HEIDELBERG UNIVERSITY HOSPITAL

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

atb applied tumor biology

# Molecular routes of colorectal cancer progression in Lynch syndrome

**Danish HNPCC Symposium**
**October 12th 2023**

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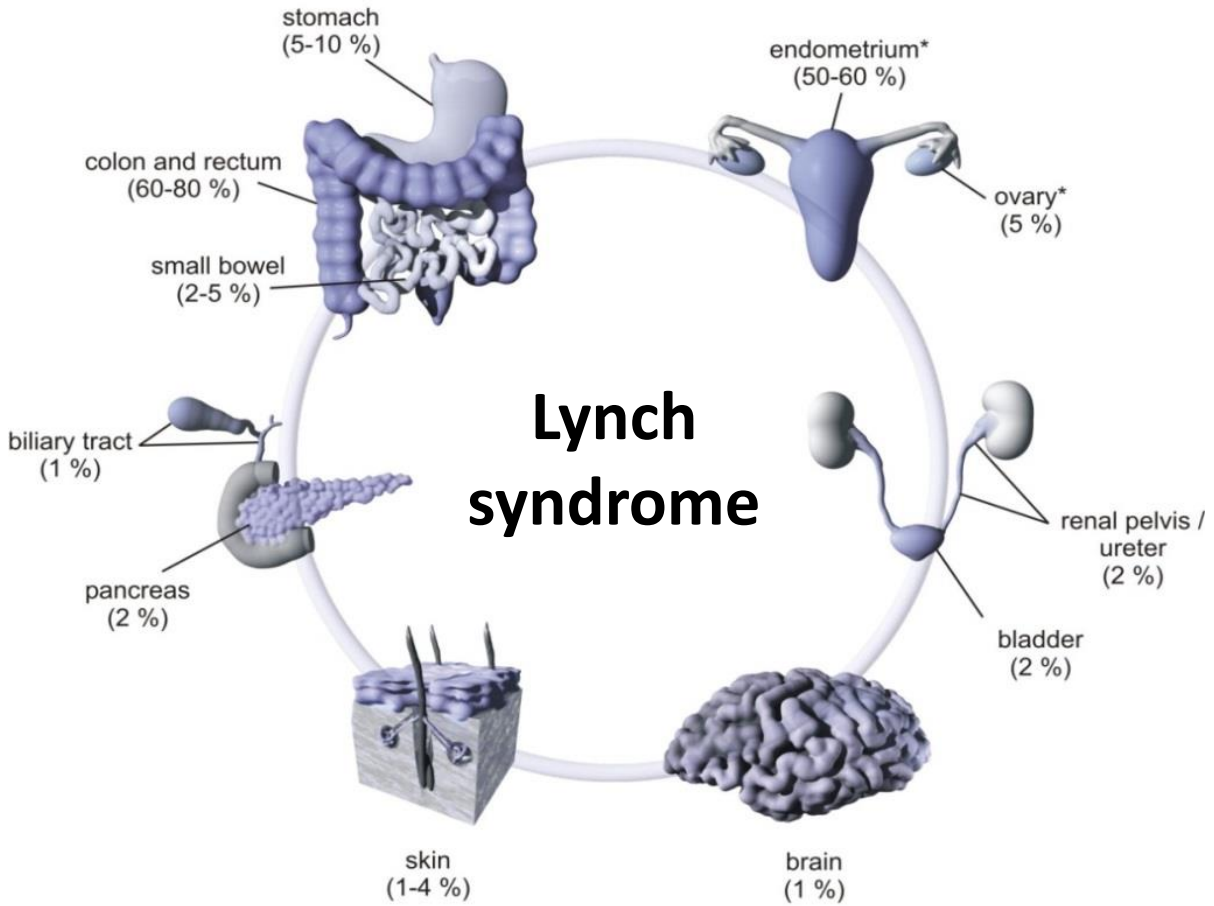
UK HD

# Conflicts of interest

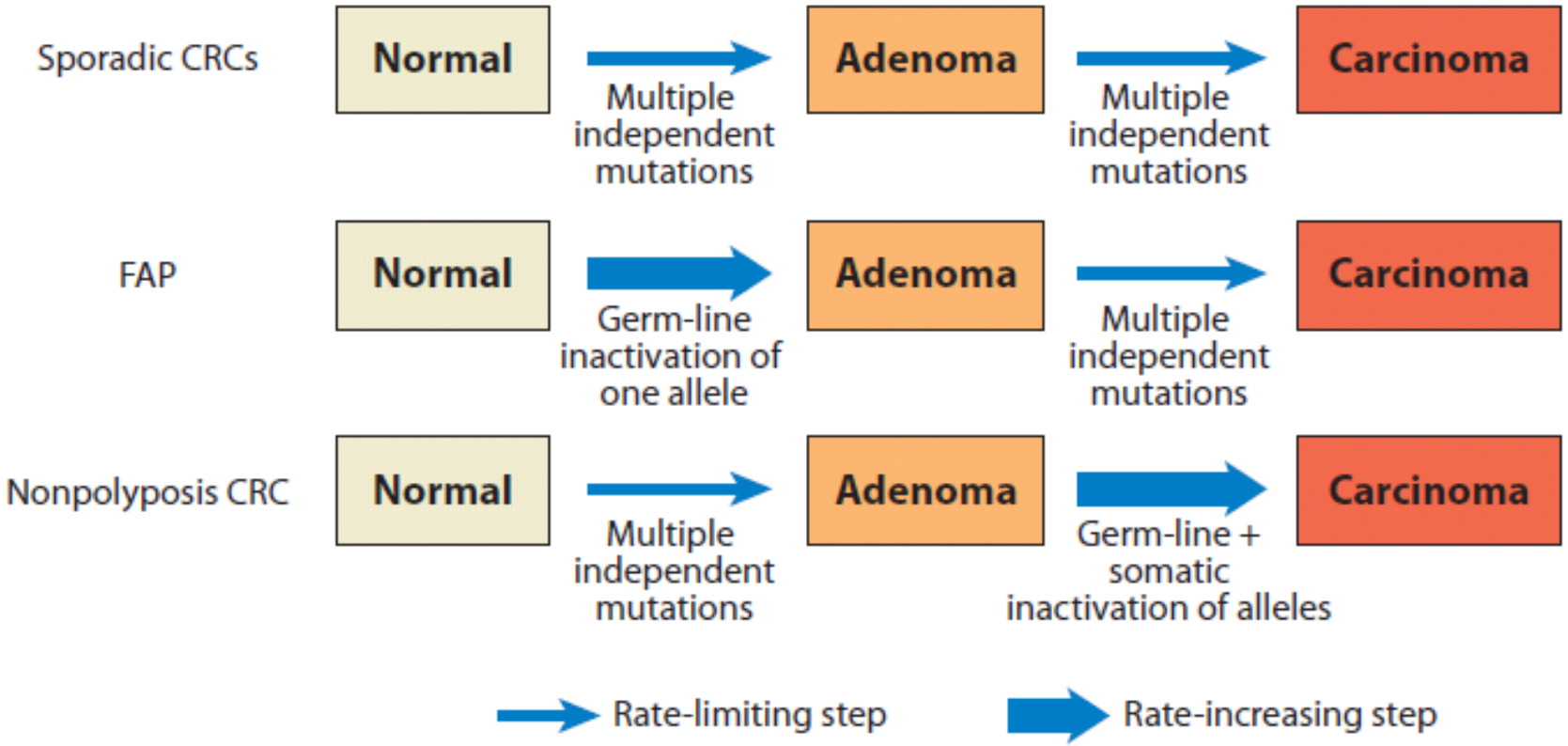
I have no potential conflict of interest to report

# Patients with cancer predisposition require prevention



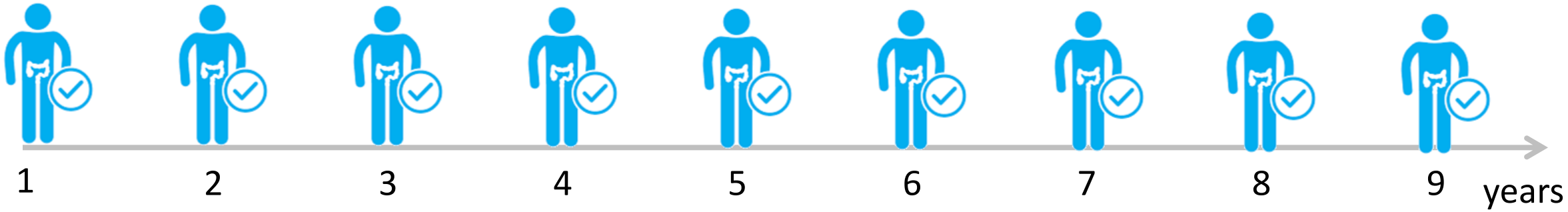
# Adenoma-carinoma dogma

"lesions that project above the surrounding mucosa are commonly termed polyps"

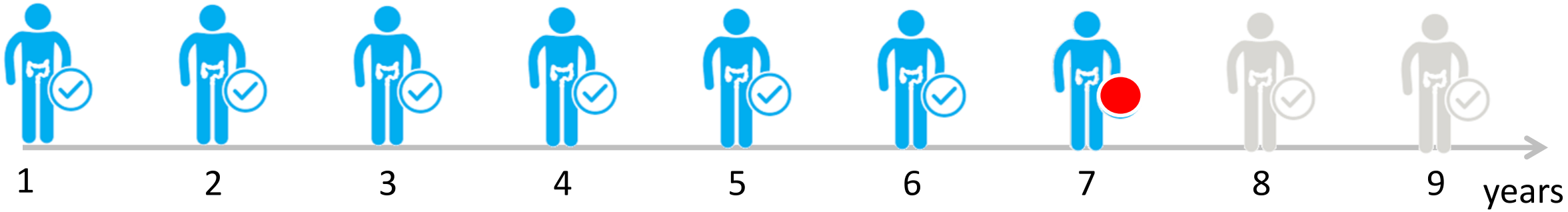



Fearon ER. Annu. Rev. Pathol. Mech. Dis. 2011
Jackman RJ, Mayo CW. *Surg Gynecol Obstet*. 1951

# Efficacy of colonoscopy



# Effectiveness of colonoscopy




There is **up to 15%** risk of developing colon cancer **in 10 years**

Jarvinen et al. *Gastroenterology* 2000; Engel et al. *Clin Gastroenterol Hepatol* 2010;
de Vos tot Nederveen Cappel et al *Dis Colon Rectum* 2002; Vasen et al *J Med Genet* 2007;
Mecklin et al. *Gastroenterology* 2007; Møller et al *Gut* 2017; Engel, Vasen, Seppälä *Gastroenterology* 2018

# Cancer risk in Lynch syndrome

Mev Dominguez-Valentin

Pål Møller

plsd.eu

Prospective Lynch Syndrome Database (PLSD) - cumulative risk for cancer by age, genetic variant, and gender

Any cancer | Carrier without previous cancer | Carrier with previous cancer | About

**Calculation of cumulative risk for cancer in selected organ(s) irrespective of cancer(s) in any other organ**

***Organ***

Colon

***Current age***

25 — 70

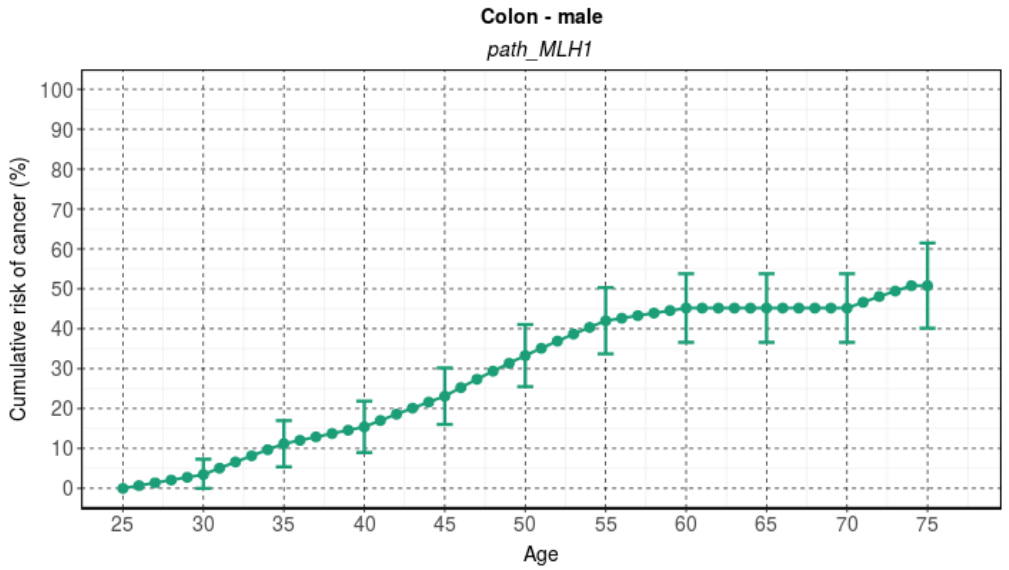
25 30 35 40 45 50 55 60 65 70

***Gender***

Male

***Genetic variant***

*path_MLH1*




**Age** **Risk (%)** **95% Confidence interval**

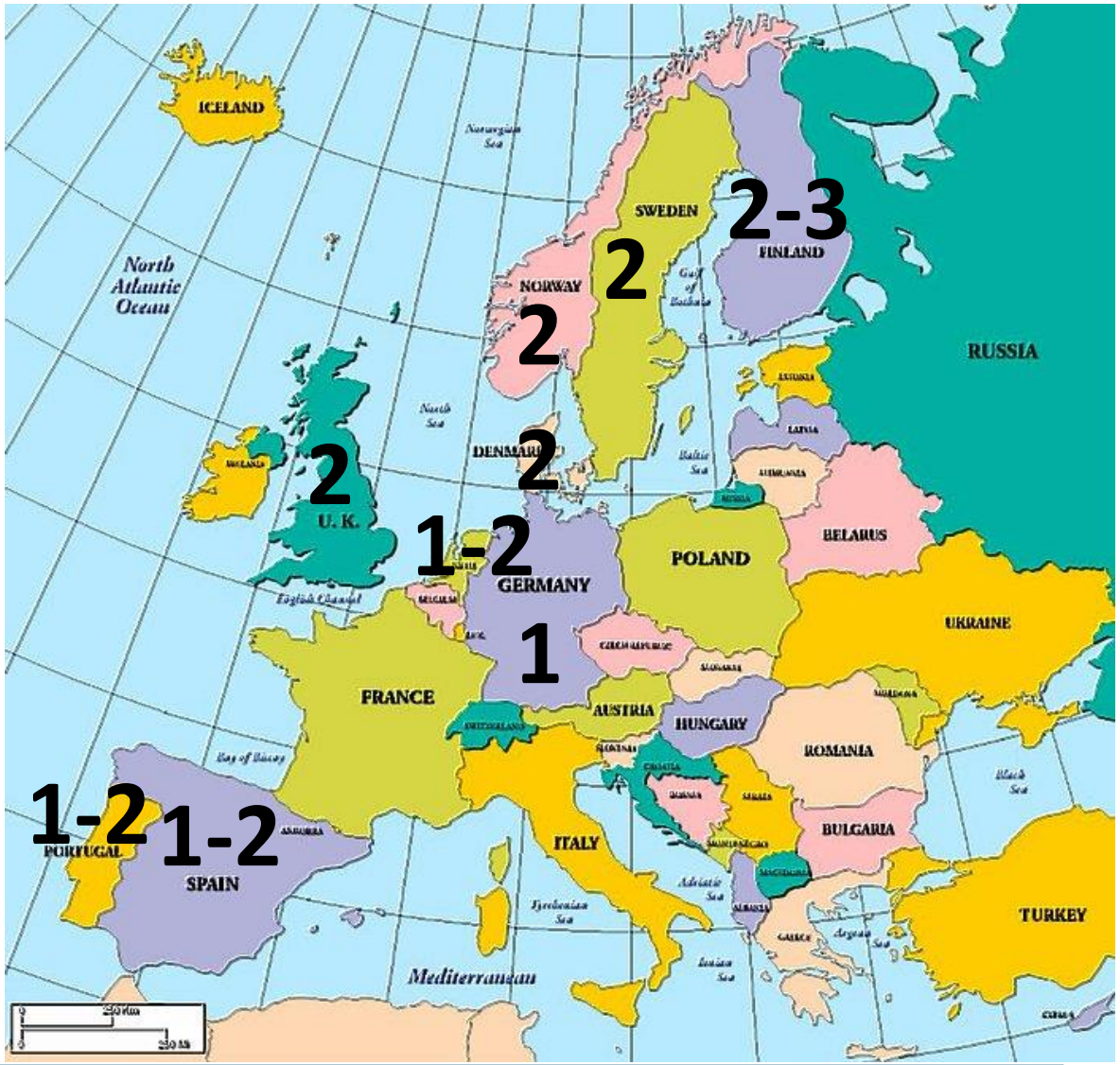
Moller et al. *Hered Cancer Clin Pract* 2022
Dominguez-Valentin et al. *Genet Med* 2020
Seppälä et al. *Fam Cancer* 2021
Moller et al. *Gut* 2017

# Shorter colonoscopy intervals, less cancers?

## 39% vs. 54%

3-yearly 1-2-yearly

Seppälä et al. *Hered. Cancer Clin. Pract.* 2017



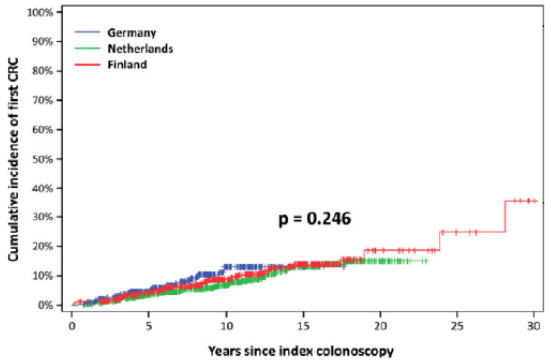
# Shorter colonoscopy intervals, less cancers?

