Lynch syndrome

Key facts

- Lynch syndrome (hereditary non-polyposis colorectal cancer (HNPCC)) is an autosomal dominant, inherited cancer predisposition syndrome that causes individuals to have a high lifetime risk of colorectal cancer.
- Women with Lynch syndrome also have a high lifetime risk of endometrial cancer, and an increased lifetime risk of developing ovarian cancer.
- Lynch syndrome occurs due to the inheritance of an alteration in one of the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*).
- Immunohistochemistry staining of the tumour tissue for mismatch repair proteins can help to identify tumours that occur due to Lynch syndrome (through abnormal staining), facilitating diagnosis of Lynch syndrome in individuals and families.
- Lynch syndrome tumours also show microsatellite instability (MSI) when a mismatch repair gene is not working properly. Testing tumour tissue for MSI can also be useful in diagnosing the condition.
- Frequent colonoscopy screening (every two years) improves survival by identifying colorectal cancers at an early stage, and by identifying and removing adenomas which may otherwise grow and develop into invasive cancers.

Clinical features

- A high lifetime risk of developing colorectal cancer (up to 68%), often at younger ages than usual.
- An increased lifetime risk of developing endometrial cancer (up to 62%), and ovarian cancer (up to 39%) in women.
- A slight increase in lifetime risk for other tumours, including upper gastrointestinal tract (stomach, small bowel, bile duct, gallbladder and pancreatic cancer), kidney, urinary tract, and brain cancer.
- Polyps (non-cancerous growths or adenomas) can develop, but not usually in high numbers (distinct from polyposis syndromes, such as FAP or MYH polyposis).
- The following are clinical clues that suggest Lynch syndrome may be present in a family:
  - Several relatives with colorectal cancer (usually 3 or more) on the same side of the family, usually across more than one generation.
  - Several relatives on the same side of the family with a combination of colorectal, endometrial and ovarian cancer.
  - Colorectal cancer occurring at a younger age than usual (often below the age of 50).
  - An individual developing more than one primary colorectal cancer, or a combination of colorectal, endometrial and ovarian cancer.

Diagnosis

- Careful assessment of family history is important to determine the likelihood of Lynch syndrome and to consider other bowel cancer predisposition syndromes, such as FAP and MYH polyposis.
- Diagnosis usually involves two steps: tumour tissue testing and genetic testing.

- Tumour tissue testing (immunohistochemistry or microsatellite instability testing) may be carried out initially to determine whether there is impaired mismatch repair function in a tumour, particularly where there is limited family history. Impaired mismatch repair is suggestive of Lynch syndrome but also occurs in 15-20% of sporadic tumours, so is not unique to Lynch syndrome.
- If tumour tissue testing results suggest Lynch syndrome is likely, a genetic test for variants in the mismatch repair genes may be offered.

Genetic basis and genetic testing

- Lynch syndrome is caused by a variant in one of the mismatch repair genes: *MLH1*, *MSH2*, *MSH6* or *PMS2*.
- These genes have an important role in the repair of DNA damage (base mismatches). Defects in mismatch repair lead to the accumulation of DNA damage across the genome, causing cancers to develop and progress.
- The risks of developing particular cancers and penetrance of Lynch syndrome are variable. There is some variability between the genes involved. *MSH6* variants appear to confer a higher probability of developing endometrial cancer, but a lower probability of developing bowel cancer. The overall probabilities of developing cancer are generally considered lower for *PMS2* variants.
- Lynch syndrome is inherited in an autosomal dominant manner. This means that a variant in one copy of a gene pair is sufficient to cause an increased risk of cancer. Each child of an individual with Lynch syndrome has a 50% (one-in-two) chance of inheriting the gene variant and also having Lynch syndrome.
- Individuals who have inherited variants in both copies of a mismatch repair gene (and are homozygous or compound heterozygous for variants in a mismatch repair gene) have been described, but these occurrences are rare. These individuals have a distinct presentation, with a high probability of developing colorectal cancer, leukaemia, brain tumours and other cancers developing in childhood. This usually occurs because both parents have Lynch syndrome.
- Laboratory analysis of *MLH1*, *MSH2*, *MSH6* and *PMS2* is widely available, and is carried out through a combination of sequencing and tests to look for larger deletions and duplications.
- Initial testing in an affected family member is preferable to determine whether the cancers are related to Lynch syndrome, and to identify the specific family variant.
- Once a specific gene variant has been identified in a family, predictive genetic testing can then be offered to at-risk relatives to identify those who carry the variant, and would therefore benefit from screening.

Clinical management

- Regular colonoscopy (every two years) usually from the age of 25 onwards for those with Lynch syndrome or at 50% risk (if testing not possible or declined) enables cancers to be detected at an early stage, and adenomas to be identified and removed.
- Continued surveillance of remaining bowel tissue is important for those who have developed colorectal cancer, as there is an increased risk of further cancers.
- It is important that women are aware of the symptoms of endometrial and ovarian cancer, and seek advice if they experience unusual vaginal bleeding or discharge, abdominal pain, discomfort or bloating, back pain or constipation.
- A total hysterectomy with bilateral salpingo-oophorectomy (BSO: surgical removal of the uterus, ovaries and fallopian tubes) is offered to most women with Lynch syndrome. This surgery significantly reduces the risk of developing endometrial and ovarian cancer. Women with a *PMS2* gene variant may be advised to have only the uterus removed and not the ovaries because their ovarian cancer risk is not thought to be greatly increased.

- There is currently no proven, effective screening for endometrial, ovarian or other Lynch syndrome-related cancers. However, screening for ovarian cancer may be available privately in some areas.
- There is mounting evidence that low dose, enteric-coated aspirin for over two years can reduce the lifetime risk of bowel cancer for those with Lynch syndrome, and may be recommended for those without contraindications.

Further reading and patient groups

- Lynch Syndrome UK
- Bowel Cancer UK
- MacMillan Cancer Support: Lynch syndrome
- Lynch syndrome gene specific guidelines, UK Cancer Genetics Group

This information is intended for educational use and was current in June 2020. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and University Hospitals Bristol NHS Foundation Trust's Clinical Genetics department.