



HEIDELBERG
UNIVERSITY
HOSPITAL



MOLECULAR ROUTES OF COLORECTAL CANCER PROGRESSION IN LYNCH SYNDROME

Danish HNPCC Symposium

October 12th 2023

Aysel Ahadova

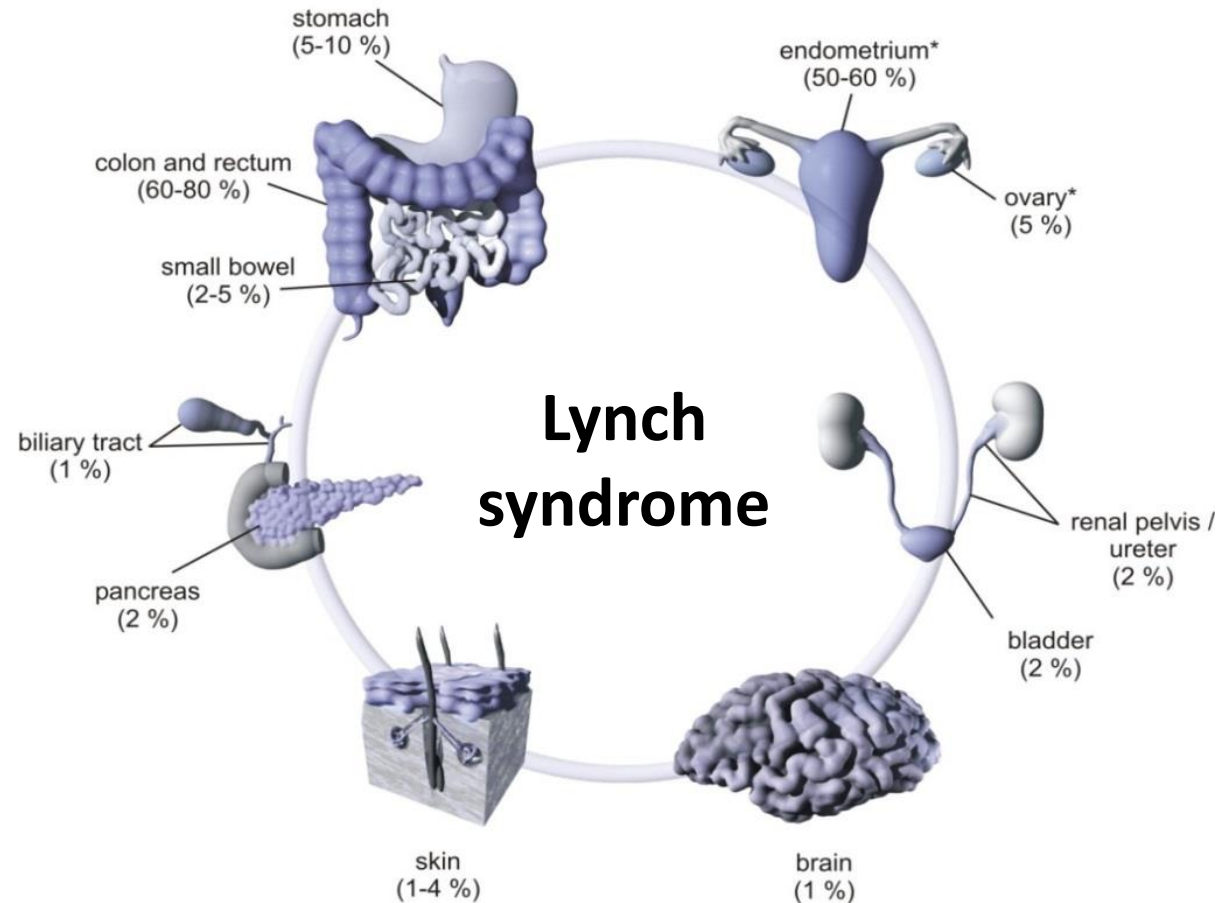
Department of Applied Tumor Biology, Institute of Pathology
Heidelberg University Hospital
Im Neuenheimer Feld 224, 69120 Heidelberg, Germany



Conflicts of interest

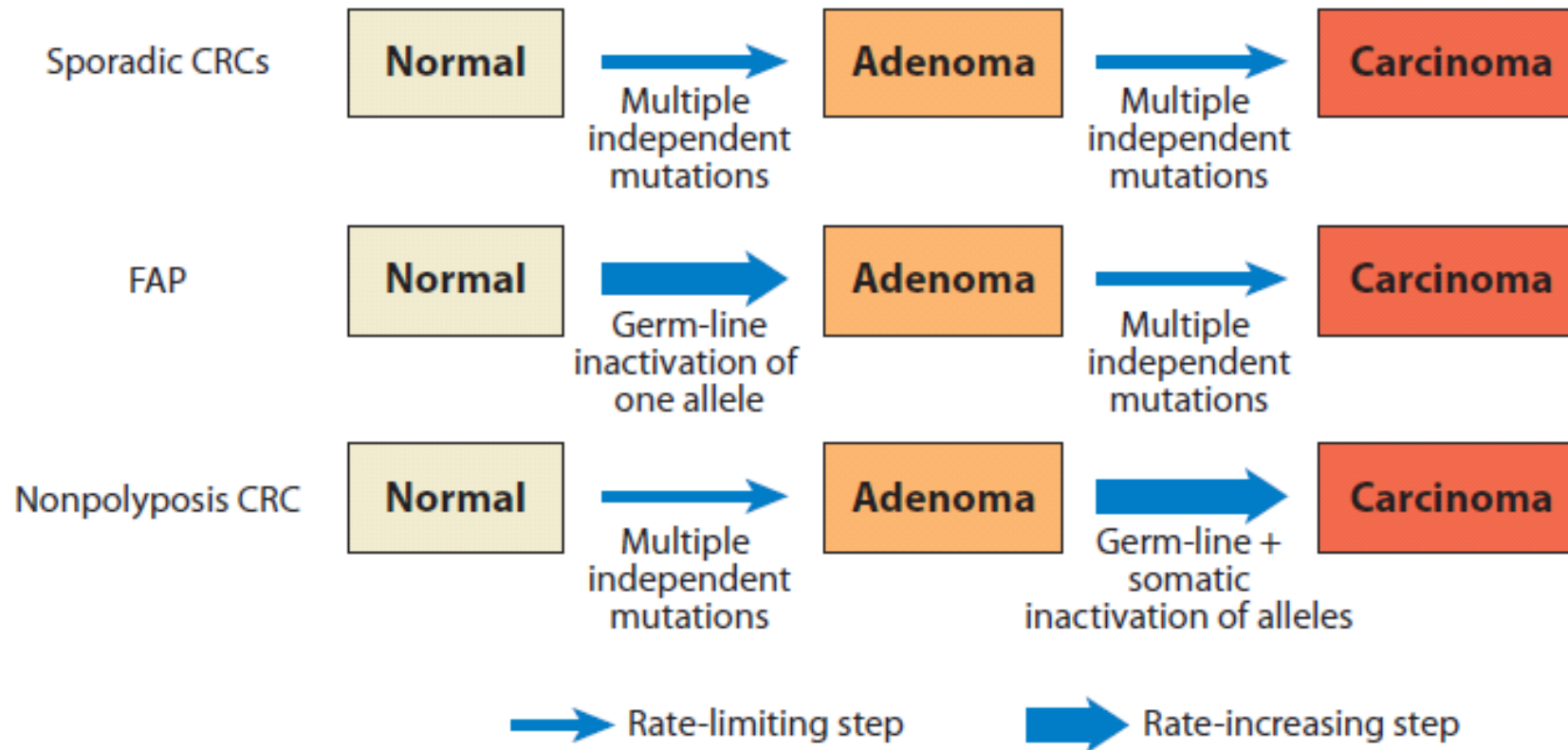
I have no potential conflict of interest to report

Patients with cancer predisposition require prevention



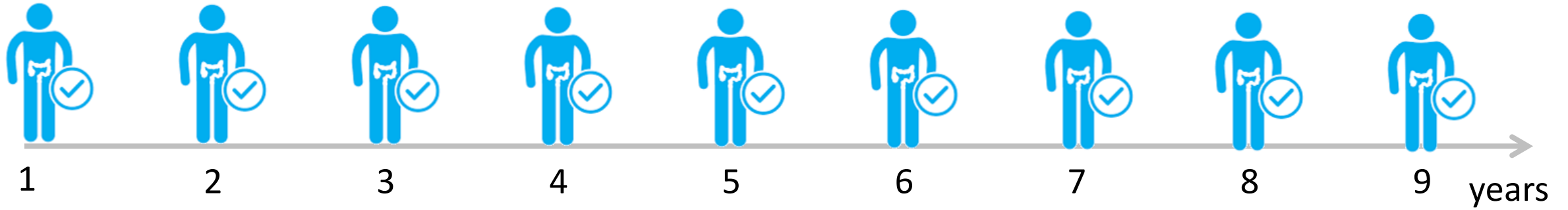
Adenoma-carcinoma dogma

“lesions that project above the surrounding mucosa are commonly termed polyps”

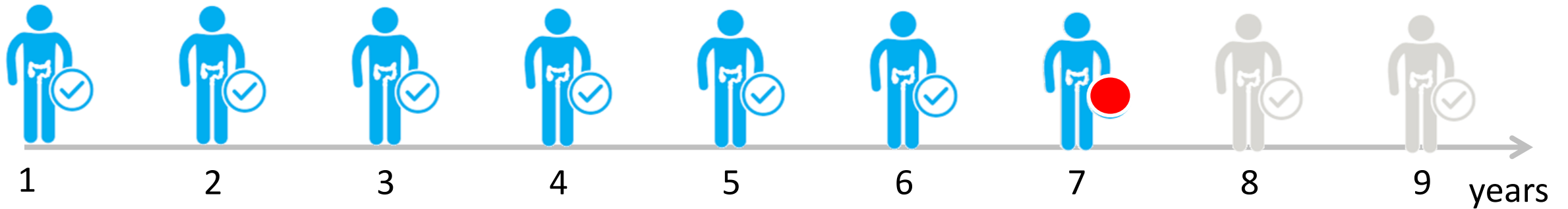


Fearon ER. Annu. Rev. Pathol. Mech. Dis. 2011
Jackman RJ, Mayo CW. *Surg Gynecol Obstet.* 1951

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

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

25

30

35

40

45

50

55

60

65

70

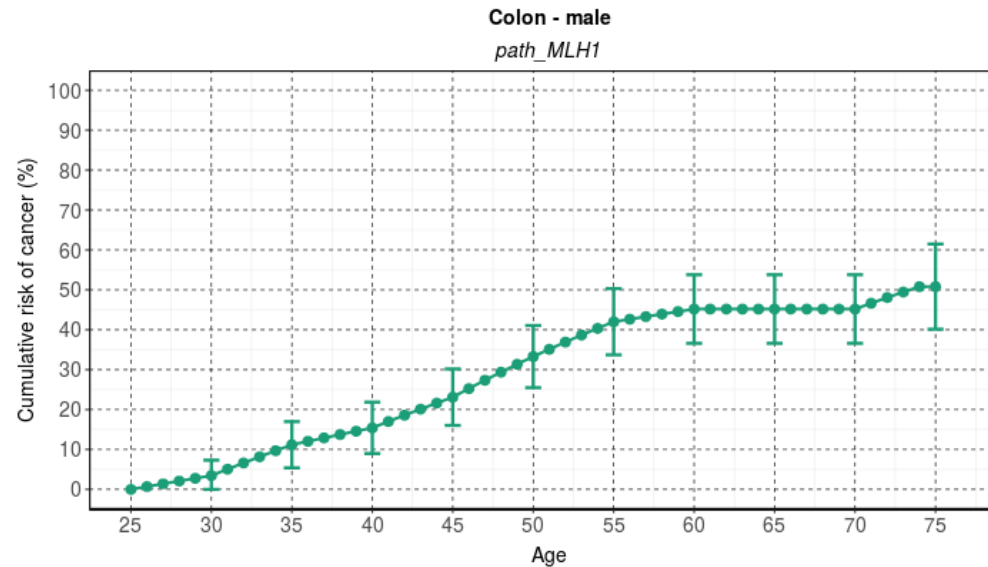
75

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



Mev
Dominguez-
Valentin



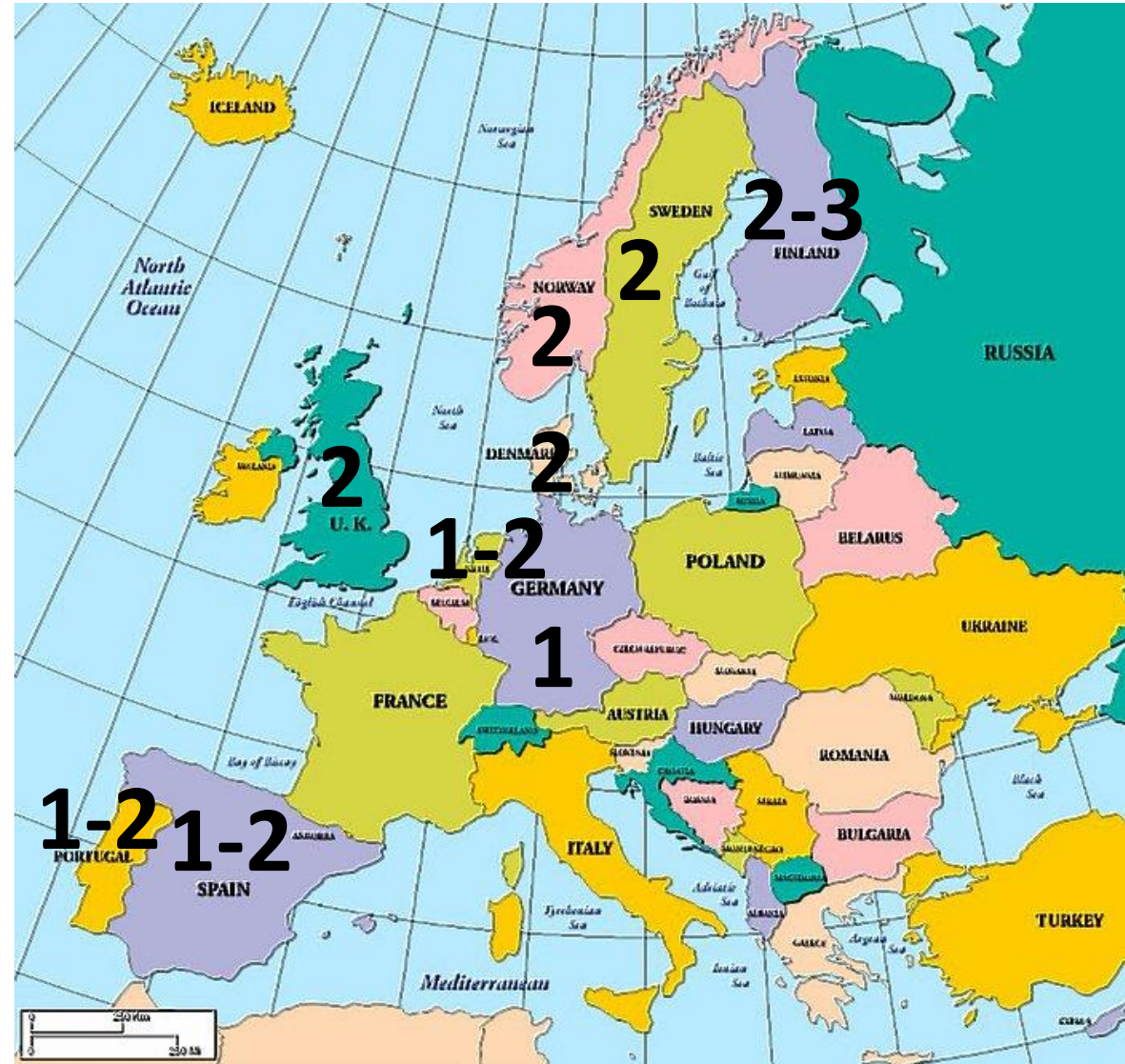
Pål Møller

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

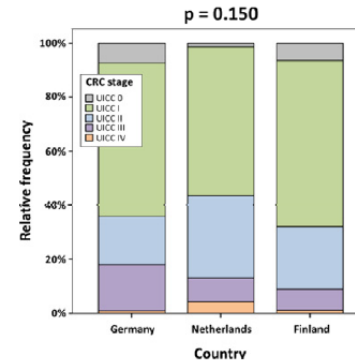
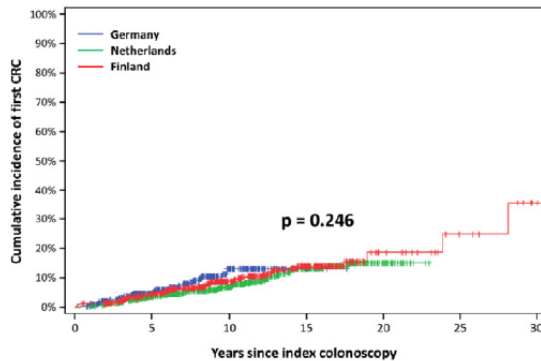
Germany
1-yearly

