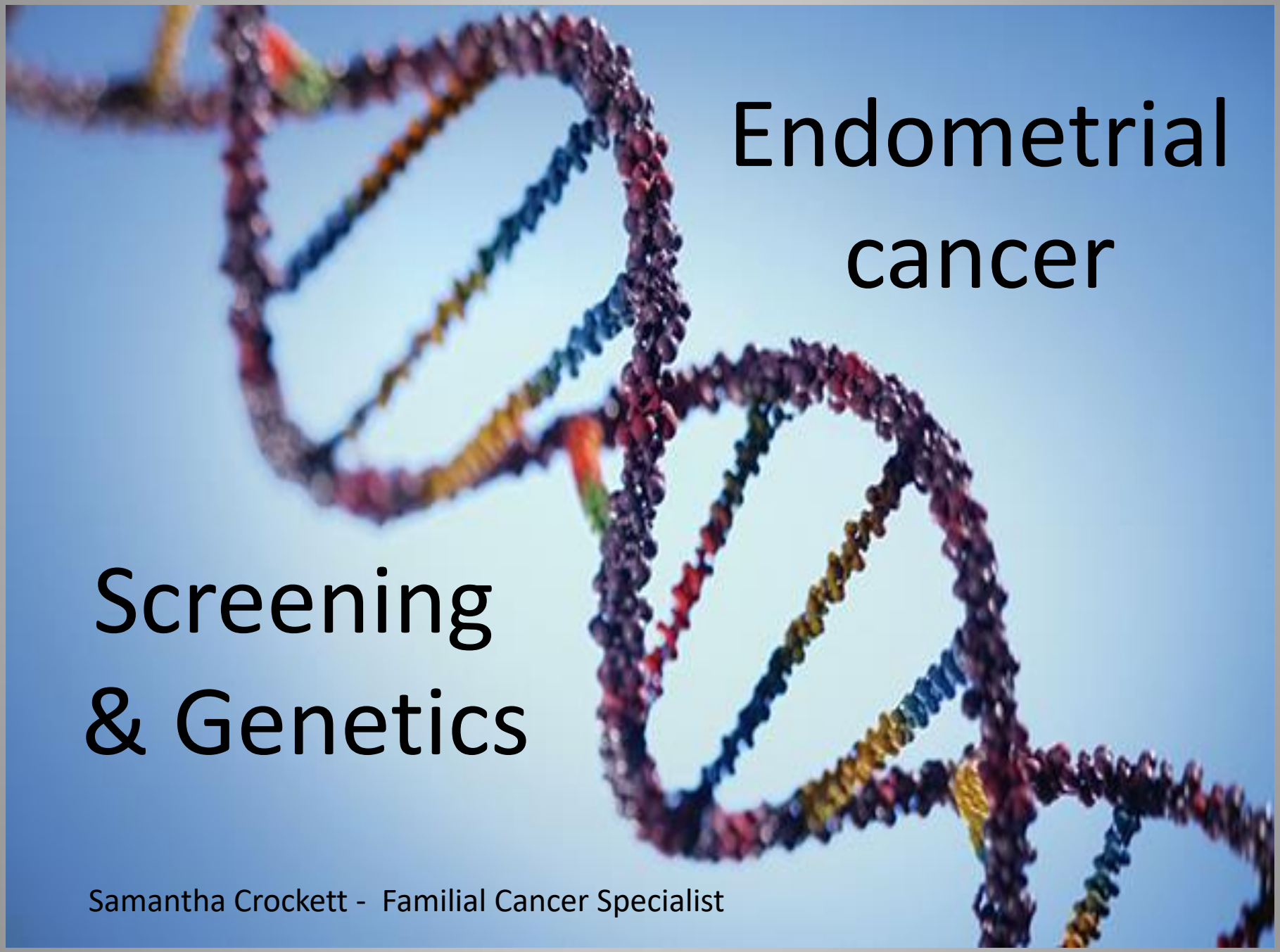


Endometrial cancer

Screening & Genetics

Samantha Crockett - Familial Cancer Specialist

Screening the general population

BGCS guidelines (2014 – due to be updated in 2020) :

