Lynch syndrome: an overview of cancer risks

1. Lynch syndrome: an overview of cancer risks

Lynch syndrome was first described in the early 20th century when affected families were identified as being at increased risk of colorectal cancer (HNPCC or hereditary non-polyposis colorectal cancer). We now know that carriers are also at higher-than-background risk of other malignancies.

Genetic assessments are increasingly important in the risk assessment, early diagnosis and management of malignancies. In its implementation guide for Lynch syndrome testing, NHS England reported a claim from Bowel Cancer UK that there were approximately 175 000 people with Lynch syndrome in the UK, but that only 5% are aware of their diagnosis. As more people are identified, primary care teams are likely to need to be able

to discuss concerns with these individuals and/or their relatives.

This article was written using information from the following references:

- Molecular testing strategies for Lynch syndrome in people with colorectal cancer (NICE DG27, 2017).
- NICE guidance on testing for Lynch syndrome in colorectal cancer (NICE NG151, 2020), endometrial cancer (NICE DG42, 2020) and pancreatic cancer (NICE NG85, 2018).
- NHS England: Implementing Lynch syndrome testing and surveillance pathways handbook v.1.2.
- Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG) Gut 2020;69:411).

Please also see our linked article on *Endometrial cancer* for more detail on the impact of Lynch syndrome on endometrial cancer risk assessment, and the subheading on non-Lynch syndrome genetic risk in our article on *Colorectal cancer*. You may also find the article on *Ovarian cancer: genetic risk* helpful.

This article was updated in October 2024.

1.1. What is Lynch syndrome?

- Lynch syndrome is a genetically inherited predisposition to developing cancer.
- It is responsible for up to 4% of colorectal cancer in the UK, often in younger patients.

- Originally, it was thought to be a risk factor for colorectal cancer only.
- We now know that it confers increased risk of other cancers, including, most commonly, endometrial, ovarian and pancreaticobiliary, but also gastric, small intestinal, urinary tract, brain, skin and other cancers. The exact risks depend on the underlying genetic defect (NHS National Genomics Education Programme).
- This has led to specific guidance on the identification and surveillance of those families affected by this condition.

1.2. Genetic basis

Individuals with Lynch syndrome usually have a defect in one of four mismatch repair genes: MLH1, MSH2 and (more rarely) MSH6 and PMS2. Even more rarely, a deletion in the EPCAM gene (not a mismatch repair gene) can impact the expression of MSH2.

Mismatch repair (or MMR) genes are responsible for manufacturing proteins which repair errors in DNA replication during cell division. Over time, accumulation of DNA errors (mutations) can cause cancer (NICE DG27 & DG42).

The specific mutation a person with Lynch has determines the specific cancers they are at risk from, and the Royal Marsden has an excellent patient resource that breaks this down (see useful resources at the end of the article).

Inheritance is **autosomal dominant**. This means that a child who has a parent with Lynch syndrome has a 50% chance of inheriting it.

Very occasionally, a mutation can arise de novo in one of these genes. In this situation, of course, only descendants rather than siblings and parents

would be at increased risk of developing cancer.

1.3. Impact on cancer risk

Colorectal cancer

Estimates of lifetime risk (defined as up to age 70y) of developing colorectal cancer (CRC) in a person with Lynch syndrome vary between 10 and 47%, depending on the MMR gene affected.

These cancers typically occur at a younger than normal age for CRC (average 44y), and tend to arise proximal to the splenic flexure. The MMR genes conferring the greatest risk for CRC are MLH1 and MSH2 (Gut 2020;69:411).

Endometrial cancer

The lifetime risk of endometrial cancer in females with Lynch syndrome is estimated to be 40–60%, which equals or exceeds the risk of colorectal cancer.

Ovarian cancer

The lifetime risk of ovarian cancer in Lynch syndrome is estimated to be 10–17%.

Other cancers

Other cancers with increased risk in Lynch syndrome include upper GI (e.g. pancreatic, cholangiocarcinoma), uroepithelial (ureter and bladder) and prostate cancer. There is currently not sufficient evidence to perform genetic testing (and subsequent cascade testing) for Lynch syndrome at the time of diagnosis of these cancers.

