When to refer a patient with a personal or family history of cancer to Clinical Genetics

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WCGS Wessex Clinical Genetics Service

Referral Guidelines

- https://www.uhs.nhs.uk/departments/genetics/for-health-professionals-the-referral-process/cancer-genetics
- Fulfilling the referral criteria does not mean a patient will be seen in the Genetics Clinic
- Referrals should be made via E-referral system. Please always include completed family history questionnaire with any cancer genetics referral

Date .....

Wessex Clinical Genetics Service
Princess Anne Hospital
Coxford Road
Southampton
SO16 5YA
Tel: 023 8120 6170
Fax: 023 8120 4346
www.uhs.nhs.uk/genetics

FAMILY HISTORY ENQUIRY FORM

This form MUST be accompanied by a referral from a healthcare professional.

Please complete this form, giving as much information as possible. If there is any information you do not know, leave that box empty. All the information you give will be kept as part of your clinical NHS record, and will be treated as confidential information.

- Please let us know the details of your family members as requested on the form. We would like to know about both relatives with and without cancer. This can be very important in assessing your chances of developing cancer.
- If you do not know the exact dates of birth and/or death, or where the person was treated is not known, then please put approximate dates and ages and whereabouts in the country the person lived.
- Please indicate whether a person is male or female since it can be difficult to know for certain names.

Please return your questionnaire as soon as possible in order for us to process the information and get back to you or your health professional. If you are unable to complete all the sections, please still return the form.

Name ……	**Date of birth** ……..
Previous surnames……	**GP Name**……
Address ……..	**GP Address**……
……	……
……	……
Tel No: ……	**Email:**……

We may contact you by phone if we need further details. We will not disclose where we are calling from to anyone apart from yourself, without your permission:

- I am happy for you to disclose where you are calling from should someone other than myself answer the phone YES / NO
- I would prefer to receive a letter from you, asking me to call the department, should you need any further details. □

If you know of anyone else in your family who has been seen by another Genetics Service or referred to Wessex Clinical Genetics Service, it would be helpful to provide some details here:

Name: ..... Date of birth:.....

Genetics Service where seen: .....

Other information if known……...

1. Relative	**Name** (including maiden and any previous names)	Date of Birth	Alive Y/N	Date of death	If your relatives suffered from cancer ……. Where cancer occurred	Age when cancer found	Hospitals where treated (+name of specialist if known)
You							
Your Own Children							
Your sisters full or half (if half, please state through mother or father)							
Your brothers full or half (if half, please state through mother or father)							
Your mother							
Your father							

Some types of inherited cancer are more common in Jewish families. Are you or any of your immediate family Jewish? Yes No

Please complete this section if you are female and have a family or personal history of breast or ovarian cancer

- At what age did your periods start? ……..
- At what age did you go through menopause? ……(if appropriate)
- Are you taking the contraceptive pill? Yes ☐ No ☐
- For how many years of your life have you been on the contraceptive pill (if at all)? ……...
- Are you taking Hormone Replacement Therapy (HRT)? Yes ☐ No ☐ If yes for how long?…….
- Have you ever had any problems with your breasts other than cancer? If so please describe the nature of this, including dates, hospital and names of specialists seen.

If you have had cancer, please give details including dates, hospital and names of specialists seen and any medication.

Please feel free to use a separate sheet of paper if you wish.

Have you had/do you have **any major illnesses** (excluding cancer) **or surgery**? Please give details including dates, hospital and names of specialists seen and any medication.

Please feel free to use a separate sheet of paper if you wish.

What are your **main questions** that you would like to discuss with the genetics service?

University Hospital Southampton NHS Foundation Trust

Wessex Clinical Genetics Service

Personal History of Cancer

Colon cancer

An individual with:

- colorectal cancer diagnosed at any age that has loss of mismatch repair proteins (MMR) on immunohistochemistry (IHC)*
- colorectal cancer diagnosed under 40 years (irrespective of MMR IHC status) *
- a parent, sibling or child diagnosed with colorectal cancer under 50 years
- two close relatives with colorectal cancer diagnosed under 60 years
- three close relatives with colorectal cancer diagnosed under 70 years
- a close relative with colorectal cancer diagnosed under 50 years AND a family history of endometrial, ovarian, urothelial, gastric or hepatobiliary cancer
- a diagnosis of or family history of a high-risk susceptibility condition, for example: Familial Adenomatous Polyposis (FAP), MutYH Associated Polyposis (MAP), Juvenile Polyposis, Peutz Jeghers syndrome, Lynch syndrome
- 10 or more colorectal adenomas