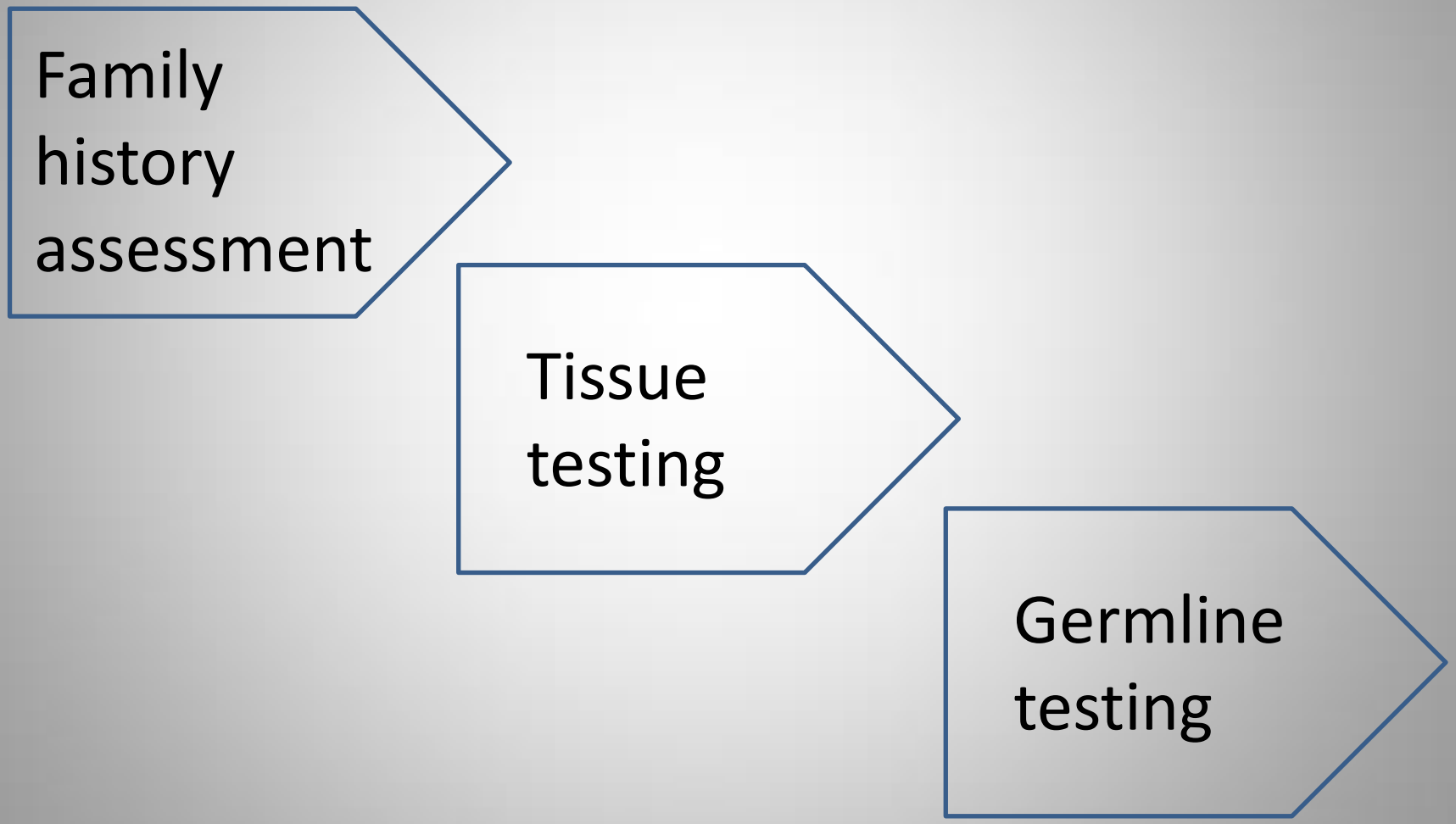
There is no evidence that screening asymptomatic women in the general population with transvaginal ultrasound scanning (TVS) or endometrial sampling reduces the mortality from endometrial cancer (EC).

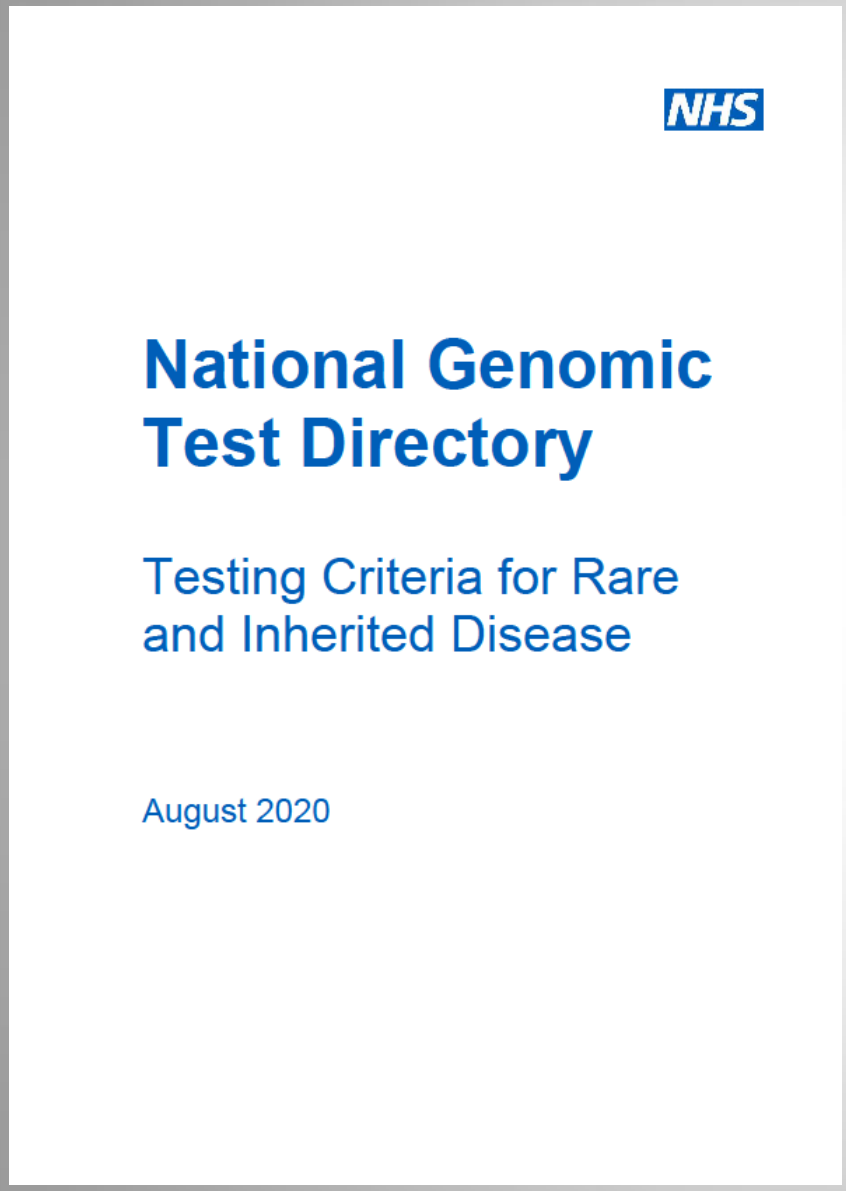
Identification of high risk women

Between 2-5% of endometrial cancer cases are thought to be inherited rather than sporadic.

Lynch syndrome – first characterised in 1966 by Professor Henry T Lynch.
Syndrome & term coined in 1984.
Also known as HNPCC.
Autosomal dominant inheritance pattern.

