



Hereditary CRC syndromes in 2026: Beyond Lynch – what you need to know (15 mins)

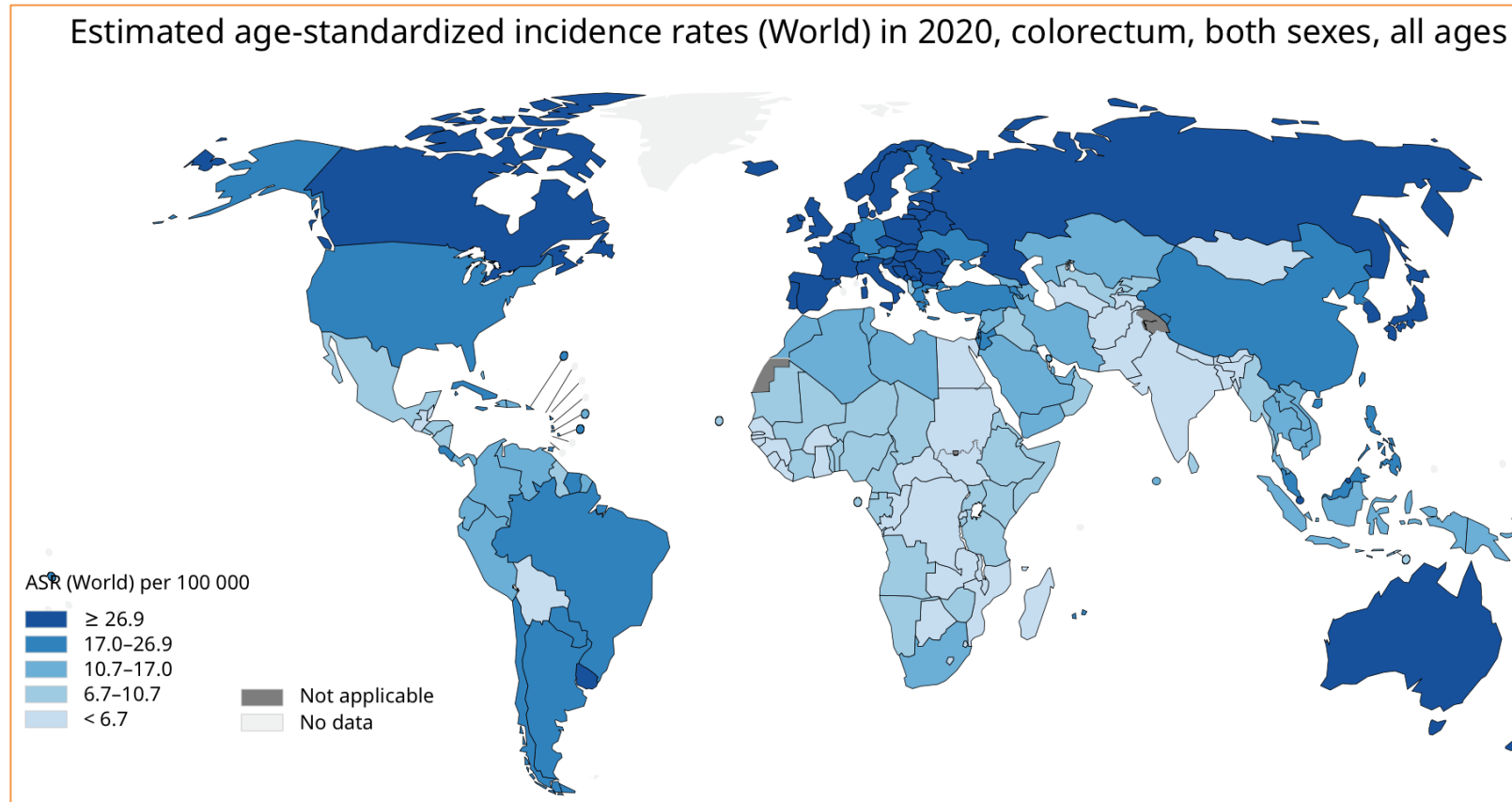
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- NHS England, Clinical Lead for LGI Cancer



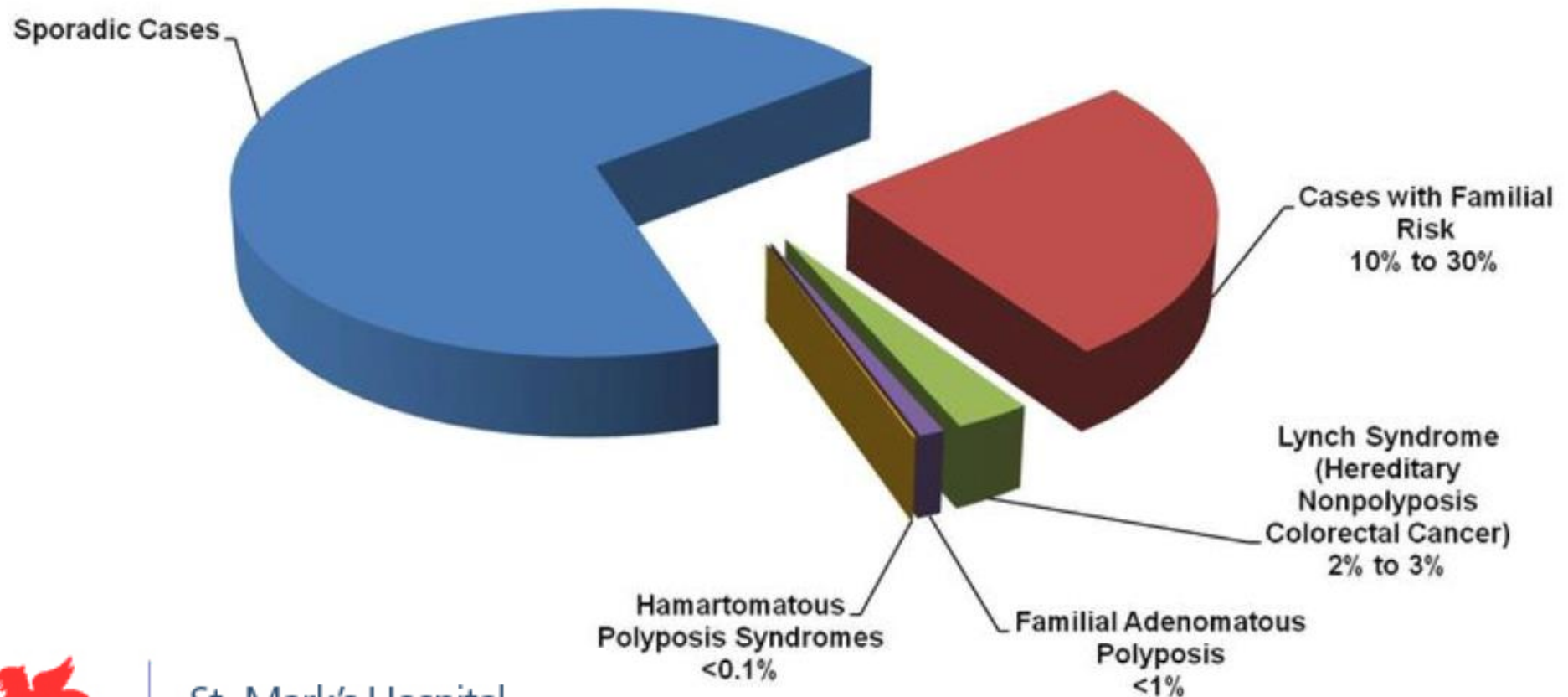
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Colorectal cancer epidemiology



In 2020 worldwide there are estimated to have been 1,931,590 new cases. There is substantial geographical variation in incidence across the world

Prevalence of hereditary causes among CRC



Q1. When should you suspect hereditary bowel cancer?

Q2. How are you going to diagnose it?

Q3. What are you going to do about it?

When to suspect hereditary CRC

- Around 30-35% of CRC's are familial BUT only **5–6%** are caused by a known inherited genetic change (mutation) passed down through families.

When should you suspect it?

