Hereditary polyposis and cancer syndromes

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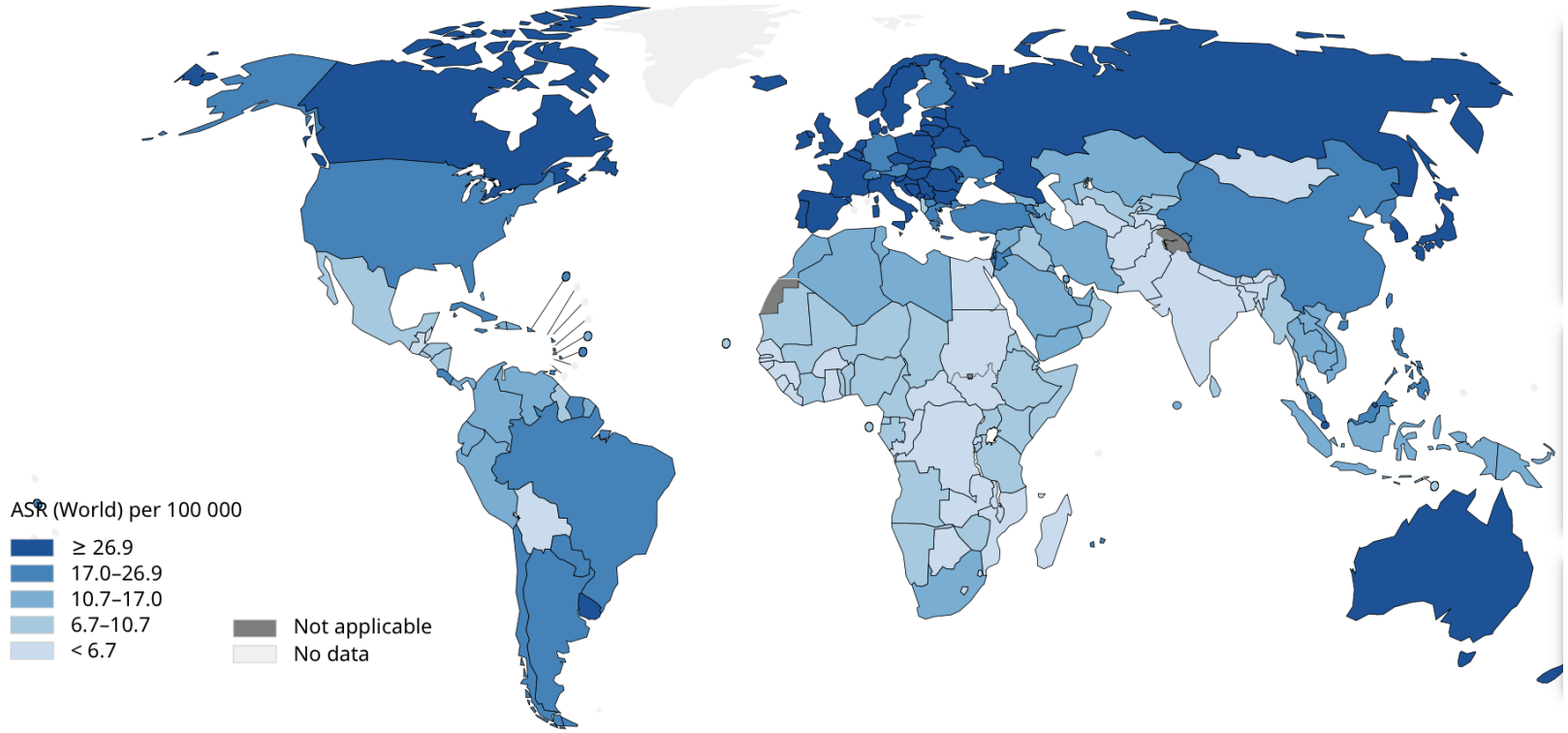
Colorectal cancer epidemiology

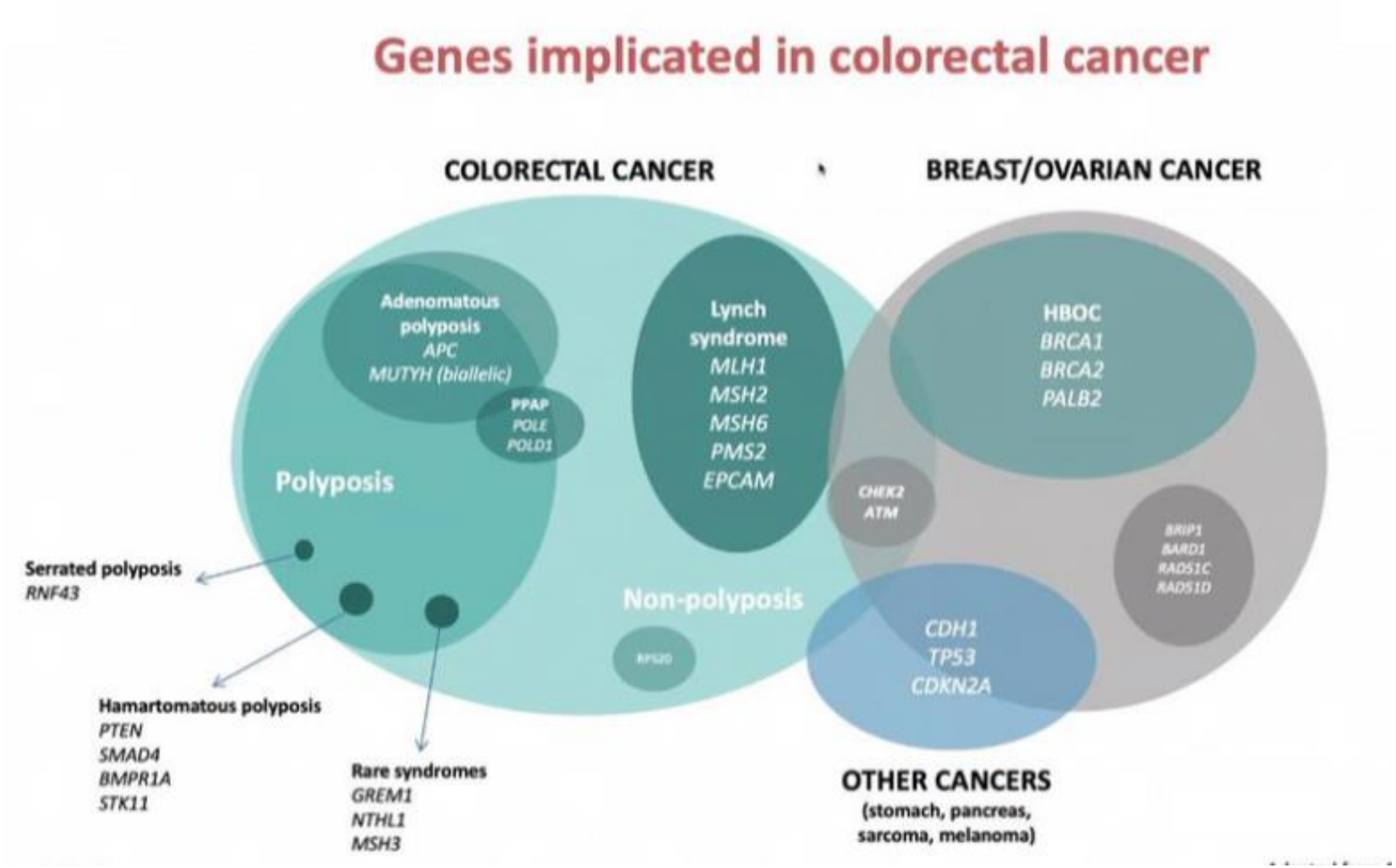
Estimated age-standardized incidence rates (World) in 2020, colorectum, both sexes, all ages



