# Implementing Lynch syndrome testing and surveillance pathways

## A handbook for Cancer Alliances

## The Ambition

The NHS Long Term Plan sets an ambition that by 2028, 75% of cancers will be diagnosed at an early stage. One of the ways this ambition will be reached is through targeted screening and personalised surveillance of those most at risk of developing cancer such as those with Lynch syndrome.

Each year, 1,100 colorectal cancers are caused by Lynch syndrome, making it the most common form of hereditary colorectal cancer (NICE, DG27). By implementing Lynch syndrome pathways nationally we have the opportunity to detect many of these at an earlier stage and also prevent cancers through risk reduction treatments and appropriate surveillance routes.

This handbook sets out guidance to support Cancer Alliances to achieve this. It has been shaped by the Lynch syndrome expert Advisory Group[1]. For any questions about the handbook please email england.cancerpolicy@nhs.net.

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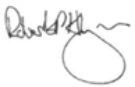
NHS England and Improvement National Clinical Director for Cancer



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[1] Acknowledgements: This handbook was developed by the NHS Cancer Programme. It has been shaped by the Lynch syndrome Advisory Group whose members include, Professor John Burn, Dr Kevin Monahan, Dr Fiona Lalloo, Kevin Peters, Steven Hardy, Julia Jessop, Michelle Timoney, David Wells, Suzy Lishman, Jessica Lewington, Dr Michael Machesney, Peter English, Momenul Haque and Robert Logan as National Endoscopy Advisor.

## Lynch syndrome what is it?

- Lynch syndrome is an inherited genetic condition caused by a germline pathogenic variant in one of four DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6 and PMS2. Pathogenic variants in another non MMR gene, known as *EPCAM*, which is next to the MSH2 gene, can also cause Lynch syndrome.

- MMR genes encode proteins that are involved in recognising and repairing errors in DNA sequence, which occur when DNA is replicated during cell division. Pathogenic variants in MMR genes can lead to impaired functioning of the MMR system and a failure to repair DNA errors. Over time, this allows mutations to accumulate, potentially leading to cancer.

- Lynch-like syndrome (LLS) is a condition where a genetic diagnosis of Lynch syndrome is suspected but cannot be confirmed using current genetic testing methods.

- Around half of all people with Lynch syndrome develop colorectal cancer. It is also responsible for a range of other cancers including endometrial, gastric, small bowel, urothelial and brain cancers. There are around 1,000 cases at these other sites each year in the UK.

- Lynch syndrome follows an autosomal dominant inheritance pattern. A child who has a parent with a pathogenic variant has a 50% chance of inheriting that pathogenic variant.

- Since 2017, the National Institute for Health and Care Excellence (NICE) has recommended that all people with colorectal cancer are tested for Lynch syndrome using Immunohistochemistry (IHC) or Microsatellite Instability (MSI) testing (DG27).

- NICE guidance on the testing of endometrial tumours for Lynch syndrome is due in late 2020.

## Case for change

- An estimated 175,000 people have Lynch syndrome in the UK but fewer than 5% of individuals know they have the condition (Bowel Cancer UK).
- In 2018, there were 35,958 new cases of colorectal cancer diagnosed in England. We estimate that between 2,200 and 3,700 of these people would be eligible for full-screen germline genetic testing for Lynch syndrome. Data provided to NCRAS by the NHS genomic laboratories suggests that only 1,212 full-screen germline genetic tests for Lynch syndrome were performed in 2018[2]. Compliance with DG27 therefore needs to be improved.
- If all people with colorectal cancer and their family members were tested for Lynch syndrome and enrolled into appropriate surveillance pathways in 2028, we would expect up to 380 more colorectal cancers to be diagnosed early. That's up to a 0.9% point increase against the Long Term plan ambition to diagnose 75% of cancers early by 2028.
- A diagnosis of deficient MMR (dMMR) can affect cancer treatment options with certain tumours being more responsive to particular chemotherapy agents. People with Lynch syndrome are also responsive to new immunotherapy drugs. It is therefore important that the initial tumour test (IHC or MSI) is done in time to inform treatment options.
- Low cost treatments and services are available to help people with Lynch syndrome manage and reduce their risk.

