Lynch Syndrome/Genomics

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Wessex Cancer Alliance Lunch & Learn Webinar

19th April 2023

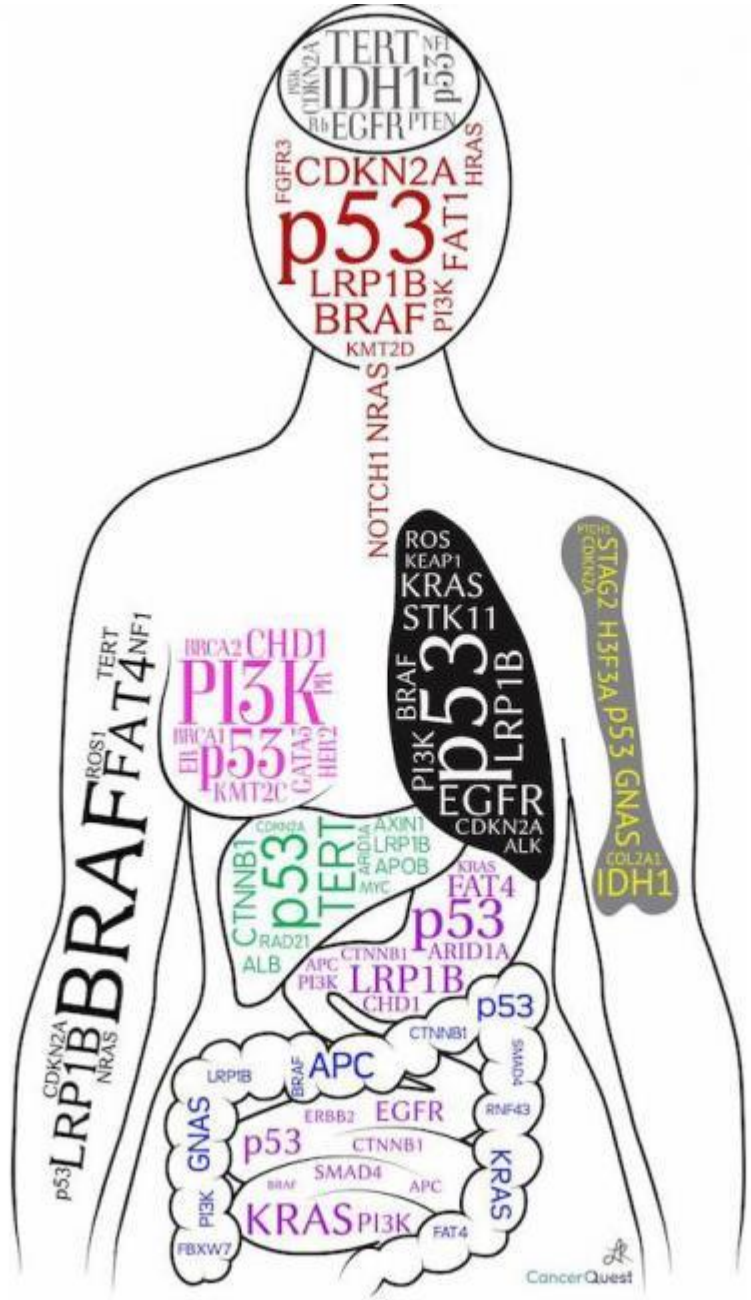
WCGS
Wessex Clinical Genetics Service

NHS
University Hospital Southampton
NHS Foundation Trust

Aim

To give a brief overview of

- Cancer genomics and Lynch Syndrome
- The National Lynch Syndrome project
- Potential impact on patients in primary care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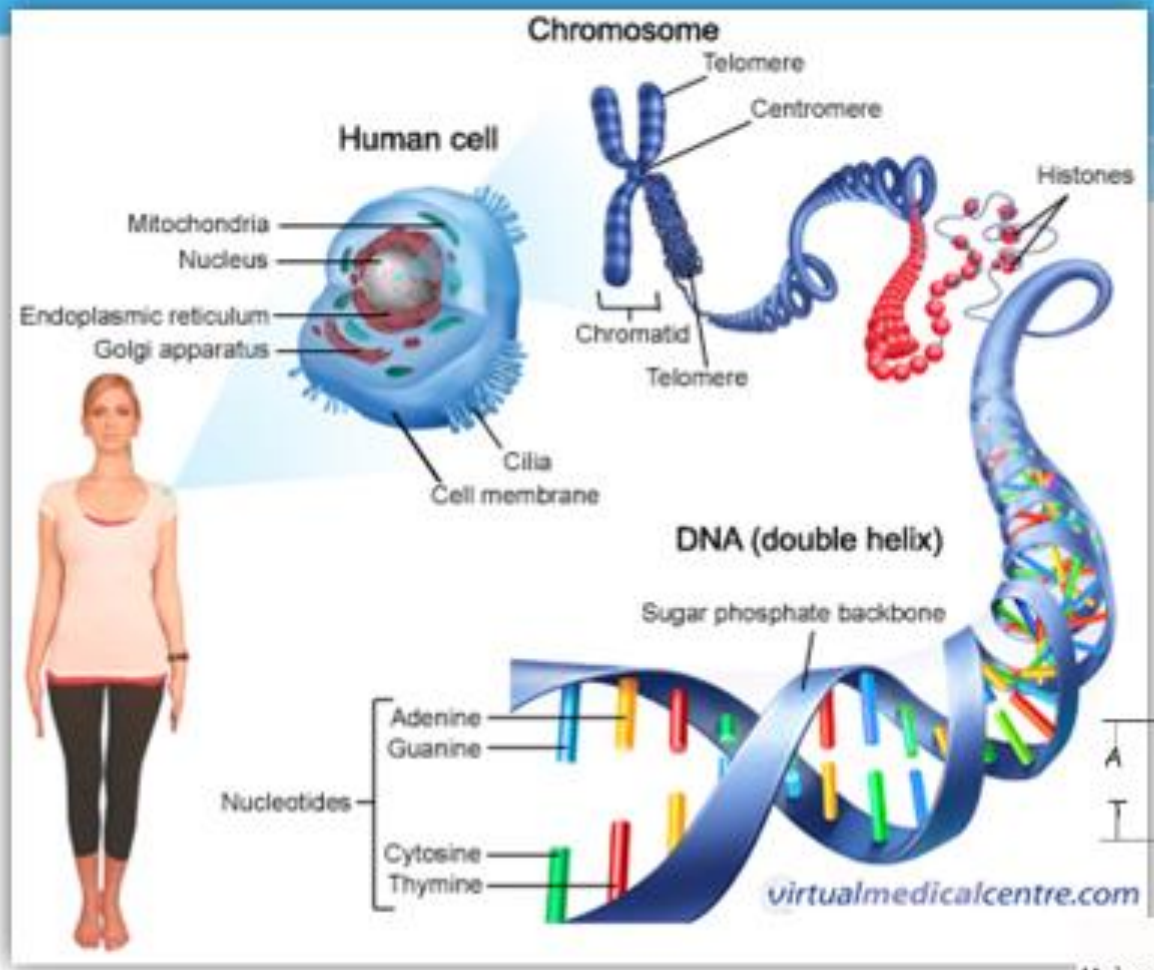
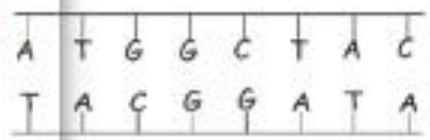
CancerQuest

