netzwerk gegen darmkrebs

European Reference Network for rare or low prevalence complex diseases

Network Genetic Tumour Risk Syndromes (ERN GENTURIS)

Erblicher Darmkrebs, Erkennung, Vorsorge, Entwicklung

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Estimated fraction hereditary cancers

Hereditary, familial

Breast Carcinoma: 5-10% (15-20%)
Ovarian Carcinoma: 15-20% (5-10%)
Colorectal Carcinoma: 5-10% (10-20%)
Retinoblastoma: 40-50% (10%)
Paraganglioma: 25-35% (8-10%)
Prostate Carcinoma: 3-5% (10-20%)

10-25% of all patients develop a secondary neoplasia, 18% are hereditary

1:10 in advanced cancer

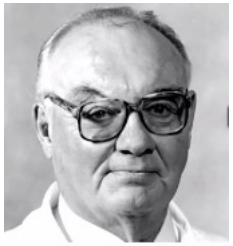
1:20 colorectal cancer

Pick-up criteria:
cancer < 50 y., syn- metachronous tumors, advanced cancer, pos. family history

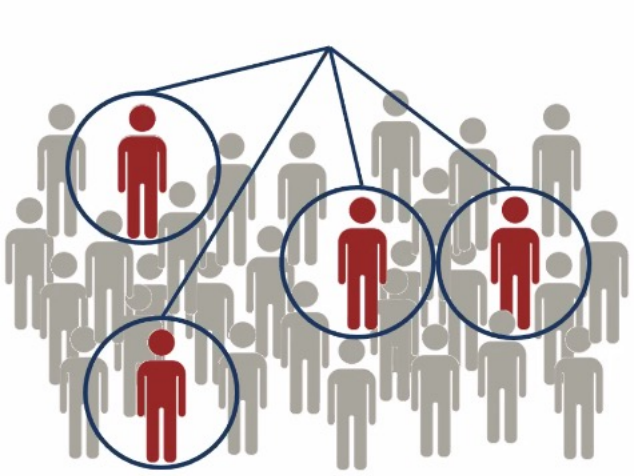
[1]Mandelker et al. 2017; Robinson et al. 2017; [2]Zhang et al. 2015; [3]Yurgelun et al. 2017; [4]Brand et al. 2018; Yurgelun et al. 2019, [5]Pritchard et al. 2016; [6]Walsh et al. 2011; Norquist et al. 2016

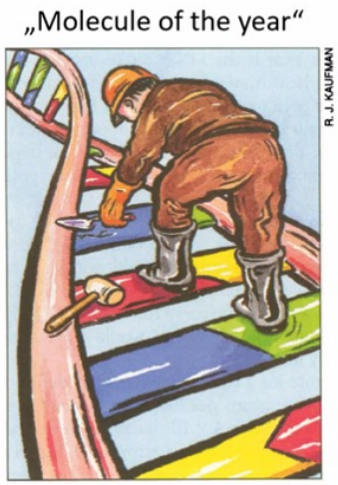
Lynch Syndrome

MMR genes: MLH1, MSH2, MSH6, PMS2
Carrier: 1:280
< 300,000 individuals affected in Germany
< 1 Mio in the US

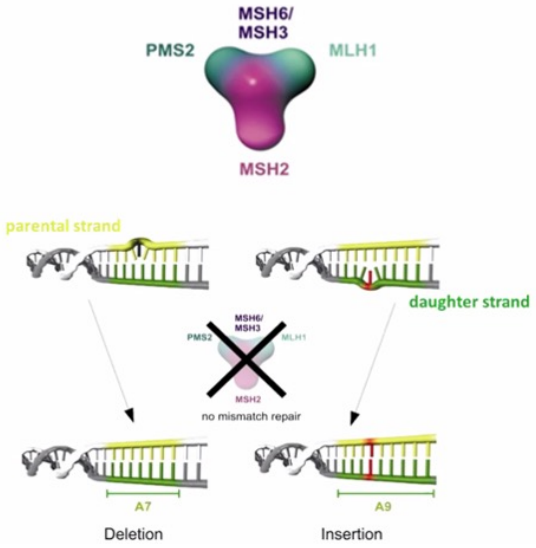


Henry T. Lynch
(1928-2019)

