Lynch Syndrome

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Overview

- What is Lynch Syndrome
- Genetics and inheritance
- Cancer Risks
- Management of cancer risks
- Reproductive options
- Research and future directions

Lynch Syndrome

(also known as Hereditary Non-Polyposis Colorectal cancer – HNPCC)

Characterised by an increased risk of certain cancers:

- **Colorectal**
- **Endometrial**
- Ovary
- Stomach
- Small intestine
- Hepatobiliary tract
- Urinary tract
- Brain
- skin

Genetics

Lynch occurs due to alterations in DNA repair genes involved in mismatch repair

- MLH1 - 50%
- MSH2 - 40%
- MSH6 - 7-10%
- PMS2 - <5%
- EPCAM - 1-3%

Mismatch Repair (MMR)

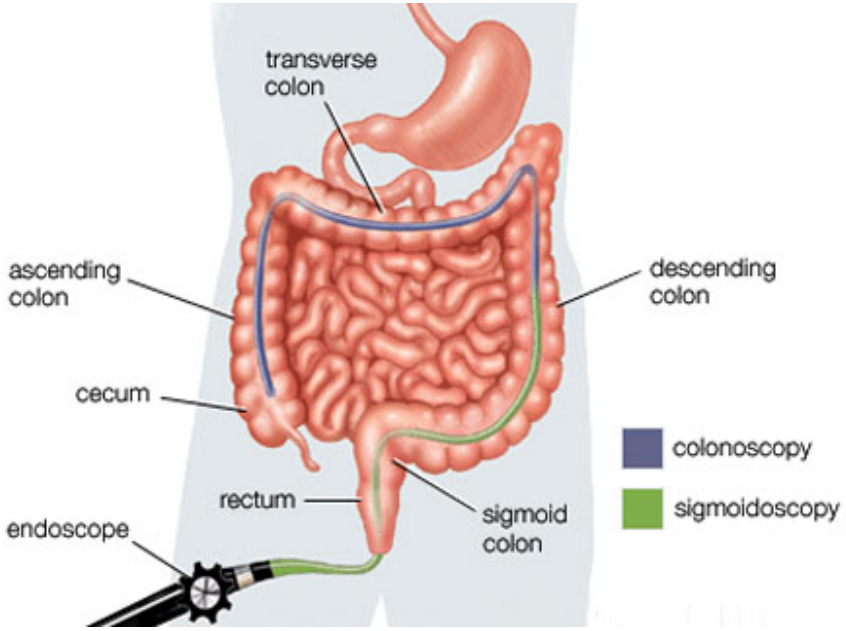
Lynch Syndrome

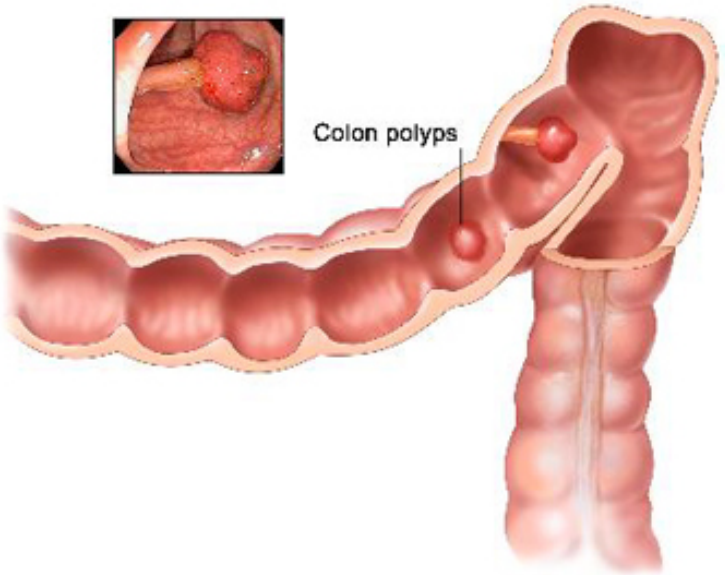
- The most common hereditary colorectal cancer (CRC) predisposing syndrome.
- 3% of CRC arise due in patients with Lynch
- Frequency estimated to be 1 in 440
- Lynch only explains about 10-25% of familial CRC
- Important to identify as has implications for the family