Guidelines for colorectal screening for moderate and high-risk groups: https://www.bsg.org.uk/wp-content/uploads/2019/12/Guidelines-for-the-management-of-hereditary-colorectal-cancer.full_.pdf

Family History of Cancer

- **In most cases, genetic testing needs to start in an affected family member**. If an affected family member is available, we recommend they are referred to their local genetics service in the first instance
- We may still make screening recommendations for unaffected individuals but are less likely to see them in clinic
- In some cases, we may organise testing on tissue samples from deceased relatives.
- Testing an unaffected individual is more likely to generate uncertain results

For Lynch (R210 testing) and polyposis gene panel (R211) see: https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-inherited-disease-eligibility-criteria-version-5.2.pdf

Known Genetic Variant in Family

- If there is a known genetic variant in the family, we can offer predictive genetic testing
- If available, include information about the individual who has been diagnosed with an inherited predisposition to cancer in the referral
- Often patients will be given a letter from their relative's genetics service

University Hospital Southampton NHS Foundation Trust

WCGS Wessex Clinical Genetics Service

TWIMC letter

Dear Relative

Re: Your family WCGS ref Gxx

Identification of a Lynch gene alteration
A member of your family has a genetic condition that causes an increased risk of cancer. Blood relatives could have inherited the same gene alteration and this letter is to advise them about the gene alteration and what further action should be taken.

What effect does the gene alteration have?
This gene alteration in your family causes a condition called Lynch syndrome. Individuals who have this condition have an increased risk of developing certain cancers, especially cancers of the bowel and in women, of the uterus. A gene carrier has a 1 in 2 chance of passing this on to their children and both men & women can inherit the gene alteration.

What action should I take?
Genetic testing can tell you whether you might benefit from extra medical checks or other measures to reduce your cancer risk. If you would like to find out more please ask your family doctor to refer you to your regional genetics service. Do contact us directly if you have any difficulty obtaining a referral.

Yours sincerely

cc our patient xx

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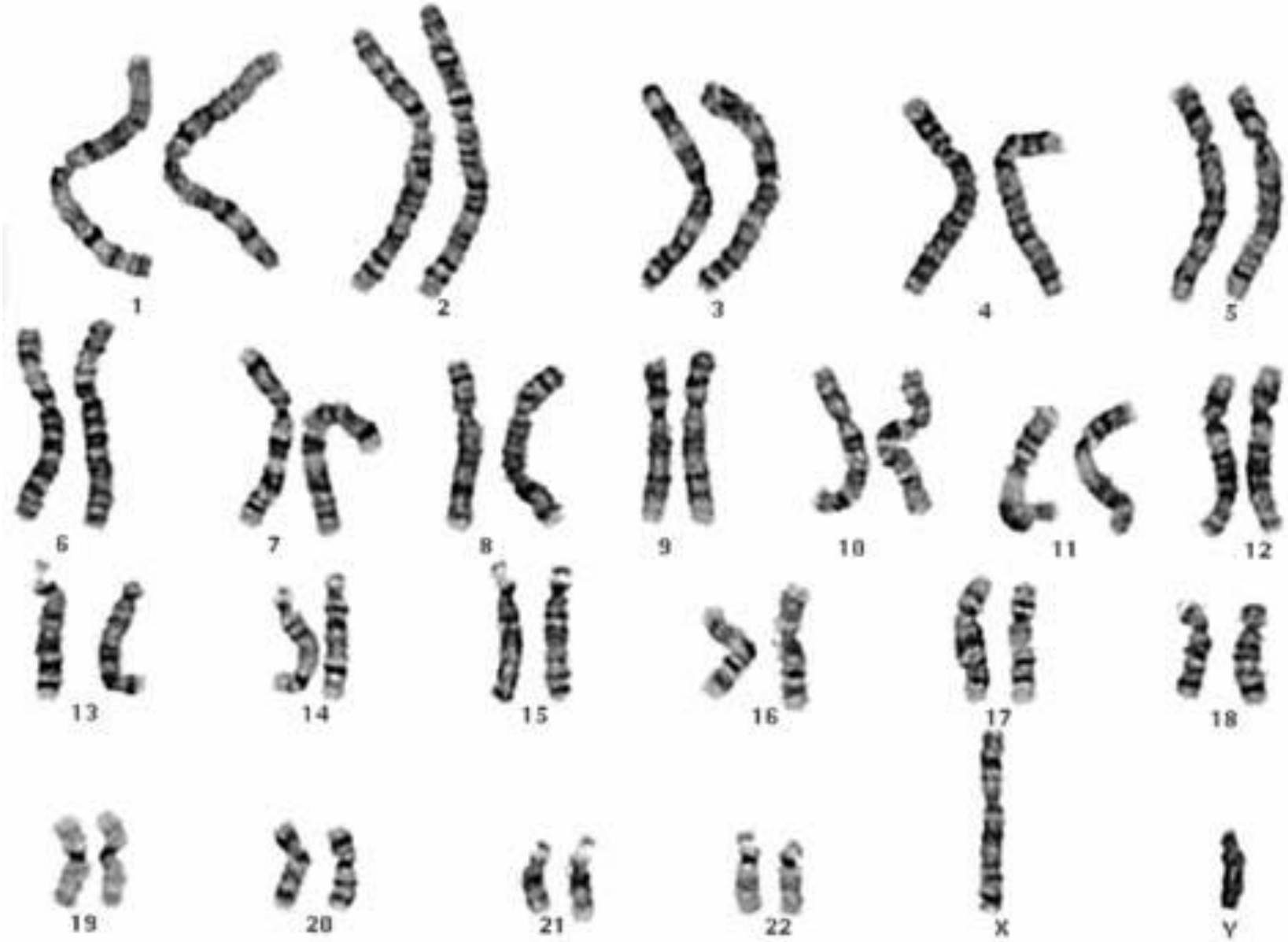
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How common are hereditary cancer