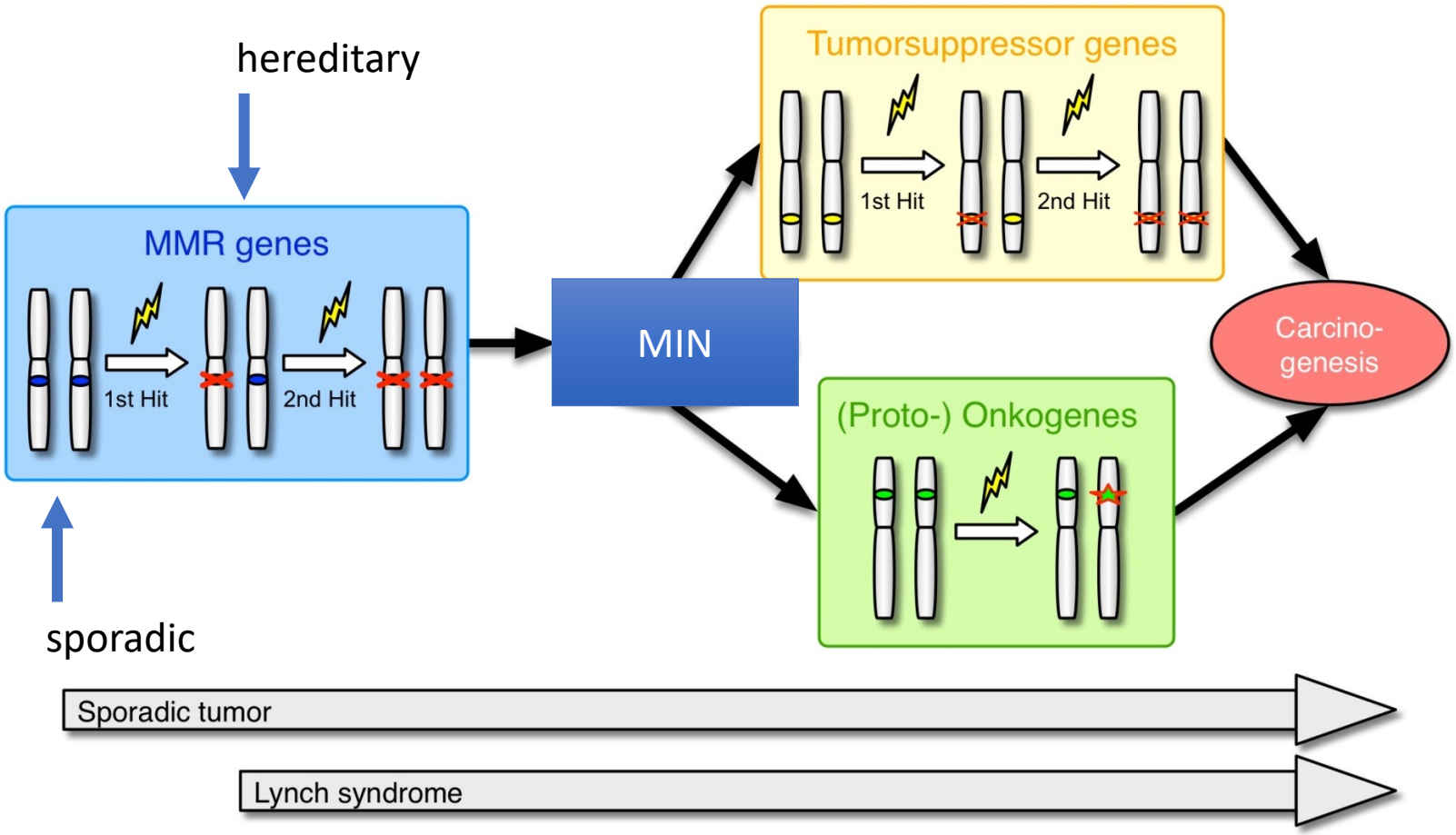




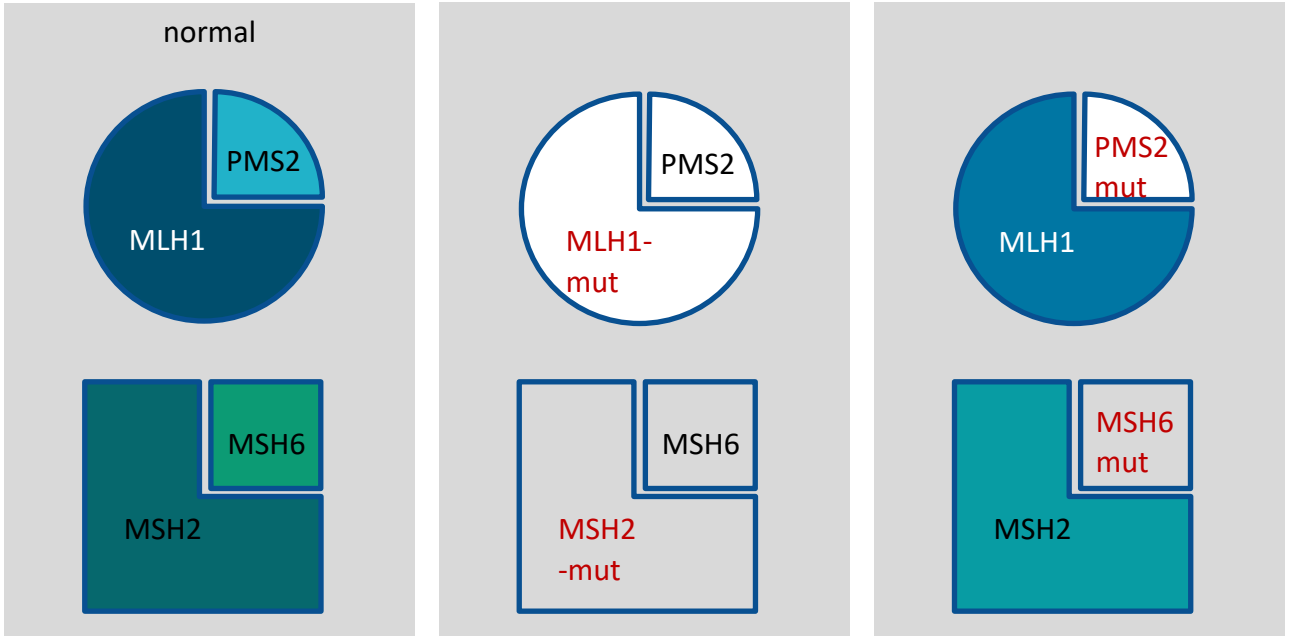
Koshland, *Science* 1994



Lynch Syndrome



Lynch Syndrome detection - immunohistochemistry

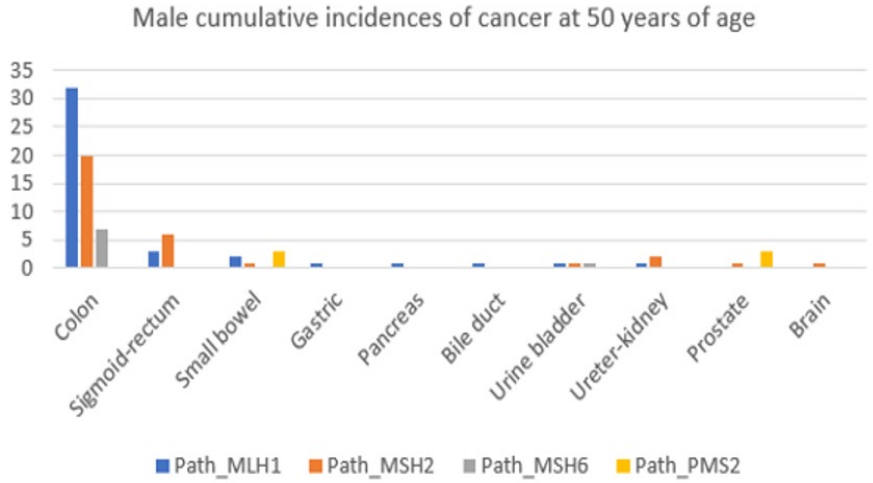