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

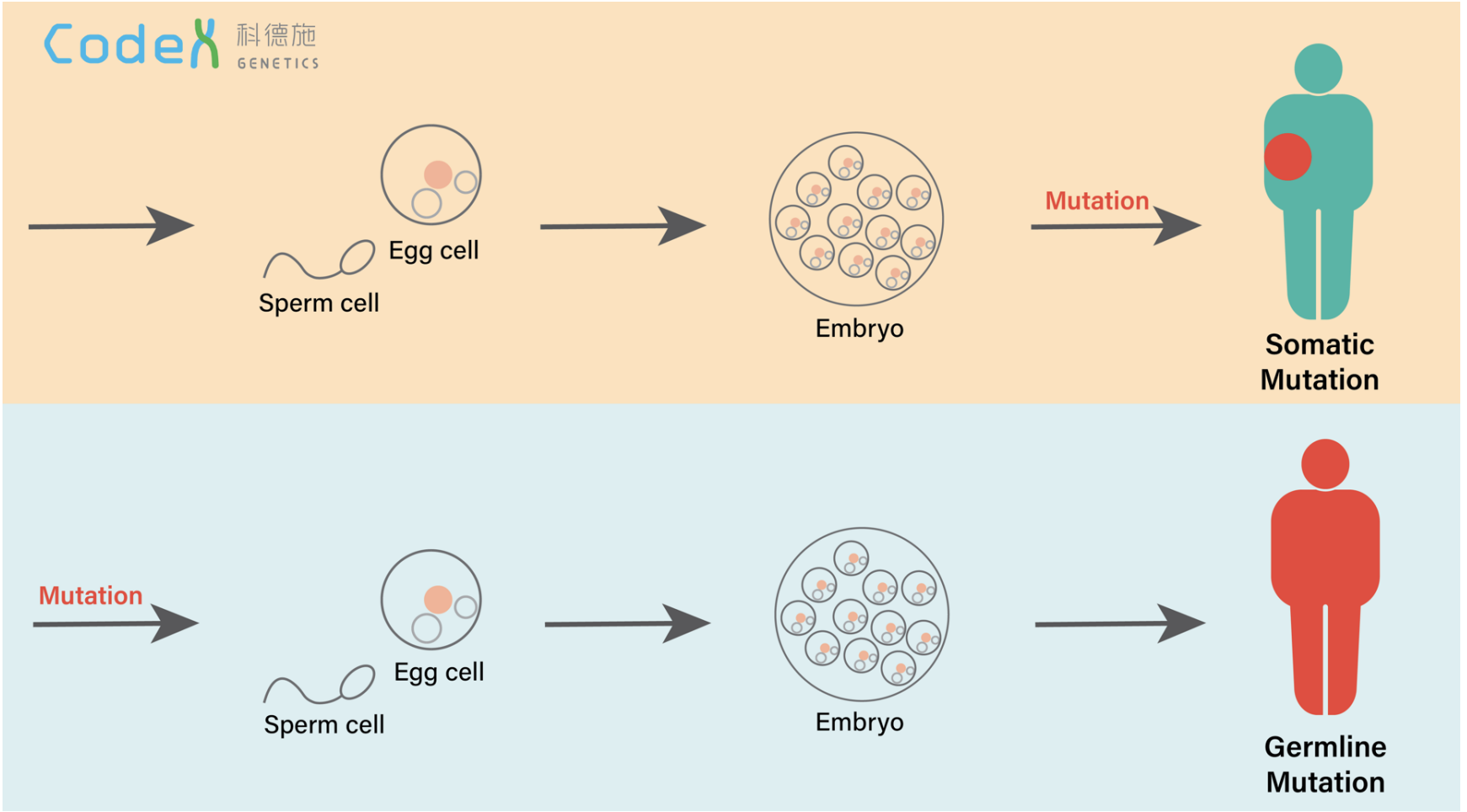
GLOBOCAN 2020

Genes implicated in colorectal cancer



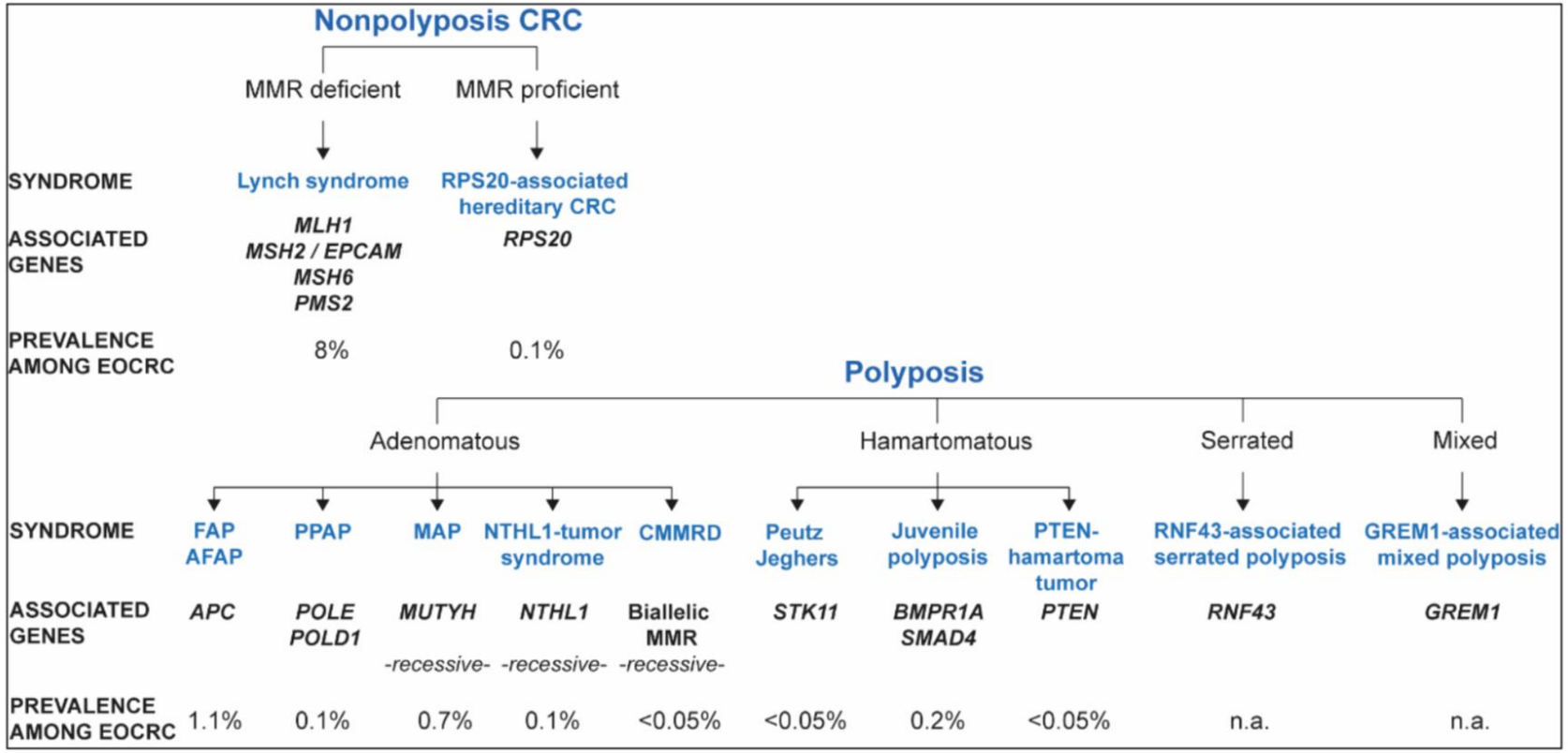
Stoffel et al. Gastro 2018

Somatic versus germline mutation



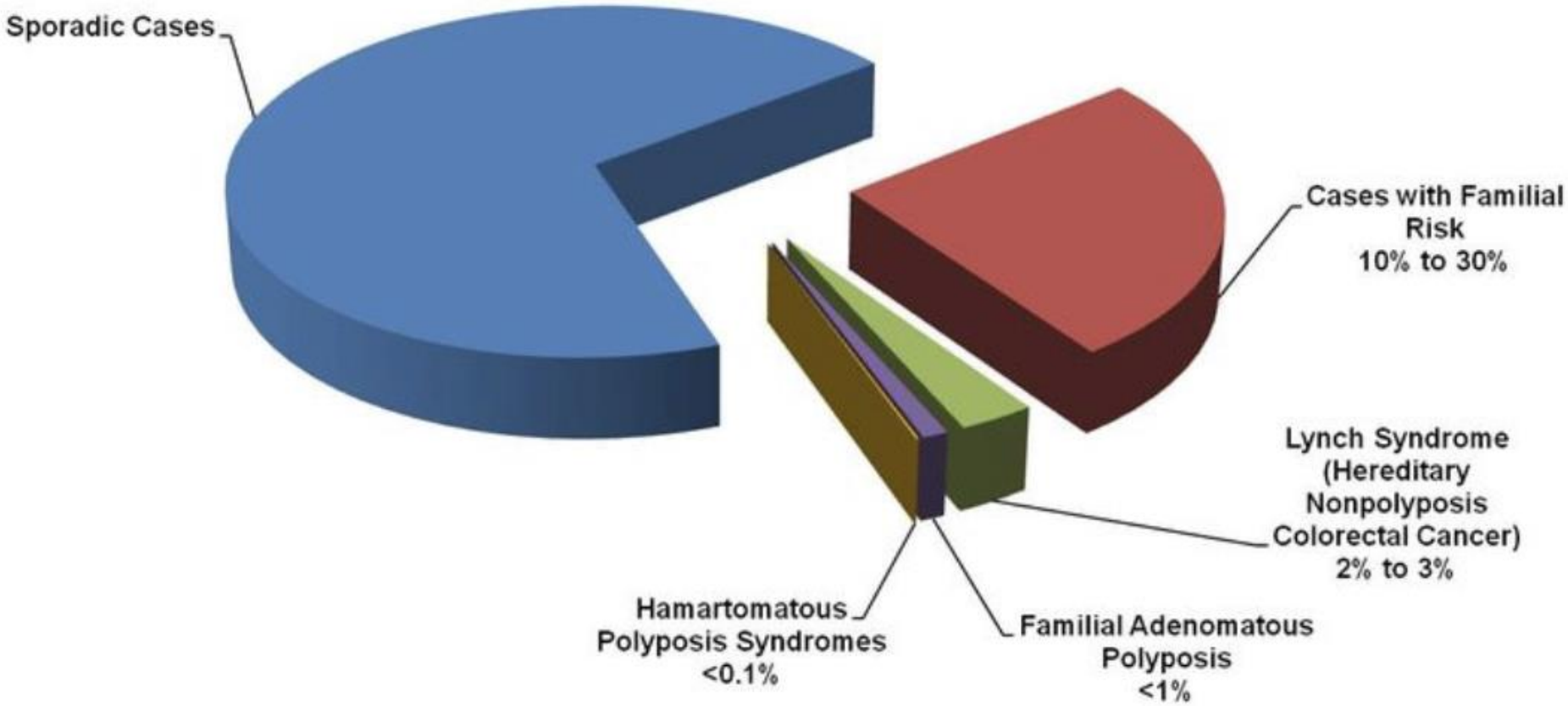
CodeX Genetics

Hereditary colorectal cancer and causal genes