- Bowel cancer before age **50**
- More than one bowel cancer
- Multiple bowel polyps
- Several close relatives with bowel or related cancers
- A family history spanning several generations
- Certain combinations of cancers (such as bowel and uterine cancer)

How to diagnose hereditary bowel cancer

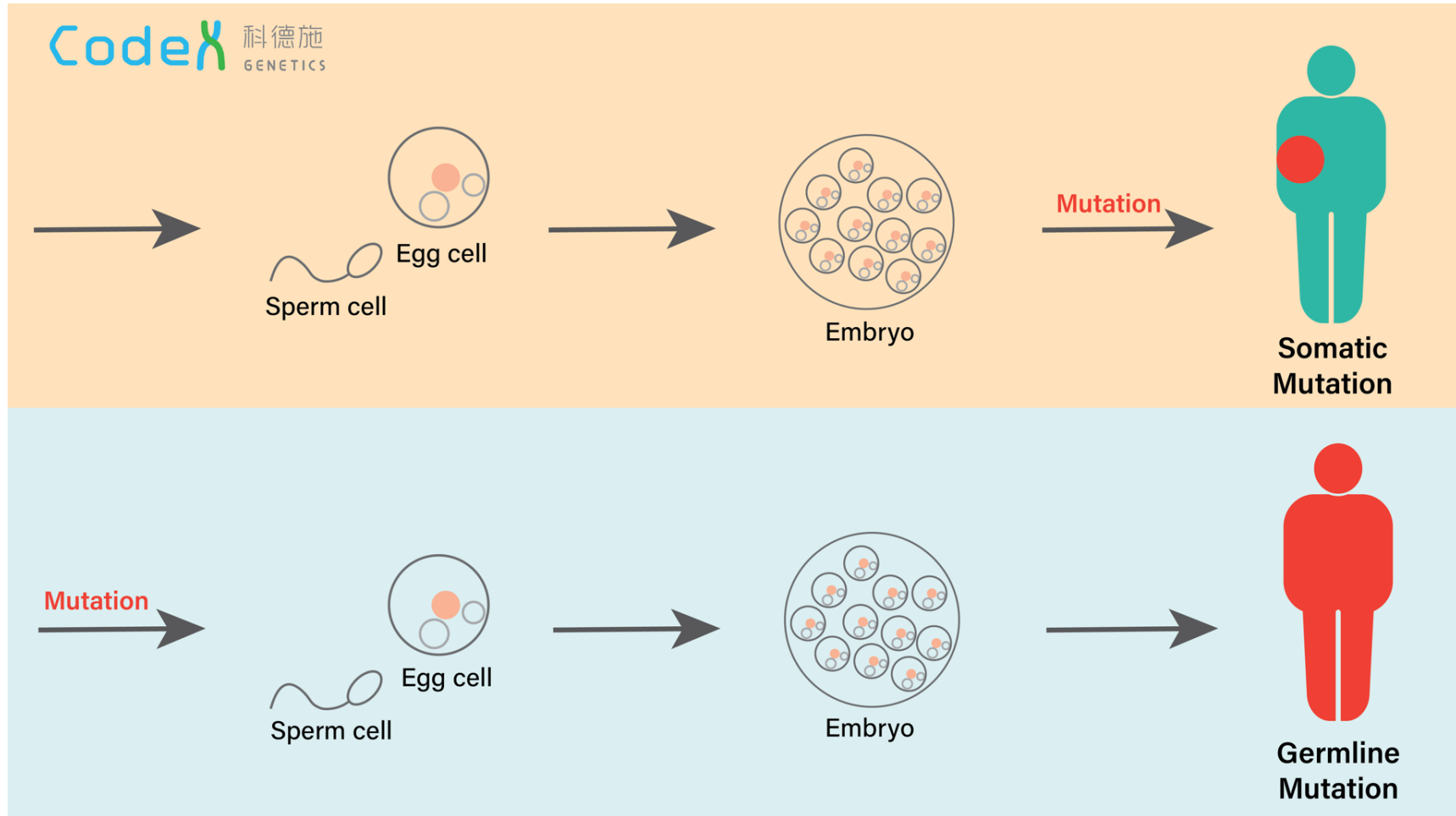
- Clinical presentation, FH & phenotype

- Endoscopy

- Histopathology

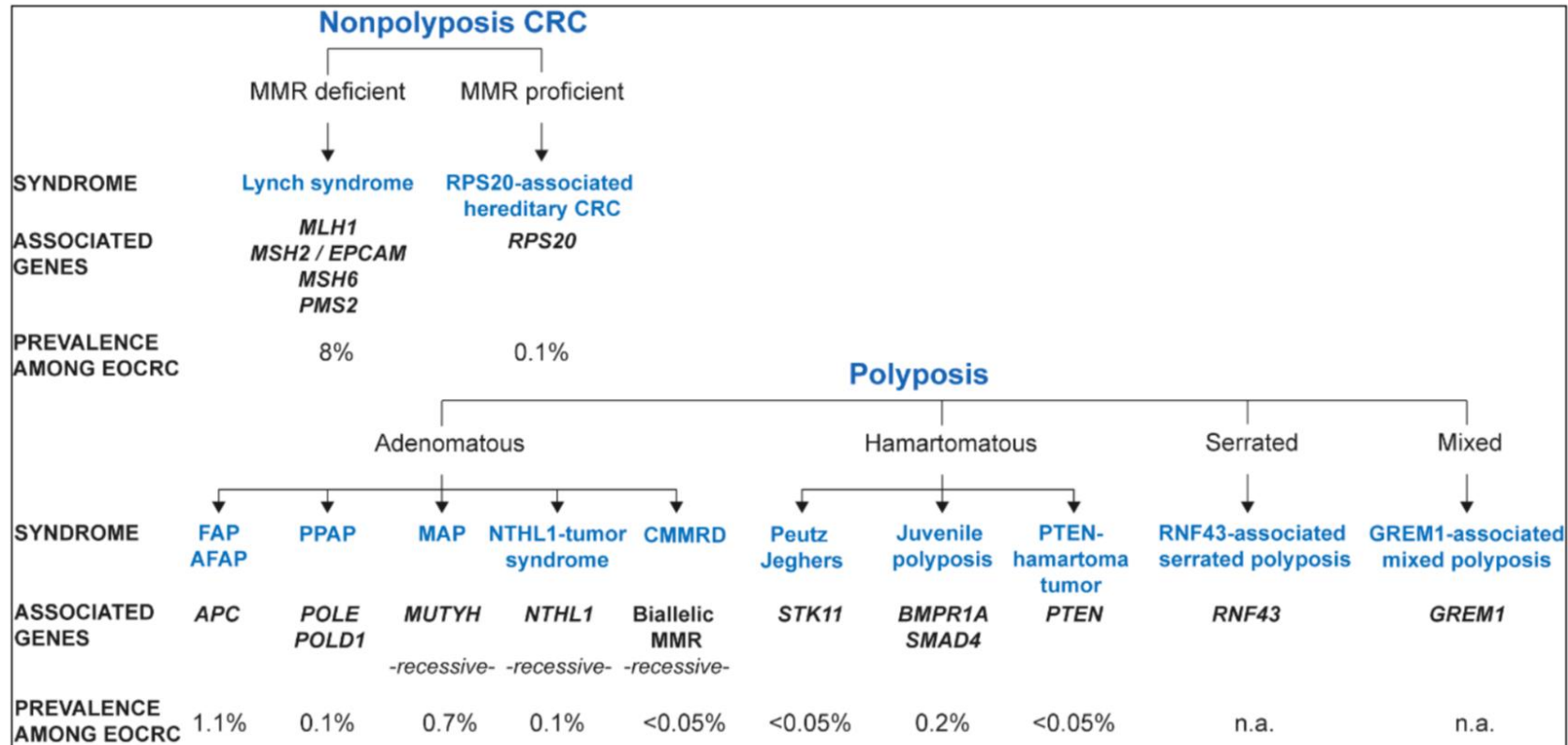
Gene testing

Somatic versus germline mutation



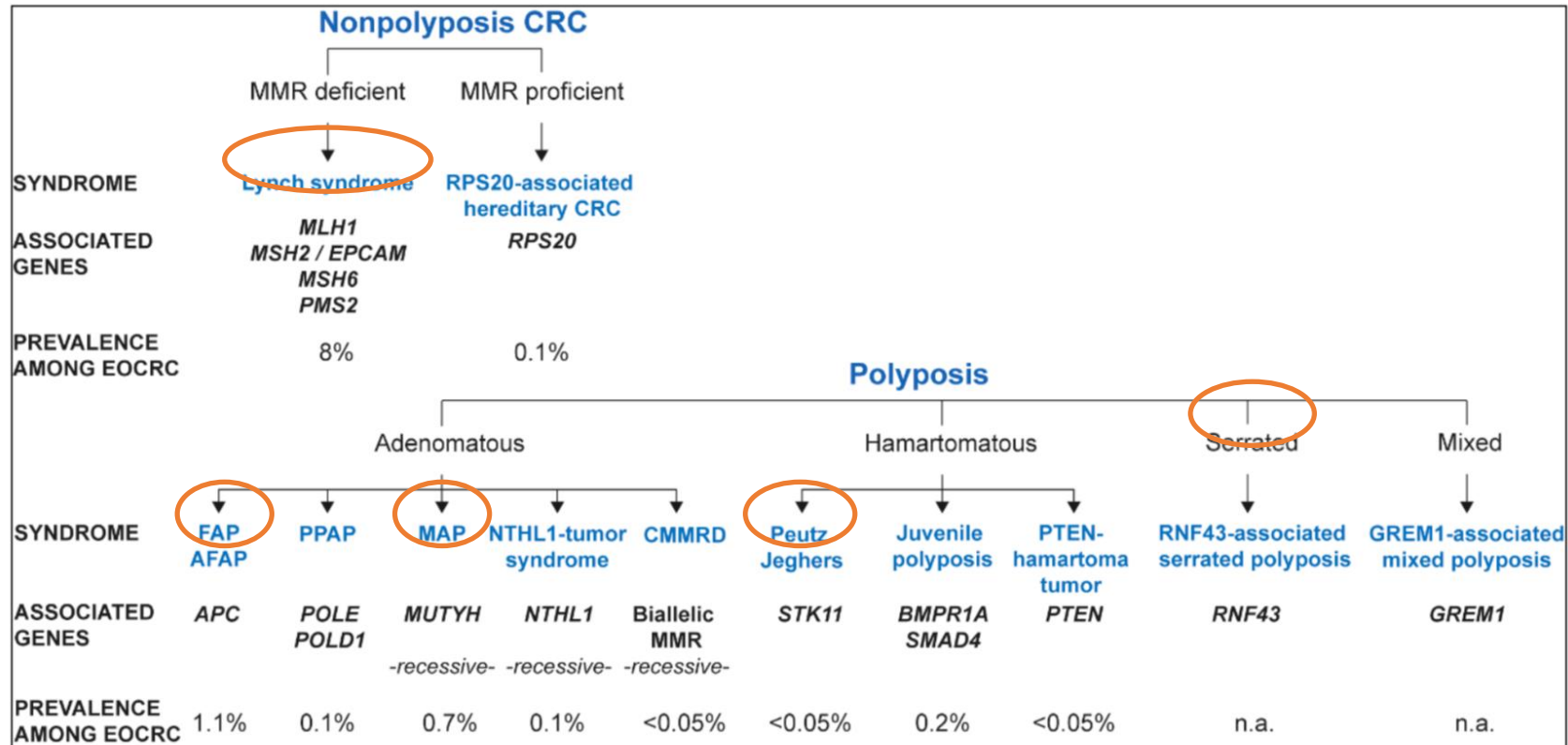
Hereditary colorectal cancer and causal genes

Polypsis versus Non-Polypsis



Hereditary colorectal cancer and causal genes

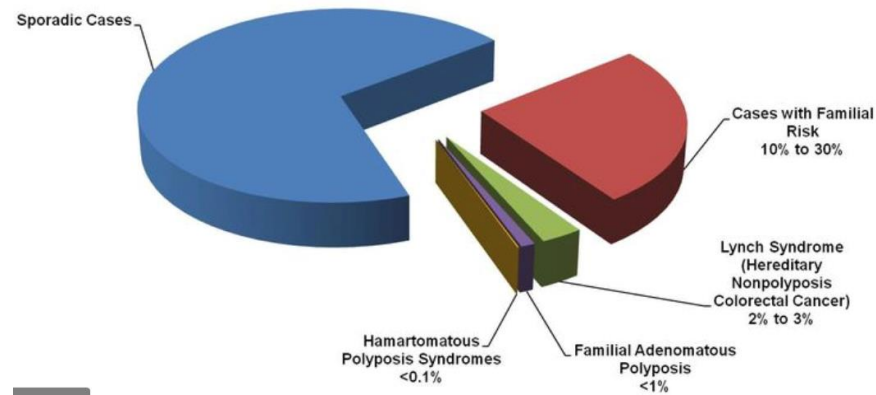