Chromosomes, genes and DNA





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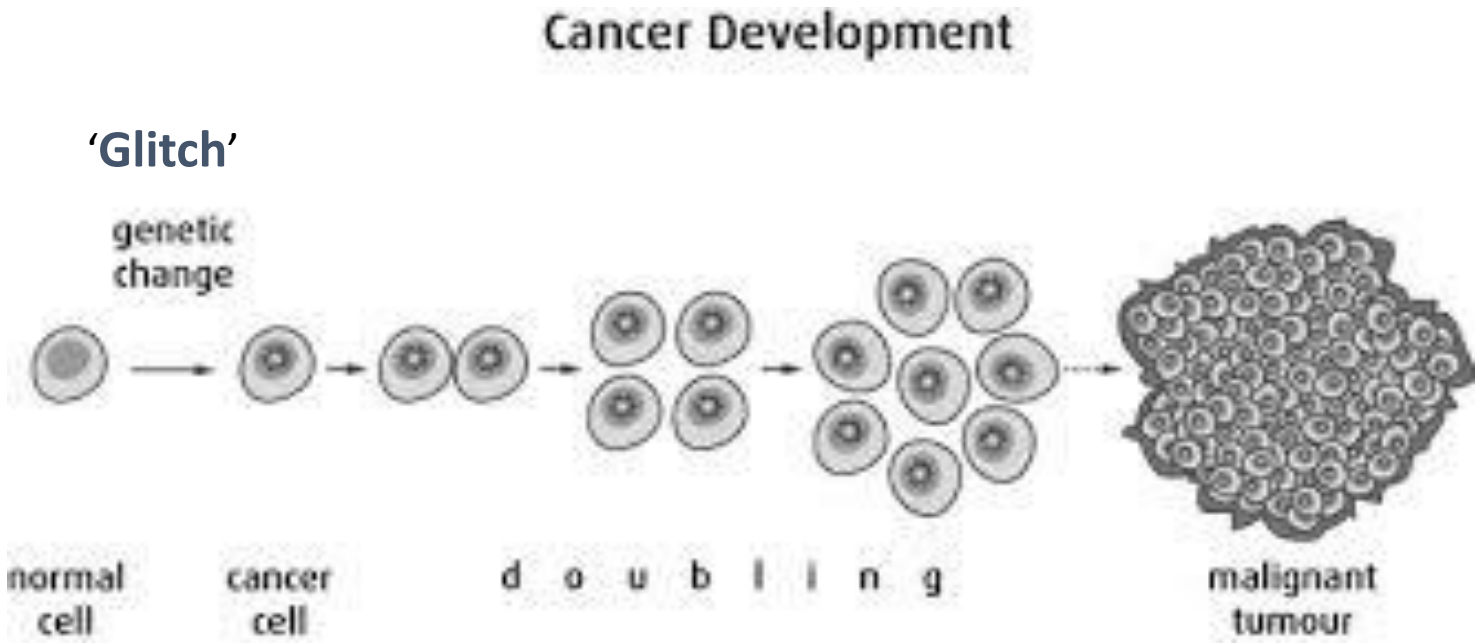
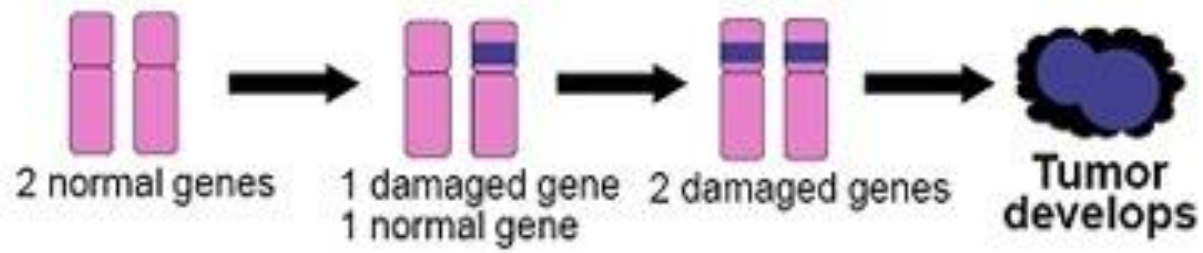
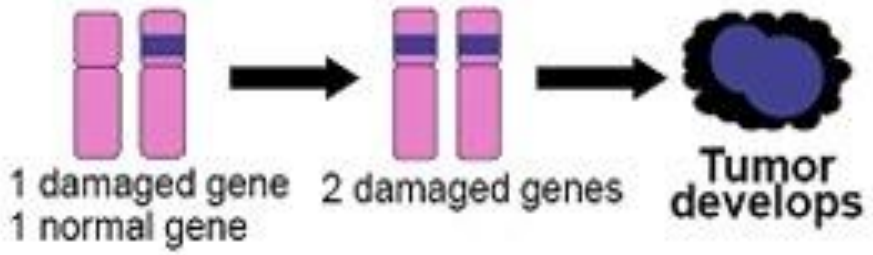
All cancer is 'genetic'....

