The British Association of Gynaecological Pathologists

Lecturer – Dr Neil Ryan

Dr Neil Ryan is the RCOG Subspecialty Trainee in Gynaecological Oncology at the Royal Infirmary of Edinburgh and a CSO/NES Clinical Lecturer at the University of Edinburgh. He completed a PhD as an MRC Clinical Research Fellow at the University of Manchester, where his work led to a change in NICE guidance on endometrial cancer testing. His research focuses on the molecular determinants of cancer risk and treatment response, with a particular interest in mismatch repair deficiency. He leads the EU PREDI-Lynch gynaecology arm and is developing translational trials to improve personalised care in endometrial and other gynaecological cancers.

The British Association of Gynaecological Pathologists

Syndromic Tumours in Gynaepath
Diagnoses not to be missed by Pathologists

- Title DR
- Speaker NEIL RYAN
- Affiliation UNIVERSITY OF EDINBURGH

- Date 14/11/2025

The British Association of Gynaecological Pathologists

Speaker disclosures

Choose one

I have no financial conflicts of interest to disclose

Lynch syndrome: Genetic Referral Pathway

Dr Neil Ryan

Gynaecology Oncology Surgeon SST and Clinical Lecturer

University of Edinburgh

Speaker Disclosures

Honoraria for GSK and Chief Medical Officer for Ellele Health (advisory role)

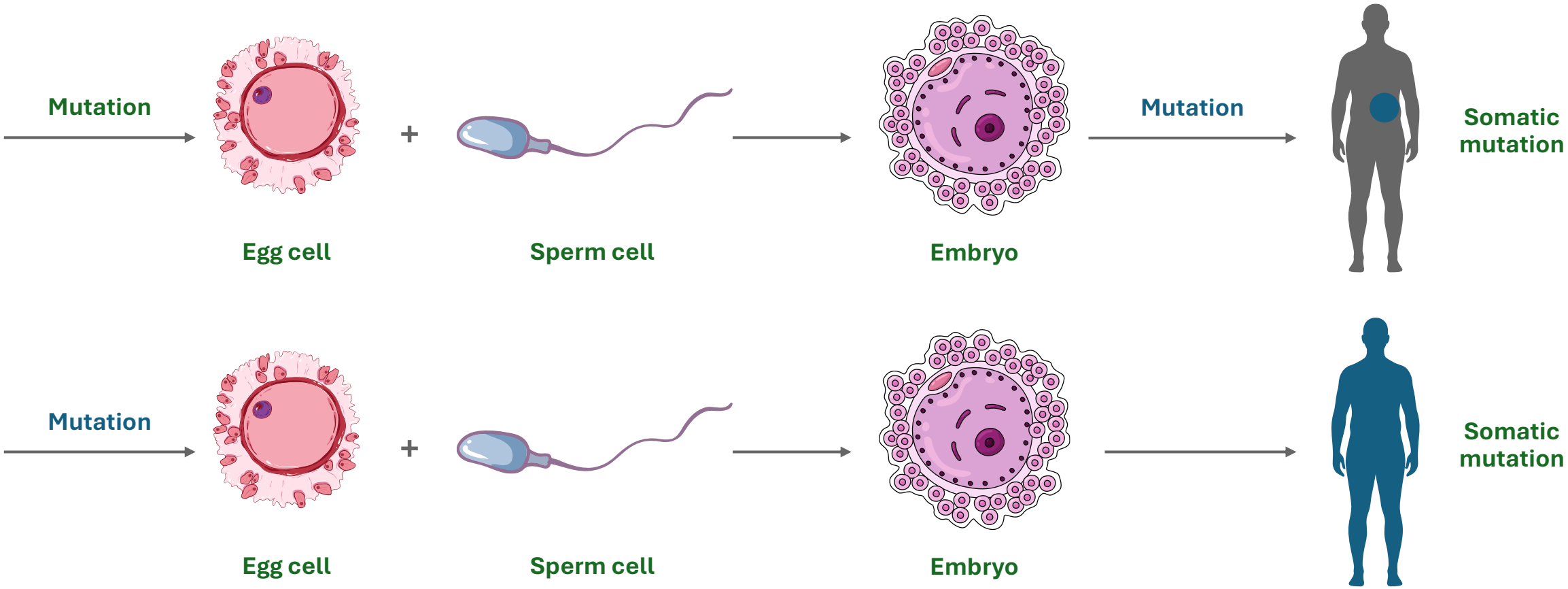
Overview

Principles of screening

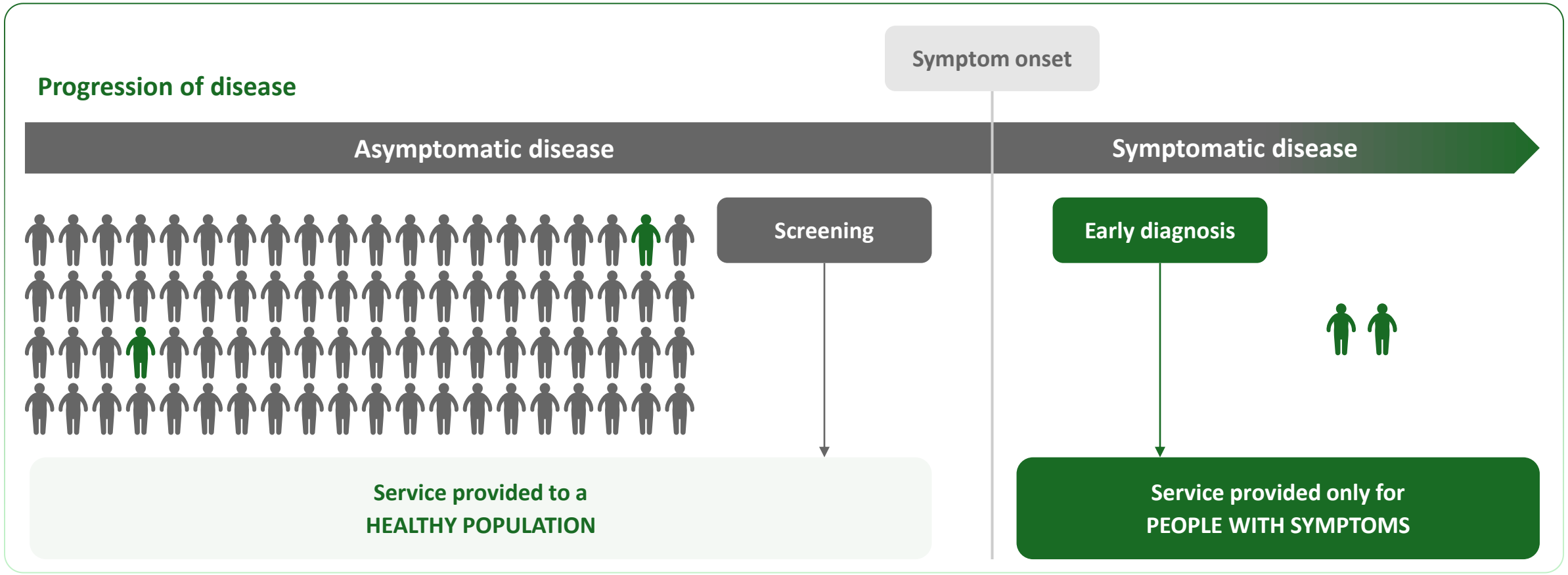
Endometrial cancer

Lynch syndrome

Take home messages


Mutation
+
Egg cell
Sperm cell
Embryo
Mutation
Somatic mutation
Mutation
+
Egg cell
Sperm cell
Embryo
Somatic mutation

Principles of screening[1]



- world health organization: screening programmes a short guide. 2020

Endometrial Cancer [1]

Cochrane Library

Cochrane Database of Systematic Reviews

EDITORIAL

The emerging epidemic of endometrial cancer: time to take action

Emma Crosbie, Jo Morrison

Cochrane Database of Systematic Reviews 2014;(12):ED000095 https://doi.org/10.1002/14651858.ED000095

Publication date: 22 December 2014

Endometrial cancer is the fifth most common cancer in women, affecting 318,000 women per year globally.[1] Incidence is higher than for ovarian cancer and is increased in developed nations, reflecting differences in lifestyle risk factors.[1] In the UK, endometrial cancer is the fourth most common cancer in women, but there is little public awareness about the disease,[2] and there is no endometrial cancer charity in the UK. There is also very little research effort on international level: a simple PubMed search using the term 'endometrial cancer' revealed 28,218 references, compared with 85,926 for 'ovarian cancer' and 289,989 for 'breast cancer'.

The incidence of endometrial cancer is rising, and more women are now dying from the disease, despite improvements in overall survival.[3] Most of the increase in incidence is due to low-grade Type 1 cancers. These are largely caused by excess oestrogen, unopposed by progesterone, and the main risk factor is obesity.
Body mass index (BMI) is the main driver for the increasing incidence in endometrial cancer globally.[4] However, survival from the more aggressive Type 2 cancers is decreasing.[3] There is therefore an urgent need for research into the aetiology, screening, prevention, and treatment of this disease.

Overall survival rates for endometrial cancer are good. In England, 77.7% of women are expected to survive their disease for five years or more.[5] However, survival stage-for-stage is similar to ovarian cancer; five-year survival is around 85% for stage I tumours, compared with 25% for women diagnosed with stage IV disease.[6] The overall relatively favourable survival may be one explanation for the lack of research and funding in this area. Another reason may be that it is commonly a disease of older women, who attract less media attention and may be less likely to discuss gynaecological problems, similar to the silence surrounding breast cancer 30 years ago. Whatever the reason, women are dying due to this relative lack of attention and research.

- Crosbie E, Morrison J. *Cochrane Database Syst Rev*. 2014.

Survival rates remain low for patients with advanced* or recurrent EC

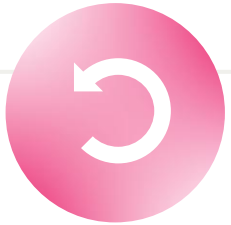
EC in the 2020s

>400,000 new cases

globally in 2020[1]

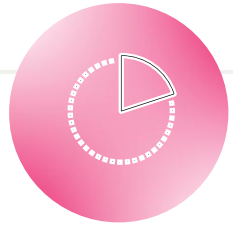
63 years

globally in 2020[1]



~13%

of EC patients have recurrent disease[3]



≤20% survival at 5 years

for patients with advanced* or recurrent EC[3,4]