Polypsis versus Non-Polypsis



What to do about hereditary CRC's?

In the context of:

- familial risk
- Lynch (HNPCC)
- Familial Adenomatous Polyposis (FAP)
- Serrated Polyposis Syndrome (SPS)
- Hamartomatous polyposis (Juvenile and Peutz-Jehgers)



Familial Risk

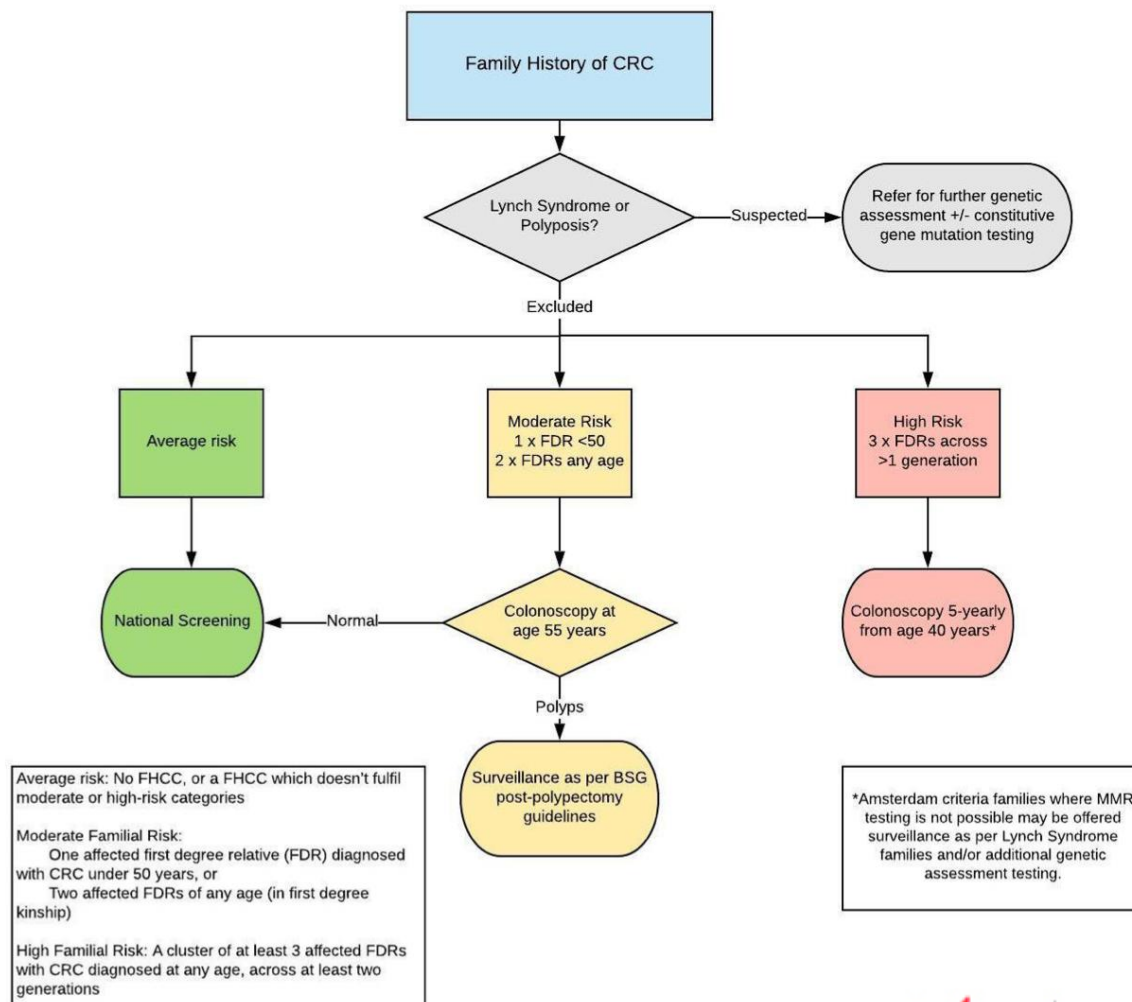


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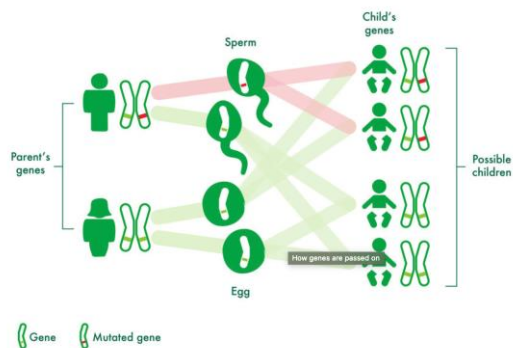
Levels of Risk and Family History

- **Average Risk:** No family history (4-5% lifetime risk)
- **Moderate Risk:** A 1st-degree relative aged <50 or (x3 risk), 2 FDR's at any age (x2-3 risk)
- **High Risk:** 3 first-degree relatives (x2-4) or a known *inherited syndrome*.

