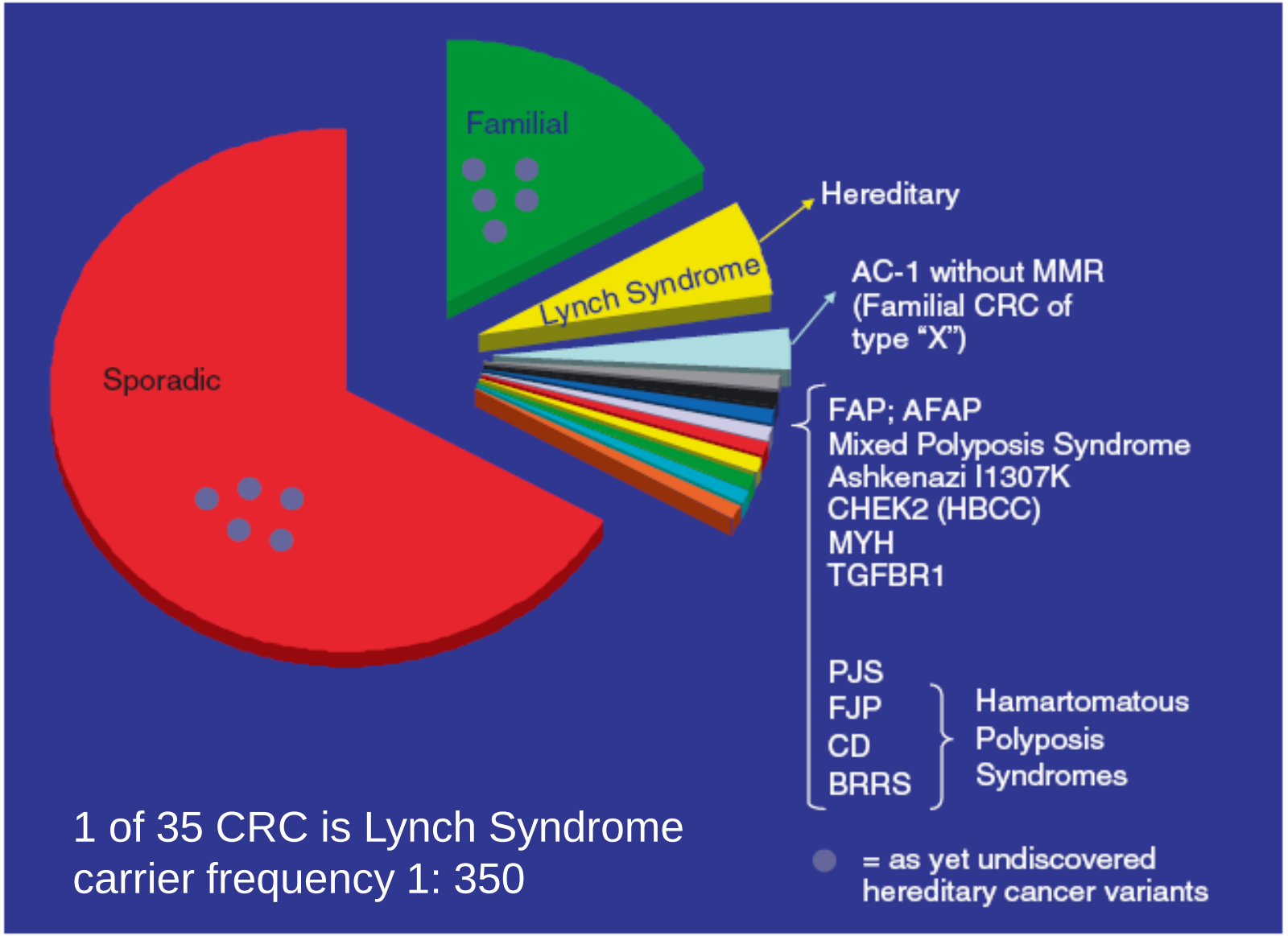
Jahrestagung
Deutsche Gesellschaft für Humangenetik

Früherkennung und Vorsorge bei erblichen Tumorsyndromen

MGZ
Medizinisch Genetisches Zentrum

Elke Holinski-Feder
MGZ-München, LMU-München

Hereditary gastrointestinal cancer



Lynch HT et al., Clin Genet 2009

Lynch Syndrome

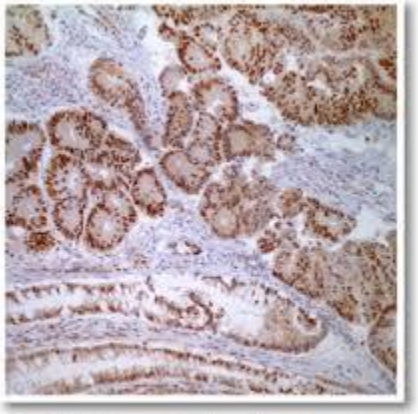
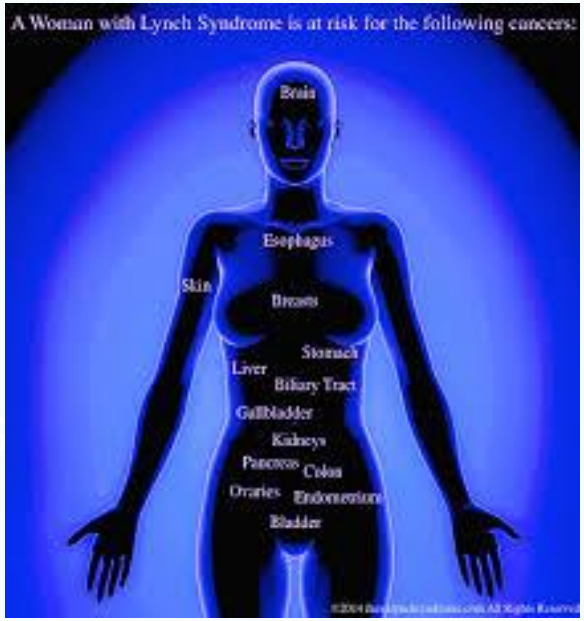
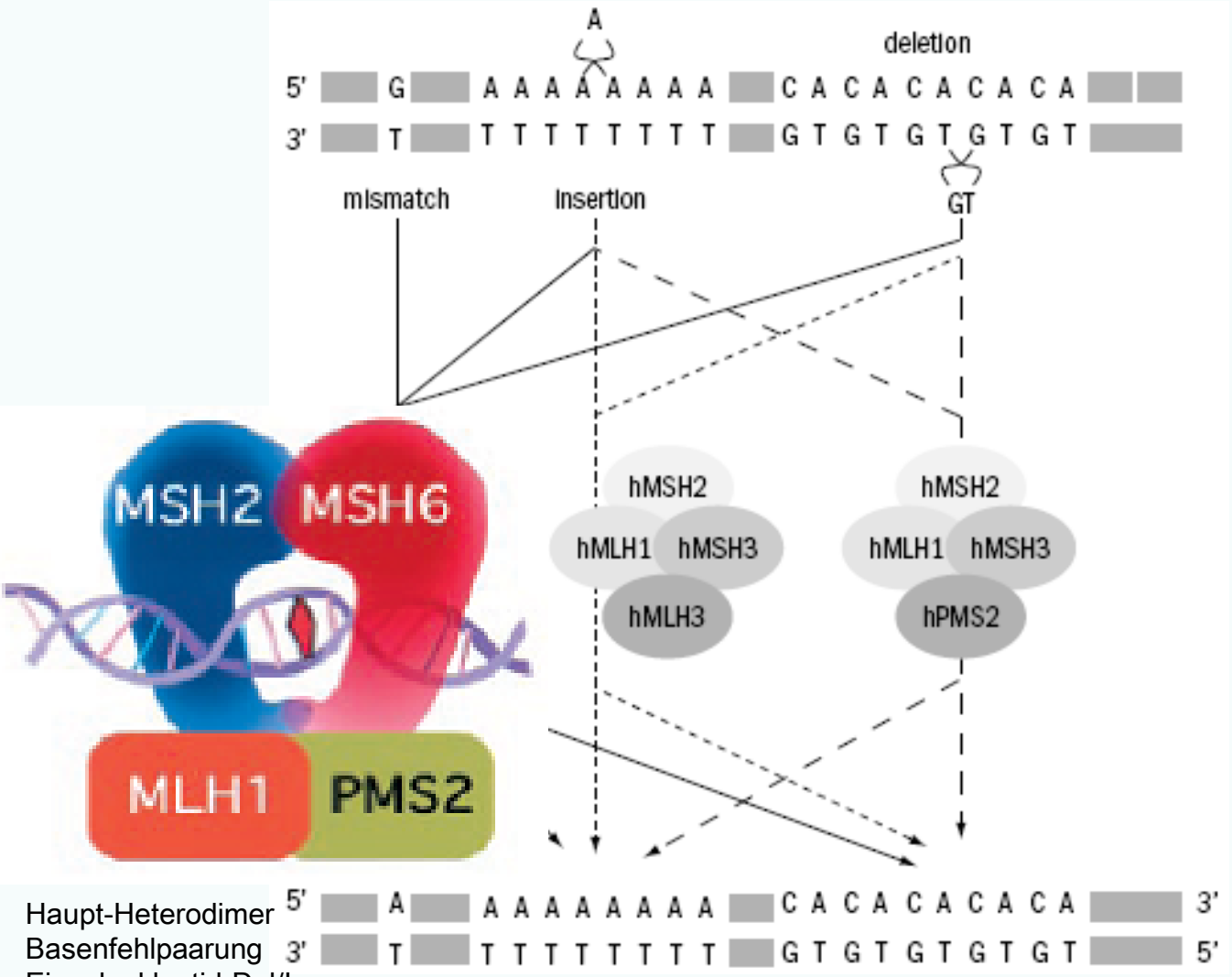


Figure 4: MSH6 (44) - nuclear labeling of adenocarcinoma cells and normal crypt epithelial cells.



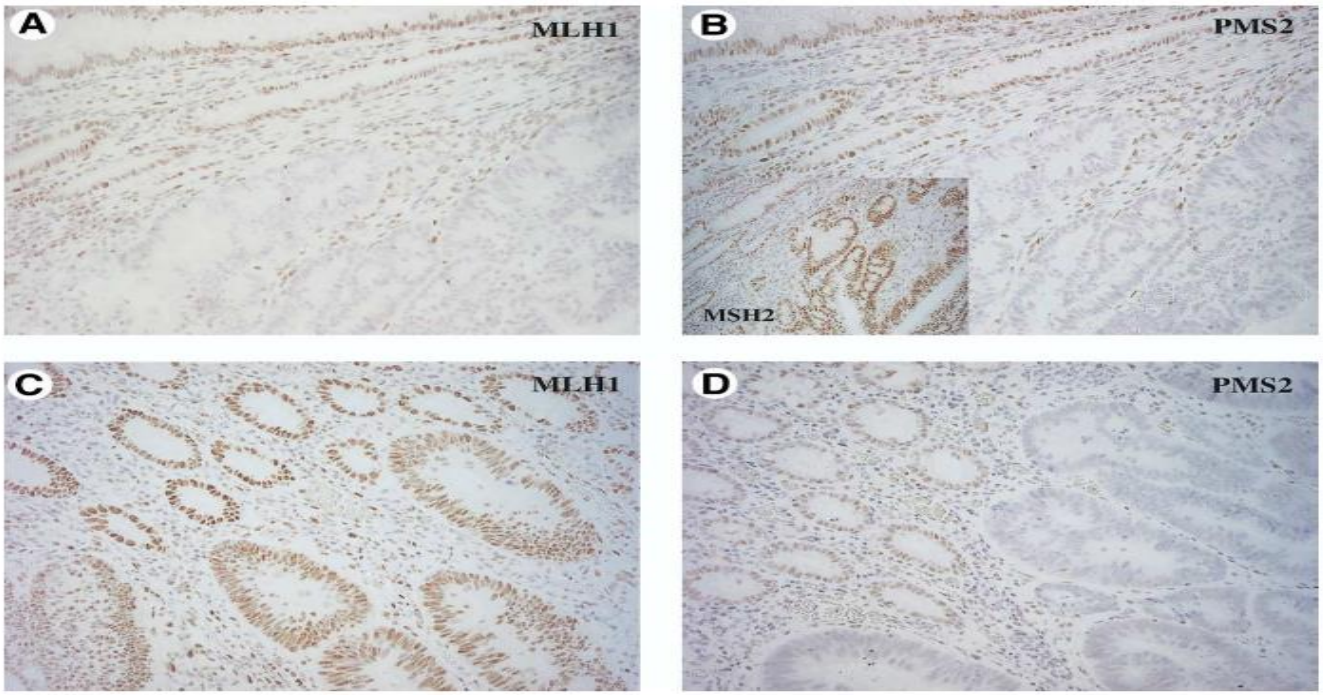
Lynch-Syndrome – microsatelliteinstability (MSI)

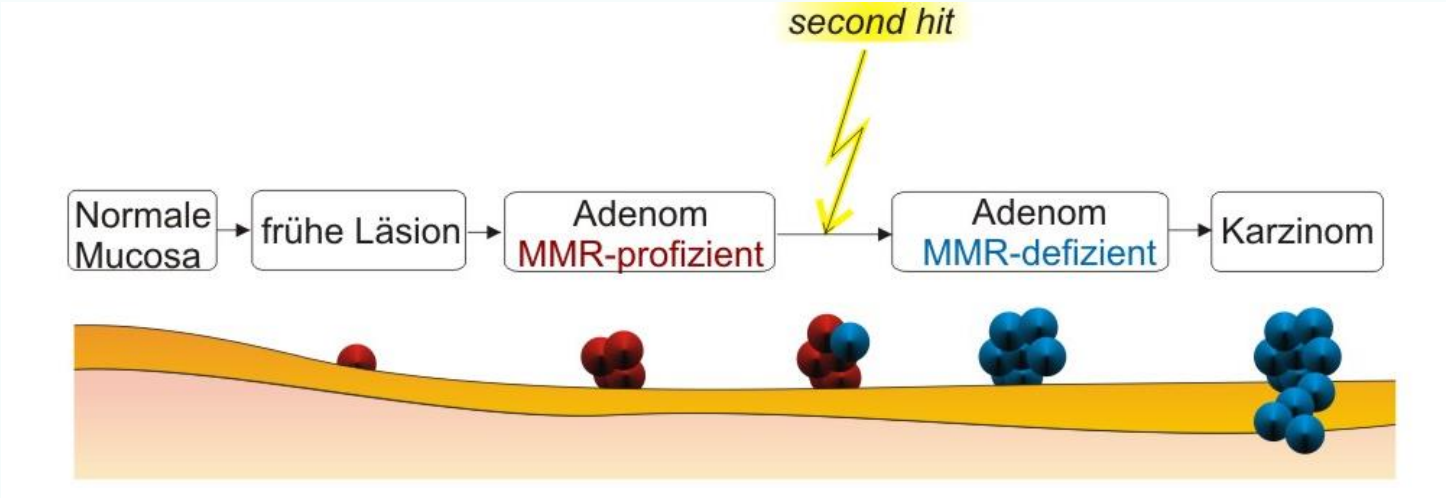


Haupt-Heterodimer
Basenfehlpaarung
Einzelnukleotid-Del/Ins
Repeat-Loops

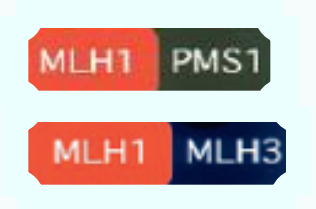
Lynch-Syndrome – immunohistochemistry (IHC)

Immunohistochemistry points towards the affected gene





Lynch-Syndrome – immunohistochemistry (IHC)



MLH1/PMS2
MSH2/MSH6
MSH6
PMS2

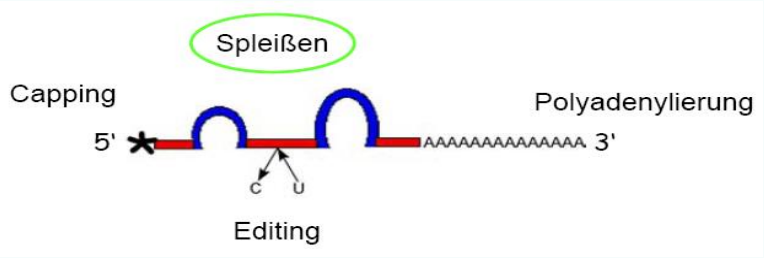
! CAVE: 6% escape in immunohistochemistry

- normal IHC for some missense mutations or late truncating mutations
  MLH1: 34% have low expression
  PMS2 mutation c.989-1G > T: 84% normal IHC, MSI-H 71%, MSI-L 19%
- Low sensitivity of IHC in adenomas