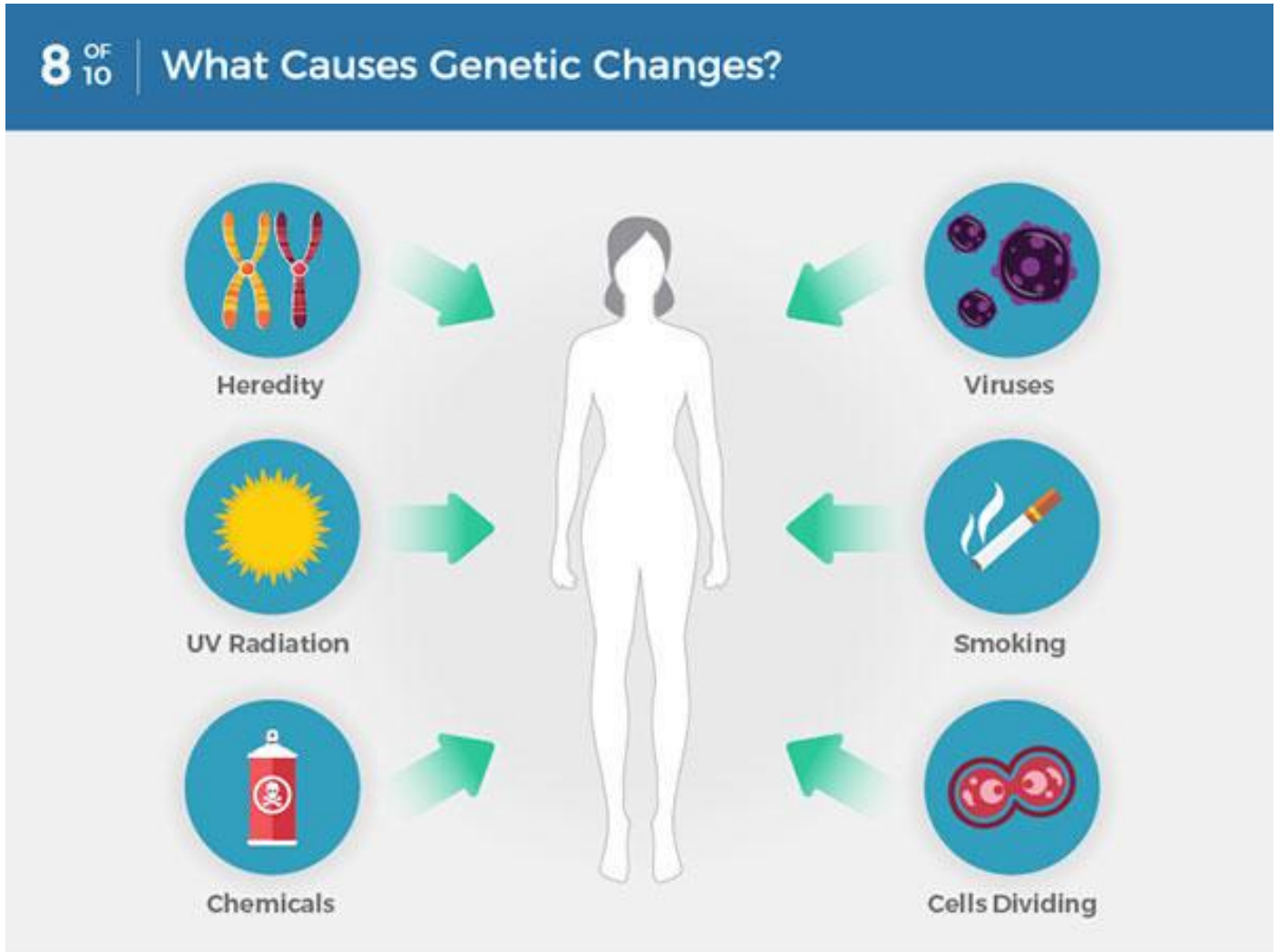


Sporadic vs. Hereditary Cancers



In hereditary cancer, one damaged gene is inherited.

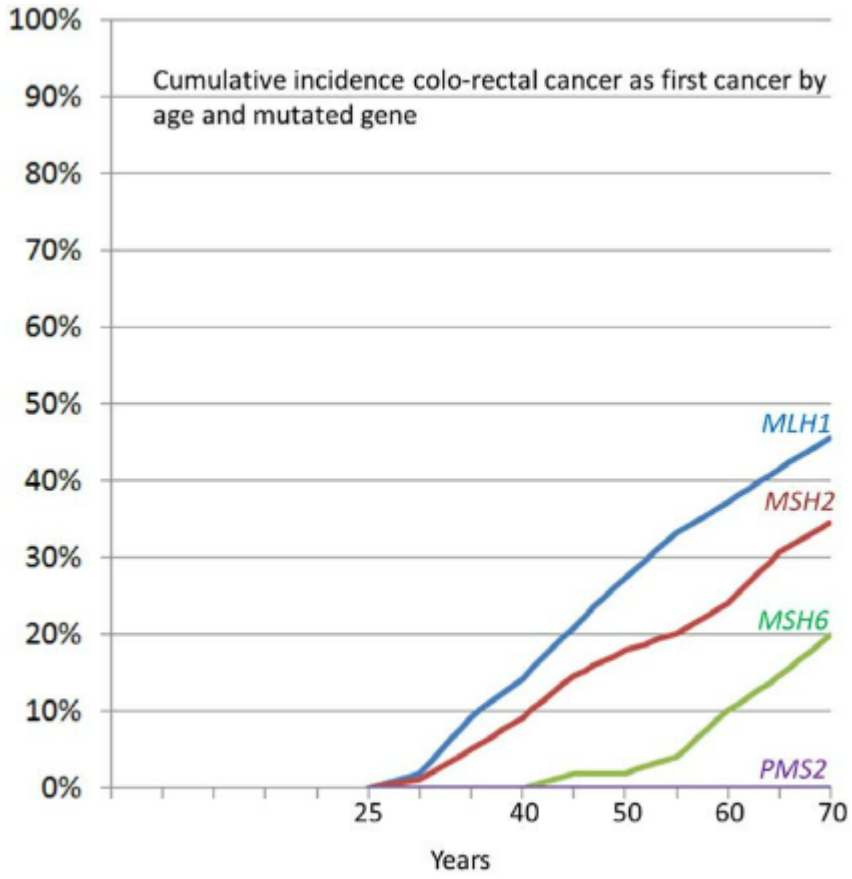



8 OF 10
What Causes Genetic Changes?
Heredity
UV Radiation
Chemicals
Viruses
Smoking
Cells Dividing

Do any of your patients have Lynch Syndrome?

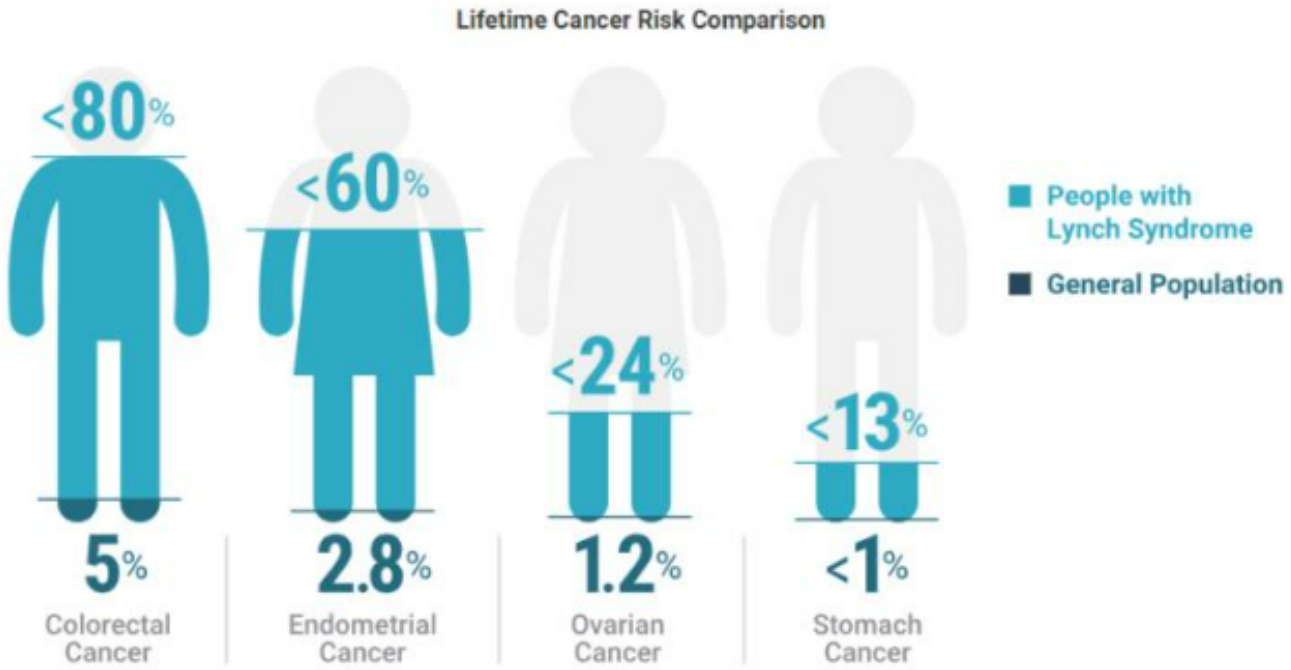
Lynch Syndrome - epidemiology

- An inherited cancer predisposition syndrome
- Increases the chance of developing a number of cancers.
- Incidence of 1 in 350 (UK Biobank, Healthy Nevada Study)
- 3.3% of CRC patients will have Lynch syndrome
- Estimated only 5% known (Bowel Cancer UK)