These include:

- **Taking aspirin** – NICE guidance (NG151) recommends people with Lynch syndrome consider taking aspirin daily for more than 2 years to prevent colorectal cancer.
- **Losing weight -** The risk of early onset colorectal cancer is more than doubled in Lynch syndrome patients who are also obese (Mathers et al)[3].
- **Stopping smoking** – people with Lynch syndrome may be at increased risk of colorectal cancer if they smoke regularly (Pande et al)[4]
- **Dietary Advice** – The CAPP2 study tested a daily supplement of resistant starch, also known as fermentable fibre in people with Lynch syndrome. This has shown a highly significant reduction over ten years in cancers in other part of the body such as the stomach, liver and pancreas. (Mathers et al in press).
- **Surgery -** Patients diagnosed with Lynch syndrome may choose to have adaptive surgery (Bowel resection, hysterectomy or oophorectomy) to reduce their risk of developing cancer.
- **Surveillance pathways to support early detection** – there is guidance on recommended surveillance pathways for people with Lynch syndrome[5] highlighted in this handbook.

[2] Data was provided to NCRAS by 12 NHS genomic laboratories providing Lynch syndrome germline testing. The quoted figure corresponds to full-screen tests performed in 2018 which may not necessarily correlate with tumours diagnosed in 2018 due to the lag effect in genetic testing; however, this figure is provided to allow an estimation of yearly testing activity compared to estimated demand.
[3] https://pubmed.ncbi.nlm.nih.gov/26282643/
[4] https://pubmed.ncbi.nlm.nih.gov/20145170/
[5] The Manchester International Consensus Group Recommendations for the Management of Gynaecological Cancers in Lynch Syndrome, Guidelines for the management of hereditary colorectal cancer from the BSG /ACPGBI/UKCGG

## Implementing the Lynch syndrome pathway

In this handbook, the Lynch syndrome pathway has been split into four stages shown below

| | |
|---|---|
| **Stage 1:Initial tumour test** | 1. Biopsy taken<br>2. Test tumour using Immunohistochemistry (IHC) or Microsatellite instability (MSI). Initial tumor testing should be completed in time to inform treatment options.[6] |
| **Stage 2:Germline testing** | 3. Test suggests cancer could be caused by Lynch syndrome<br>4. If not already done, consent to perform germline testing<br>5. Perform germline testing. This test should take no longer than 4 weeks to complete |
| **Stage 3: Management of index case** | 6. If Lynch syndrome is confirmed, communicate results to patient and refer to genetics service.<br>7. Agree a screening and management plan and refer to relevant services |
| **Stage 4: Cascade testing and surveillance of family members** | 8. Cascade testing of at-risk family members |

[6] The turnaround times outlined in this handbook for the initial tumour test and genetic test are based on the timescales GLHs will be working to as they become firmly established. It is recognised that there will be a ramp up period whilst Cancer Alliances work with GLHs to streamline pathways and embed these standards.