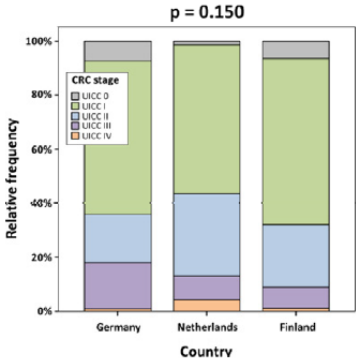
Recommended colonoscopy intervals in Lynch syndrome

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

Outcome in 2747 patients

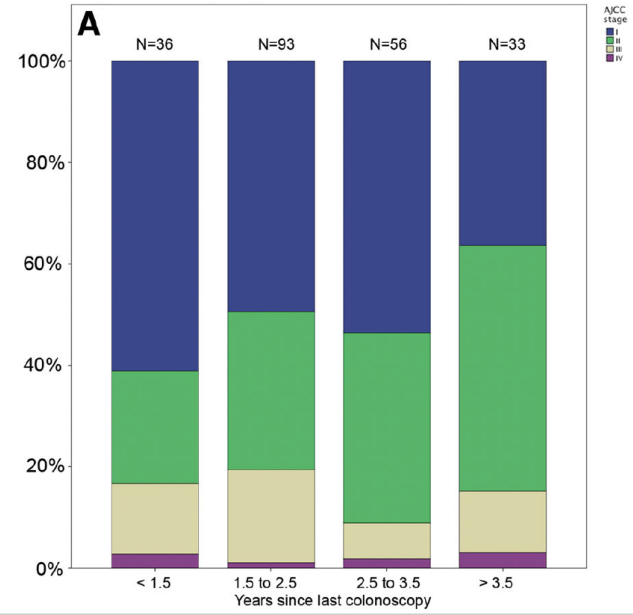
No reduction of CRC risk or tumor stage with shorter intervals




Gastroenterology

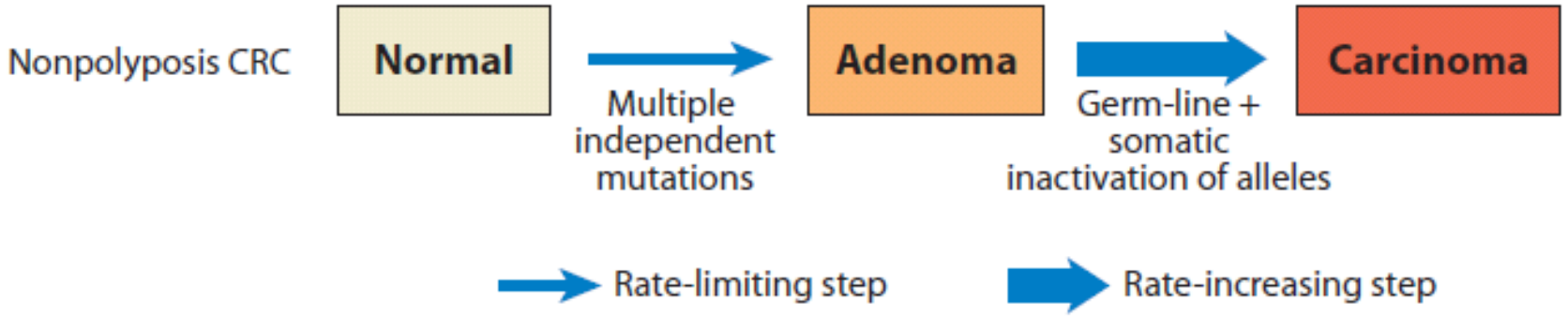
3-country study

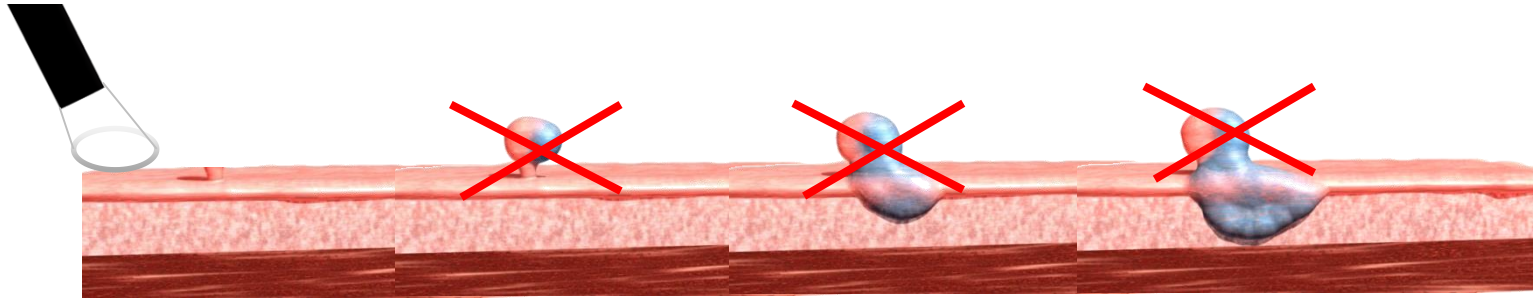



PLSD

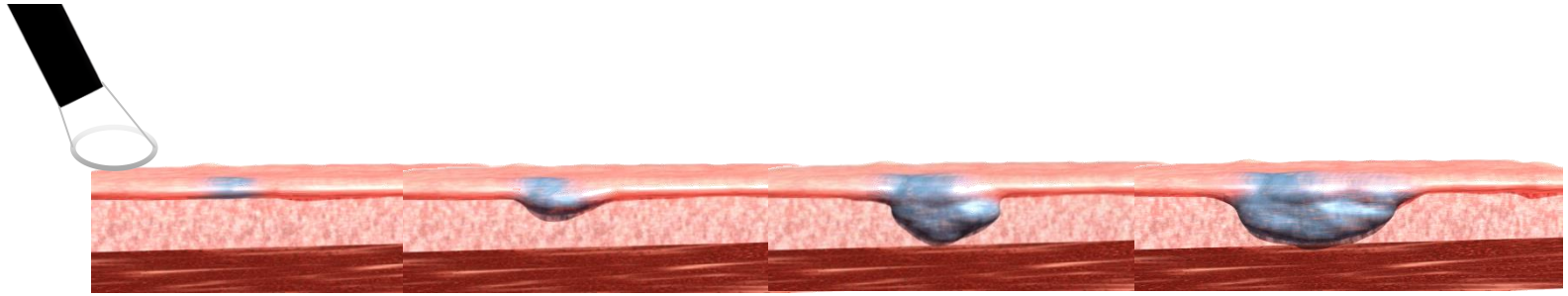
Engel, Vasen, Seppälä et al. *Gastroenterology* 2018
Seppälä et al. *Hered Cancer Clin Pract* 2019

# It does not add up



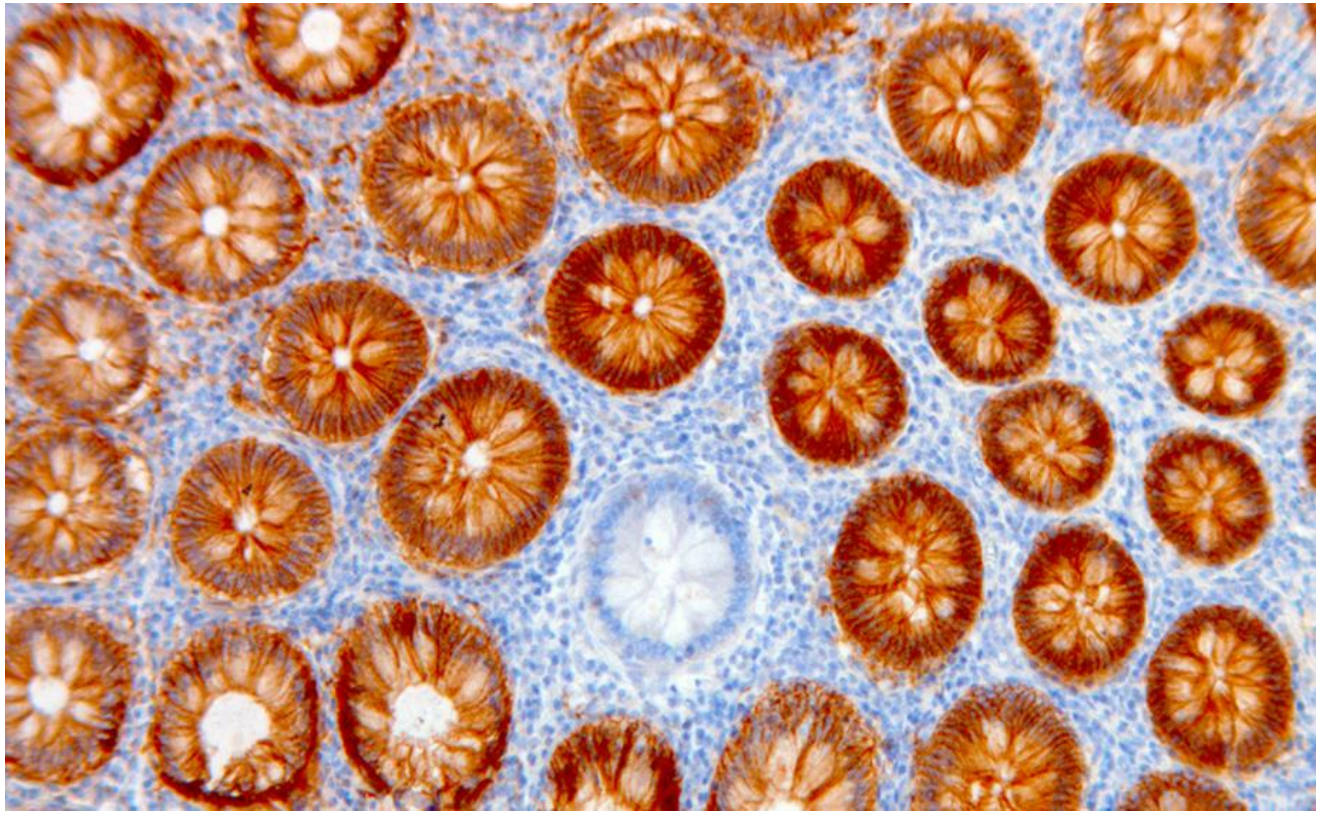
**classical progression of CRC**



**non-polypous progression of CRC?**

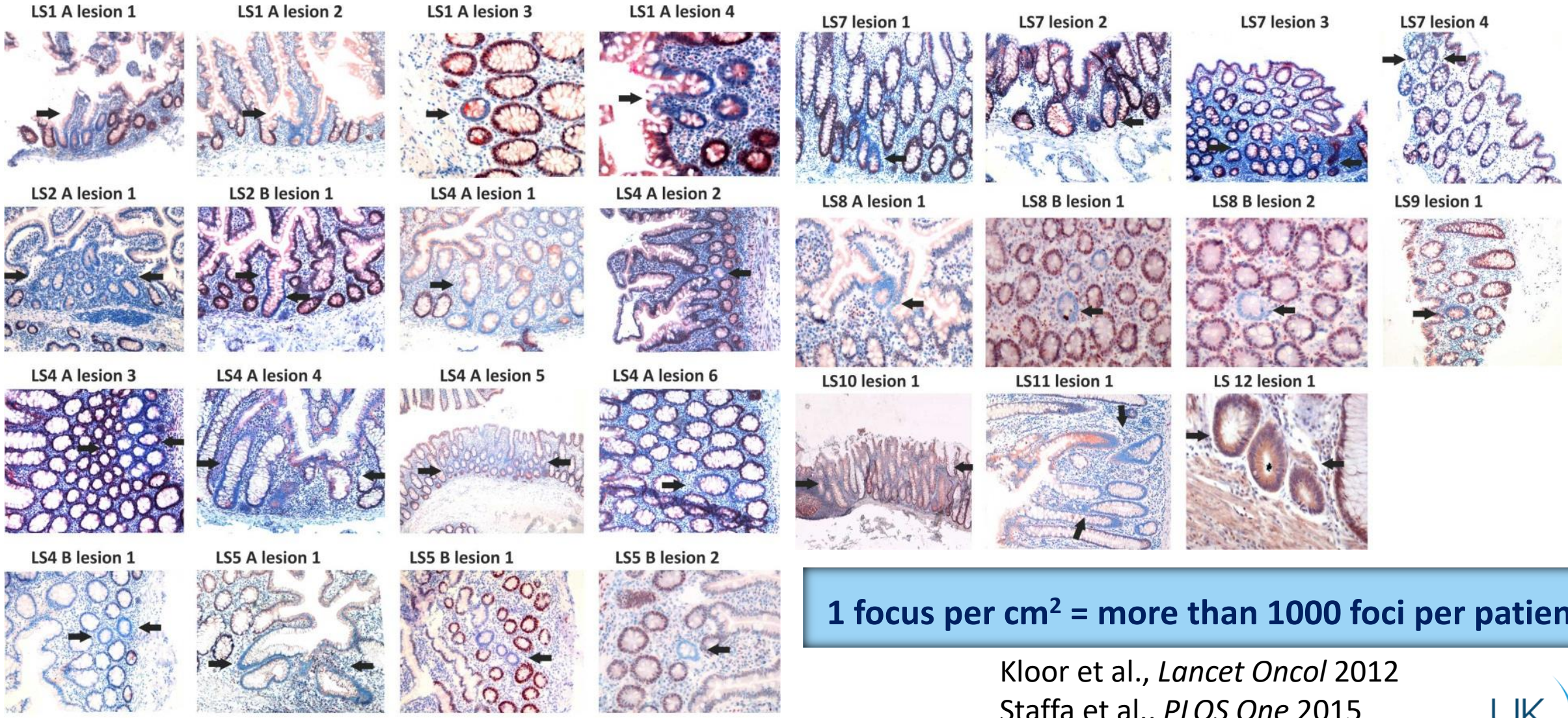
# Non-polypous precursors: evidence from pathology

## **M**is**M**atch **R**epair-**D**eficient **Cr**ypt **F**oci



EPCAM staining

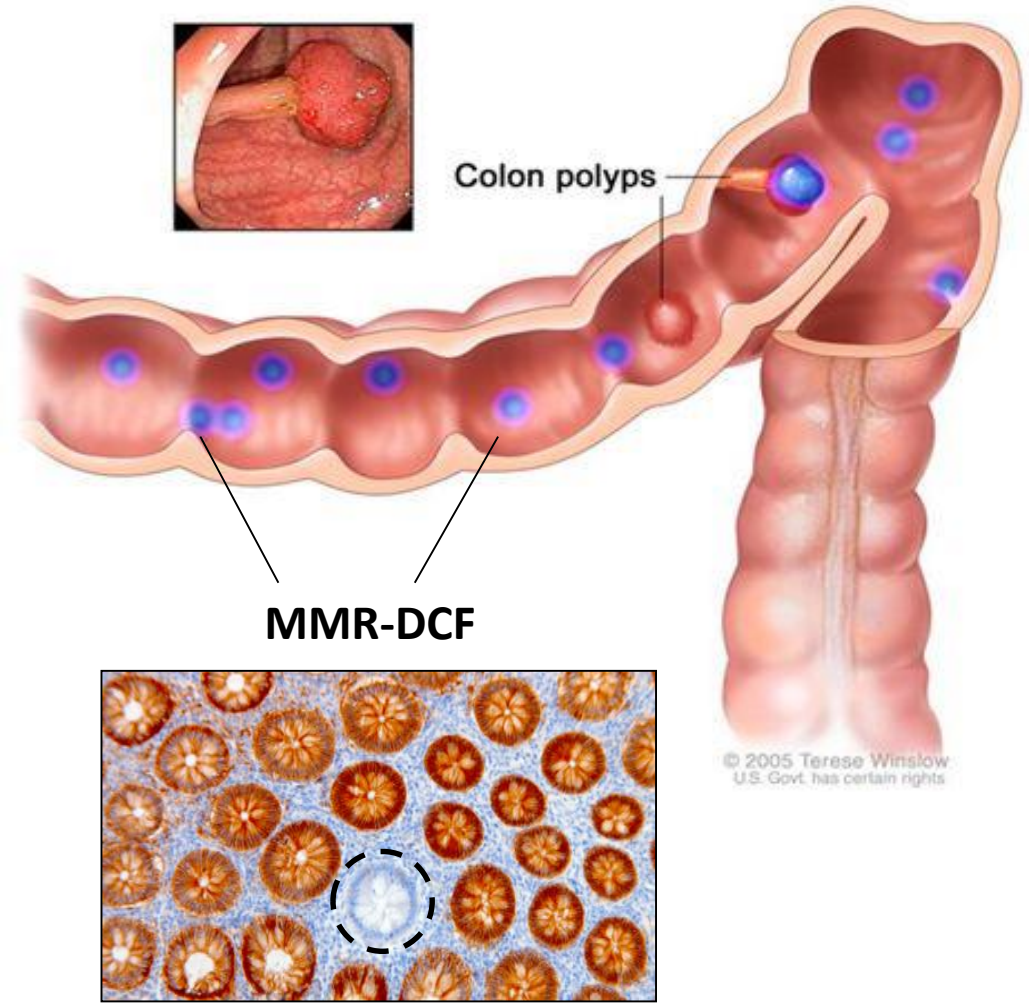
# Non-polypous precursors: evidence from pathology