Pål Møller et al. Gut 2017;66:464-472

Lynch syndrome predisposes to certain cancer types:



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The main concerns are:

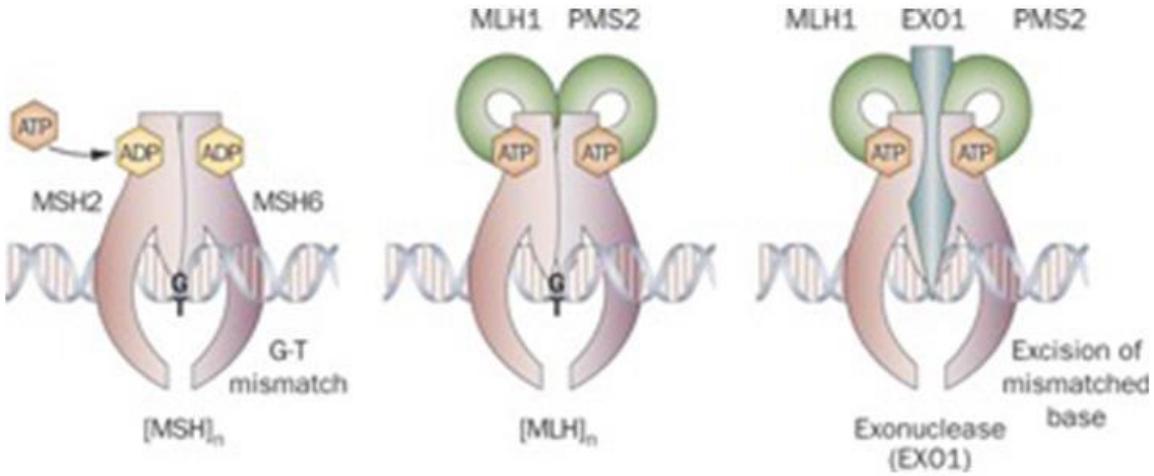
- **Colorectal**
- **Endometrial**

Other less frequent cancers:

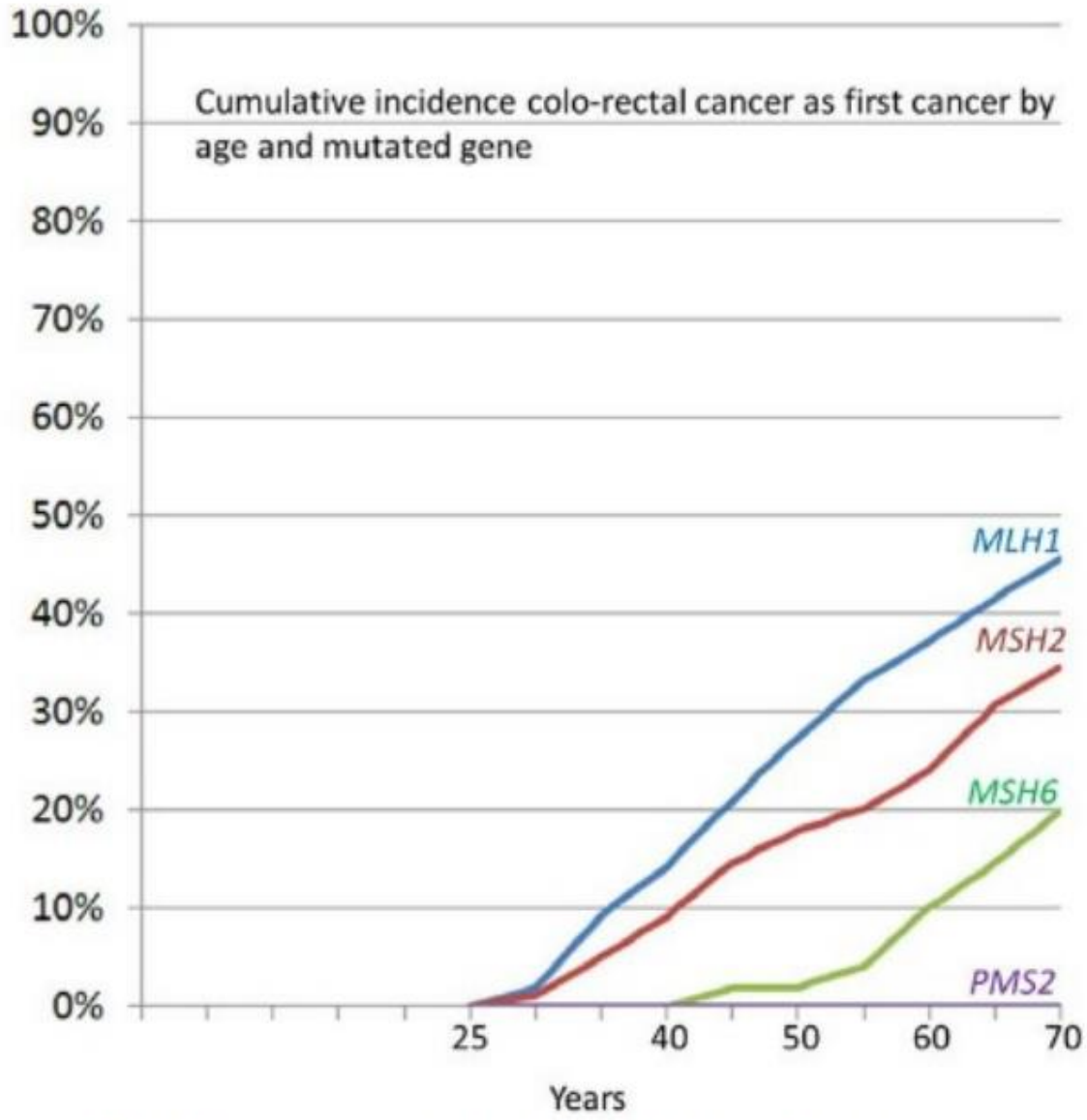
- Ovarian
- Urinary tract
- Gastric
- Small intestine
- Hepato-biliary and pancreatic
- Sebaceous gland (and adenoma)
- Central Nervous System

Lynch syndrome is caused by germline pathogenic variants in one of four DNA Mismatch Repair (MMR) genes:

- *MLH1*
- *MSH2*
- *MSH6*
- *PMS2*
- *EPCAM :* which may inactivate *MSH2*



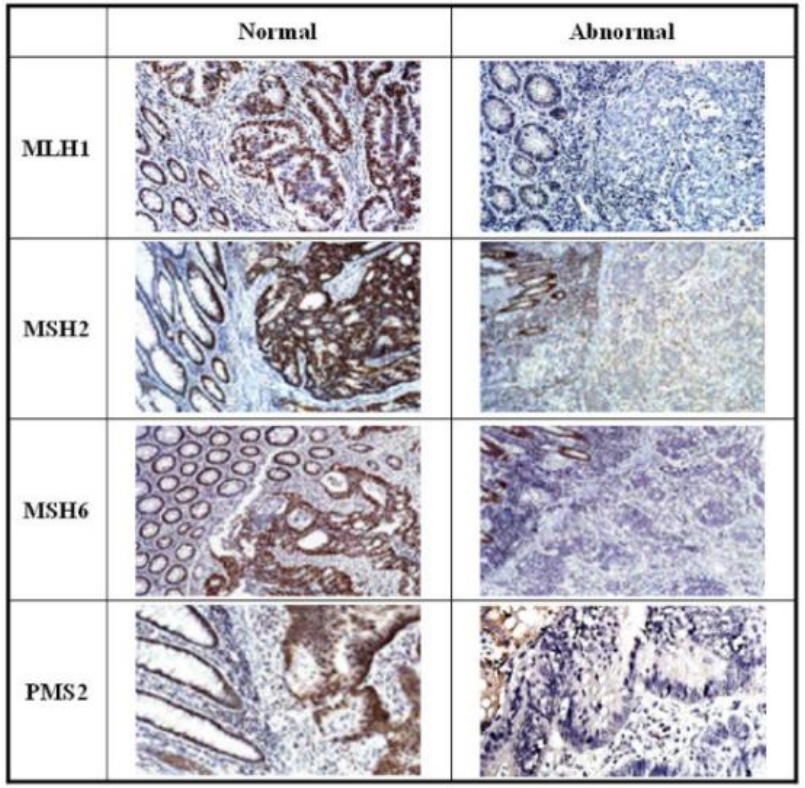
Cumulative colorectal cancers



Pål Møller et al. Gut 2017;66:464-472

Cancers due to LS are characterised by deficient MMR (dMMR), which usually manifest as:

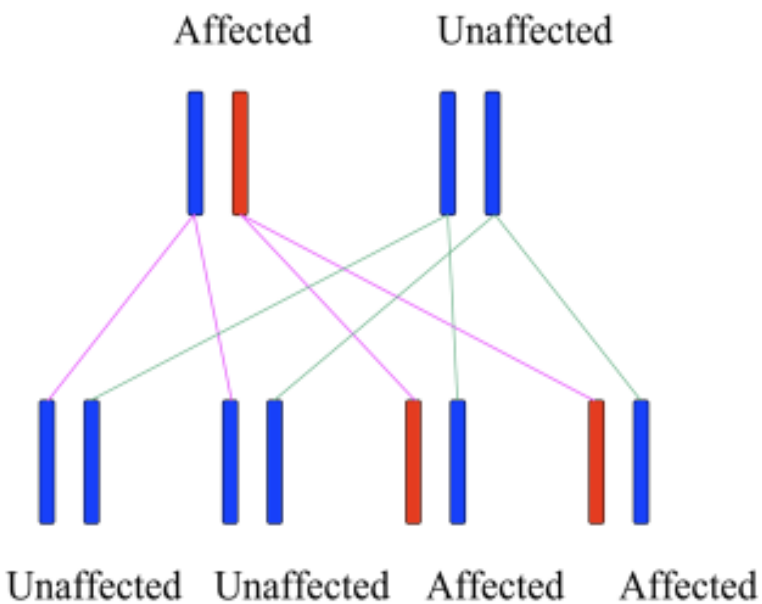
- Microsatellite instability (MSI)
- Loss MMR protein expression on immunohistochemistry (IHC)



IHC stains: Samples stained with antibodies for MLH1, MSH2, MSH6 and PMS2

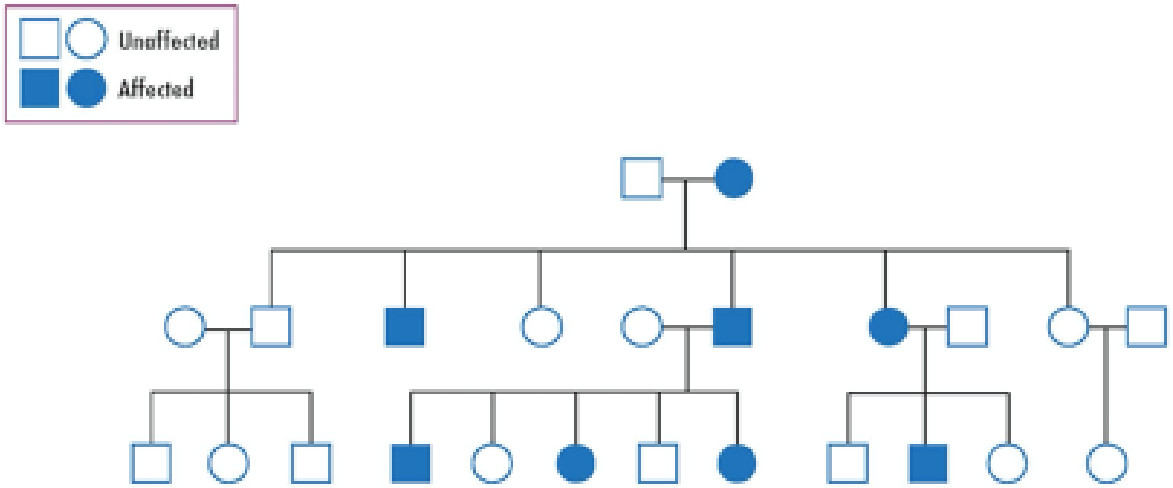
https://www.researchgate.net/figure/Immunohistochemical-IHC-stains-for-MLH1-MSH2-MSH6-and-PMS2-proteins_fig2_51195594