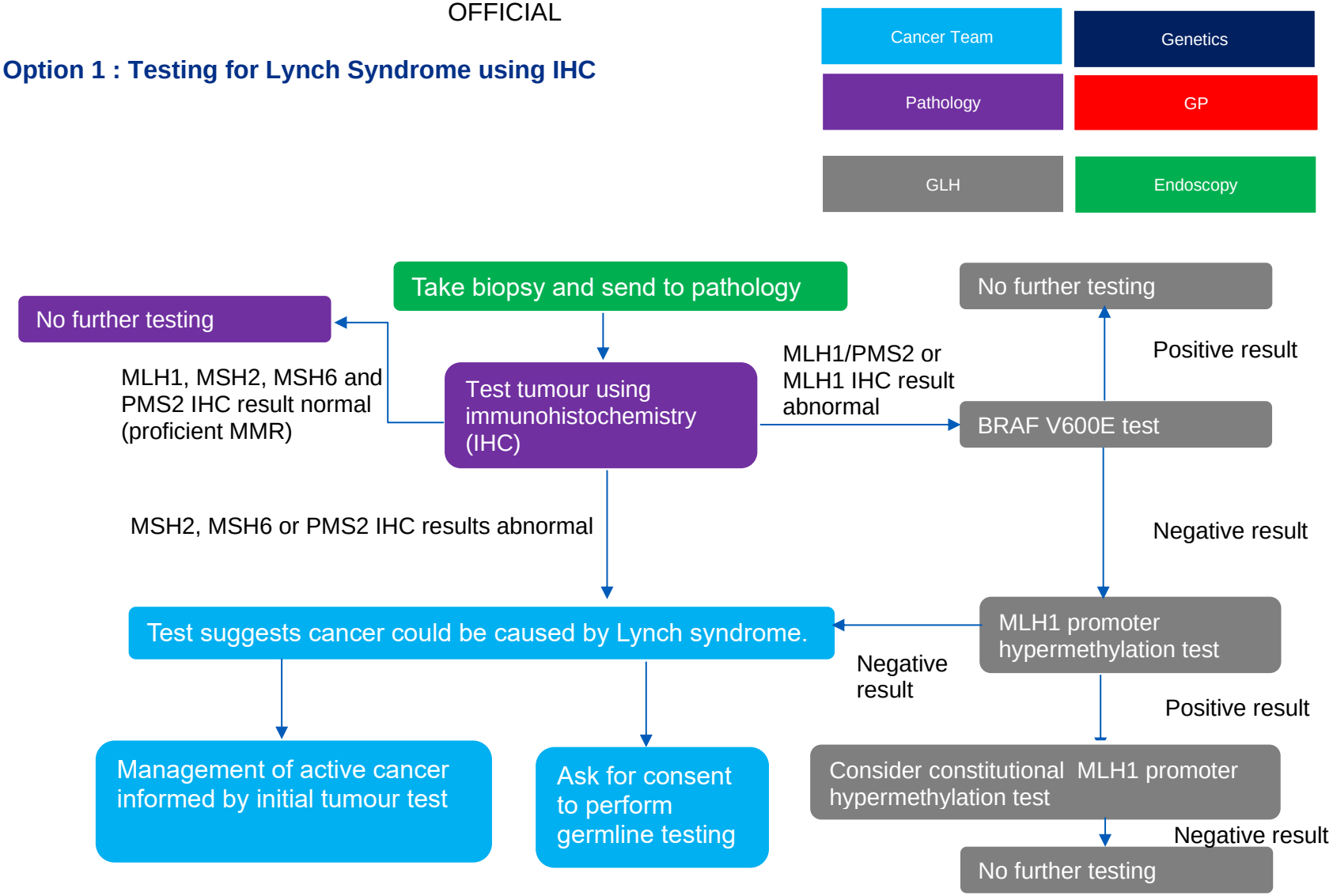
## Stage 1: Initial Tumour Test

DG27 NICE guidance recommends all people with colorectal cancer are tested for Lynch syndrome using one of two initial tumour tests, IHC or MSI.

Where no pathway currently exists, a pathway of IHC or MSI should be established. A genetic pathway (MSI) will naturally slot into the cancer gene panel sequencing being rolled out nationally.

Notes:
NICE guidance, Testing strategies for Lynch syndrome in people with endometrial cancer currently out for consultation states that endometrial tumours should be tested using IHC. Once this guidance is finalised, Cancer Alliances should make sure there is appropriate IHC provision and funding to meet the needs of those with endometrial cancer.