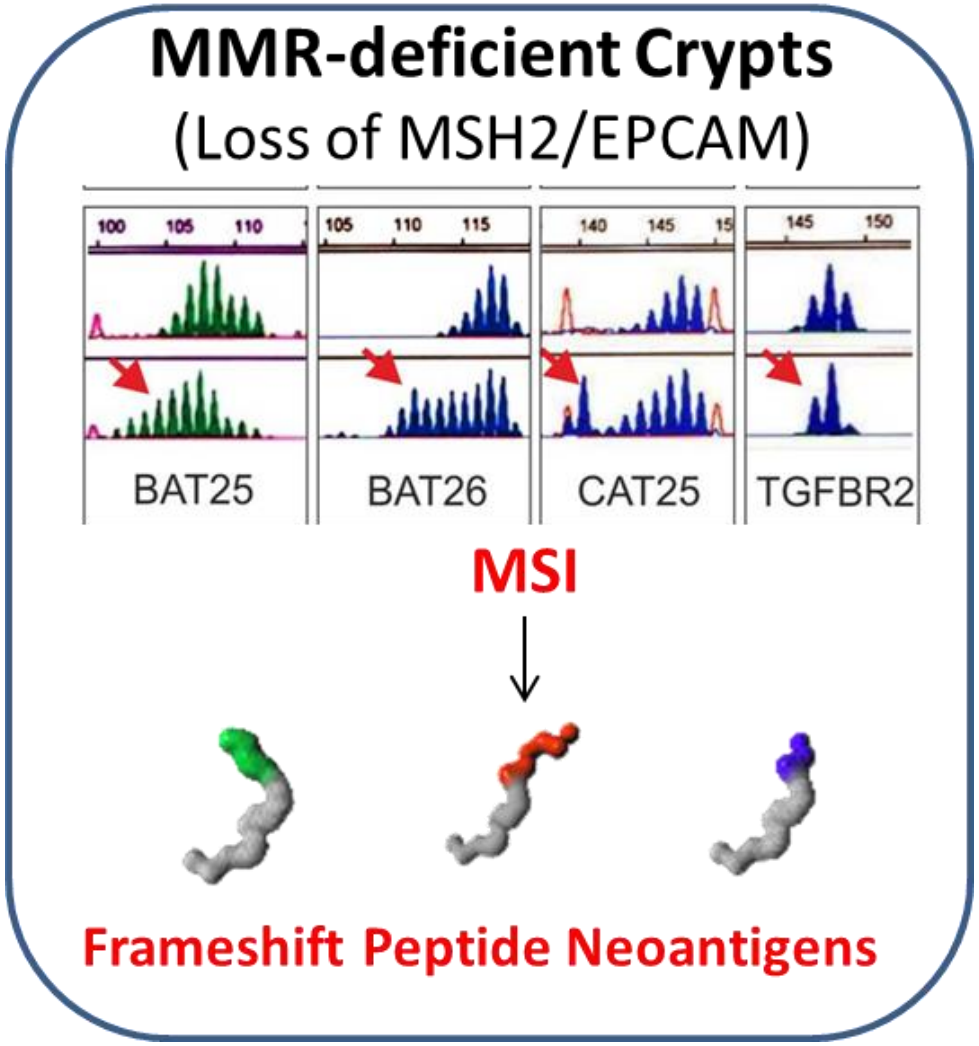



**1 focus per cm$^2$ = more than 1000 foci per patient**

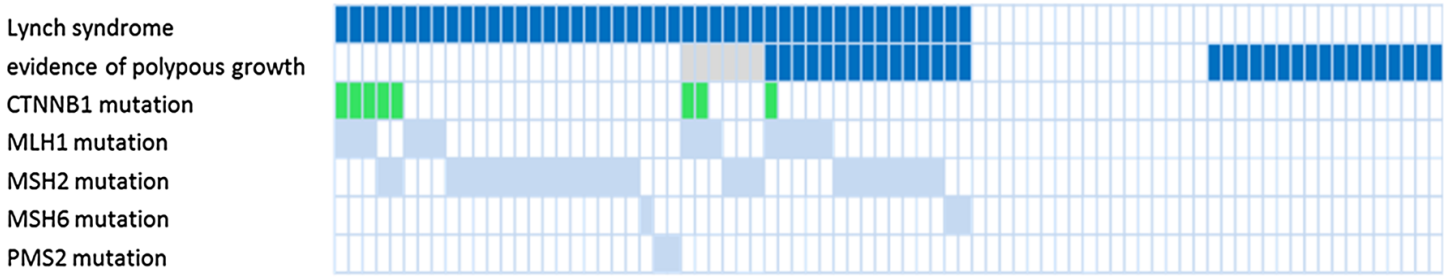
Kloor et al., *Lancet Oncol* 2012
Staffa et al., *PLOS One* 2015

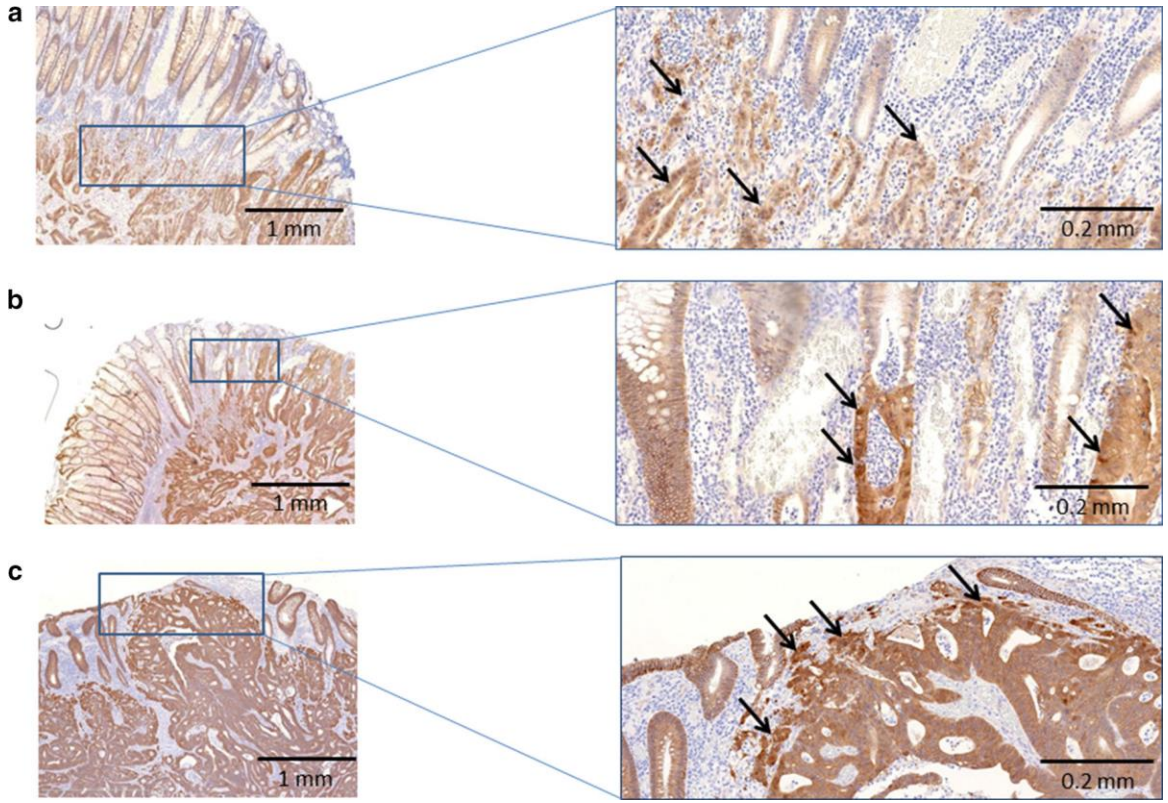
# Cancer-driving potential of MMR-DCF

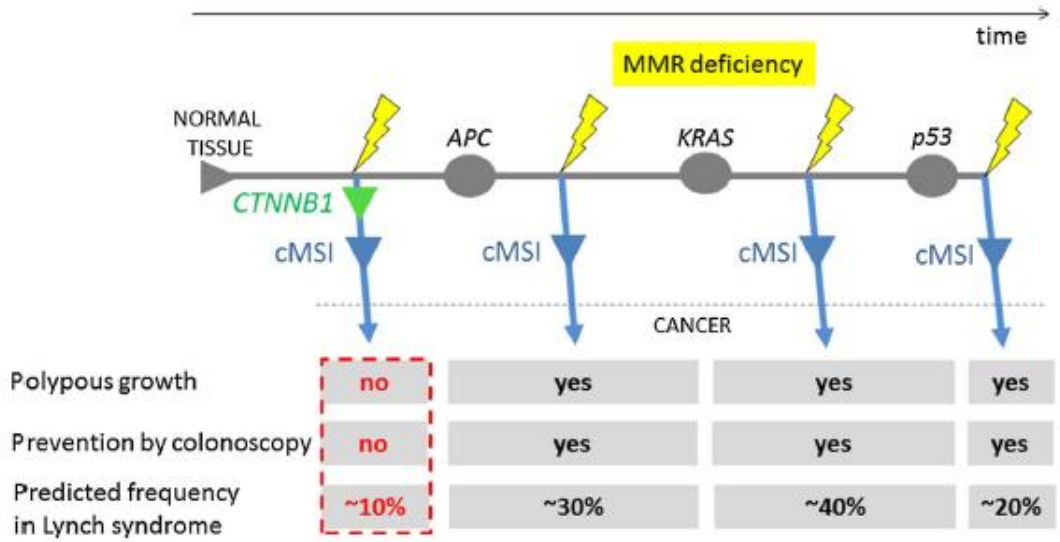


# Can LS CRC progress from a non-polypous precursor?



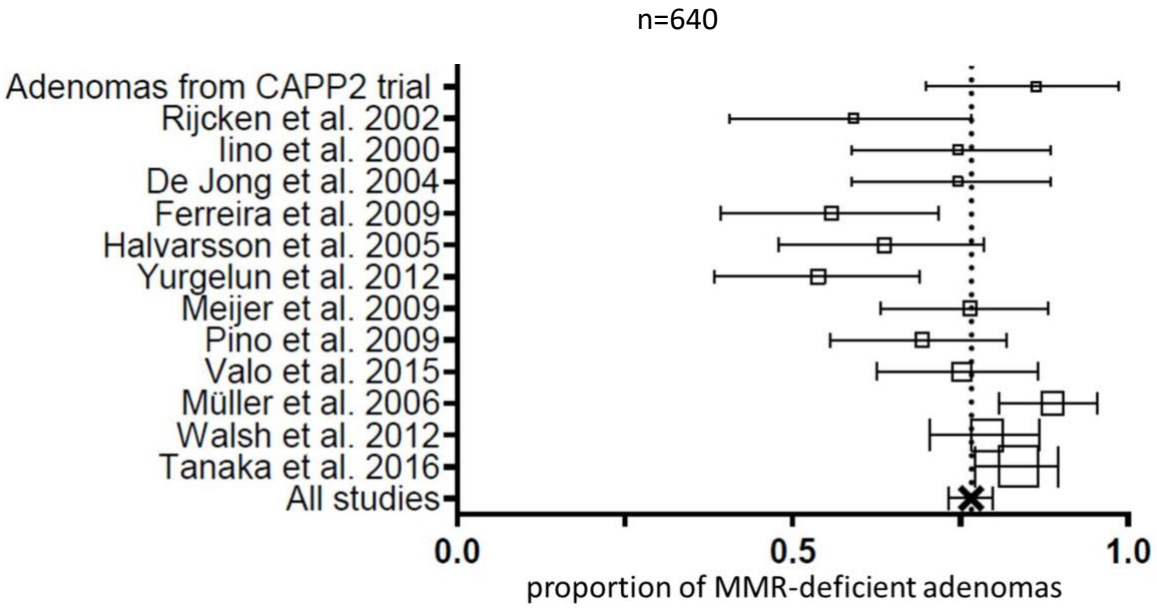



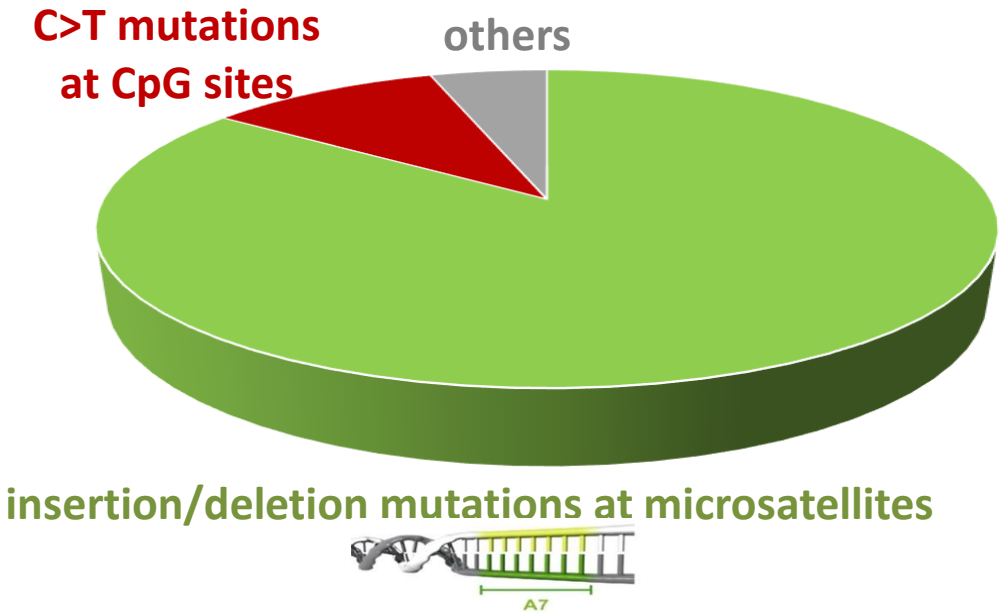

Ahadova et al. *Fam Cancer* 2016

# When does the MMR deficiency occur?

## Evidence from adenomas



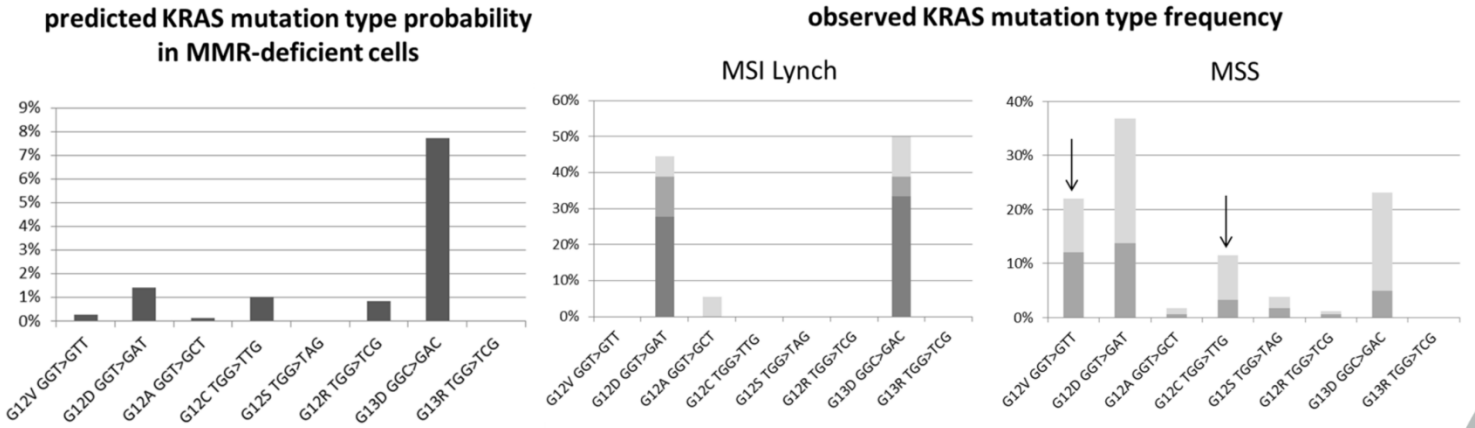

## Evidence from carcinomas

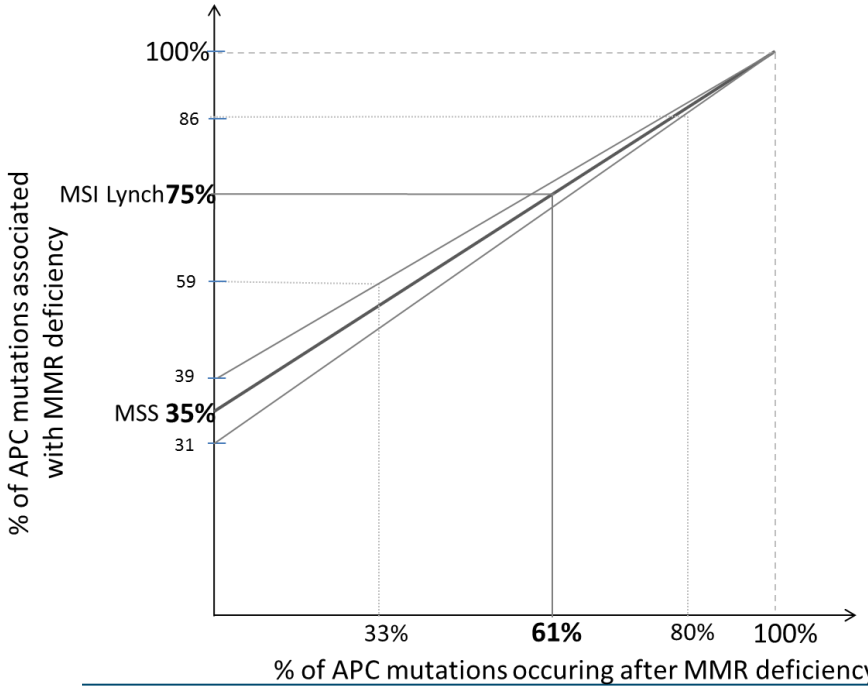


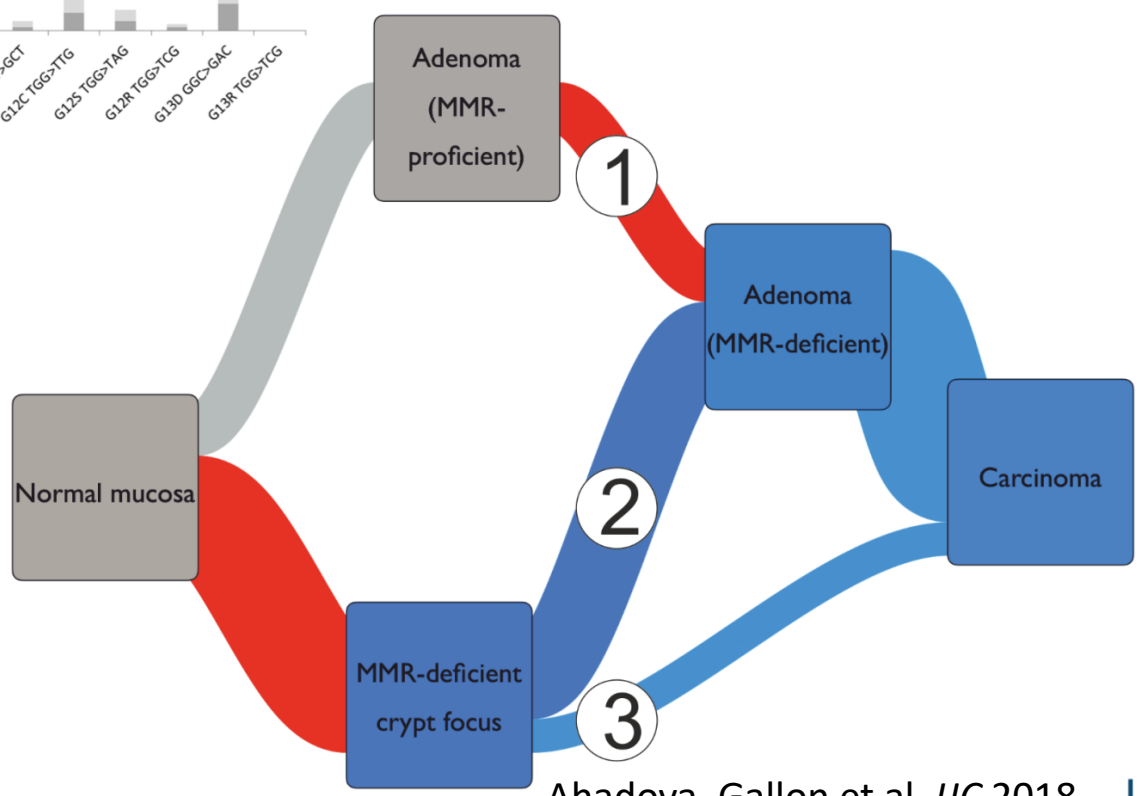

- 77% of LS-assocaited adenomas are MMR-deficient
- LS-associated adenomas carry cMS mutations  in target genes