13.9% of CRCa are genetic

Criteria to test?

10% fulfill the criteria for testing

7.8% DO NOT fulfill the criteria

Genetics and treatment

- Is surgery needed?
- Will immunotherapy work for this pt
- If Lynch surgery options?
  - Remove the whole bowel
  - Surveillance
  - Bowel movements

Frequency of Lynch

UK figures thought to be 1:280

(from biobank data may be 1:400)

Prevalence 1:400 UK => 200,000 affected people

Only 5% of those affected know they have this defect

*……..there are **190,000** people to find…….*

How is LS detected?

- Amsterdam criteria (family patterns)
- Colorectal cancer (NICE 2017 DG27)
  - all colorectal cancers should be tested
- Endometrial cancer (NICE 2020 DG42)

Why the importance?

- Recognition of the importance of genetics in cancer
- 95% of people with this condition do not know they have it
- Many of the LS cancers can be prevented through
  - screening & surveillance
  - health education
  - risk reducing surgery
  - medication
- Benefits for the patient
- Benefits for the healthcare system

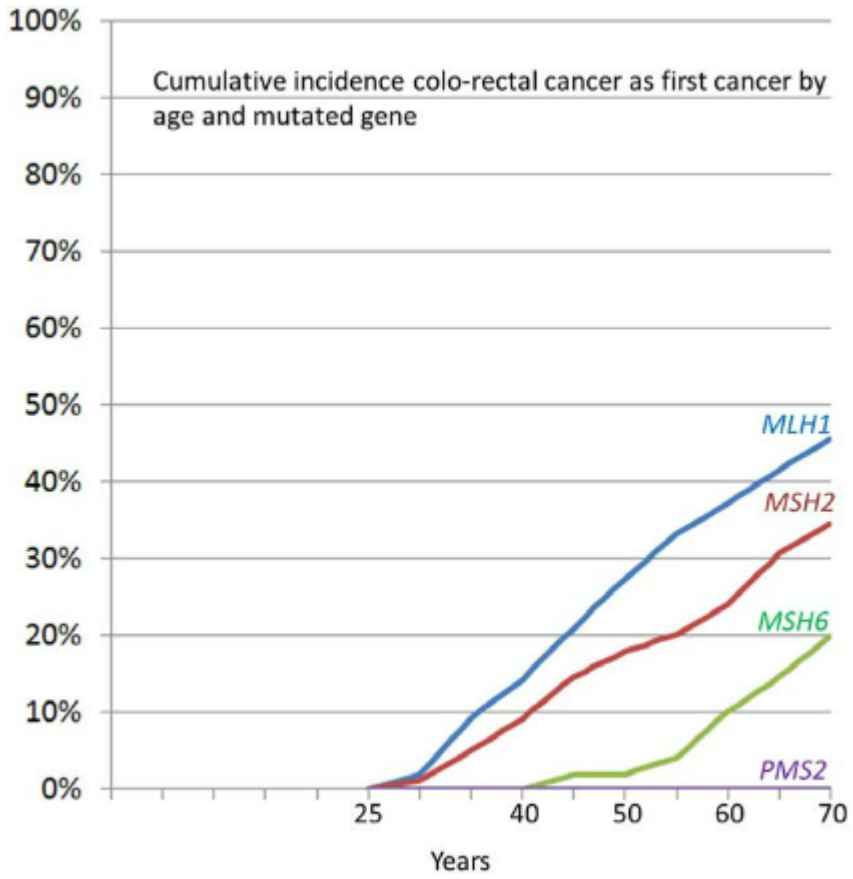
What cancers occur?