Grindedal, Heredit Cancer Clin Pract, 2014

Lynch-Syndrome – mutation spectrum

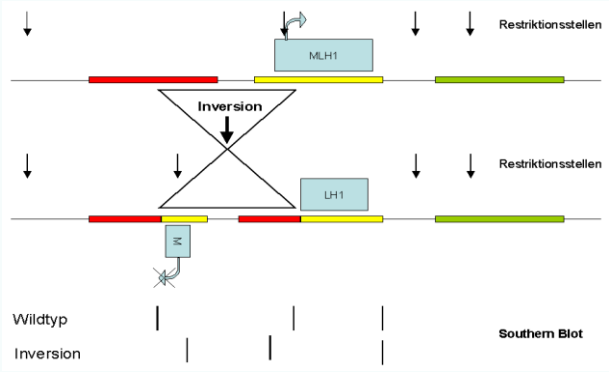
Point mutations



Chromosomal rearrangements

Intragenic inversion, normal sequencing and MLPA

Transgenic inversions with fusion transcrips



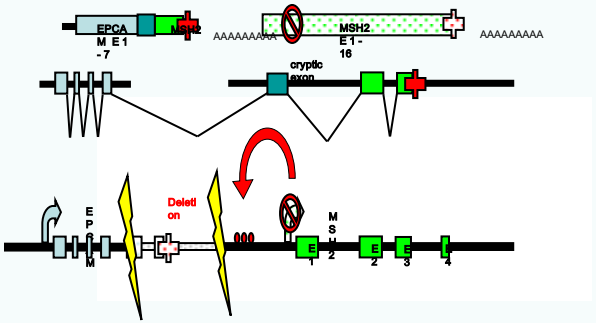
Regulatory mutations

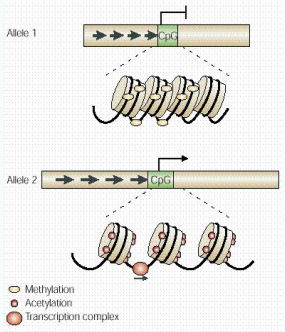
EPCAM-deletion, variable size

Promotermethylation in MLH1

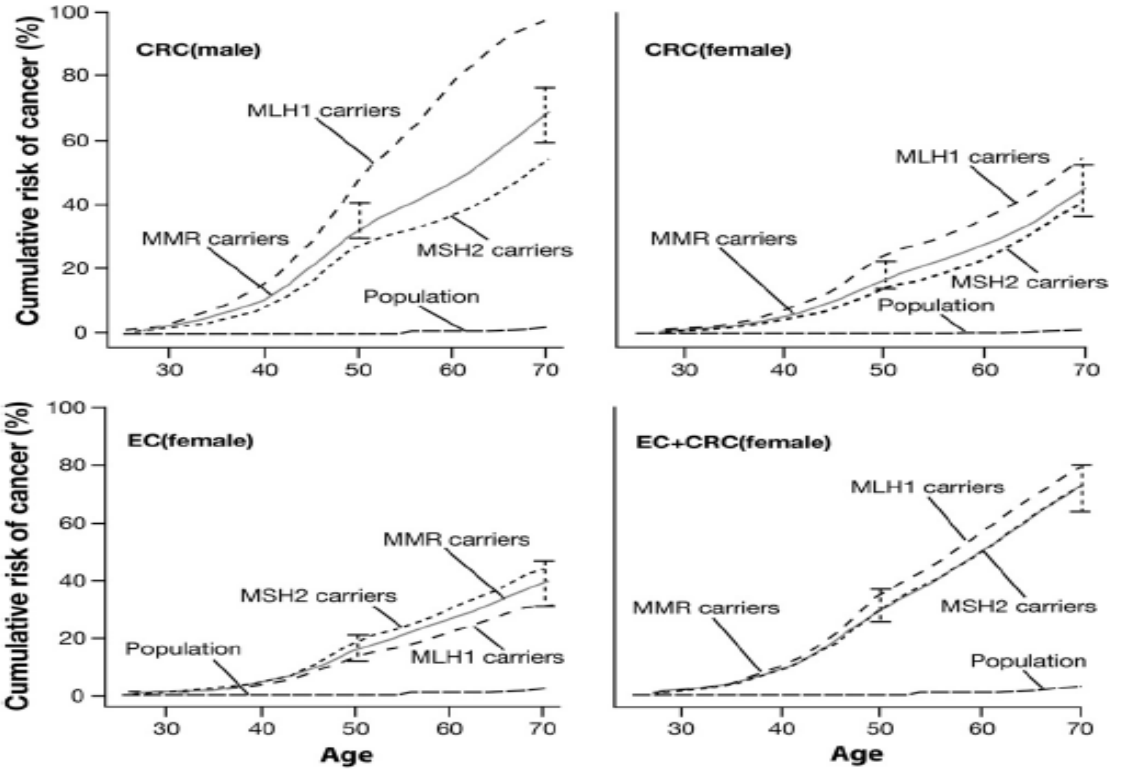
consitutive

somatic





Lynch-Syndrome – cancer risk – common cancers

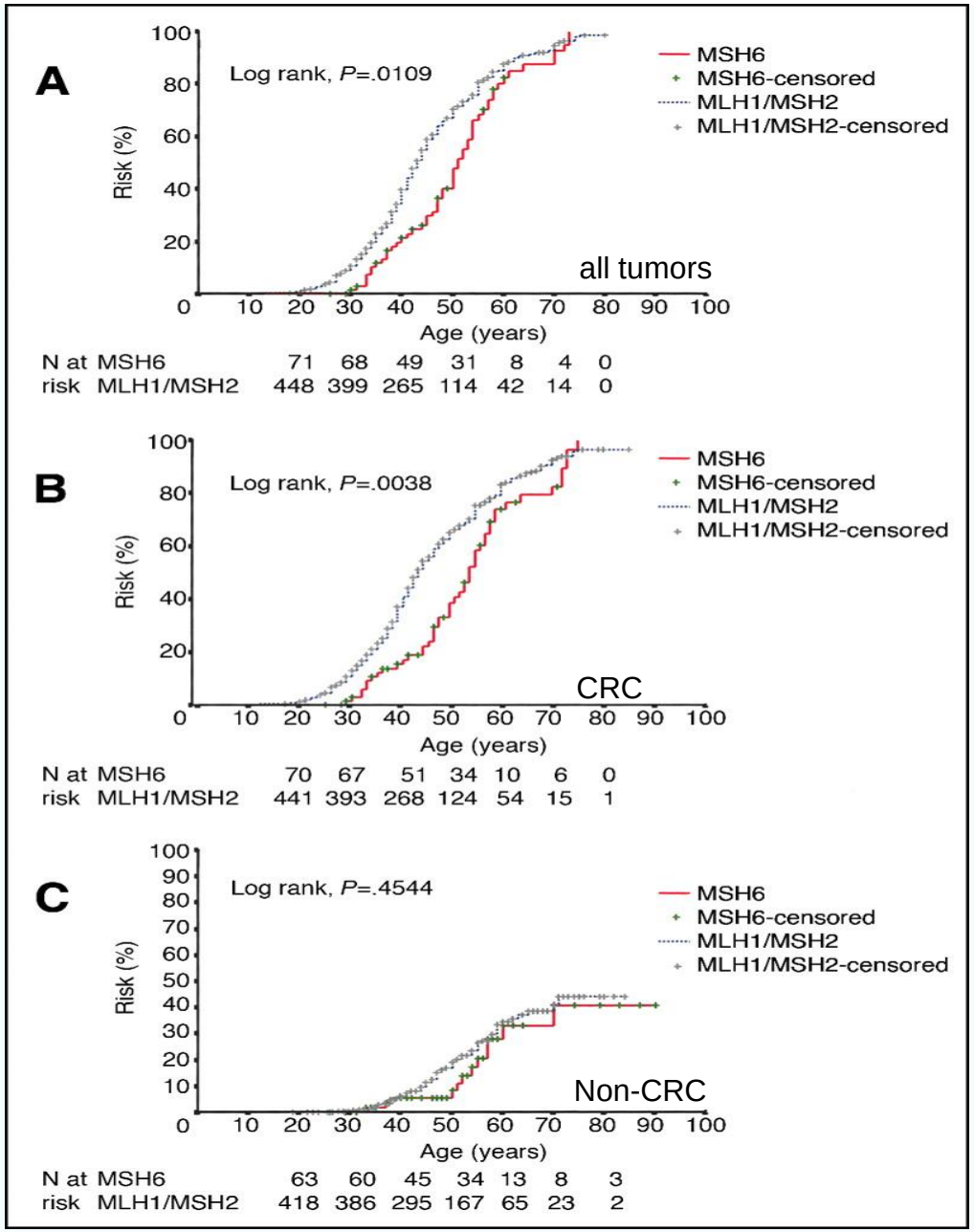


Age, y	Colorectal Cancer: Carriers: All	*MLH1*	*MSH2*	*MSH6*
20	0 (0-1)	0 (0-1)	0 (0-1)	0
30	2 (1-3)	1 (0-3)	2 (1-5)	0 (0-1)
40	5 (3-8)	6 (3-11)	8 (4-13)	1 (0-3)
50	13 (9-19)	14 (8-27)	20 (13-30)	3 (2-6)
60	24 (17-35)	28 (16-49)	36 (23-54)	6 (4-12)
70	35 (25-49)	41 (25-70)	48 (30-77)	12 (8-22)
80	42 (30-60)	49 (29-85)	52 (31-90)	18 (13-30)

Age, y	Endometrial Cancer: Carriers: All	*MLH1*	*MSH2*	*MSH6*
20	0	0	0	0
30	0 (0-1)	0 (0-1)	0 (0-1)	0
40	2 (1-4)	1 (0-4)	2 (0-7)	1 (0-2)
50	8 (4-15)	9 (3-19)	8 (3-21)	3 (1-8)
60	23 (12-38)	32 (12-55)	18 (8-53)	9 (5-19)
70	34 (16-58)	54 (20-80)	21 (8-77)	16 (8-32)
80	35 (17-60)	57 (22-82)	21 (9-82)	17 (8-47)

Bonadona et al., JAMA 2011 Stoffel et al., Gastroenterology 2009,

Lynch-Syndrome – cancer risk – common cancers



Age, y	Colorectal Cancer: Carriers All	*MLH1*	*MSH2*	*MSH6*
20	0 (0-1)	0 (0-1)	0 (0-1)	0
30	2 (1-3)	1 (0-3)	2 (1-5)	0 (0-1)
40	5 (3-8)	6 (3-11)	8 (4-13)	1 (0-3)
50	13 (9-19)	14 (8-27)	20 (13-30)	3 (2-6)
60	24 (17-35)	28 (16-49)	36 (23-54)	6 (4-12)
70	35 (25-49)	41 (25-70)	48 (30-77)	12 (8-22)
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Age, y	Endometrial Cancer: Carriers All	*MLH1*	*MSH2*	*MSH6*
20	0	0	0	0
30	0 (0-1)	0 (0-1)	0 (0-1)	0
40	2 (1-4)	1 (0-4)	2 (0-7)	1 (0-2)
50	8 (4-15)	9 (3-19)	8 (3-21)	3 (1-8)
60	23 (12-38)	32 (12-55)	18 (8-53)	9 (5-19)
70	34 (16-58)	54 (20-80)	21 (8-77)	16 (8-32)
80	35 (17-60)	57 (22-82)	21 (9-82)	17 (8-47)

Bonadona et al., JAMA 2011 Stoffel et al., 2009,

Lynch-Syndrome – cancer risk – common cancers

Age, y	Colorectal Cancer: Carriers: All	*MLH1*	*MSH2*	*MSH6*
20	0 (0-1)	0 (0-1)	0 (0-1)	0
30	2 (1-3)	1 (0-3)	2 (1-5)	0 (0-1)
40	5 (3-8)	6 (3-11)	8 (4-13)	1 (0-3)
50	13 (9-19)	14 (8-27)	20 (13-30)	3 (2-6)
60	24 (17-35)	28 (16-49)	36 (23-54)	6 (4-12)
70	35 (25-49)	41 (25-70)	48 (30-77)	12 (8-22)
80	42 (30-60)	49 (29-85)	52 (31-90)	18 (13-30)

Colorectal cancer

***PMS2* male**		***PMS2* female**	
1.27	0.00 to 3.51	0.46	0.00 to 1.52
4.63	0.01 to 9.04	0.92	0.00 to 2.42
7.11	1.76 to 12.17	4.74	0.22 to 9.05
18.75	5.60 to 30.06	10.56	2.42 to 18.01

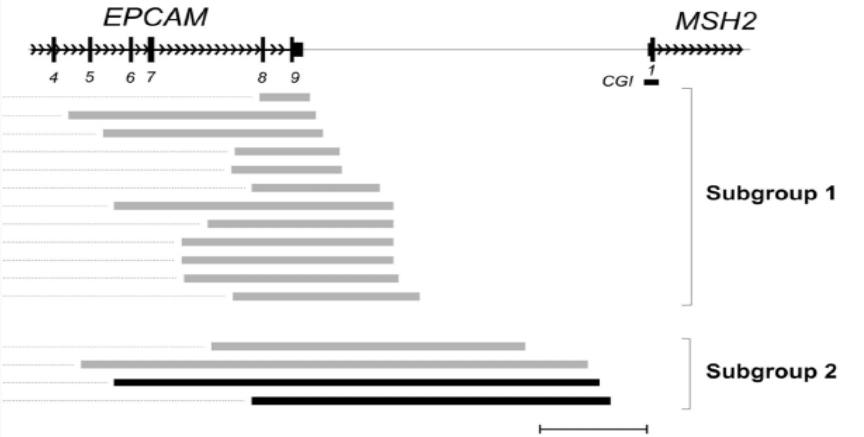
Age, y	Endometrial Cancer: Carriers: All	*MLH1*	*MSH2*	*MSH6*
20	0	0	0	0
30	0 (0-1)	0 (0-1)	0 (0-1)	0
40	2 (1-4)	1 (0-4)	2 (0-7)	1 (0-2)
50	8 (4-15)	9 (3-19)	8 (3-21)	3 (1-8)
60	23 (12-38)	32 (12-55)	18 (8-53)	9 (5-19)
70	34 (16-58)	54 (20-80)	21 (8-77)	16 (8-32)
80	35 (17-60)	57 (22-82)	21 (9-82)	17 (8-47)

Endometrial cancer

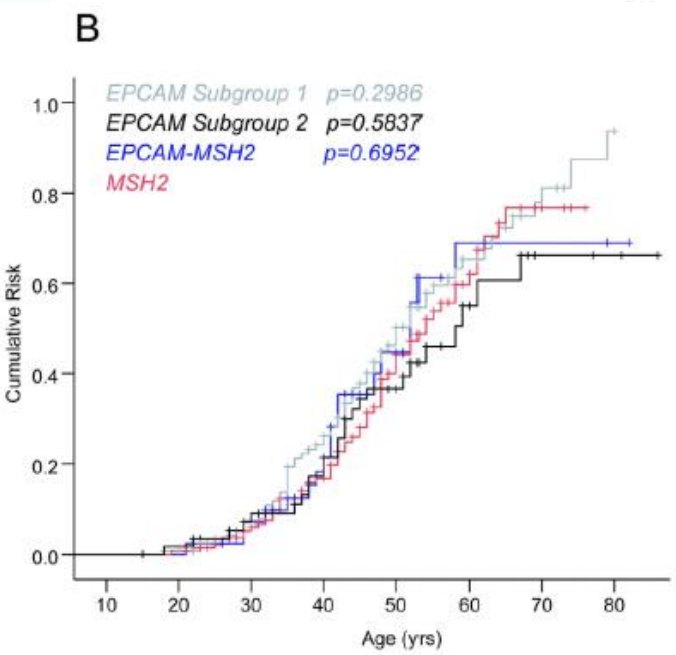
***PMS2* female**	
0.19	0.00 to 0.84
0.69	0.00 to 2.79
7.11	0.52 to 13.26
11.78	2.61 to 20.09