Polyposis versus Non-Polyposis



Maria Alvarez et al. Cells 2021

Prevalence of hereditary causes among CRC



Surgery in FAP

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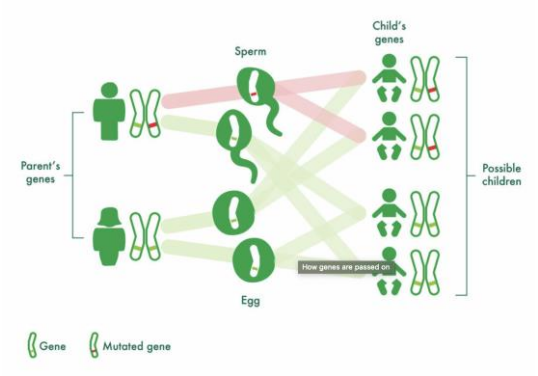
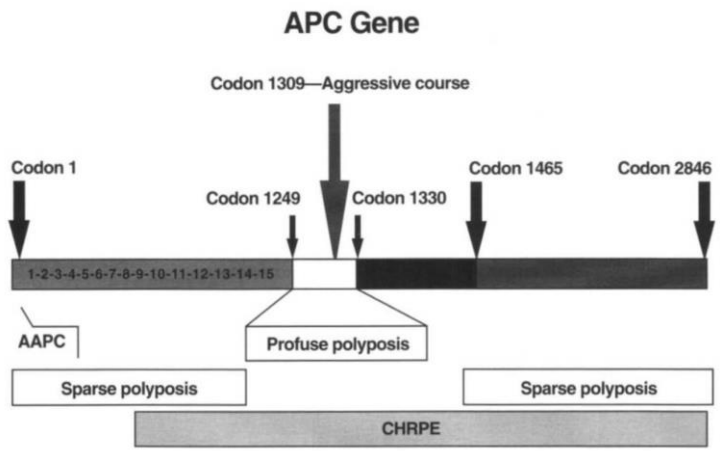
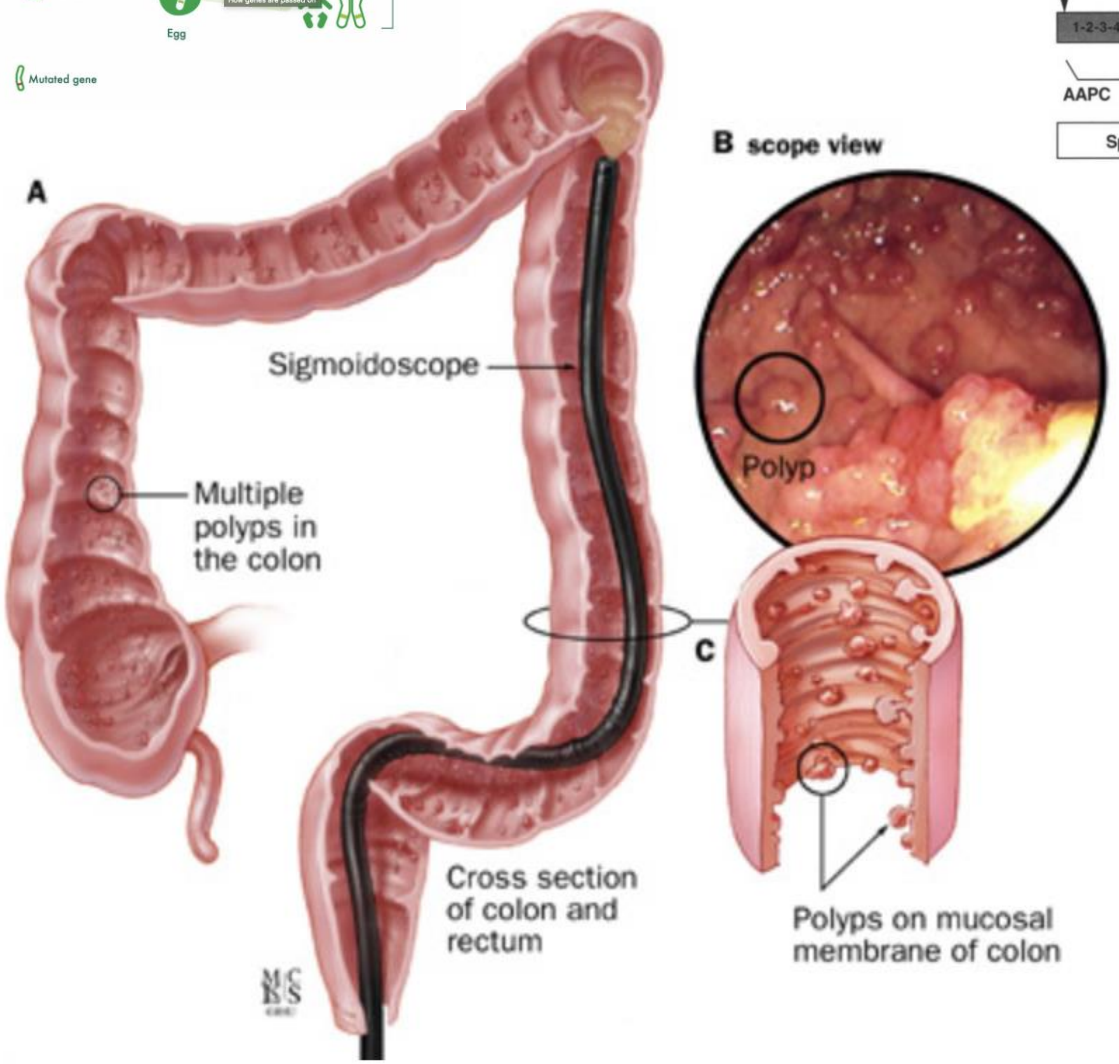
FAP