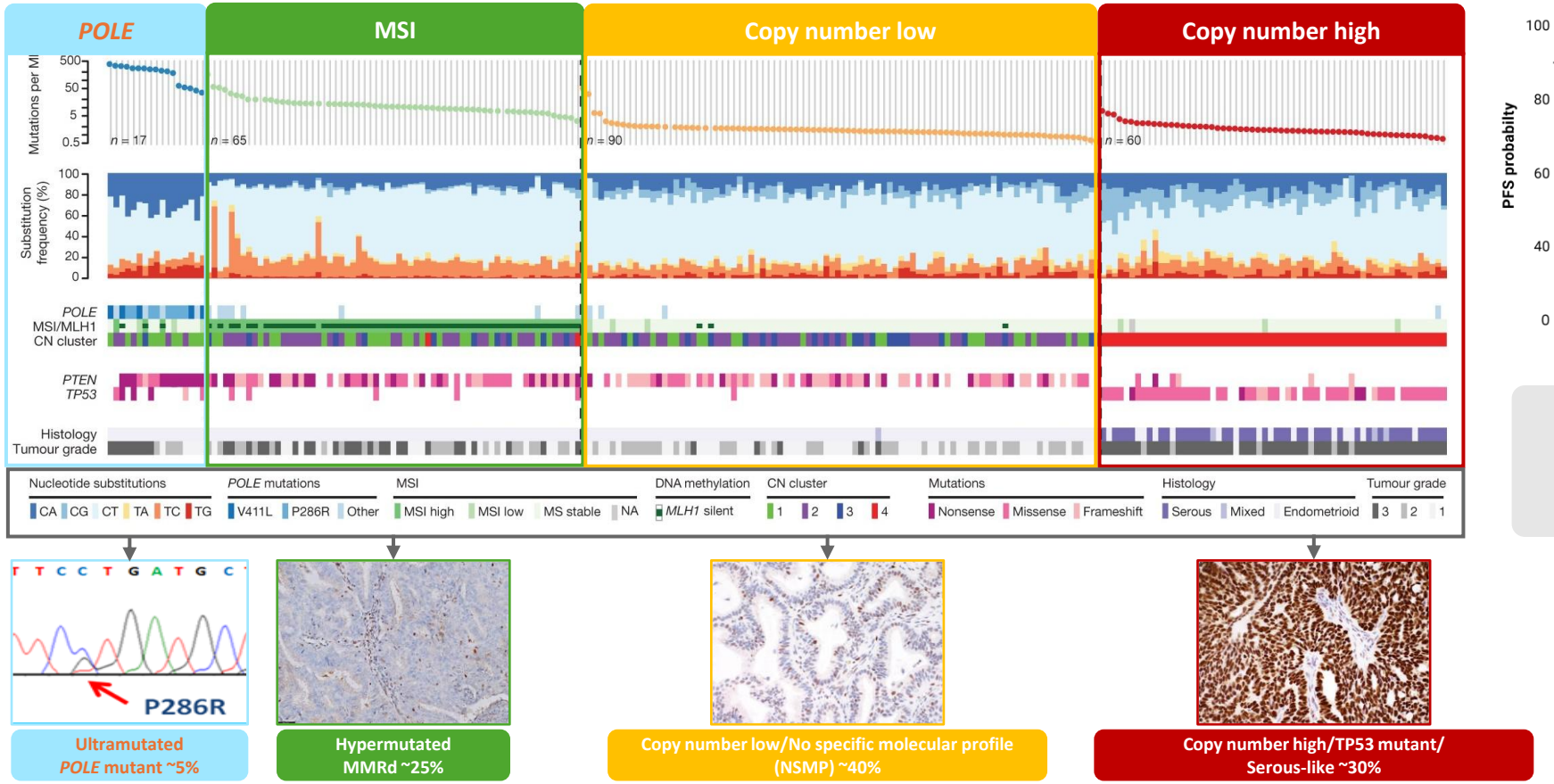
*Stage IV

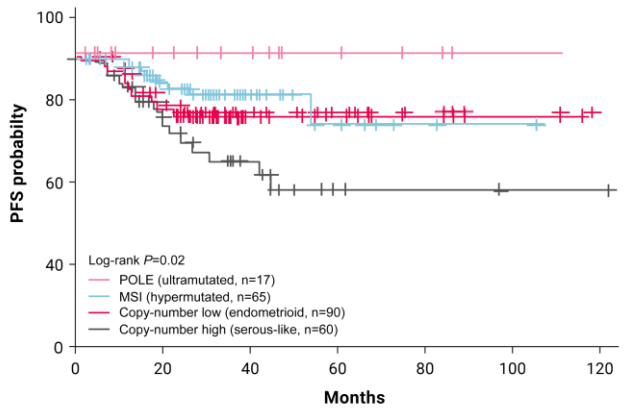
EC, endometrial cancer.

1. World Health Organization International Agency for Research on Cancer. Accessed from: https://gco.iarc.fr/today/data/factsheets/cancers/24-Corpus-uteri-fact-sheet.pdf . 2. Colombo N *et al.* Ann Oncol. 2016;27;16-41. 3. Huijgens A, Mertens H. Facts Views Vis ObGyn. 2013;5:179-186; 4. Cancer Research UK. Uterine cancer survival statistics. Accessed from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/survival#heading-Three .

Molecular classification & Endometrial cancer[1-3]

Molecular classification



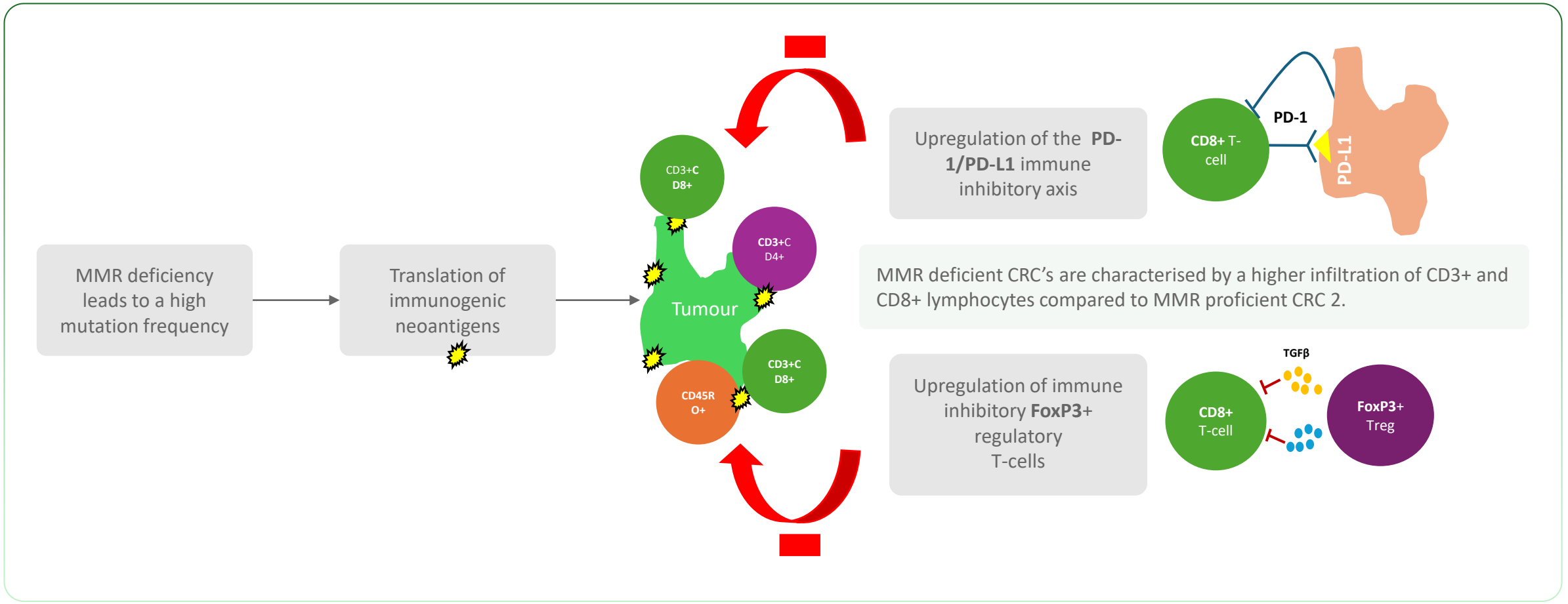


PFS of EC patients stratified by TCGA molecular subtype, established by comprehensive genomic analyses

Figure from Tillmans et al, 2024

Images provided courtesy of speaker with relevant permissions obtained.

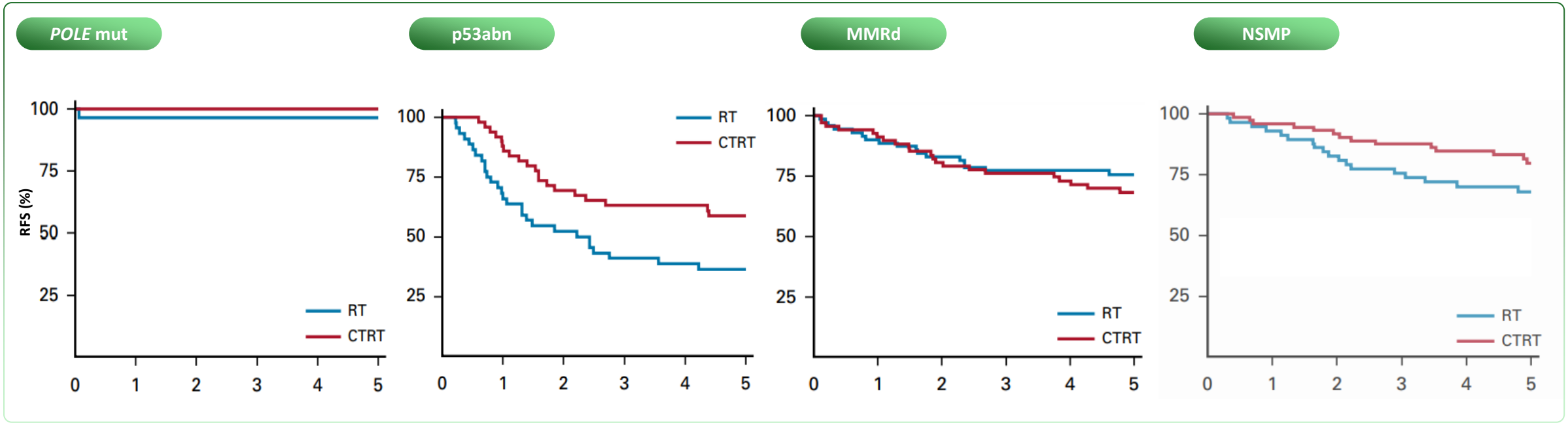
EC, endometrial cancer**; NSMP**, no specific molecular profile; **PFS,** progression-free survival**; POLE,** DNA polymerase epsilon; **TCGA,** The Cancer Genome Atlas; **TP53,** tumor protein p53



Thank you Dr Neal Ramchander

FoxP3, Forkhead box P3; **MMR,** mismatch repair; **PD**, programmed death-1; **PD-L1, p**rogrammed death-ligand 1

PORTEC 3 – molecular markers[1]



POLE mut	p53abn	MMRd	NSMP
5-year RFS: 100% (CTRT) v 96.6% (RT) HR, 0.02; 95% CI, < 0.01 to >10^5; P_{cox} = .637	5-year RFS: 58.6% (CTRT) *v* 36.2% (RT) HR, 0.52; 95% CI, 0.30 to 0.91; P_{cox} = .637	5-year RFS: 68.0% (CTRT) *v* 75.5% (RT) HR, 1.29; 95% CI, 0.68 to 2.45; P_{cox} = .429	5-year RFS: 79.7% (CTRT) *v* 67.7% (RT) HR, 0.68; 95% CI, 0.36 to 1.30; P_{cox} = .246

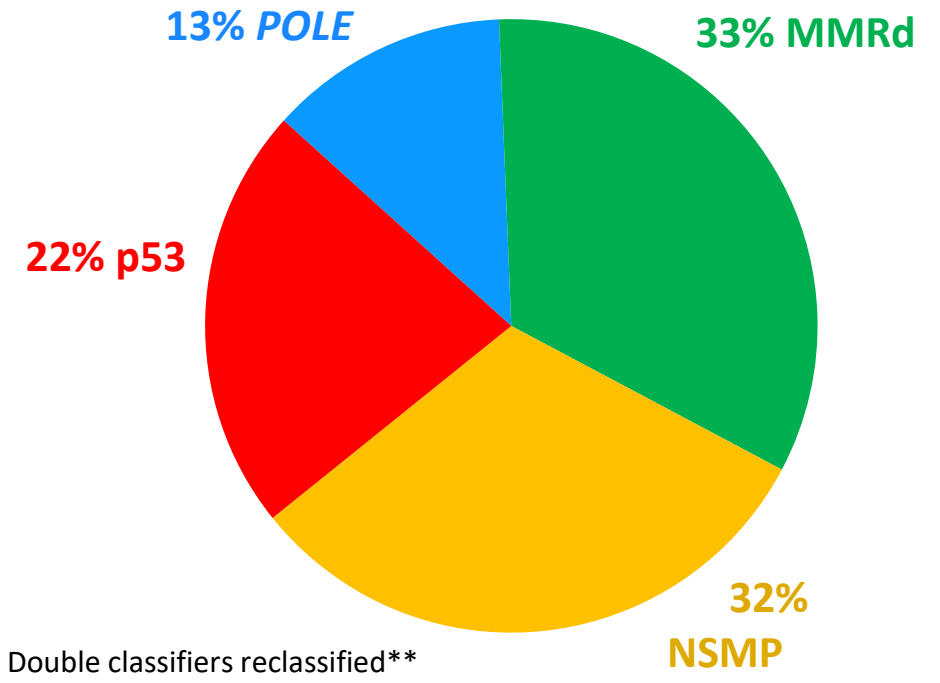
- ***POLE* mut:** Excellent prognosis, regardless of adj. treatment
- **P53abn:** Worst prognosis; greatest benefit from adj chemotherapy
- **MMRd:** Intermediate prognosis, no benefit from adj chemotherapy
- **NSMP:** Intermediate prognosis, maybe some benefit (ns)

CTRT, chemoradiotherapy; **HR**, hazard ratio; **MMRd,** Mismatch repair deficient; **NSMP,** no specific molecular profile; **p53abn,** p53 abnormal; **POLE,** DNA polymerase epsilon; **POLEmut,** POLE ultramutated; **RFS,** recurrence-free survival; **RT,** radiotherapy