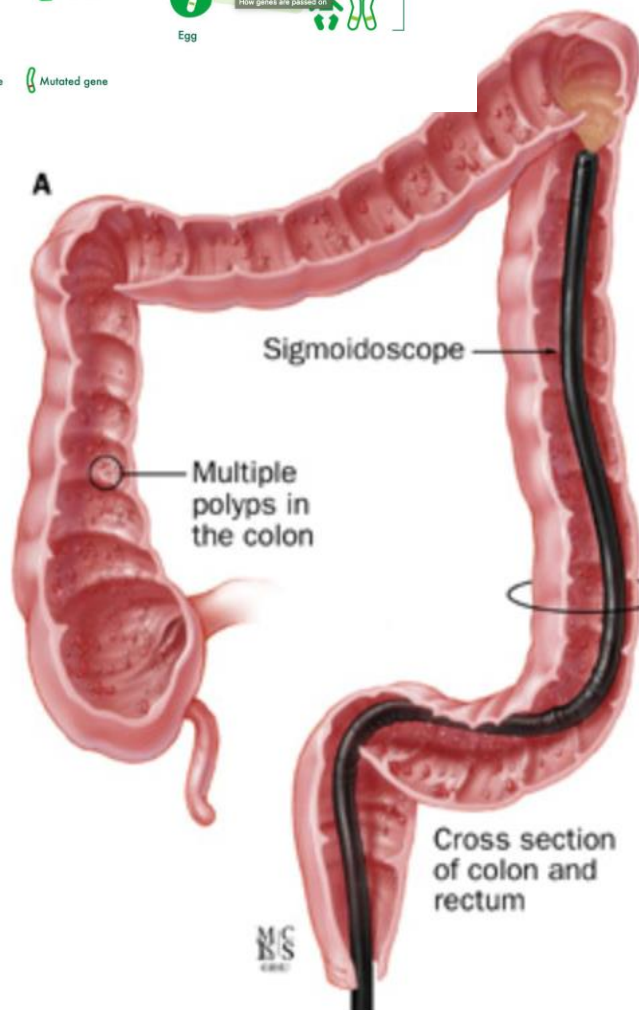
Screening guidelines for Family History



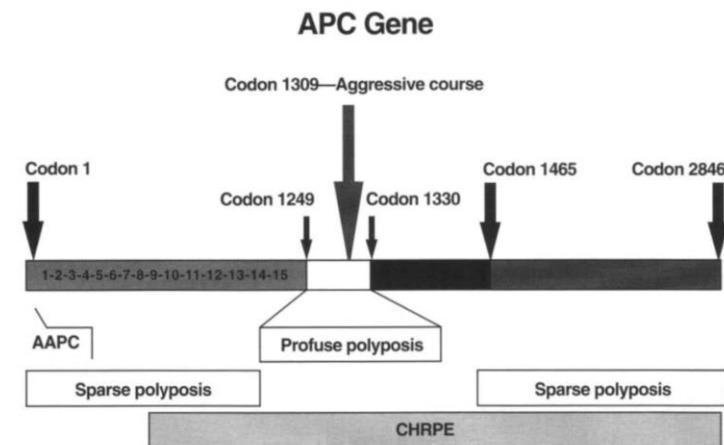
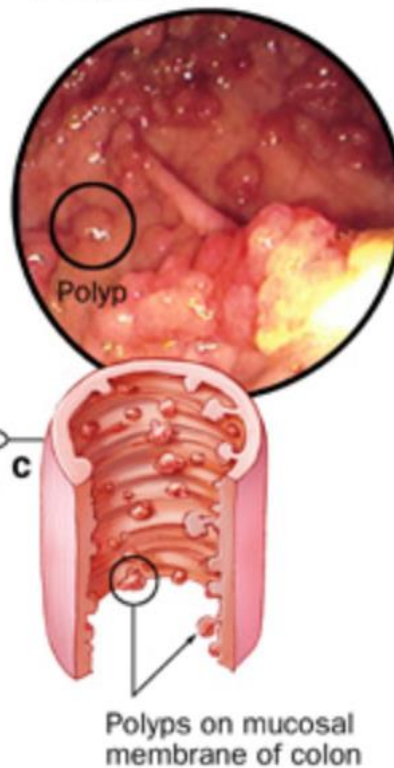
Familial Adenomatous Polyposis (FAP)



FAP



B scope view



- Colorectal cancer, up to 100% if polyps not removed
- Desmoid tumor, 10% to 20%
- Small bowel (intestines), 4% to 12%
- Pancreatic/ampullary cancer, 2%
- Papillary thyroid cancer, 2% to 25%
- Hepatoblastoma, 1.5%
- Brain or central nervous system tumor, less than 1%
- Stomach cancer, 5%
- Bile duct cancer, slightly increased risk
- Adrenal gland cancer, slightly increased risk

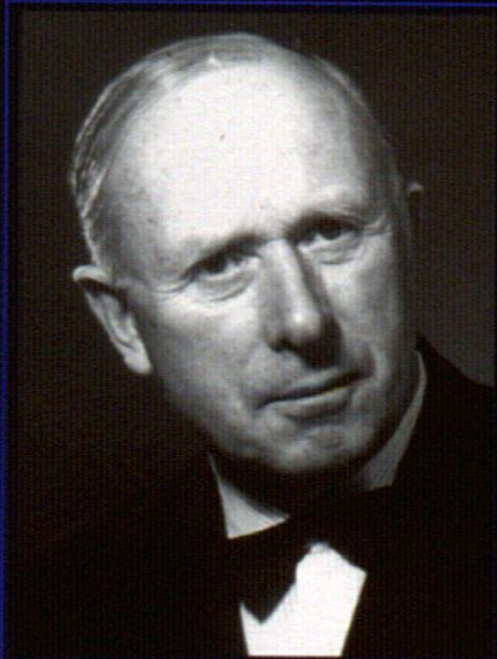
Two patient groups

- Young patients with known FAP – no evidence of cancer
(2/3)
- Patients of any age with new diagnosis of FAP (+/- cancer)
(1/3)

Evolution of surgical management of FAP

Choices:

- proctocolectomy and ileostomy
- total colectomy and IRA (1948 -)
- pouch operation (1976 -)