- Colorectal (3% of all CRCA)
- Endometrial (3% of all endometrial)
- Ovarian
- Stomach
- Small Intestine
- Pancreas
- Hepatobiliary
- Urinary (ureter, bladder)
- Prostate
- Skin – sebaceous adenoma, carcinoma, keratacanthoma
- CNS glioblastoma
- Sarcoma

Cancer Site	Main Symptoms	Lifetime Risk				Amenable to Surveillance	Prophylactic Surgery Recommended
		MLH1	*MSH2*	*MSH6*	*PMS2^*		
Colorectal	Bleeding, pain, change in bowel habit	45%	43%	15%	1%	Yes - Colonoscopy around every 2 years	No
Endometrial	Abnormal vaginal bleeding or discharge, postmenopausal bleeding, pain	43%	57%	47%%	26%	No- evidence not clear if of benefit	Yes
Ovarian	Bloating, pain, decreased appetite, nausea	10%	17%	13%	0%	No- evidence not clear if of benefit	Yes
Prostate	Decreased flow, blood in the urine, pain	17%	32%	18%	38%	Yes - prostate specific antigen levels (ongoing study NCT 00261456)	No
Gastric	Pain, decreased appetite, black stool, indigestion, feeling full	7%	8%%	5%	0%	Yes - gastroscopy around every 2 years	No
Bladder/ Ureter/ Kidney	Pain, increased urinary frequency, blood in the urine	8%	25%	11%	0%	No- no reliable test	No
Pancreas	Bloating, pain, decreased appetite, nausea	6%	1%	1%	0%	No	No
Breast	Lump, pain, abnormal nipple discharge/bleeding	12%	12%%	13%	NK	Yes - routine breast screening	No*

Notes: ^PMS2 results limited as very few individuals in source data. *Mastectomy is possible however the lifetime risk in Lynch is not significantly more than a woman's risk of breast cancer who does not have Lynch. Therefore, Mastectomy is not indicated.

Cumulative colorectal cancers



Pål Møller et al. Gut 2017;66:464-472

Preventing Colorectal Cancer in LS

- Colonoscopy screening every two years
  - From age 25y for MLH1, MSH2, EPCAM
  - From age 35y PMS2, MSH6

- May be under local High Risk Screening who offer regular recall
- From April 2023 National Register with the Bowel Cancer Screening Program

- Screening ceases at age 75yr as risk outweighs benefits

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.

NICE National Institute for Health and Care Excellence

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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.

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

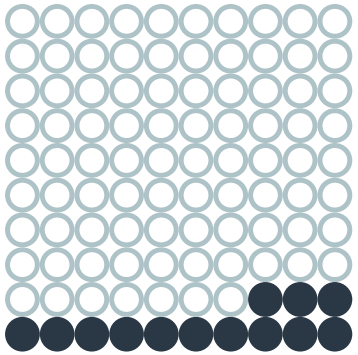
The CAPP2 study was carried out in people with Lynch syndrome. It compared taking aspirin (600 mg every day) with taking a dummy tablet.

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.

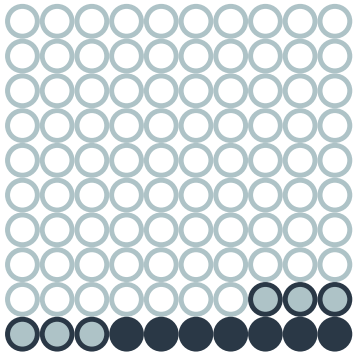
Bowel cancer among people who did not take aspirin



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

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

The future….

- National register of the current 5% known LS
- Exact Aspirin dose (CAPP3) ?based on wt <70kg/ >70kg
- Diet and effect on the whole GI tract
- Role of FIT? Australia FIT every 2y (35-44yr) with 5yr colonoscopies
- Vaccinations – as strong immune response
- Circulating cell-free DNA
- Cytology based or urine endometrial cancer detection
- Immunotherapy

Are there ways to identify a cancer sooner?

- Screening
  - FIT
  - Breast
  - Cervical
- Urine
  - Cytology
- Blood
  - Tumour markers
  - DNA/RNA from the cancer
- Imaging
  - Consider use of AI

Galleri® PILOT

Circulating DNA

50-77

Not being investigated for a cancer

Not recently had cancer

Pick up for 50 known cancer in asymptomatic

University Hospital Southampton NHS Foundation Trust

Questions

Wessex Clinical Genetics Service