- Leon-Castillo *et al,* 2020, J Clin Oncol 38:3388-3397

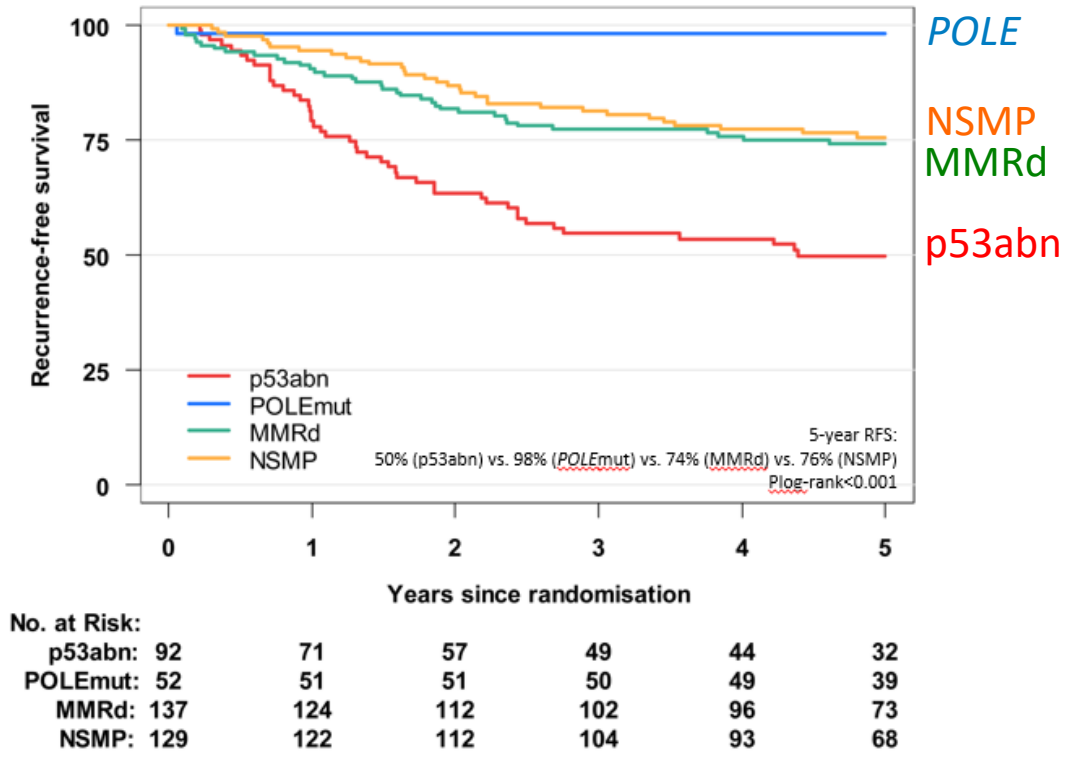
PORTEC 3 – molecular markers[1]

PORTEC-3 HR-EC trial cohort N=410



Double classifiers reclassified**

N=410 (PORTEC-3)[1]

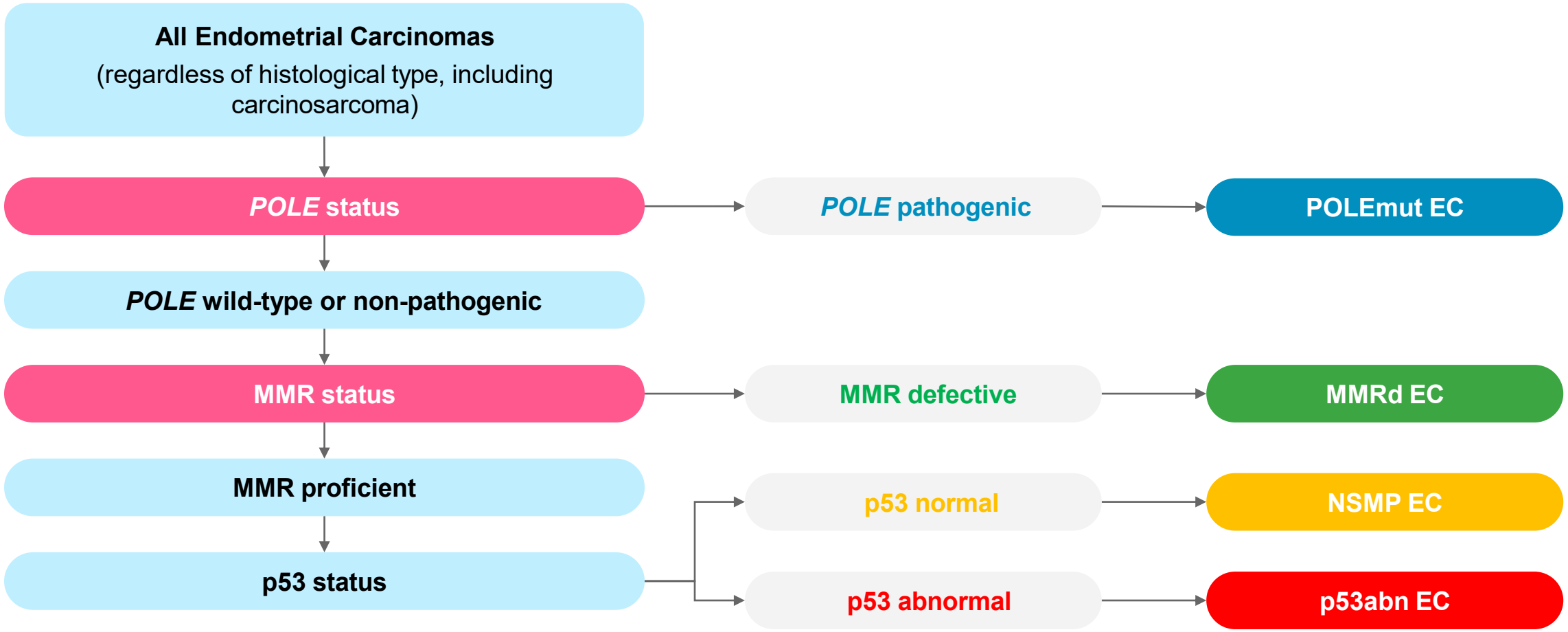


**Leon Castillo *et al,* J Pathol 2020

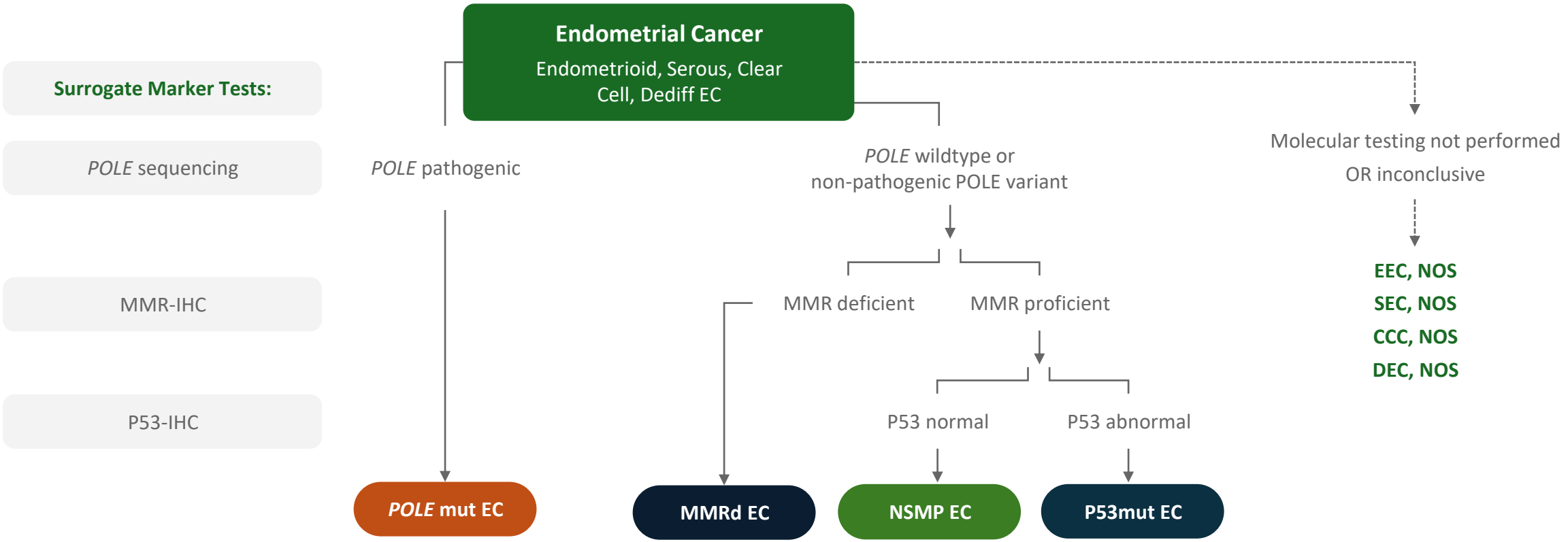
EC, endometrial cancer; **MMRd,** Mismatch repair deficient; **NSMP,** no specific molecular profile **p53abn,** p53 abnormal; **POLE,** DNA polymerase epsilon; **POLEmut,** POLE ultramutated; **RFS**, recurrence-free surviva

1. Leon-Castillo *et al,* 2020, J Clin Oncol 38:3388-3397

PROMISE Algorithm for molecular classification in clinical practice[1]



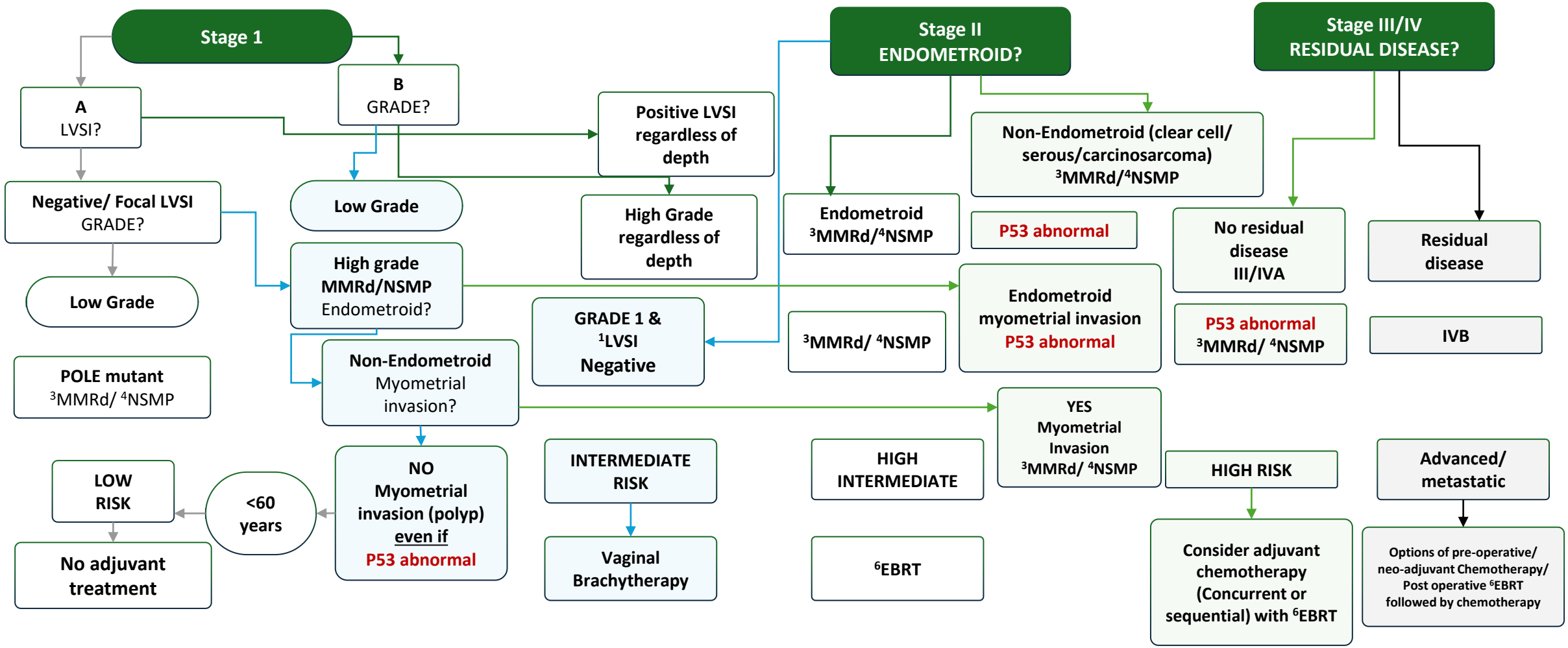
Paradigm Shift in Endometrial Cancer Classification[1]



Adapted from Vermij *et al.* Histopathology. 2020.

EC, endometrial cancer; **IHC**,immunohistochemistry ; **NSMP**, no specific molecular profile; **POLE**, DNA polymerase epsilon; **POLE**, DNA polymerase epsilon mutated; **P53**, protein p53

1. Vermij L *et al*. Histopathology. 2020;76(1):52-63.



Adapted from Al-Booz H. Int J Gynecol Cancer 2021.

EBRT, external beam radiation therapy**; LVSI,** lymphovascular space invasion; **MMRd,** mismatch repair deficient; **NSMP,** no specific molecular profile; **ER,** estrogen receptor; **LVSI**, lymphovascular space involvement; **p53abn,** mutated tumour protein p53; **POLE,** DNA polymerase epsilon;

- Al-Booz H. Int J Gynecol Cancer. 2021;31(9):1313-1314.