- 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

1. Young patients with known FAP – no evidence of cancer (2/3)

2. Patients of any age with new diagnosis of FAP (+/- cancer) (1/3)

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Evolution of surgical management of FAP

Choices:

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

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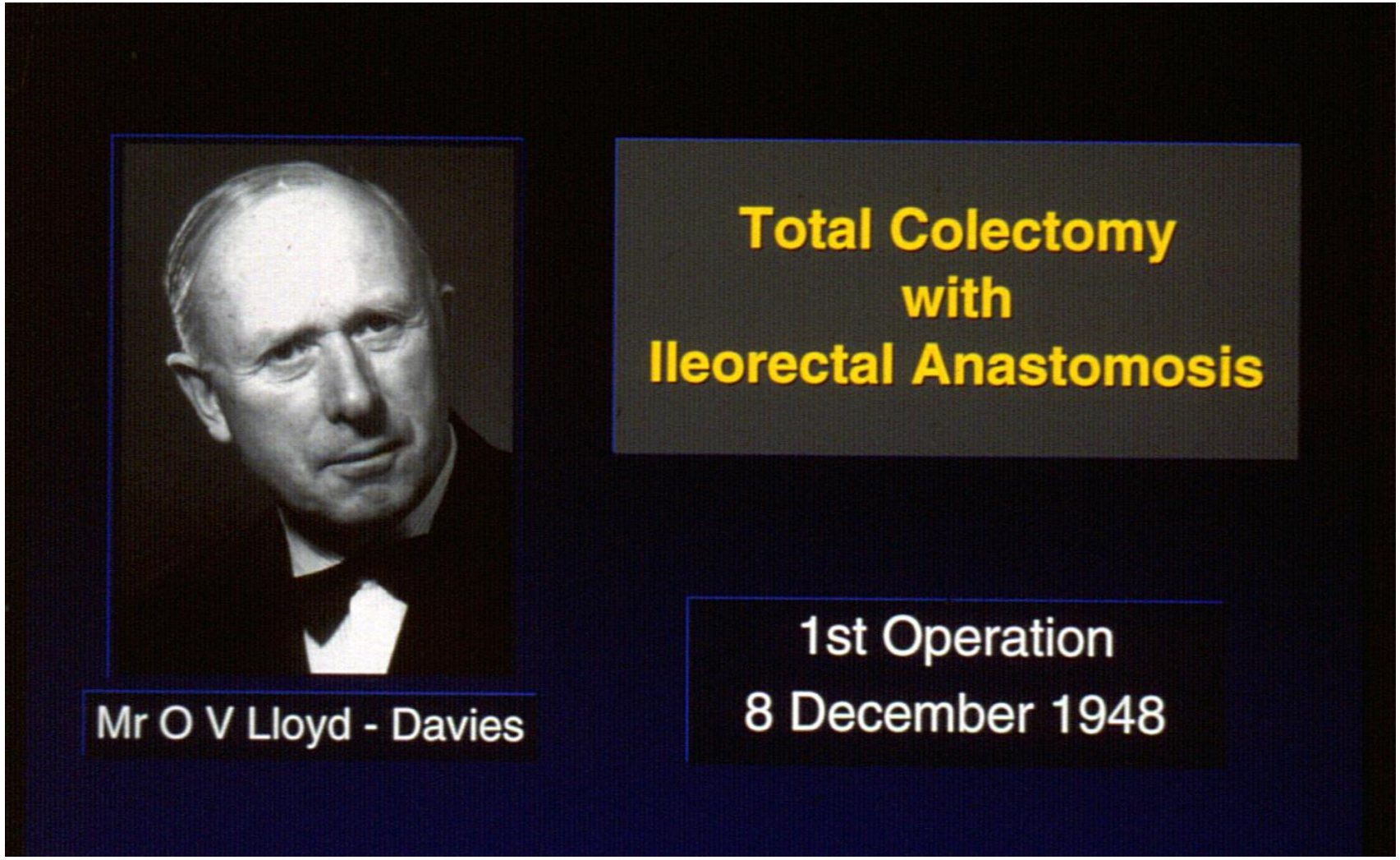

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Sir Alan Parks PRCSE

Restorative Proctocolectomy (Ileal Pouch)

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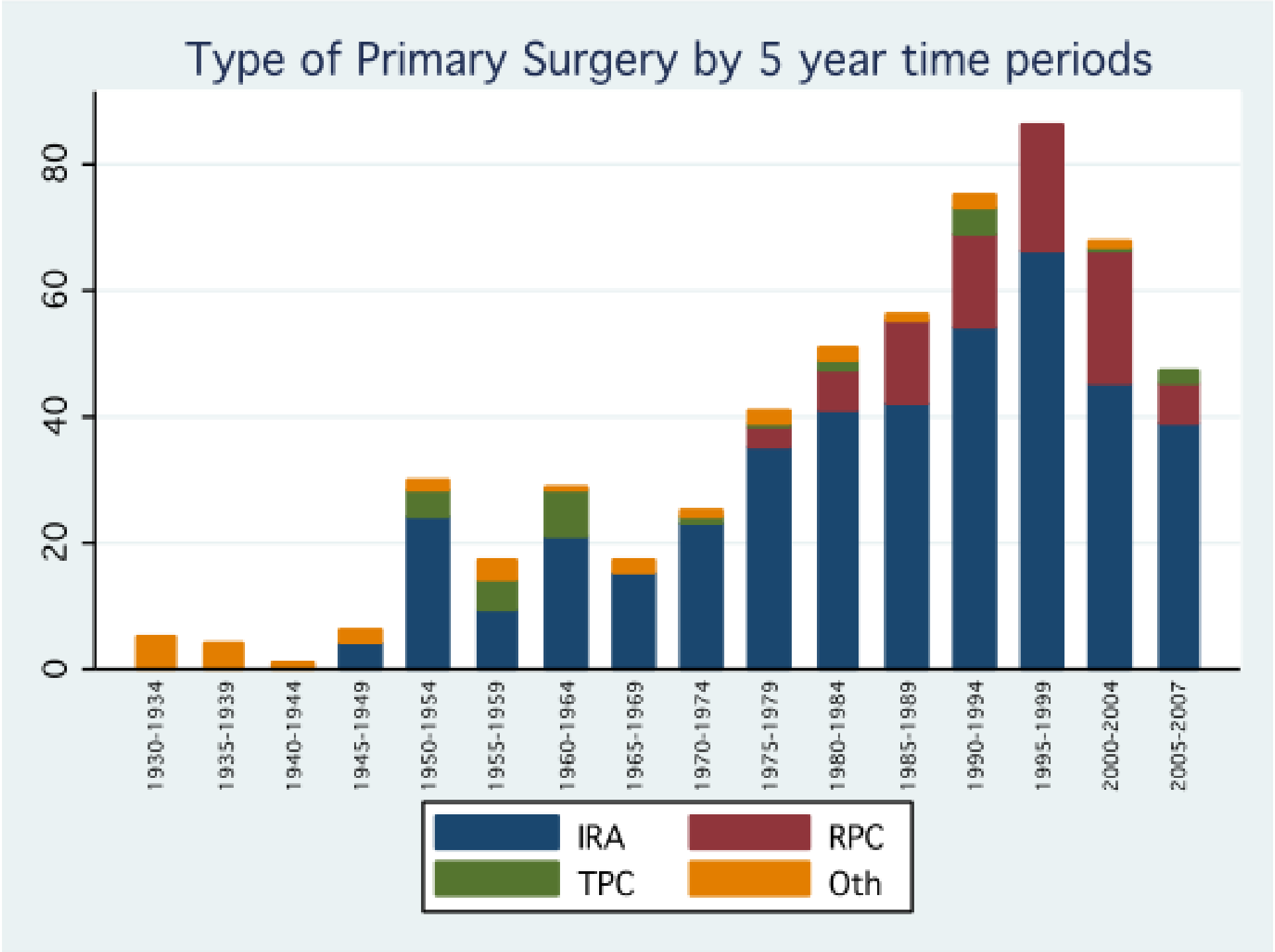
Type of Primary Surgery by 5 year time periods
0
20
40
60
80
1930-1934
1935-1939
1940-1944
1945-1949
1950-1954
1955-1959
1960-1964
1965-1969
1970-1974
1975-1979
1980-1984
1985-1989
1990-1994
1995-1999
2000-2004
2005-2007
IRA
RPC
TPC
Oth