Ahadova, Gallon et al. *IJC* 2018

# Mutational signature of MMR deficiency in initiating somatic mutations



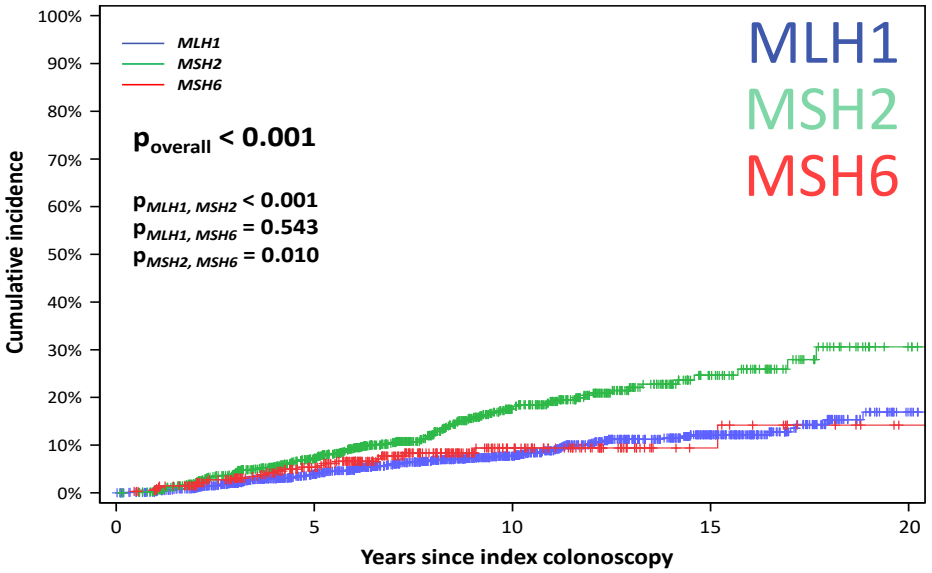



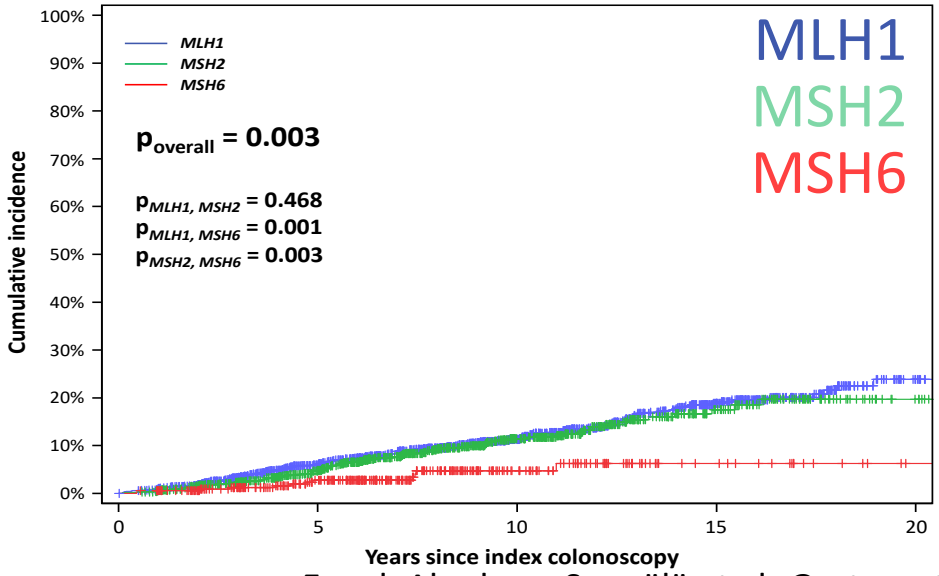

Ahadova, Gallon et al. *IJC* 2018

# Incident cancer risk is different among different MMR variant carriers

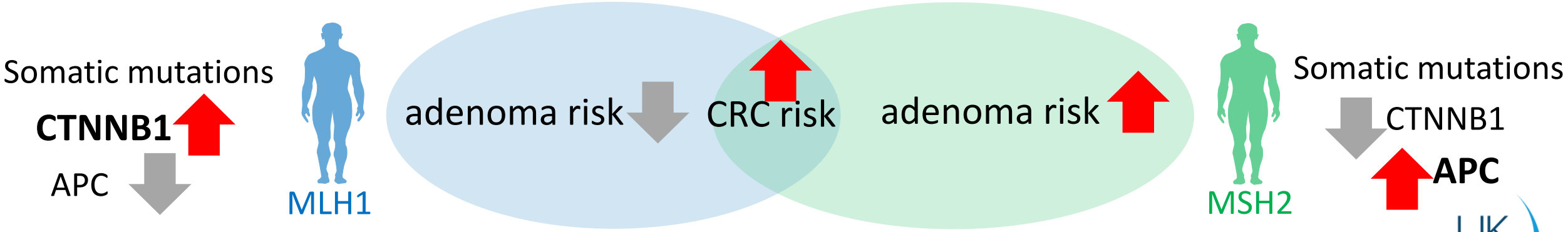
## Risk for advanced adenoma



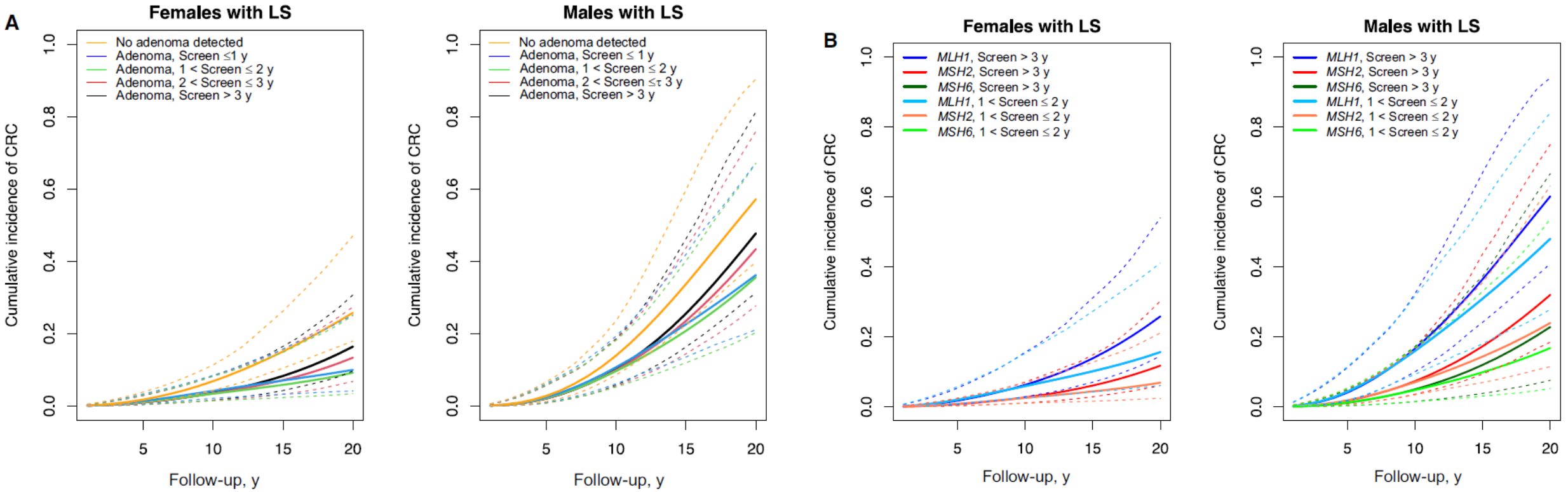

## Risk for incident cancer




Engel, Ahadova, Seppälä et al. *Gastroenterology* 2020



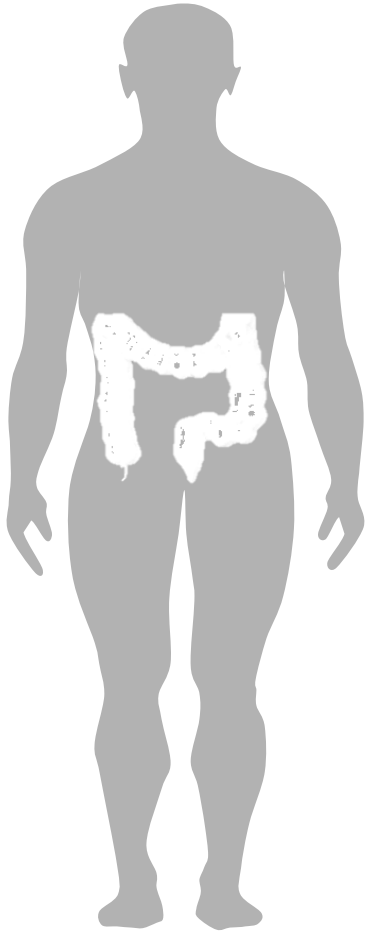
# *MLH1* carriers and carriers without adenomas at first colonoscopy show highest CRC incidence under surveillance




Aronson et al. *JNCI* 2023

# *CTNNB1* is an oncogene, but not a classical one

***CTNNB1* requires a monoallelic hit for activation**



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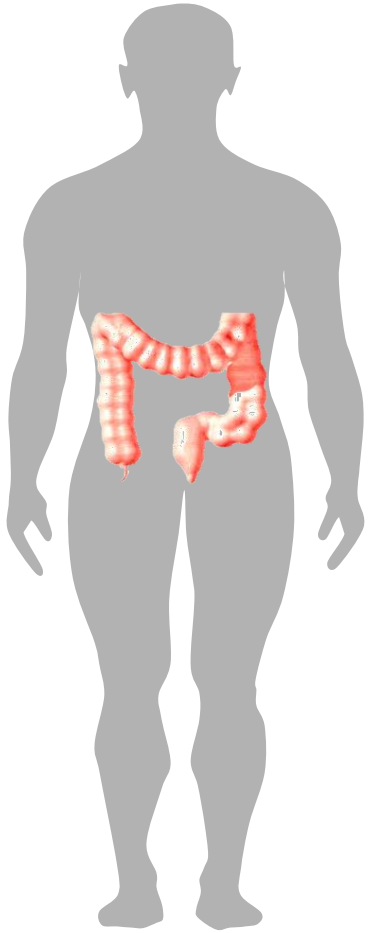
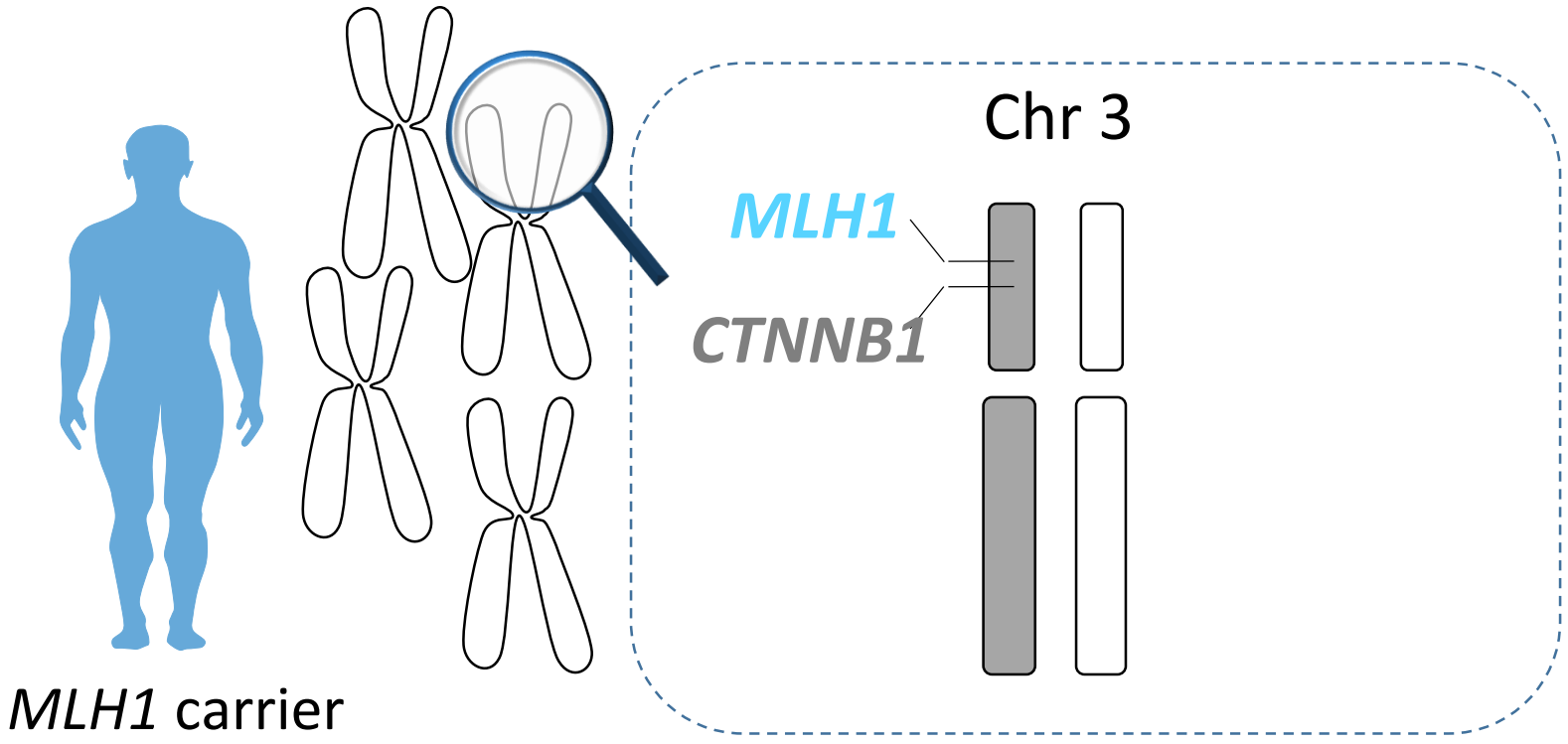


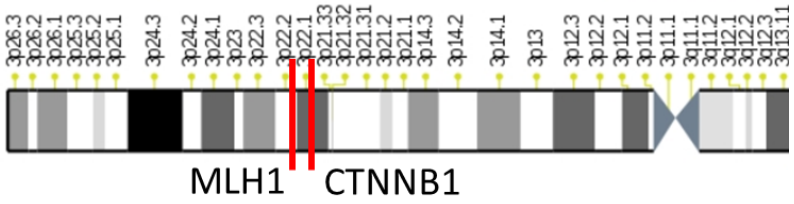
***CTNNB1* requires a biallelic hit for activation**