AUTOSOMAL DOMINANT INHERITANCE



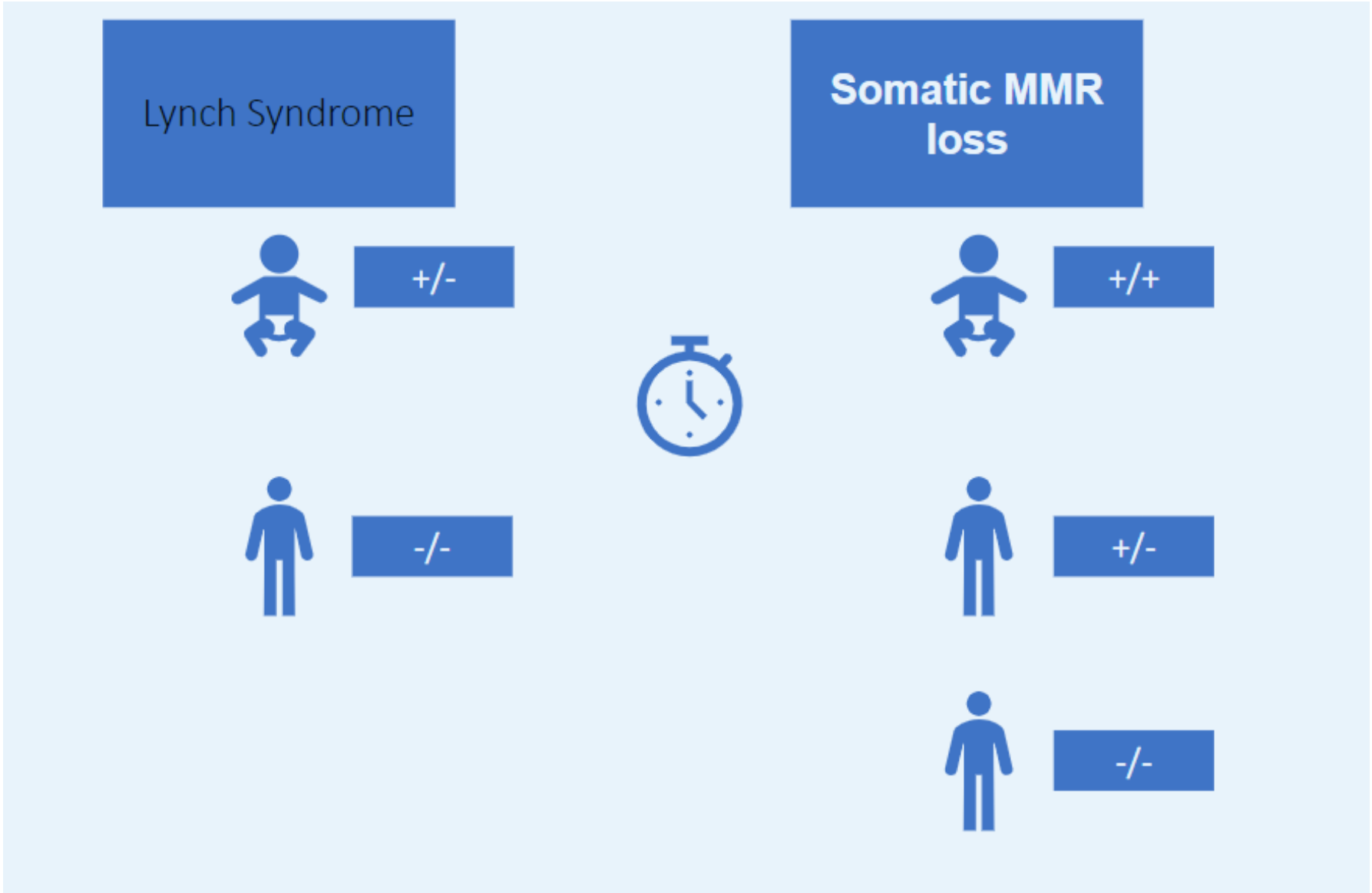
- One normal copy of a gene and one with a gene variant (mutation).
- Offspring at 50% risk.

AUTOSOMAL DOMINANT



Characteristics of Autosomal Dominant Inheritance

- Multiple generations are affected.
- Males and females are equally likely to be affected.
- Male to male transmission occurs.
- Each offspring of an affected parent has a 50% chance of being affected and a 50% chance of being unaffected.


Lynch Syndrome
+/-
-/-
Somatic MMR loss
+/+
+/-
-/-

Lynch Syndrome: Expert Consensus Recommendations October 2016

- The development of a national Lynch Syndrome registry
- A Quality assured surveillance programme for L.S patients
- A dedicated clinical champion for hereditary CRC within every colorectal MDT

Lynch Syndrome – NHS National Plan

- 2017 NICE guideline DG27 recommend all colorectal cancers tested for MMR proteins deficiency (by IHC or MSI)
- 2020 NICE guideline DG42 for endometrial cancers

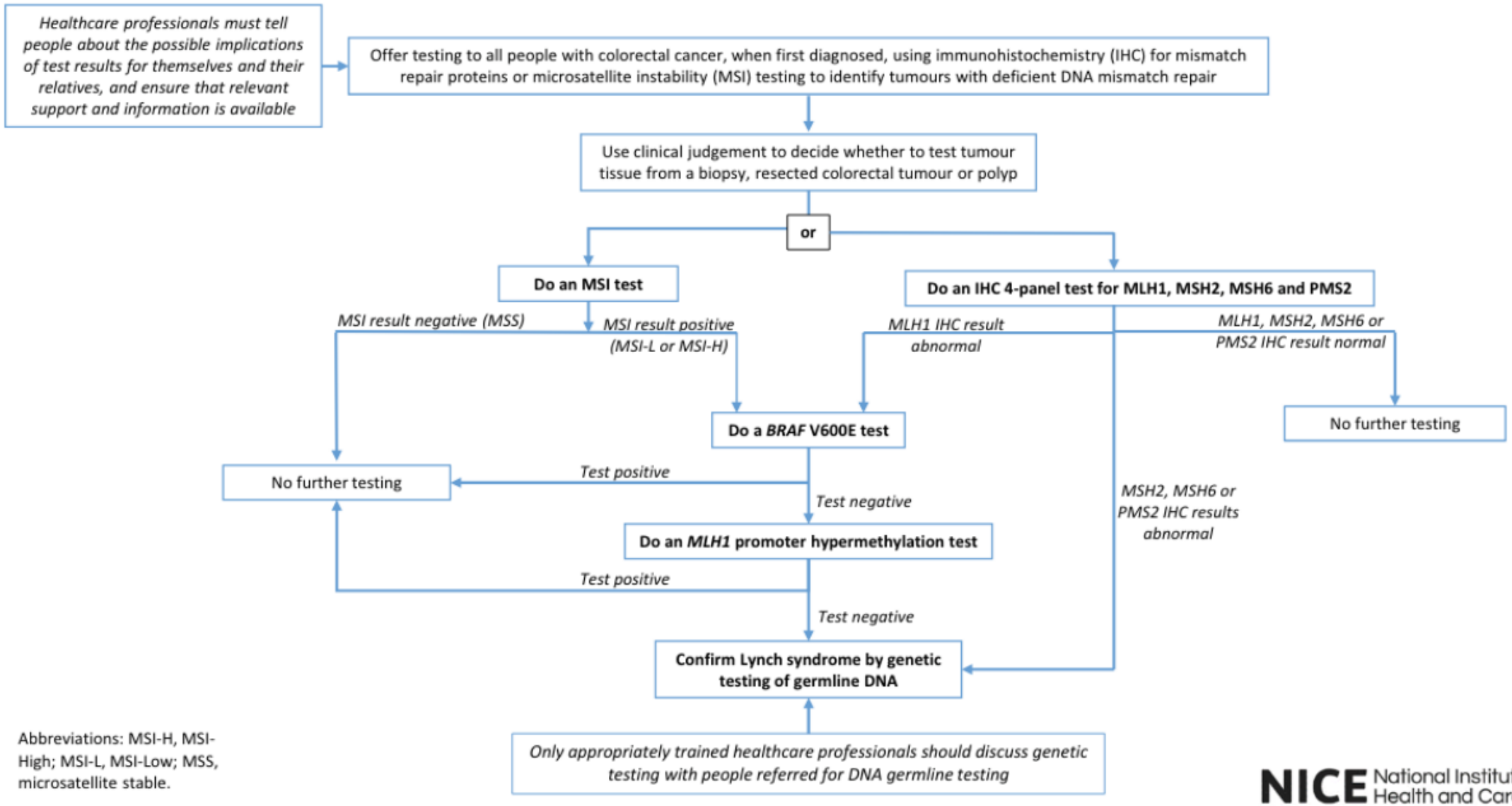
- NHS Long Term Plan 2019 stated more people to have cancers identified at an early stage (75% by 2028)