The Netherlands
1-2-yearly

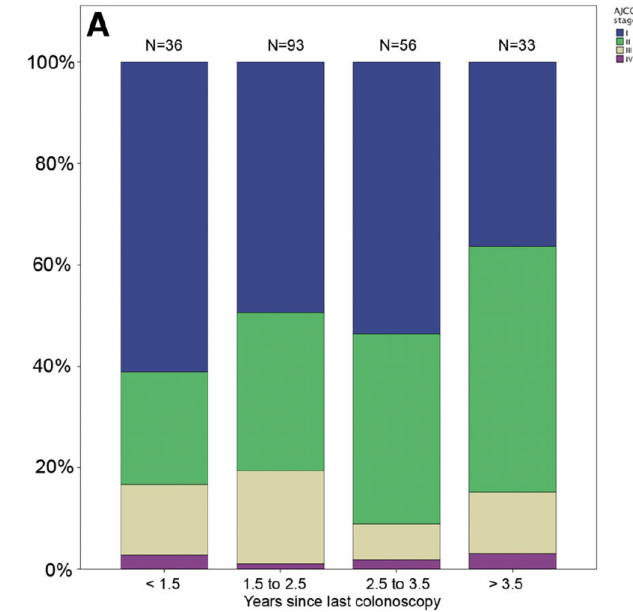
Finland
2-3-yearly

Outcome in 2747 patients

No reduction of
CRC risk or tumor
stage with shorter
intervals



Gastroenterology

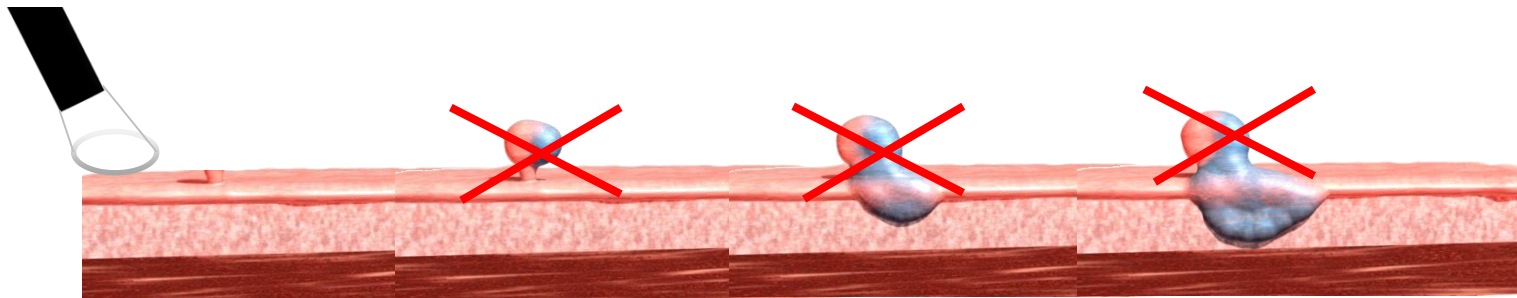
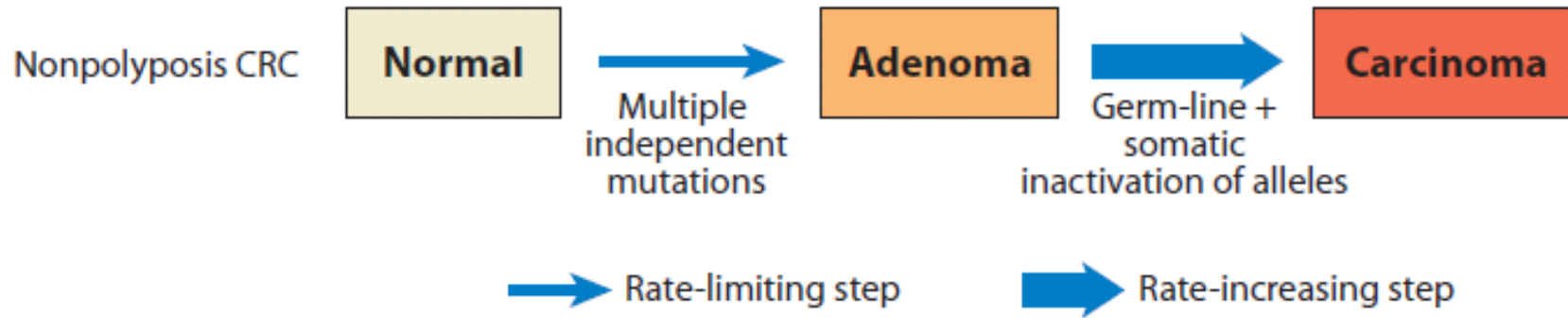


PLSD

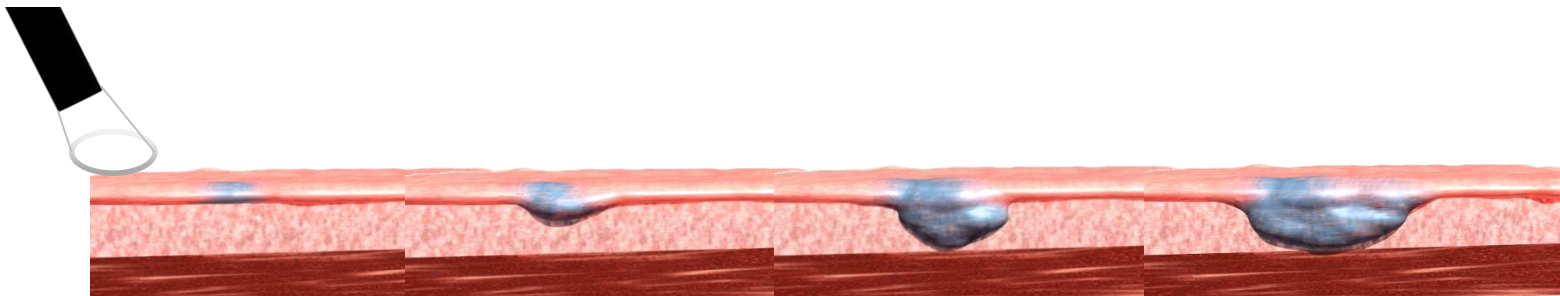
3-country study

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

It does not add up



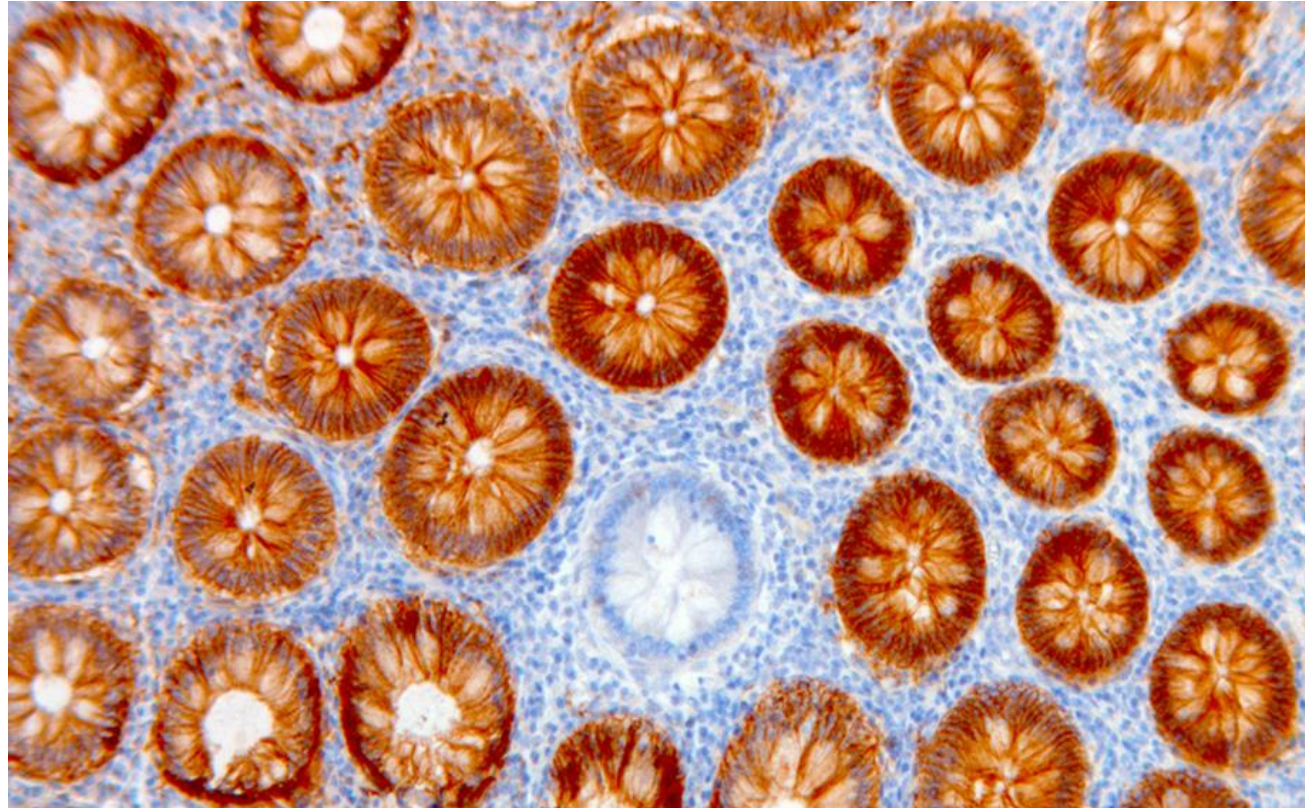
classical progression of CRC



non-polypous progression of CRC?

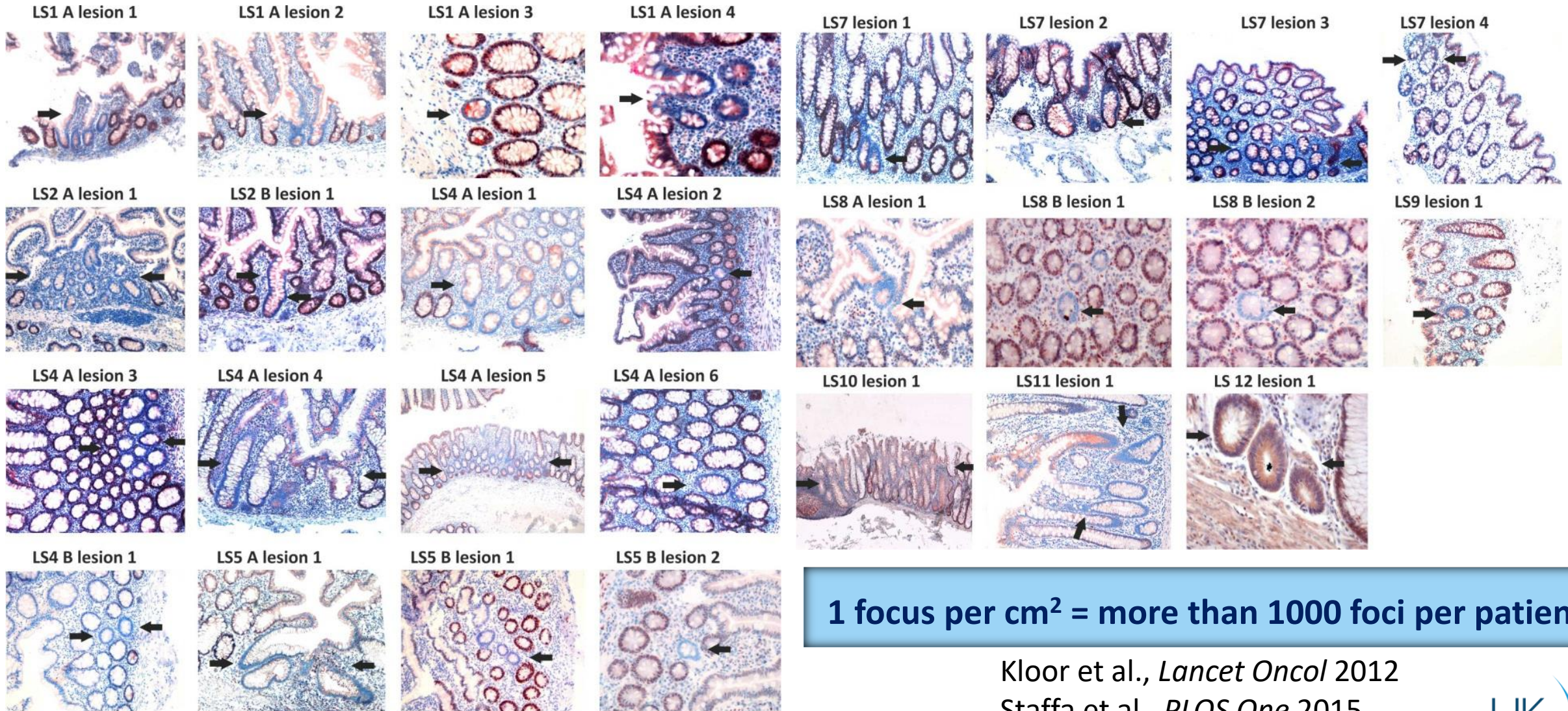
Non-polypous precursors: evidence from pathology

MisMatch Repair-Deficient Crypt Foci



EPCAM staining

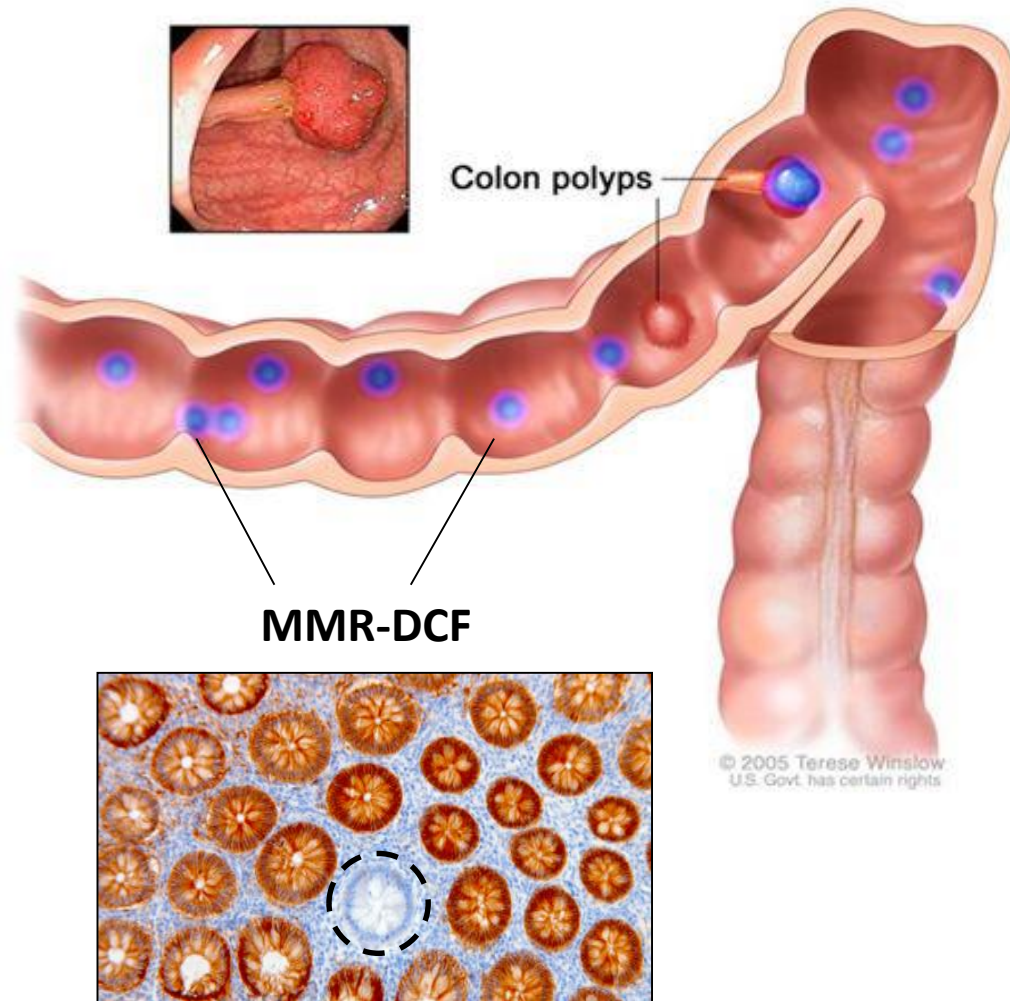
Non-polypous precursors: evidence from pathology



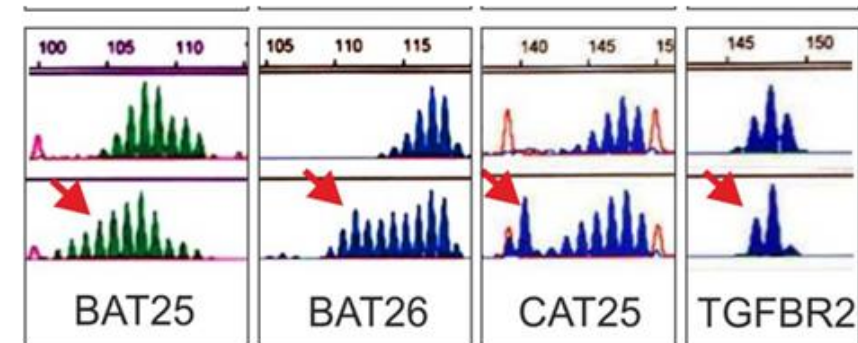
1 focus per cm² = more than 1000 foci per patient

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

Cancer-driving potential of MMR-DCF



MMR-deficient Crypts (Loss of MSH2/EPCAM)