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

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

Which operation should we do?

Risk factors for proctectomy:

- 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

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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

Which operation - general guide

Total colectomy & IRA

- low density polyposis (<5 rectal polyps)
- convert to pouch as older or if polyp density increases

Pouch

- high density genotype/phenotype (>20 rectal polyps and especially 1309 mutation)

Surgery in Lynch syndrome

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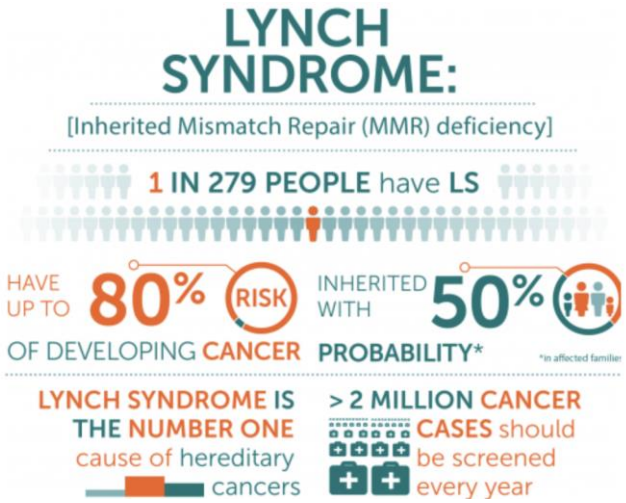
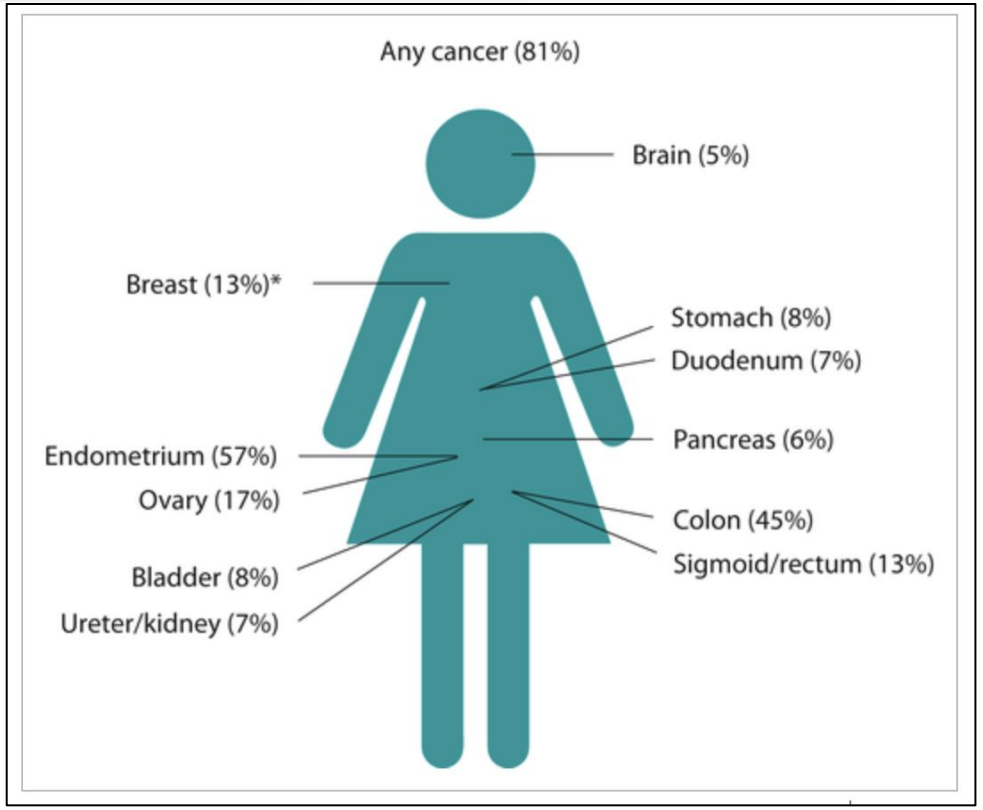
Lynch Syndrome

Microsatellite Instability (MSI).
Germline mutations of DNA Mismatch repair
MLH1
PMS2 (complexes with MLH1)
MSH2
MSH6 (complexes with MSH2)