- NHS Planning and Contracting Guidance for 2020/21 included the L.S pathway and as such it has been identified as a priority for the Cancer Alliances and the GMSAs

The Case for Change

- Estimated 175,000 people have L.S in the UK but only around 5% get diagnosed
- Genetic testing for L.S is only being done in 25% of eligible cases
- Good results using immunotherapeutics in MMR deficient tumours
- Low cost interventions reduce the cancer risk in Lynch syndrome
    - Aspirin
    - Weight loss
    - Stopping smoking
    - Surgery – bowel resection, hysterectomy, oophorectomy
    - Surveillance – colonoscopy, pilot for urothelial cancer in Newcastle

Pathway for Testing for Lynch Syndrome using IHC



Abbreviations: MSI-H, MSI-High; MSI-L, MSI-Low; MSS, microsatellite stable.

NICE National Institute for Health and Care Excellence

R210 Inherited MMR deficiency (Lynch syndrome)

Testing Criteria

All new diagnoses of colorectal and endometrial cancer should have tumour MSI / IHC as outlined in the cancer test directory and the Lynch syndrome handbook for Alliances in order to identify dMMR tumours

1. **Clinical Criteria for germline testing in an affected individual**
   a. The proband has a dMMR tumour where results of BRAF and/or MLH1 hypermethylation testing suggest Lynch syndrome
   b. The proband is diagnosed with colorectal cancer ≤ 40 , irrespective of the dMMR status of the tumour
   c. The affected proband comes from a modified Amsterdam criteria positive family irrespective of the dMMR status of the tumour
   d. (Wimmer score =>3)

What is happening now

- Colonoscopy via National Bowel Screening program from April 2023
- Lynch Champion in every CRC and Gynae MDT
- Immunohistochemistry at biopsy to test for MMR protein deficiency on every patient with CRC or endometrial cancer regardless of age at diagnosis
- Genetic testing for Lynch syndrome in all eligible patients

Resources for Primary Care

Lynch Syndrome online training for primary care clinicians - RM Partners

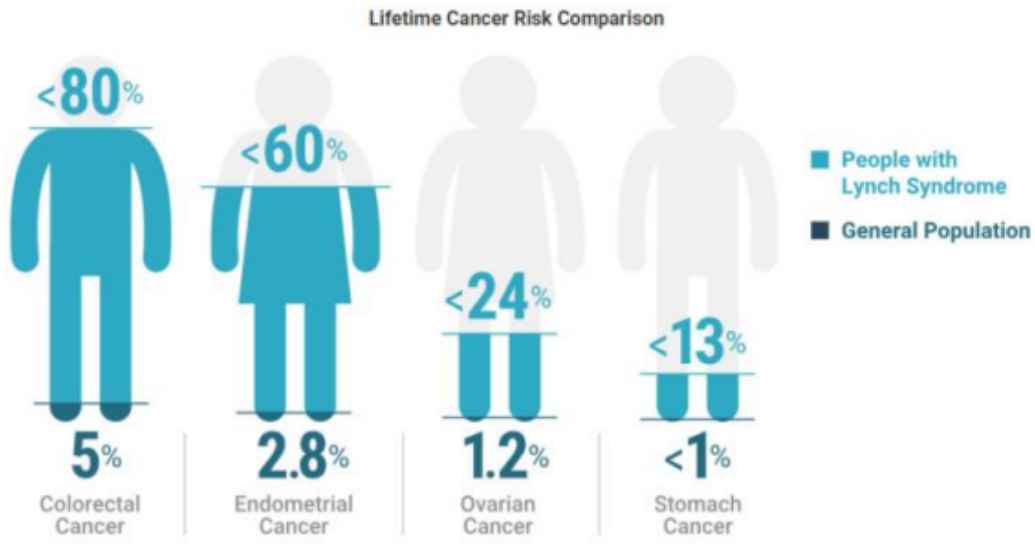
www.plsd.eu Prospective Lynch Syndrome Database

UKCGG leaflets and guidelines - Cancer Genetics Group Cumulative risks, Management Guidelines and Gene specific management recommendations

Lynch syndrome quick guide for Primary Care clinicians

Recommendations for Lynch syndrome patients & their family

Lynch syndrome is a cancer predisposition syndrome in which the main concerns are **colorectal** and **endometrial** cancer. There is also a risk of other cancers, although less frequently.



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Highest Risk
Colorectal
Endometrial

Increased Risk
Ovarian
Urinary tract
Gastric
Small intestine
Hepato-biliary
Pancreatic
Sebaceous gland
CNS

Coding Lynch syndrome as a 'problem' in the primary care record (this information is not considered within insurance applications as per ABI code of Genetic testing and Insurance)
Colonoscopy every 2 years: Chromoendoscopy (with dye spray) is the preferred choice - From the age of **25** for pathogenic variants in ***MLH1, MSH2*** or ***EPCAM*** genes - From the age of **35** for pathogenic variants in ***PMS2*** and ***MSH6*** genes
We recommend a ***low threshold for investigations*** if your patient present with symptoms which could be

For now most specialised centres recommend 150 mg daily for individuals with average weight, and 300 mg for individuals with BMI above 30
One-off screening for Helicobacter pylori: Eradication may reduce the risk of gastric cancer by half
Gynaecological surveillance: Currently there is limited evidence about the utility of gynaecological surveillance for early detection of endometrial and ovarian cancer Risk reducing surgery is offered because there is no effective screening test. However, this should be a personalised decision, generally offered from the age of 40, once they have completed their families, taking into consideration their risk factors, genetic mutation, personal preferences and quality of life Consider referral of women around the age of 40 for a discussion about surgery
Family planning for pathogenic variant carriers: Consider referral to clinical genetics for a discussion about embryo selection
First degree relatives (parents, siblings & children): Referral may be discussed from the age of 18, ideally prior the age at which screening commences We recommend a ***low threshold for investigations*** if relatives present with symptoms which could be associated with LS, regardless of age If the familial pathogenic variant is ***MLH1, MSH2 or EPCAM*** and the unaffected relative is **>25y** and declines genetic testing, refer to specialised centre for colonoscopy – 2 yearly If the familial pathogenic variant is ***PMS2 or MSH6*** and the unaffected relative is **>35y** and declines genetic testing, refer to specialised centre for colonoscopy – 2 yearly

Aspirin [NICE 2020]

- CAPP2 study clear reduction (50%) in colorectal cancer
- Age 25-65y

NNT 25 pt on 600mg aspirin to prevent 1 CRCa over 15yrs (and beyond)

- CAPP3 study underway to work out dose
- Why? Some of the CRCA are denova (they don't come from an adenoma, aspirin thought to reduce the risk in the colonoscopy screening interval)
- **STOPPING?** Fatal GI bleed risk 1:1000 by age 80y, so risk outweighs the benefits, and believed ongoing benefit of previous aspirin course

Lynch syndrome: should I take aspirin to reduce my chance of getting bowel cancer?