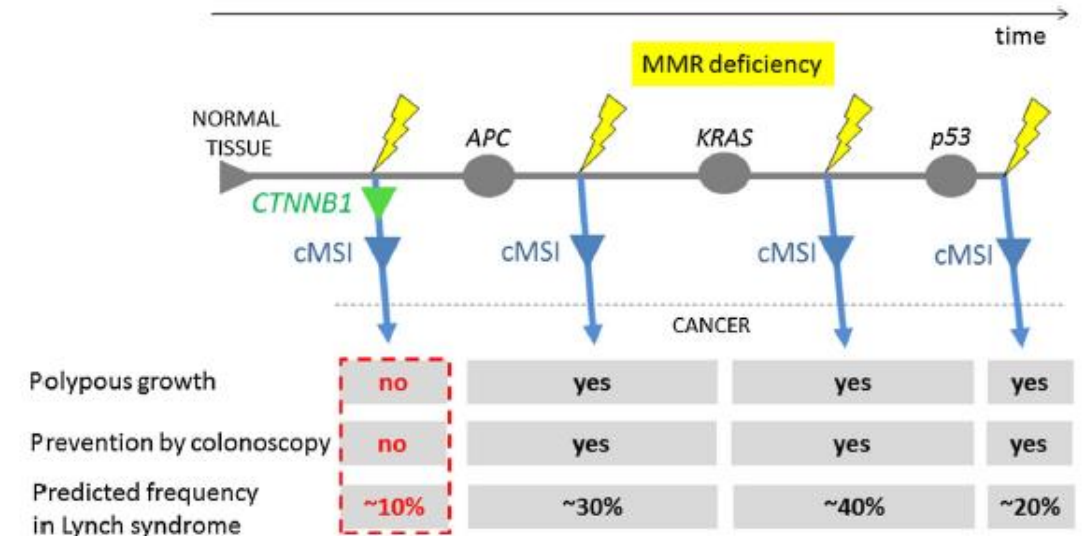
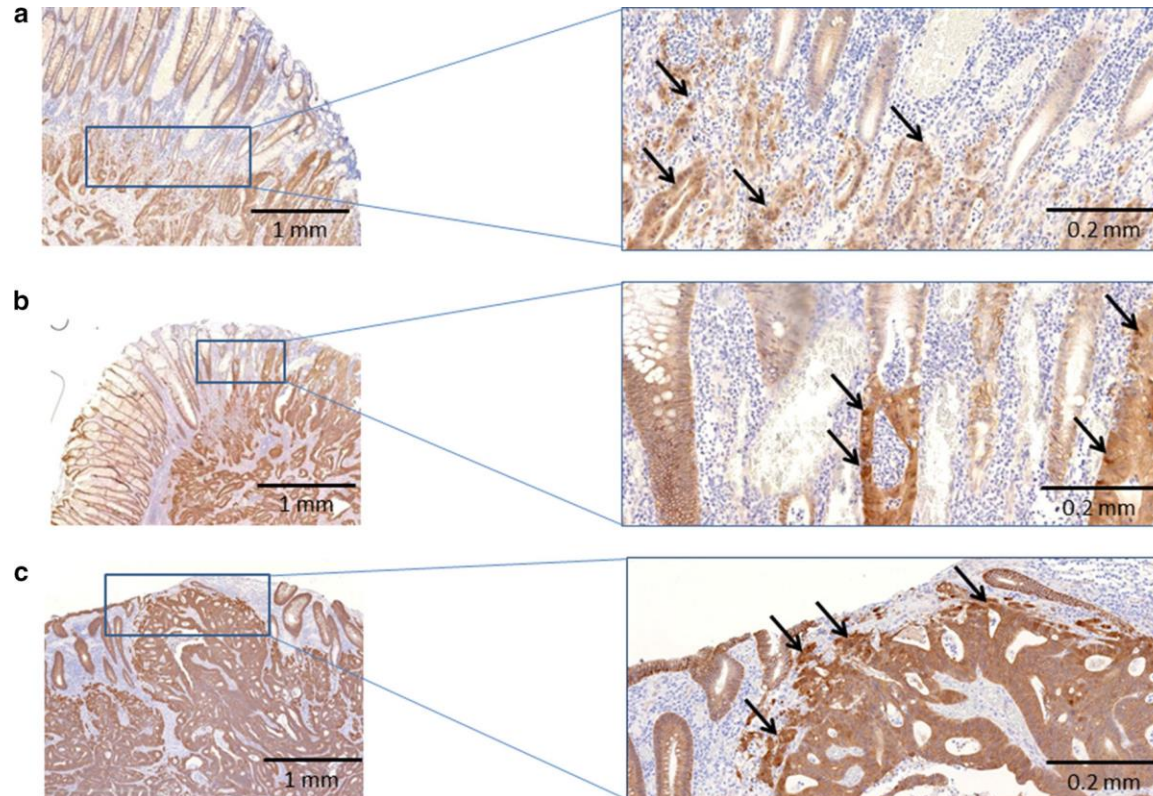
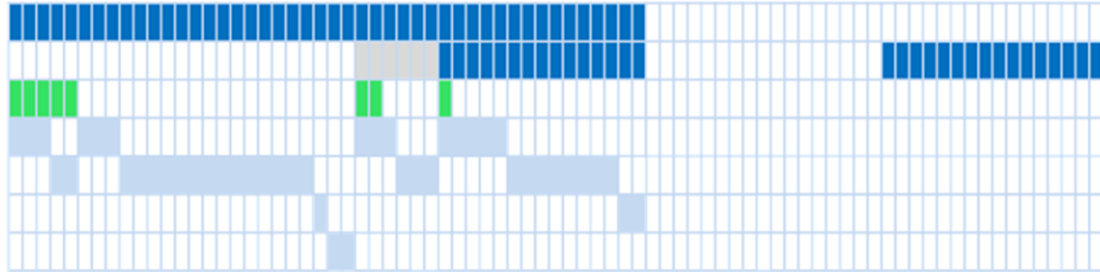


MSI

Frameshift Peptide Neoantigens

Can LS CRC progress from a non-polypous precursor?

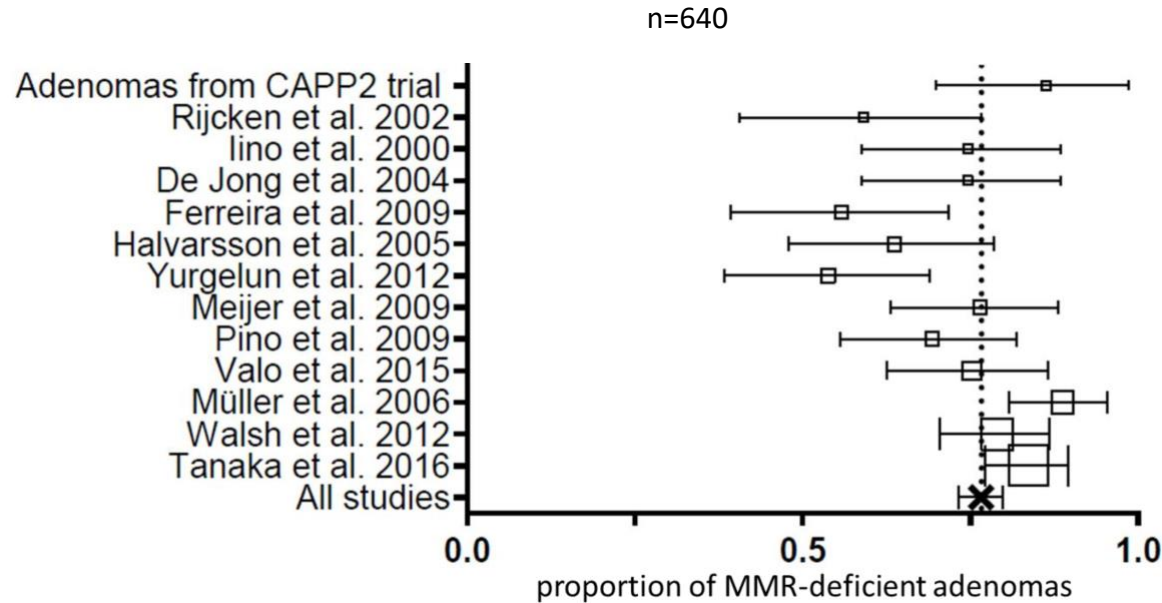
Lynch syndrome
evidence of polypous growth
CTNNB1 mutation
MLH1 mutation
MSH2 mutation
MSH6 mutation
PMS2 mutation



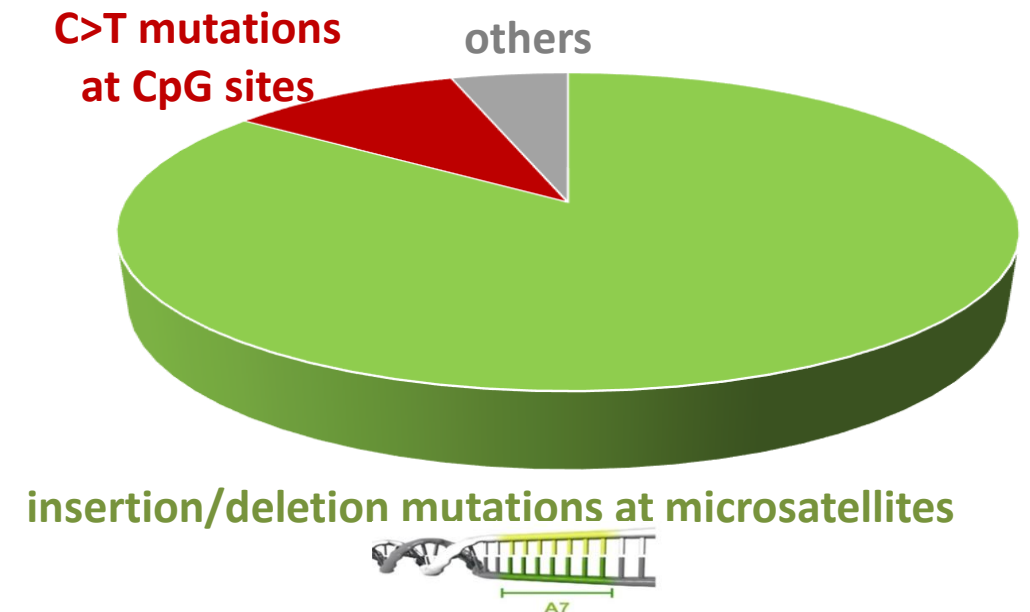
Ahadova et al. *Fam Cancer* 2016

When does the MMR deficiency occur?

Evidence from adenomas



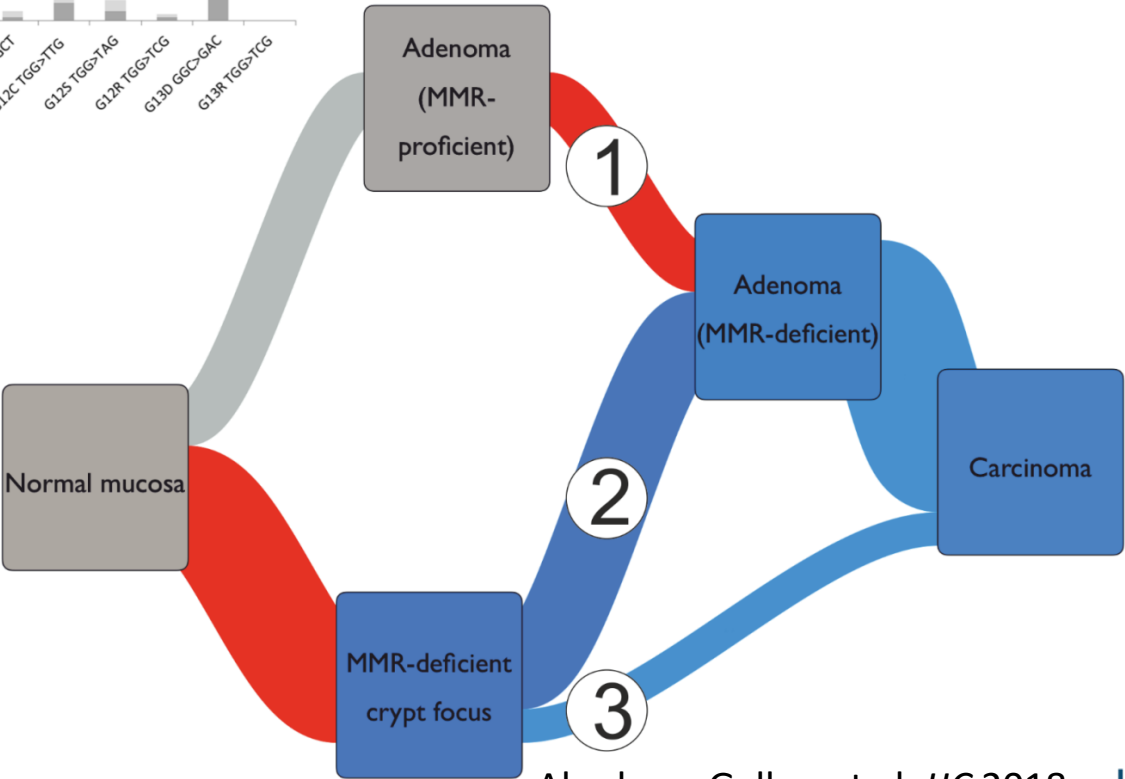
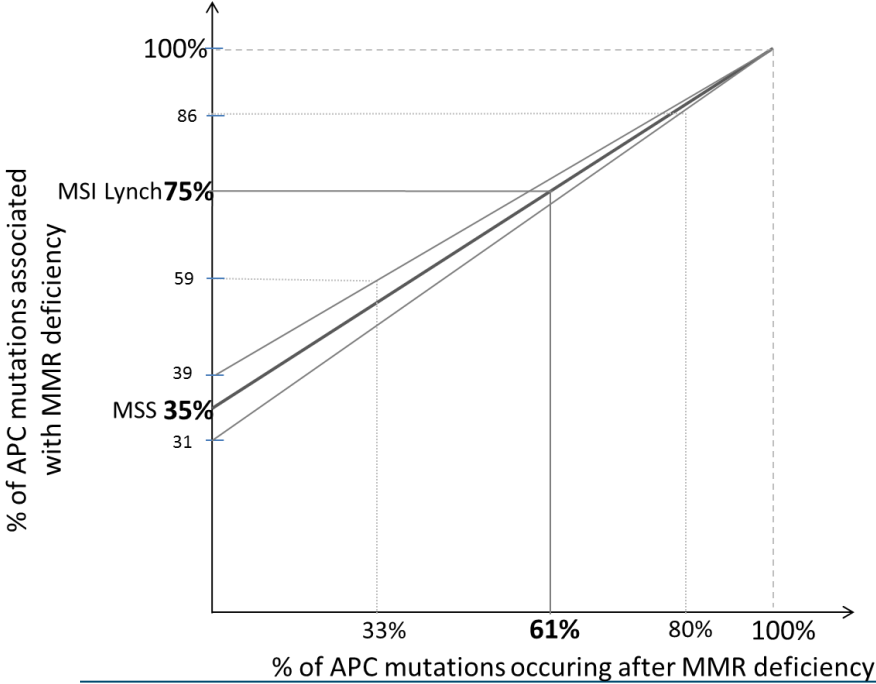
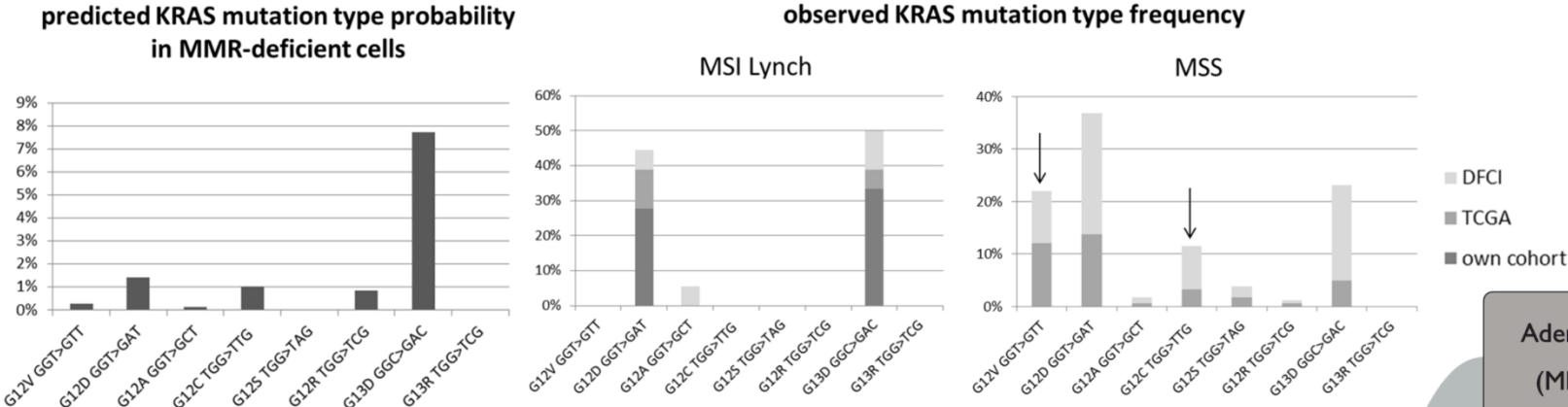
Evidence from carcinomas