Mr O V Lloyd - Davies

**Total Colectomy
with
Ileorectal Anastomosis**

**1st Operation
8 December 1948**

Sir Alan Parks PRCSE

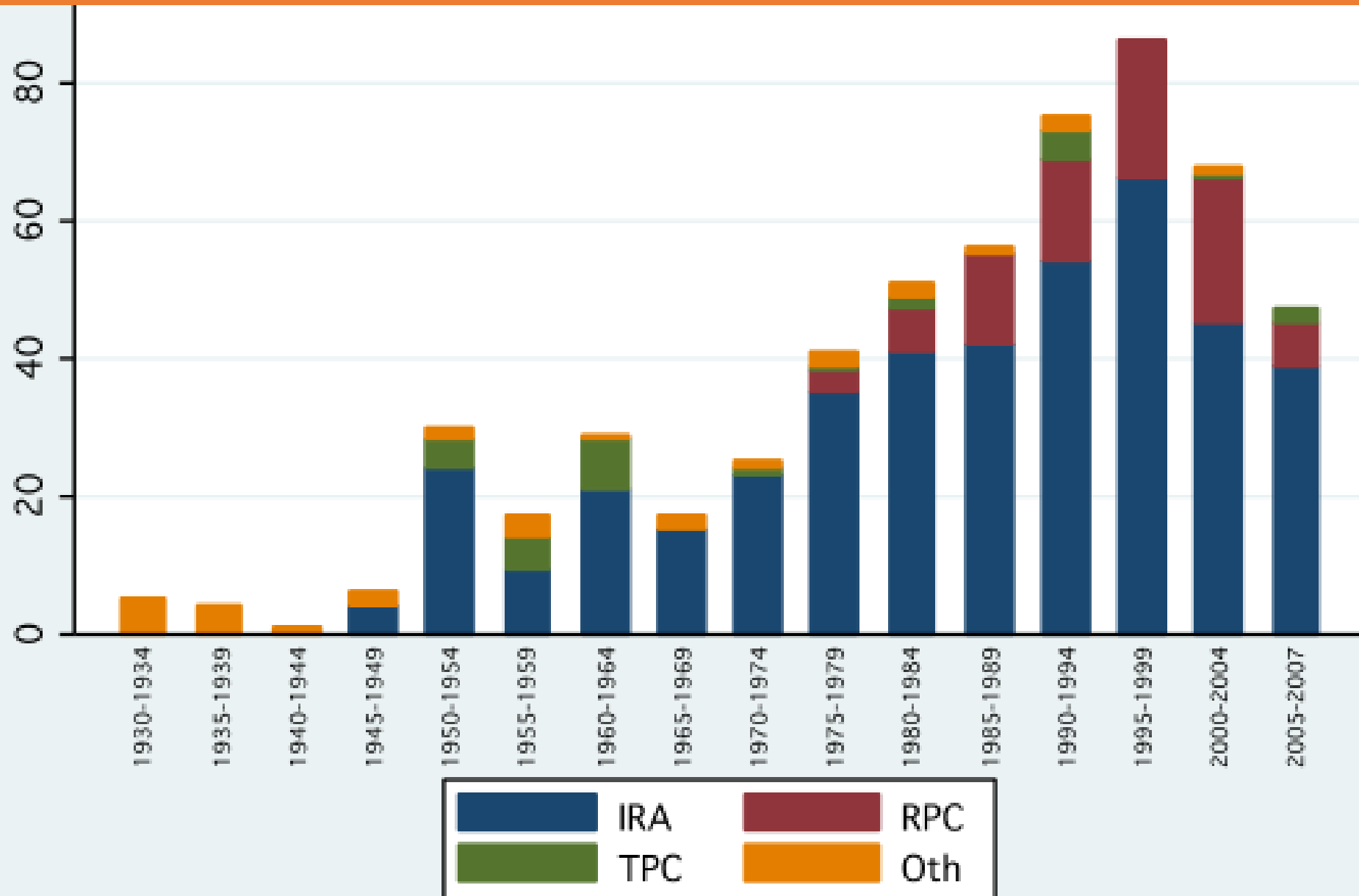
Restorative
Proctocolectomy
(Ileal Pouch)



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Type of procedure by 5 – year periods



Issues with pouch surgery / benefits of IRA

- Complication rate higher than colectomy & IRA
- Sexual and urological dysfunction
- Female fecundity
- Pouch function

Which operation should we do?

Risk factors for needing secondary proctectomy:

- Age
- Genetic mutation
- Rectal polyp density
- Colonic polyp density
- Patient choice

Which operation should we do?

Risk factors for requiring primary proctocolectomy:

- Age
- Mutation APC codons 1250-1450 (HR 3.9)
- Rectal polyp density >20 (HR 30)
- Colonic polyp density >500 (HR 2.5)
- Patient choice

Sinha A et al. Br J Surg 2010; 97: 1710-1715

FAP Risk Factors for secondary proctectomy

St Mark's Hospital, UK

427 patients with IRA for FAP

48 developed rectal cancer

77 required proctectomy for worsening polyposis

Sinha A et al. Br J Surg 2010; 97: 1710-1715

Rates of IRA conversion to pouch at St Mark's

*if **you** start with an IRA, you can usually convert it to a pouch*

- 390 FAP patients with IRA performed at St Mark's since 1948
- 68 (17%) required conversion
- conversion to pouch not possible in 6 (9%):
 - desmoid disease in 5
 - short small bowel mesentery in 1

Von Roon et al. Dis Colon Rectum 2007; 50: 1-10

Surgical management - general guide

Total colectomy & IRA

- low density polyposis (<20 rectal polyps)
- convert to pouch if rectal polyp density increases

Primary Pouch

- high density phenotype (>20 rectal polyps, 1309 mutation)

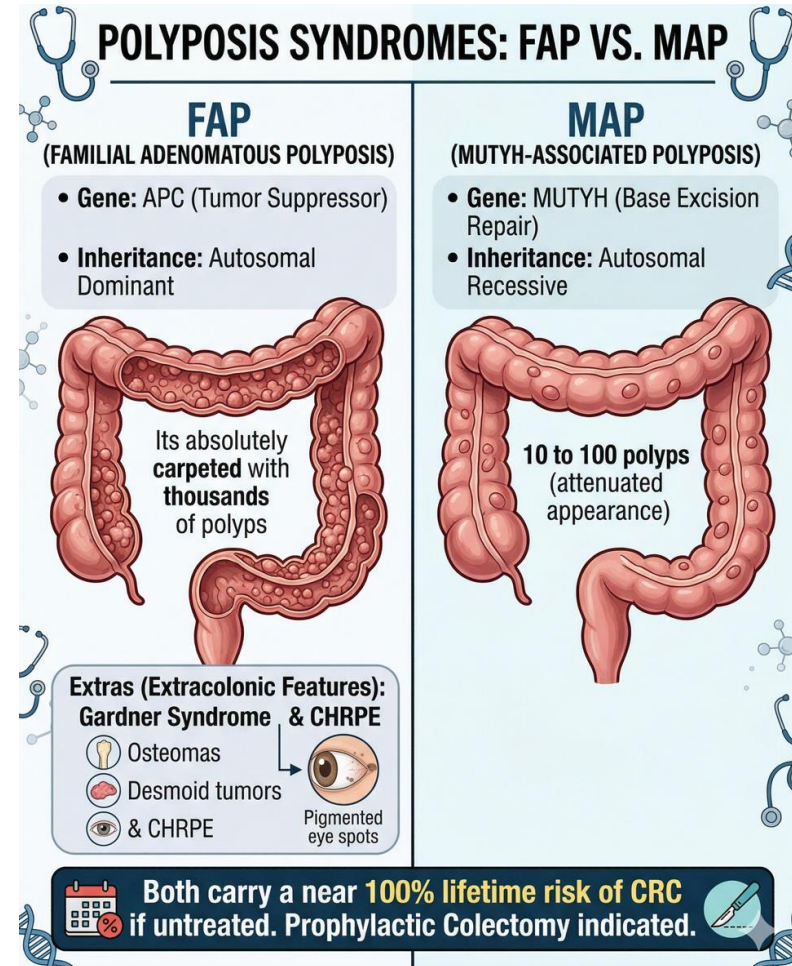
Ongoing surveillance

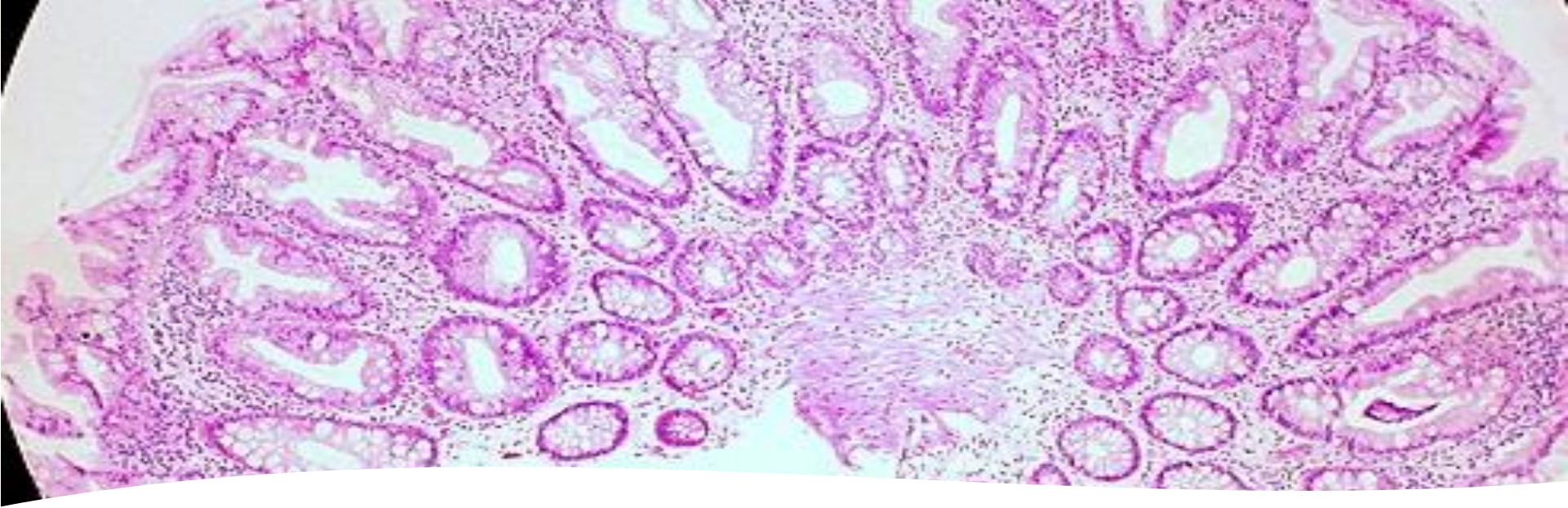
- Upper GI, rectal remnant or pouch +/- desmoid disease

Other hereditary cancers?