FIGO 2023 staging system prognostic risk groups[1]

	Molecular classification				
	***POLE*mut**	**dMMR**	**NSMP low-grade+ERpos**	**NSMP high-grade/ERneg***	**p53abn**
Confined to the uterine corpus					
No myoinvasion, limited to polyp/endometrium	IAm *POLE*mut	IAI	IAI	IAI	IC
Myoinvasion <50%, no/focal LVSI	IAm *POLE*mut	IA2	IAI	IA2	IICm p53abn
Myoinvasion >50%, no/focal LVSI	IAm *POLE*mut	IB	IB	IB	IICm p53abn
Confined to the uterus (uterine corpus ± cervical invasion)					
Cervical stromal invasion, no/focal LVSI	IAm *POLE*mut	IIA	IIA	IIA	IICm p53abn
Uterine corpus ± cervical invasion, substantial LVSI**	IAm *POLE*mut	IIB	IIB	IIB	IICm p53abn
Local and/or regional spread beyond uterus					
Spread to ovary or fallopian tube (except for #)	IIIAI	IIIAI	IIIAI	IIIAI	IIIAI
Involvement of uterine subserosa or spread through the uterine serosa	IIIA2	IIIA2	IIIA2	IIIA2	IIIA2
Metastasis or direct spread to the vagina and/or the parametrium	IIIB	IIIB	IIIB	IIIB	IIIB
Metastasis to the pelvic peritoneum	IIIB2	IIIB2	IIIB2	IIIB2	IIIB2
Metastasis to the pelvic lymph nodes	IIICI	IIICI	IIICI	IIICI	IIICI
Metastasis to the para-aortic lymph nodes	IIIC2	IIIC2	IIIC2	IIIC2	IIIC2
Locally advanced					
Invasion of bladder mucosa and/or intestinal mucosa	IVA	IVA	IVA	IVA	IVA
Low-grade endometrioid carcinoma of both the endometrium + ovary #					
Myoinvasive <50%, no/focal LVSI, overian tumour pT1a	IA3	IA3	IA3	IA3*	IA3
Metastatic or residual disease after surgery					
Local and/or regional spread with residual disease	III with residual disease				
Invasion of bladder musosa and/or intestinal mucosa with residual disease	IVA with residual disease				
Peritoneal metasis beyond pelvis	IVB				
Distant metastasis	IVC				

Table adapted from Concin et al. 20251

Green denotes low risk for recurrence; yellow denotes intermediate risk; orange denotes high-intermediate risk and red denotes high risk; grey denotes uncertain risk classification because of lack of data.

2023 FIGO stage IIC carcinomas other than p53 abnormal are not depicted in this table.

When molecular classification is known, the FIGO stage should be reported with an annotation of m (for molecular) followed by the specific molecular subtype. There are two specific molecularly defined FIGO stages, namely stage IAm POLEmut (stages I and II disease with a pathogenic POLE mutation) and stage IICm p53abn (stages I and II disease with a p53 abnormality and myometrial invasion).

*The molecular subgroup NSMP high-grade/ERneg consists of either high-grade NSMP cases or ERneg NSMP cases. Thus, in low-grade endometrioid carcinomas of both the endometrium + ovary, only the ERneg cases of the molecular subgroup NSMP high-grade/ERneg apply.

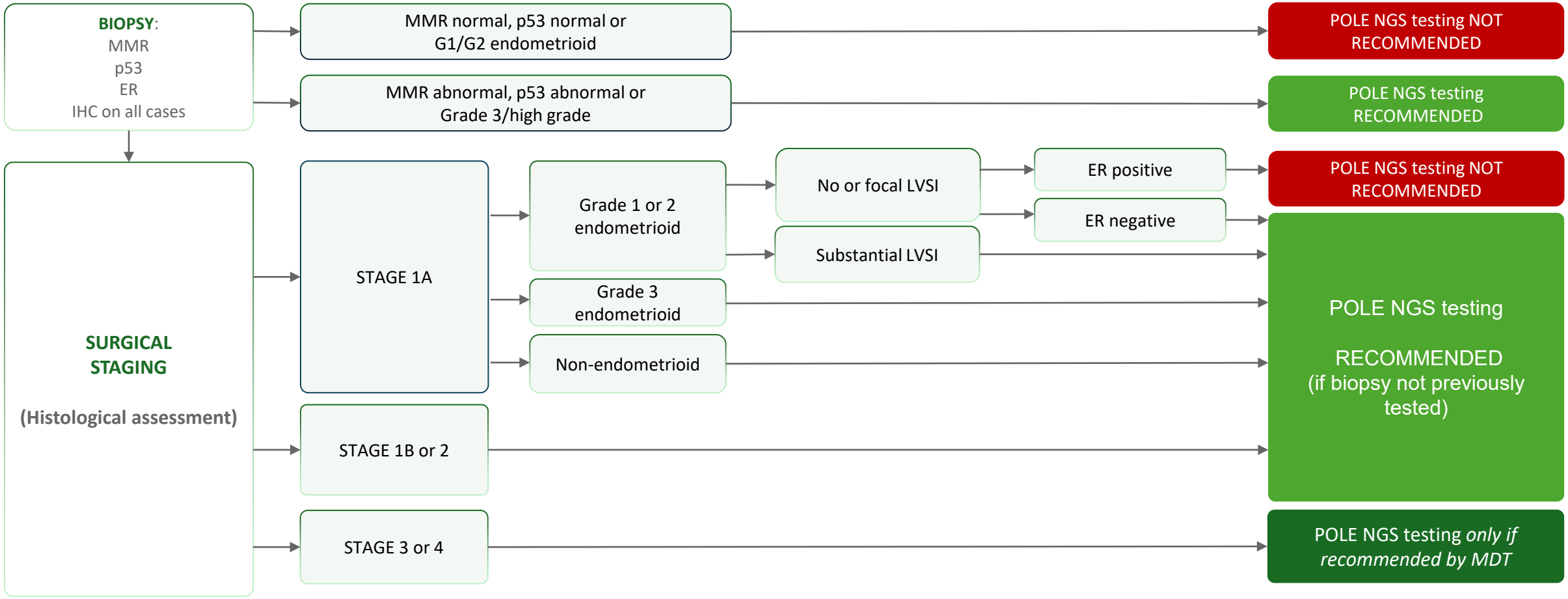
**Substantial LVSI is defined according to WHO criteria by ≥4 vessels in at least one H&E slide.

dMMR, mismatch repair deficient; **ER,** estrogen receptor; **FIGO**, International Federation of Gynecology and Obstetrics; **LVSI,** lymphovascular space invasion; **NSMP,** no specific molecular profile; **p53abn,** mutated tumour protein p53; **POLEmut,** DNA polymerase epsilon mutation

1. Concin N *et al*. Lancet Oncol. 2025;26(8):e423-e435- Update 2025. Presented at ESGO 2025, 20–23 Feb, Rome, Italy

SIMPLIFIED BAGP/BGCS POLE NGS Testing guidance[1]

All endometrial carcinomas regardless of histological type



BAGP, British Association of Gynaecological Pathologists; **BCGS**, British Gynaecological Cancer Society; **ER,** estrogen receptor; **G**, grade; **IHC,** immunohistochemistry; **LVSI**, lymphovascular space invasion; **MDT**, multidisciplinary team; **MMR,** mismatch repair; **NGS**, next generation sequencing; **POLE,** DNA polymerase epsilon

- Oaknin A *et al*. Ann Oncol. 2022;33;860-877

Gynecologic Oncology 156 (2020) 194–202

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journal homepage: www.elsevier.com/locate/ygyno

Clinical outcomes of patients with *POLE* mutated endometrioid endometrial cancer

Marina Stasenko [a], Irina Tunnage [a], Charles W. Ashley [b], Maria M. Rubinstein [c], Alicia J. Latham [c, d], Arnaud Da Cruz Paula [b], Jennifer J. Mueller [a, d], Mario M. Leitao Jr. [a, d], Claire F. Friedman [c, d], Vicky Makker [c, d], Robert A. Soslow [b, d], Deborah F. DeLair [e], David M. Hyman [c, d], Dimitriy Zamarin [c, d], Kaled M. Alektiar [d, f], Carol A. Aghajanian [c, d], Nadeem R. Abu-Rustum [a, d], Britta Weigelt [b, d], Karen A. Cadoo [c, d, *]

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[b] Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
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[d] Weill Medical College of Cornell University, New York, NY, USA
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[f] Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

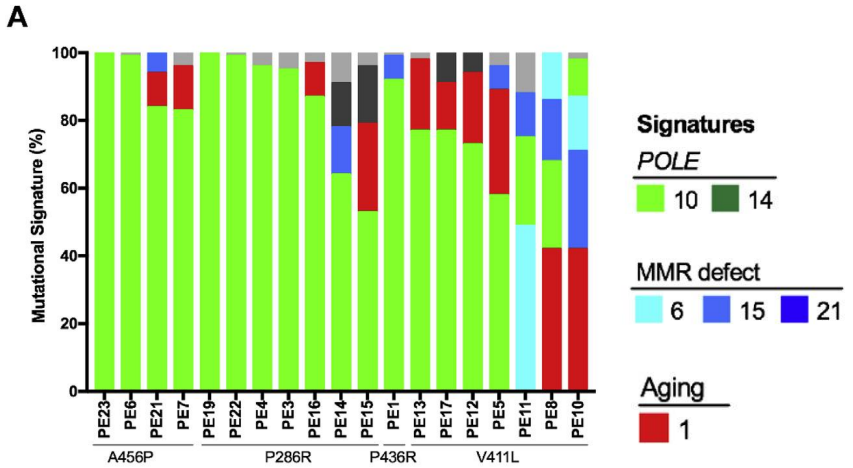
A B S T R A C T

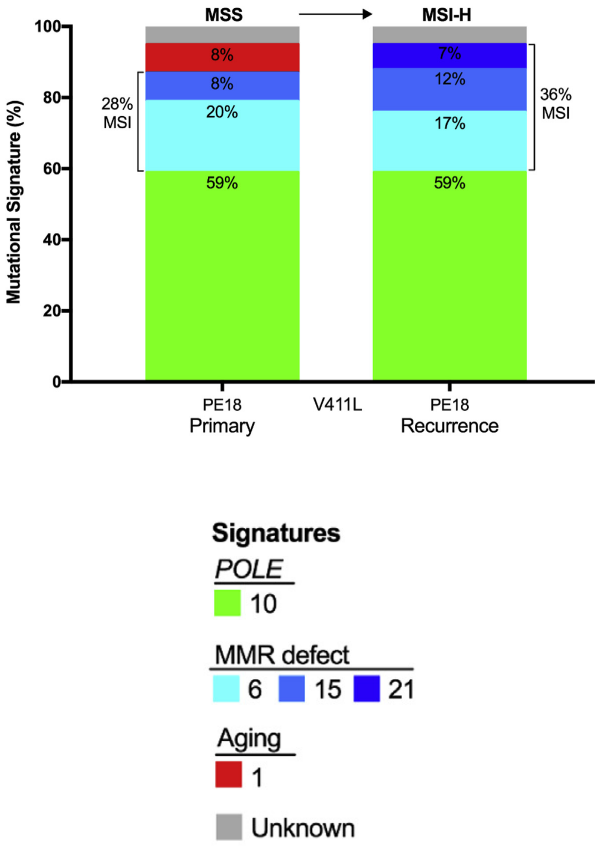
Objectives: Assess outcomes of a clinical cohort of patients with endometrioid endometrial cancer (EEC) harboring somatic *POLE* exonuclease domain mutations (EDMs).

Methods: Patients were consented to a protocol of tumor-normal massively parallel sequencing of 410–468 cancer related genes. EECs subjected to sequencing from 2014 to 2018 were reviewed. Tumors with somatic *POLE* EDMs were identified. EECs were assessed for microsatellite instability (MSI) using MSIsensor and immunohistochemical analysis for mismatch repair (MMR) proteins.

Results: Of the 451 EECs sequenced, 23 had a *POLE* EDM (5%): 20 primary and 3 recurrent tumors sequenced. Nineteen cases (83%) were stage I/II and 4 (17%) were stages III/IV. Thirteen EECs (57%) were of FIGO grades 1/2, 10 (43%) grade 3. All patients were treated with surgery and 17 (89%) received adjuvant therapy. Five (22%) demonstrated loss of DNA MMR protein expression, none were due to Lynch syndrome. MSIsensor scores were conclusive for 21 samples: 19 were microsatellite stable and 2 MSI-high. After median follow-up of 30 months, 4/23 (17%) developed recurrences: 3 with initial grade 3 stage I and 1 with grade 1 stage III disease. One patient with grade 2 stage IV EEC had progressive disease after treatment.