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

Ahadova, Gallon et al. *IJC* 2018

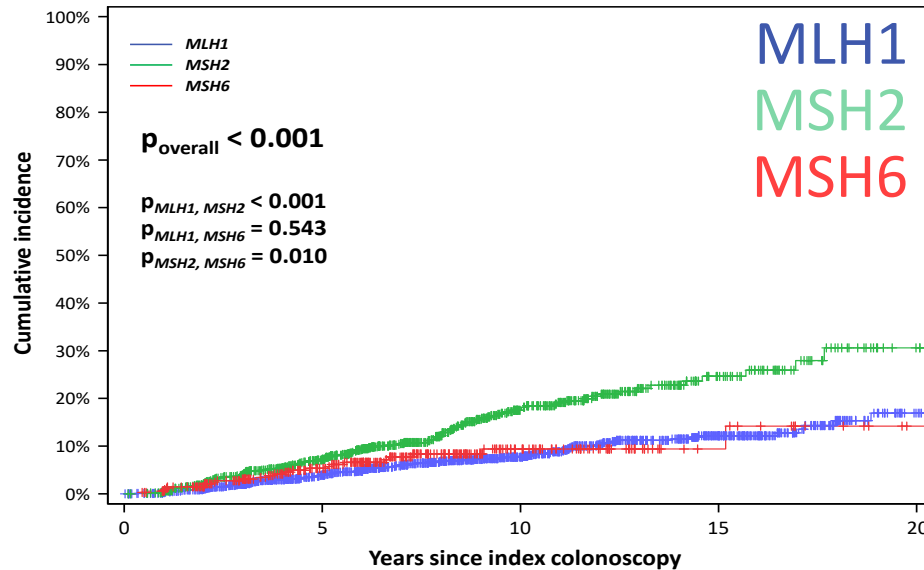
Mutational signature of MMR deficiency in initiating somatic mutations



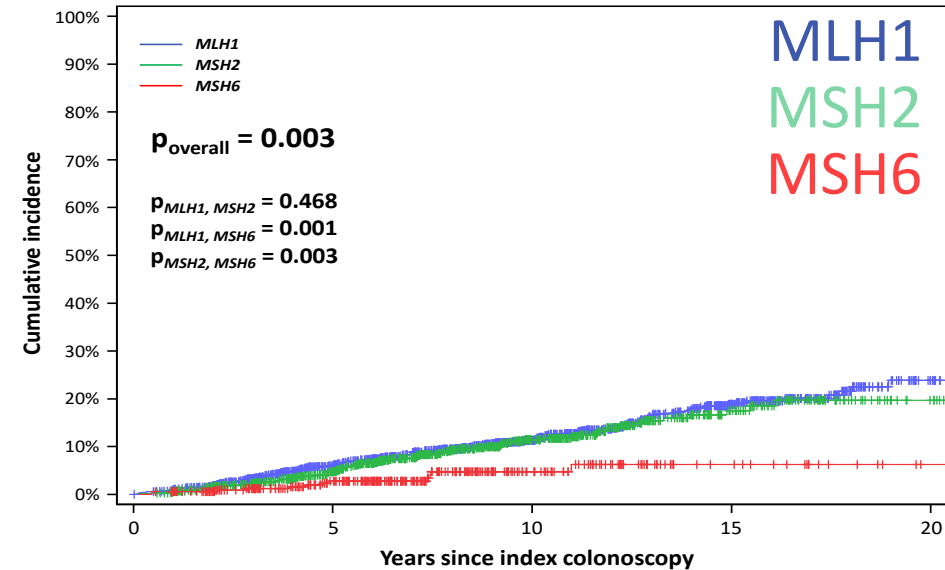
Ahadova, Gallon et al. *IJC* 2018

Incident cancer risk is different among different MMR variant carriers

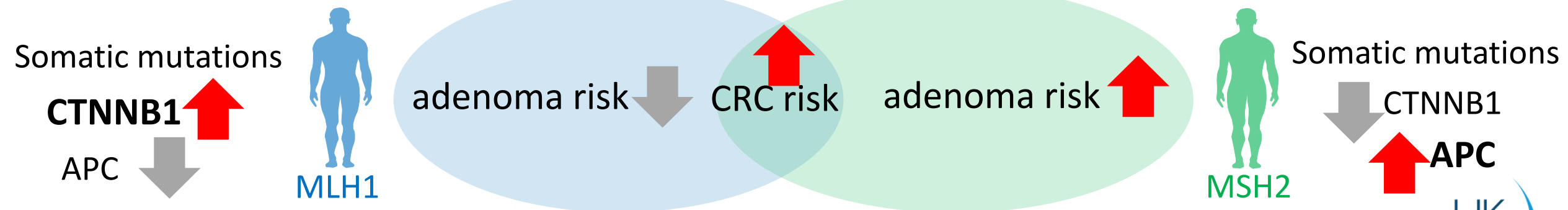
Risk for advanced adenoma



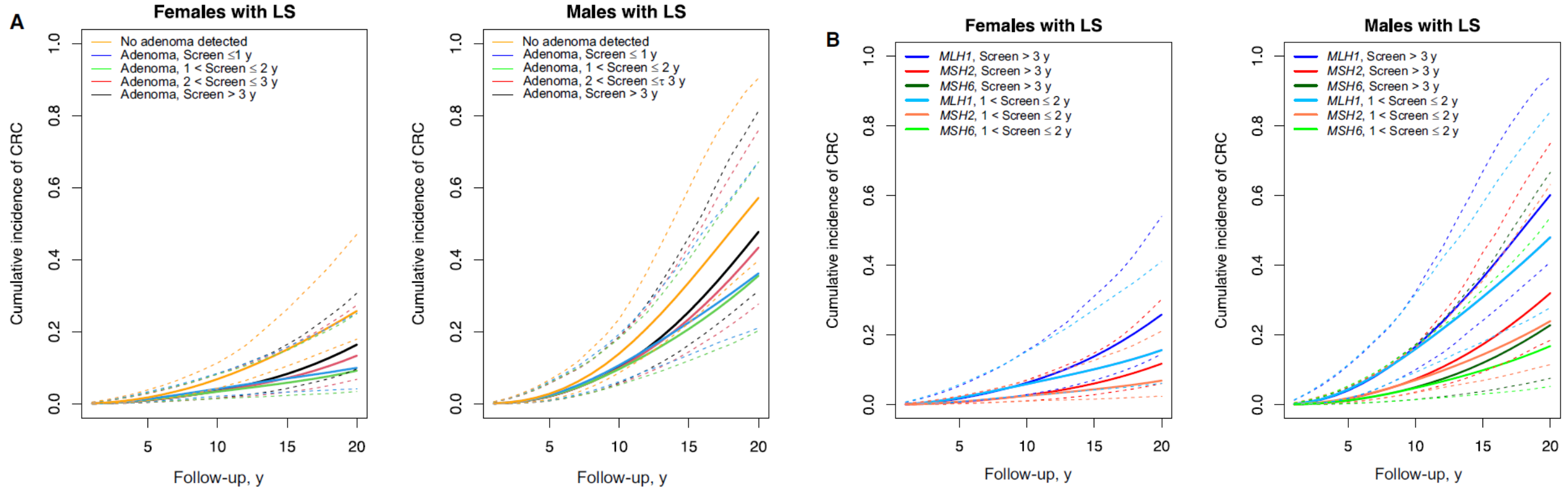
Risk for incident cancer



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



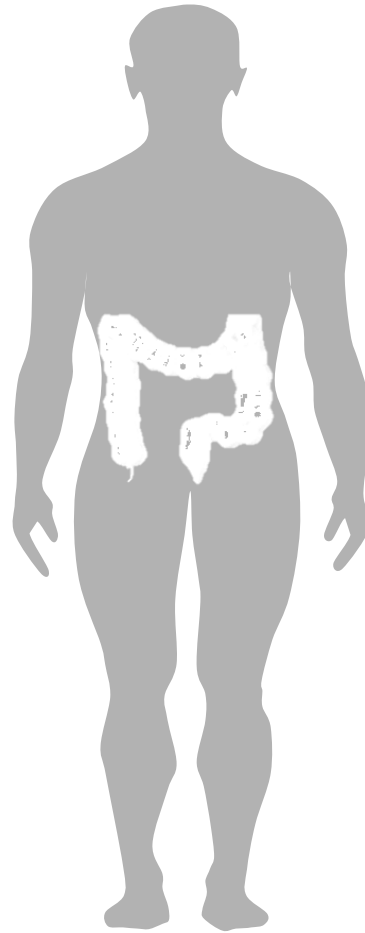
MLH1 carriers and carriers without adenomas at first colonoscopy show highest CRC incidence under surveillance



Aronson et al. *JNCI* 2023

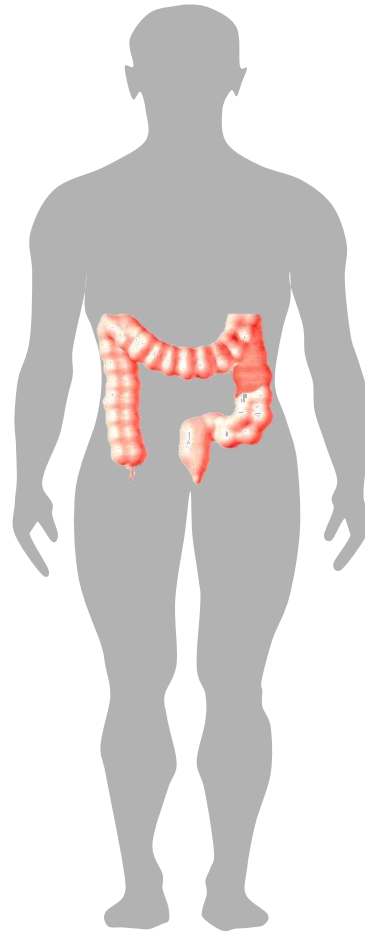
CTNNB1 is an oncogene, but not a classical one

CTNNB1 requires a
monoallelic hit for
activation



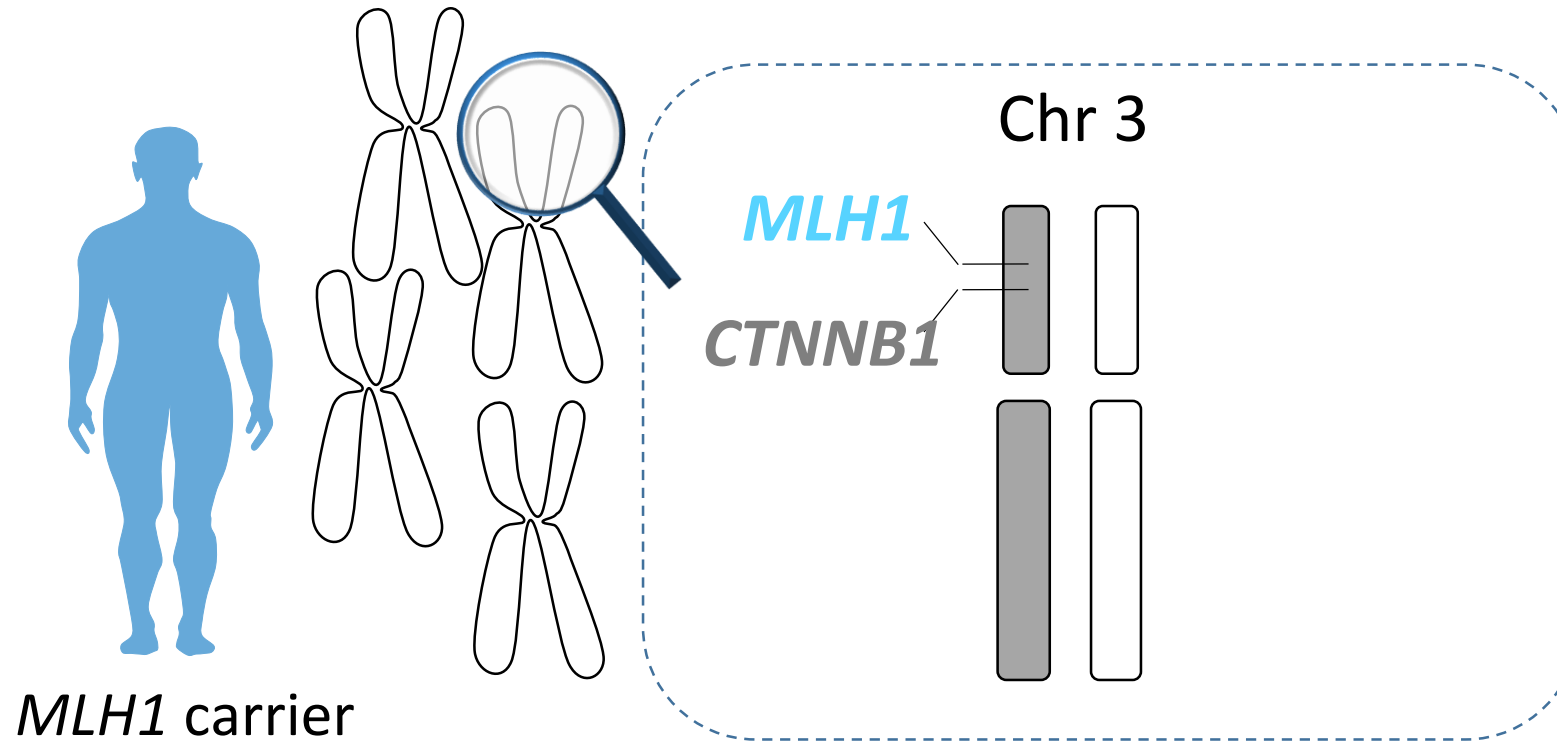
CTNNB1 is an oncogene, but not a classical one

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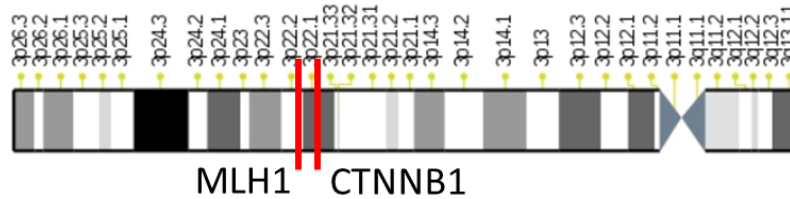
CTNNB1 requires a biallelic hit for activation

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

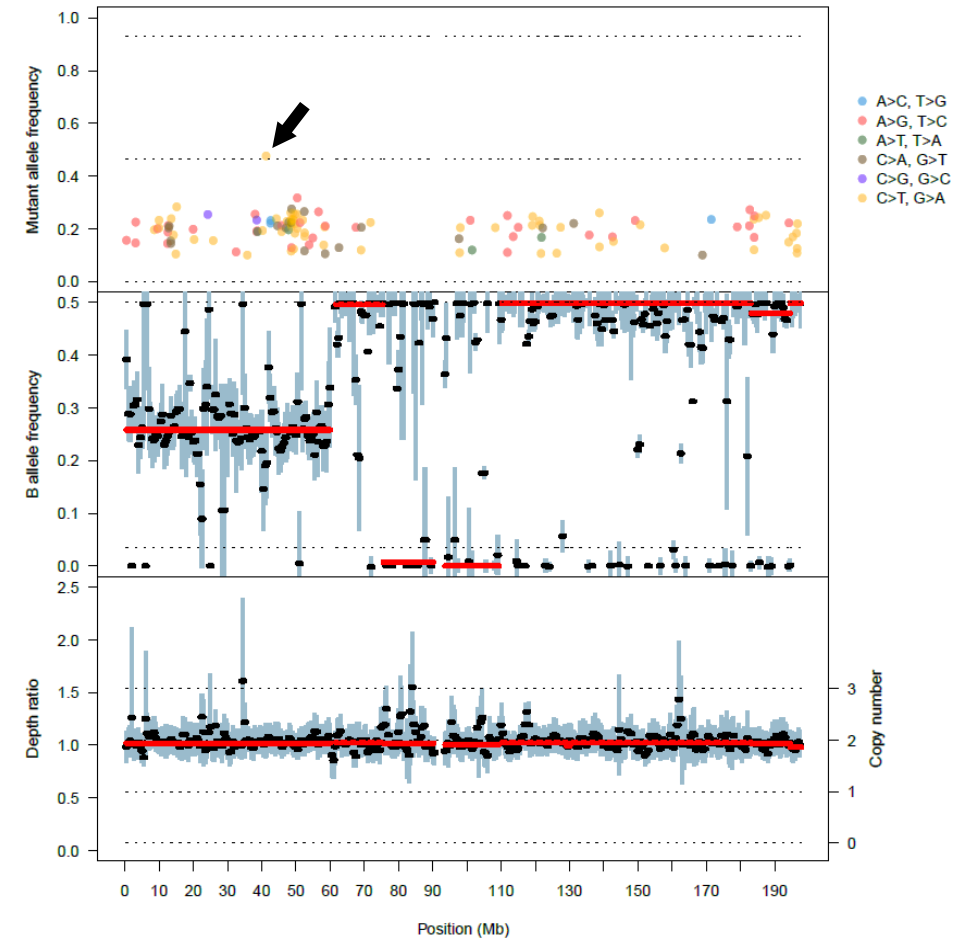


Single genetic event switches *MLH1* off and *CTNNB1* on?