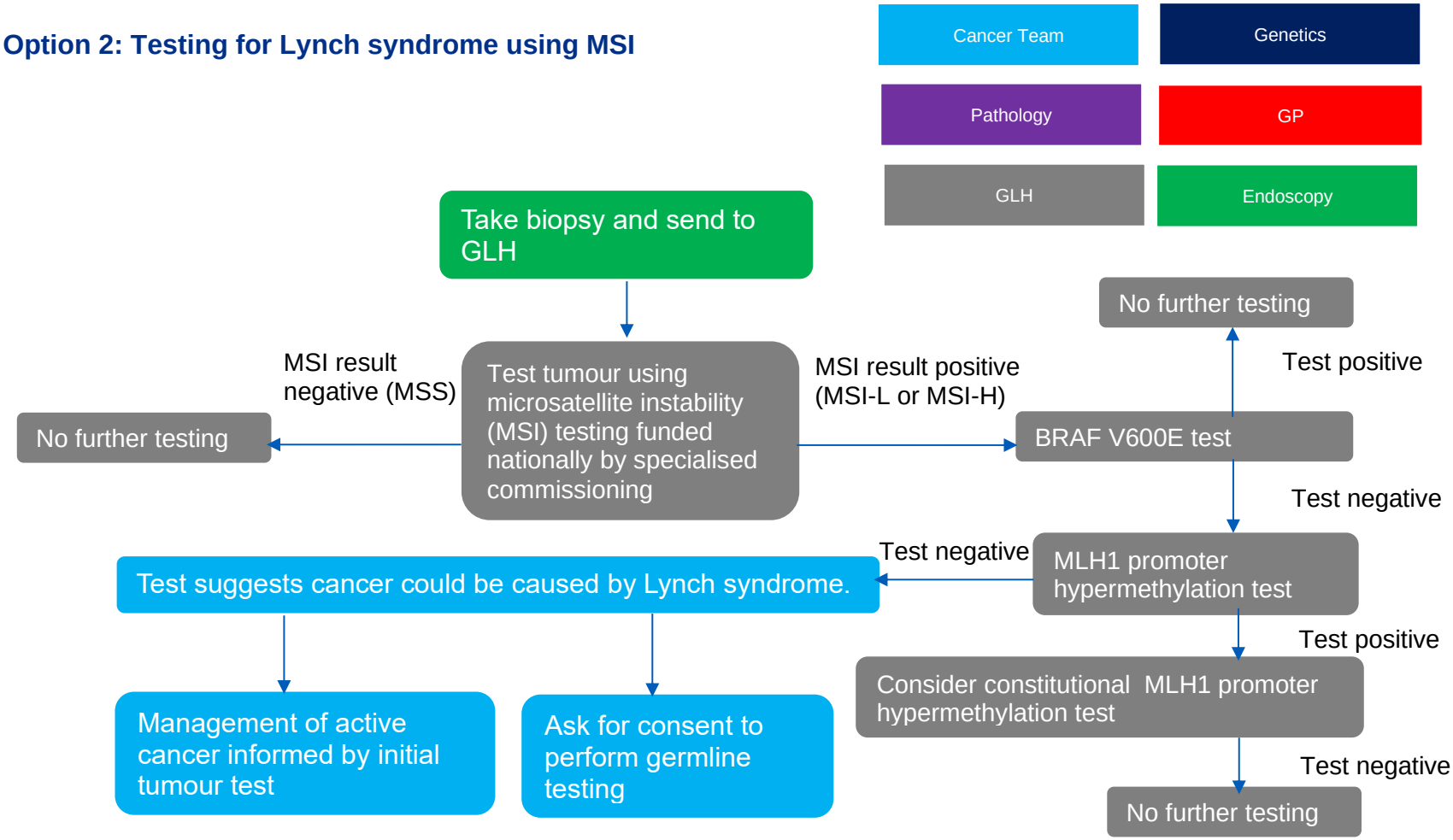
## Option 1 : Testing for Lynch Syndrome using IHC




Notes:

- A biopsy should be sent directly from endoscopy to pathology for IHC testing. Patients may present by alternative routes and consideration should still be made for Lynch syndrome testing
- The initial tumour test should be a part of standard pathology and germline testing should be part of a mainstreaming approach
- Informed consent for germline testing is mandatory, but not for preceding steps in the diagnostic pathway. A decision can be taken locally on whether to take informed consent before the initial tumour test or before the germline test.
- IHC testing should be completed within 7-10 days