Conclusions: Patients with *POLE* EDM EEC have been shown to have a favorable prognosis. In this real-world cohort of patients, *de novo* metastatic disease and recurrences in initially uterine-confined cases were observed. Further research is warranted before incorporating the presence of *POLE* EDM into decision-making regarding adjuvant therapy.





Adapted from Figure from Stasenko M *et al*[1]

mages provided are courtesy and responsibility of speaker

- Stasenko M *et a*l. Gynecol Oncol. 2020;156(1):194-202

Patterns of cytotoxic T-cell densities in immunogenic endometrial cacners reveal a potential mechanism for differences in immunotherapy efficacy[1]

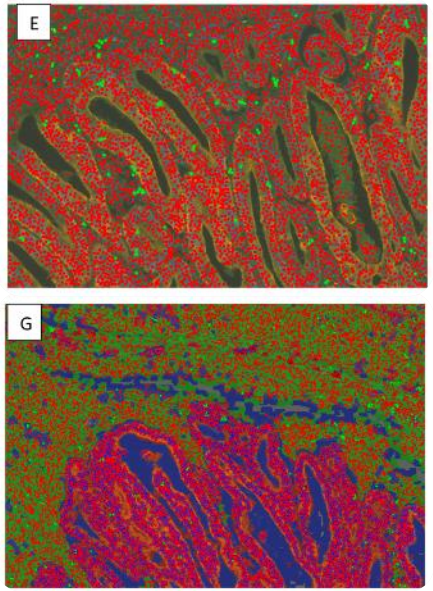
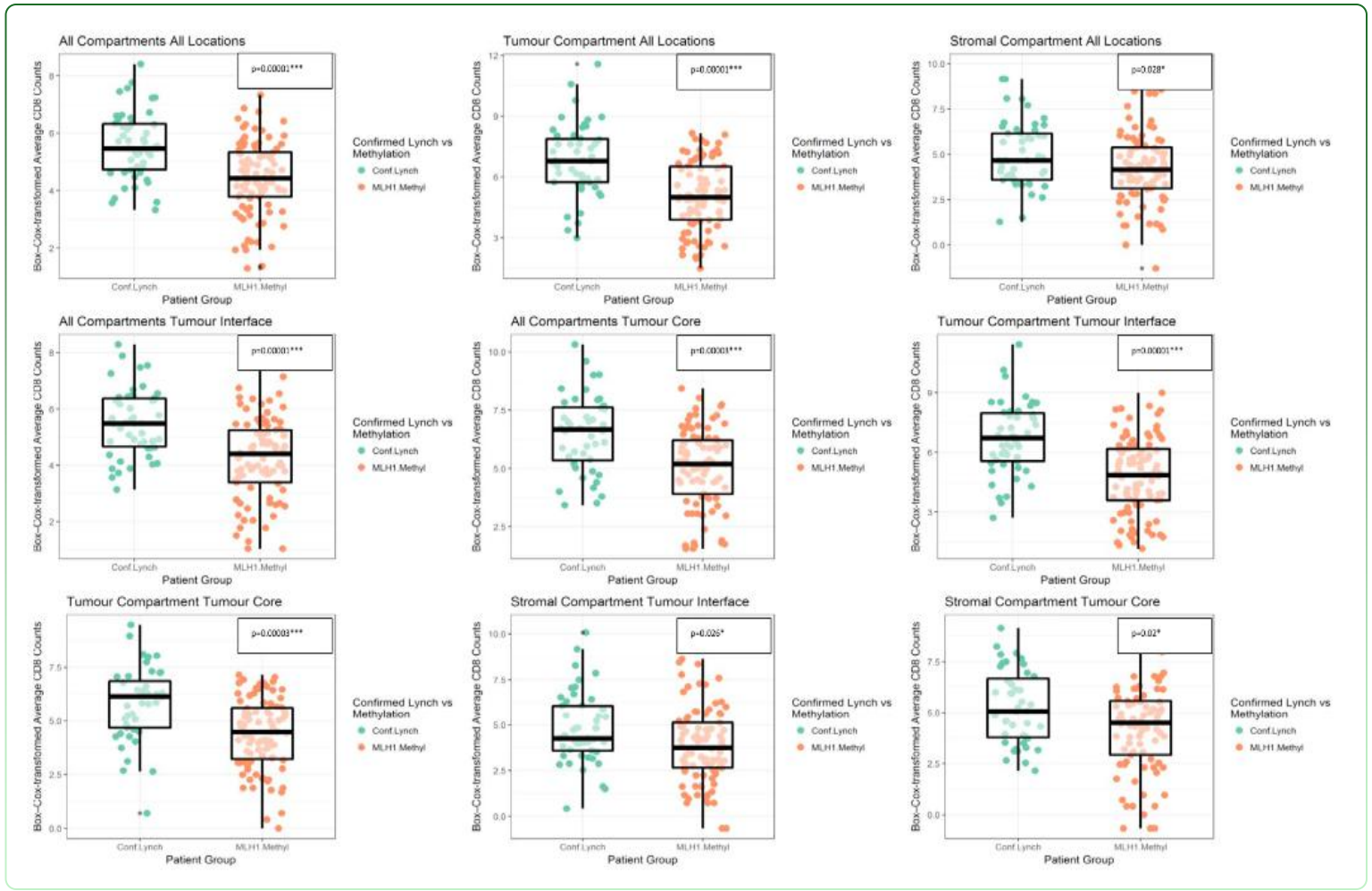


Figure 3 Box and whisker plots comparing the CD8+ counts of confirmed Lynch syndrome endometrialcancers versus MLH1_methylated endometrial cancers in various tumour locations.



MLH1, **MutL Homolog 1**

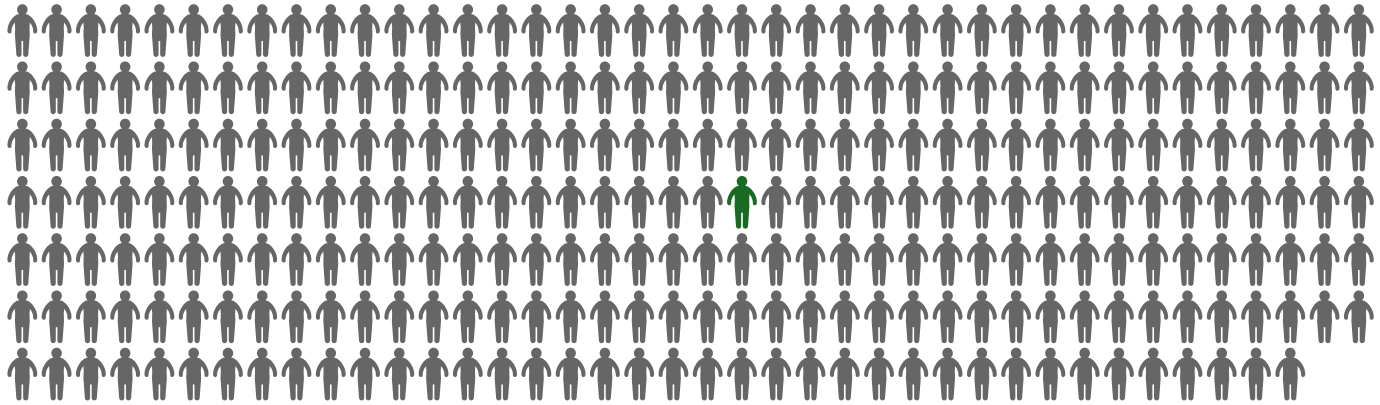
- Ryan N *et a*l. BMJ Oncol. 2024;3(1):e000320

What is Lynch syndrome?

Lynch syndrome is an autosomal dominant cancer predisposition syndrome arising from a dysnfunctional DNA mismatch repair (MMR) system

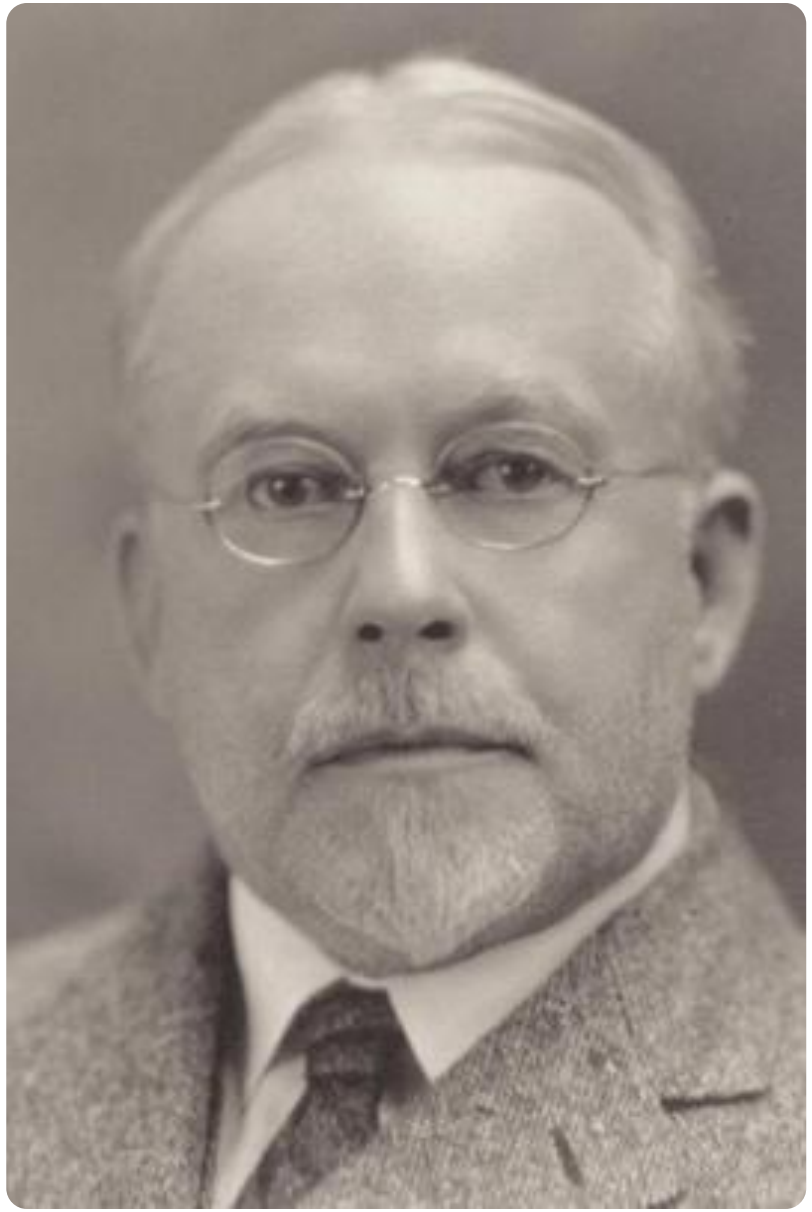
Up to 95% of Lynch syndrome carriers are unaware

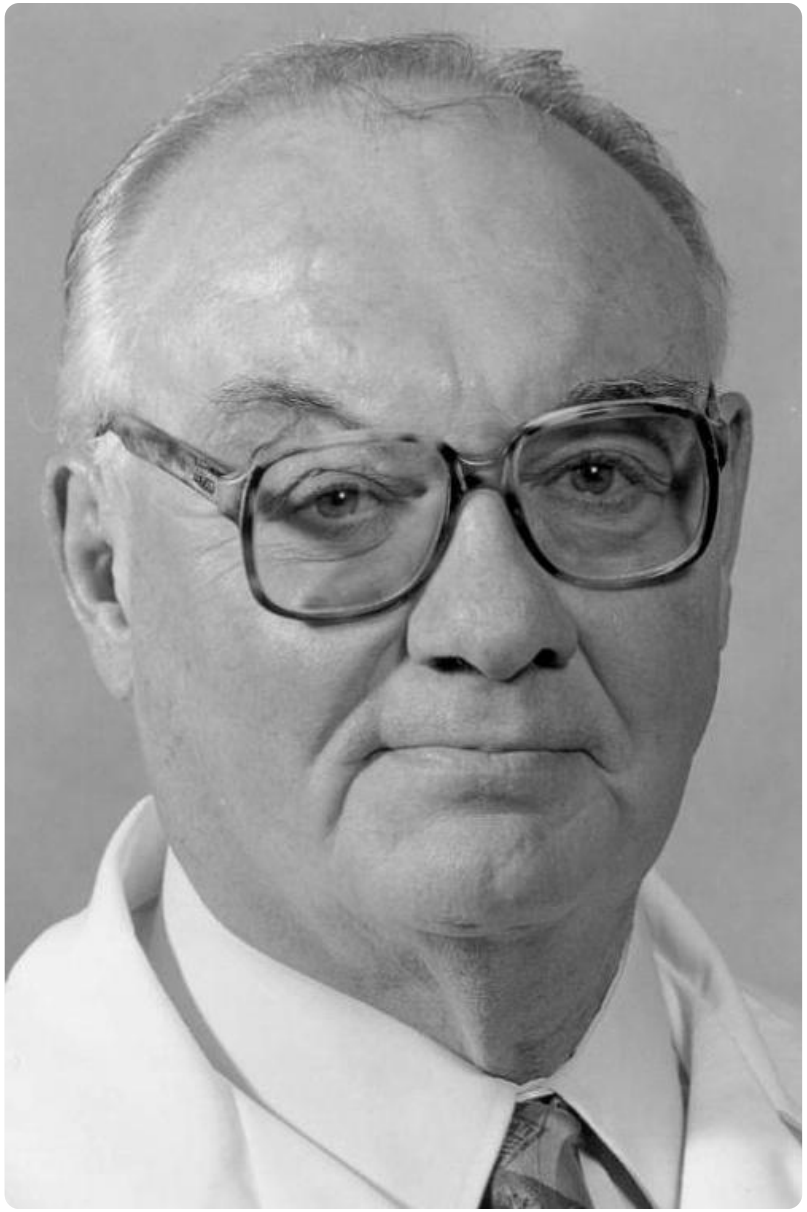
Lynch syndrome may occur in up to **1 in 278** people