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

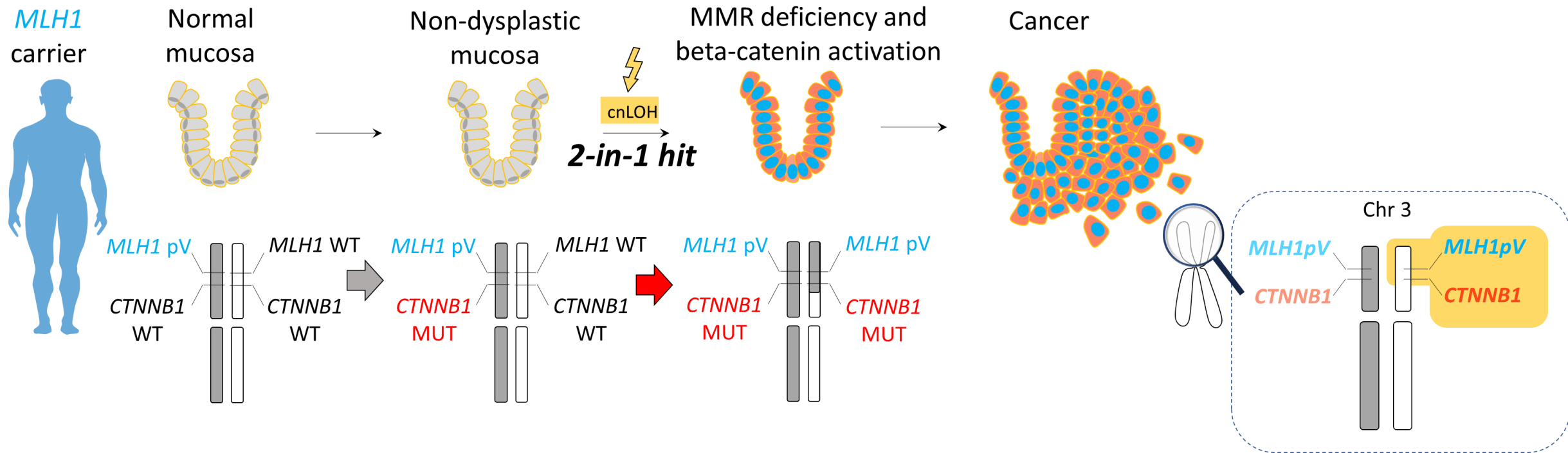


Ca14	3pter	52 Mbp	3p21.2
Ca15	3pter	49 Mbp	3p21.31
Ca17	3pter	54 Mbp	3p21.1
Ca19	3pter	59 Mbp	3p14.2
Ca20	3pter	56 Mbp	3p14.3



Ahadova et al. *Gastroenterology* 2023

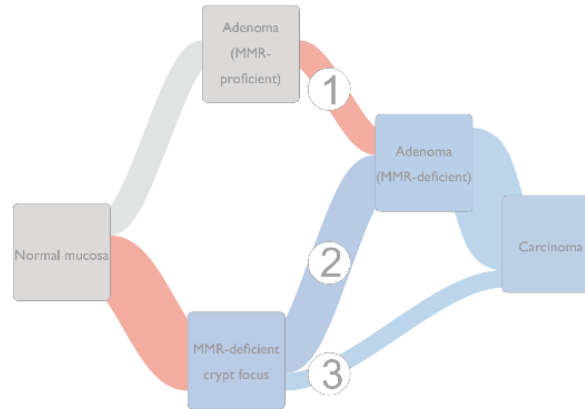
Two-in-one hit model of carcinogenesis



Ahadova et al. *Gastroenterology* 2023

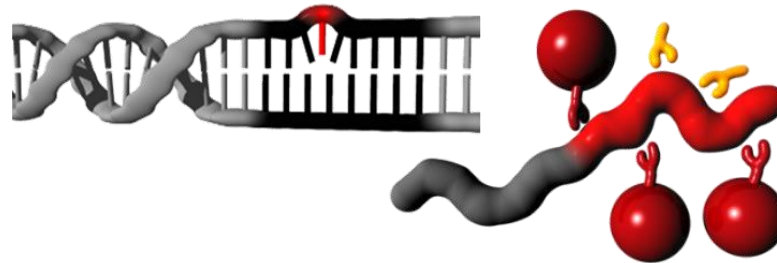
Potential explanations for the limited effect of colonoscopy

pathway heterogeneity/other precursors



unpreventable cancer?

MSI pathogenesis/high immunogenicity/strong immune infiltration



lesion regression?

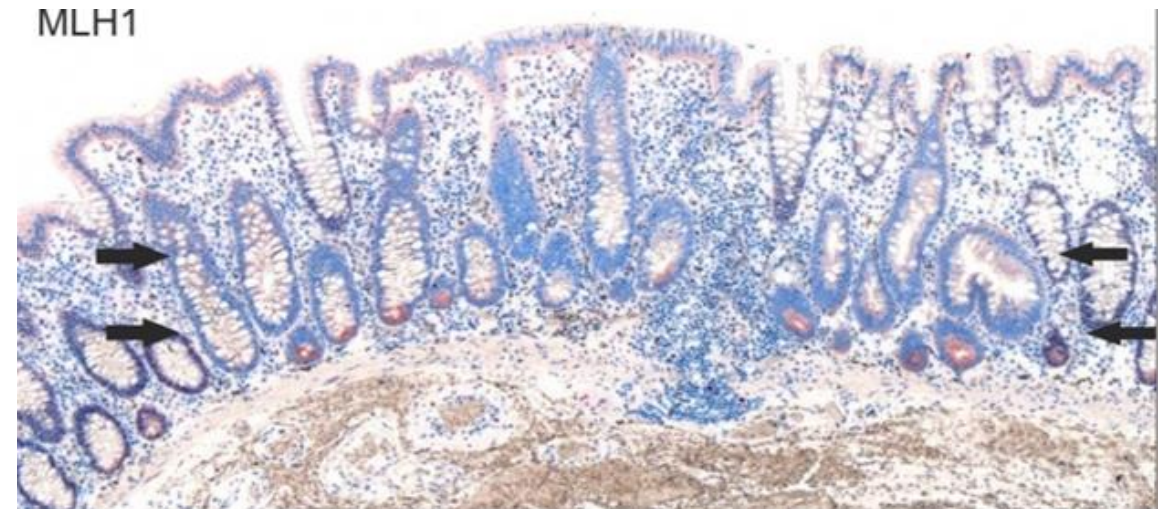
Low probability of progression from MMR-DCF

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

>1000 MMR-deficient foci per patient



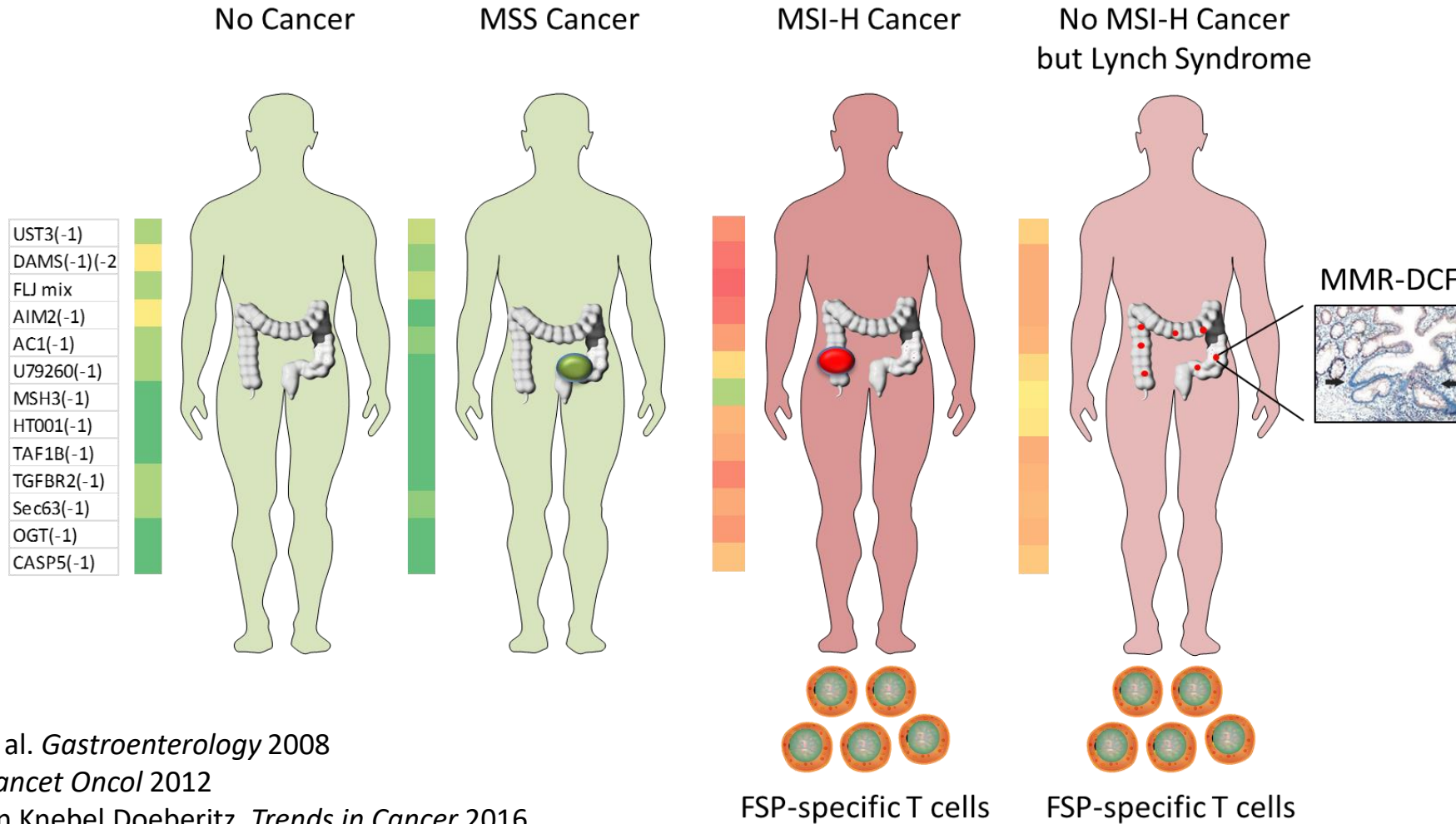
<0.5 progressing to cancer



Kloor et al. *Lancet Oncol* 2012

What happens to all those MMR-DCF?