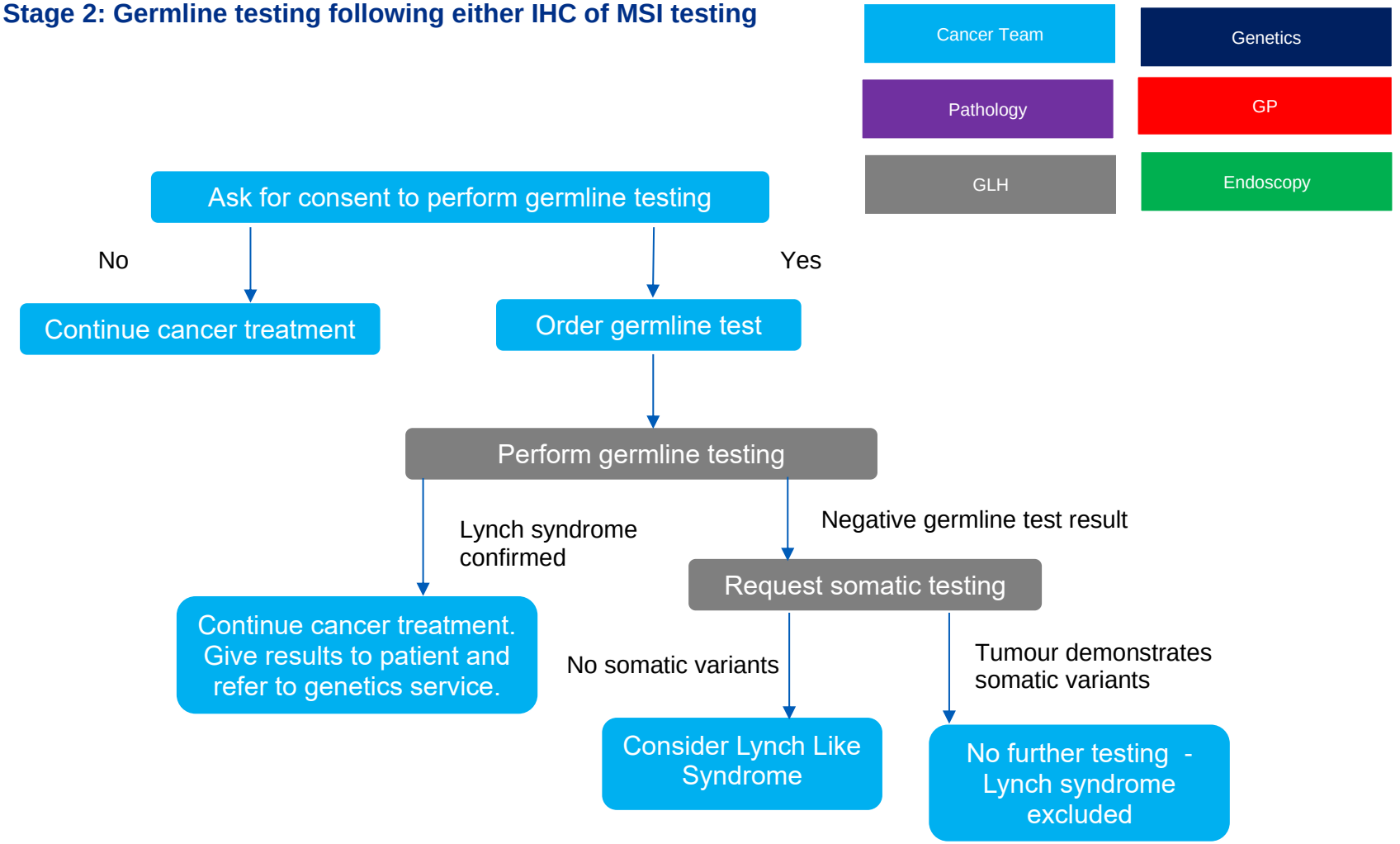
## Option 2: Testing for Lynch syndrome using MSI




Notes:

- A biopsy should be sent directly from endoscopy to the relevant GLH for genetic analysis. Patients may present by alternative routes and consideration should still be made for Lynch syndrome testing
- The initial tumour test should be a part of standard pathology and germline should be part of a mainstreaming approach
- Informed consent for germline testing is mandatory, but not for preceding steps in the diagnostic pathway. A decision can be taken locally on whether to take informed consent before the initial tumour test or before the germline test.
- Steps across this pathway and the time taken to complete the test may differ depending on the MSI assay used by the GLH. MSI, BRAF and hypermethylation testing should be completed before the MDT, and results communicated to the patient within 4 weeks.