Diagnosis of Lynch Syndrome - historically emphasis on bowel cancer in families





R210 Inherited MMR deficiency (Lynch syndrome) Testing Criteria

1. Living affected individual (proband) with Lynch-related cancer where the individual +/- family history meets one of the following criteria. The proband has:

a. **Colorectal or endometrial cancer** (when first diagnosed, any age; as per NICE guidance,) OR

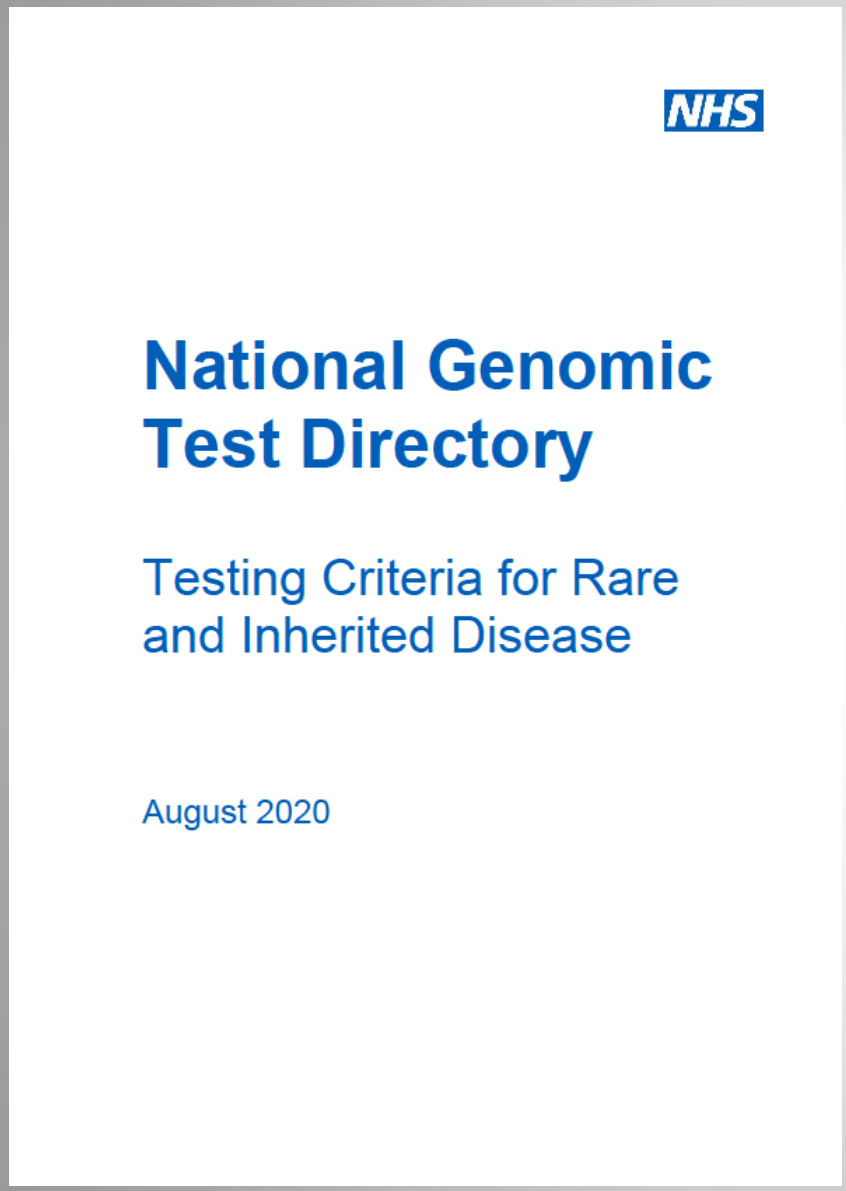
b. Any lynch-related cancer* (<50 years), OR

c. Two Lynch-related cancers (any age, one is colorectal or endometrial), OR

d. Lynch-related cancer and ≥ 1 first degree relative has Lynch-related cancer (both occurred <60 years, one is colorectal or endometrial), OR

e. Lynch-related cancer and ≥ 2 relatives (first / second / third degree relatives) have Lynch-related cancer (all occurring <75 years, one is colorectal or endometrial), OR

f. Lynch-related cancer and ≥ 3 relatives (first / second / third degree relatives) have Lynch-related cancer (occurring any age, one is colorectal or endometrial)



*Lynch-related cancers comprise:

Colorectal cancer,
Endometrial cancer,
Epithelial ovarian cancer,
Pancreatic cancer,
Ureteric cancer,
Transitional cell cancer of renal pelvis,
Gastric cancer,
Hepatobiliary tract cancer (excluding liver cancer except cholangiocarcinoma),
Small bowel cancer,
Glioblastoma,
Pancreatic cancer,
Prostate cancer,
Multiple sebaceous adenomata,
Multiple sebaceous epitheliomas,
Multiple keratoacanthomas,
Sebaceous carcinoma,
Endocervical cancer

Order of testing

1. Microsatellite testing or immunohistochemistry (NOTE: IHC is out of Scope for this test directory)

If microsatellite stability and/or normal IHC are demonstrated, no further testing is indicated in the individual whose tumour has been tested

2. Exclusion of MMR deficiency due to somatically acquired MLH1 hypermethylation via tumour testing for BRAF p.(V600E) OR MLH1 hypermethylation in living proband if:

a. Proband has colorectal cancer or endometrial cancer, AND

b. Tumour shows high/intermediate MSI and/or loss of staining of MMR protein(s) on IHC

If acquired MLH1 hypermethylation is demonstrated (i.e. MLH1 hypermethylation in tumour tissue with normal methylation observed in normal tissue) no further testing is indicated in the individual whose tumour has been tested

3. Germline Lynch syndrome panel test in living affected individual (proband) with Lynch-related cancer. The proband has:

a. Lynch-related cancer, AND

b. Tumour featuring high/intermediate MSI or loss of staining of MMR protein(s) on IHC, AND

c. If colorectal or endometrial, tumour which is normal on testing of: BRAF p.(V600E) and/or MLH1 hypermethylation analysis (BRAF p.(V600E) is not indicated in the endometrial testing pathway)