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Lynch Syndrome cancer risks

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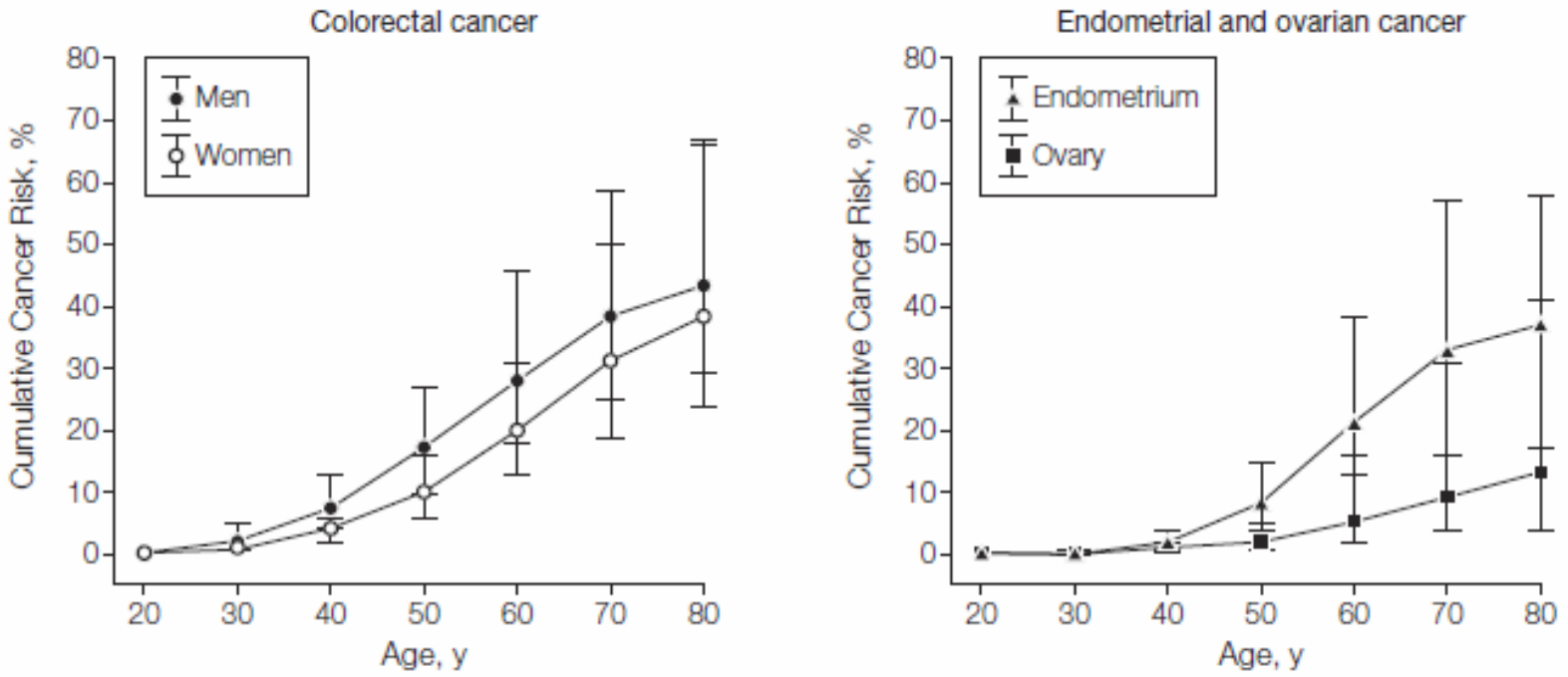
Figure. Cumulative Risks of Cancer by Age for All Genes



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.

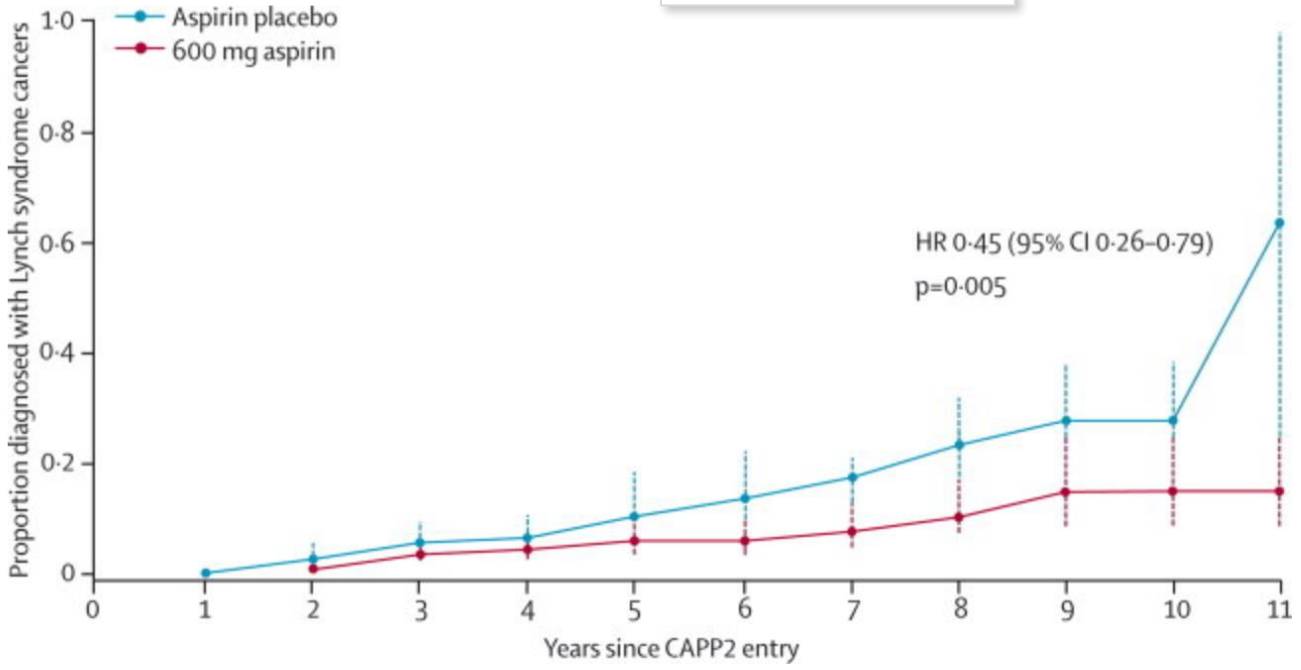
Banadona V L et al. JAMA, 2011

Aspirin chemoprevention

Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial

John Burn, Anne-Marie Gerdes, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Moeslein, Sylviane Olschwang, Diane Eccles, D Gareth Evans, Eamonn R Maher, Lucio Bertario, Marie-Luise Bisgaard, Malcolm G Dunlop, Judy W C Ho, Shirley V Hodgson, Annika Lindblom, Jan Lubinski, Patrick J Morrison, Victoria Murday, Raj Ramesar, Lucy Side, Rodney J Scott, Huw J W Thomas, Hans F Vasen, Gail Barker, Gillian Crawford, Faye Elliott, Mohammad Movahedi, Kirsi Pylvanainen, Juul T Wijnen, Riccardo Fodde, Henry T Lynch, John C Mathers, D Timothy Bishop, on behalf of the CAPP2 Investigators

Lancet 2011; 378: 2081–87



Time to first Lynch syndrome cancer in participants randomly assigned to aspirin compared with those assigned to aspirin placebo

Role of prophylactic colonic resection - what surgery?

- Usually do not recommend prophylactic colonic resection

- If develop colorectal cancer suggest more extensive resection (i.e. total colectomy and Ileorectal anastomosis if Colonic CRC OR proctocolectomy if rectal cancer)

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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 in ‘high risk’ patients once tumour resected

For carriers of Lynch Syndrome

-Do not undertake prophylactic surgery

-If they develop colon cancer undertake total colectomy and survey the rectum

-If they develop rectal cancer can consider a pouch or segmental resection

How do I do the operations for hereditary cancers?

- Total colectomy & IRA
- Restorative proctocolectomy (ileoanal pouch)

What matters to the patient?