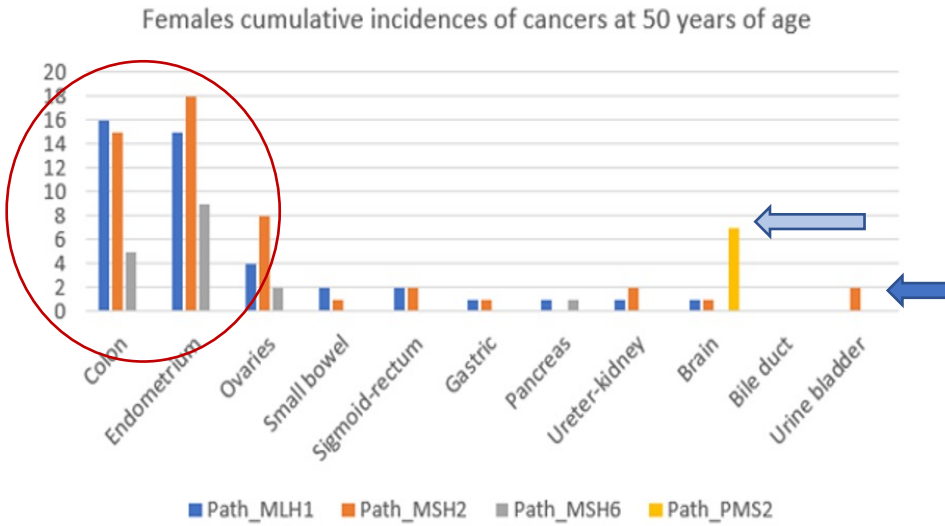
Appropriate tumors: CRC, EC

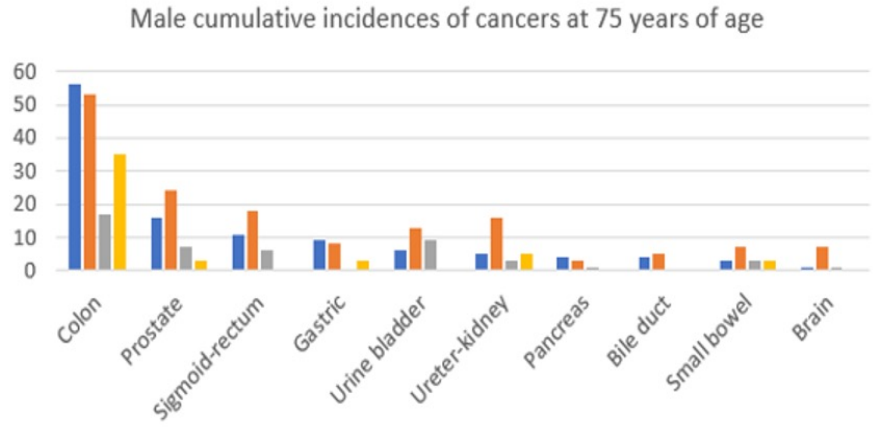
Screening for Lynch Syndrome by immunohistochemistry

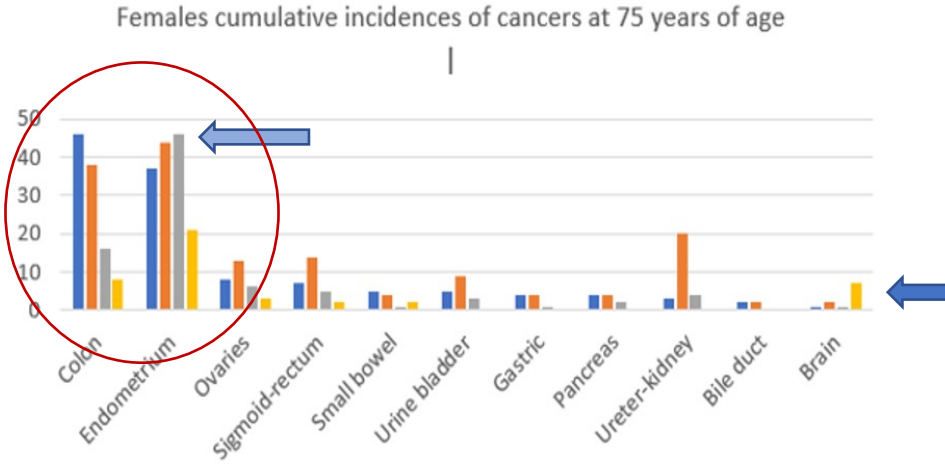
- all colorectal cancers
- endometrial cancer < 60 years