4. Somatic Lynch syndrome panel test in:

a. Living affected individual (proband) with Lynch-related cancer. The proband has:

b. Colorectal or endometrial cancer, AND

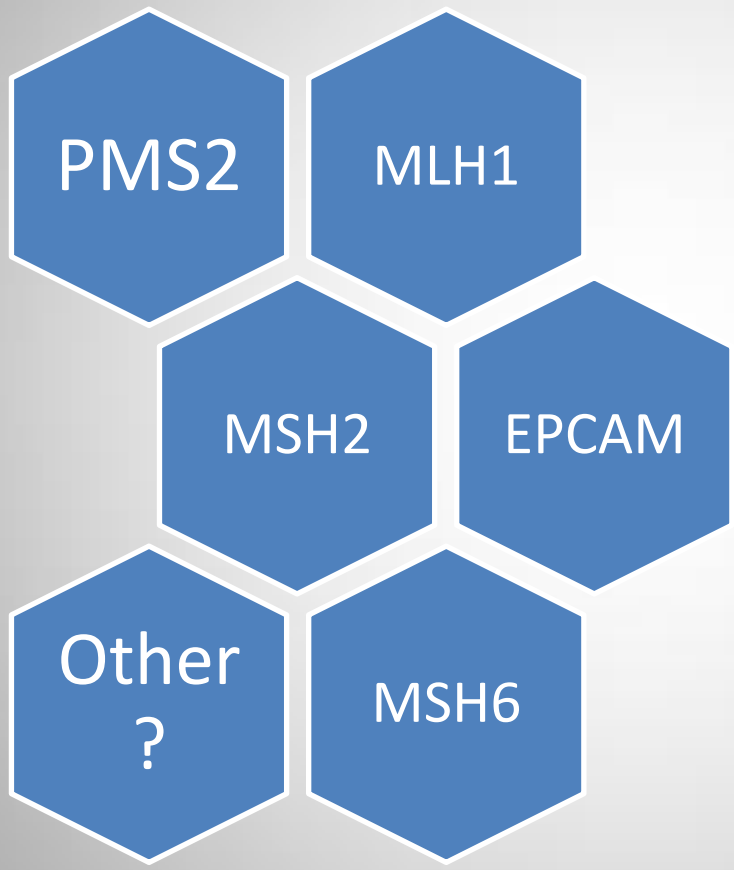
c. Tumour featuring high/intermediate MSI or loss of staining of MMR protein(s) on IHC, AND

d. Tumour is normal on testing of: BRAF p.(V600E) and/or MLH1 hypermethylation analysis (BRAF p.(V600E) is not indicated in the endometrial testing pathway), AND

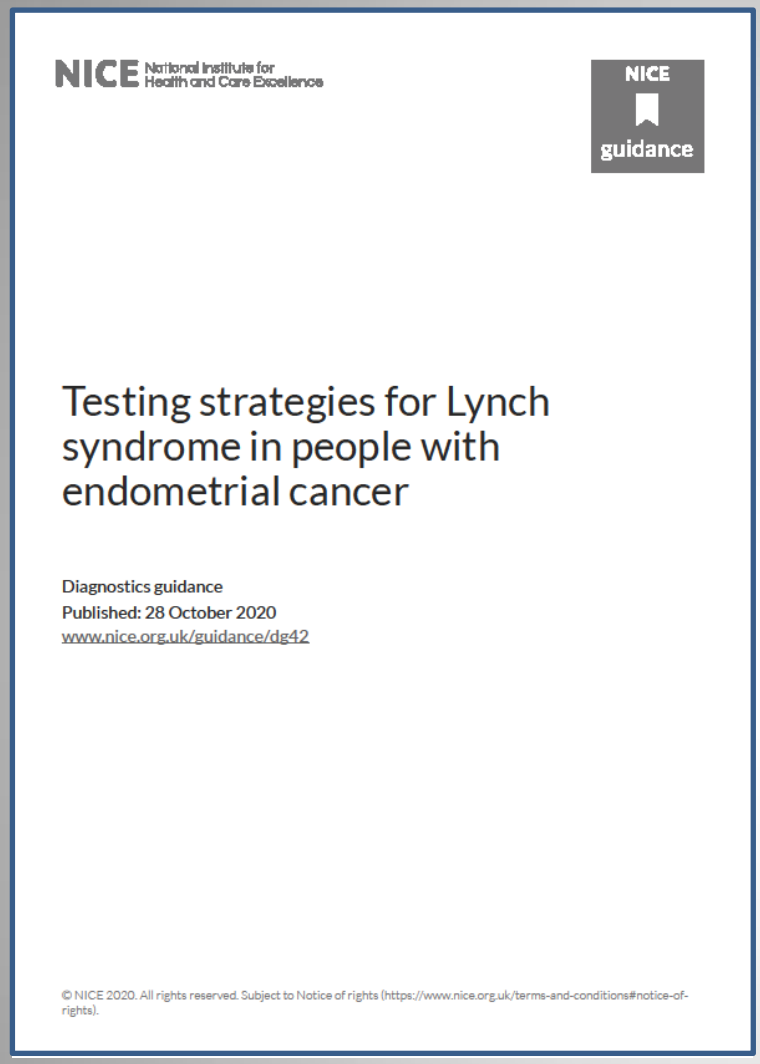
e. Germline Lynch panel did not reveal a pathogenic mutation, AND

f. Personal/family pattern of disease whereby demonstration of acquired MMR mutations (and therefore exclusion of constitutional MMR abnormality) enables downscaling of surveillance

Lynch Syndrome genes



FAP
MUTYH associated polyposis
Cowden syndrome
Peutz-Jeghers syndrome
PTEN hamartoma syndrome