Bonadona JAMA 2011; ten Broeke JCO 2015

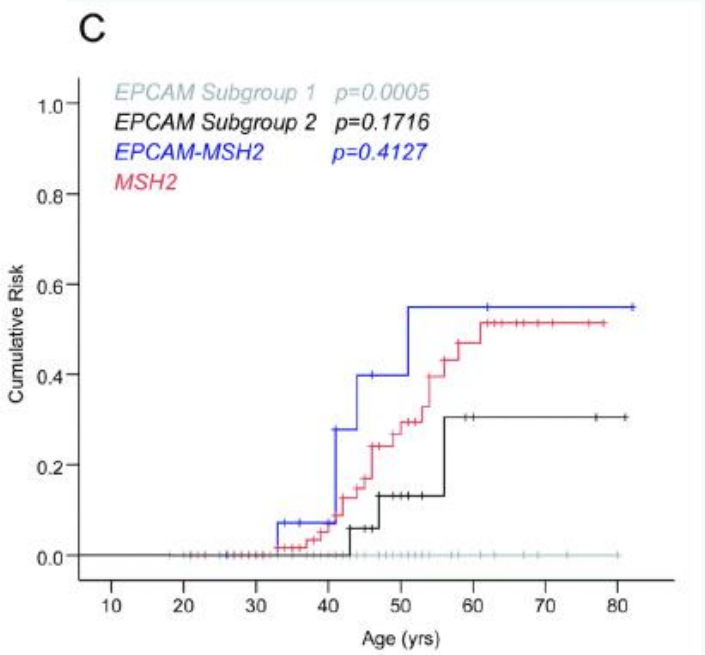
Lynch-Syndrome – cancer risk – common cancers



EPCM deletion



Colrectal cancer



Endometrial cancer

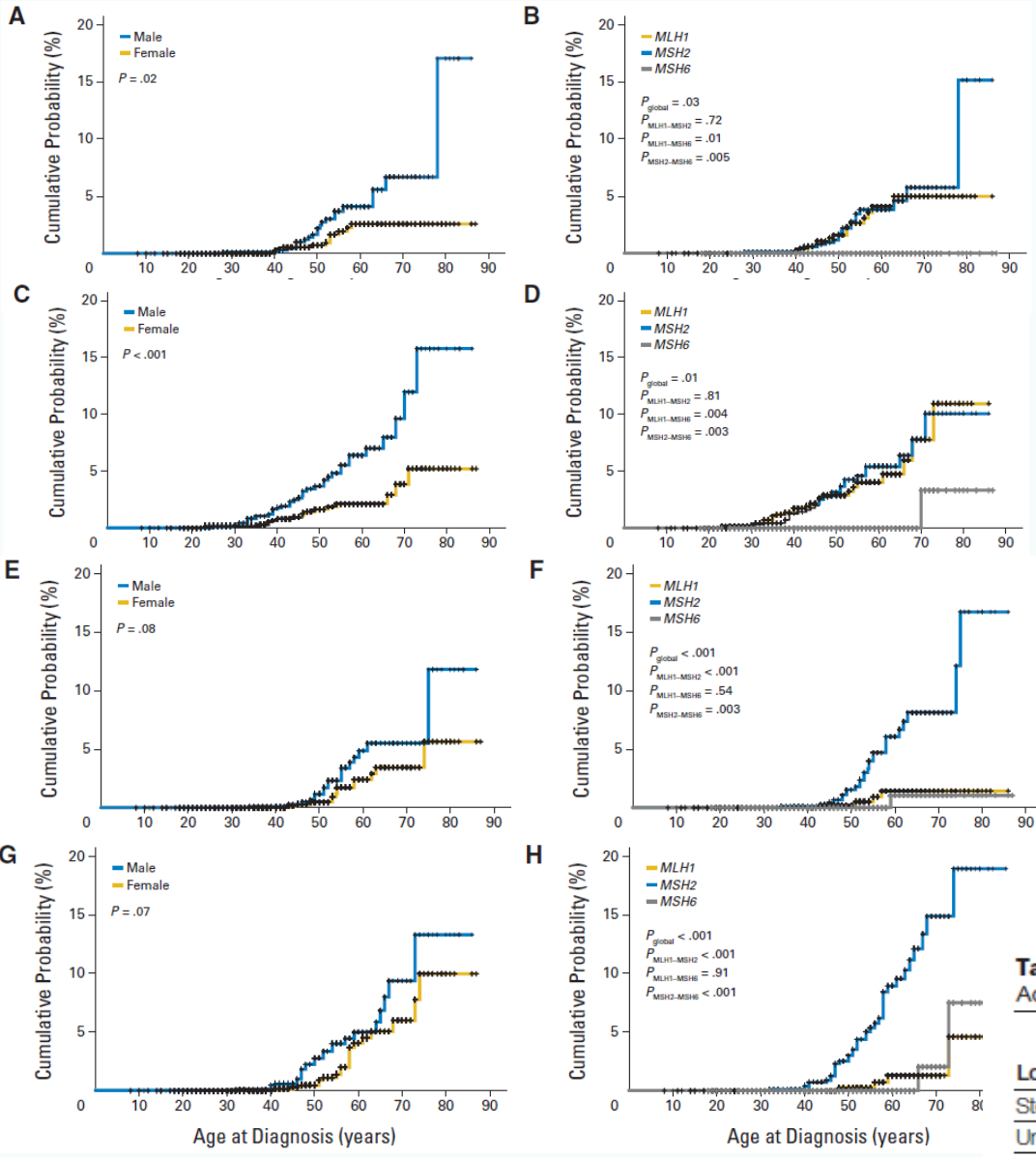
Kempers et al., Lancet Oncology 2011

Lynch-Syndrome – cancer risk – rare cancers

	Male %	95% CI	Age median	Female %	95% CI	Age median
Stomach	6,7	3,1 – 10,3	51	2,6	1,1 – 4,1	49
Small bowel	12.0	5,7 – 18,2	46	3,9	1,2 – 6,5	46
Urinary bladder	5.5	2,7 – 8,3	53	3,5	1,4 – 5,5	55
Urothelium	9.4	4,6 – 14,1	52	6,0	2,9 – 9,1	57
Breast				14,4	9,5 – 19,3	52
Ovary				8,0	5,8 – 10,3	44
Prostate	9.1	4,4 – 13,8	59			

Engel et al., JCO 2012; Bonadona et al., JAMA 2011

Lynch-Syndrome – cancer risk – rare cancers



Stomach

Small bowel

Urinary bladder

Urothelial cancer

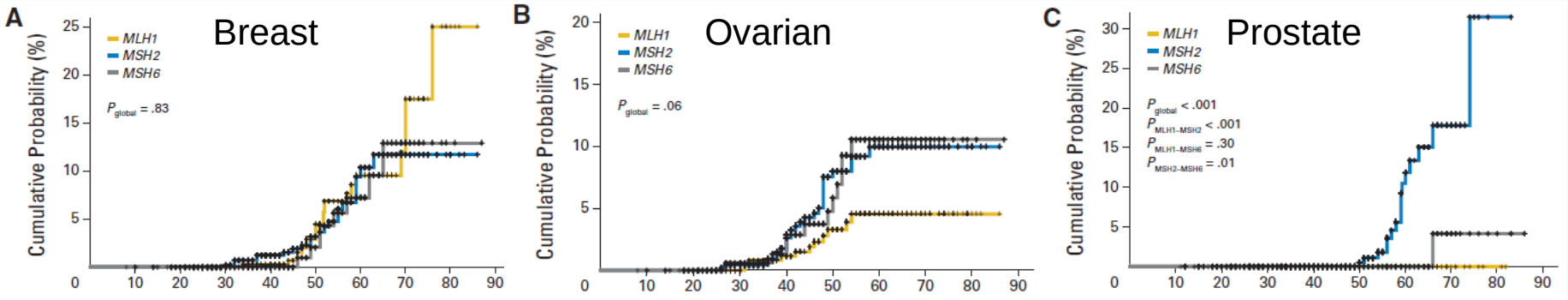
Table 4. Cumulative Risks of Other Hereditary Nonpolyposis Colorectal Canc
According to the Mutated Gene[a]

	Cumulative Cancer Risk at 70 Years, % (95% Confid		
Localization	*MLH1*	*MSH2*	*MSH6*
Stomach	6 (0.2-17)	0.2 (0-10)	0
Urothelium	0.2 (0-2.6)	2.2 (0.6-8)	0.7 (0-2.1)
Small bowel	0.4 (0.1-3)	1.1 (0-5)	0
Biliary tract	1.9 (0-15)	0.02 (0-0.2)	0

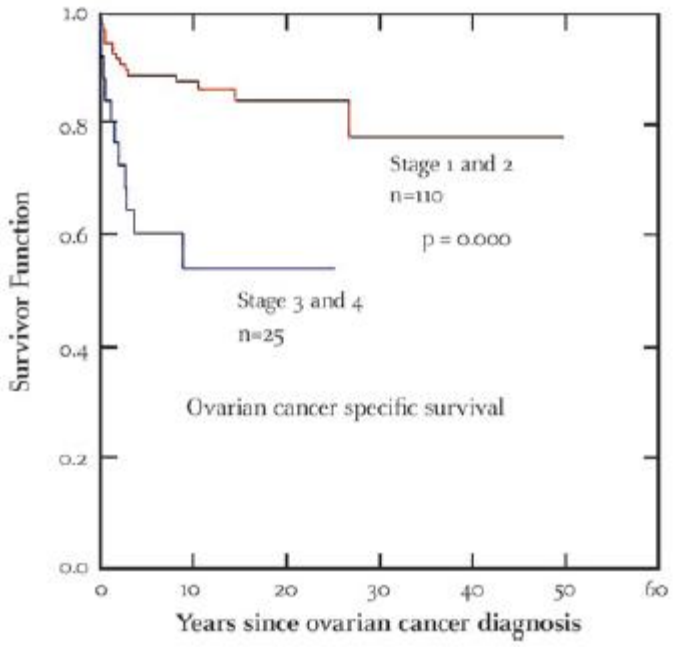
[a]See eTable 4 (available at http:www.jama.com) for the number of affected individuals and the numb

Engel et al., JCO 2012; Bonadona et al., JAMA 2011

Lynch-Syndrome – cancer risk – rare cancers



Age, y	Ovarian Cancer: Carriers: All	*MLH1*	*MSH2*	*MSH6*
20	0	0	0	0
30	0	0	0 (0-1)	0
40	1 (0-1)	0 (0-2)	1 (0-3)	0
50	3 (1-5)	4 (0-11)	4 (1-9)	0 (0-1)
60	7 (2-21)	15 (1-45)	11 (2-28)	1 (0-2)
70	8 (2-37)	20 (1-65)	24 (3-52)	1 (0-3)
80	8 (2-39)	20 (1-66)	38 (3-81)	1 (0-3)



Grindedal EM, J Med Genet 2010; Bonadona JAMA 2011; Engel JCO 2012;

Lynch-Syndrome - pick-up strategies

Sensitivity

Amsterdam-Criteria:	40-80% (MSI-H 70%)
Bethesda-Criteria:	15-20% (MSI-H 53%)
They miss:	12-28%

Recommendation: IH and MSI-analysis for all CRC and EC < 60 years

Lynch-Syndrome - epidemiology

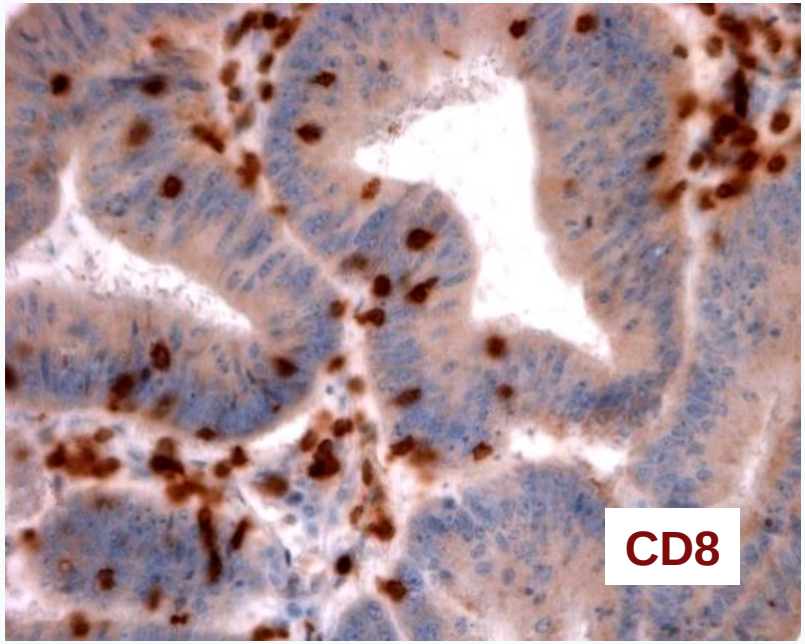
Prevalence

CRC	MSI-H app. 13% mutation positive app. 3%
EC	MSI-H app. 20% mutation positive app. 2-4%
SC	MSI-H app. 38% mutation positive app. 14%
SB	MSI-H app. 30% mutation positive 76%

GeneReeviews; Steinke V., IJC 2014

Lynch-Syndrome - immunology

- Infiltration with activated cytotoxic T-cells
- Crohn ‘s like reaction
- T3/T4,N0
- Good prognosis

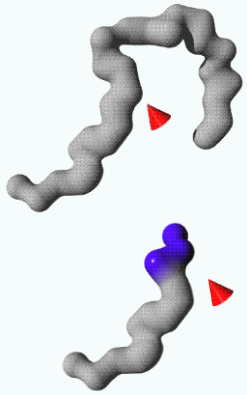


Coding microsatellite

TGT . AAA . AAA . AAA . ACG . TGC . TGG . CTA . GCT . GA.....