Systemic immune responses in Lynch syndrome

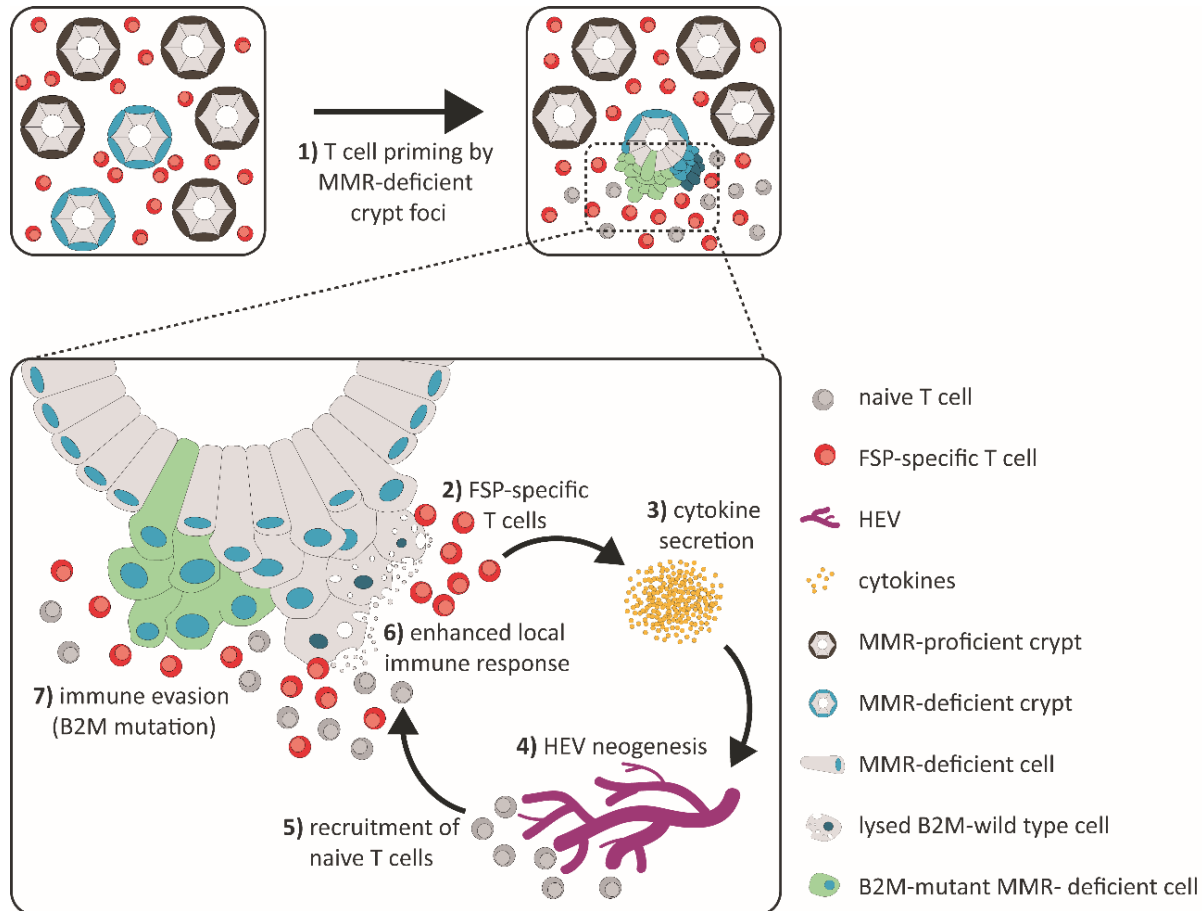


Schwitalle et al. *Gastroenterology* 2008

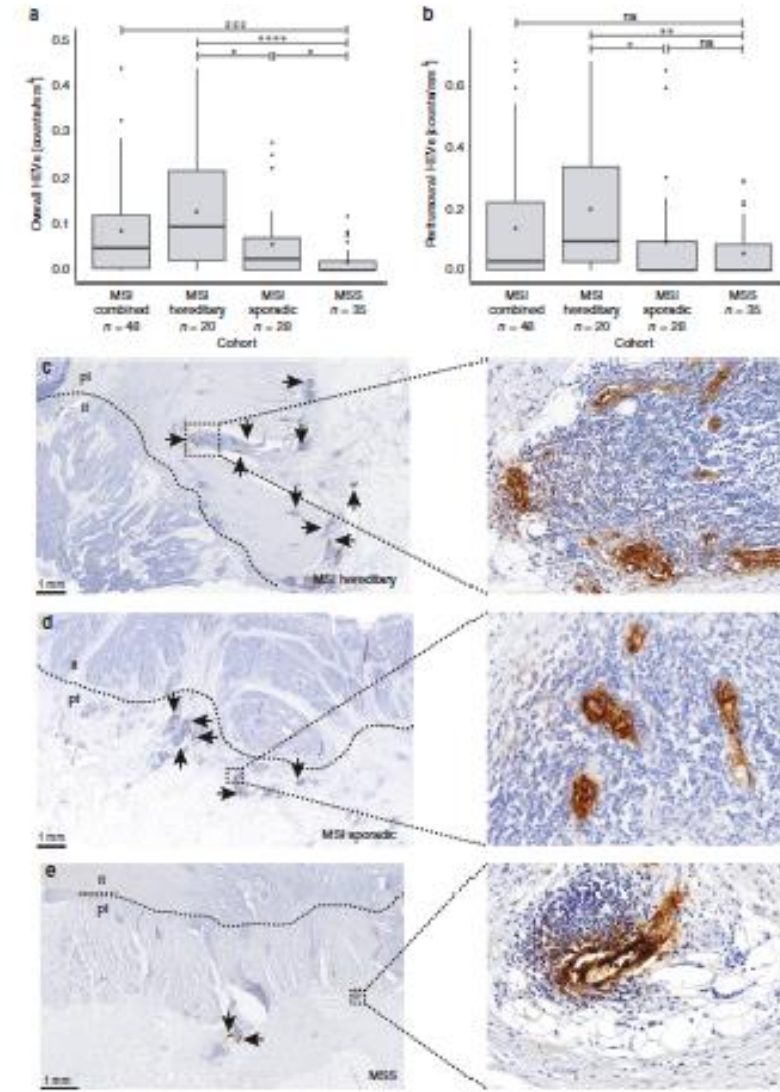
Kloor et al. *Lancet Oncol* 2012

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

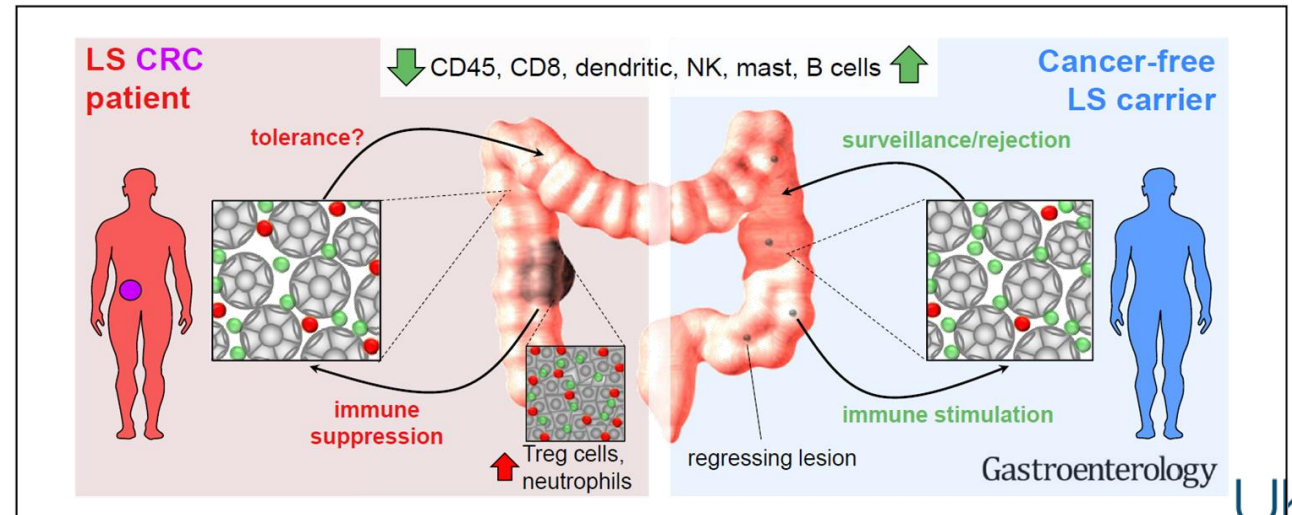
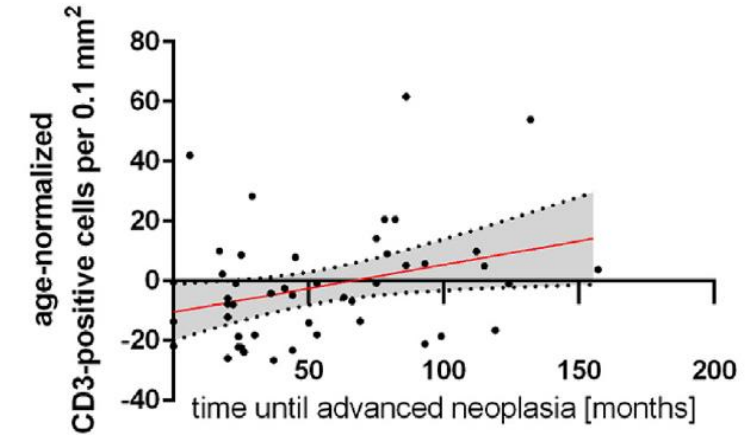
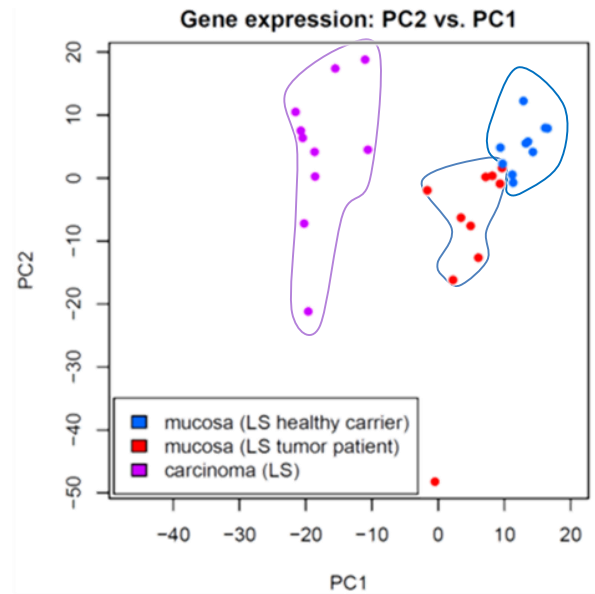
Local immune responses in Lynch syndrome



Pfuderer et al. *Br J Cancer* 2019



Local T cell responses in tumor-free Lynch syndrome patients



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 Macrae¹

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

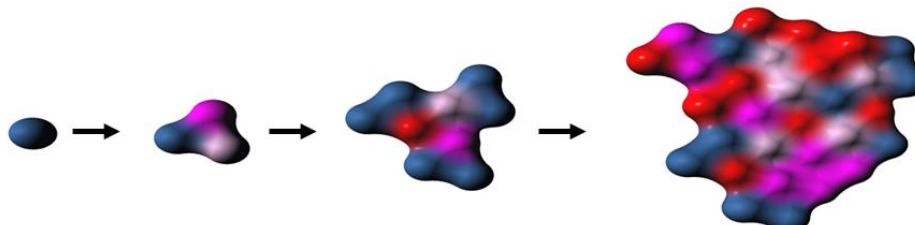
© The Author(s), under exclusive licence to Springer Nature B.V. 2023

Macrae. *Fam Cancer* 2023

Van Liere et al. *Fam Cancer* 2023

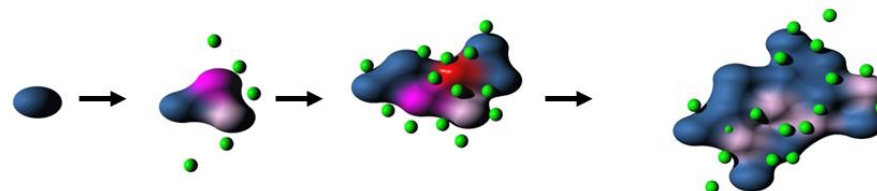
Alternative prevention strategies

A. MSI tumor evolution
without immune surveillance



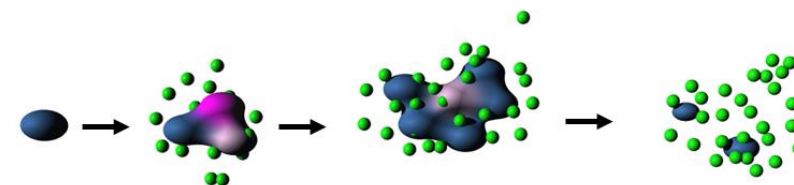
*Uncontrolled outgrowth of
immunogenic tumor*

B. MSI tumor evolution
under immune surveillance



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

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

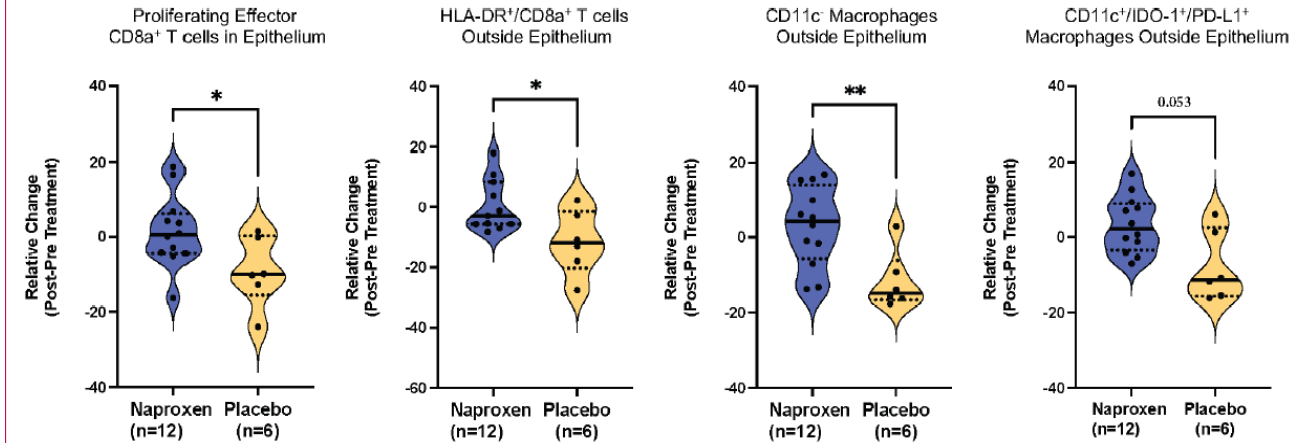
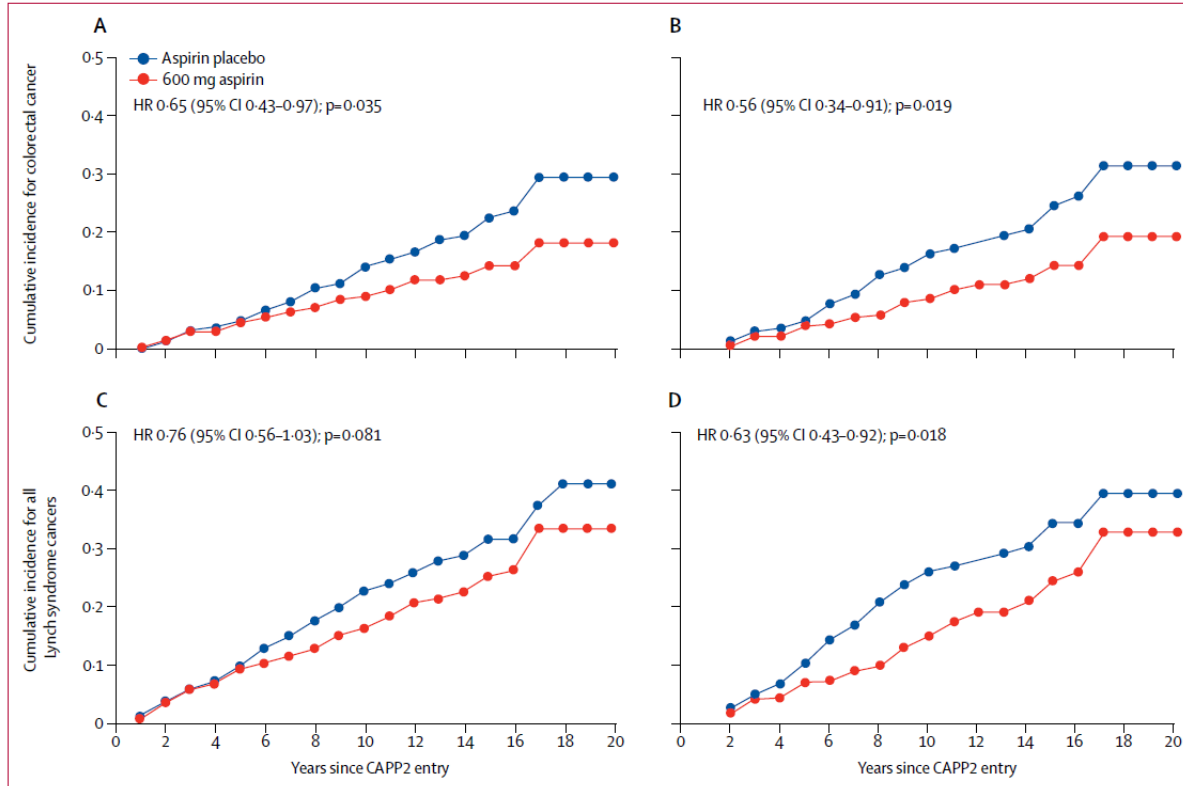


*Elimination of
precancerous lesions, no
tumor development*

<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

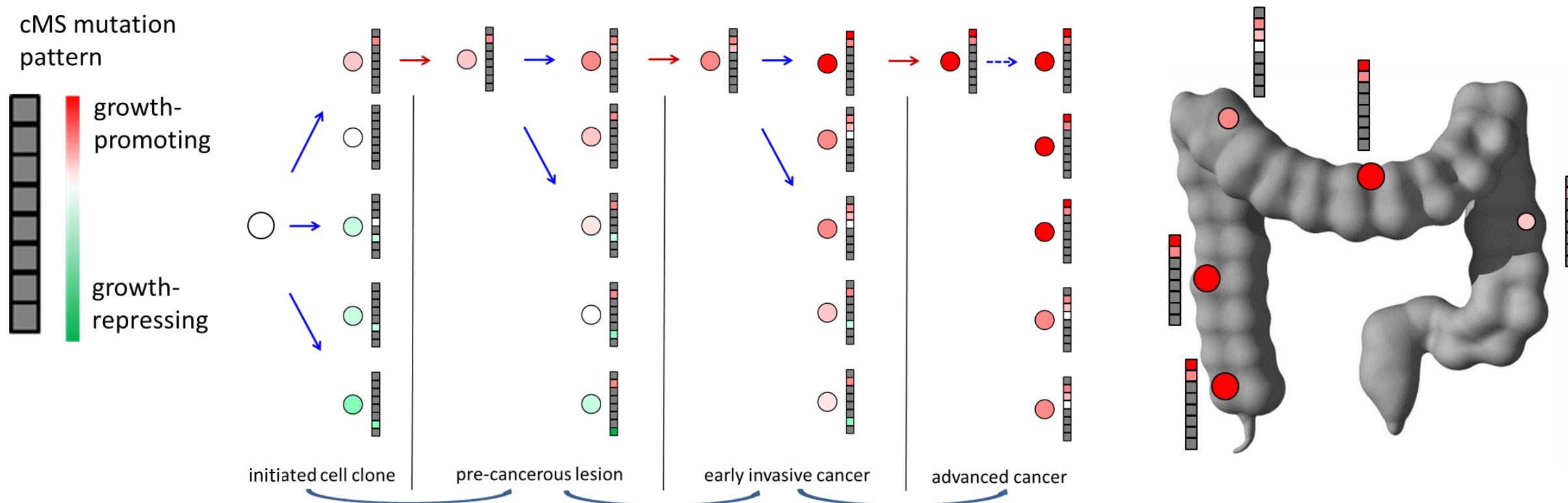
Alternative prevention strategies: NSAIDs



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

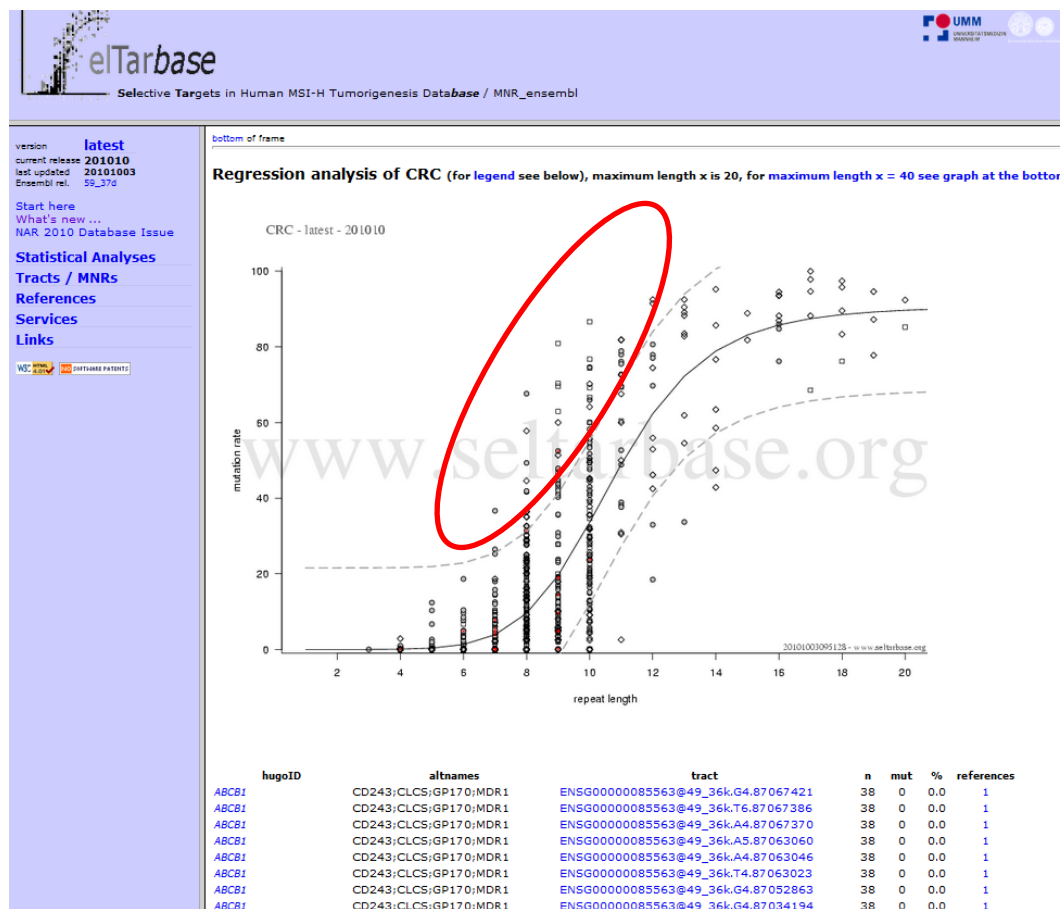
Burn et al. *Lancet* 2020

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
<i>TGFB2</i>	A10	73.8*	14.5*
<i>TAF1B</i>	A11	78.9*	58.3*
<i>AIM2</i>	A10	51.7*	50.0*
<i>ASTE1</i>	A11	78.0*	25.0*
<i>ACVR2</i>	A8	67.6*	13 [§]
<i>CASP5</i>	A10	47.6*	11.4*
<i>NDUFC2</i>	A9	40.3*	20 [§]
<i>SLC22A9</i>	A11	69.6*	23 [§]
<i>MSH3</i>	A8	42.0*	19.4*
<i>SMAP1</i>	A10	48.0*	20 [§]
<i>OR7E24</i>	T11	62 [§]	30 [§]
<i>KIAA2018</i>	T11	59 [§]	27 [§]
<i>JAK1</i>	T8	0 [§]	30 [§]
<i>C18ORF34</i>	T10	29 [§]	30 [§]