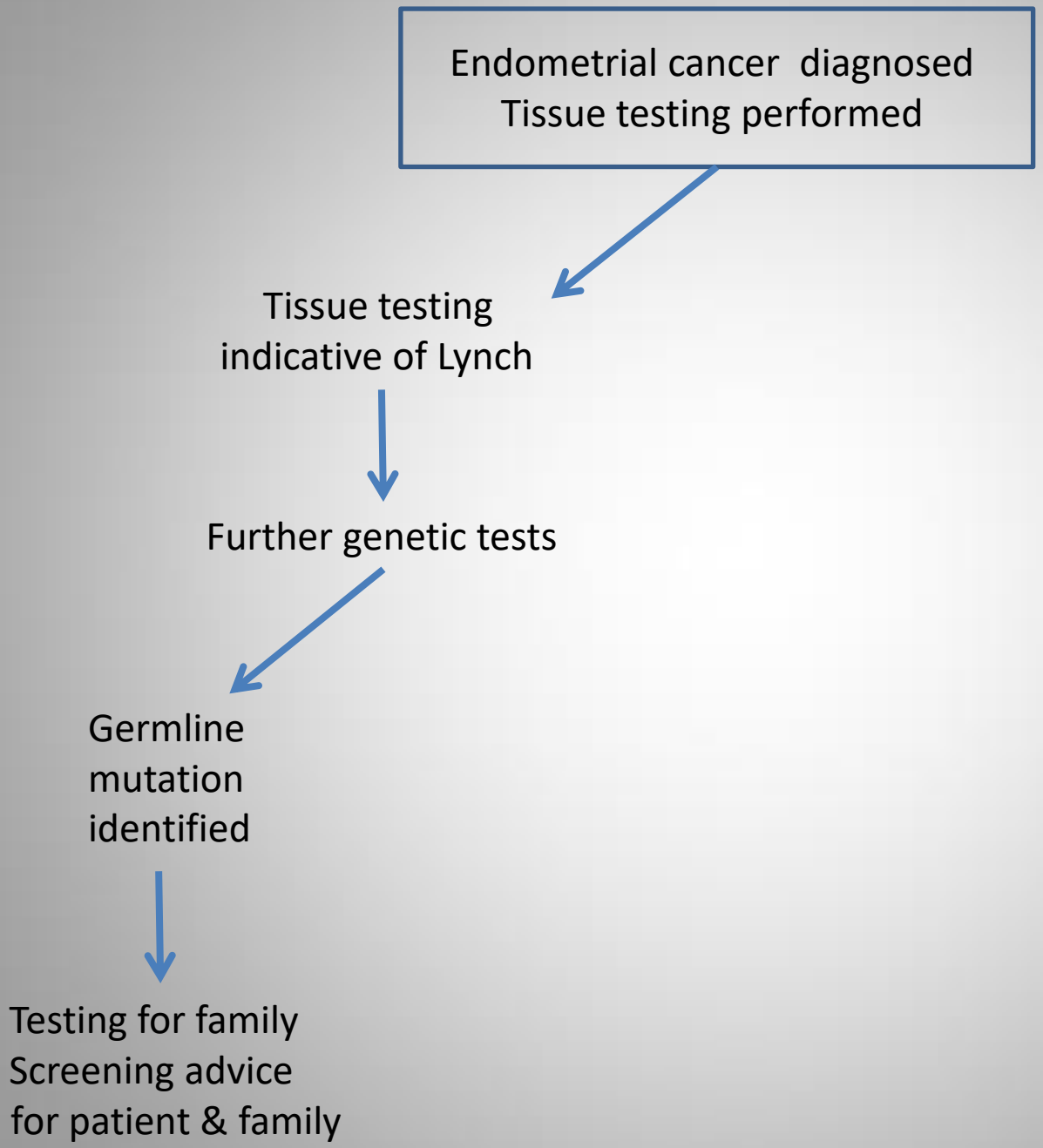
Offer testing for Lynch syndrome to people who are diagnosed with endometrial cancer.

Use immunohistochemistry (IHC) to identify tumours with mismatch repair (MMR) deficiency.

It is likely that people and their families will benefit substantially if Lynch syndrome is identified after endometrial cancer is diagnosed

Testing for Lynch syndrome for people with endometrial cancer is likely to be a cost-effective use of NHS resources

Published October 2020


Endometrial cancer diagnosed
Tissue testing performed
Tissue testing indicative of Lynch
Further genetic tests
Germline mutation identified
Testing for family
Screening advice for patient & family

Management Guidelines for *MLH1* Mutation Carriers

Male *MLH1* approximate risks*

Cancer type	*MLH1* mutation carrier (up to 75)	Population lifetime risk
Colorectal	57%	7%
Endometrial	-	-
Ovarian	-	-
Upper gastrointestinal	22%	5%
Ureter/kidney	5%	3%
Urinary Bladder	7%	2%
Brain	<1%	<1%
Prostate	Similar to population/ may be increased	18%

Female *MLH1* approximate risks*

Cancer type	*MLH1* mutation carrier (up to 75)	Population lifetime risk
Colorectal	48%	6%
Endometrial	37%	3%
Ovarian	11%	2%
Upper gastrointestinal	11%	4%
Ureter/kidney	4%	2%
Urinary Bladder	5%	<1%
Brain	2%	<1%
Prostate	-	-

Approximate *MLH1*– age-dependent cumulative cancer risks*

Current age	Male colorectal	Female colorectal	Endometrial	Ovarian
30	5%	0%	0%	0%
40	16%	12%	2%	2%
50	34%	21%	15%	6%
60	45%	32%	27%	10%
70	53%	44%	35%	11%
75	57%	48%	37%	11%