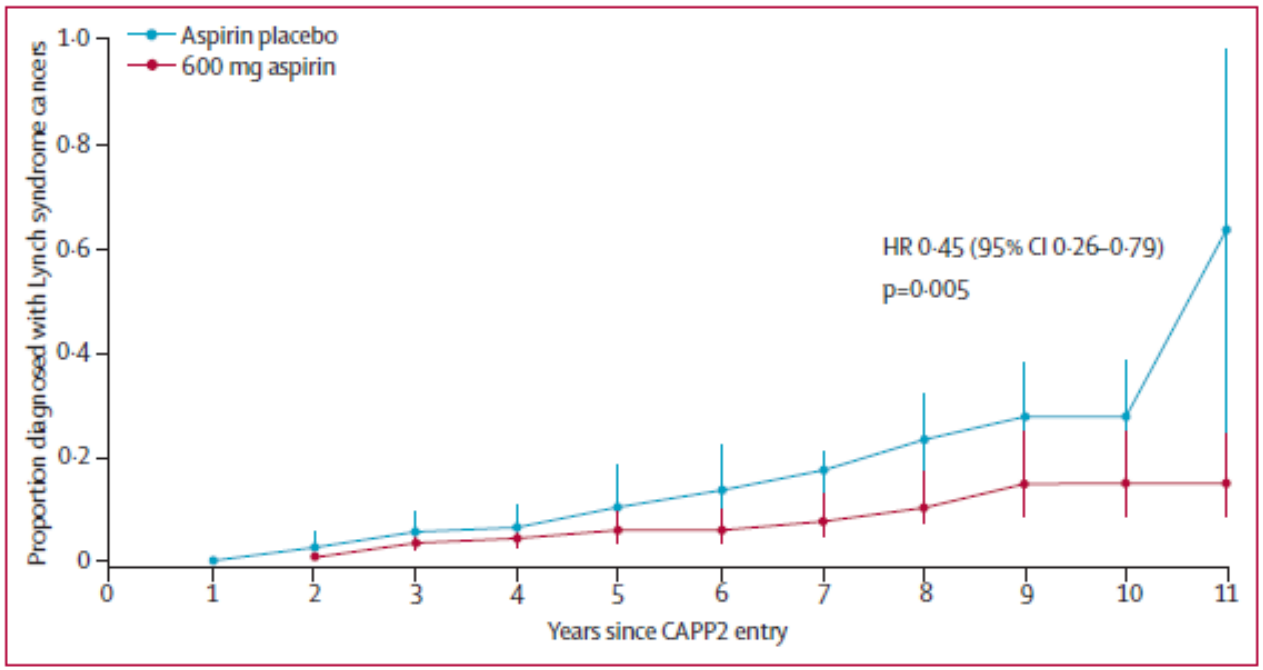
C K K K T C W L A

FSP *neo*-Sequenz



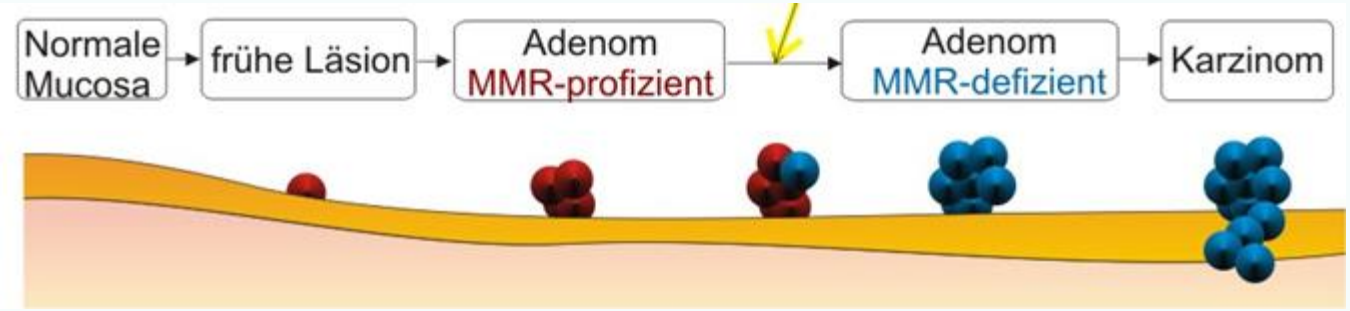
M. Kloor

Lynch-Syndrome - chemoprevention



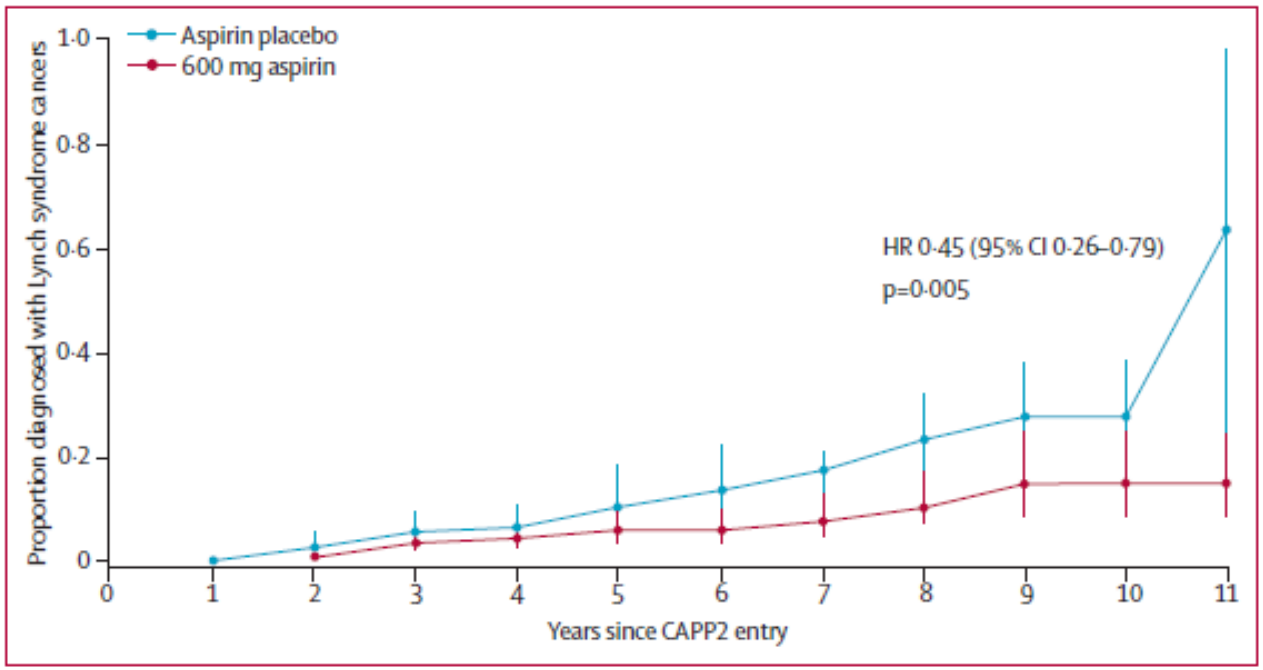
Mallorca Group

All patients should consider regular daily aspirin starting with their regular surveillance. HP erradication may be beneficial.

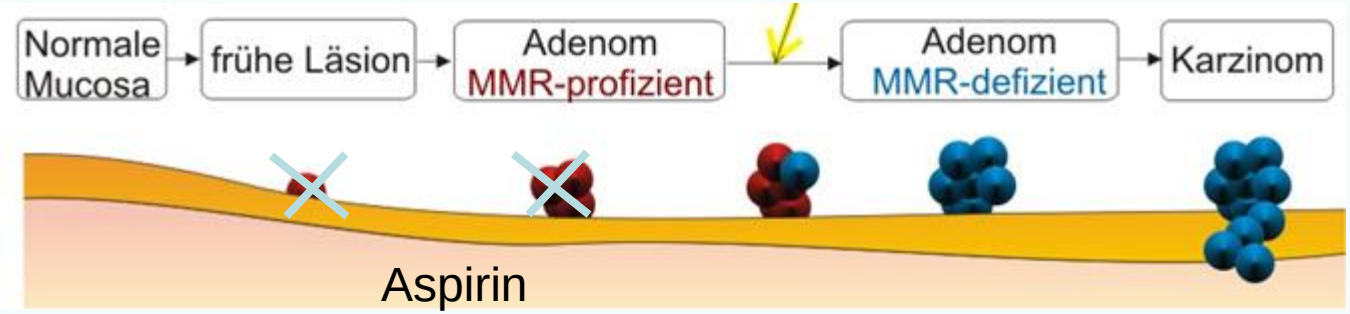


Burn J; Lancet 2011

Lynch-Syndrome - chemoprevention



Mallorca Group
All patients should consider regular daily aspirin starting with their regular surveillance. HP erradication may be beneficial.



Burn J; Lancet 2011

Lynch-Syndrome cancer survival

	10 year survival %	5 year survival %	
Colorectum			
Endometrium	75-85		20% ultimatively die
Ovary	80-85		80% FIGO I/II
Stomach		20-25	
Small bowell		30-35	43% duodenum, 33% jejunum
Urothelium, bladder		> 90 low grade	
		60-70 high grade	
Prostate	72		Gleason score high

Vasen H. et al., GUT 2013

Lynch-Syndrome surveillance recommendations

Cumulative risks

- high risc for MLH1 and MSH2 at young ages
- lower risc for MSH6 and PMS2 at higher ages

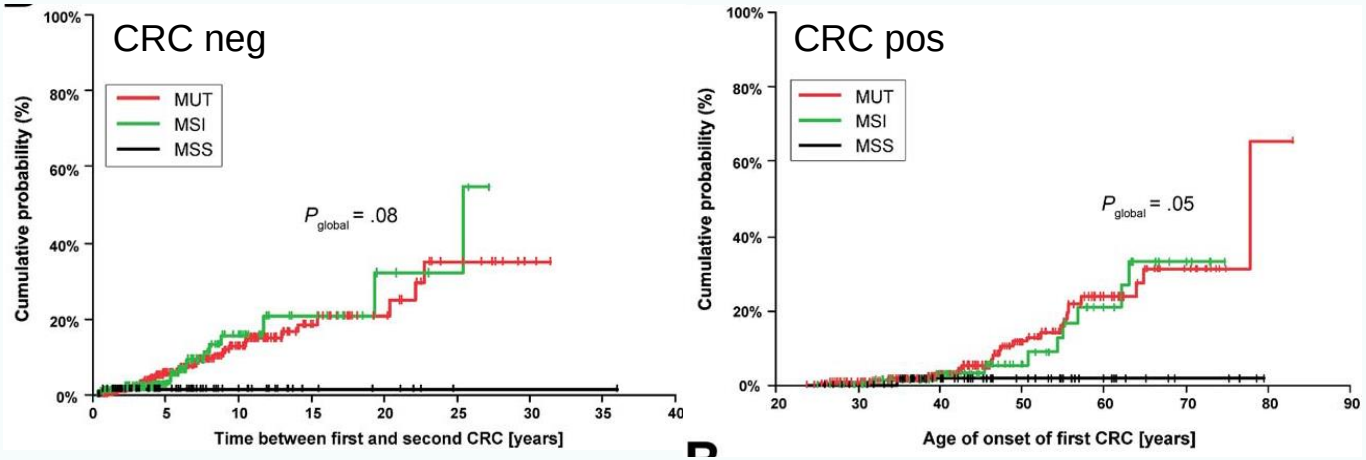
Current surveillance recommendation

- colonoscopy from 25 years on (male MLH1 from 20 years on)
- gastroscopy from 35 years on (duodenum, jejunum)
- gynaecological ultrasound from 25 years on
- abdominal ultrasound, urine testing

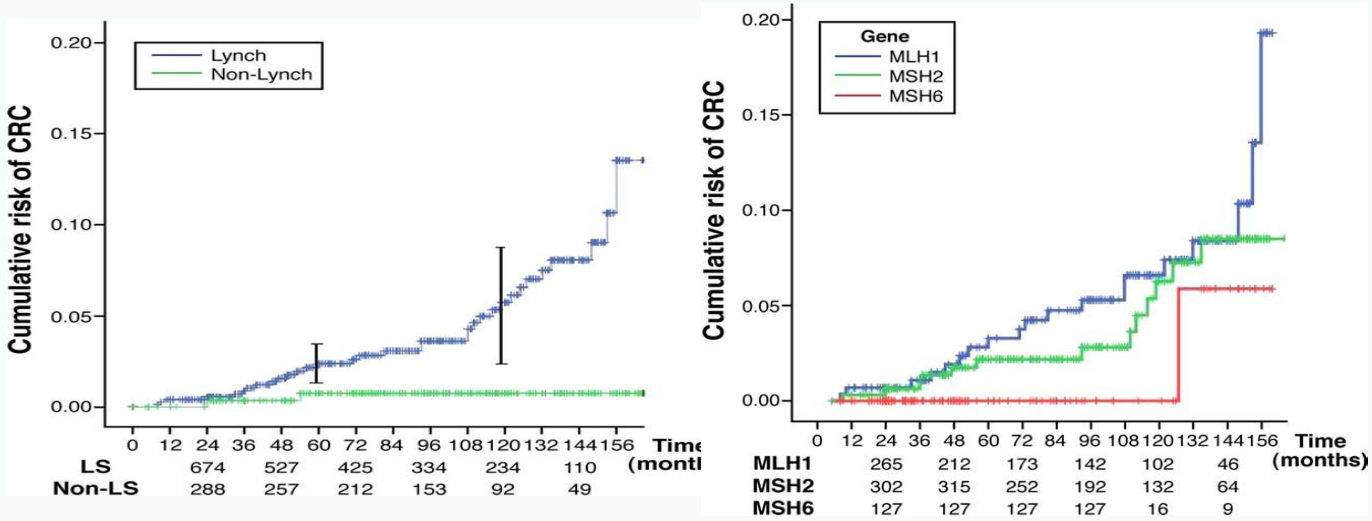
Risc adapted surveillance

- later onset and longer intervals for MSH6 and PMS2

Lynch-Syndrome surveillance



1126 individuals
Interval 1 year

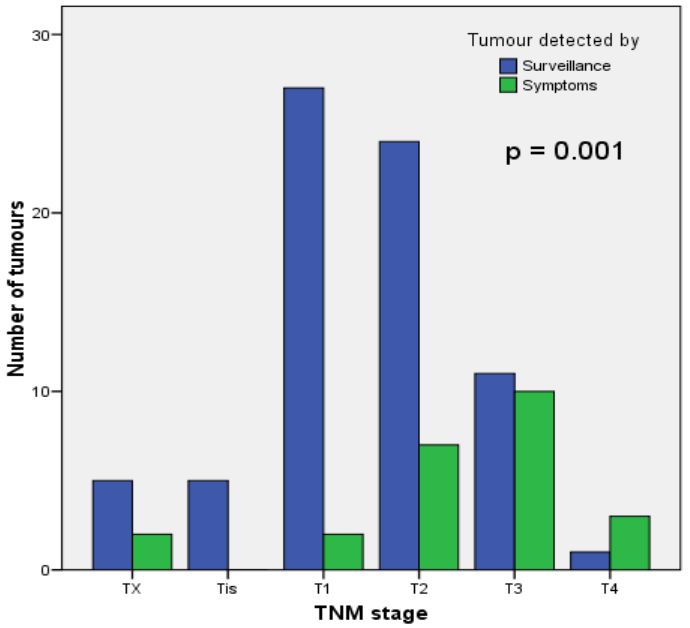


745 individuals
Interval 1-2 years

Engel at al., Clin Gastoeterol. and Hepatol. 2010; Vasen et al., Gastroenterology 2010

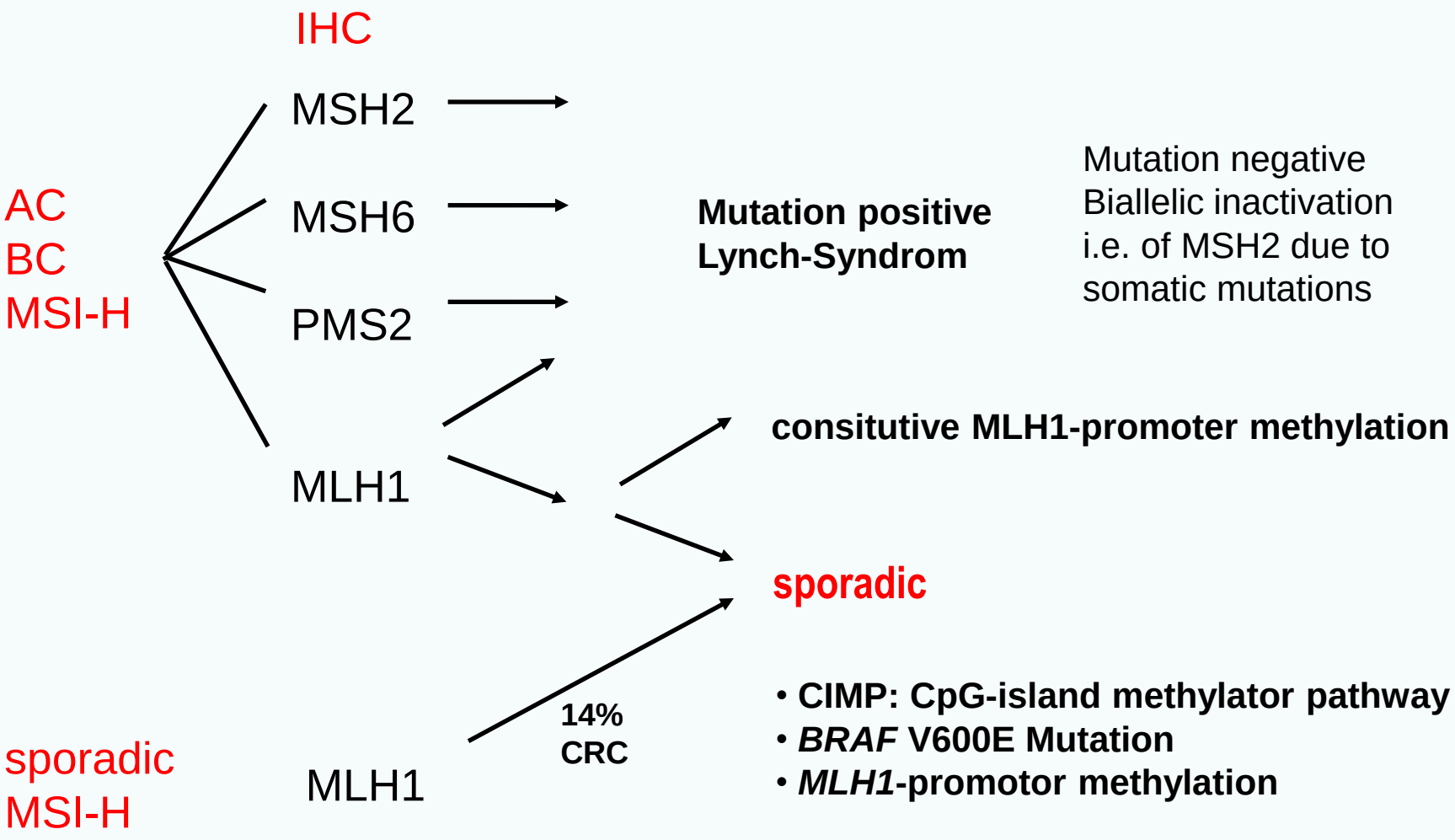
Lynch Syndrome – surveillance

- Cumulative risk at 60 years for CRC 23%
- 104 CRC in 1126 patients
  - 72% at yearly surveillance endoscopy
  - 17% symptomatic
  - Significant different TNM stages (p=0.01)
- Adenoma at baseline endoscopy
  - Risk for further adenomas RR 2.6
  - Risk for further carcinomas RR 3.9



Engel et al., Clin Gastroenterol Hepatol 2009

Lynch-Syndrome - phenocopies



Familial colorectal cancer type X (FCCTX)