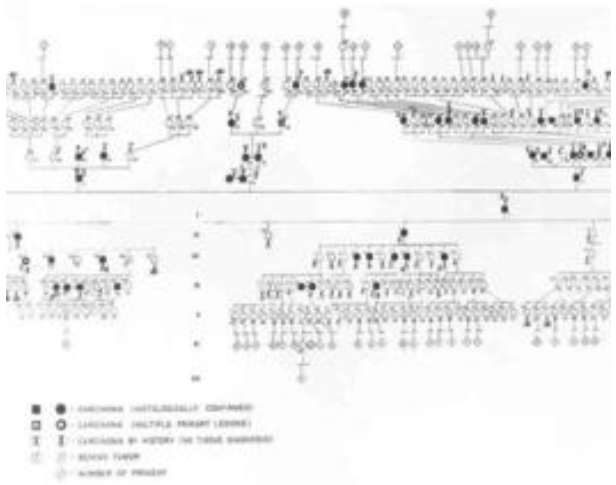


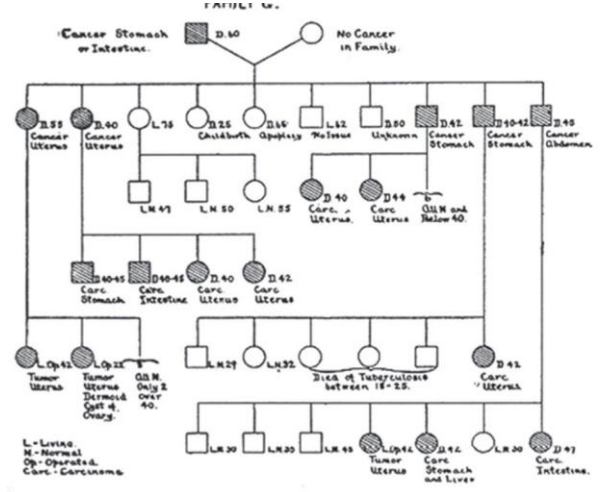
making it the most common inherited cause of cancer

DNA, deoxyribonucleic acid; **MMR,** mismatch repair

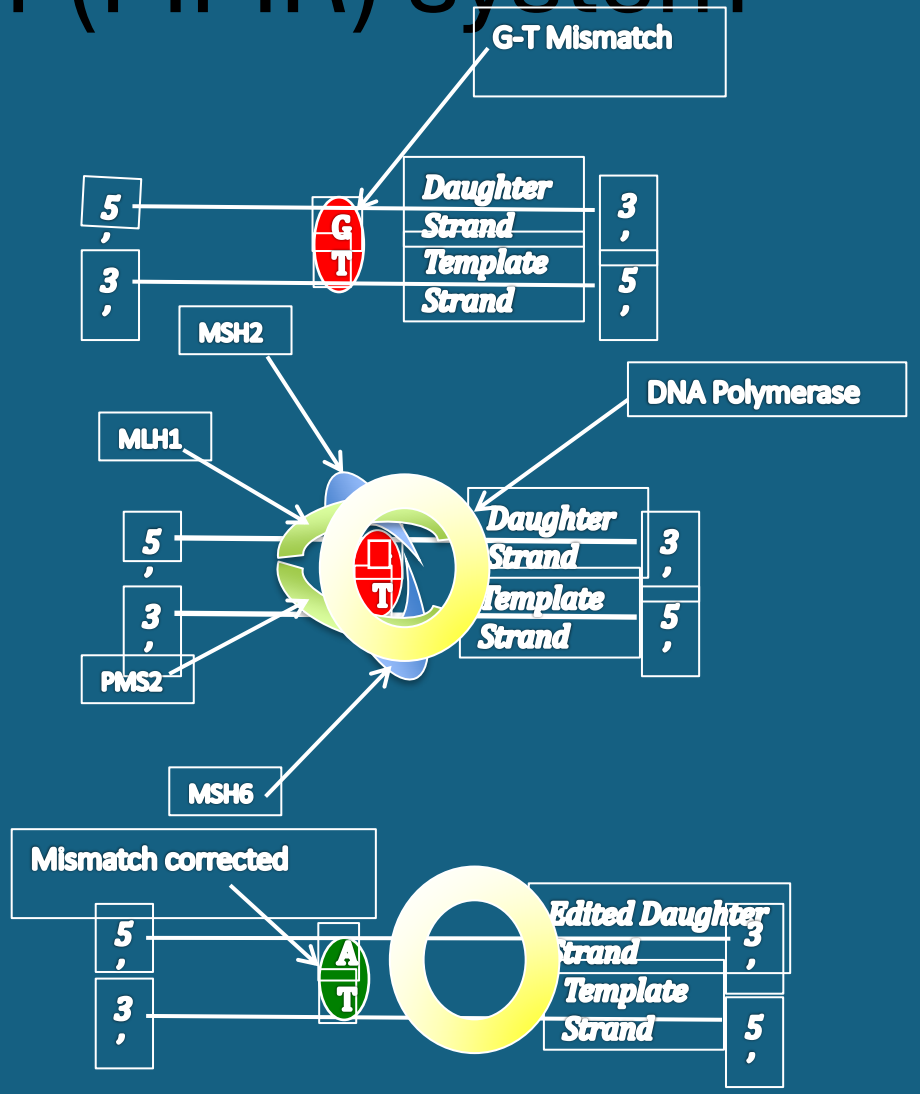




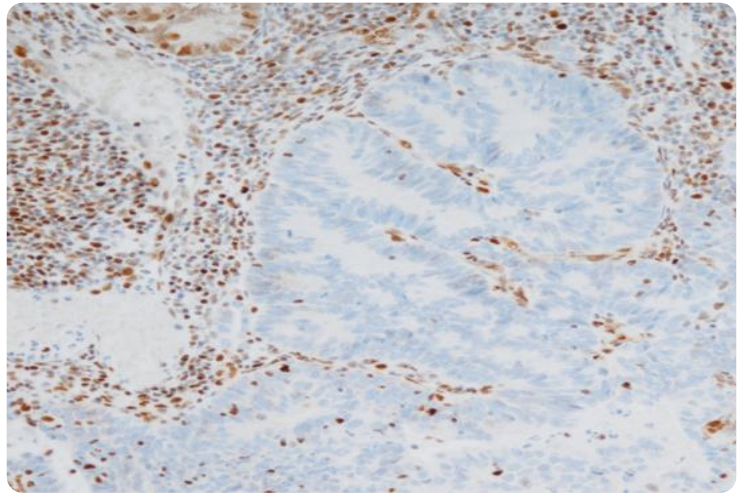


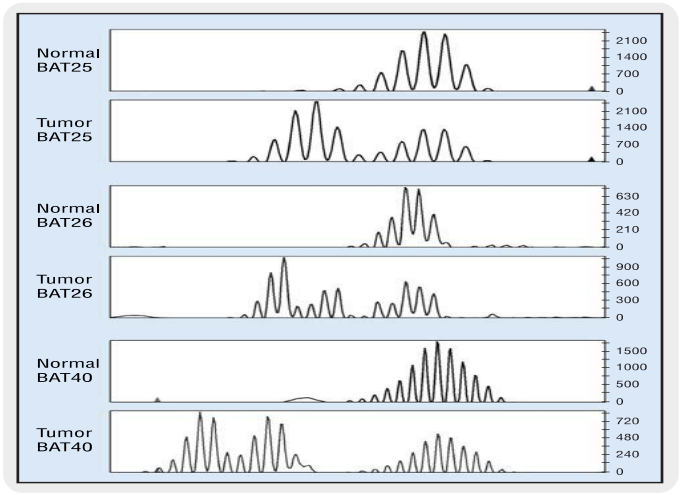

Cancer Stomach or Intestine.
No Cancer in Family
L-Living
N-Normal
Op-Operated.
Canc-Carcinoma

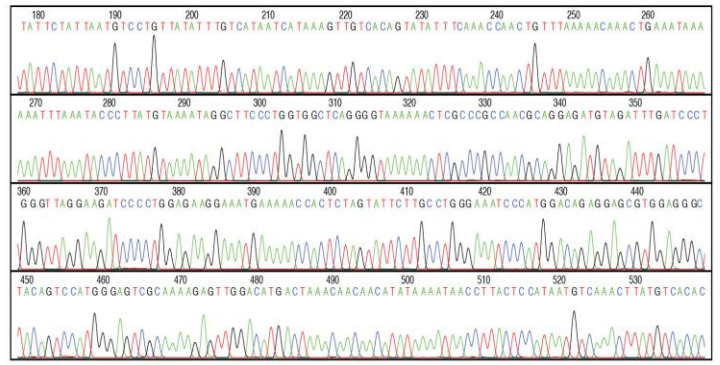
Mismatch repair (MMR) system



Thank you Dr Neal Ramchander







DNA sequence data from an automated sequencing machine

PLOS MEDICINE[1]

PLOS MEDICINE

RESEARCH ARTICLE

The proportion of endometrial tumours associated with Lynch syndrome (PETALS): A prospective cross-sectional study

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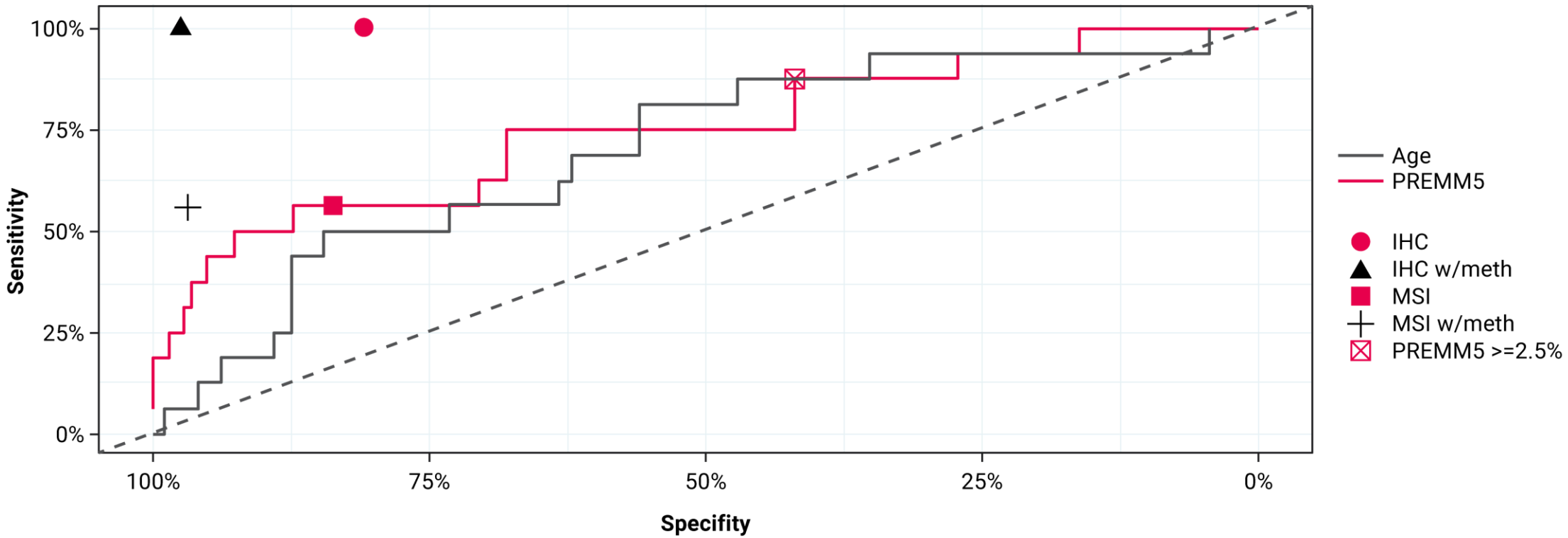
- Ryan NAJ *et al*. PLoS Med. 2020;17(9):e1003263


100%
75%
50%
25%
0%
Sensitivity
100%
75%
50%
25%
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Specifity
Age
PREMM5
IHC
IHC w/meth
MSI
MSI w/meth
PREMM5 >=2.5%

SPECIAL ARTICLE | Genetics inMedicine

Open

The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome

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Purpose: There are no internationally agreed upon clinical guidelines as to which women with gynecological cancer would benefit from Lynch syndrome screening or how best to manage the risk of gynecological cancer in women with Lynch syndrome. The Manchester International Consensus Group was convened in April 2017 to address this unmet need. The aim of the Group was to develop clear and comprehensive clinical guidance regarding the management of the gynecological sequelae of Lynch syndrome based on existing evidence and expert opinion from medical professionals and patients.