Hereditary cancer management - MAP

- MUTYH-associated polyposis (MAP) is characterized by the development of multiple colorectal polyps and a high lifetime risk of colorectal cancer (80-90%).
- It is caused by mutations in both copies of the *MUTYH* gene and is inherited in an autosomal recessive manner.
- **Surveillance:** Regular colonoscopy every 1 to 2 years, typically starting between ages 18 and 20.
- **Upper Endoscopy:** starting around ages 30 to 35.
- **Intervention:** Polypectomy, or potential surgical removal of the colon (colectomy) if polyp burden becomes unmanageable.



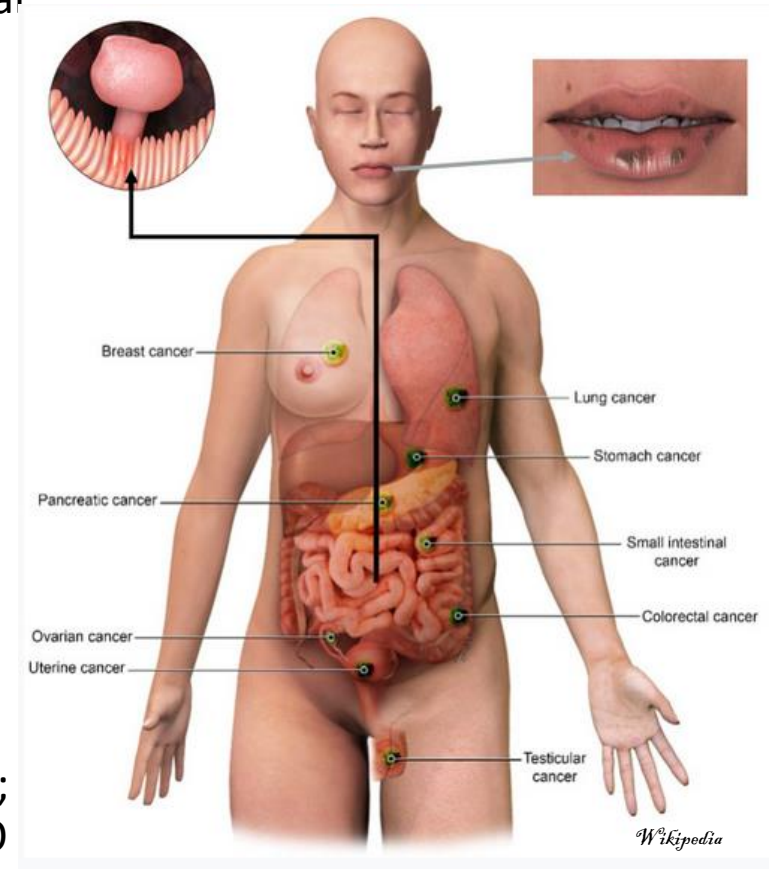


Serrated Polyposis Syndrome (SPS)

- Serrated polyposis syndrome (SPS) is a rare medical condition defined by the growth of many serrated polyps in the large bowel.
- **Diagnosis:**
 - Five or more serrated polyps above the rectum that measure at least 5 mm wide, with at least two measuring 10 mm or larger.
 - More than 20 serrated polyps of any size spread throughout the colon, with at least five located above the rectum.
- **Management:**
 - Regular screening colonoscopy and polypectomy
 - Surgery for bowel deterioration (polyp numbers, malignancy)
 - Screening for family members

Peutz-Jehgers Polyposis Syndrome

- Peutz-Jeghers syndrome (PJS): hamartomatous polyposis syndrome characterized by gastrointestinal polyposis, distinctive dark freckling, and a high lifetime risk of cancer. Caused by changes in the *STK11* gene.
- Associated with a >90% cumulative lifetime risk (of intestinal (e.g., colorectal, gastric, and small bowel) and extra-intestinal (e.g., breast, pancreas, cervix, uterus, ovary, testes, and lung) cancers.
- Patients require lifelong intensive cancer surveillance.
- Small bowel obstruction is a frequent complication; up to 70% of individuals require laparotomy for SBO by the age of 18 years.



Screening guidance for inherited syndromes

Indication for surveillance	Category	Modality	Age to commence (years)	Interval
Family history of CRC	Average risk	National screening	National screening age	As defined by national screening
	Moderate risk	Colonoscopy	55	Post-polypectomy guidelines
	High risk*	Colonoscopy	40	5 yearly until age 75 years
Lynch syndrome	MMR gene pathogenic variant carriers			
	<i>MLH1</i> and <i>MSH2</i> gene carriers	Colonoscopy	25	2 yearly until age 75 years
	<i>MSH6</i> and <i>PMS2</i> gene carriers	Colonoscopy	35	2 yearly until age 75 years
Lynch-like syndrome	Stomach, small bowel and pancreas	Not indicated outside a clinical trial		
	Individuals with deficient MMR tumours without hypermethylation/BRAF pathogenic variant and no pathogenic constitutional pathogenic variant in MMR genes, and no evidence of biallelic somatic MMR gene inactivation (and their unaffected FDRs) .	Colonoscopy	25	2 yearly until age 75 years
Serrated polyposis syndrome	Affected individuals (WHO 2019)	Colonoscopy	From age of diagnosis	1–2 yearly until age 75 years
	FDRs of affected individuals	Colonoscopy	40 (or 10 years earlier than the index case)	5 yearly until age 75 years
Multiple colorectal adenomas (MCRAs)	10 or more adenomas without constitutive pathogenic variants in <i>APC</i> or <i>MUTYH</i>	Colonoscopy	From age of diagnosis	1–2 yearly until age 75 years
Familial adenomatous polyposis (FAP)	<i>APC</i> pathogenic variant carriers	Colonoscopy	12 to 14	1–3 yearly depending on phenotype
		Gastroscopy and duodenoscopy	25	As per Spigelman classification
		Sigmoidoscopy/pouchoscopy	From time of colectomy	1–3 yearly depending on phenotype
	Individuals with an FDR with a clinical diagnosis of FAP (ie, “at-risk”) and in whom a constitutional pathogenic variant has not been identified	Colonoscopy	12 to 14	5 yearly until national screening age
		Gastroscopy and duodenoscopy	Commence only if clinical diagnosis made of colorectal polyposis phenotype	As per Spigelman classification
<i>MUTYH</i> -associated polyposis (MAP)	<i>MUTYH</i> gene pathogenic variant carriers	Colonoscopy	18 to 20 years	Annual
		Gastroscopy and duodenoscopy	35	As per Spigelman classification
Peutz-Jeghers syndrome (PJS)	<i>STK11</i> gene pathogenic variant carriers	Upper gastrointestinal endoscopy, colonoscopy and video capsule endoscopy	8	see main text
Juvenile polyposis syndrome (JPS)	<i>SMAD4</i> and <i>BMPR1A</i> pathogenic variant carriers	Colonoscopy	15	1–3 yearly depending on phenotype
	<i>SMAD4</i> pathogenic variant carriers	Gastroscopy and duodenoscopy	18	1–3 yearly depending on phenotype
	<i>BMPR1A</i> pathogenic variant carriers	Gastroscopy and duodenoscopy	25	1–3 yearly depending on phenotype

*Amsterdam criteria families where MMR testing is not possible may be offered surveillance as per Lynch syndrome families and/or additional constitutional testing. CRC, colorectal cancer; FDR, first degree relative; MMR, mismatch repair.

Lynch syndrome

Lynch Syndrome

Microsatellite Instability (MSI).