Amsterdam Criteria

60 % MSI Lynch Syndrome

40 % MSS heterogenous, polygenic

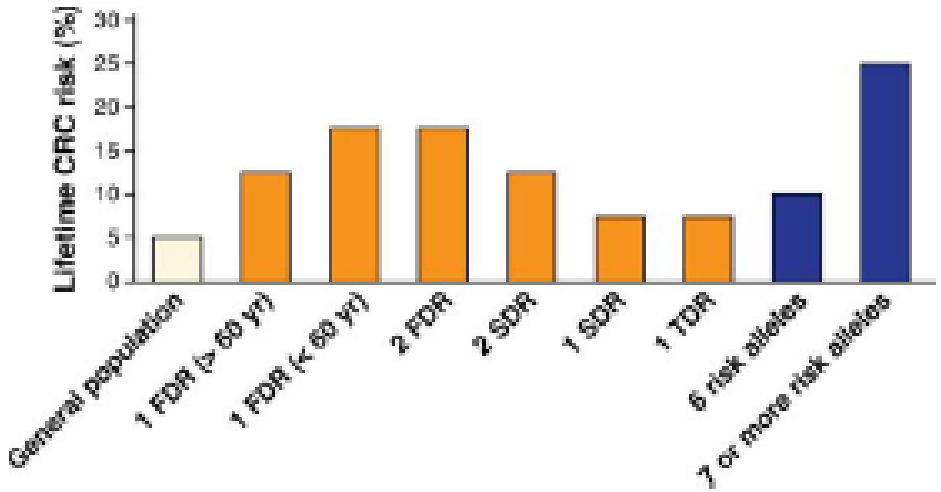
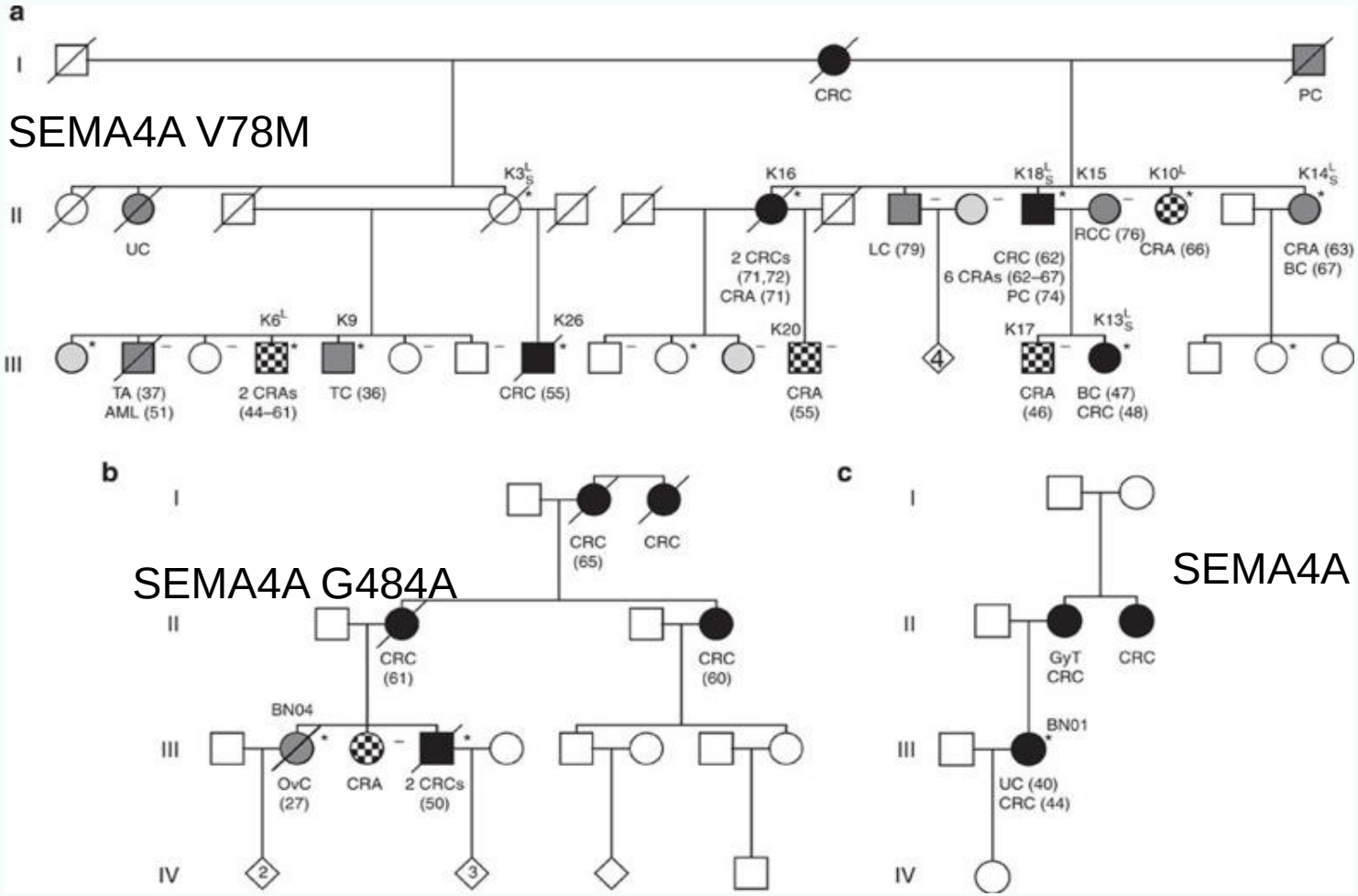


Table 1. Risk of Colorectal Cancer Associated With Susceptibility Alleles Identified in Genome-Wide Association Studies

SNP	Gene	Chromosomal region	Per allele[a]	Heterozygous gene carriers[a]	Homozygous gene carriers[a]	Reference
rs16892766	*EIF3H*	8q23.3	1.25 (1.19–1.32)	1.27 (1.20–1.34)	1.43 (1.13–1.82)	Tomlinson et al[28]
rs6983267 (rs7014346)		8q24.21	1.24 (1.17–1.33)	1.35 (1.20–1.53)	1.57 (1.38–1.80)	Tomlinson et al[26]
			1.17 (1.12–1.23)	NA	NA	Zanke et al[29]
			1.22 (1.12–1.32	1.04 (0.90–1.20)	1.47 (1.25–1.74)	Haiman et al[30]
			1.19 (1.15–1.23)	NA	NA	Tenesa et al[31]
rs10795668		10p14	0.89 (0.86–0.91)	0.87 (0.83–0.91)	0.80 (0.74–0.86)	Tomlinson et al[28]
rs3802842		11q23.1	1.11 (1.08–1.15)	NA	NA	Tenesa et al[31]
			1.17 (1.12–1.22)	1.18 (1.11–1.25)	1.35 (1.22–1.49)	Pittman et al[33]
rs4779584	*CRAC1 (HMPS)* region	15q13.3	1.23 (1.14–1.34)	1.17 (1.06–1.30)	1.70 (1.35–2.14)	Jaeger et al[27]
rs4939827	*SMAD7*	18q21.1	0.85 (0.80–0.91)	0.84 (0.75–0.94)	0.73 (0.64–0.83)	Broderick et al[32]
			1.20 (1.16–1.24)	NA	NA	Tenesa et al[31]

Lynch HT et al., Clin Genet 2009

Familial colorectal cancer type X (FCCTX)



SEMA4A V78M

SEMA4A G484A

SEMA4A S326F

CRC at a median age of 62 years, mainly distal localisation
Possibly increased risk for associated tumors
Not ready for routine testing

Schulz E, Nature Communications 2014

Familial colorectal cancer type X (FCCTX) - surveillance

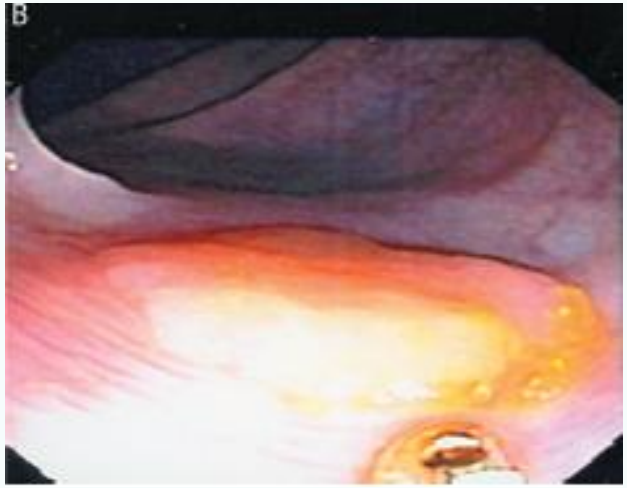
Risc seems to confined to colorectum
no accelerated adenoma carcinoma sequence

Current surveillance recommendations

- Colonoscopy every five years starting 10 years bevore the earlies tuor event in the family

Schulz E, Nature Communications 2014

Serrated polyposis



Serrated polyposis - definition

WHO clinicial diagnostic critera for serrated polyposis

- > five serrated polyps proximal to the sigmoid colon with at least two greater than 10 mm
- at least one serrated polyo proximal to the sigmoid colon an an individual who has a first-degree relative with serrated polyposis
- > 20 serrated polyps of any size, but distributed throughout the colon

	Edelstein 44 patients	Edelstein 64 patients	Jasperson 52 patients
Mean age at diagnosis of polyps	52 %	53 y	51 y
Mean age of diagnosis of cancer		56 y	48 y
Recurrend polyps	68 %		82 %
Personal history of CRC		9 %	16 %
Number of polyps			53 (9-277)
Peronal history of extracolonic cancer	28 %	16 %	37 % (24 % 1˚)
Positive family history polyps	5 %		10 %
smoking			49 %

Serrated polyposis – clinical phenotypes

Three different clinical phenotypes

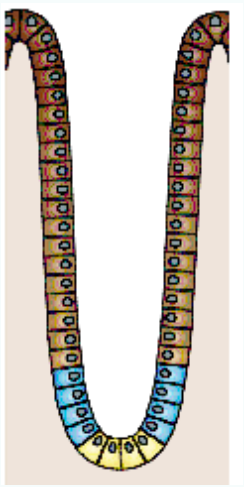
	Hyperplastic polyposis phenotype		
	Right	*Left*	*Mixed*
Serrated polyps	310	309	585
Hyperplastic polyps	193 (62%)	287 (93%)	524 (90%)
Sessile serrated polyps	113 (36%)	21 (7%)	45 (8%)
Traditional serrated adenomas	4 (1.3%)	1 (0.3)%	16 (2%)

		Hyperplastic polyposis phenotype		
	Total population	*Right (n = 55)*	*Left (n = 18)*	*Mixed (n = 42)*
Patients with colorectal cancer	29 (25%)	15 (27%)	5 (28%)	9 (21%)
Mean age at diagnosis	63 ± 13	59 ± 10	64 ± 18	68 ± 14
Median age at diagnosis	63 (33–91)	61 (38–70)	62 (33–82)	67 (47–91)
Cancer site				
Right	15	6	1	8
Left	8	5	3	1
Rectum	7	5	1	1
Family history of colorectal cancer (%)	44 (38%)	19 (35%)	6 (33%)	19 (45%)

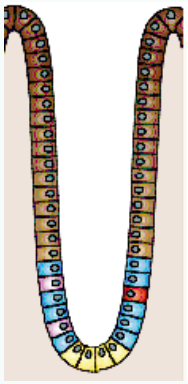
Kalady MF, Dis Colon Rectum 2011

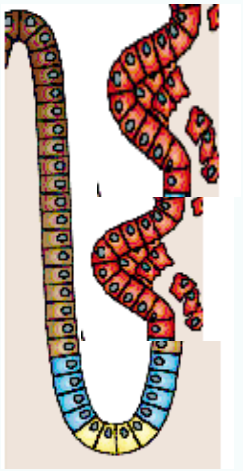
Serrated polyposis - histology

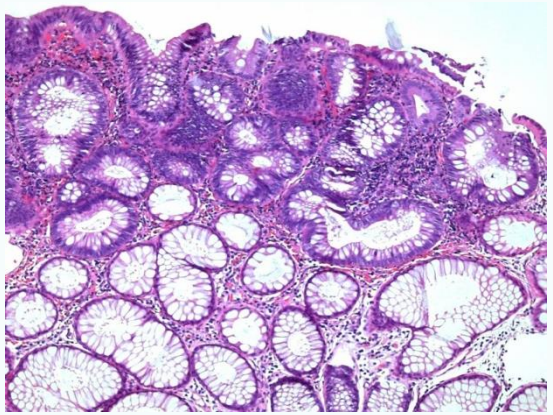
Adenomatous polyp



APC → K-Ras → LOH 18q21 → p53 CIN







Top down neoplasia

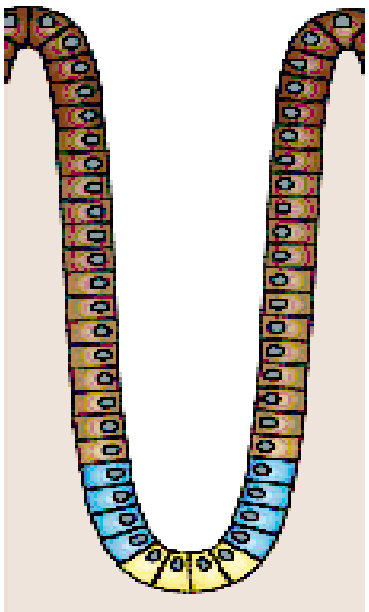
Cancer pathways

CIN	chromosomal instability	~70 %
MSI	microsatellite instability	~2-5% Lynch Syndrome
CIMP	CpG island methylation	~ 25%

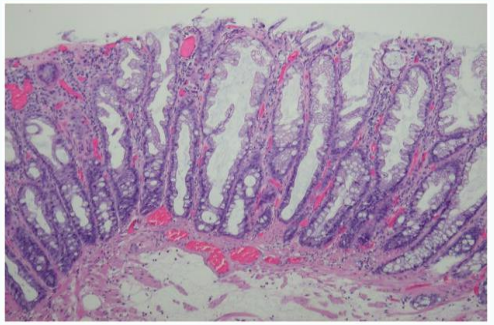
Serrated polyposis - histology

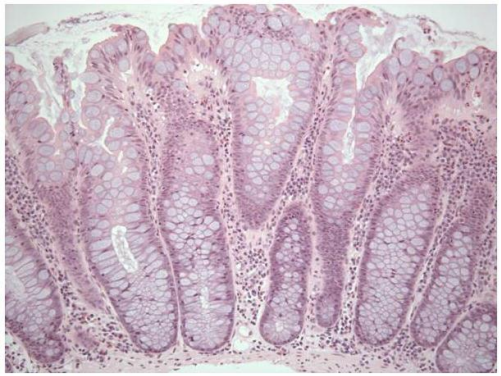
Hyperplastic polyp

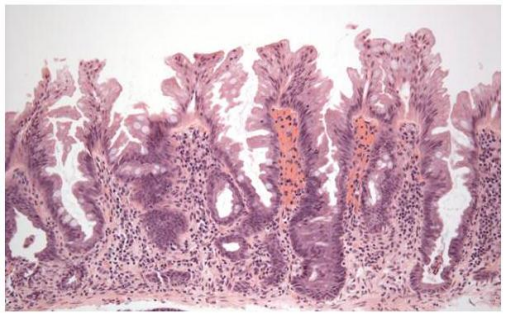
- Microvesicular hyperplastic polyp (MVHP)
- Goblet cell hyperplastic polyp
- Mucin poor hyperplastic polyp



decreased apoptosis



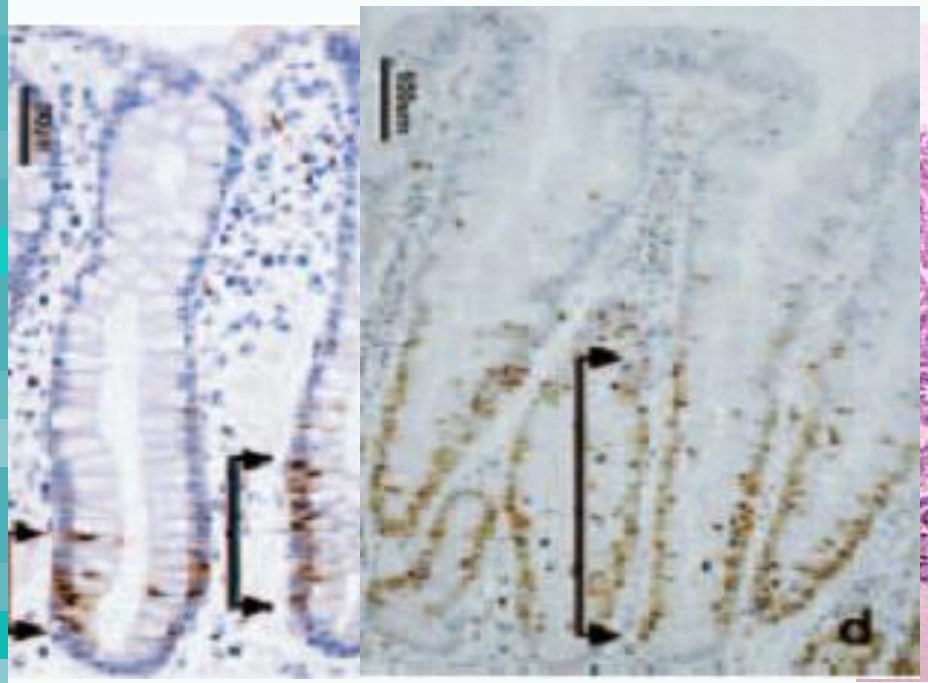


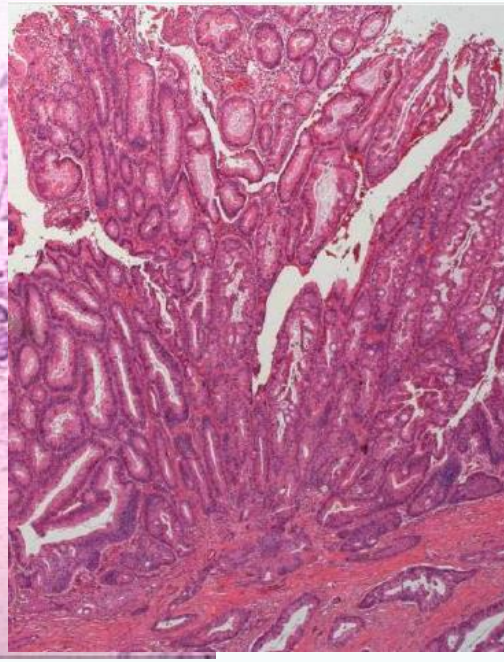


Douglas Am J Gastroenterol. 2012

Serrated polyposis - histology

Histology





(Reu, Pathology LMU)