# Why are *CTNNB1* mutations associated with *MLH1* Lynch syndrome?

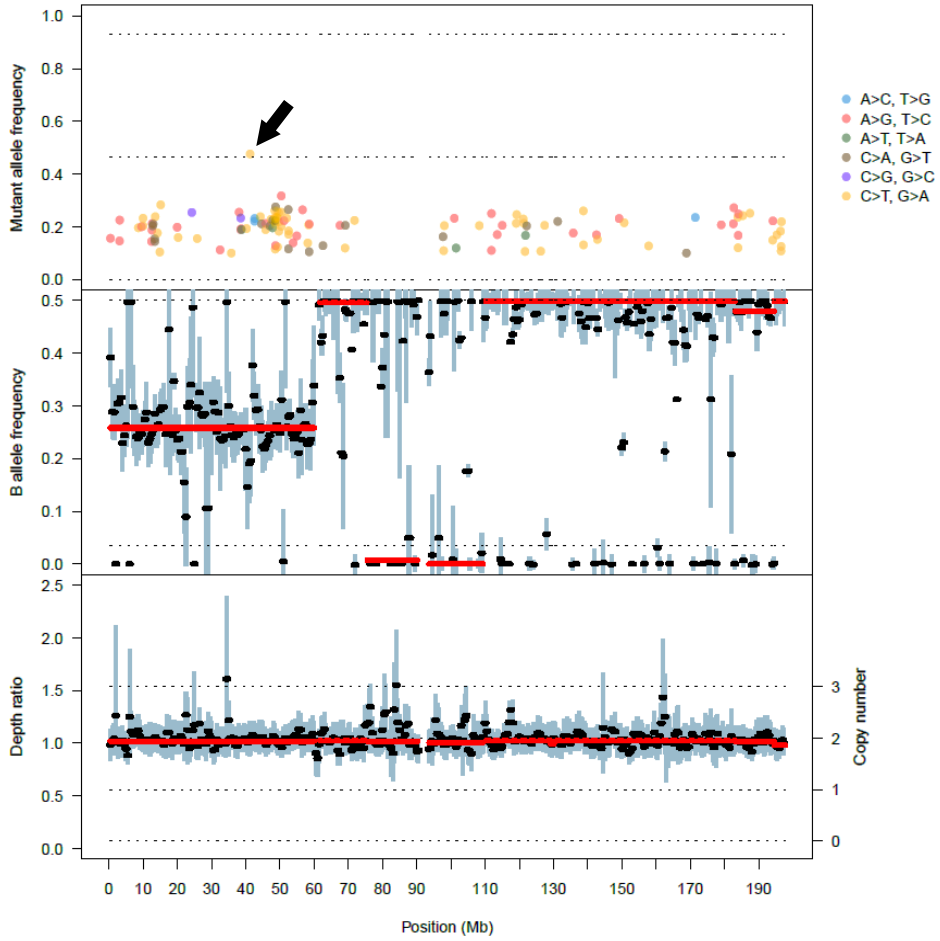



**Single genetic event** switches *MLH1* **off** and *CTNNB1* **on**?

# cnLOH is responsible for biallelic *MLH1* inactivation and *CTNNB1* activation

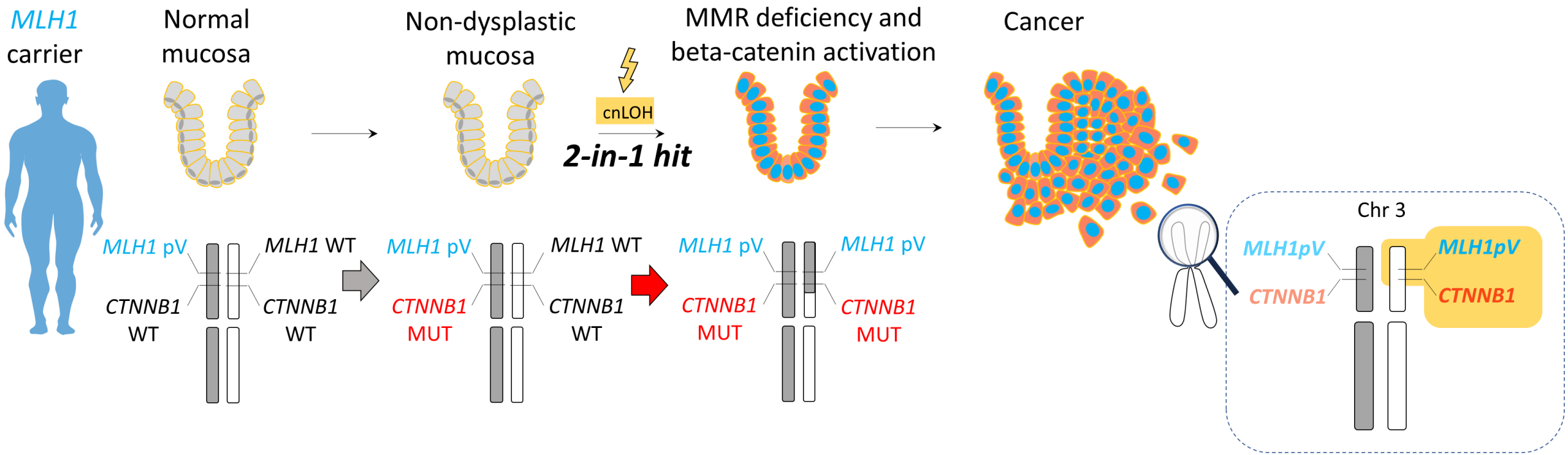



| | | | |
|---|---|---|---|
| **Ca14** | 3pter | 52 Mbp | 3p21.2 |
| **Ca15** | 3pter | 49 Mbp | 3p21.31 |
| **Ca17** | 3pter | 54 Mbp | 3p21.1 |
| **Ca19** | 3pter | 59 Mbp | 3p14.2 |
| **Ca20** | 3pter | 56 Mbp | 3p14.3 |




Ahadova et al. *Gastroenterology* 2023

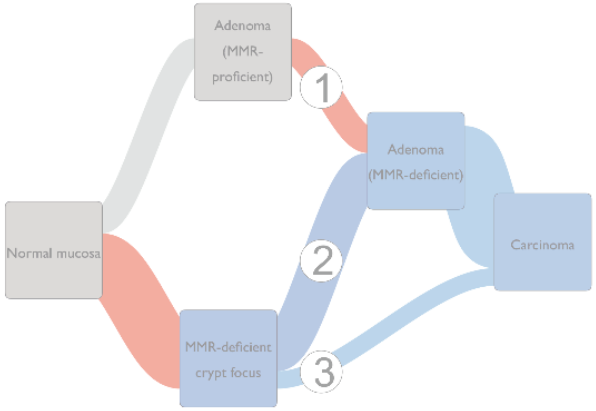
# Two-in-one hit model of carcinogenesis




Ahadova et al. *Gastroenterology* 2023

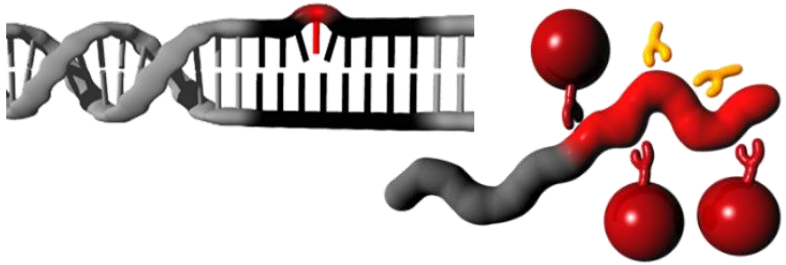
# Potential explanations for the limited effect of colonoscopy

pathway heterogeneity/other precursors




unpreventable cancer?

MSI pathogenesis/high immunogenicity/strong immune infiltration



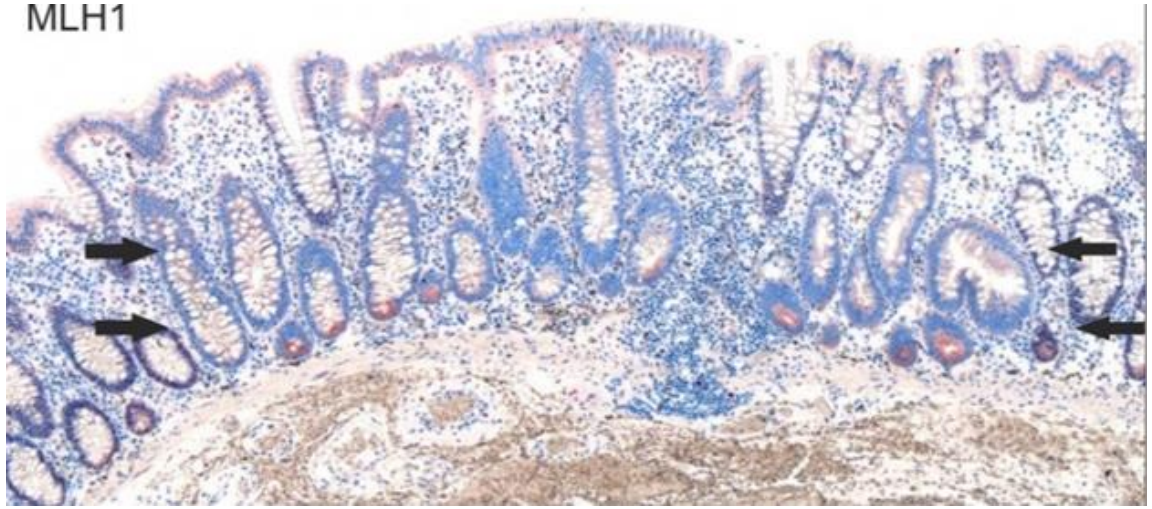
lesion regression?

# Low probability of progression from MMR-DCF

Stark contrast between the prevalence of MMR-deficient crypts and LS penetrance

>1000 MMR-deficient foci per patient

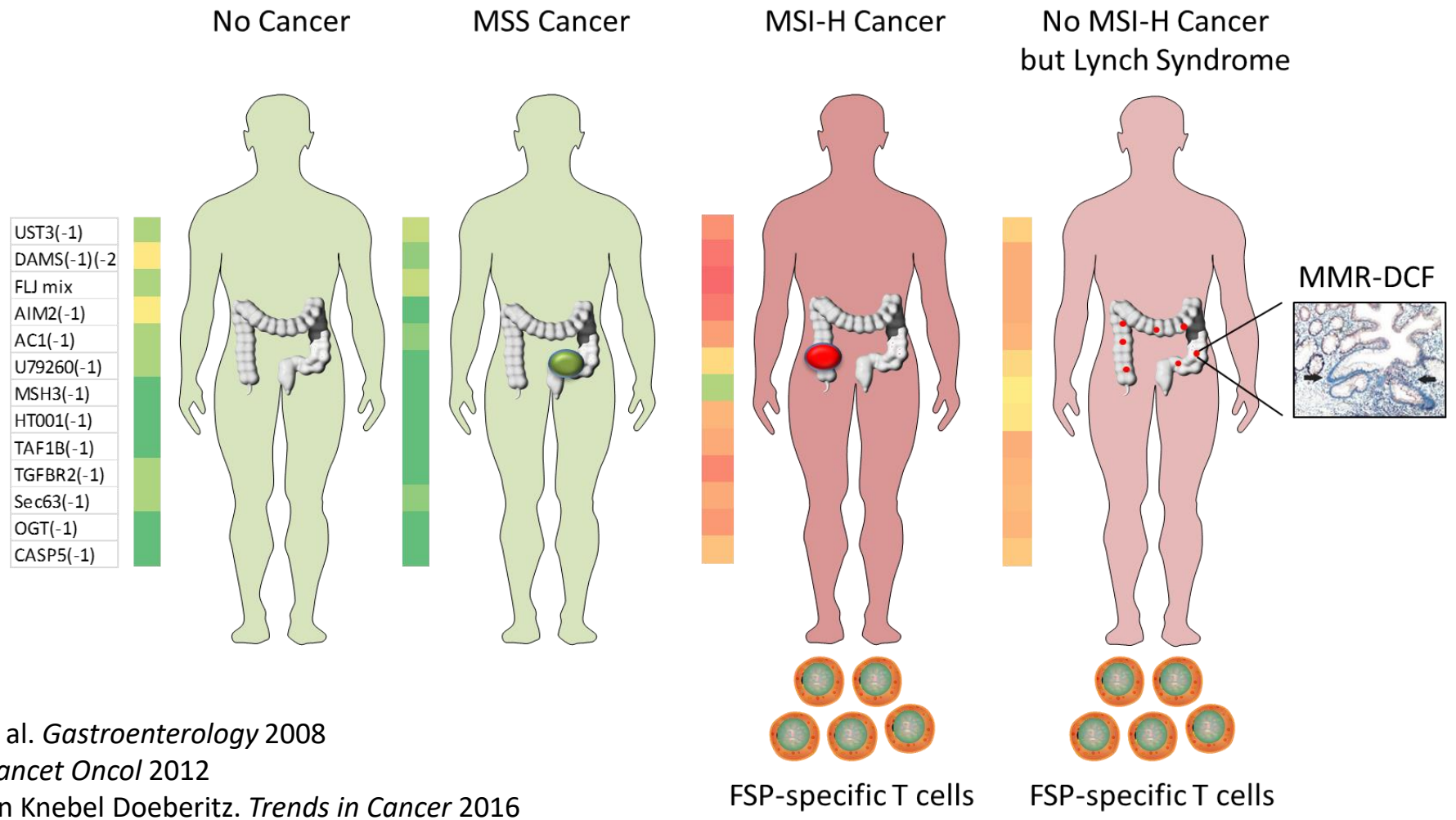
<0.5 progressing to cancer




Kloor et al. *Lancet Oncol* 2012

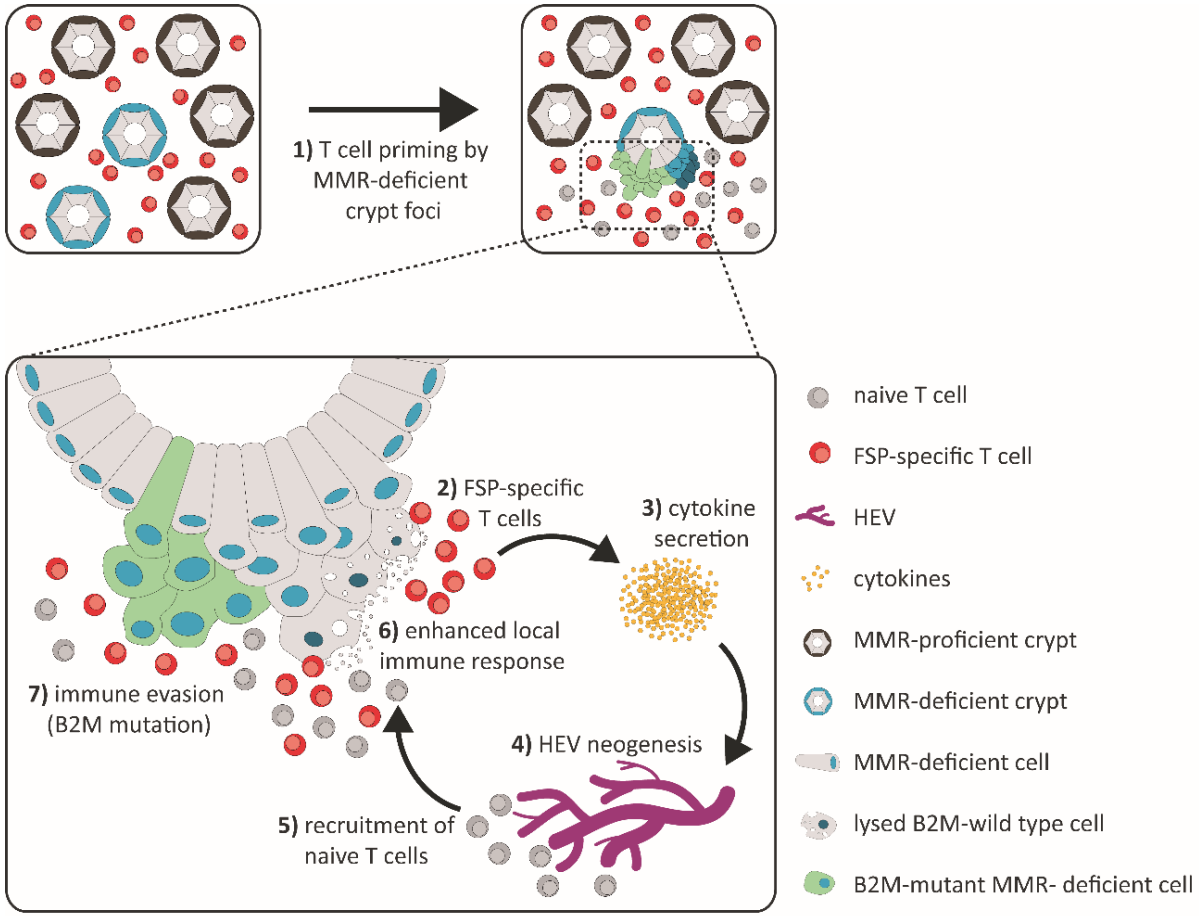
**What happens to all those MMR-DCF?**

# Systemic immune responses in Lynch syndrome

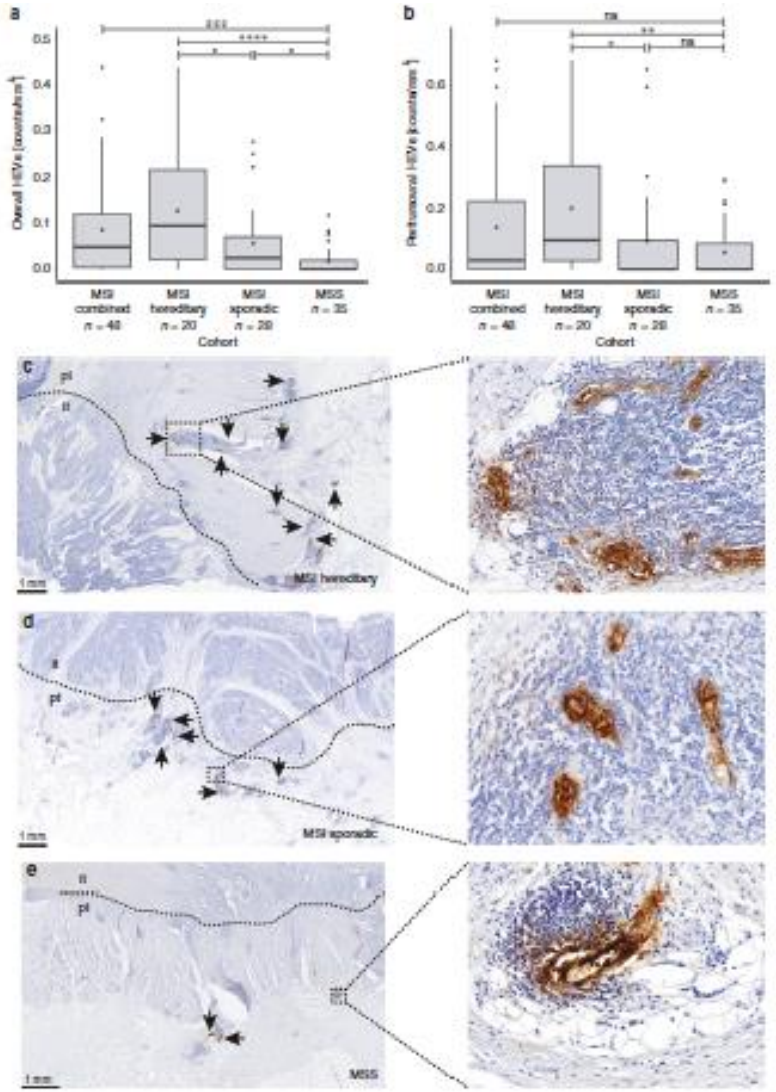



Schwitalle et al. *Gastroenterology* 2008
Kloor et al. *Lancet Oncol* 2012
Kloor and von Knebel Doeberitz. *Trends in Cancer* 2016

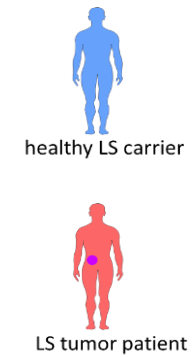
# Local immune responses in Lynch syndrome