Patient decision aid

What is the option?

Having Lynch syndrome means you are more likely to get certain cancers, including bowel cancer. Taking aspirin every day can help reduce your chance of getting bowel cancer. **There are pros and cons to taking aspirin**. This decision aid can help you and your healthcare team decide together if taking aspirin is right for you. It's important to talk to your GP or specialist care team if you are thinking about taking aspirin, because it's not suitable for everyone.

How likely am I to benefit?

If you take aspirin you are less likely to get bowel cancer, although some people will get bowel cancer even if they take aspirin. The diagrams on page 3 show the results of a study in people with Lynch syndrome. This looked at the effect that taking aspirin for 2 to 4 years had on the chance of getting bowel cancer, compared with taking a dummy tablet. The protective effect wasn't seen straightaway, but it continued for many years after people stopped taking aspirin.

Regular colonoscopies, to spot cancers early if they develop, are recommended for people with Lynch syndrome whether they take aspirin or not. Your specialist team will tell you what other things you can do to reduce your risk of bowel and other cancers.

It is not possible to know in advance what will happen to any one person.

What are the possible side effects of aspirin?

The most common side effects include indigestion, bruising more easily and cuts taking longer to stop bleeding. Between 1 and 10 people in every 100 get these side effects (so 90 to 99 people in 100 do not). Less commonly, aspirin can cause ulcers in the stomach and small bowel, but there are no reliable figures on how often this happens.

More rarely, aspirin can cause major bleeding in the gut: between 1 and 10 people in 10,000 get this (so 9,990 to 9,999 people in 10,000 do not). Aspirin can also make a type of stroke known as haemorrhagic stroke (bleeding inside the brain) worse if it happens. Other rare side effects have also been reported occasionally. There is more information about these in the leaflet that comes with the medicine.

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Other things to think about

- **Aspirin is most likely to make a difference to your chance of getting bowel cancer if you take it every day for at least 2 years.**
- The older you are, the more likely you are to get side effects.
- Aspirin may not be suitable for you if you have certain other conditions, for example if you have stomach ulcers or bleeding problems now or have had them in the past, or if you have had allergic-type reactions to similar medicines.
- For pregnant women:
  - There is no good evidence that aspirin causes harm to the baby in early pregnancy when taken at lower doses, or at higher doses taken short term.
  - There is not much evidence about taking aspirin at higher doses long term in pregnancy.
  - **Talk to your healthcare team before taking aspirin after 30 weeks of pregnancy.**
- Aspirin is not recommended if you are breastfeeding.
- Manufacturers have not applied for a licence to cover using aspirin to reduce the chance of getting bowel cancer, so this would be an 'off-label' use. That's why it is not mentioned in the leaflet that comes with the medicine.
  (There is more information about licensing of medicines at www.nhs.uk.)
- Aspirin has not been shown to reduce the chance of getting other cancers linked to Lynch syndrome.

There are still some things that are not known about taking aspirin to reduce the chance of bowel cancer if you have Lynch syndrome:

- It is not known how long aspirin should be taken for (in the study described on page 3, people took aspirin for 2 to 4 years). There is some evidence that the benefits increase the more years you take aspirin.
- The possible harms from taking higher doses of aspirin for many years are not certain.
- The best dose of aspirin to take is not known:
  - A study comparing different doses is going on at the moment, but it will be several years before the results are known.
  - In the study described on page 3, people took 600 mg aspirin per day. This is much higher than the dose of aspirin used long term in other conditions.
  - The higher the dose, the more likely you are to get side effects. But a lower dose might not work so well at reducing the chance of bowel cancer.

  Talk to your healthcare team about the best dose for you.

The NICE website has information about how this decision aid was produced and the evidence it is based on.

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Effect of aspirin on the chance of getting bowel cancer: results of the CAPP2 study

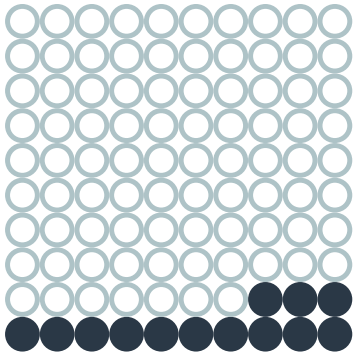
The CAPP2 study was carried out in people with Lynch syndrome. It compared taking aspirin (600 mg every day) with taking a dummy tablet.

People were followed up in the study for an average of 10 years.

The diagrams below show the number of people per 100 who got bowel cancer over that time.

Aspirin made most difference to the chance of getting bowel cancer in people who took it for at least 2 years, so only the effect for those people is shown here.

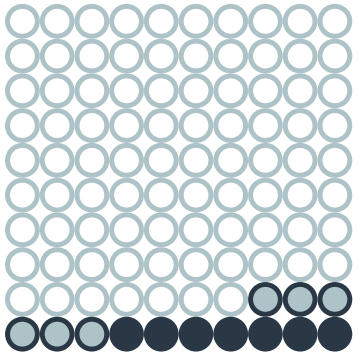
Bowel cancer among people who did not take aspirin



On average, for every 100 people who did **not** take aspirin, over 10 years:

- 87 people **did not** get bowel cancer
- 13 people **got** bowel cancer

Bowel cancer among people who took aspirin for at least 2 years



On average, for every 100 people who took aspirin for at least 2 years, over 10 years **93 people did not get bowel cancer**, but **7 people did**:

- 6 people **did not get** bowel cancer **because they took aspirin**
- 87 people **did not get** bowel cancer, but would not have done whether they took aspirin or not.
- 7 people **got** bowel cancer, even though they took aspirin.

It is not possible to know in advance what will happen to any one person

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Reducing stomach cancer

- One off test for Helicobacter Pylori
- Irradicate if found and 50% reduction in stomach cancer risk

- Added benefit of reduced risk of GI side effects from aspirin

Preventing Gynaecology Cancer in LS

- No effective screening – adhoc
- Gynae review every 1-2yr to discuss:
  - Red flag symptoms
  - Aspirin (50% reduction in endometrial Ca in CAPP2, power not high enough to recommend)
  - Contraception (LNG IUD)
- Risk reducing surgery (hysterectomy & bilateral salpino-oophorectomy)
  - Once family complete MLH1 or MSH2
  - Age 45y MSH6 or PMS2

Role of primary care

- Correct coding in healthcare records
- Helicobacter Pylori test & treat
- Aspirin – use decision aid tool
- Ensure on BCSP register if new registration
- Consider appropriate genetic counselling for family planning
- Consider risk reducing surgery
- **Low threshold** to investigate and refer – think other cancers…..

..take home message….

- Only 5% know they have the defective gene
- High risk of cancer (colorectal, endometrial…)
- Variable penetration
- Cancer risk can be reduced by
  - Colonoscopy screening
  - Aspirin
  - Risk reducing surgery
  - Low threshold to investigate