Lynch and Bowel Cancer

- Risk of Bowel cancer 50-80% mean age 44-61yrs in MLH1 and MSH2 mutation carriers
- Risk in MSH6 mutation carriers is 20-40%
- Risk in PMS2 mutation carriers is 15-20%
- 2/3 bowel cancer occur in the proximal colon
- When matched for stage, Lynch bowel cancers have a better prognosis than non-lynch bowel cancers
- Increased chance of developing a second bowel cancer therefore bowel cancers treated with full colectomy

Bowel Surveillance





Bowel surveillance

- Usually begins from 25 years, can be earlier depending on family history
- Colonoscopy every 2 years
- This reduces the incidence of bowel cancer

Endometrial cancer

- 2% of all endometrial cancers are due to Lynch syndrome
- Up to 60% lifetime risk in MLH1 and MSH2 mutation carriers
- Studies based on high-risk families have estimated the mean age of onset to be 48yrs
- Although bowel cancer risks lower in MSH6 and PMS2 mutation carriers, endometrial cancer risks similar to those seen in MLH1 and MSH2 mutation carriers
- Better prognosis than for non-Lynch endometrial cancers

Endometrial Surveillance and Risk-reducing surgery

- Many cancers detected through reporting of symptoms
- Evidence regarding whether pipelle biopsy and transvaginal ultrasound surveillance improves outcome are conflicting
- Patients can be referred for these investigations on an annual basis from 40 years
- Risk-reducing hysterectomy (and removal of ovaries) has been shown to be effective in significantly reducing the risk of endometrial and ovarian cancers
- Surgery is performed once a woman has completed her family, usually around the age of 40 years

Ovarian Cancer

- Lifetime risk in MLH1 and MSH2 mutation carriers 4-12%
- No specific risk estimates in MSH6 or PMS2 mutation carriers
- Mean age of onset is 42yrs
- Surveillance has not been proven to improve outcome
- Risk-reducing surgery – removal of ovaries recommended from 40yrs at the time of hysterectomy

Gastric Cancer

- Lifetime risk 6-13%
- Greatest risk seems to be in men with a MSH2 mutation
- Mean age of diagnosis is 56 yrs
- In families with a history of gastric cancer surveillance with upper GI endoscopy can be considered from 30yrs every 2-3yrs but evidence that this is effective is limited therefore not routinely recommended