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

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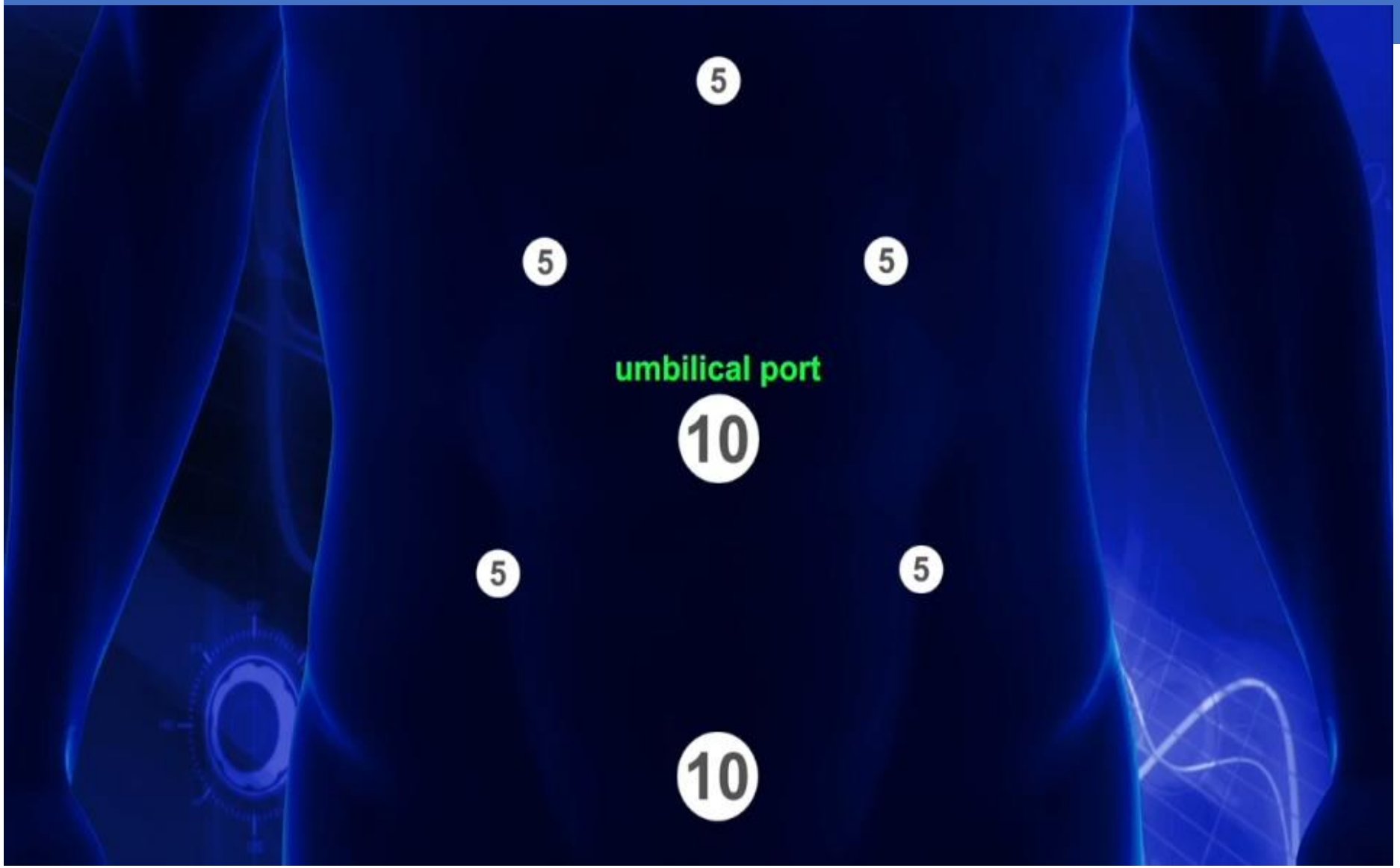
‘Near-total’ colectomy & ileo-distal sigmoid anastomosis (NTC—IDSA)

a modification of the

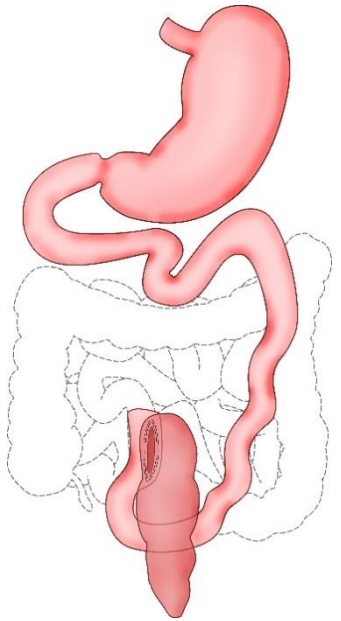
Total Colectomy and Ileorectal Anastomosis (TC-IRA)