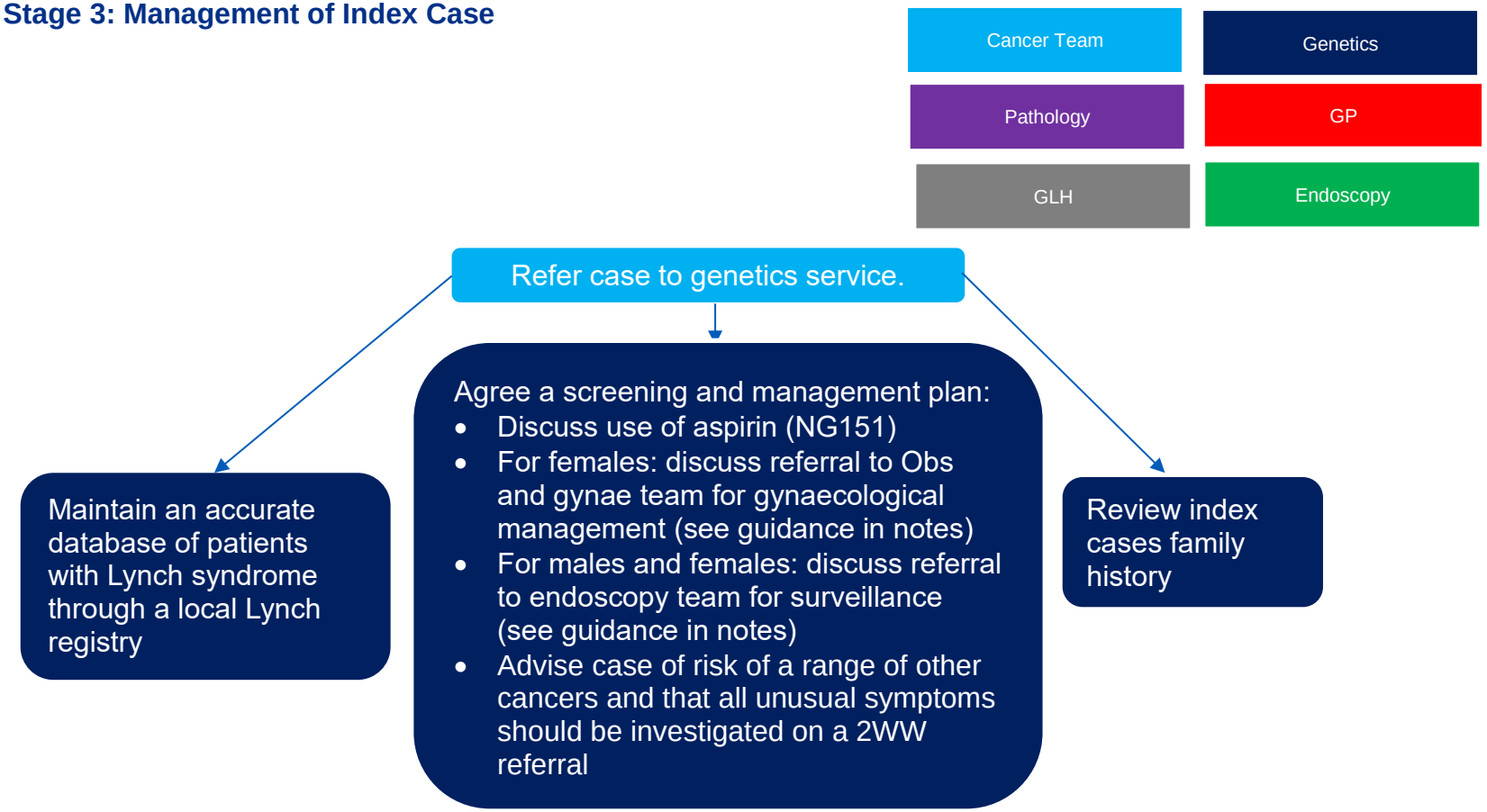
## Stage 2: Germline testing following either IHC of MSI testing




Notes:

- Germline testing should be part of a mainstreaming approach
- If the germline test is negative but the patient has a significant family history of cancer or was diagnosed under age 30, consider referral to clinical genetics service
- A germline test should be completed, and results communicated to the patient within 4 weeks.