Risk compared with population risk

If you prefer more specific numbers, particularly if you have a patient who knows their specific gene defect, see the table below, adapted from the excellent Royal Marsden 'A beginner's guide to Lynch syndrome'; you will find the link in the useful resources box at the end of the article.

Male approximate risks

Cancer type	Population risk	MLH1	MSH2	MSH6	
Colorectal	7%	57%	51%	18%	
UGI	5%	22%	20%	8%	
Ureter/kidney	3%	5%	18%	As population risk	
Urinary/bladder	2%	7%	13%	8%	
Brain	<1%	<1%	8%	2%	
Prostate	18%	Similar to population or may be increased	24%	Similar to population or may be increased	

Female approximate risks

Cancer type	Population risk	MLH1	MSH2	MSH6	
Colorectal	6%	48%	47%	20%	
Endometrial	3%	37%	49%	41%	
Ovarian	2%	11%	17%	11%	
UGI	4%	11%	13%	4%	
Ureter/kidney	2%	4%	19%	6%	
Urinary/bladder	<1%	5%	8%	1%	
Brain	<1%	2%	3%	1%	

1.4. What is the role of primary care?

Guidance from NICE and accumulating evidence, especially from the CAPP (Cancer Prevention Programme) trials, will lead to increased primary care

involvement in genetics referrals and probably discussions with patients about risk-reduction options. Patients presenting with concerns about family history of cancer are often motivated to act on lifestyle and other advice aimed at risk reduction. This is an opportunity to give some high-impact brief advice and signposting.

Let's consider some scenarios where we might get involved.

1.5. Referring for genetic assessment when we are concerned about colorectal cancer risk

Usually, our involvement will begin once the diagnosis of Lynch syndrome has been made in the patient or their family member. However, we *may* be concerned about genetic colorectal cancer risk in patients without confirmed Lynch syndrome.

The updated BSG guidelines (Gut 2020; 69:411) define moderate and high genetic risk of colorectal cancer using the criteria below:

- Moderate risk: refers to one first-degree relative diagnosed with colorectal cancer under the age of 50y, or two first-degree relatives diagnosed with colorectal cancer at any age.
- High risk: refers to families with a cluster of at least three affected first-degree relatives with colorectal cancer diagnosed at any age, across at least two generations, where the individual concerned is a first-degree relative of at least one affected individual.

In addition, we should be asking about a history of multiple Lynch syndrome-related cancers occurring in the same family line.

If you are seeing someone concerned about ovarian or breast cancer risk,

you will find separate articles addressing this.

1.6. Testing for Lynch syndrome in people WITH a cancer diagnosis

NICE recommends that the following groups are tested for Lynch syndrome as part of their secondary care:

- All people with **colorectal cancer**. This will usually initially be by immunohistochemistry (IHC) analysis of a tumour sample and further testing as required (NICE 2017, DG27).
- All people with **endometrial cancer** (NICE 2020, DG42).
- Index case identification should trigger **cascade testing:** a methodical search for affected individuals by testing relatives of index cases for the genetic mutations:
    - Genetic testing is recommended for first-degree relatives (mum, dad, siblings, children) of individuals with confirmed Lynch syndrome.
    - If the index genetic test is negative, no further testing is needed.

Is this happening?

In January 2018, Bowel Cancer UK carried out a freedom of information request to find out whether hospitals across the UK were testing all bowel cancer patients for Lynch syndrome at the time of diagnosis. At that time, only 17% of hospitals in the UK were testing all bowel cancer patients in line with clinical guidance. The situation may well now have changed, but be aware that we are all likely to have patients who would have been eligible

for testing if it had been part of the guidance at the time they were diagnosed, but they have not been tested.

Role of primary care

- Act on cascade testing letters as we receive them.
- Discuss Lynch syndrome testing and status, if appropriate, at cancer care reviews for those with colorectal and endometrial cancers diagnosed prior to the widespread availability of testing.
- We may need to assess risk and consider a genetics referral where there is a strong family history of colorectal or other cancers (especially those associated with Lynch syndrome) which were diagnosed prior to current guidance, or where testing was not carried out at diagnosis (see above).
- Add the READ code of Lynch syndrome to ensure clarity of risk assessment in the future.