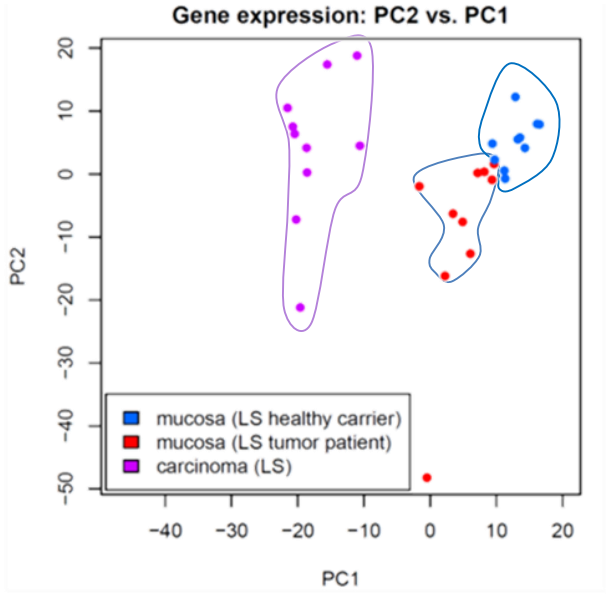

Pfuderer et al. *Br J Cancer* 2019

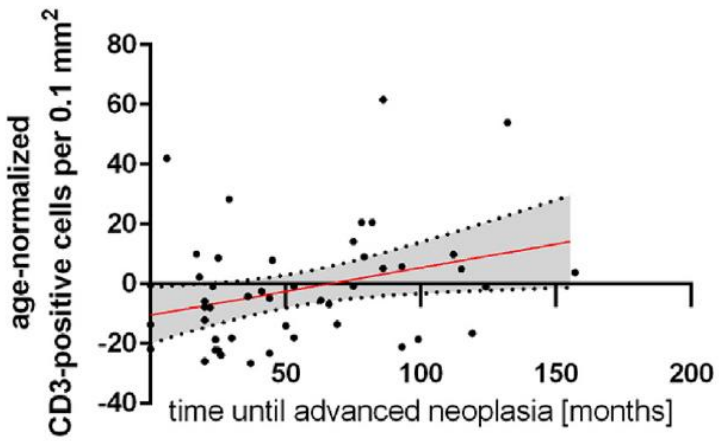


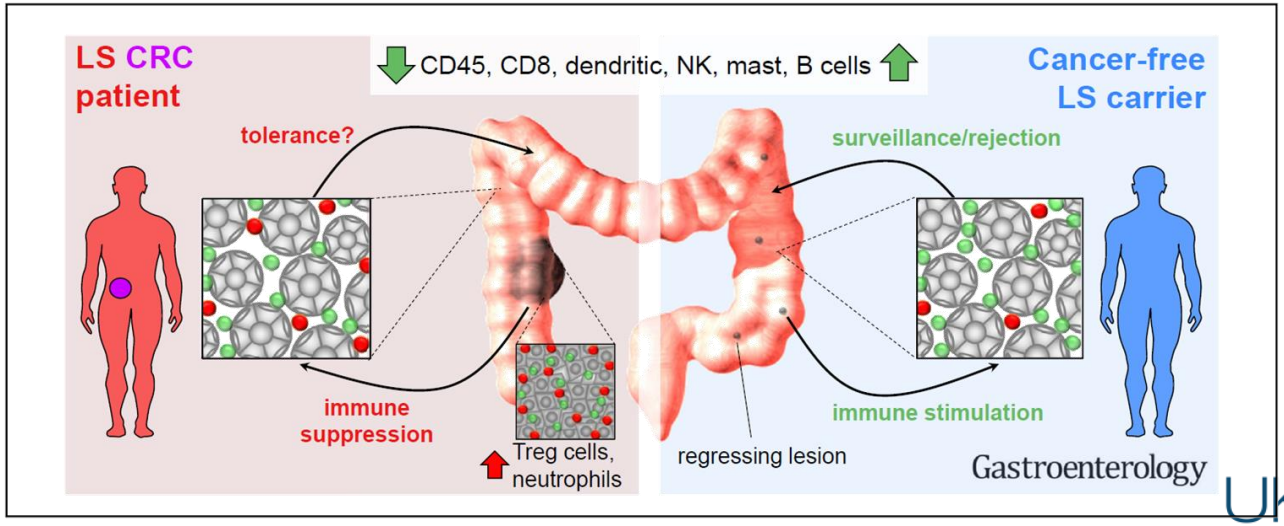
# Local T cell responses in tumor-free Lynch syndrome patients


770 immune-relevant genes




Bohaumilitzky et al. *Gastroenterology* 2022
Kupfer (editorial). *Gastroenterology* 2022

# What is the way to go?

## Balancing the burden and benefits of colonoscopy in Lynch Syndrome

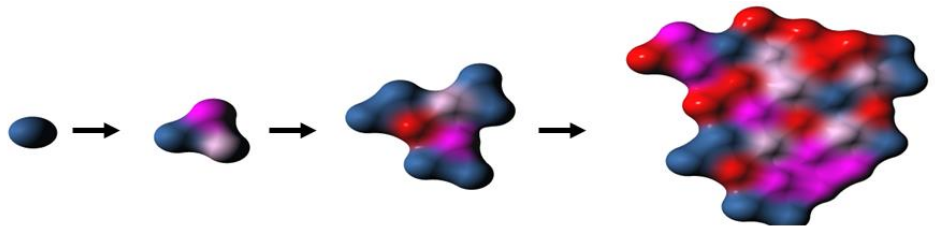
Finlay Macrae[1]

Accepted: 12 August 2023 / Published online: 15 September 2023


Macrae. *Fam Cancer* 2023
Van Liere et al. *Fam Cancer* 2023

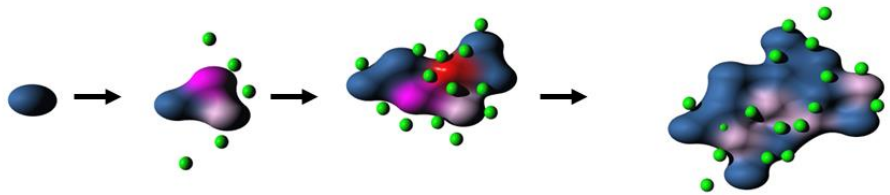
# Alternative prevention strategies

**A.** MSI tumor evolution without immune surveillance



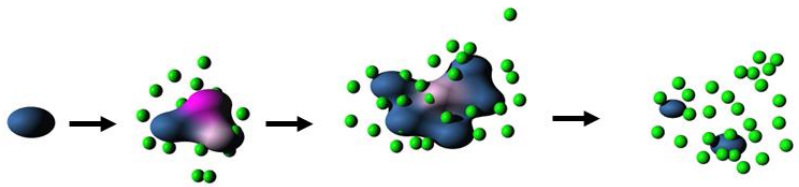
*Uncontrolled outgrowth of immunogenic tumor*

**B.** MSI tumor evolution under immune surveillance



*Tumor with limited immunogenicity („Immuno-Editing“)*

**C.** MSI tumor evolution with immune stimulation (e.g. by vaccination)

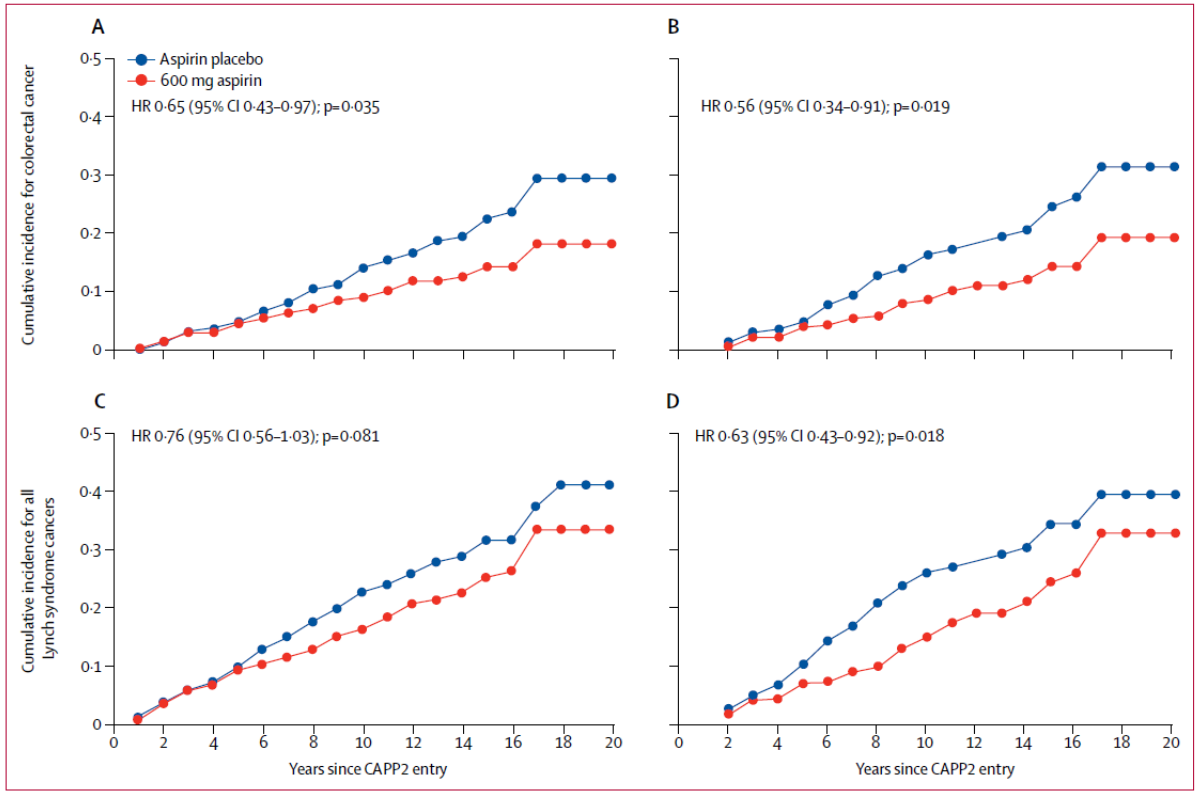


*Elimination of precancerous lesions, no tumor development*

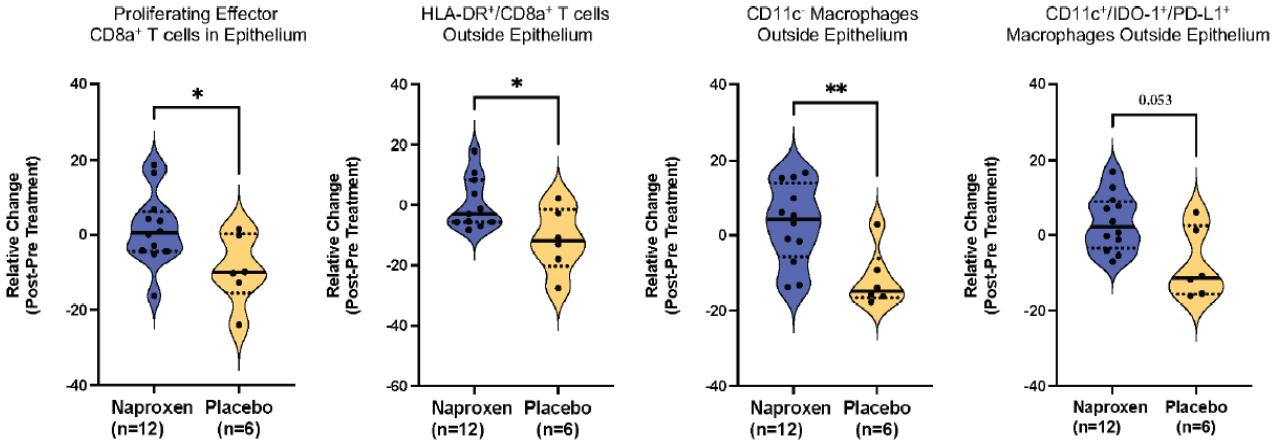
https://www.dkfz.de/en/presse/pressemitteilungen/2020/dkfz-pm-20-60-Vaccination-against-altered-proteins-could-prevent-cancer-development.php
https://cancercommunity.nature.com/posts/immune-surveillance-and-immunoediting-in-microsatellite-unstable-cancers

Ballhausen et al. *Nat Com* 2020

# Alternative prevention strategies: NSAIDs

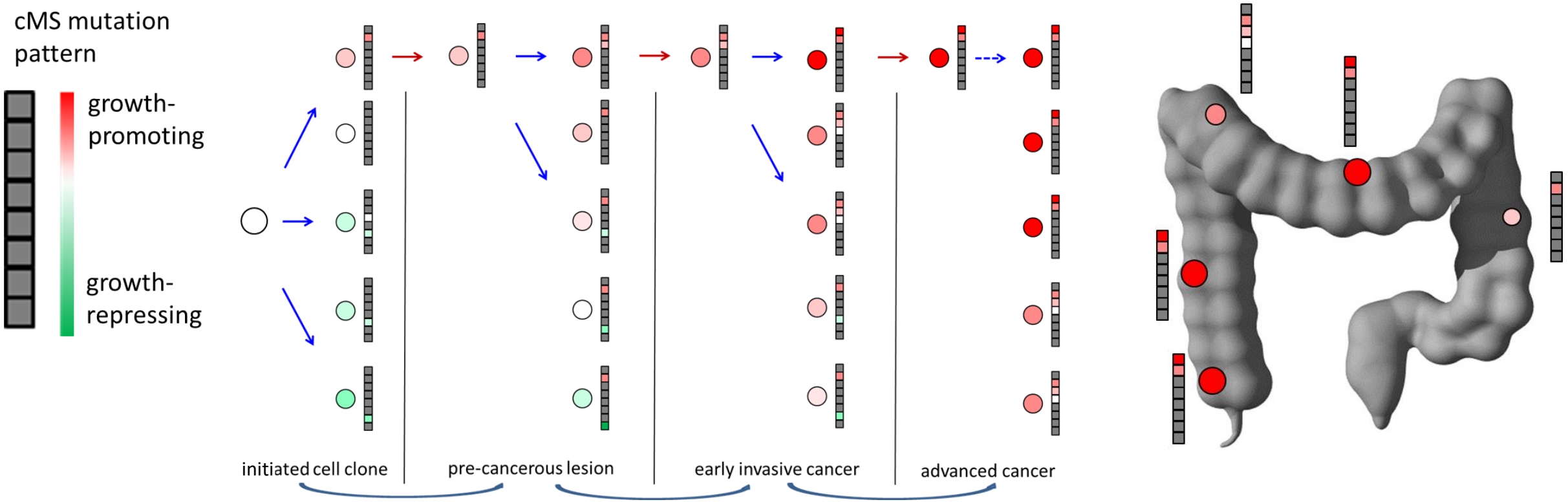



Burn et al. *Lancet* 2020



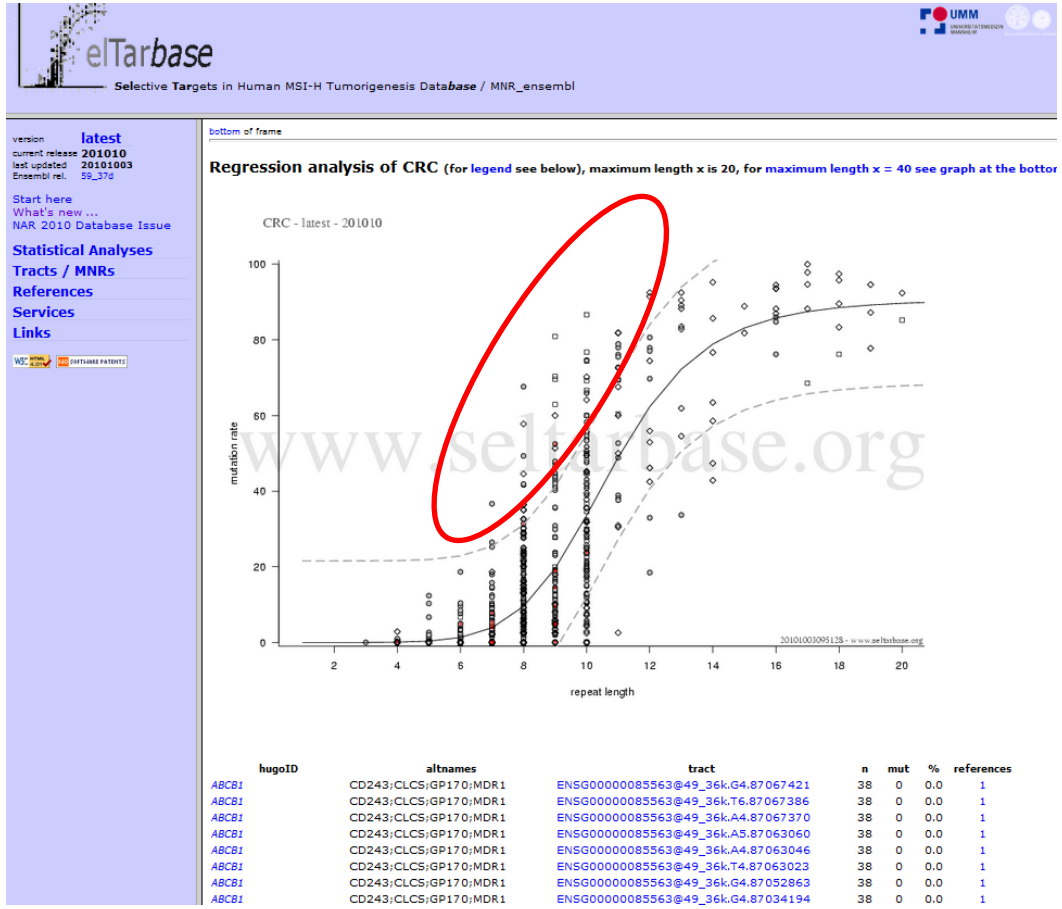

Bowen et al. *Front Immunol* 2023
Reyes-Ulribe et al. *Gut* 2021

# Alternative prevention strategies: vaccines




Kloor and von Knebel Doeberitz. *Trends in Cancer* 2016

# Potential vaccine targets are shared




| | | Mutation frequency (%) | |
|---|---|---|---|
| | Repeat type | MSI-H CRC | MSI-H endometrial cancer |
| *TGFBR2* | A10 | 73.8* | 14.5* |
| *TAF1B* | A11 | 78.9* | 58.3* |
| *AIM2* | A10 | 51.7* | 50.0* |
| *ASTE1* | A11 | 78.0* | 25.0* |
| *ACVR2* | A8 | 67.6* | 13§ |
| *CASP5* | A10 | 47.6* | 11.4* |
| *NDUFC2* | A9 | 40.3* | 20§ |
| *SLC22A9* | A11 | 69.6* | 23§ |
| *MSH3* | A8 | 42.0* | 19.4* |
| *SMAP1* | A10 | 48.0* | 20§ |
| *OR7E24* | T11 | 62§ | 30§ |
| *KIAA2018* | T11 | 59§ | 27§ |
| *JAK1* | T8 | 0§ | 30§ |
| *C18ORF34* | T10 | 29§ | 30§ |