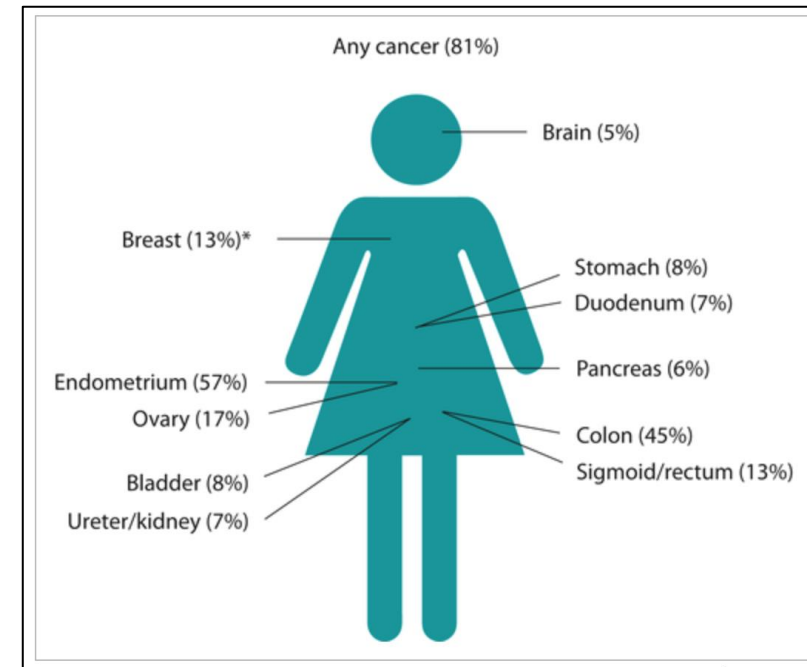
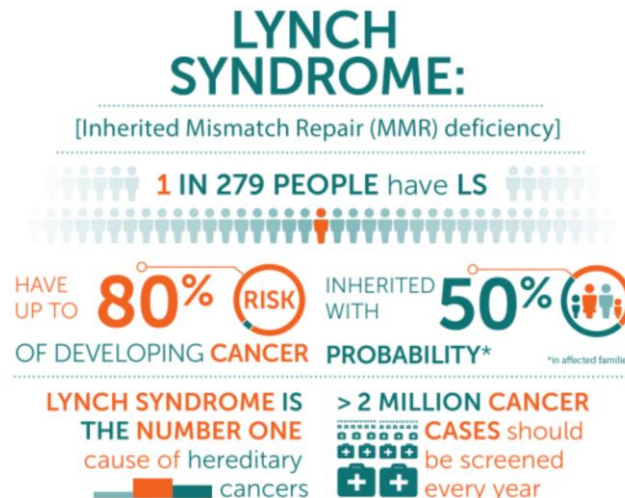
Germline mutations of
DNA Mismatch repair

MLH1

PMS2 (complexes with MLH1)

MSH2

MSH6 (complexes with MSH2)



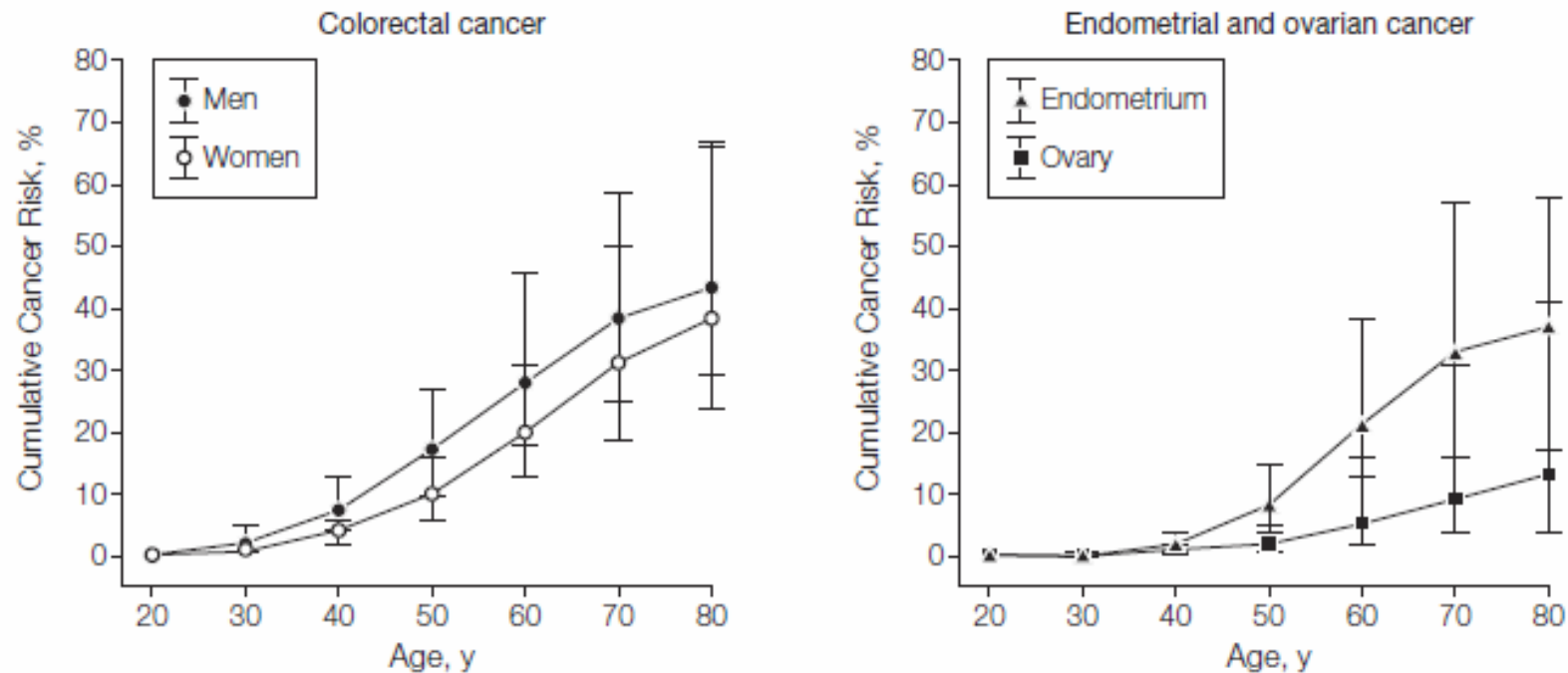
Autosomal dominant



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Lynch Syndrome cancer risks

Figure. Cumulative Risks of Cancer by Age for All Genes



See eTable 3 (available at <http://www.jama.com>) for the number of affected individuals and the number of family members contributing to the likelihood for risk estimation. Error bars indicate 95% confidence intervals.

Role of prophylactic colonic resection - what surgery?

- Usually do not recommend prophylactic colonic resection
- If known Lynch develop colorectal cancer suggest more extensive resection (i.e. total colectomy and Ileorectal anastomosis if Colonic CRC OR proctocolectomy if rectal cancer)

Colorectal disease April 2017

Risk of metachronous colorectal cancer following colectomy in Lynch syndrome: a systematic review and meta-analysis

C. C. Anele^{*†} , S. O. Adegbola^{*†}, A. Askari[‡], A. Rajendran[§], S. K. Clark^{*†}, A. Latchford[§] and O. D. Faiz^{*†}

Aim Lynch syndrome (LS) accounts for 2–4% of all colorectal cancer (CRC) cases, and is associated with an increased risk of developing metachronous colorectal cancer (mCRC). The role of extended colectomy in LS CRC is controversial. There are limited studies comparing the risk of mCRC following segmental colectomy and extended colectomy. The objective of this systematic review is to evaluate the risk of developing mCRC following segmental and extended colectomy for LS CRC and endoscopic compliance.

Method A systematic review of major databases was performed using predefined terms. All original articles published in English comparing the risk of mCRC in LS patients after segmental and extended colectomy from 1950 to January 2016 were included.

Results The search retrieved 324 studies. Six studies involving 871 patients met the inclusion criteria. Of these, 705 (80.9%) underwent segmental colectomy and 166 (19.1%) extended colectomy. Average follow-up

was 91.2 months. The mCRC rate was 22.8% and 6% in the segmental and extended colectomy groups, respectively. The segmental group were over four times more likely to develop mCRC (OR 4.02, 95% CI: 2.01–8.04, $P < 0.0001$). mCRC occurred in patients after segmental colectomy despite 1–2-yearly postoperative endoscopic surveillance.

Conclusion This result suggests that extended colectomy reduces the risk of mCRC by over four-fold compared with segmental colectomy. mCRC occurred in the segmental group despite postoperative endoscopic surveillance. This needs to be borne in mind when deciding on the appropriate surgical management of LS patients with CRC. We recommend that extended colectomy should be considered for patients with confirmed LS CRC.

Keywords Segmental colectomy, extended colectomy, metachronous colorectal cancer, Lynch syndrome

‘This result suggests that extended colectomy reduces the risk of mCRC By over four-fold compared with segmental colectomy.... We recommend that Extended colectomy should be considered for patients with confirmed LS CRC’

Summary – what surgery for Lynch?