Management recommendations*

1	Screening	• **Colorectal screening**: 2-yrly colonoscopy from age 25 to 75—review at 75 • **Gastric screening**: Helicobacter pylori one-off screening • **Cervical screening**: As part of the NHS cervical screening programme • No additional cancer screening is currently recommended outside of a research setting; **symptom awareness** to be advised
2	Risk-reducing surgery	• Offer risk-reducing **hysterectomy with BSO**, once childbearing is complete, no earlier than age of 35- 40 (risks and benefits to be discussed) • HRT should be offered until age 51 in women who have not had a ER positive breast cancer
3	Chemoprevention	• Discuss pros and cons of **aspirin chemoprevention** from age 25 to 65 (GP to prescribe): 150mg OD if ≤70kg or 300mg OD if >70kg **(expert opinion)**
4	Research	• **Research studies**: e.g. **IMPACT** (prostate cancer screening study) and **EUROPAC** (pancreatic cancer screening study)
5	Cancer management	• **Targeted therapies** may be available as a treatment option for certain cancer types (immune checkpoint inhibitors e.g. pembrolizumab) • **Surgical management of colon cancer**: discussion regarding pros and cons of segmental vs. extensive resection may be appropriate • **Adjuvant 5-FU chemotherapy** may not be appropriate for patients with Dukes' B colorectal cancers*
6	Family matters	• Facilitate **cascade testing** in at-risk family members • Discuss **reproductive options**

***See FAQ document for further information**: for questions or comments contact: Bianca.DeSouza@gstt.nhs.uk

25/11/2019

https://www.ukcgg.org/information-education/documents-websites/

lscarisk.org

Not secure | lscarisk.org

PLSD
Prospective Lynch Syndrome Database

Prospective Lynch Syndrome Database (PLSD) - cumulative risk for cancer by age, genetic variant, and gender in carriers subject to colonoscopy

Any cancer | Carrier without previous cancer | Carrier with previous cancer | About

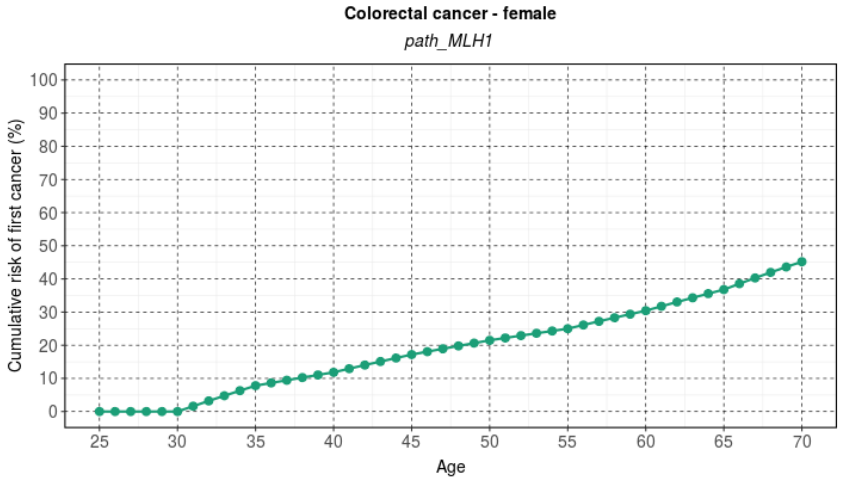
Calculation of cumulative risk for first cancer