Cancer risks in Lynch syndrome

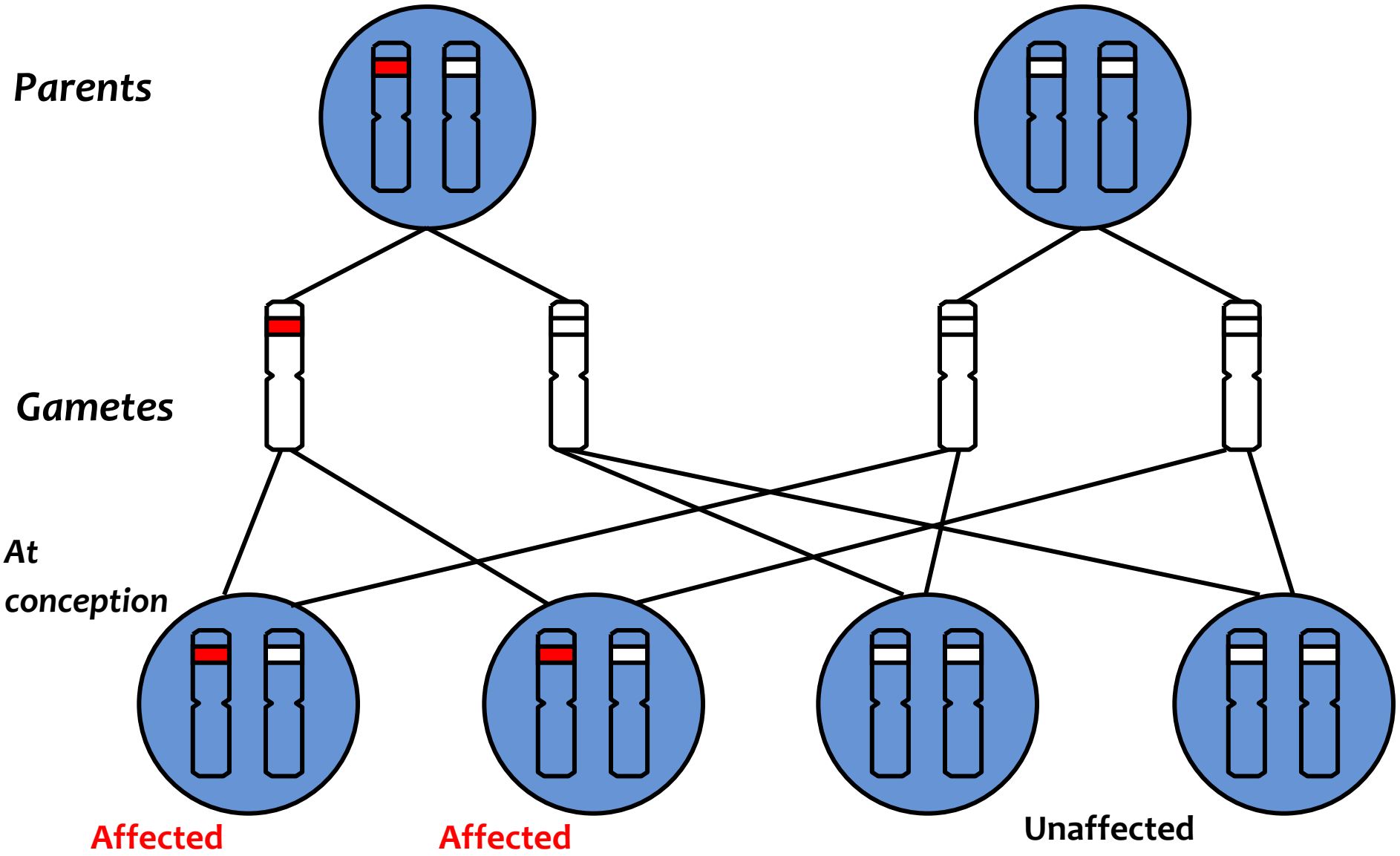
Cancer Type	Risk in MLH1 and MSH2 mutation carriers	Mean age of onset	Population risk
Colon	50-80%	44-61 yrs	5.5%
Endometrial	25-60%	48-62 yrs	2.7%
Stomach	6-13%	56 yrs	<1%
Ovary	4-12%	42.5 yrs	1.5%
Hepatobiliary	1.4- 4%	-	<1%
Urinary Tract	1-4%	55yrs	<1%
Small bowel	3-6%	49yrs	<1%
Brain	1-3%	50yrs	<1&
Sebaceous neoplasms	1-9%	-	<1%

Surveillance for other cancers

- Small bowel – upper GI endoscopy or capsule endoscopy every 2-3yrs from 30yrs to be considered
- Urinary tract – annual urine analysis from 30yrs to be considered

Evidence that the above strategies are useful is limited therefore not routinely performed but considered in those with a strong family history of these types of cancer.

Autosomal dominant inheritance



Autosomal Dominant inheritance

- Every child of a parent with Lynch syndrome has a 50% chance of inheriting the mutation
- This chance is not affected by whether the child is male or female
- If a child has not inherited the mutation they will not pass it on to subsequent generations
- Carrying a mutation means the individual has a significantly *increased* risk of cancer but does not mean that they *will* develop cancer

Other important issues relating to Lynch syndrome

- Cancer risks in adulthood therefore do not usually offer genetic tests to children
- Reproductive options
- Sharing information with family members

Research Studies

- COGS2
- IMPACT
- CAPP

Summary

- Lynch syndrome gives rise to increased risks of bowel and endometrial cancers as well as some other cancers
- If a parent has Lynch there is a 50% chance that each child will inherit the mutation which has caused the condition
- It is beneficial to know that cancers in a family have occurred due to Lynch as this allows a better assessment of cancer risks and the utilisation of strategies to reduce cancer risk