110)**	61	7	35	7	0

Although the number of hospitals that carry out testing on all people diagnosed with bowel cancer under the age of 50 has increased, many of them still do not do this as a reflex test. 38% responded that all testing is done via referral and only **56%** perform the test as a reflex test.

A similar picture exists in individual nations. In England, only **49** (54%) trusts carry out the test as a reflex test. In Scotland, only **50%** of molecular tests are done as a reflex test and Wales only carries out testing on referral. All HSCTs in Northern Ireland carry out reflex testing.

Stage of testing

In the UK, only **12** (11%) hospitals routinely carry out molecular testing at diagnosis and prior to any treatment for bowel cancer. **70%** of all tests take place post treatment and **19%** of trusts use a combination depending on clinical context.

The majority of hospitals in England (**77%**) provide testing post treatment with only **7** (8%) taking place pre-treatment. **31%** of health boards in Scotland do perform the test pre-treatment but in Wales all testing is done post-treatment.

Number of hospitals	Pre-treatment	Post-treatment	Both
England	7	69	14
Scotland	4	4	5
Wales	0	2	0
Northern Ireland	1	2	2

Which test

3. Which of the following molecular tests does your trust use to identify people who could have Lynch syndrome?

Country	IHC	MSI	BRAF	MLH1	Combination
England	39	17	0	1	31
Scotland	1	0	0	0	12
Wales	1	1	0	0	0
Northern Ireland	2	0	0	0	2

41% of hospitals in the UK have chosen to use a combination of molecular tests for Lynch syndrome. In Scotland **92%** of health boards use a combination of tests. The most common combination is using MSI and IHC. In England MMR IHC is used in **43%** of all trusts.

Communication

4. Are the results of the screening test communicated to the patient?

71% of hospitals in the UK (**74%** in England) stated that they do communicate the results of the molecular test to patients.

In the UK a total of **21** hospitals stated that the decision of whether the result is communicated to a patient is either at the discretion of the clinician, and may not be discussed unless there is a positive result, or that the decision is made after being referred to the genetics team.

Number of hospitals	Yes	No/unanswered	Other
England	67	7	16
Scotland	8	1	4
Wales	1	1	0
Northern Ireland	2	2	1

Reasons for not offering testing

In England **40** trusts said they did not test all patients diagnosed with bowel cancer under the age of 50 for Lynch syndrome. 18 out of the 40 trusts provided responses on whether they intend to implement the guidance. Three of these said that they intend to implement testing while **10** have no plans at all to introduce such testing in the near future.

Trusts in England which do not currently perform Lynch syndrome testing on bowel cancer patients under age 50	
Intend to implement	3
Being looked into	4
No information	1
No plans	10
No response	22

The main reasons given for not introducing testing centred around finances and practicality. Similarly to 2015, two trusts also mentioned that they were waiting to implement testing until guidance from NICE is published.

> "Yes, there are plans for introducing MSI testing. However we are awaiting NICE verdict on the testing. This verdict is anticipated to be given in October 2016."

> "Reflex testing is not in place; this has recently been requested by the surgeons via MDT and is being looked into by the pathology department. It is necessary for us to establish the costs of the tests and calculate how these would be funded before committing to reflex testing all patients diagnosed with bowel cancer under the age of 50."

> "The Trust has been trying to establish funding for this service. The four antibodies were optimised by a biomedical scientist doing an MSc and some private patients have had the test done as a reflex in the lab. Some/most/all patients with colorectal cancer are referred

to the Regional Genetics Service and they have both MMR immunohistochemistry and PCR MSI testing. NICE are also looking into MMR testing for all colorectal cancers."

In Wales one health board mentioned that a request had been made that the issue of testing for Lynch syndrome should be coordinated at an all-Wales level by Pathology/Genetics/Molecular departments but that they are still awaiting a response.

Discussion

Our findings show that since the publication of our 2015 Freedom of Information request there has been an increase of 46% in the number of hospitals offering molecular testing for Lynch syndrome in people diagnosed with bowel cancer under the age of 50 in the UK. While this is a positive step forward, evidence from our recent follow-up FOI request shows that there is still variation across a number of areas in the testing pathway – from whether the test is carried out as a reflex test or upon referral, to whether the test is carried out before or after treatment and which molecular test is used. Our findings show that in some parts of the UK there is still some work to do to ensure a consistent approach that enables this testing to take place automatically, as a reflex test, at diagnosis of bowel cancer.