Methods: Stakeholders from Europe and North America worked together over a two-day workshop to achieve consensus on best practice.

Results: Guidance was developed in four key areas: (1) whether women with gynecological cancer should be screened for Lynch syndrome and (2) how this should be done, (3) whether there was a role for gynecological surveillance in women at risk of Lynch syndrome, and (4) what preventive measures should be recommended for women with Lynch syndrome to reduce their risk of gynecological cancer.

Conclusion: This document provides comprehensive clinical guidance that can be referenced by both patients and clinicians so that women with Lynch syndrome can expect and receive appropriate standards of care.

Genetics in Medicine (2019) https://doi.org/10.1038/s41436-019-0489-y

Keywords: Lynch syndrome; endometrial cancer; screening surveillance; guidance

- Crosbie EJ *et al*. Genet Med. 2019;21(10):2390-2400

Testing strategies for Lynch syndrome in people with endometrial cancer

Draft SW pathway for MMR IHC for endometrial cancer (DG42)

For the identification of patients with Lynch syndrome

All patients with suspected endometrial tumours being biopsied/resected – **given information leaflet**

MDT/ Clinical team

Local Cell Pathology laboratories

All endometrial tumour biopsy or resection specimens (FFPE) for **MMR IHC (MLH1, MSH2, PMS2, MSH6)**

No loss of staining

Cell Path report to MDT/clinical team: MMR proficient **Lynch syndrome unlikley**

In the presence of a strong clinical or family history referral to clinical genetics should be considered even if MMR IHC proficient.

Loss of MSH2, MSH6 or isolated PMS2

Cell Path report to MDT/clinilcal team: MMR (MSH2, MSH6 or PMS2) deficient **Lynch syndrome likley**

Loss of MLH1 or MLH1+PMS2

SWGLH

Send sample to SWGLH (NBT) for **MLH1 methylation analysis**

Send sample to SWGLH (NBT) for **MLH1 methylation analysis**

Cell Path report to MDT/clinical team: MMR (MLH1) deficient but MLH1 hypermethylated **Lynch syndrome unlikely**

MDT/clinical team to consider referral to Clinical Genetics

IHC, immunohistochemistry; **MDT**, multidisciplinary team; **MMR,** mismatch repair

An audit of current endometrial cancer mismatch repair testing and onward genetic referral in the United Kingdom and Republic of Ireland between March 2022 to March 2023.

Fifteen centres contributed data

2353

Number of endometrial cancers included in this audit

91%

Of endometrial cancers had tumour-based MMR testing

28%

Of tested endometrial cancers were MMR deficient

55%

Of those who should have had genetic testing had recorded germline results

<1%

Of this cohort had confirmed Lynch syndrome. (The prevalence should be 3%[1])

MMR, mismatch repair

An audit of current endometrial cancer mismatch repair testing and onward genetic referral in the United Kingdom and Republic of Ireland between March 2022 to March 2023

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2353

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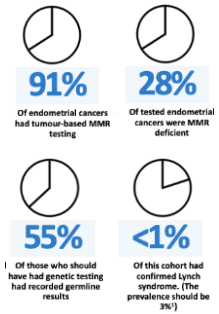
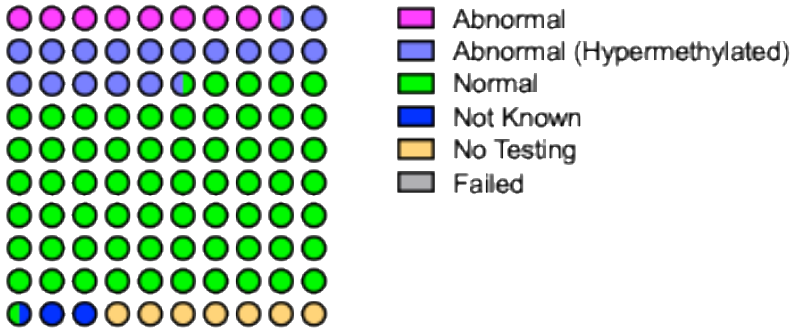
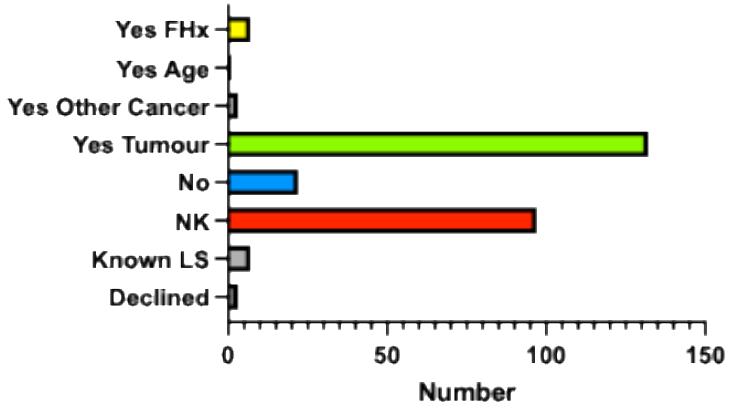


Outcomes of Tumour Based Testing



91% Of endometrial cancers had tumour-based MMR testing (n=2353)

Referral to Genetics when indicated

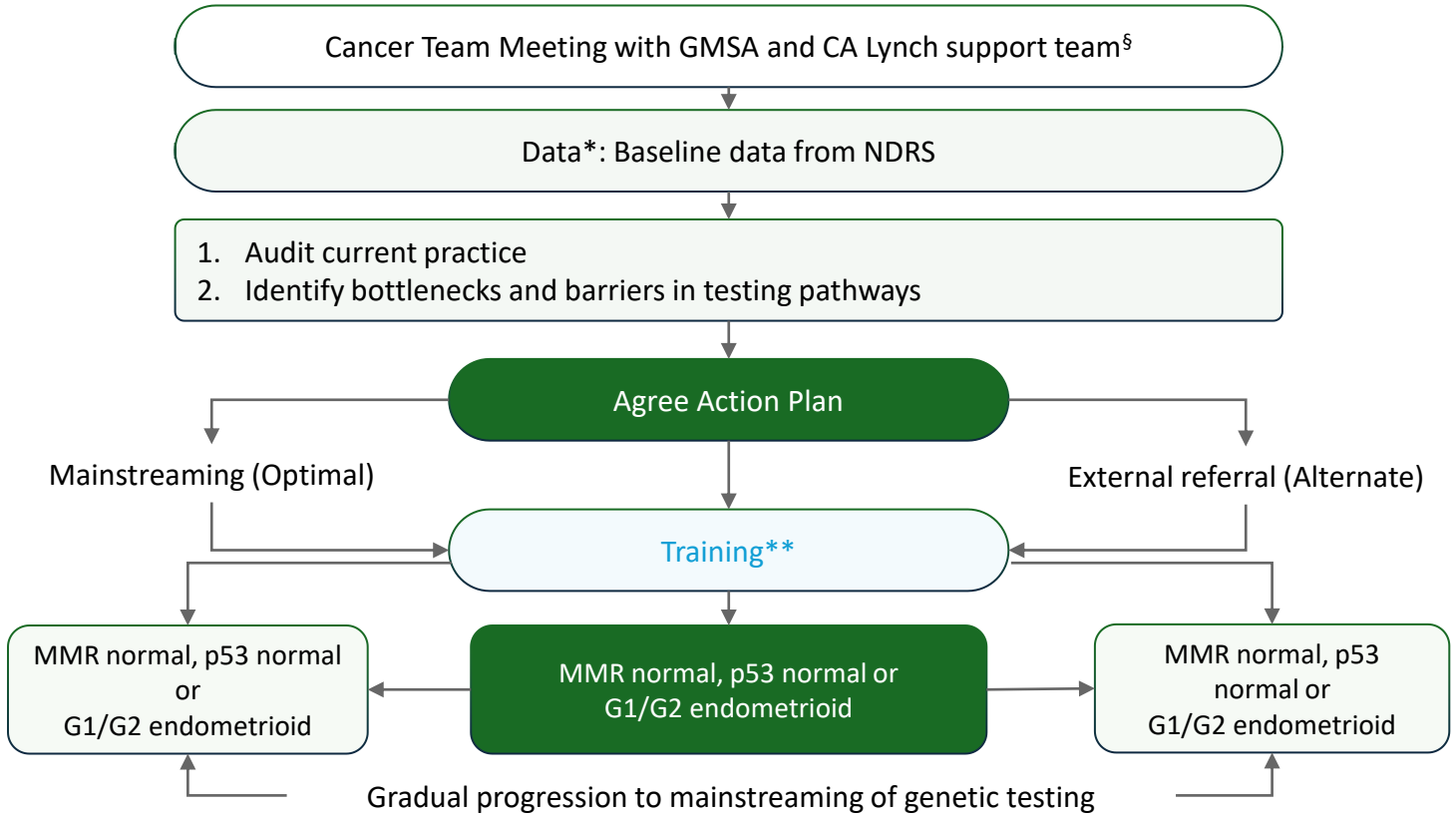


55% Of those who should have had genetic testing has recorded germline results (n=2353)

MMR, mismatch repair

The English National Lynch Syndrome transformation project: an NHS Genomic Medicine Service Alliance (GMSA programme)[1]

Kevin J Monahan, Neil Ryan, Laura Monje-Garcia, Ruth Armstrong, David N Church, Jackie Cook, Alaa Elghobashy, Fiona Lalloo, Sally Lane, Frank D McDermott, Tracie Miles, Steven A Hardy, Adele Tyson, Valerie Ya Wen Wang, Anna Kim, Simone Gelinas, Francesca Elmslie, Adam C Shaw



§ Meeting with:
1. Cancer team members: Lynch syndrome champion, cancer nurse specialist, pathologist
2. Genomic medical service alliance (GMSA) team: Regional medical lead and regional
3. Lynch syndrome nurse
4. Cancer alliance (CA): Project management team

*Data:
1. National disease registration service (NDRS) monitoring framework
2. Audit: Locally performed audit of testing outcomes in 30 consecutive cancer patients

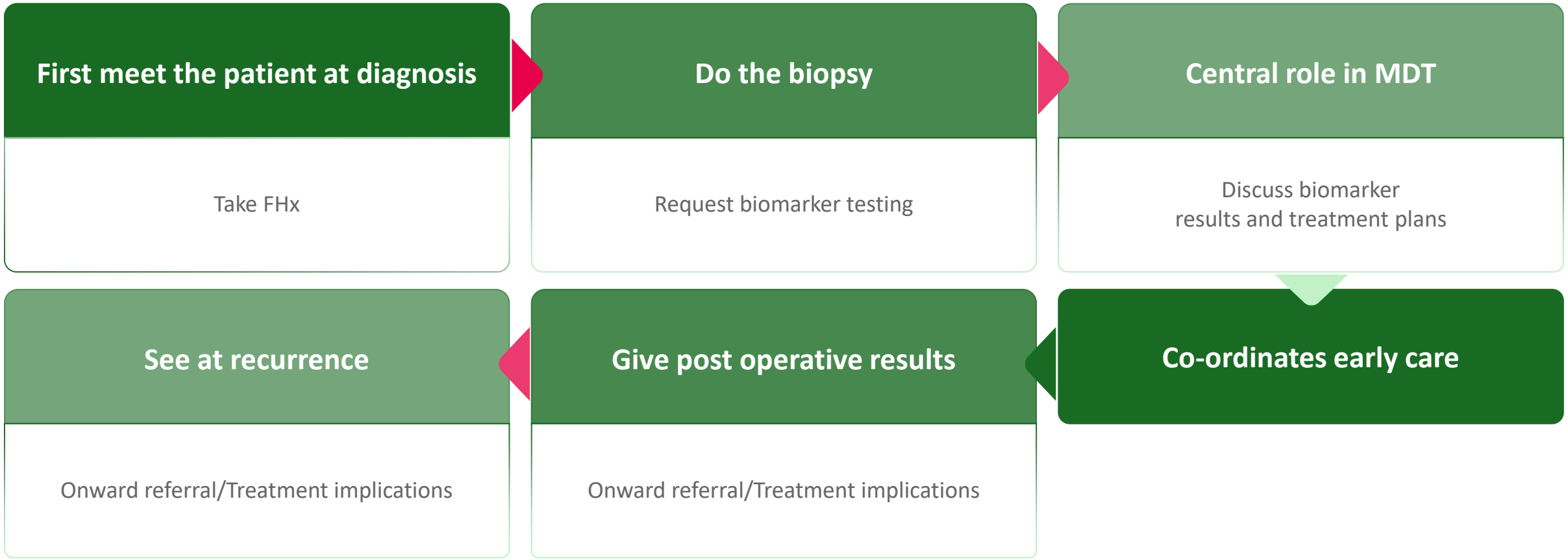
**Training:
1. Online training module completion
2. Participate in national and regional workshops
3. One-one support from GMSA team on site

Figure 1 Flow chart for support of delivery of LS diagnosis by cancer teams (details of this pathway are outlined in the section 'effective diagnostic delivery with mainstreaming').