New patients with cancer and possible Lynch Syndrome

- Undertake segmental colectomy if diagnosis not established
- Confirm or refute diagnosis once tumour resected
- Continue screening

For patients with established Lynch Syndrome

- Screening
- Do not undertake prophylactic surgery
- If they develop colon cancer consider total colectomy and survey the rectum
- If they develop rectal cancer can consider a pouch or segmental resection

How do we manage hereditary cancers?

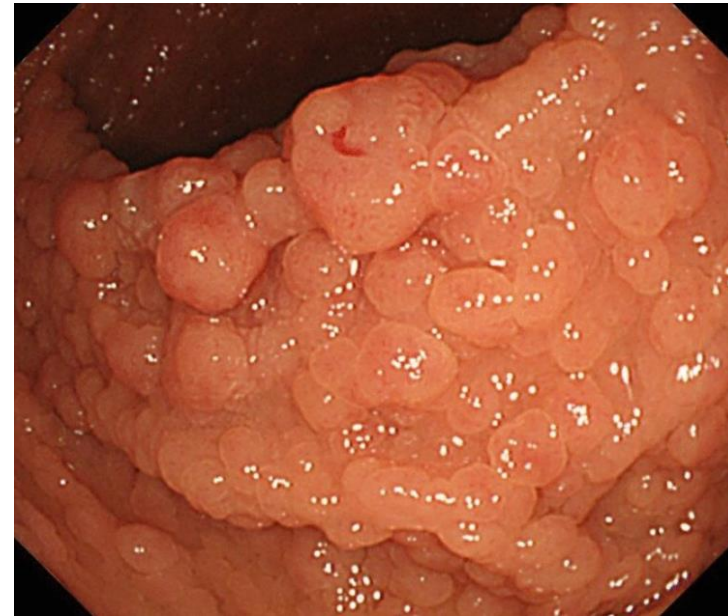
Registry of patients

Essential for:

- Family history and genetic testing
- Surveillance endoscopy planning
- Multidisciplinary decision-making

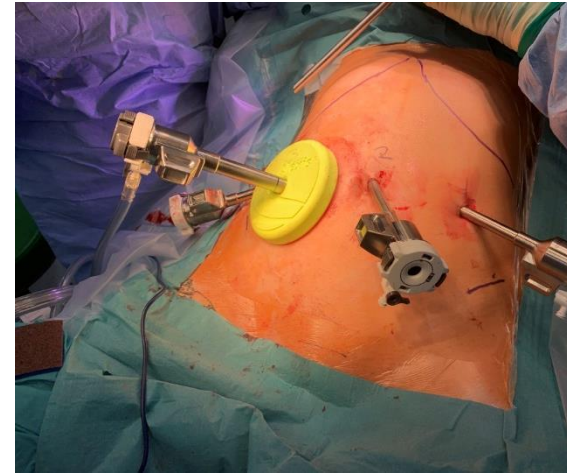
The need for high-quality endoscopy

- Patients often want to avoid or defer surgery where possible
- This demands highly capable endoscopists dedicated to this area
- Therapeutic endoscopy (advanced polypectomy) skills are essential



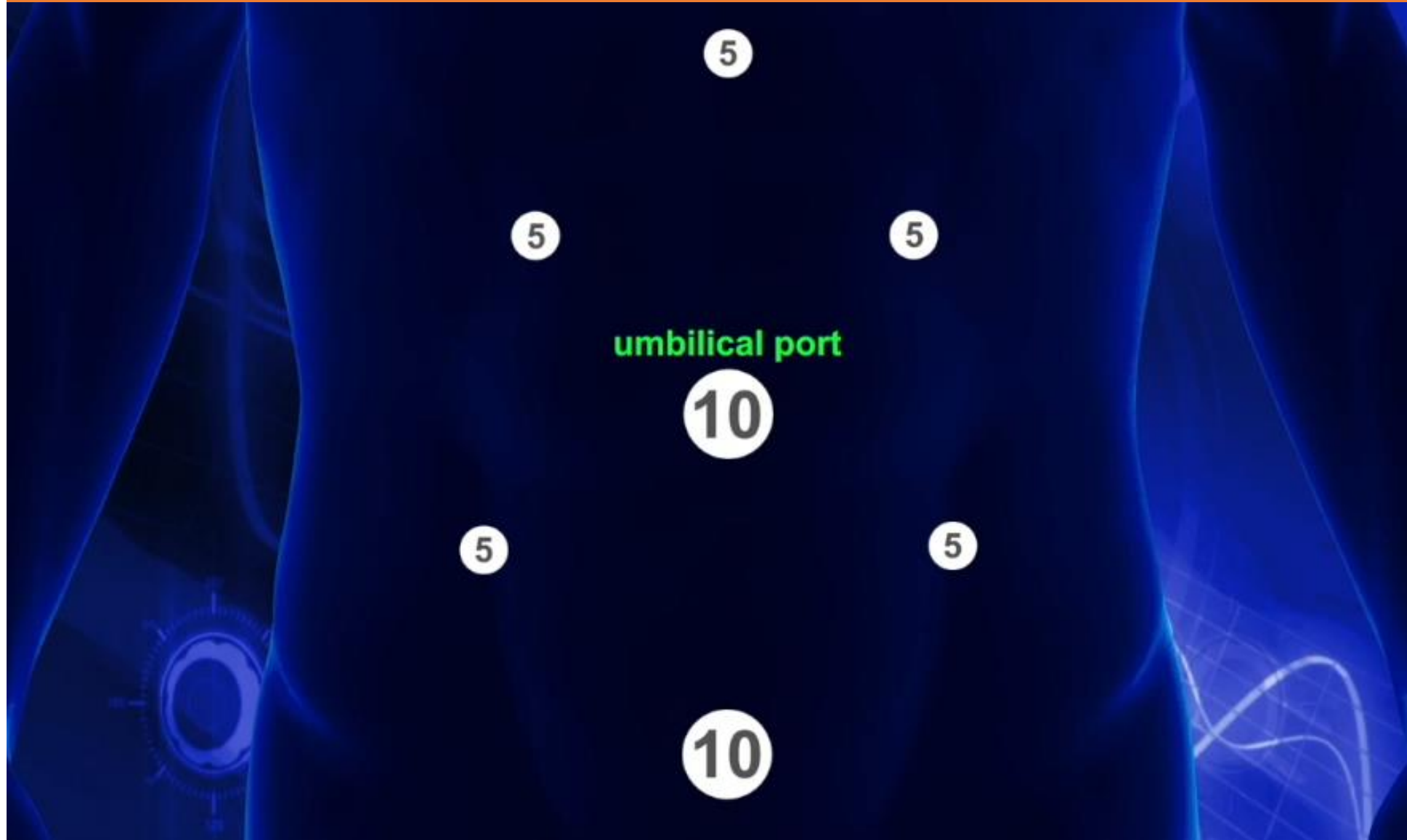
Surgery - what matters to the patient?

- Achieve prevention of cancer
- Low/zero major complication profile
- Good cosmesis



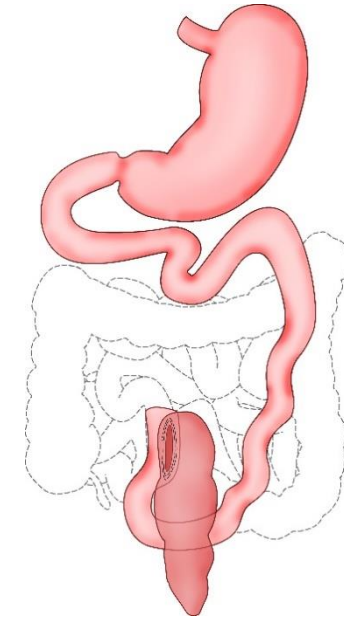
Robotic pouch surgery

Near-total colectomy & ileo-distal sigmoid anastomosis



Total Colectomy (TC-IRA) versus NT-IDSA

Outcome	TC-IRA (n=106)	NT- IDSA (n=52)	P -value
Overall complication free rate	64 (60.4)	38 (73.1)	0.115
Reoperation	13 (12.3)	0 (0)	0.005
Mortality	Nil	Nil	



Conclusions

- FAP – prophylactic colorectal surgery for all (IRA/IDSA or Pouch)
- Lynch – not for colorectal prophylactic surgery
- Lifelong screening – develop a registry, MDT and centralise OR refer on



Thank you