Two years on from the publication of the RCPath Dataset, which stated that "we now consider MMR immunohistochemistry a core dataset item for patients under 50 years at time of diagnosis" only half of hospitals carry out molecular testing as a reflex test, with the remaining hospitals carrying out molecular testing upon referral i.e. at the request of the clinical team. The lack of consensus on when to test (pre or post treatment) and which combination of tests to use requires further research to determine the optimum strategy for the management of patients and their relatives.

We recognise that there are financial, resource and capacity barriers to implementing the guidance. However there are examples of hospitals in the UK that have developed localised approaches to overcome some of these challenges. For example, Central Manchester Foundation Trust has developed regional centralised services to ensure a streamlined approach to testing. Adopting such a regionalised approach for molecular testing for Lynch syndrome might alleviate some of the pressures on smaller trusts to develop high quality in-house testing.

Both Scotland and Northern Ireland are leading the way in ensuring that all hospitals are testing patients under the age of 50 through the development of national approaches to testing. This may be a model that should be considered in England and Wales to ensure that there is a systematic approach to testing for Lynch syndrome. This would ensure most people with Lynch syndrome are identified and can subsequently be offered surveillance programmes to receive regular colonoscopy, which can reduce mortality from bowel cancer by 72% in this group of patients.

We hope that there will be a positive NICE recommendation on whether using molecular testing for Lynch syndrome in all bowel cancer patients would represent a cost-effective use of NHS resources. We know from a National Institute for Health Research (NIHR) study[vii] that testing everyone under the age of 70 would be cost-effective.

It is imperative that these guidelines stipulate consensus on a clear referral pathway on who to test, when to test and what test to use to reduce variation in practice. We hope the publication of this guidance will help to further encourage adoption of reflex testing and we hope to see a further increase in the number of patients for whom this testing is available.

Recommendations

1. All hospitals should ensure that molecular testing for Lynch syndrome takes place automatically, at diagnosis, as a reflex test.
2. All hospitals should carry out regular audits to determine whether molecular testing of tumours for Lynch syndrome is taking place at diagnosis of bowel cancer.
3. A central anonymised database (registry) of people identified as having Lynch syndrome must be developed. This must be a systematic process with patient consent obtained by a clinician at the point of diagnosis. This would increase our knowledge and understanding of Lynch syndrome, including knowing how many people are affected by the genetic condition and whether there are any regional differences in treatment, care and outcomes.
4. A positive NICE decision on molecular testing for Lynch syndrome in people diagnosed with bowel cancer.
5. Nationwide initiatives to ensure a consistent, systematic approach to molecular testing for Lynch syndrome should be established.
6. Further research is needed to determine the optimum pathway and combination of tests to use for identifying Lynch syndrome in people diagnosed with bowel cancer.

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[i] UK colorectal cancer patients are inadequately assessed for Lynch syndrome, Adelson et al, Frontline Gastroenterology (2013), http://fg.bmj.com/content/early/2013/08/09/flgastro-2013-100345

[ii] Screening for the Lynch Syndrome, Hampel et al, NEJM (2005) http://www.nejm.org/doi/full/10.1056/NEJMoa043146

[iii] I Dove-Edwin, P Sasieni, H J W Thomas, Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer:16 year, prospective, follow-up study. BMJ 2005. http://www.bmj.com/content/331/7524/1047?goto=reply

[iv] A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome, Snowsill et al (2014) http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0005/125978/FullReport-hta18580.pdf

[v] Dataset for colorectal cancer histopathology reports, RCPath (2014) https://www.rcpath.org/resourceLibrary/dataset-for-colorectal-cancer-histopathology-reports--3rd-edition-.html

[vi] Data briefing: Reflex testing for Lynch syndrome in people diagnosed with bowel cancer under the age of 50 Kaur, A (2015) https://www.bowelcanceruk.org.uk/campaigning/never-too-young/read-our-reports/

[vii] A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome, Snowsill et al (2014) http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0005/125978/FullReport-hta18580.pdf