Cancer type
Colorectal cancer

Current age
25 — 70
25 30 35 40 45 50 55 60 65 70

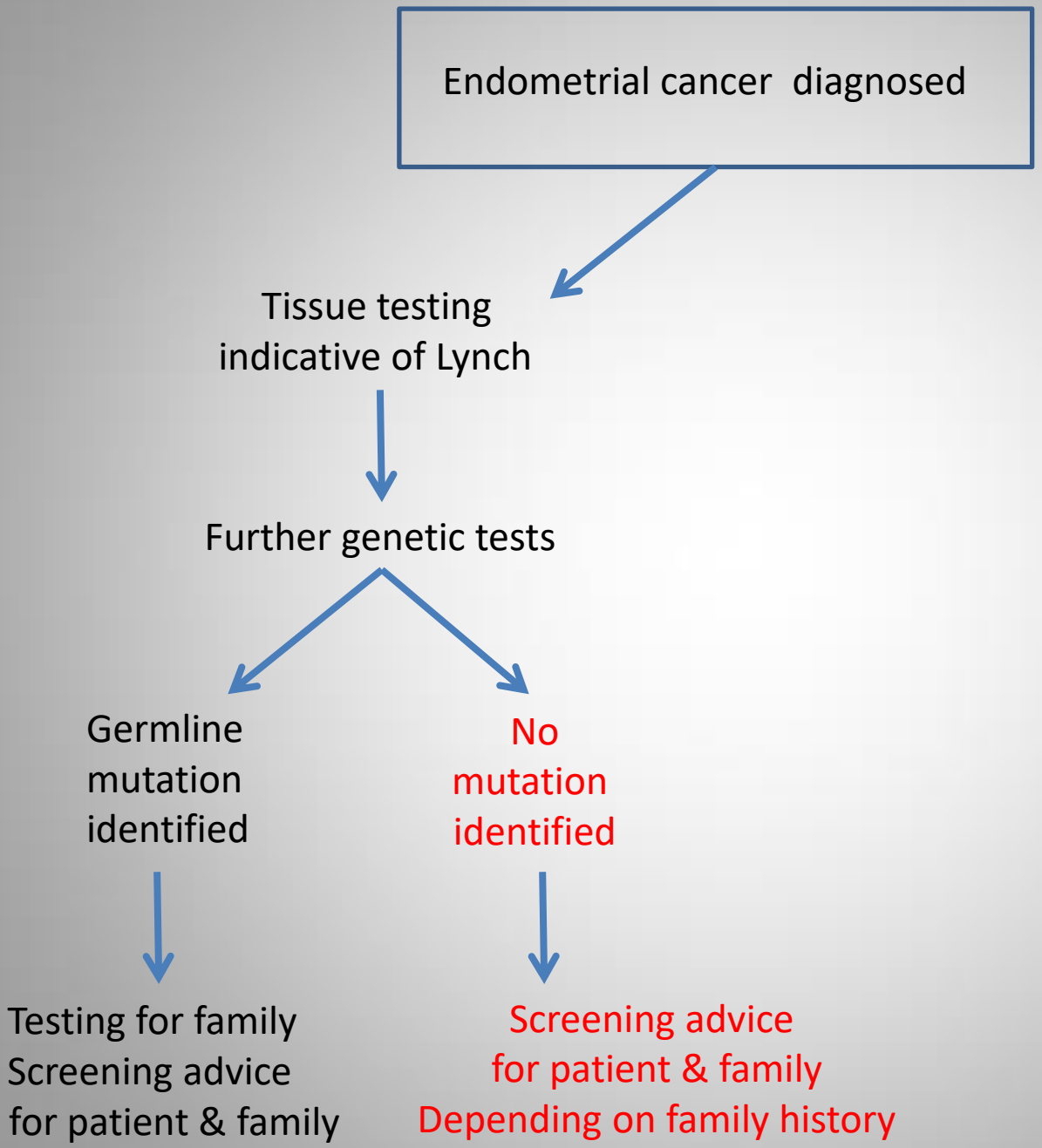
Gender
Female

Genetic variant
path_MLH1



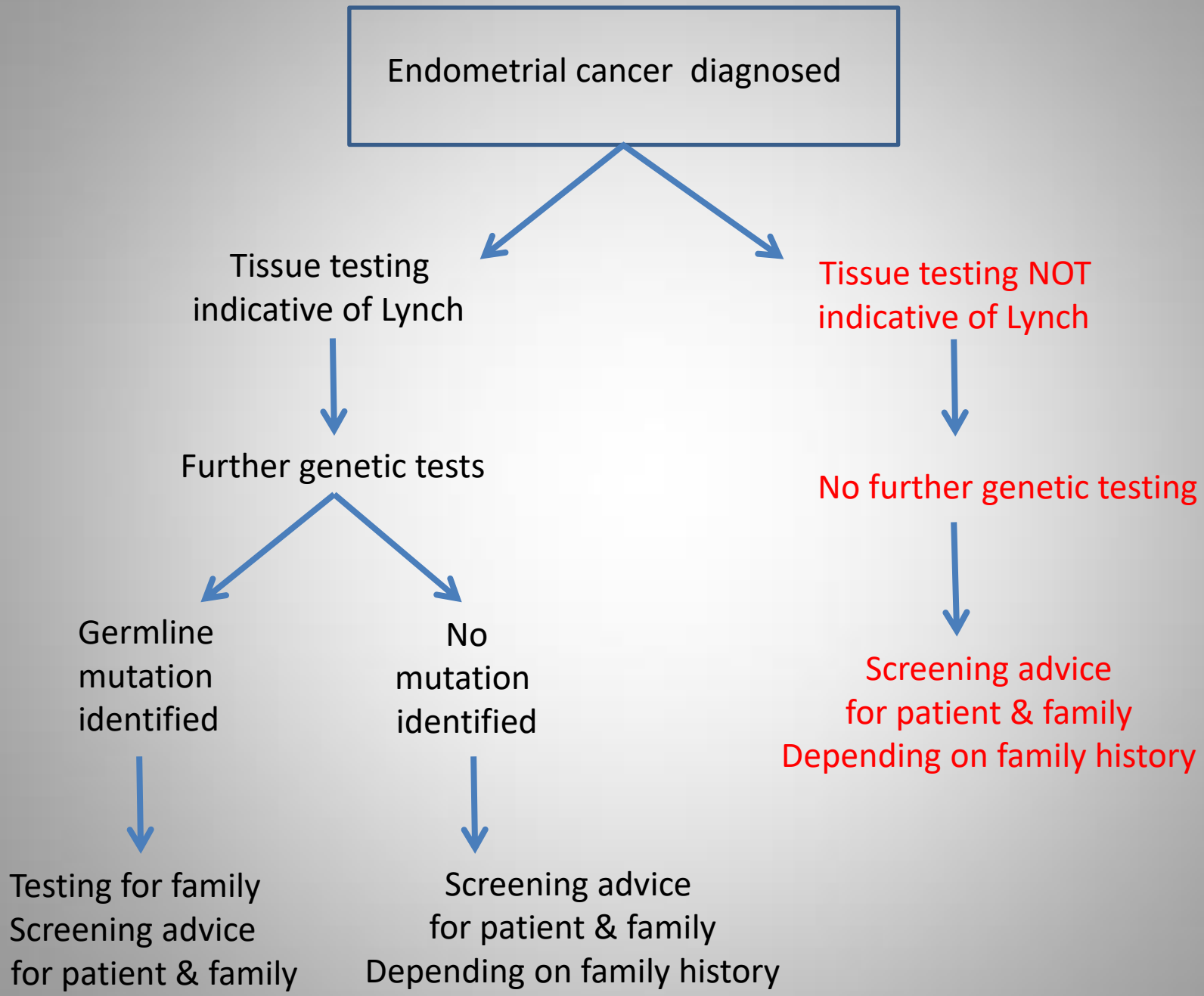
Age	Risk (%)
25	0
40	12
50	21
60	30
70	45

Lscarisk.org


Endometrial cancer diagnosed
Tissue testing indicative of Lynch
Further genetic tests
Germline mutation identified
No mutation identified
Testing for family
Screening advice for patient & family
Screening advice for patient & family
Depending on family history

Bowel screening guidance

Risk Category	Screening	Age and Frequency
Population	FIT test (faecal immunochemical test) Flexible sigmoidoscopy	60-74 years, 2 yearly. Over 74 by request-call helpline 0800 707 6060 One-off at 55 years (not yet available everywhere)
Moderate Risk **(One FDR under 50, or 2 FDRs at any age)**	Colonoscopy	One-off at 55 years
High Risk (MMR testing normal) **(3 FDRs at any age, 2 generations, proband is an FDR of one of these)**	Colonoscopy	40-75 years, 5 yearly
High Risk (MMR testing not possible and Amsterdam positive)	Colonoscopy	As per Lynch syndrome
Lynch Syndrome	Colonoscopy	2 yearly 25-75 for MLH1, MSH2, EPCAM 35-75 for MSH6, PMS2