Lynch Syndrome – tumor risk









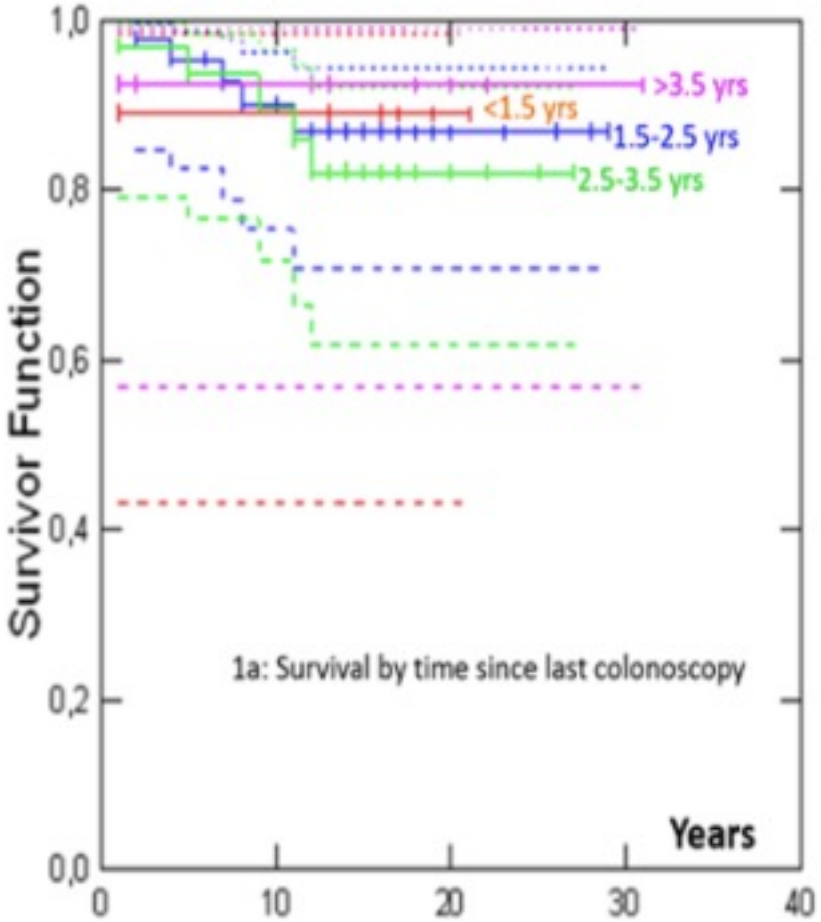
PLSD : Prospective Lynch Syndrome database, Moller 2023

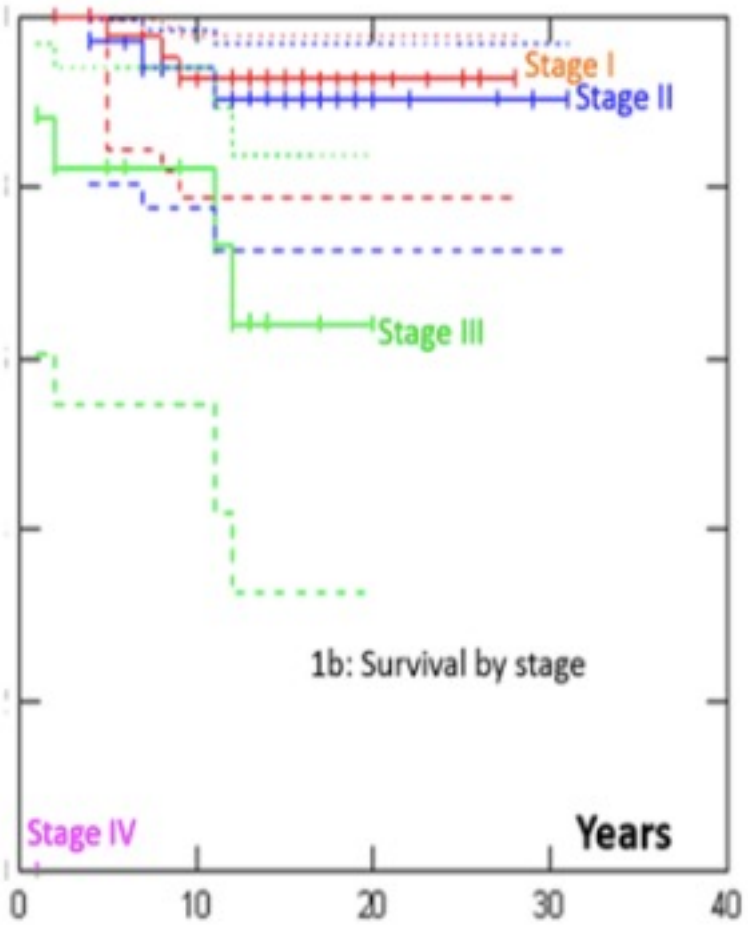
Lynch Syndrome survival - overall

Group	Number cases	5-year survival (95% CI)	10-year survival (95% CI)
Any cancer	301	90% (86 to 93)	87% (83 to 91)
Colorectal cancer	140	94% (90 to 98)	91% (84 to 95)
Endometrial cancer	71	98% (88 to 99.8)	98% (88 to 99.8)
Ovarian cancer	19	88% (60 to 97)	89% (60 to 97)
Upper GI cancer	24	58% (36 to 75)	53% (31 to 71)
Urinary tract cancer	17	82% (51 to 93)	73% (42 to 89)