1.7. After diagnosis

Secondary care is responsible for identification, risk assessment, future surveillance and risk-reduction surgery in people with Lynch syndrome, but it is useful for us to understand what this will involve and how we can support it.

Index cases will be given letters requesting onward referral to local genetics services for close family members to take to their GP. **This is where we will become involved**.

Once identified, people with Lynch may be offered risk-reducing strategies,

including:

- Surveillance.
- Lifestyle measures.
- Chemoprophylaxis with aspirin.
- Risk-reduction surgery.

Symptomatic presentations

We should remain aware of the potential for symptomatic presentations of any of the cancers identified as higher risk, and have an even lower threshold for referral for investigations if a person with Lynch syndrome presents with any relevant symptoms.

1.8. Surveillance for people with Lynch syndrome

The exact nature of recommended surveillance will depend on the genetic defect identified, but may include the following.

Colorectal cancer screening

People with confirmed Lynch syndrome will be enrolled by secondary care into the NHS Bowel Cancer Screening Programme for endoscopic surveillance in line with the screening intervals set out in the BSG/ACPGBI/PHE guidelines for the management of hereditary colorectal cancer. This will vary depending on the specific gene defect.

Typically:

- Every 1–2y starting at age 20–25y OR
- 2–5y before the youngest age of cancer diagnosis in that family if this is <25y.

All those diagnosed with Lynch syndrome should be added to the Lynch registry (by the clinical genetics team). This should include information on the specific MMR mutation. The National Disease Registration Service will then provide the NHS Bowel Cancer Screening Programme with a list of people who need screening.

Patients may ask primary care about how they will be followed-up. We can help by explaining the process and encouraging uptake of the surveillance.

Pancreatic cancer surveillance

NICE suggests considering surveillance for pancreatic cancer for people with Lynch syndrome **AND** any first-degree relatives with pancreatic cancer (NICE 2018, NG85).

Surveillance will usually involve endoscopic ultrasound, MRCP or MRI scanning.

We should ensure that our patients with Lynch syndrome are aware of this, and that we refer on to secondary care for further consideration of surveillance if they report a diagnosis of pancreatic cancer in a parent, child or sibling.

There is currently no proven form of screening for endometrial cancer or ovarian cancer. Risk-reduction surgery is therefore usually recommended (see below).

Let's now consider strategies for cancer risk reduction in people with Lynch syndrome.

1.9. Lifestyle advice

Lifestyle advice for people with Lynch syndrome is the same as for the general population, and we should take the opportunity to reiterate the main points.

Of note:

- Support weight loss: the risk of early-onset colorectal cancer is more than doubled in Lynch syndrome patients who are also obese.
- Smoking cessation: there is some evidence that people with Lynch syndrome who smoke regularly can lower their risk of bowel cancer by stopping, and they may be motivated to do so at a time when they are newly aware of their increased genetic risk.

1.10. Aspirin chemoprophylaxis

NICE guidance (NG151) recommends that people with Lynch syndrome consider taking aspirin daily for more than 2 years to prevent colorectal cancer. This is based on accumulating evidence, including that from the CAPP2 study; optimal dosage is being investigated further in the CAPP3 study (Lancet 2020; 395:1855).

This is likely to be initiated in secondary care. If we take over prescribing, we should consider indication prescribing, e.g. *Aspirin xxmg per day to reduce the risk of colorectal cancer until XXXX.*

Note that while CAPP2 (see below) used high doses of aspirin, NICE and most secondary care departments are currently recommending 150mg daily until CAPP3 reports on optimal doses.

What's the evidence?

The CAPP2 study was an international, double-blind, randomised controlled trial in which 861 people (82% from Europe) aged over 25y and with Lynch syndrome took either placebo or **600mg** aspirin per day for 2 years (Lancet 2020;395:1855). The trial showed that:

- **For people with Lynch syndrome, taking aspirin in this way resulted in a significant reduction in colorectal cancer incidence, starting 5 years AFTER starting aspirin and persisting for over a decade after stopping aspirin.**
- **There may have been a slight reduction in non-colorectal cancer risk at the later stages of the study, but this did not reach statistical significance at the time of publication.**
- **Serious adverse events while taking aspirin did not differ significantly from the placebo group. The authors comment that this may be influenced by the relatively young age of this group of people during the treatment phase, who would in any case be at lower risk of bleeding and gastric ulceration.**

How might it work?