Endometrial cancer diagnosed
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Tissue testing NOT indicative of Lynch
Further genetic tests
No further genetic testing
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No mutation identified
Screening advice for patient & family Depending on family history
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Bowel screening guidance

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Lynch Syndrome	Colonoscopy	2 yearly 25-75 for MLH1, MSH2, EPCAM 35-75 for MSH6, PMS2

Bowel screening

- Gold standard = colonoscopy (+ dye spray for mutation carriers)

- Women who have already had gynae surgery +/- radiotherapy may well find colonoscopy quite uncomfortable

- If colonoscopy cannot be tolerated ➔ CT colonography
- Future – MRI colonography & capsule colonoscopy

- Also – H.Pylori testing
- Discuss upper GI screening depending on family history
- Use of aspirin in mutation carriers to prevent polyp formation

Advice for relatives :

Bowel screening as per guidelines

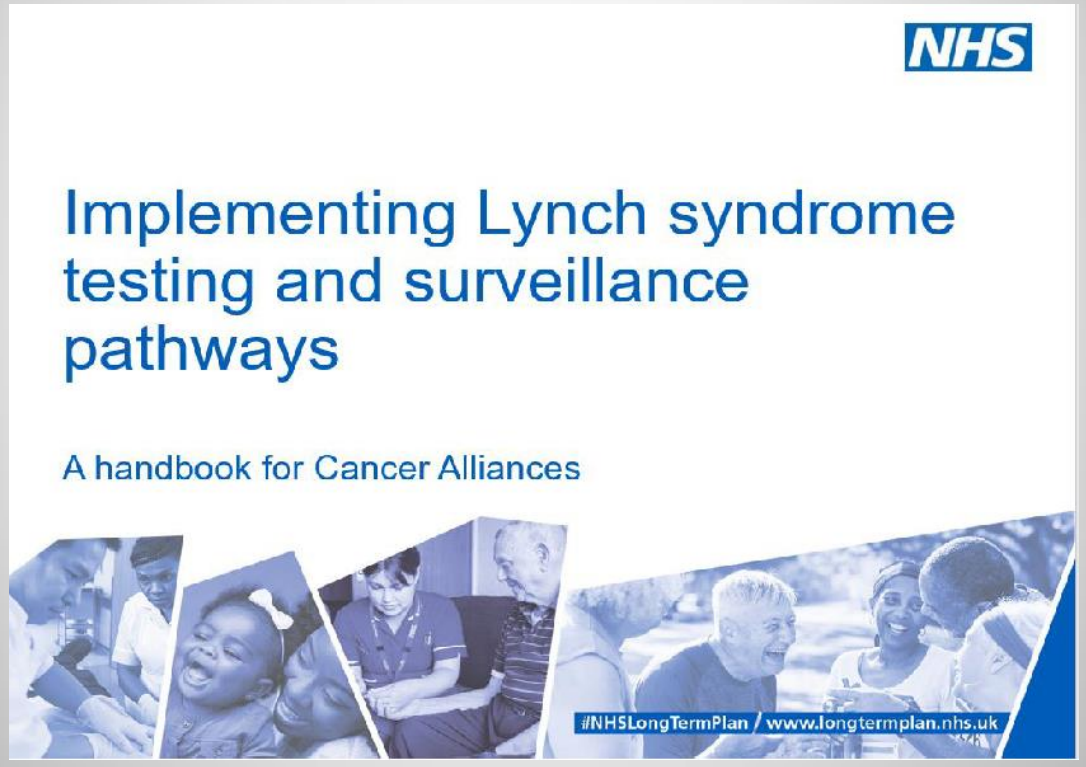
For gene carriers –

- To be symptom aware with regard to endometrial issues
- Low threshold for investigating any irregular bleeding etc
- Consider risk reducing gynae surgery once family complete

Genetic investigations

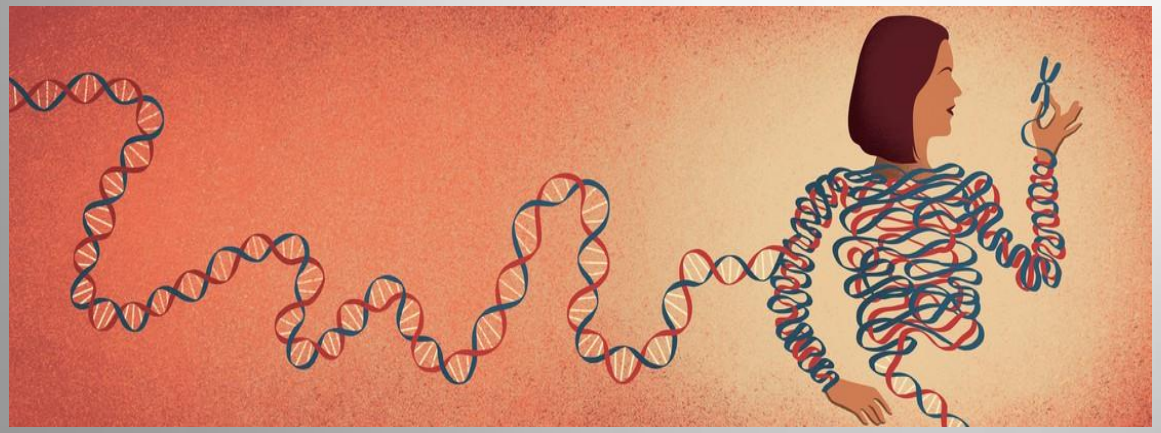
Currently – if tumour indicative of Lynch then patient needs to be referred to Tertiary Genetics for germline testing to identify any specific genetic mutations.

Future -



Consultation document – could be implemented in a similar way to Mainstreaming BrCa1/2 testing for ovarian cancer/PPC patients.

Any questions ?



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February 2021