Møller et al., Gut. 2015
Møller et al., Gut. 2016

Lynch Syndrome survival - CRC

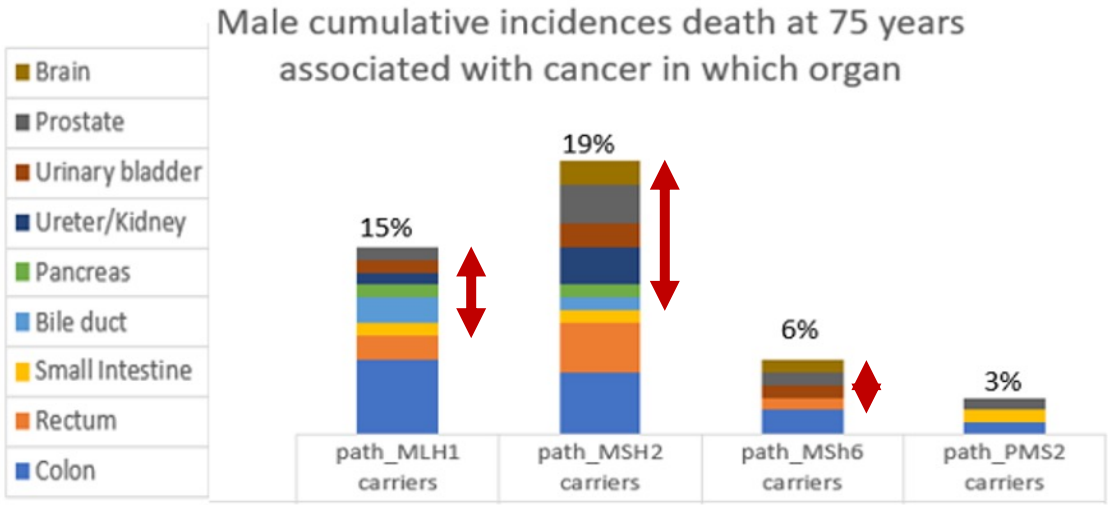


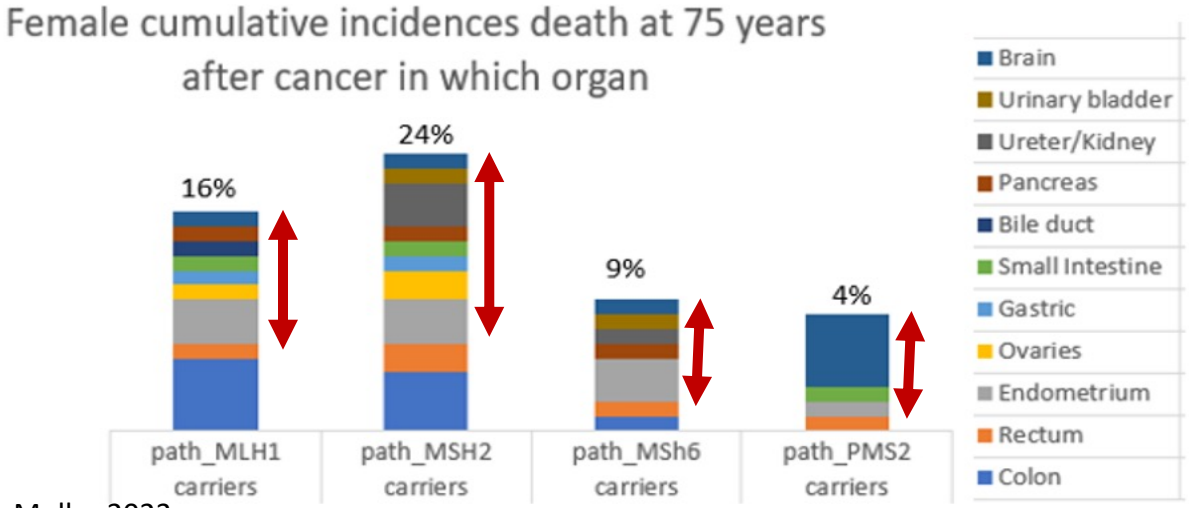


Mev Dominguez-Valentin et al., BMC 2019

Lynch Syndrome – deaths

The majority of deaths result from extraintestinal cancers





PLSD : Prospective Lynch Syndrome database, Moller 2023

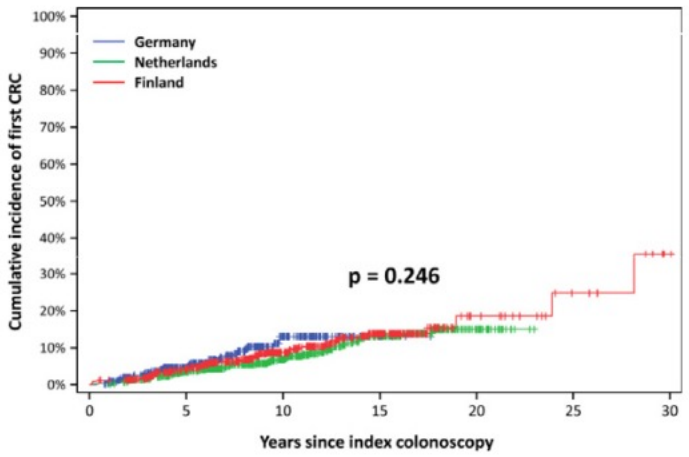
Lynch Syndrome surveillance

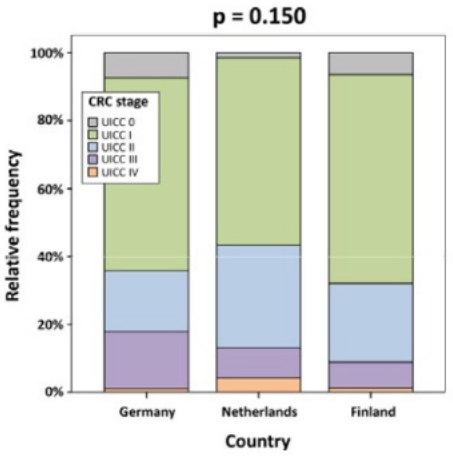
Recommended colonoscopy intervals in Lynch syndrome