<http://www.seltarbase.org>

shared mutations



shared FSP neoantigens

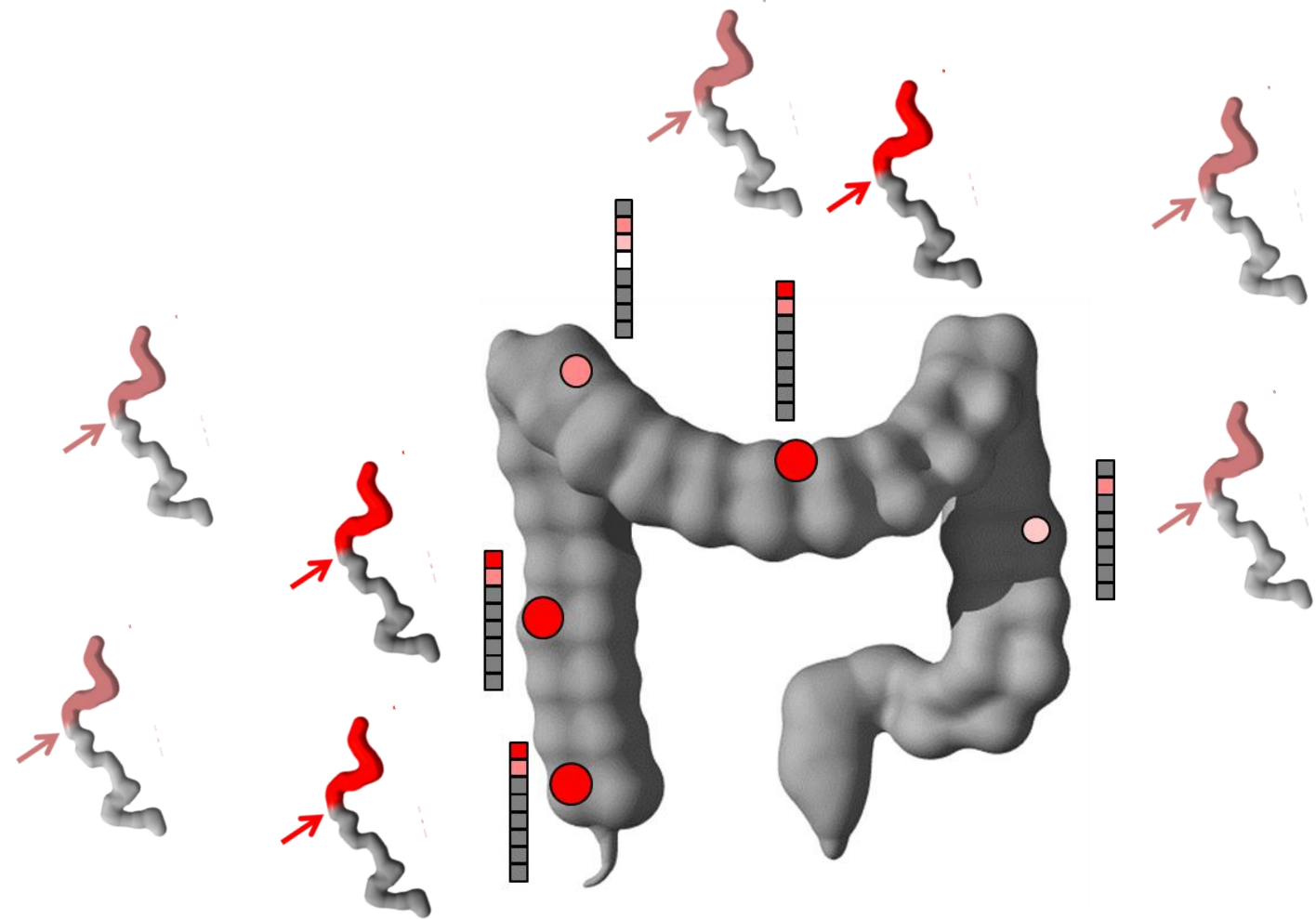
...and predictable

SOLGÅR NED

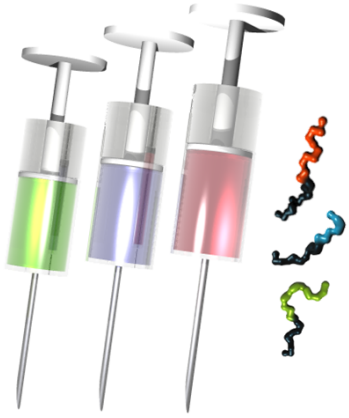
OLG ÅRN ED

SOL GÅR NED

LGÅ RNE D

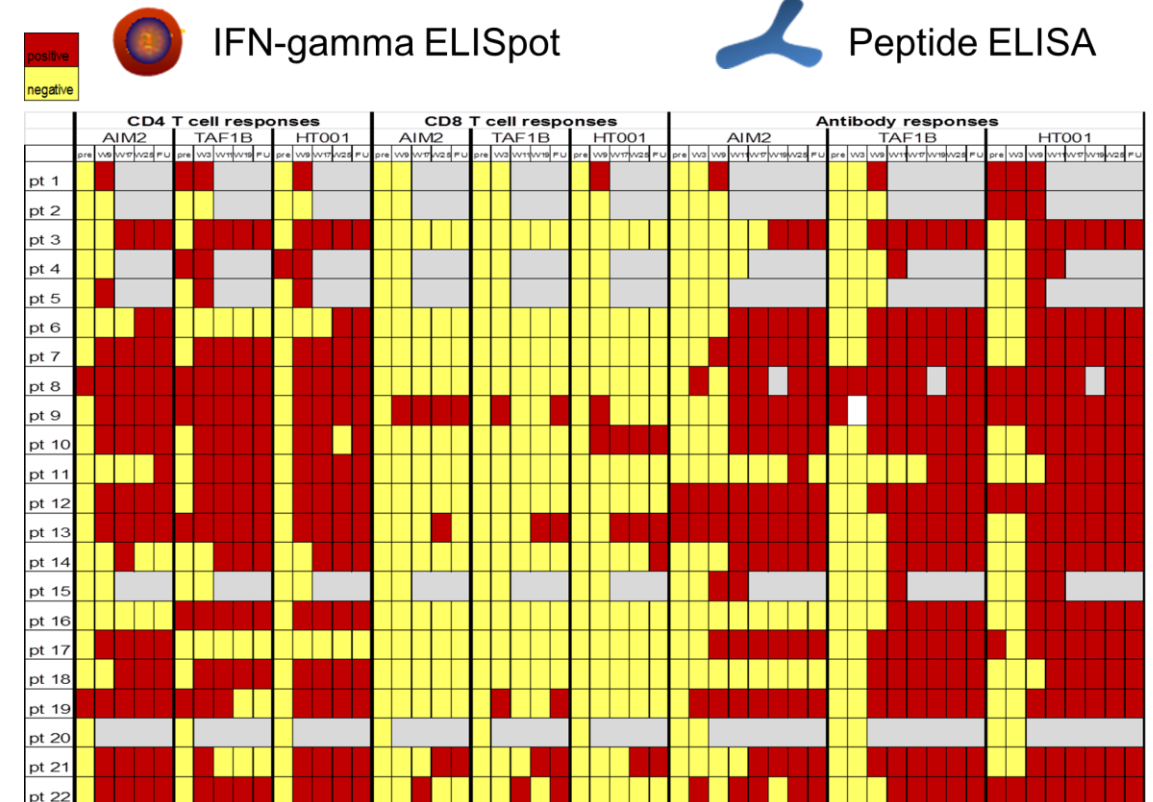


First safety trial



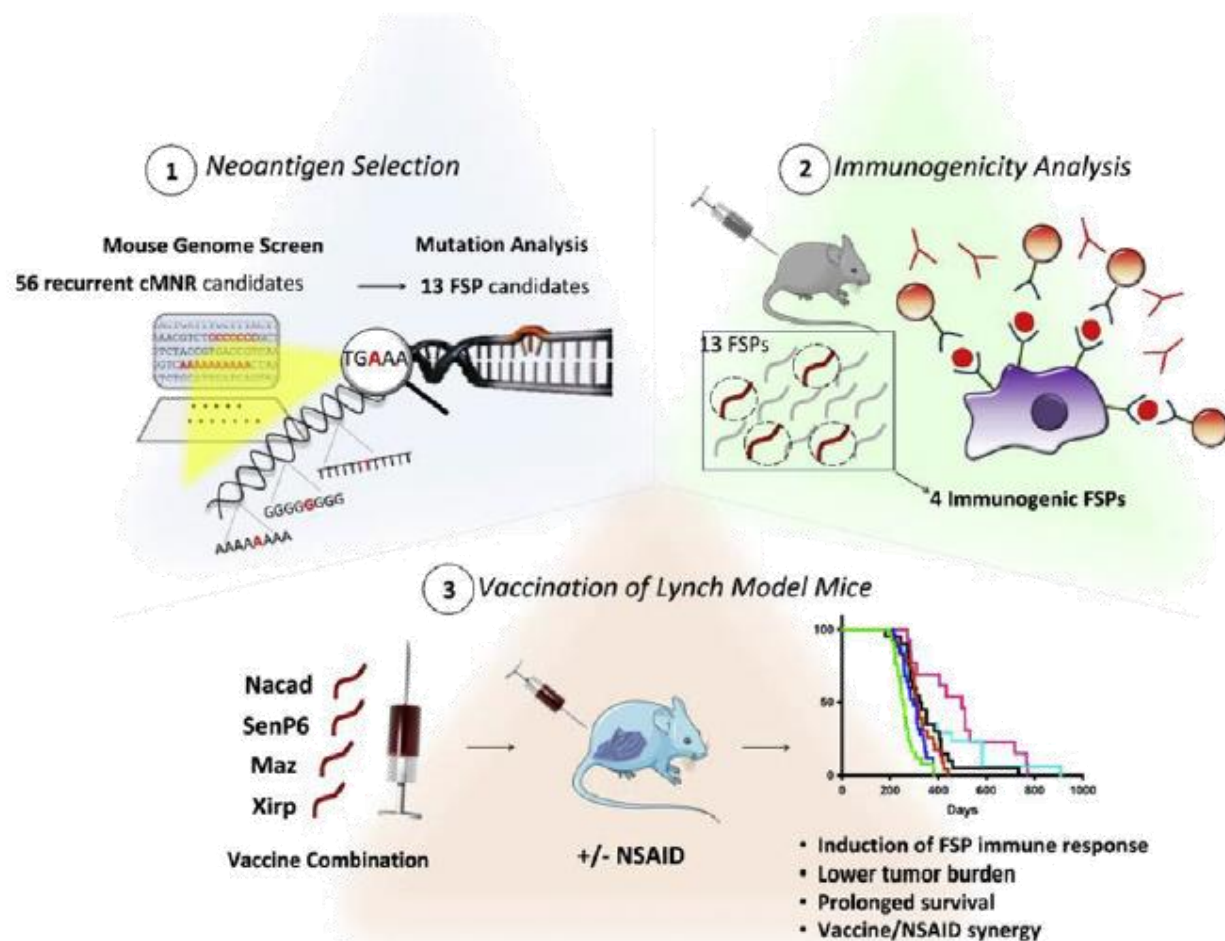
	cMS type	Mutation frequency (CRC) [§]	Mutation frequency (EC) [§]
TAF1B(-1)	A11	74.6%	50.0%
HT001(-1)	A11	86.2%	92.9%
AIM2(-1)	A10	81.6%	71.4%