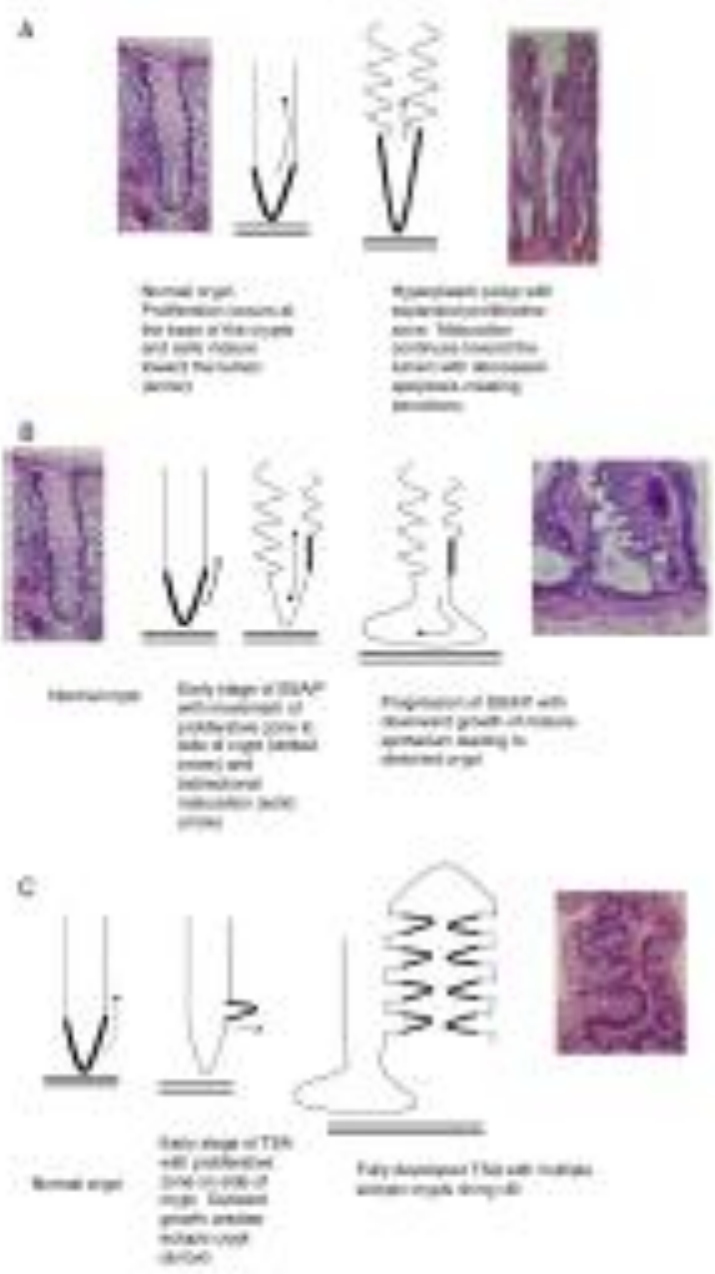
Bottom up neoplasia, would be missed by regular biopsy

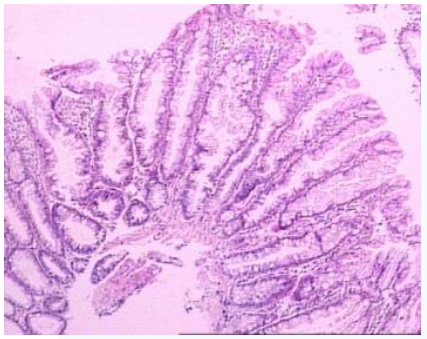
Serrated polyposis - histology

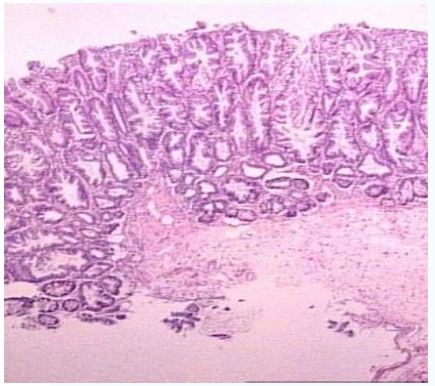
Hyperplastic polyp HP
70-90% of all serrated lesions

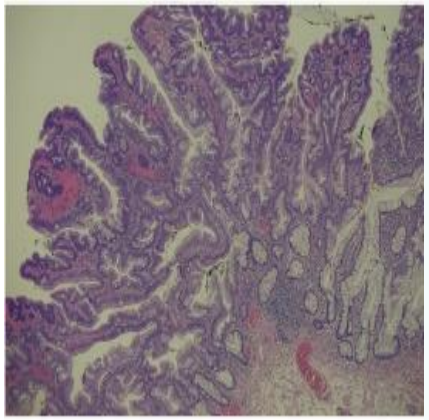
Sessile serrated adenoma SSA
5-25% of all serrated lesions

Traditional serrated adenoma TSA
2% of all serrated lesions



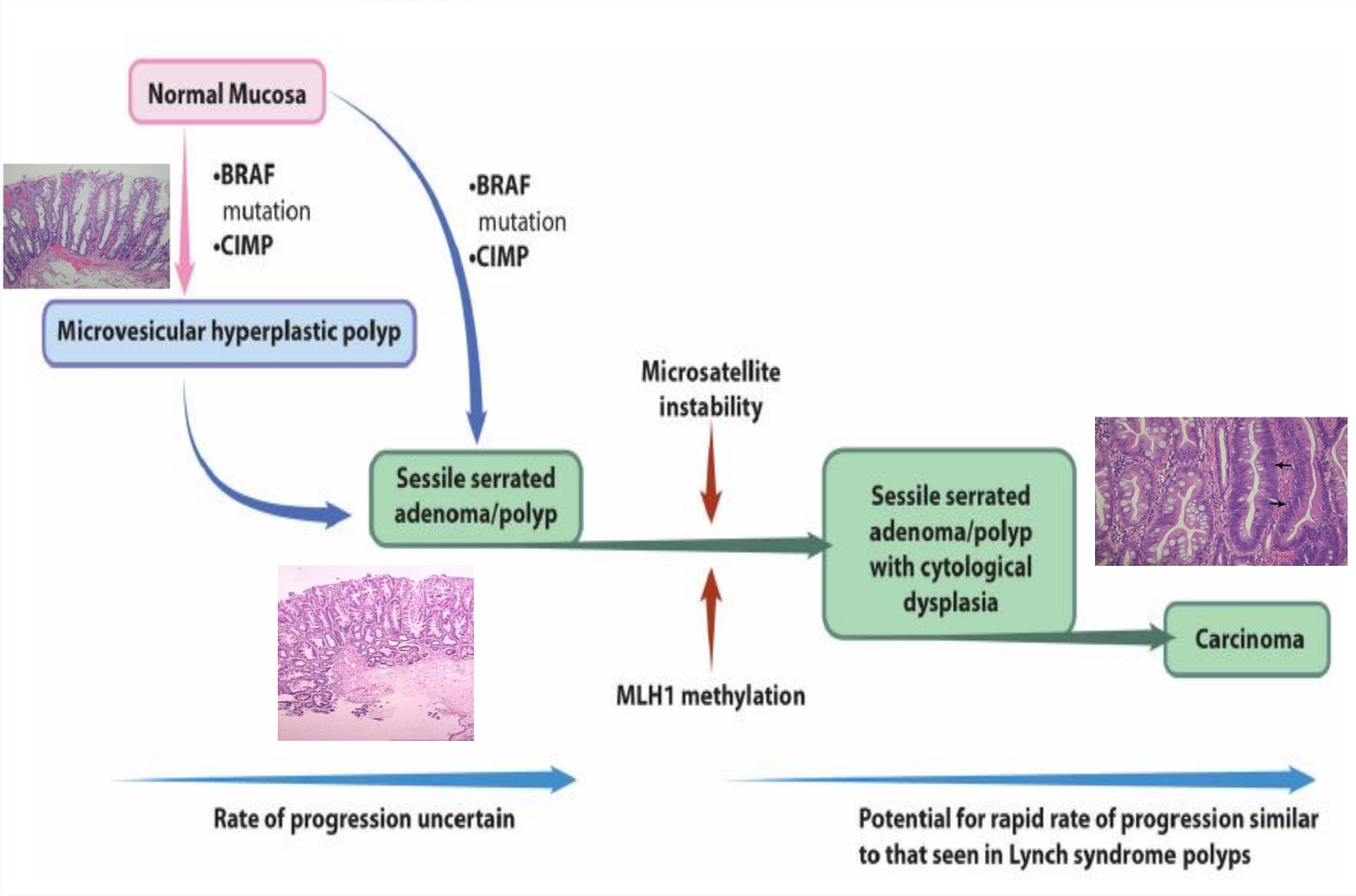






Snover et al., 2011

Serrated polyposis – CIMP pathway histology



Rex DK, Am J Gastroenterol. 2012

Serrated polyposis - CIMP pathway histology

CIN

MIN

CIMP

	CIMP-high	*MLH1* methylation	MSI	*BRAF* mutation	*KRAS* mutation
Conventional adenoma	+	–	–	–	++
CIN CRC	+/–	–	–	+/–	++
Lynch CRC	–	–	+++	–	++
HP[a]	+	–	–	+	+
SSA/P	+++	–	–	+++	–
SSA/P with cytological dysplasia	+++	++	++	+++	–
CIMP-high CRC	+++[b]	+++	+++	+++	–
TSA	++	–	–	+[c]	+[c]

	Shape	Mean Size	Prevalence	Location	Pre-cancerous
HP	flat, sessile	small, often ≤ 5mm	very common	left colon	no
SSA/P	flat, sessile	larger* than HP	Common**	right colon	yes
TSA	sessile, pedunculated	larger than HP	rare	left colon	yes

Rex DK, Am J Gastroenterol. 2012

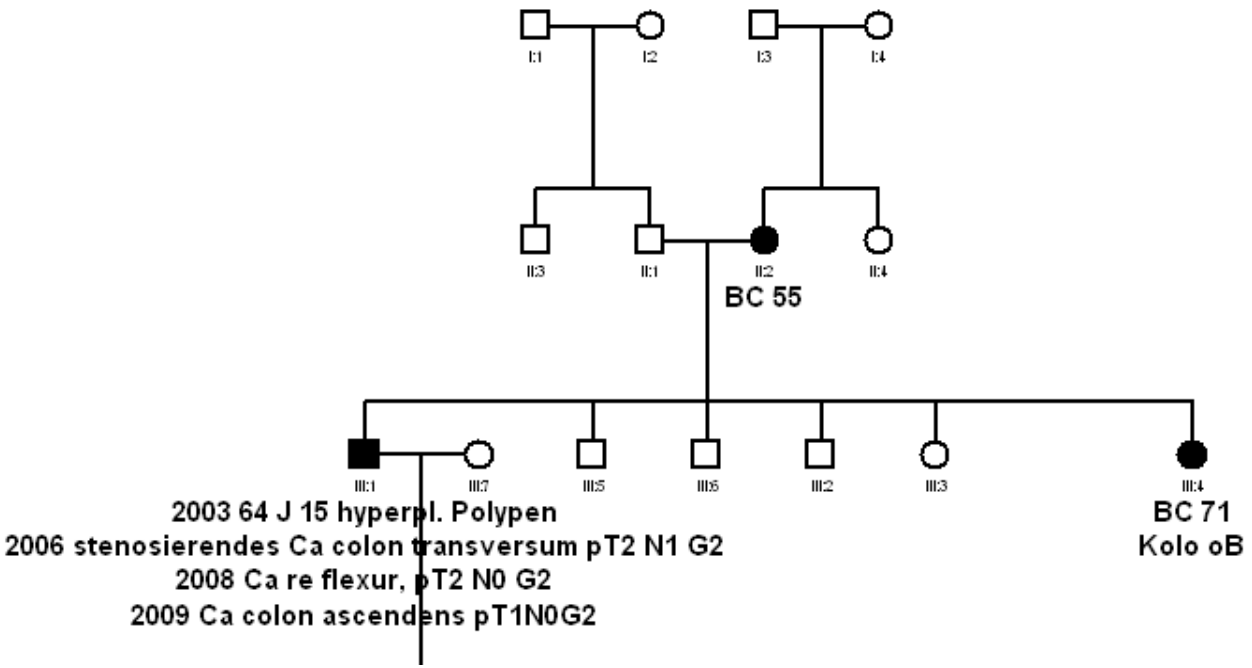
Serrated polyposis - surveillance recommendation

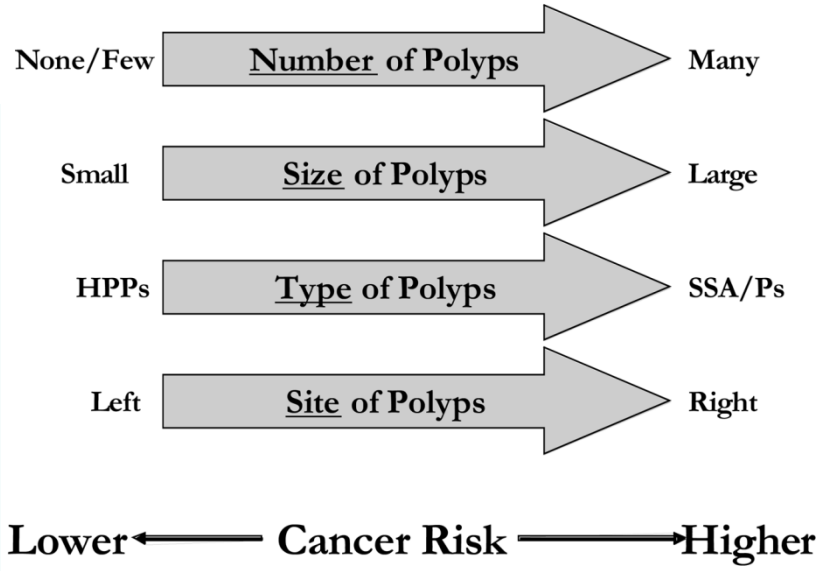
Histology	Size	Number	Location	Interval in years
HP	< 10 mm	any number *	rectosigmoid	10 ***
HP	≤ 5 mm	≤ 3	proximal to sigmoid	10
HP	any	≥ 4	proximal to sigmoid	5
HP	> 5 mm	≥ 1	proximal to sigmoid	5
SSA/P or TSA	< 10 mm	< 3	any	5
SSA/P or TSA	≥ 10 mm	1	any	3
SSA/P or TSA	< 10 mm	≥ 3	any	3
SSA/P	≥ 10 mm	≥ 2	any	1–3 ***
SSA/P w/dysplasia	any	any		1–3 ****