Germany	The Netherlands	Finland
1-yearly	1-2-yearly	2-3-yearly

Outcome in 2747 patients

No reduction of CRC risk or tumor stage with shorter intervals

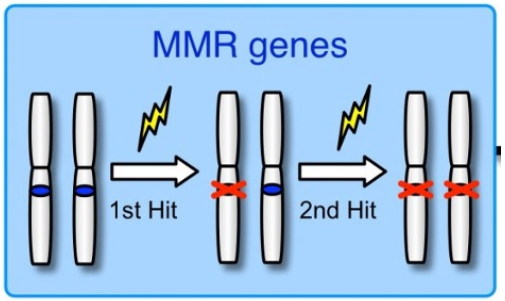




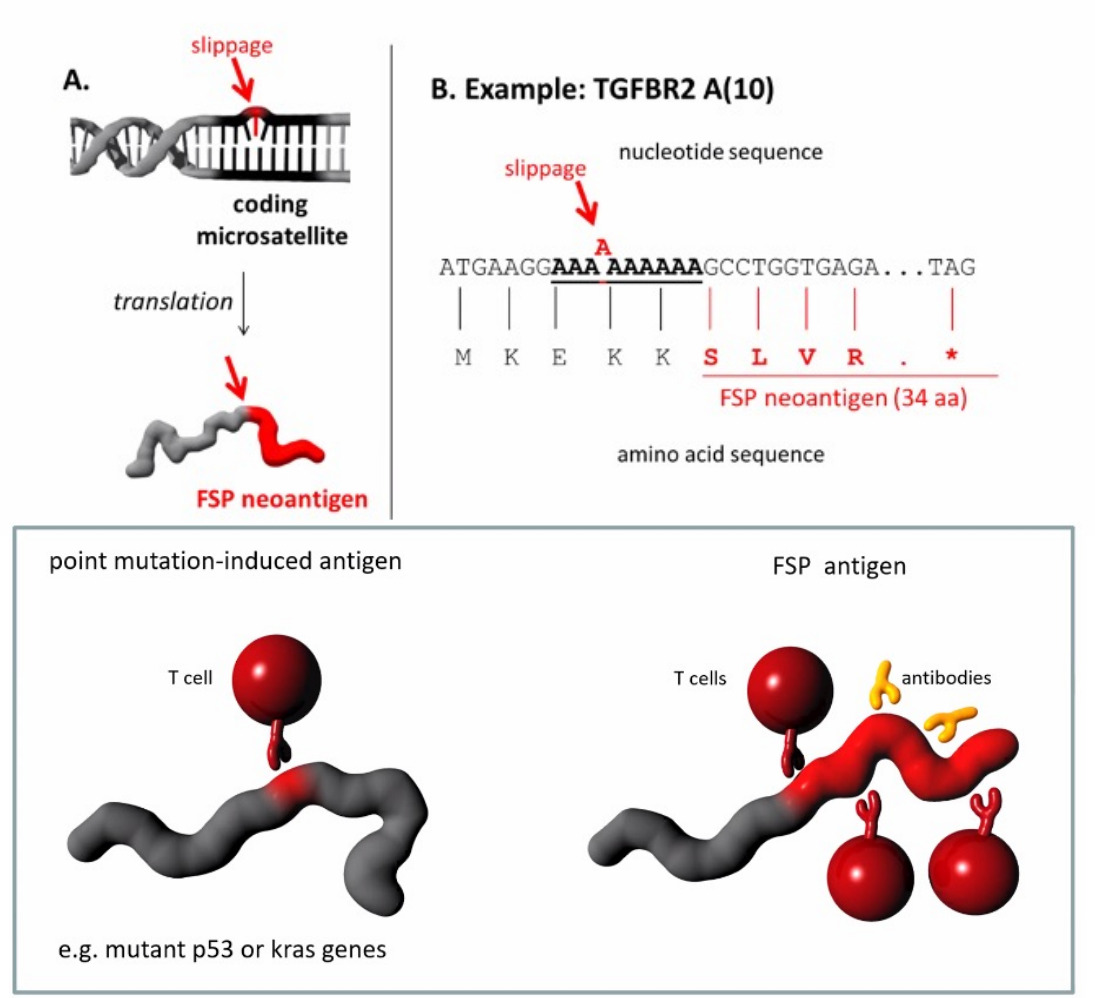
Engel et al., Gastroenerology 2018

Lynch Syndrome – therapy

hereditary

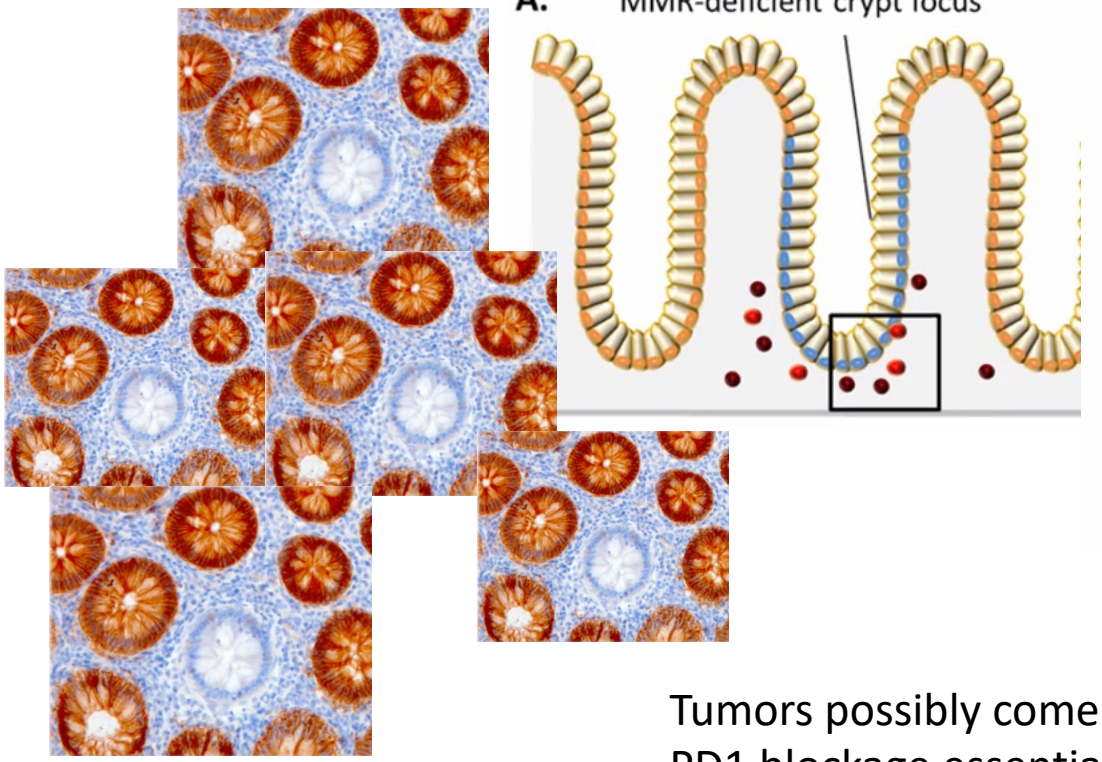


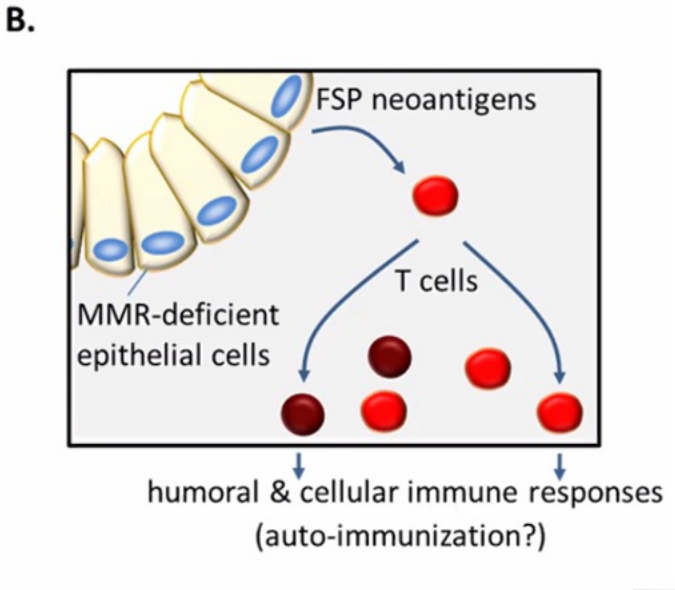
sporadic



Kloor et al. Int J Cancer. 2010 Sep 1;127(5):1001-10.

Lynch Syndrome – therapy





Tumors possibly come and go
PD1 blockage essential also for associated tumors
Resistance by mutations in ß2 microglobulin

Lynch Syndrome – prevention