CA, cancer alliance; GMSA, genomic medical service alliance; LS, Lynch syndrome; MMR, mismatch repair; **NDRS**, National Disease Registration Service

- Monahan KJ *et al*. BMJ Oncol. 2023;2(1):e000124

Surgeon

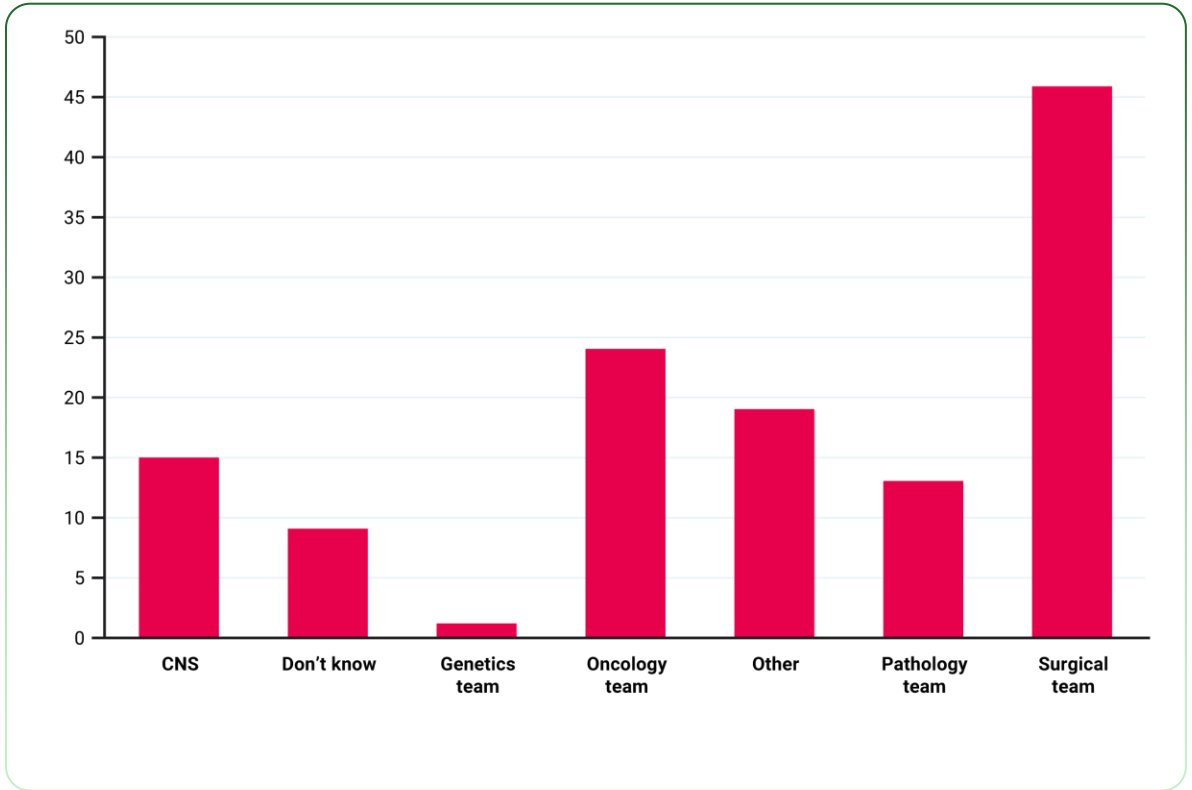


This slide reflects speaker experience

FHx: Family history, **MDT;** multidisciplinary team.

The English National Lynch Syndrome transformation project[1]

MDT member responsible for dealing with results



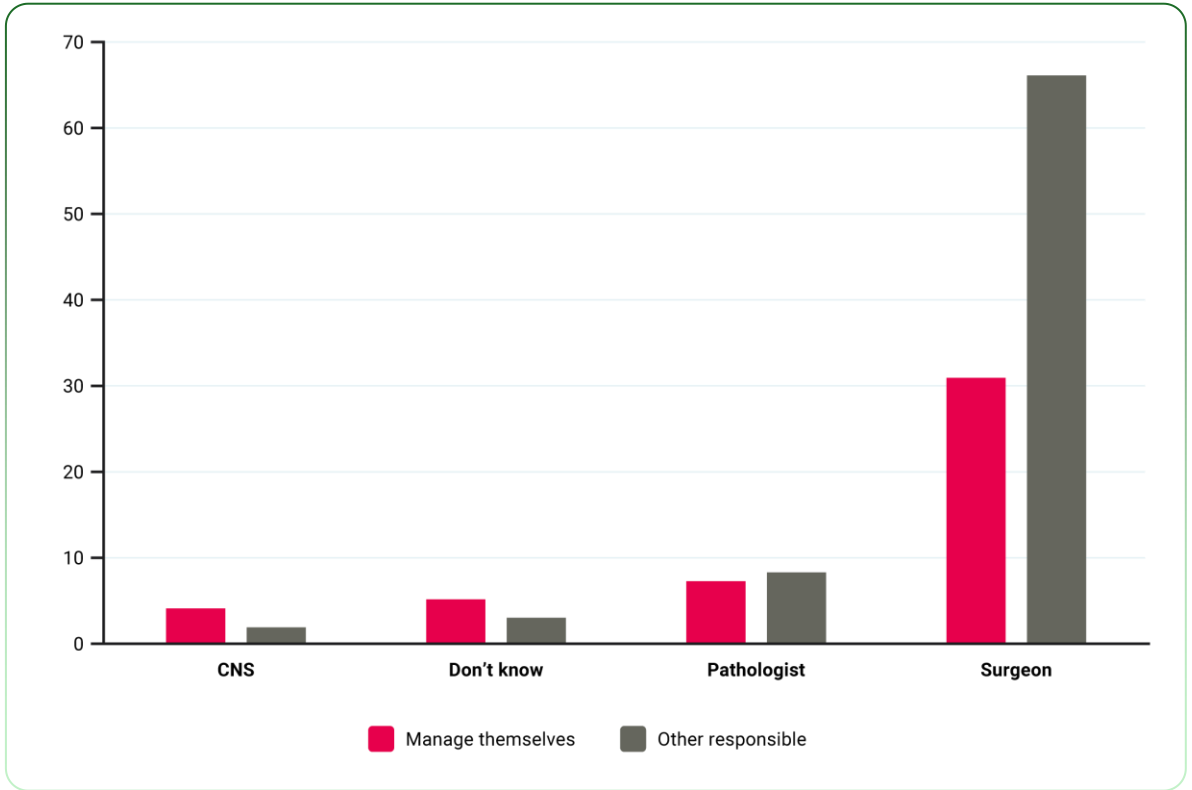


Figure 2 Cancer multidisciplinary team (MDT) member responsible for (A) receiving and actioned a somatic testing results (B) Respondent's specialty (blue columns); and opinion about which specialists they feel should manage these patients (red columns). The majority of respondents felt that someone else should be managing their patients at high risk of hereditary colorectal cancer (from baselines survey of LS champions). Y-axis=numbers of respondents.

CNS, cancer nurse specialist; **LS,** Lynch syndrome; **MDT;** multidisciplinary team.

- Monahan KJ *et al*. BMJ Oncol. 2023;2(1):e000124

Mainstreaming

1 → 2 → 3 → 4 → 5

Oncologist

Refers the BC patient to a genetic counsellor to discuss BRCA testing

Gen

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Pathologist, Clinical Scientist + Bioinformatician

Laboratory DNA analysis

Gen

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Oncologist

Receiving BRCA status + determines treatment options

The average waiting time for a genetics appointment in the UK is 12-15 weeks

BRCA t been inconsistent and unsuccessful, with only 15-30% of eligible patients being referred for testing

TAKE home

MMR results save lives

Surgeons are the conductors of the patients journey so should lead:

- On biomarker testing
- Biomarker results
- Consider implications

We should all aim to mainstream

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3 Health Economics Group, University of Exeter Medical School, University of Exeter, Exeter, Devon, UK

4 The Lynch Syndrome and Family Cancer Clinic, St Mark's Hospital and Academic Institute, Harrow, London, UK Imperial College London, London, UK

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UNCERTAINTIES

Should women with Lynch syndrome be offered gynaecological cancer surveillance?

NAJ Ryan, [1,2] T Snowsill, [3] E McKenzie, KJ Monahan, [4] D Nebgen[5]

What you need to know

- Lynch syndrome is an inherited genetic condition associated with an increased risk of endometrial and ovarian cancer in women
- Limited low quality evidence from observational studies show that gynaecological surveillance detects cancers in women with Lynch syndrome; but it is uncertain if this improves survival, and the optimal testing strategy is not established
- Inform women with Lynch syndrome about their risk of developing cancer and initiate a discussion about their preference for risk reducing surgery which is definitive, or options for annual review and gynaecological surveillance, explaining their risks and benefits

Guidelines published in 2020 by the National Institute for Health and Care Excellence (NICE) recommend testing for Lynch syndrome in women with the Prospective Lynch Syndrome database (http://www.plsd.eu). For a woman with Lynch syndrome, the lifetime risk of endometrial or ovarian cancer is 40-60% and 10-17%, respectively, the incidence increasing with age beyond 40 years.[2]

Data sources and selection strategy

We searched CENTRAL, Medline, Embase, and the Cochrane Database of Systematic Reviews for articles in English from the database inception to February 2021. Our search yielded 974 records. After removal of duplicates, 719 were available to screen. Screening was done by two independent reviewers using the Rayyan platform (https://www.rayyan.ai). Of these, 49 underwent full title review. Full manuscripts (not conference abstracts) are summarised in the supplementary table. All the studies identified were observational in nature. Our systematic review also identified four guidelines that addressed gynaecological surveillance in Lynch syndrome carriers; these are detailed in table 1.

- Ryan N *et al*. BMJ. 2021;374:n2020

UK, European, US and National Comprehensive Cancer Network gynaecological surveillance recommendations for women with Lynch syndrome

Guidelines	UK 2019[6]	ESMO 2016[7]	ASCO 2015[8]	NCCN2021[9]
Symptom awareness Education	Yes, age 25	Yes	Yes	Yes
Gynaecological examination	Yes	Yes	Yes	-
Pelvic ultrasound	No	Yes	Yes	No†
CA125	No	Not stated	No	No†
Endometrial biopsy	No	Annually from age 30-35	Annually from age 30-35	Every 1-2 years from age 30-35
Hysterectomy and bilateral salpingo-oophorectomy	Yes‡	Yes	Yes	Yes
Research needed	Yes	-	-	-

†Can consider at the physician's preference. ‡No earlier than 35-40 years and preoperative endometrial biopsy and pelvic ultrasound. United Kingdom (UK) Manchester guidelines (NICE does not currently offer a recommendation on surveillance), European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN).

PREDI-LYNCH funded with 13,6 million Euro

The European initiatitive will develop validated, non-invasive biopsy tests for cancer prediction in people with Lynch Syndrome.

European Commission

PREDI-LYNCH Project Overview

Funding

€13.6 million from the EU Horizon Missions programme

Coordination

Oslo University Hospital

Partners

28 organisations across Europe

UK Lead

Edinburgh University (€1.4 million share)

Goal

Early cancer detection in individuals with **Lynch syndrome** – the most common hereditary cancer syndrome linked to colorectal, endometrial, and other abdominal cancers.

Innovation

Development of an **AI-integrated liquid biopsy** screening method using different technologies such – affordable, non-invasive, and predictive.

Summary

We all need a degree of genetic fluency

Genetic testing saves lives through prevention and treatment

We need to do better in LS screening in endometrial cancer

Gynaecological cancer surveillance is controversial but it maybe we need better tools

Genetic risk in gynaecological cancer should be managed by an expert supported by an expert MDT

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Thank you

THE UNIVERSITY of EDINBURGH