Rex DK, Am J Gastroenterol. 2012

Serrated polyposis

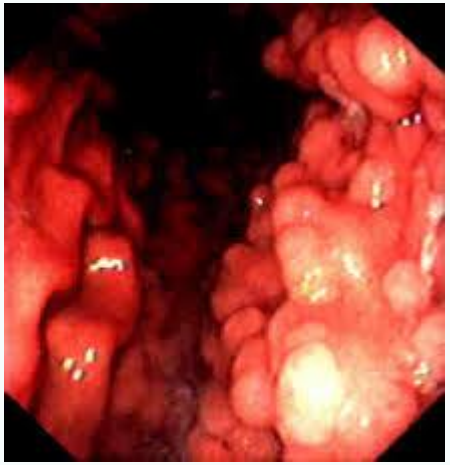
all CRCs
BRAF positive
MSI-H
MLH1-neg





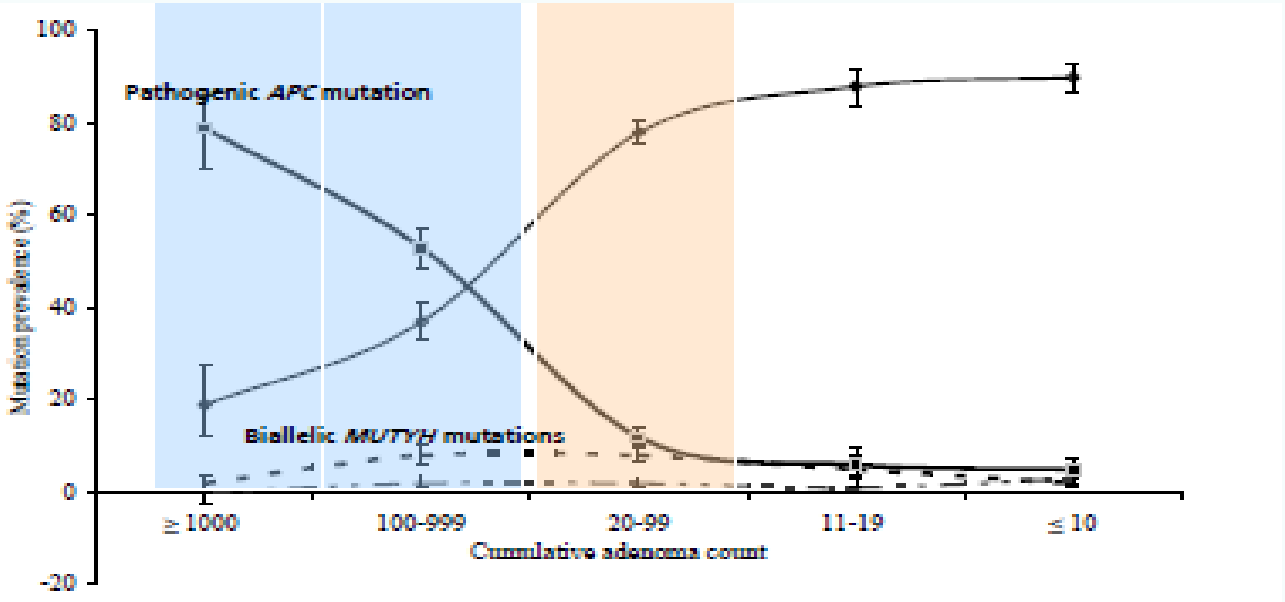
Rex DK, Am J Gastroenterol. 2012

Adenomatous polyposis



Adenomatous polyposis – FAP MAP

Cumulative adenoma count / Alteration	Classic Polyposis ≥ 1000 (n=111) N	Classic Polyposis ≥ 1000 (n=111) % (95%CI)	Classic Polyposis 100-999 (n=557) N	Classic Polyposis 100-999 (n=557) % (95%CI)	Attenuated Polyposis 20-99 (n=1193) N	Attenuated Polyposis 20-99 (n=1193) % (95%CI)
Pathogenic *APC* mutation	88	79.3 (75.4-83.2)	294	52.8 (48.0-57.3)	141	11.8 (10.0-13.8)
Pathogenic biallelic *MUTYH* mutations	2	1.8 (0.5-3.1)	47	8.4 (5.8-11.1)	95	8.0 (6.4-9.6)
Pathogenic monoallelic *MUTYH* mutation	0	0	10	1.8 (0.5-3.1)	29	2.4 (0.9-3.9)
Non-pathogenic *APC/MUTYH* alteration	21	4.5 (1.5-10.2)	206	6.1 (4.3-8.2)	928	9.1 (7.6-10.9)



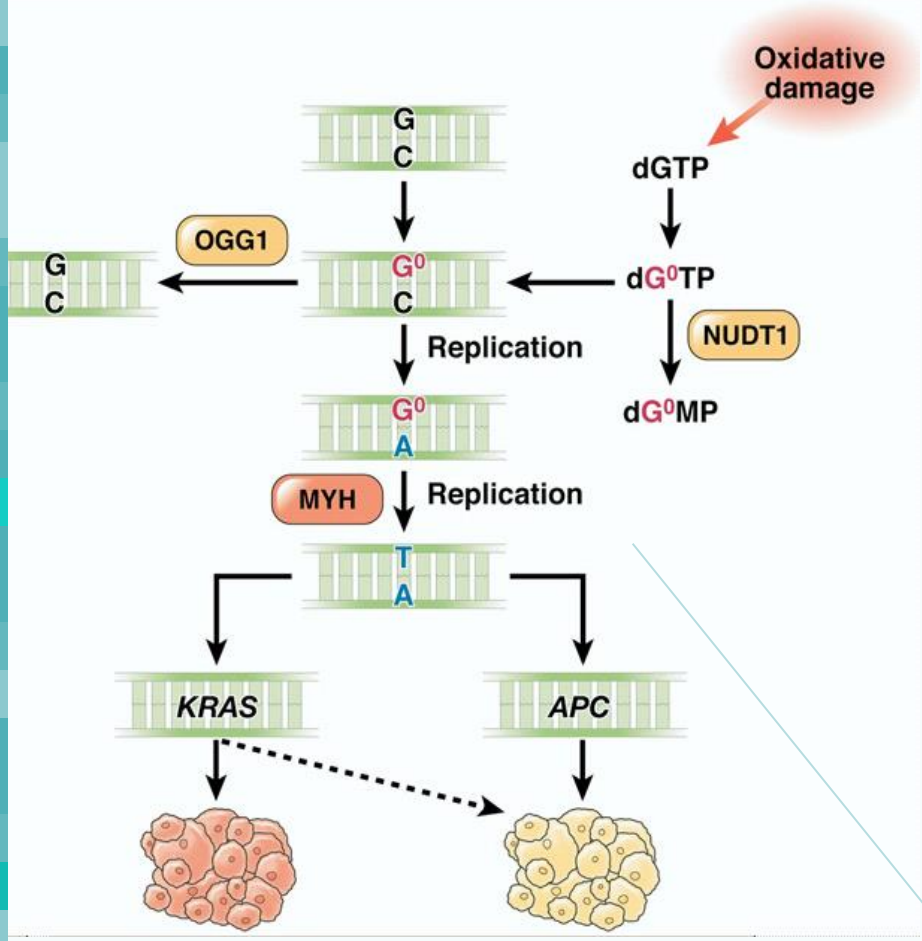
FAP
Mutations in APC
Dominant

MAP
Mutations in MUTYH
Recessive

Attenuated FAP
No mutation in 60% of the patients in these genes

Grover , Havard Boston

Adenomatous polyposis - MAP



MUTYH Funktion:
Korrektur von Fehlpaarung zwischen 8-Oxoguanin und Adenin.

MUTYH Ausfall:
G:C -> T:A Transversionen in Zielgenen:
APC
KRAS: c. 34G>T (G12C)

CIMP
HHP
SSA

CIN
Adenome

MSI
Adenome, Lynch-Tumorspektrum
Kurze Adenom-Karzinom-Sequenz

Castells, A., Gastroenterology 2008, 135: 1857

Adenomatous polyposis - PPAP

PPAP polymerase proofreading-associated polyposis

POLD1, POLD2, POLD3, POLD4, POLE, POLE3, POLE4

POLE: mutation prevalence in CRC 1,5 %
mutation prevalence in polyposis cohorts: 4-7 %
hot spot mutation p.Leu424Val, other missense mutations
mean age at polyposis diagnosis 35 years
CRC between 27 and 63 years, evenly distributed
duodenal adenomas, gastric fundic gland polyps
associated tumors: ovary, neuroendocrie CC, glioblastoma
highly variable clinical phenotype, de novos

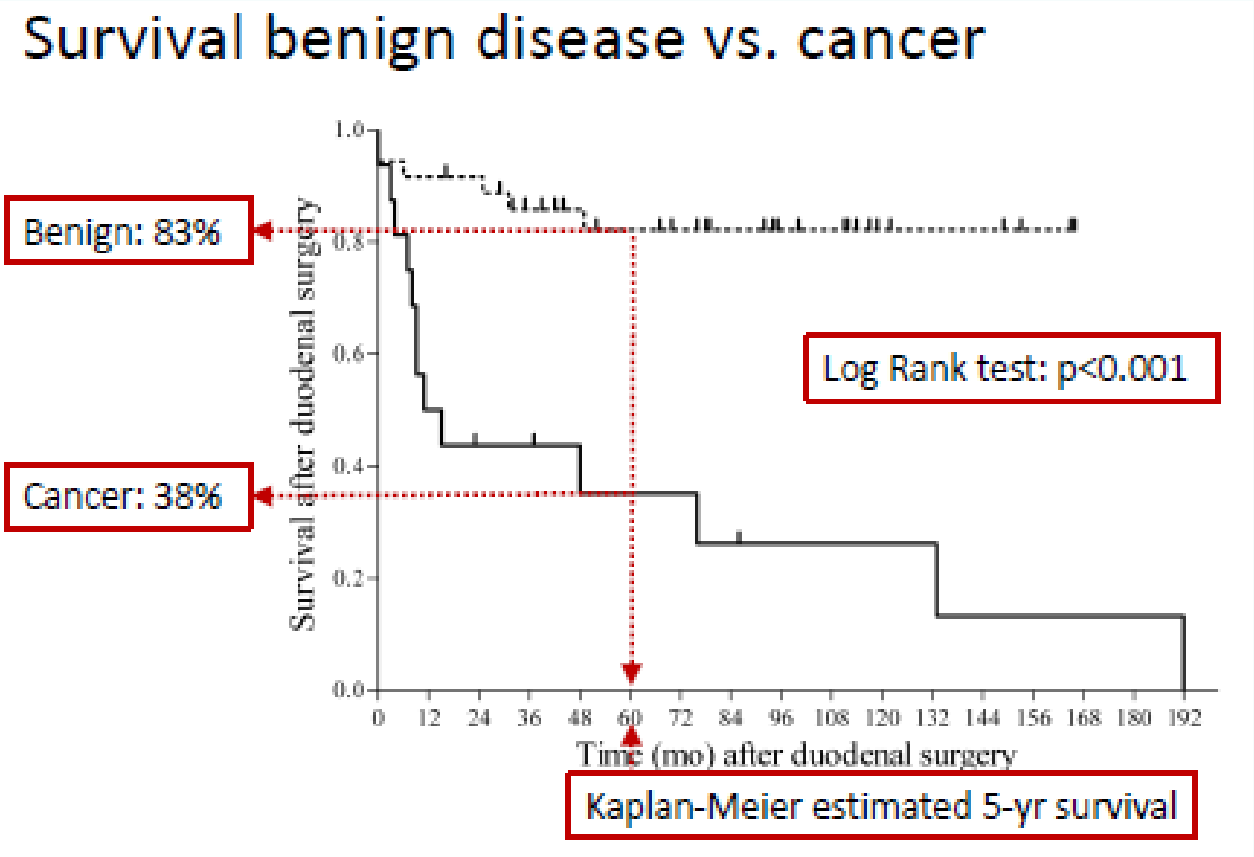
POLD1: singel mutations
polyposis phenotype

Spier I, IJC 2014, Hansen MF, Fam Cancer 2015

Adenomatous polyposis - Small bowel adenomas

52 dudenal polyposis, mean age 48 years

Pre-surgery endoscopy	16 carcinomas
	36 adenomas (2 post-OP carcinomas)
OP-proceedure	13 Whipple´s operation
	8 pylorus-sparing pancreaduodenectomy
	22 pancreas-sparing duodenectomy

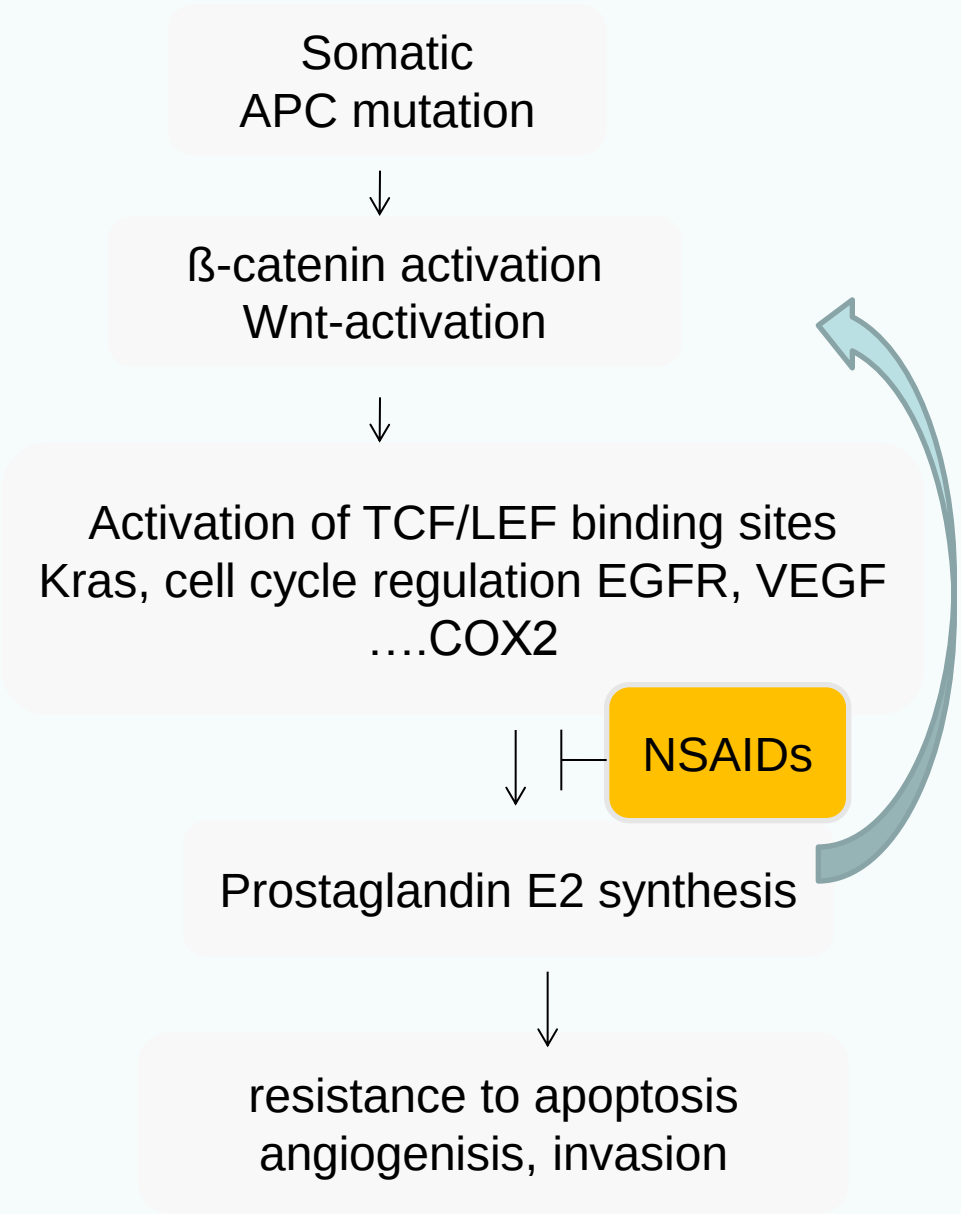


Nagengast et al., 2011

Adenomatous polyposis - clinical studies

Literature	patients	medication	duration	side effects	results
Nagent 1993	24 IRA	2x200mg Sulindac/plac.	9 months	n.d.	adv. duod. adenomas cell proliferation duodenum rectum
Giardiello 2012	22 IRA no surg.	2x150 mg Sulindac/plac.	9 months	no	number 44% size 34%
Steinbach 2000	77 IRA	30 2x400mg Celecoxib 32 2x 100mg Celecoxib 15 placebo	6 months		number 28% size 30% number 12% size 14% number 4.5% size 4,5%
Cruz-Correa 2002	12 IRA	2x150mg Sulindac variable 1x150mg	12-36 months	50% erosions	number 12 months p=0,039 number 36 months p=0,006
Burn 2011	62	600mg aspirin +/- RS	12 months > 12 months	no	size 3,8 -> 5,5 mm size 3,0 -> 6,0 mm