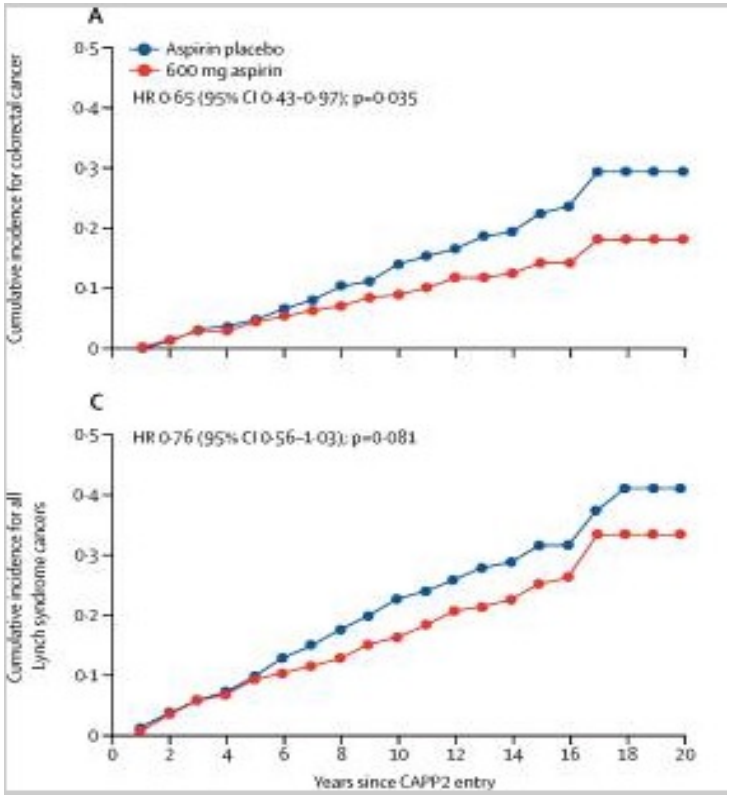
- <u>Aspirin</u>:
  - Long term reduction of CRC
  - Necessary dosis unclear

  Currently no general recommendation

  Can be discussed with male MLH1

- <u>Oral contraceptives</u>:
  - General risk reduction for ovary and endometrial cancer
  - Not data for patients for Lynch Syndrome

  Currently no general recommendation

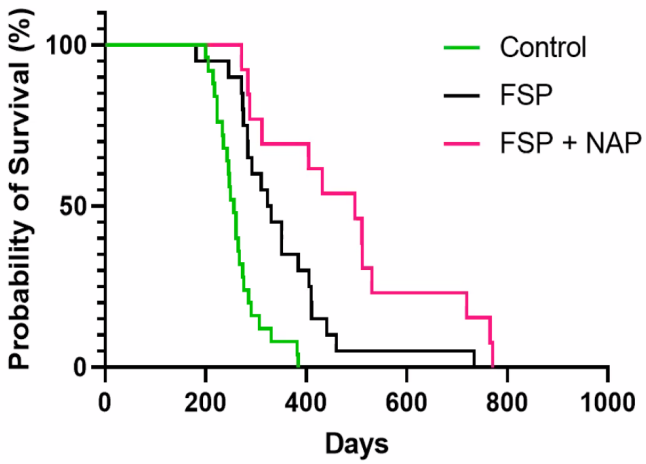


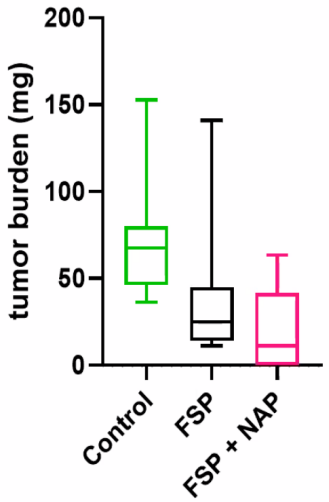
Burn et al., Lancet 2020

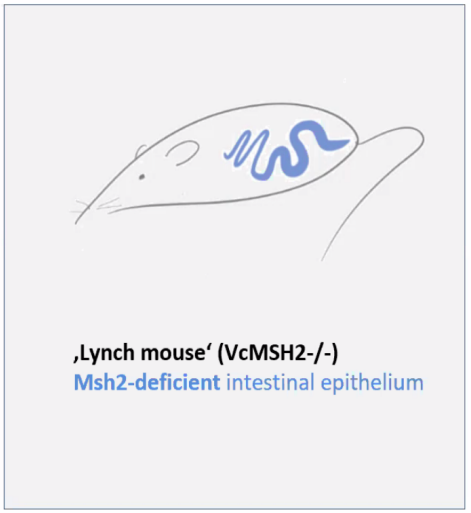
Lynch Syndrome – future prevention

FSP vaccine prolongs life and reduces tumor burden in Lynch mice

- Synergy with chemoprevention (naproxen [NAP])