http://www.seltarbase.org

***shared mutations*** → ***shared FSP* neoantigens**

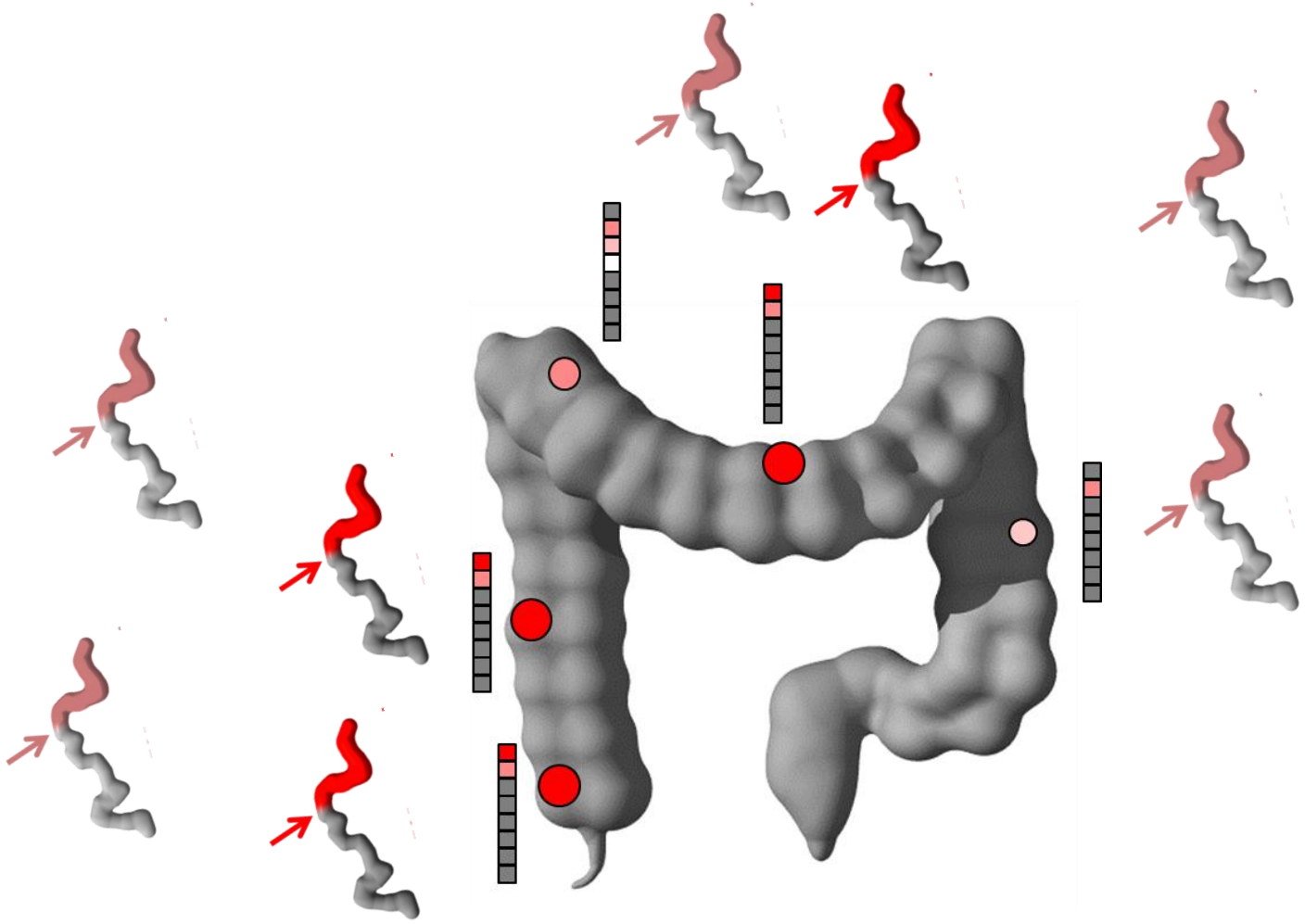
# …and predictable

SOLGÅRNED

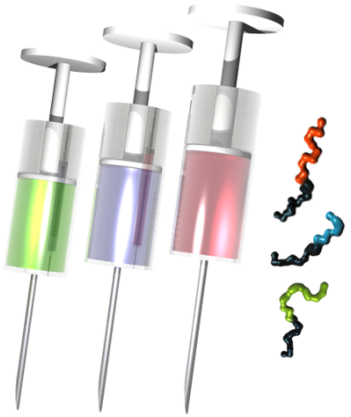
OLG ÅRN ED

SOL GÅR NED

LGÅ RNE D

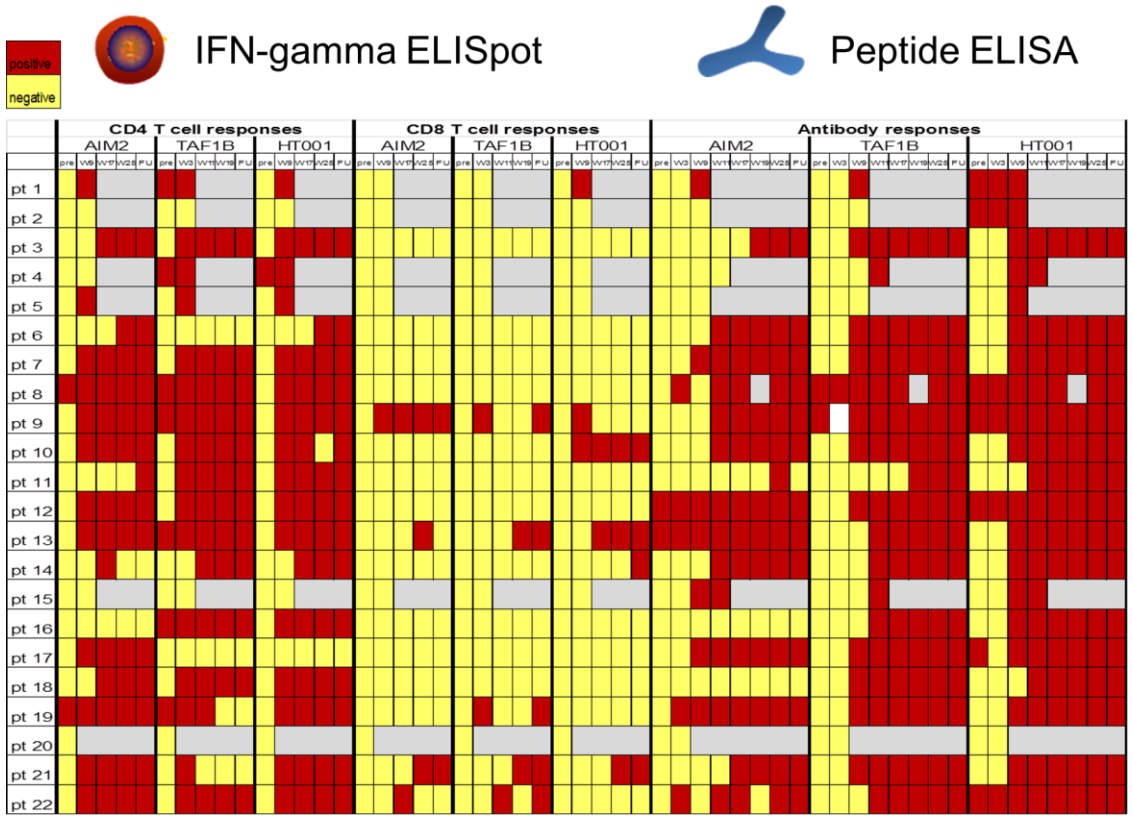


# First safety trial



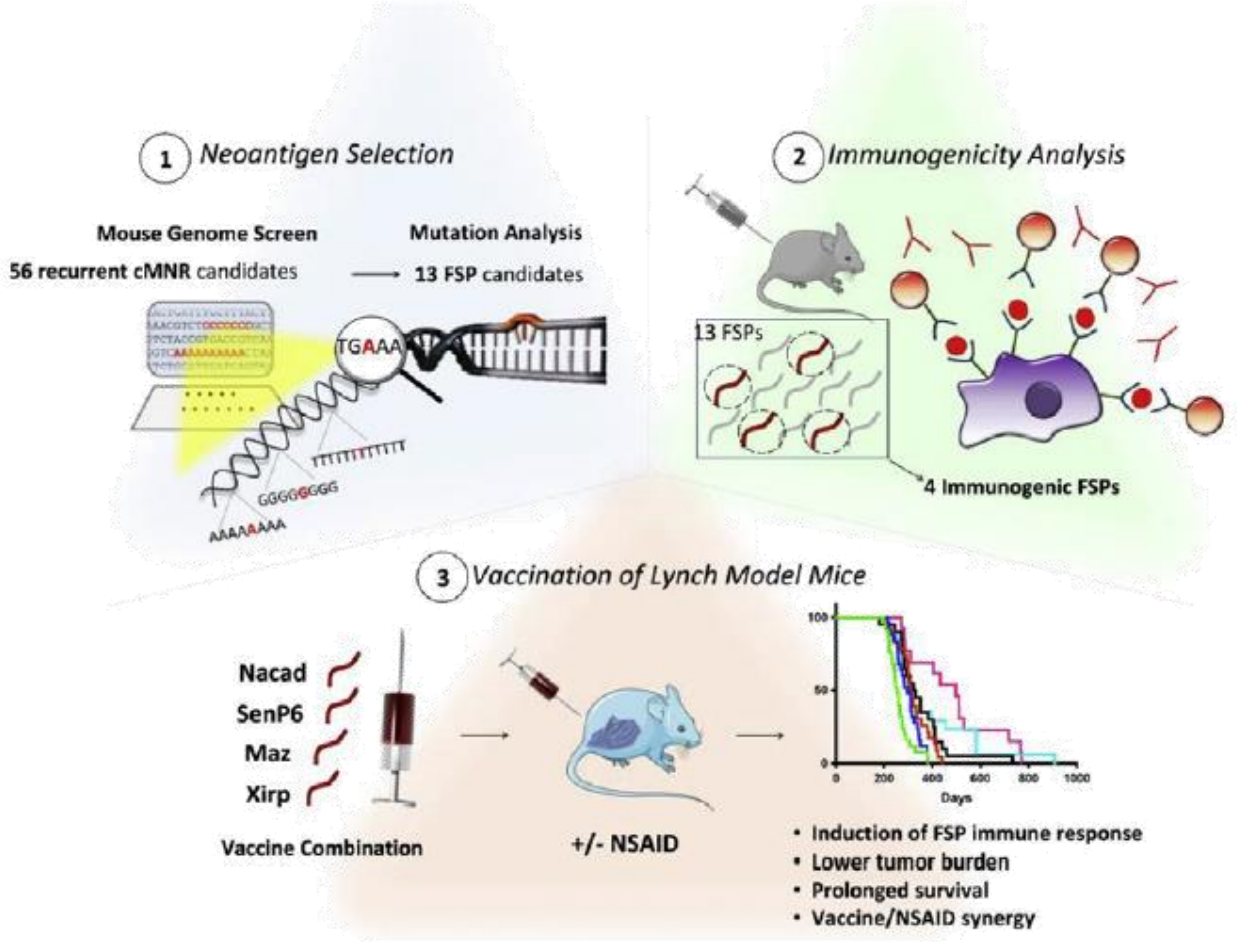
| | cMS type | Mutation frequency (CRC)§ | Mutation frequency (EC)§ |
|---|---|---|---|
| TAF1B(-1) | A11 | 74.6% | 50.0% |
| HT001(-1) | A11 | 86.2% | 92.9% |
| AIM2(-1) | A10 | 81.6% | 71.4% |

- Significant T cell and humoral immune responses in all patients vaccinated per protocol
- No systemic side effects
- Local injection site reactions in 3 patients, reflecting strong immunogenicity of the FSP antigens



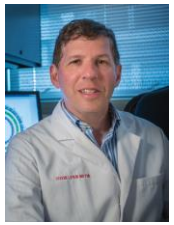

Kloor et al. *Clin Cancer Res* 2020

# First proof-of-concept




CANCER MOONSHOT

NCI *HHSN261201 0391*



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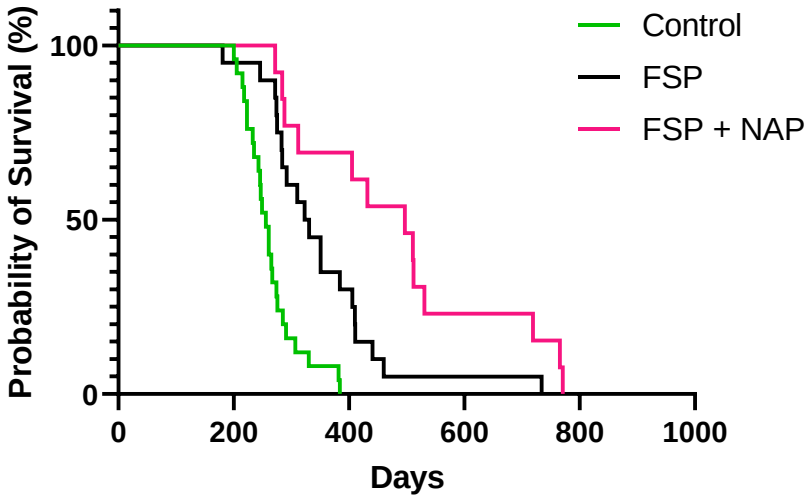
Shizuko Sei, DCP, NCI