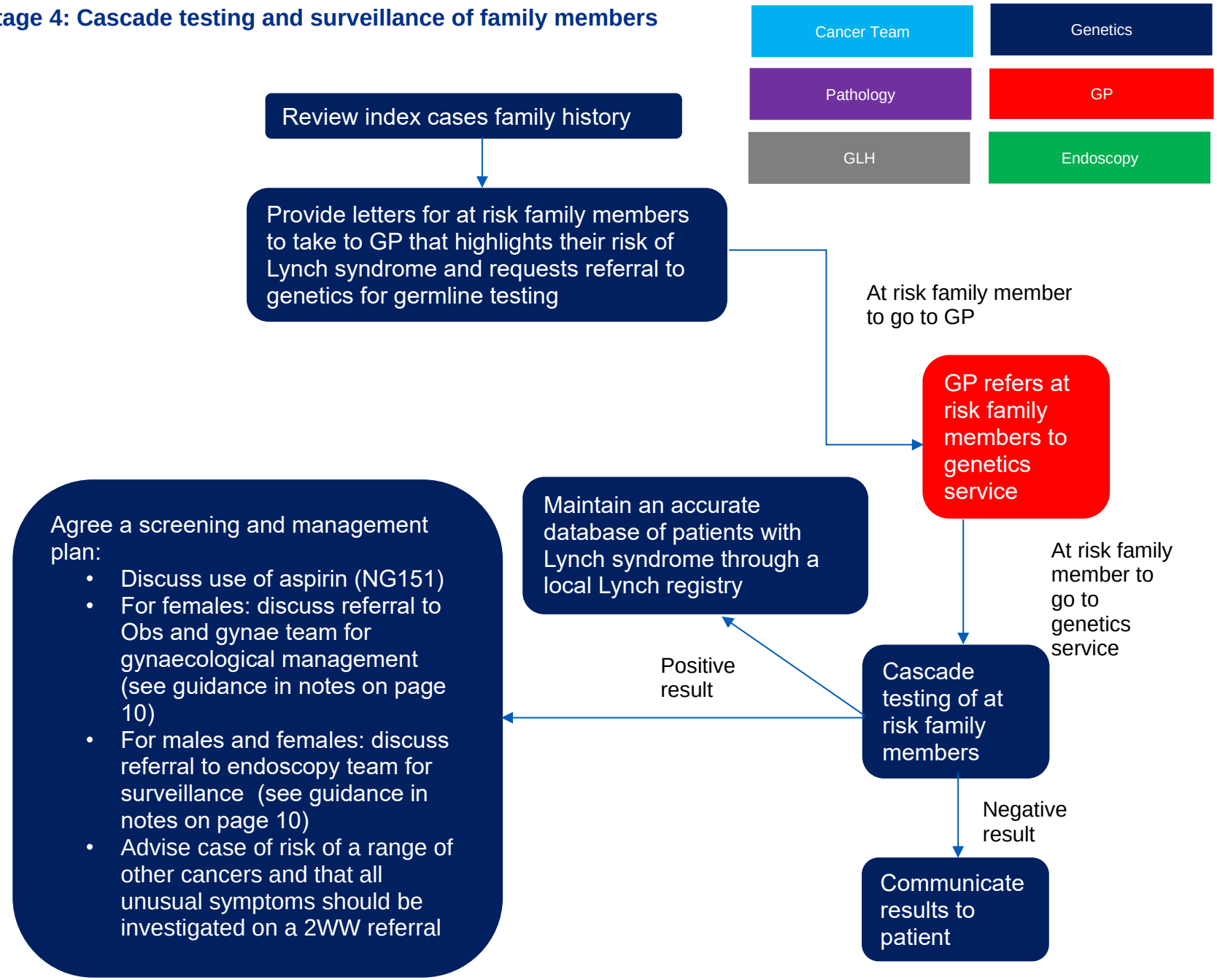
## Stage 3: Management of Index Case




Notes:

- Recommendations for the management of gynaecological cancers in Lynch syndrome.
- Public Health England is working with an expert Advisory Group to consider the appropriateness and feasibility of referring people with Lynch and Lynch like syndrome for surveillance into the NHS Bowel Cancer Screening Programme. Should it be, a recommendation will then be made for consideration by NHS England and Improvement. For now patients with Lynch syndrome should receive colonoscopy at trust level by a screening accredited colonoscopist, in accordance with Guidelines for the management of hereditary colorectal cancer from the BSG/ACPGBI/PHE
- A local Lynch registry can be as simple as an excel sheet. What is important is a database is kept of patients diagnosed with Lynch syndrome

## Stage 4: Cascade testing and surveillance of family members



## Commissioning responsibilities

Implementation of the Lynch syndrome pathway is included in the NHS Planning and Contracting Guidance for 20/21 and has been identified as a priority for Cancer Alliances

| Stage | Funding responsibility |
|---|---|
| Initial Tumour test | IHC: Clinical Commissioning Groups (CCGs) are responsible for providing funding to pathology services for IHC testing<br>MSI: MSI is included in National Genomic Test Directory and is therefore funded nationally by specialised commissioning |
| Germline testing | Germline testing for Lynch syndrome is included in the National Genomic Test Directory and is therefore funded nationally by specialised commissioning |
| Surveillance and management of people with Lynch syndrome | CCG's are responsible for funding surveillance pathways for people with Lynch syndrome including colonoscopy and gynaecological prevention strategies |

## How to achieve success

**Appoint a clinical lead for the pathway**
All trusts should appoint an individual to take on responsibility for implementing this pathway. In November 2019 we wrote to Cancer Alliances asking them to nominate a 'Trust Surveillance Lead.' This lead is well placed to also champion implementation of the Lynch pathway across various specialties.

**Establish a regional Lynch network to support and develop the delivery of a cross-system service**
Bring together key stakeholders (pathology, endoscopy, GLHs, clinical genetics service, cancer team, surgical team and Cancer Alliances) bi-annually as part of a Lynch syndrome network to review delivery of service standards and to support service development. Develop regional expert centres who will be able to provide clinical advice and training to dedicated local leads within cancer MDTs and manage regional patient registries.

The Improvement Hub provides a number of useful resources that can support service improvement including guidance, modelling tools, and webinars.

**Coproduction and codesign with people who use the services**
Coproduction, working together with patients and their families in codesigning ideas should be used to develop and implement the pathway. Identify how you will ensure patient and carer feedback is welcomed, listened to and acted upon throughout the pathway as a measure of experience of care. Bite size guides are available for participation patient insight and feedback.

**Work with GPs**
Work with GPs to prepare for a rise in the number of people presenting and asking for a referral to the genetics service due to risk of Lynch syndrome. Make sure they are aware of referral pathways and who to signpost any questions on to. You can use local networks for communication such as newsletters and GP events.

**Set up communication templates**
The Lynch pathway crosses over a number of specialities and will require good communication between teams. Create templates that clearly communicate requests and that enable consistency across the pathway. Example templates can be found on the NICE website.

## Support Resources

- NICE DG27 guidance 'Molecular testing strategies for Lynch syndrome in people with colorectal cancer'
- NICE NG151 guidance 'Colorectal cancer.' Recommendation 1.1 Prevention of colorectal cancer in people with Lynch syndrome
- NICE guidance out for consultation: Testing strategies for Lynch syndrome in people with endometrial cancer
- NICE has developed a 'Resource Impact Template: Molecular strategies for Lynch Syndrome in people with colorectal cancer' that allows Alliances to input their local population data. This will show how many people will be expected to go through each stage of the Lynch syndrome pathway for both MSI and IHC tests and the associated cost.
- NICE has also developed a 'Resource impact report: Molecular testing strategies for Lynch syndrome in people with colorectal cancer' that outlines the costs of tests across the Lynch syndrome pathway.
- The National Genomic Test Directory
- 'It's time to test' campaign material from Bowel Cancer UK