Control vs FSP, $P < 0.0001$ Control vs FSP + NAP, $P < 0.0001$ Control vs FSP, $P = 0.0024$ Control vs FSP + NAP, $P = 0.0002$

Gebert et al. Gastroenterology 2021

Lynch Syndrome – surveillance

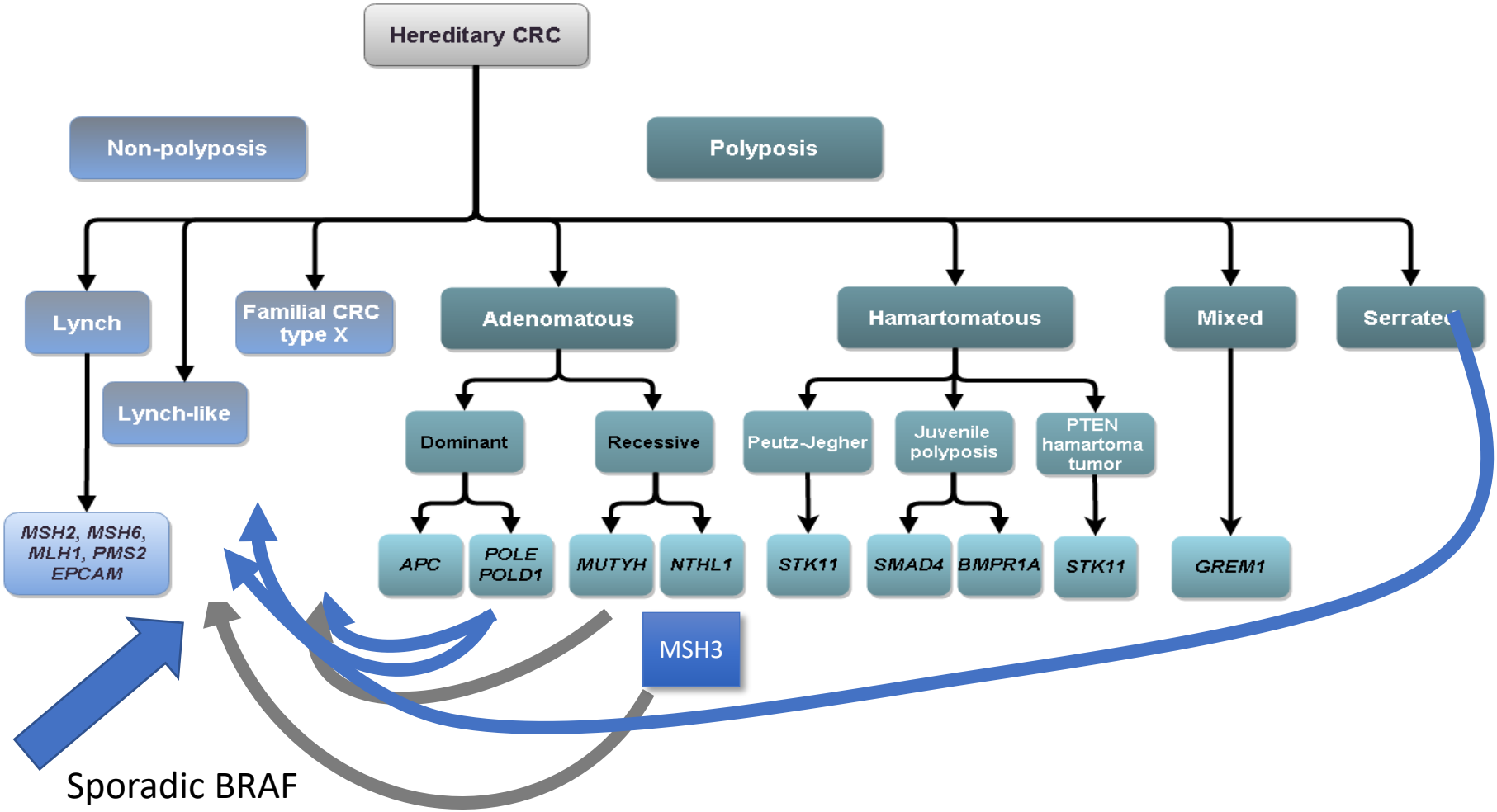
5.23.	Konsensbasierte Empfehlung	2013
EK	HNPCC-Patienten und Risikopersonen sollen in der Regel ab dem 25. Lebensjahr jährlich koloskopiert werden. alle 1-2 Jahre	

5.26.	Konsensbasierte Empfehlung	2013
EK	Bei HNPCC-Patienten und Risikopersonen mit HNPCC sollte ab dem 35. Lebensjahr zusätzlich regelmäßig eine ÖGD durchgeführt werden. ab 30. Jahre	

5.24.	Evidenzbasierte Empfehlung	2013
Empfehlungsgrad **B**	Bei weiblichen HNPCC-Patienten und Risikopersonen sollte ab dem 25. Lebensjahr zusätzlich zur jährlichen gynäkologischen Untersuchung ein transvaginaler Ultraschall im Hinblick auf Endometrium- und Ovarialkarzinome durchgeführt werden. optional	

5.25.	Konsensbasierte Empfehlung	2013
EK	Bei weiblichen HNPCC-Patienten und Risikopersonen sollte ab dem 35. Lebensjahr zusätzlich jährlich eine Endometriumbiospsie durchgeführt werden.	
	Konsens optional	

Differential diagnosis



Summary

- Lynch syndrome rather four syndromes than just one
- App. 4-5% of all CRC is LS (1 von 20-25 CRC patients), carrier frequency 1:280
- CRC < 50 years of age
- ≥ 2 HNPCC tumors in one patient
- ≥ 3 HNPCC tumors in the family
- Appropriate treatment improves prognosis
- Surveillance and early detection also of associated tumors especially saves lifes
- Development of vacination

HNPCC / Lynch syndrom is a common disease – that is commonly not diagnosed.