Bob Shoemaker, DCP, NCI

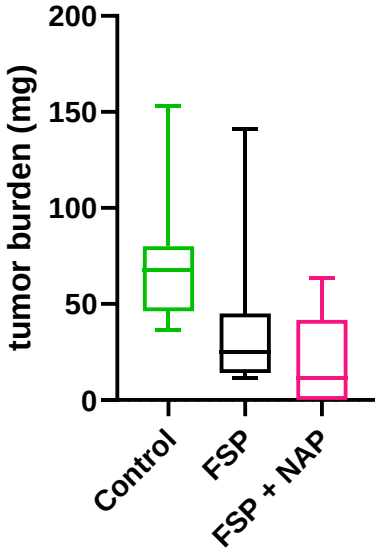
Asad Umar, DCP, NCI

Gebert et al. *Gastroenterology* 2021

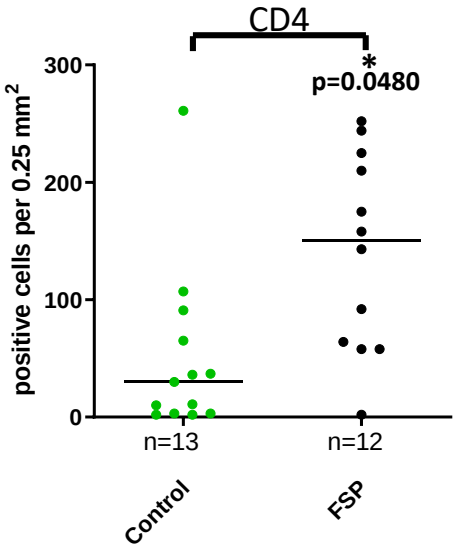
# First proof-of-concept

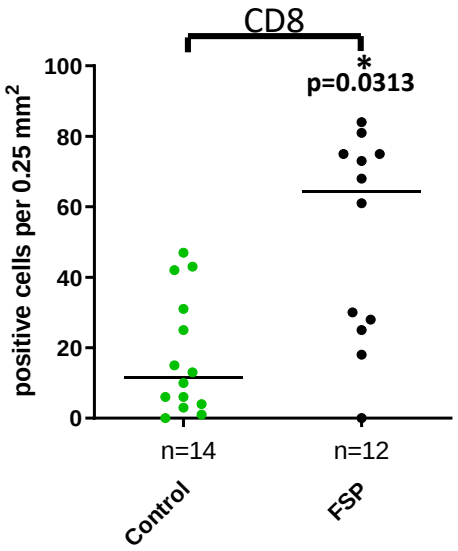



Control vs FSP, $P < 0.0001$ Control vs FSP + NAP, $P < 0.0001$



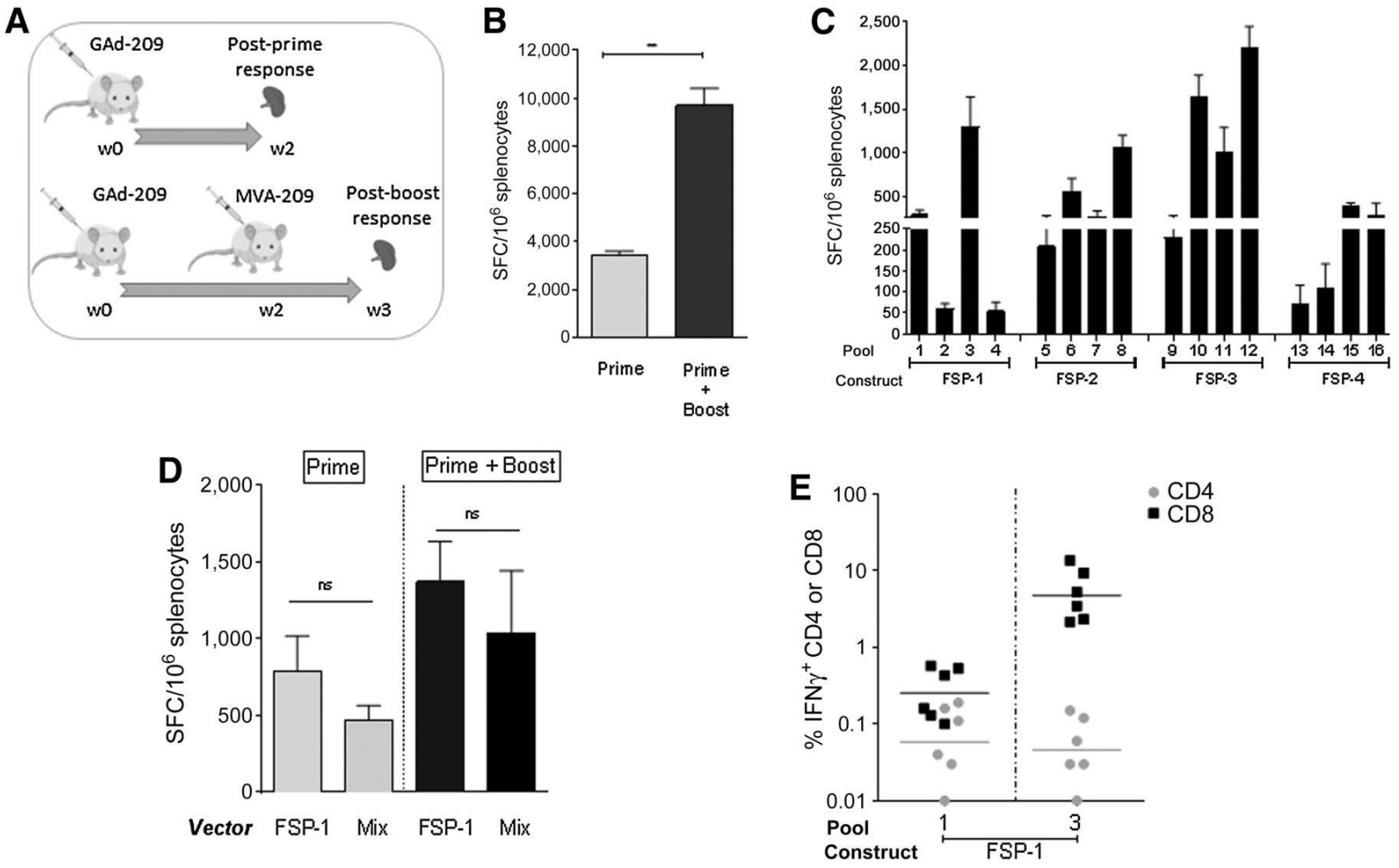

Control vs FSP, $P = 0.0024$ Control vs FSP + NAP, $P = 0.0002$



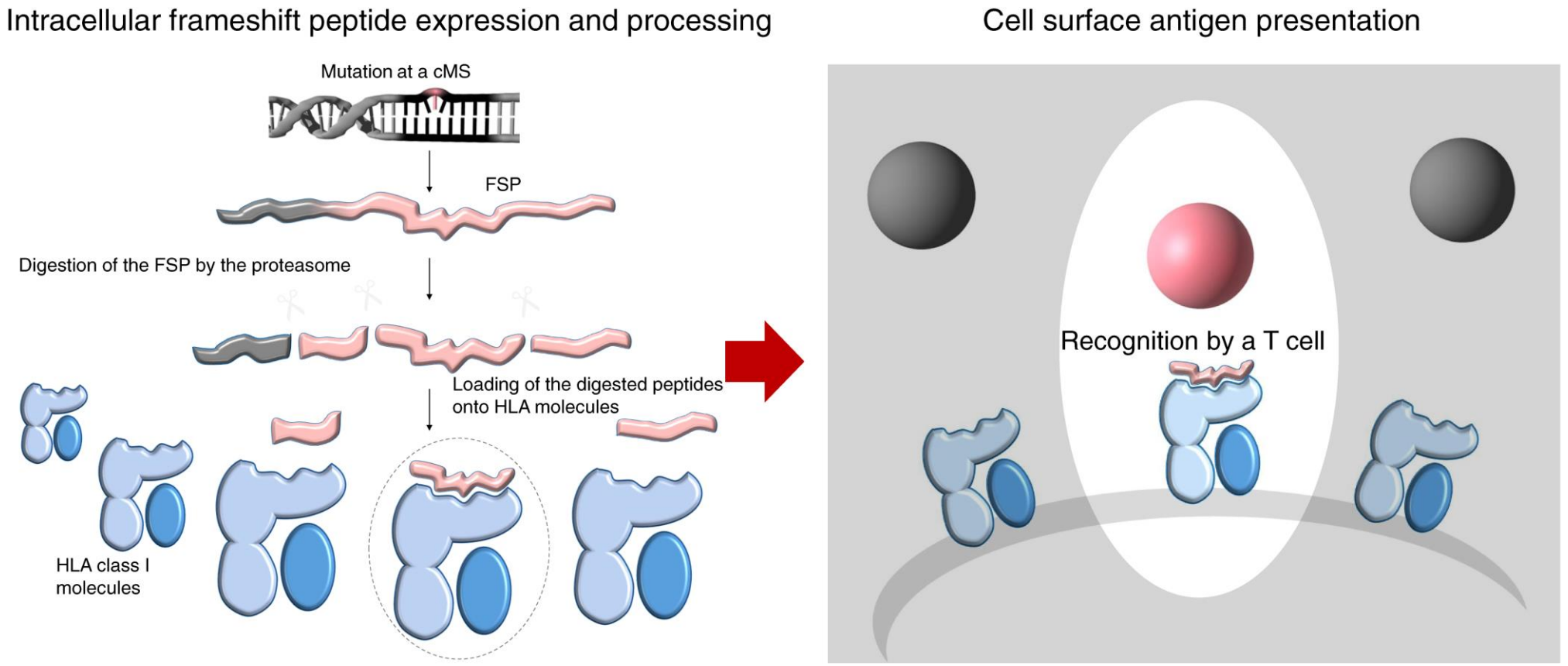

Gebert et al. *Gastroenterology* 2021

# First proof-of-concept



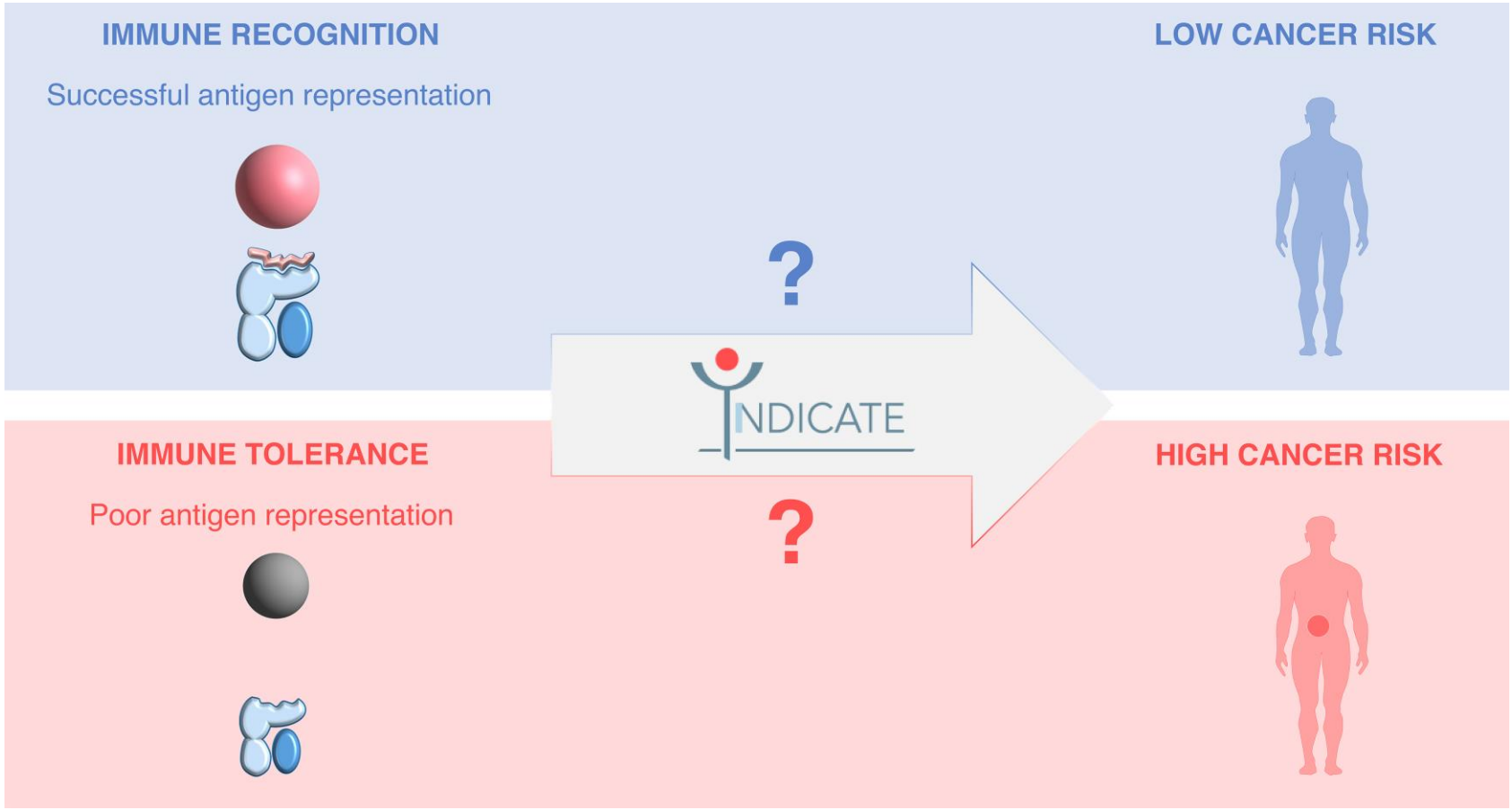

Leoni et al. *Cancer Res* 2020

# Next generation vaccines: personalized, HLA type-adapted




Ahadova et al. *Int J cancer* 2022

# HLA type as a possible risk modifier and a factor for vaccine efficiency

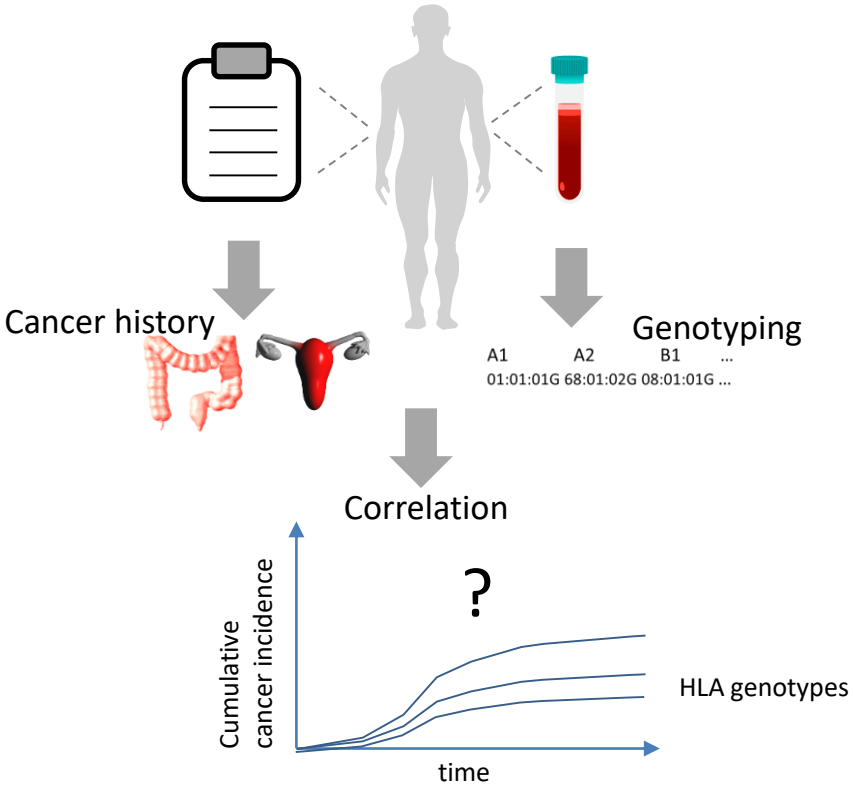



Ahadova et al. *Int J cancer* 2022

# INDICATE – **Indi**vidual **ca**ncer risk by HLA **type**

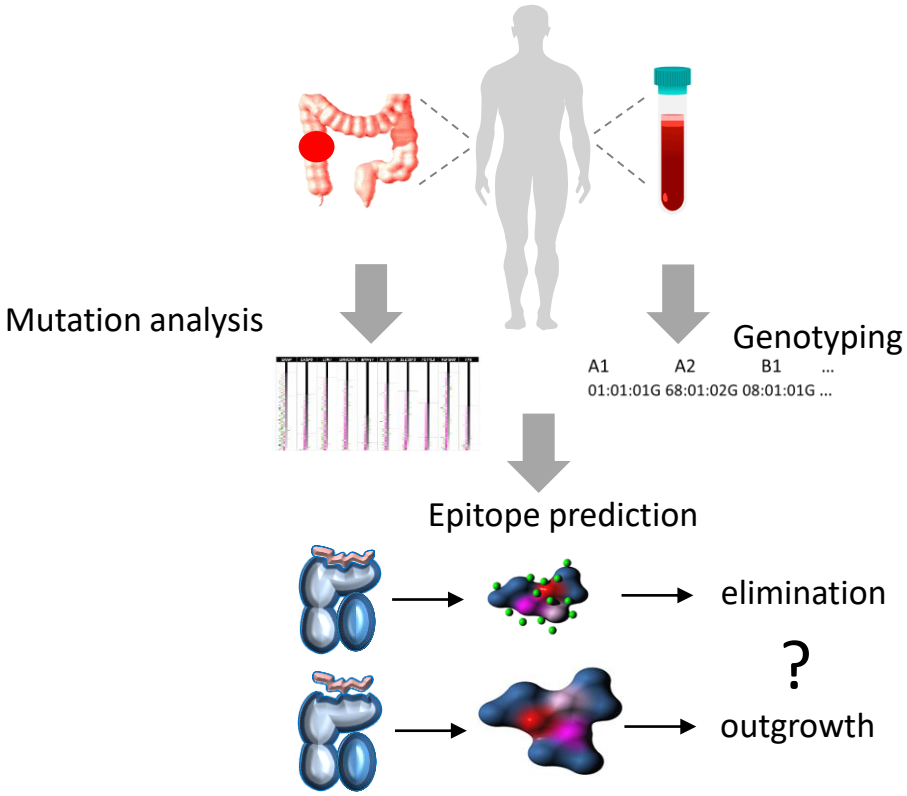
## Part 1: Epidemiological research

HLA genotype and cancer risk

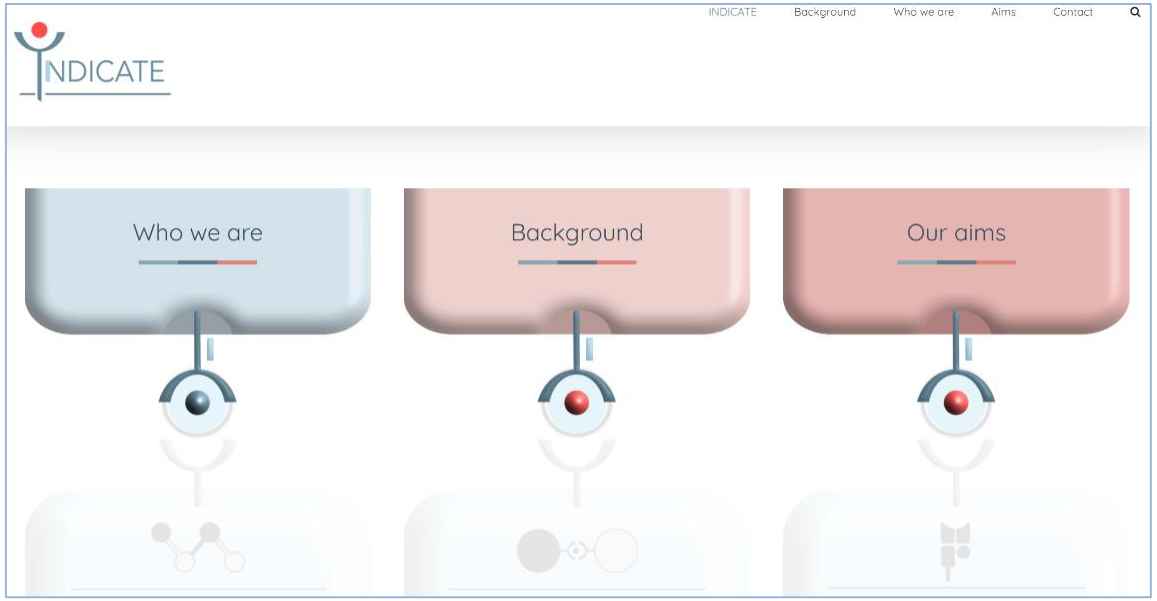


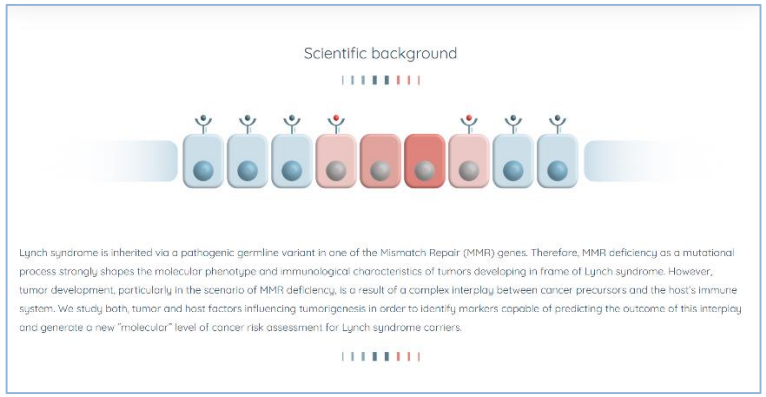

## Part 2: Molecular biology research

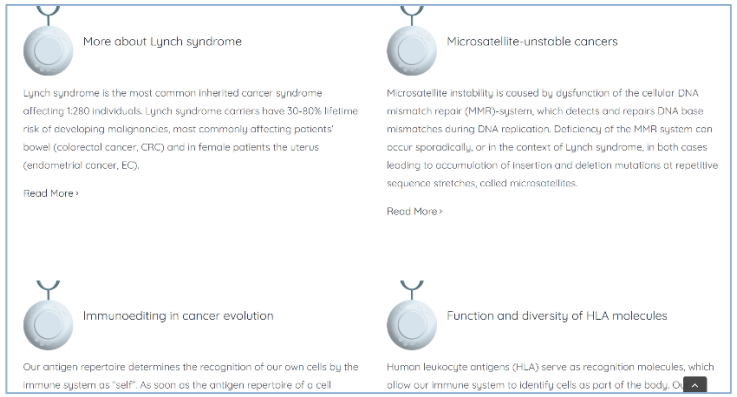
HLA-dependent tumor antigen selection



# INDICATE – **Indi**vidual **ca**ncer risk by HLA **type**




*www.indicate-lynch.org*

# Growing Network of INDICATE

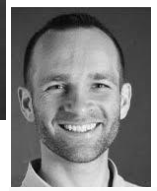
## Newcastle


John Burn


Michael Jackson


Richard Gallon


Mauro Santibanez-Koref



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Johannes Witt


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Saskia Haupt


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## Helsinki


Toni Seppälä


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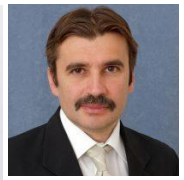
Jaana Koski-Alhainen


Kirsi Pylvänäinen

## Budapest


Vince Grolmusz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Noah Helderman


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Ian Frayling
Julian Sampson

John Burn
Richard Gallon

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(German Cancer Aid)

**German Consortium for Familial Intestinal Cancer**