The mechanism of action of aspirin in reducing the incidence of colorectal cancer in Lynch syndrome is thought to be anti-inflammatory. This is similar to previously-observed benefits of NSAIDs and aspirin in reducing the incidence of cancers where studies had a primary endpoint of

cardiovascular disease.

What next?

Determining the optimal dose and duration of treatment. CAPP3 will address this. It has recruited 1882 Lynch syndrome carriers and closed to new recruits in March 2019. First results are likely to be published in 2025.

1.11. Risk-reduction surgery

This may be advised for some people with Lynch syndrome, and may include:

- Bilateral salpingo-oophorectomy (BSO) and/or hysterectomy (ideally between the ages of 35 and 45y).
- Prophylactic subtotal colectomy.

This decision will be made with the person in secondary care, and will take account of their individual risk as well as stage of life, e.g. whether they have completed their family.

What about HRT after risk-reduction BSO surgery in Lynch syndrome?

The RCOG and Royal Marsden recommend that women who have had risk-reduction BSO surgery should be offered HRT up to age 51y, providing they have not had an ER-receptor positive breast cancer (in this situation, HRT use should be discussed with the oncologist).

If we in primary care are uncertain, we can and should seek advice from secondary care.

1.12. *H. Pylori* testing and Lynch syndrome

The BSG also recommends one-off screening of people with Lynch syndrome for *Helicobacter pylori* and eradication therapy, as appropriate (Gut 2020;69:411).

This is because of the higher proportion of intestinal-type gastric cancer associated with Lynch syndrome, and increased bleeding risk with aspirin chemoprophylaxis.

1.13. A role for resistant starch?

Resistant starch is a component of dietary fibre found in bananas, grains, pulses, potatoes and seeds.

The CAPP2 European study team (Cancer Prev Res (Phila) 2022;15:623) reported on a double-blind, randomised trial that involved people with Lynch syndrome taking a 30g daily supplement of resistant starch or placebo for up to 4 years, with 20 years' follow-up. Although epidemiological studies have previously suggested a preventive effect of dietary fibre against CRC in the general population, this was surprisingly not reproduced in the CAPP2 study involving people with Lynch syndrome.

However, there was a significant reduction in cancer of other organs associated with Lynch syndrome, especially **upper GI, but not endometrial**.

Site of cancer (20y incidence)	Placebo (n=455)	30g of resistant starch daily (n=463)
Colorectal cancer	53	52
Non-colorectal cancer	48	27
Upper gastrointestinal cancer	21	5
Endometrial cancer	16	15

The team had also postulated a synergistic effect of aspirin and resistant starch, but this was not demonstrated. The mechanism of action of resistant starch is thought to be due to fermentation in the bowel and production of substances such as butyrate, which are thought to have anticancer properties.

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- We will be seeing more requests for genetic referral as people diagnosed with colorectal and endometrial cancer are tested for Lynch syndrome.
- Secondary care should test for Lynch syndrome in ALL patients diagnosed with colorectal cancer and endometrial cancer.
- Support patients presenting for cascade testing for Lynch syndrome after a family diagnosis. Consider also identifying those with significant family history and referring to genetics if appropriate.
- Refer people with Lynch syndrome for consideration of pancreatic cancer surveillance screening if there is a history of a first-degree relative with pancreatic cancer.
- If someone has Lynch syndrome, aspirin for at least 2 years and surveillance by colonoscopy is recommended.
- The BSG also recommends one-off screening of people with Lynch syndrome for *Helicobacter pylori* and eradication therapy, as appropriate.

Search for patients with a diagnosis of Lynch syndrome. Are they taking prophylactic aspirin? If so, is the repeat prescription clear about indication and length of treatment?

Useful resources:

Websites (all resources are hyperlinked for ease of use in Red Whale Knowledge)

- NICE - patient decision aid on Lynch syndrome and aspirin
- CAPP3 – Cancer Prevention Programme
- The Royal Marsden NHS Foundation Trust – Lynch syndrome a beginner's guide

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