Adenomatous polyposis - chemoprevention



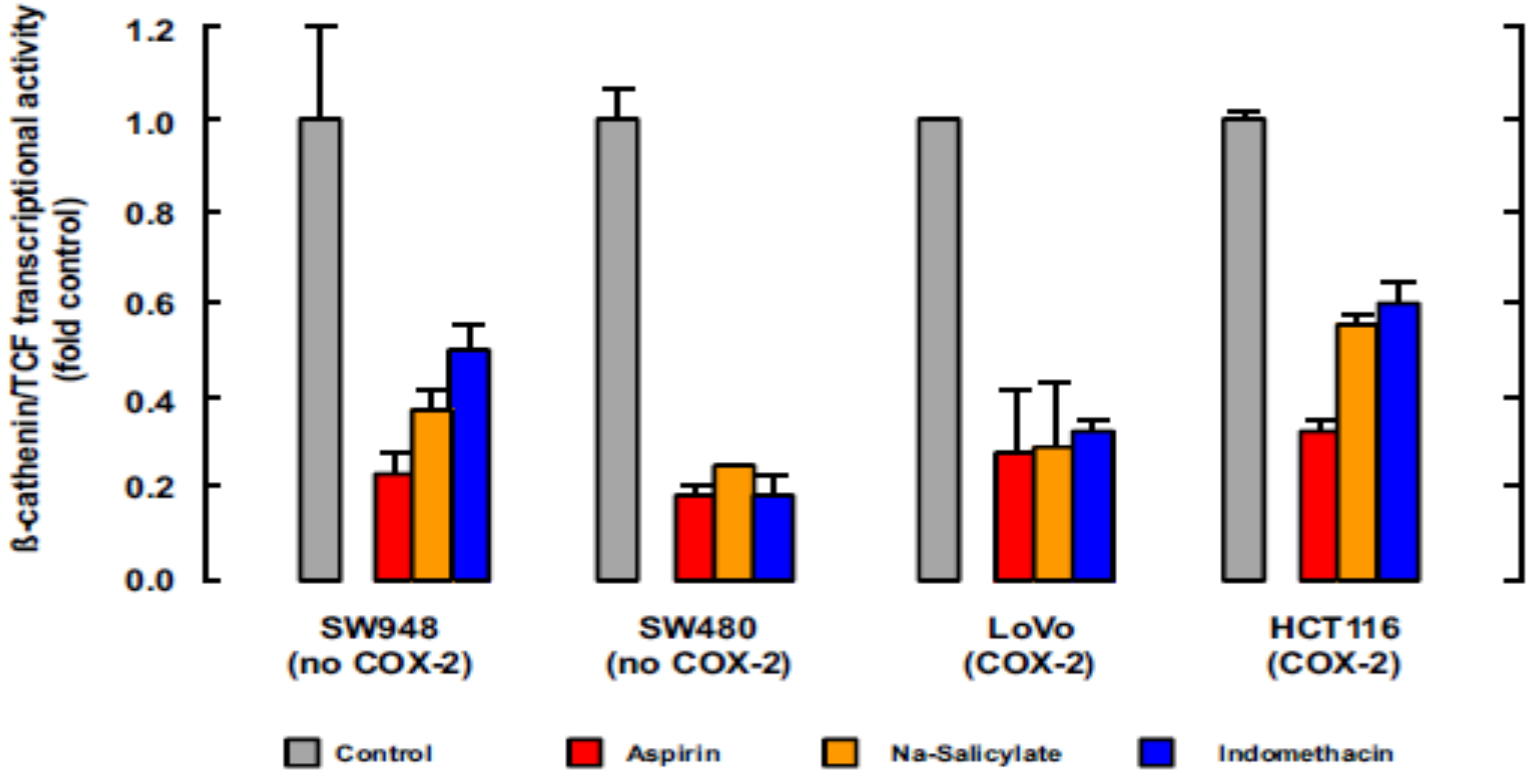
COX2 low in normal tissue, epithel, endothel, duodenum > colon
40-50% in adenoma
80-90% in CRC

COX2 expression induced by growth factors, oncogenes, tumor promoters, infammatory cytokines

Adenomatous polyposis - chemoprevention

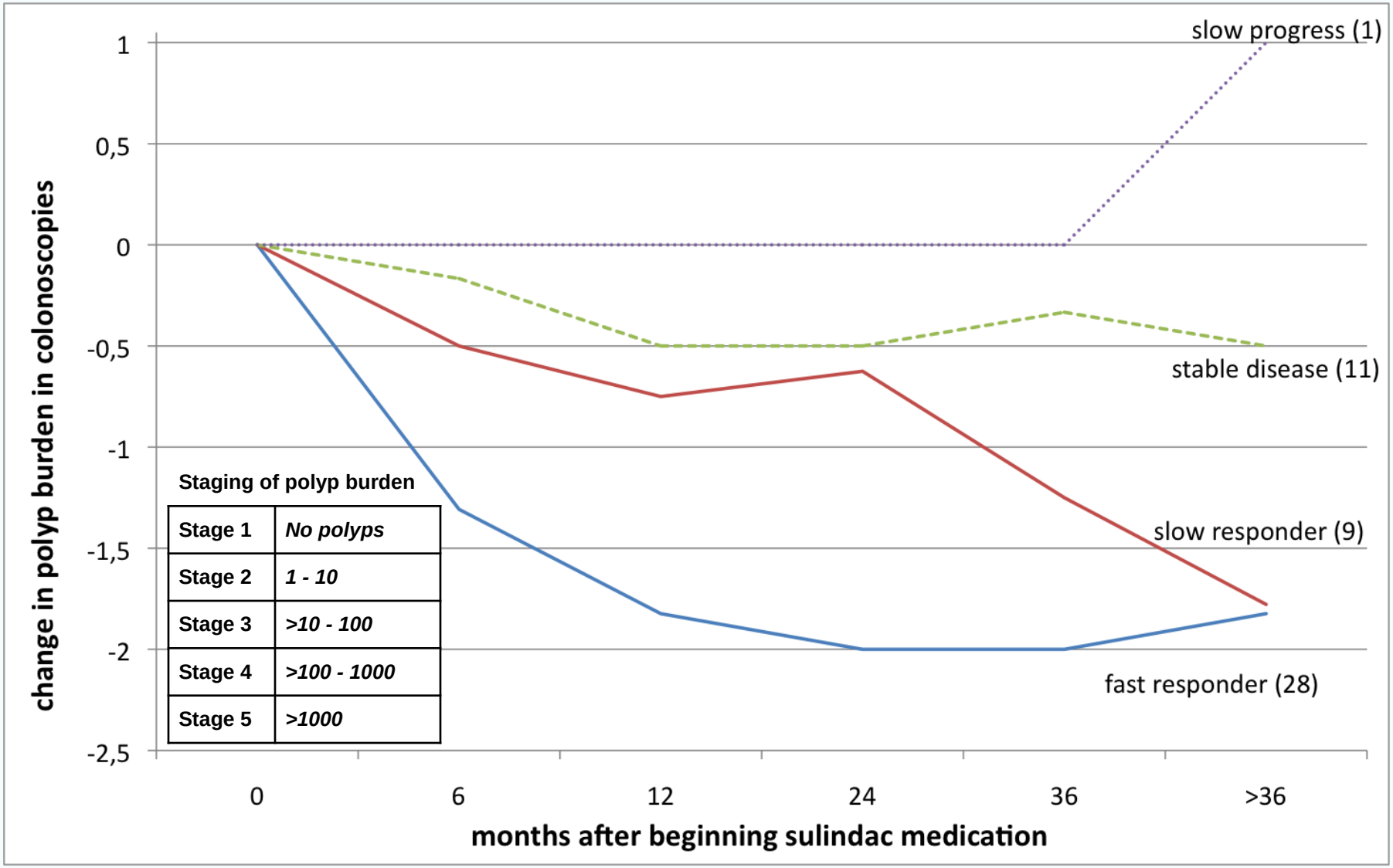
NSAIDs

COX independent

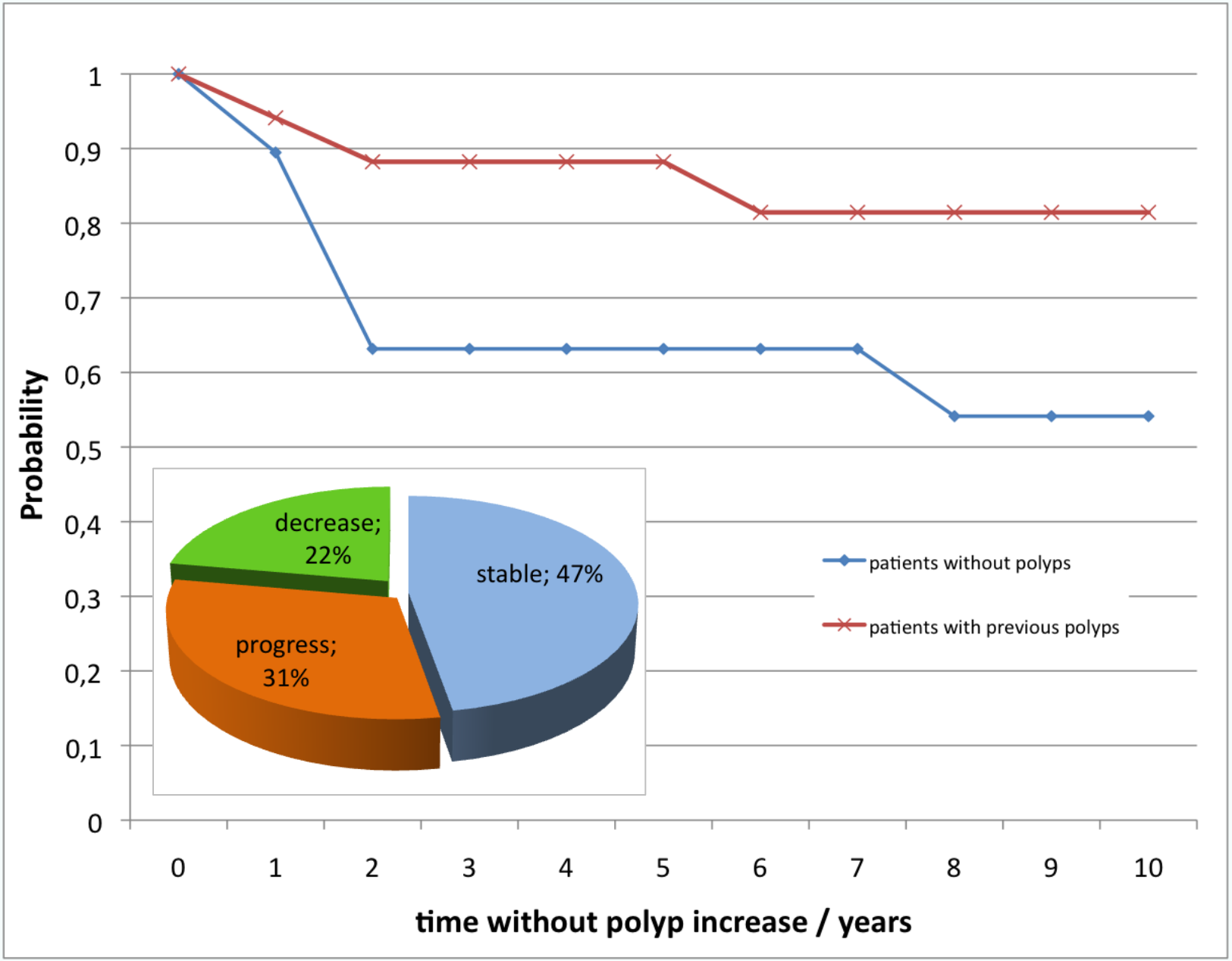


Schrör, Best Practice Research Clinical Gastro. 2011

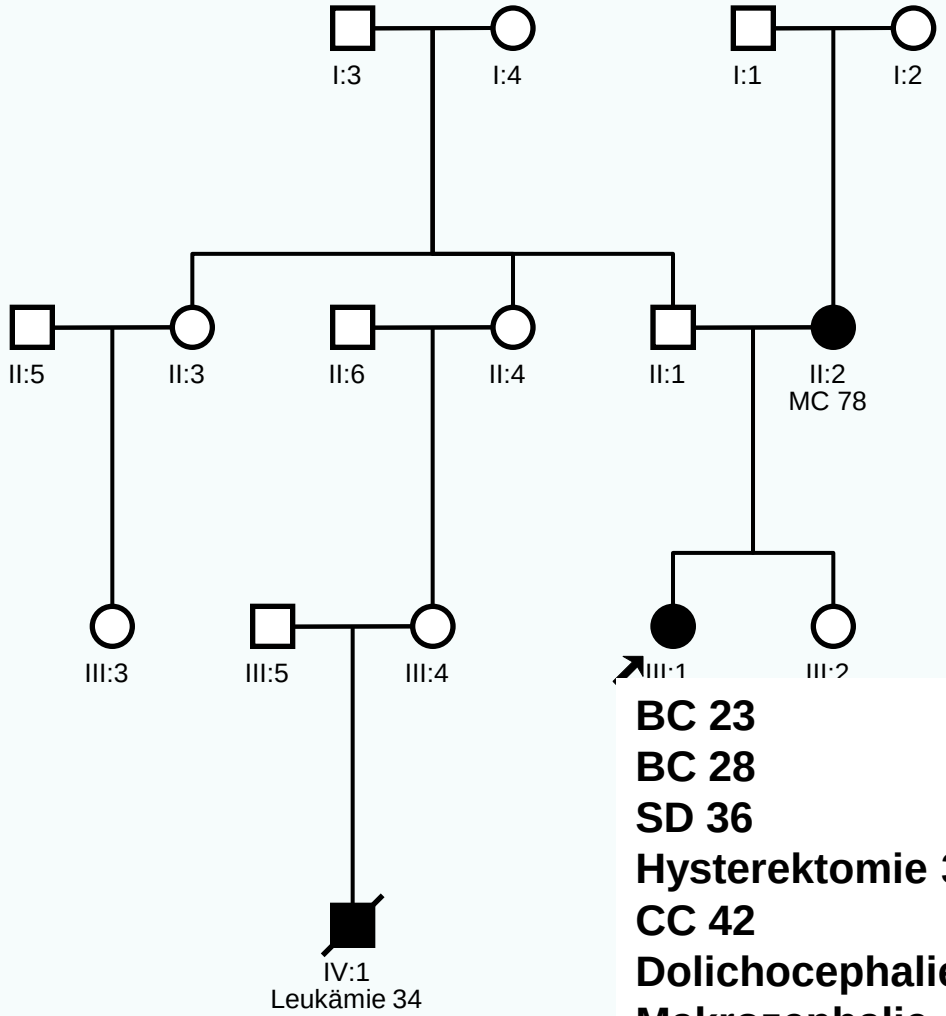
Adenomatous polyposis - chemoprevention



Adenomatous polyposis - chemoprevention



Cowden-Syndrom



Mutationen: PTEN-Gen
Hautmanifestation: 90%
Fibroadenome: 75%
BC: 25-30% (38-46Jahre)
SD-Adenome: 75%
FTC, PTC: 10%
Uterusfibrome: häufig
Uteruskarzinom: 5-10%

BC 23
BC 28
SD 36
Hysterektomie 38
CC 42
Dolichocephalie
Makrozephalie
Keine Hautmanifestation

Cowden Syndrom Gen

Summary

Lynch Syndrome

Common cancers	colon, rectum, endometrium
Less common	Stomach, small bowel, urinary bladder, urothelium, breast ,ovary, prostate
Tumor risk	MSH2 > MSH1…. MSH6 > PMS2 EPCAM-Deletion: CRC risk as for MMR-gene mutation EC risk depends on deletion size
Surveillance	does not prevent cancers reduces mortality significantly
Prophylactic surgery	recommendation only for MLH1 and MSH2 chemoprevention should be offered

Serrated polyposis

SSA	right sided, increased cancer risk also for first degree relatives can be familiar and can mimic Lynch-Syndrome

Adenomatous polyposis

FAP	small bowel cancer highest mortality chemoprevention should be offeredfor colonic polyps

Other polyposis Syndromes

PJS, CS….	Always carefully check histology


Many thanks for
your attention
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MGZ
Medizinisch Genetisches Zentrum