Near-total’ colectomy & ileo-distal sigmoid anastomosis

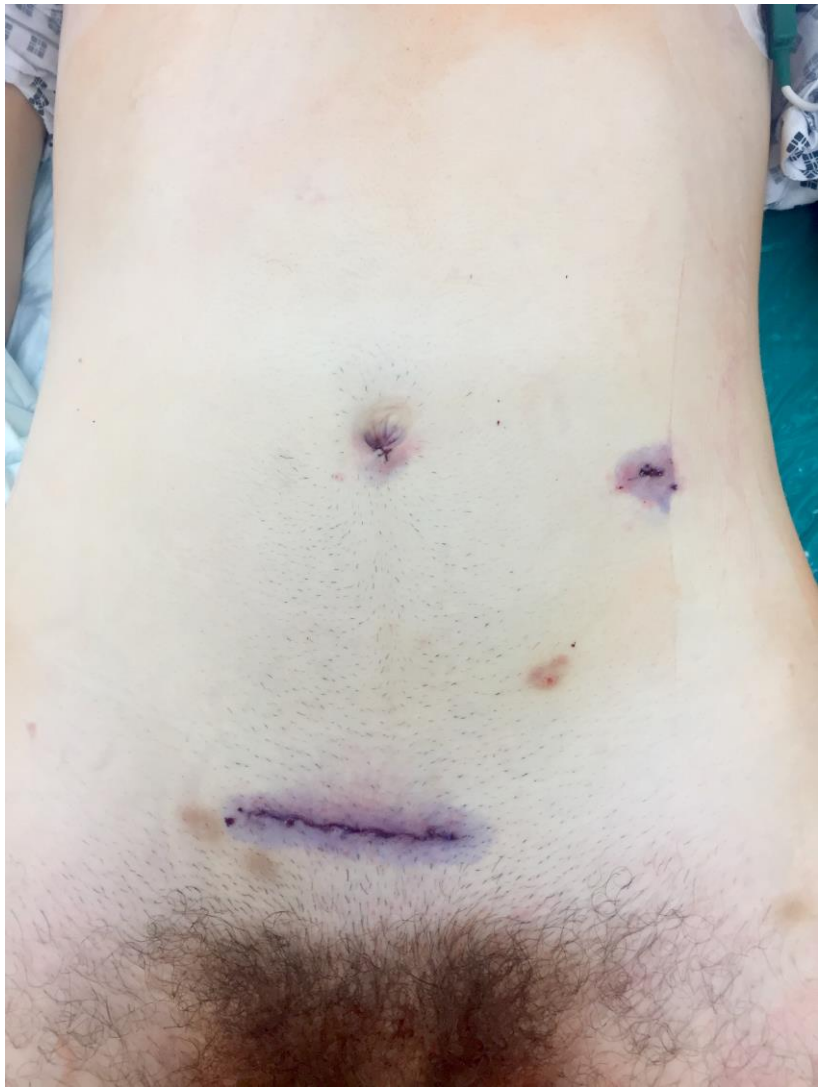


Total Colectomy (TC-IRA) versus NT-IDSA

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	

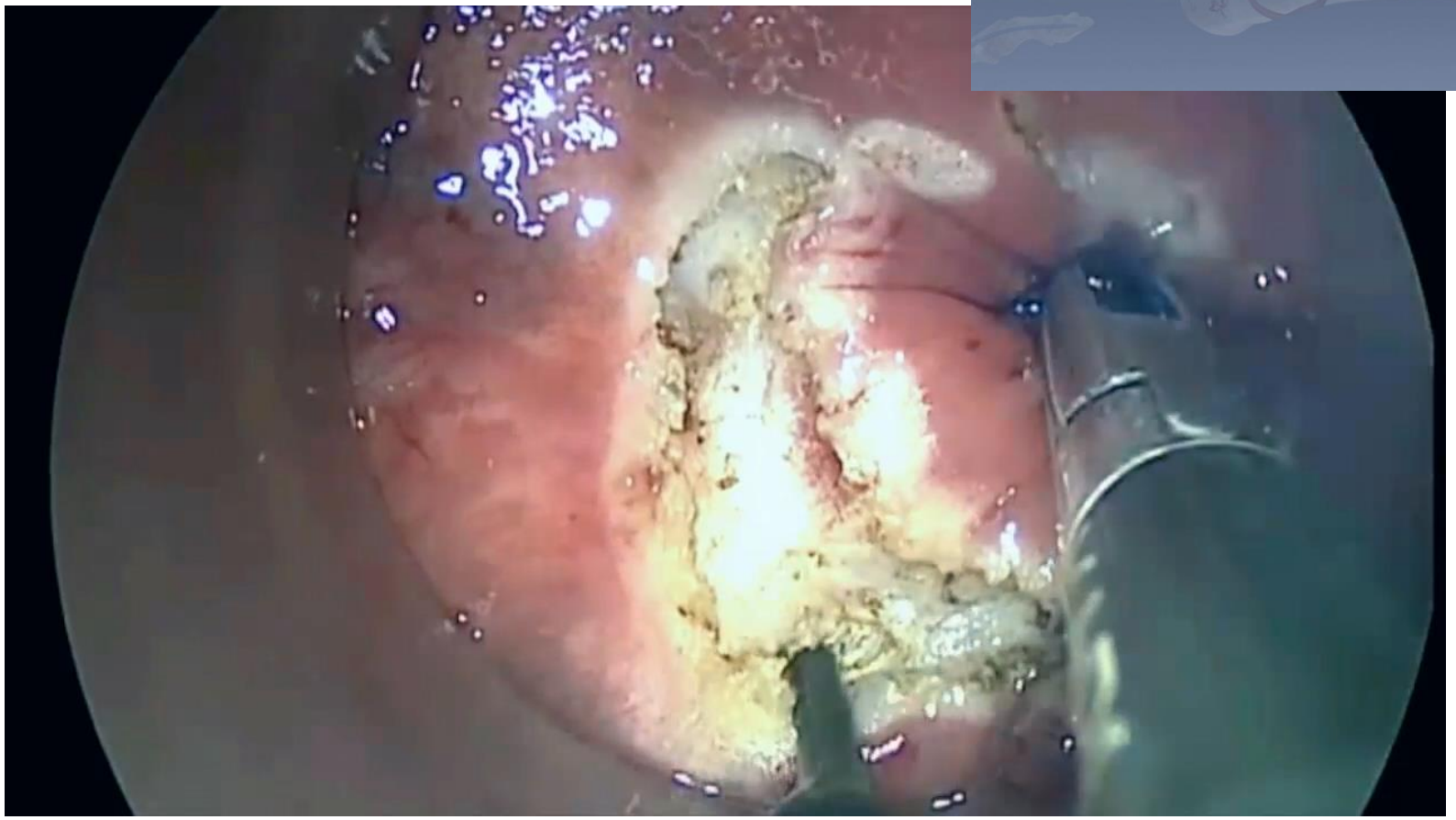


Gelport + 2

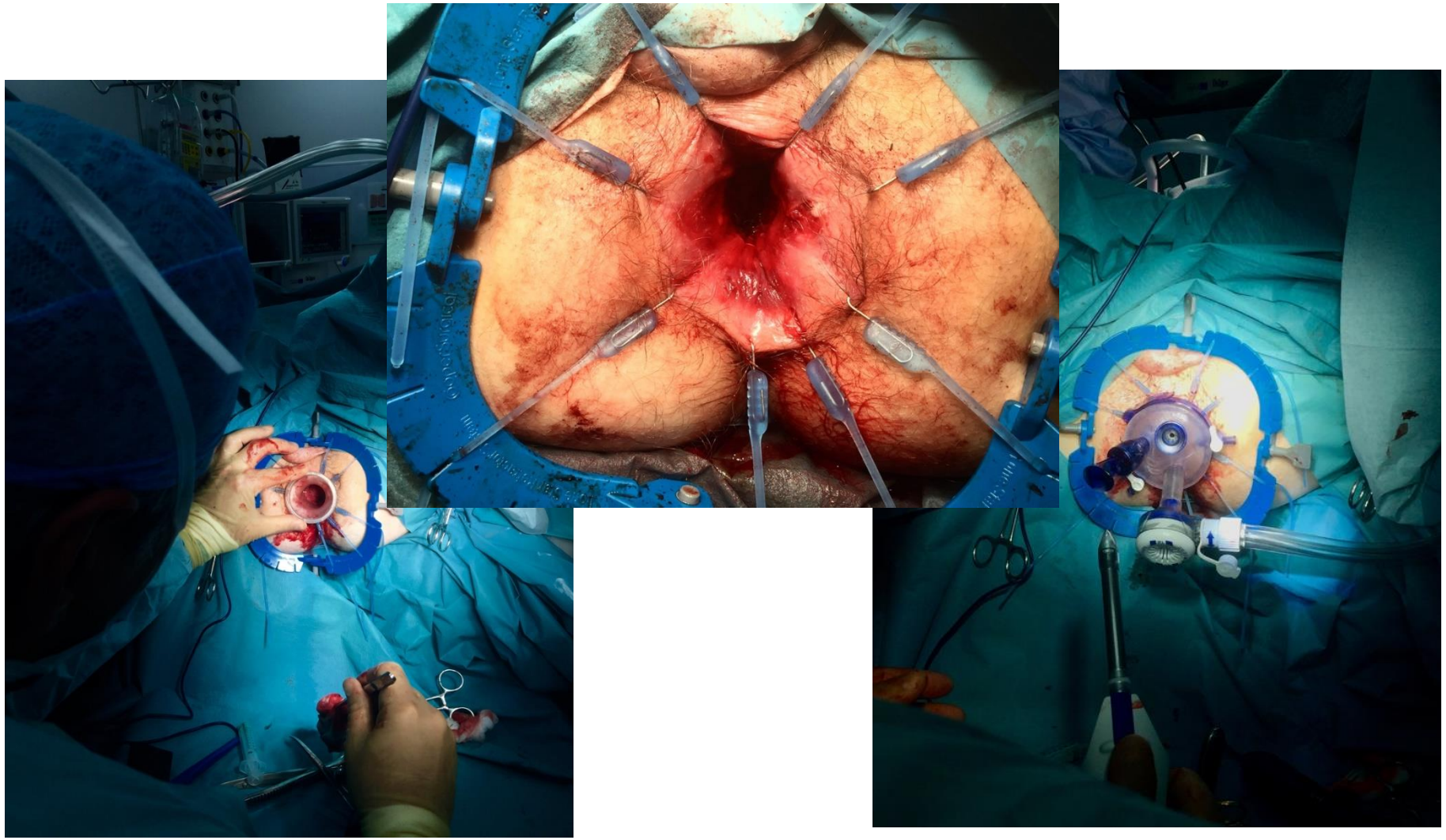


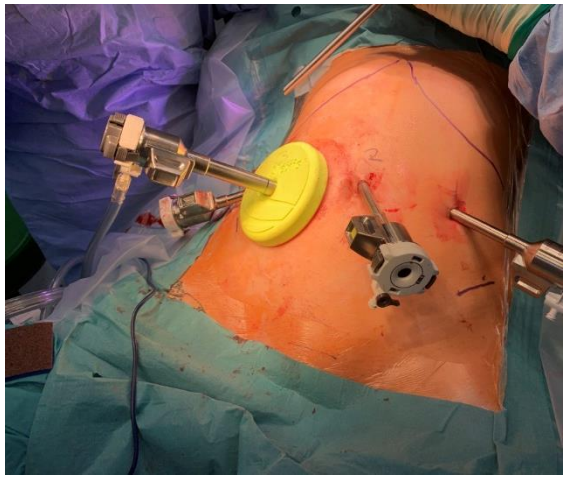
Restorative proctocolectomy

RPC



TaTME





Robotic pouch surgery

Conclusions

- FAP – prophylactic surgery for all. Decision to preserve rectum on basis of i. phenotype ii genetics
- Lynch – not for prophylactic surgery. Extend resection for CRC in known carriers. Segmental resection only for CRC when Lynch not confirmed
- Operative procedures – do what I do!

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Thank you

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