- 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

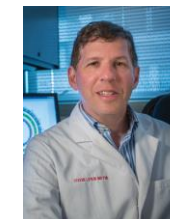


Kloor et al. *Clin Cancer Res* 2020

First proof-of-concept



CANCER MOONSHOT
NCI HHSN261201 0391



Steven Lipkin
Weill Cornell
University, NY



Winfried Edelmann,
Einstein College of
Medicine, NY



Shizuko Sei,
DCP, NCI



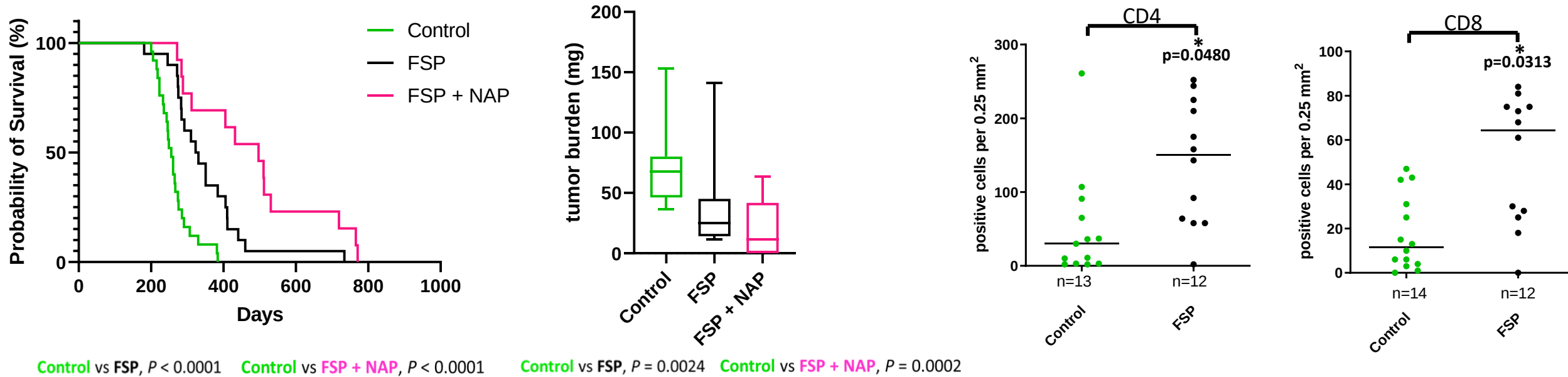
Bob Shoemaker,
DCP, NCI



Asad Umar,
DCP, NCI

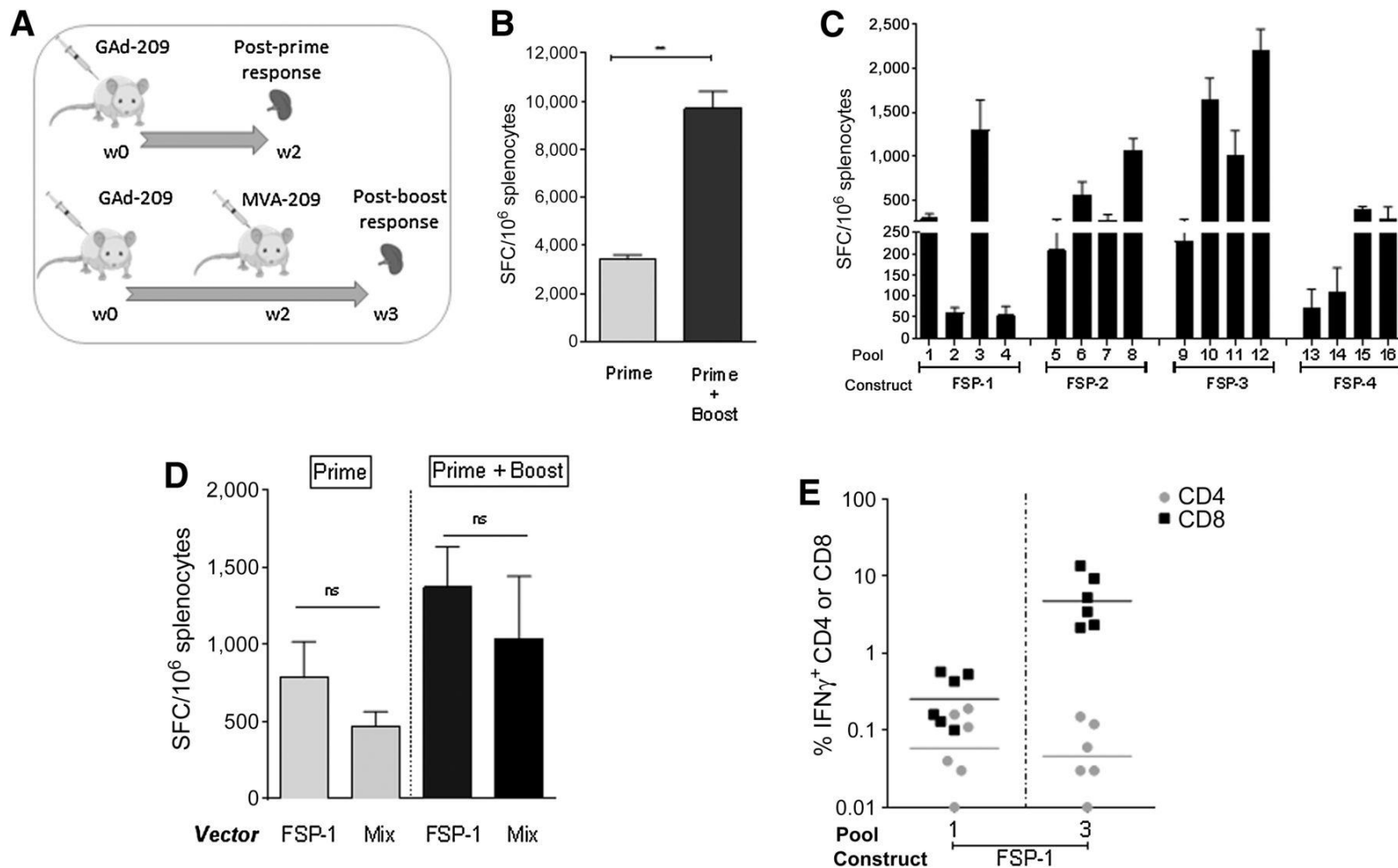
Gebert et al. *Gastroenterology* 2021

First proof-of-concept



Gebert et al. *Gastroenterology* 2021

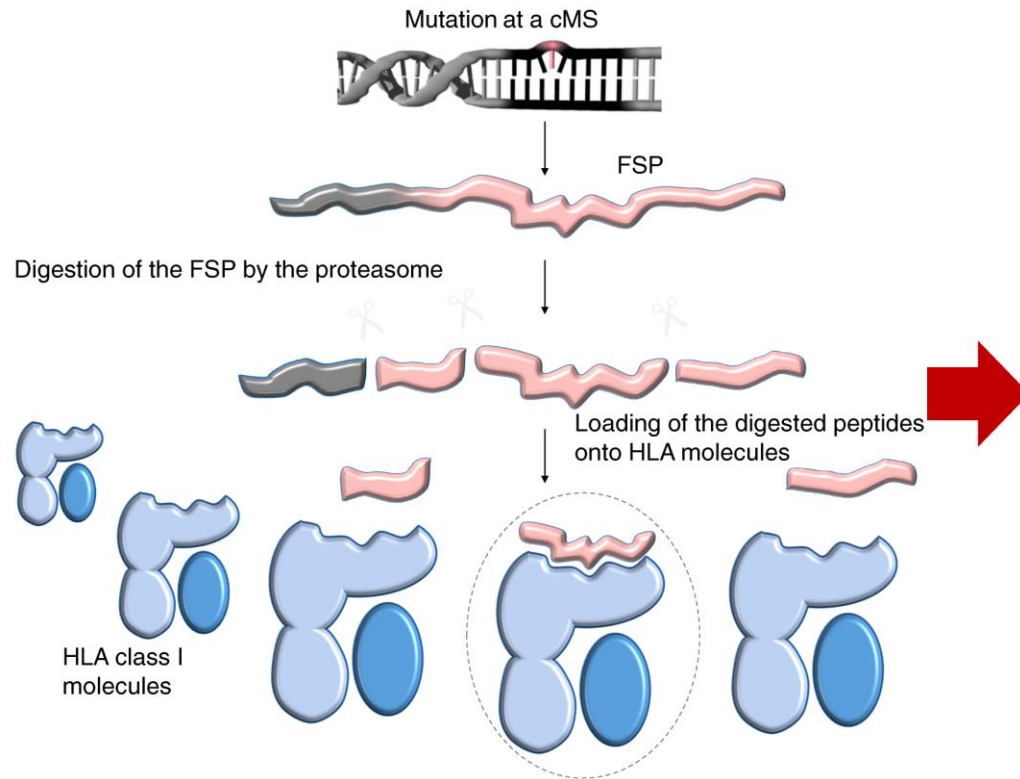
First proof-of-concept



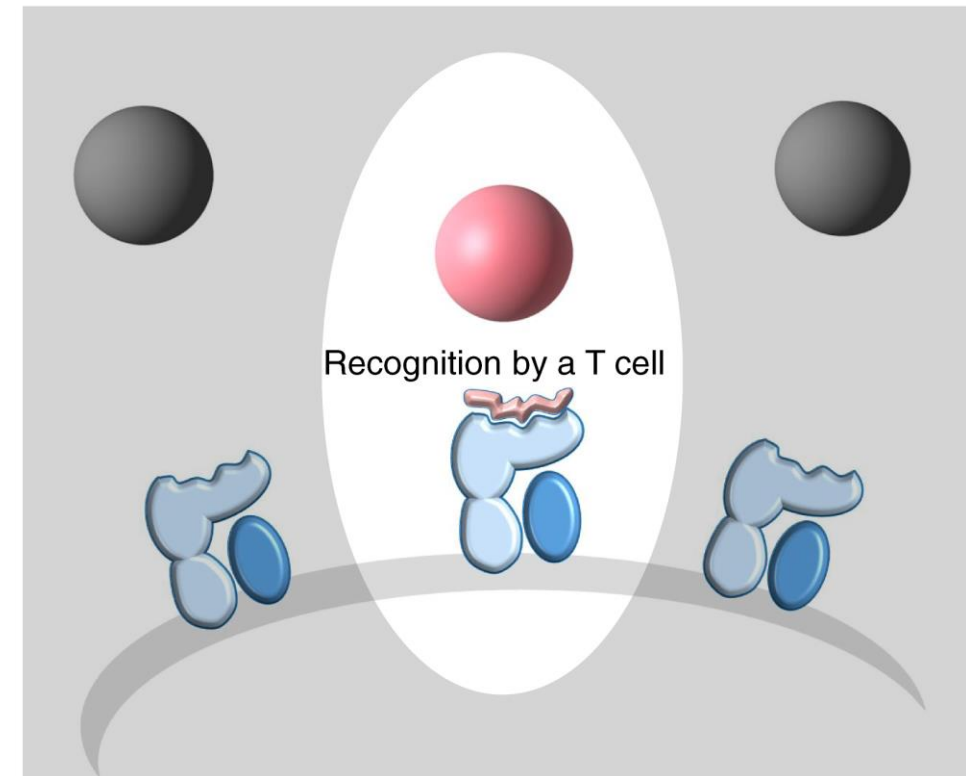
Leoni et al. *Cancer Res* 2020

Next generation vaccines: personalized, HLA type-adapted

Intracellular frameshift peptide expression and processing

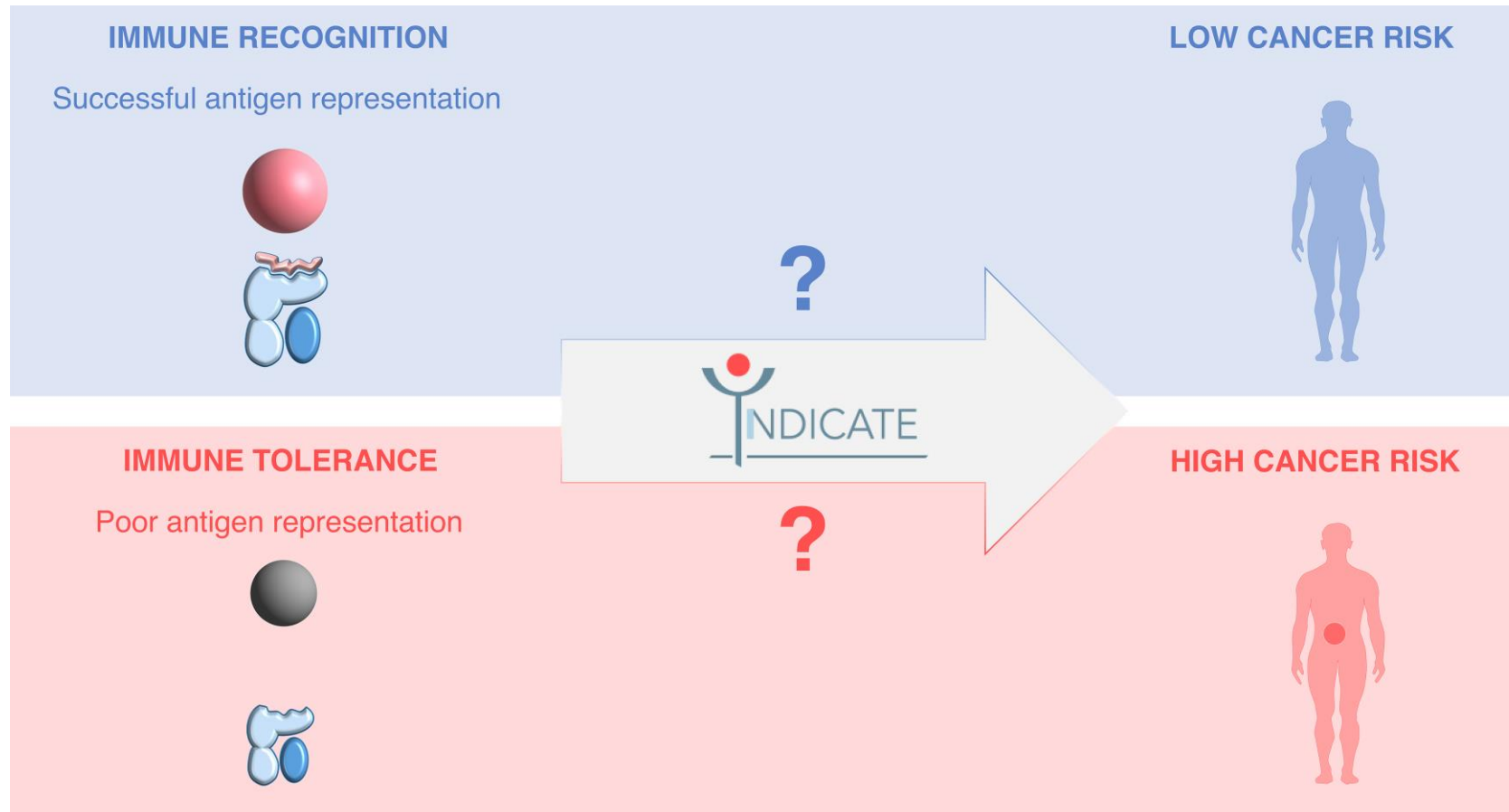


Cell surface antigen presentation



Ahadova et al. *Int J cancer* 2022

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



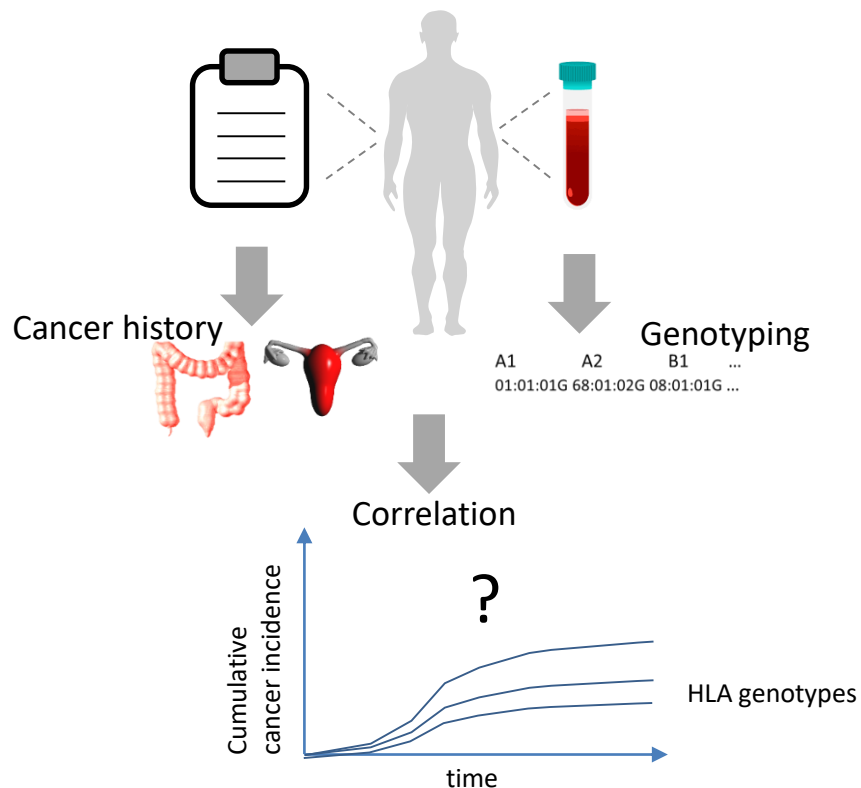
Ahadova et al. *Int J cancer* 2022

INDICATE – Individual cancer risk by HLA type



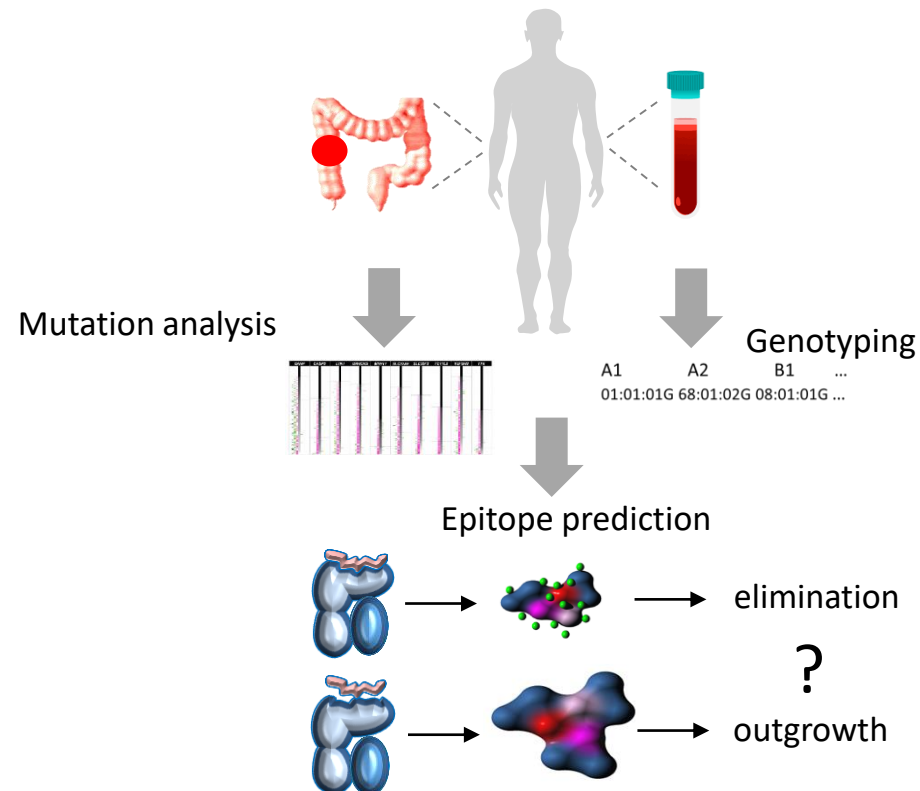
Part 1: Epidemiological research

HLA genotype and cancer risk

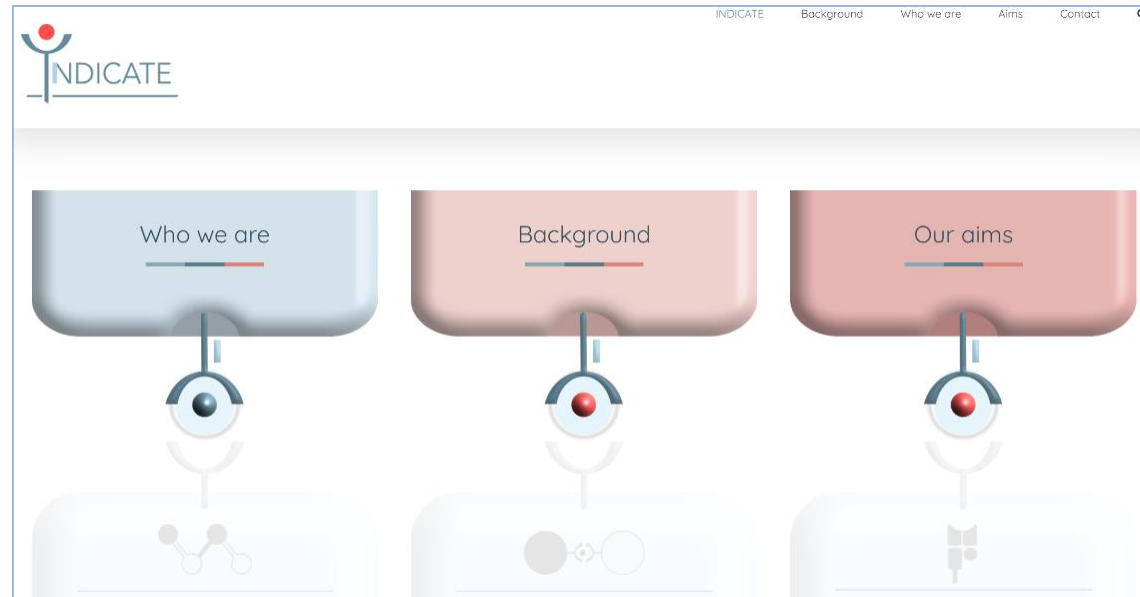


Part 2: Molecular biology research

HLA-dependent tumor antigen selection



INDICATE – Individual cancer risk by HLA type



Scientific background

Lynch syndrome is inherited via a pathogenic germline variant in one of the Mismatch Repair (MMR) genes. Therefore, MMR deficiency as a mutational process strongly shapes the molecular phenotype and immunological characteristics of tumors developing in frame of Lynch syndrome. However, tumor development, particularly in the scenario of MMR deficiency, is a result of a complex interplay between cancer precursors and the host's immune system. We study both, tumor and host factors influencing tumorigenesis in order to identify markers capable of predicting the outcome of this interplay and generate a new "molecular" level of cancer risk assessment for Lynch syndrome carriers.

More about Lynch syndrome

Lynch syndrome is the most common inherited cancer syndrome affecting 1280 individuals. Lynch syndrome carriers have 30-80% lifetime risk of developing malignancies, most commonly affecting patients' bowel (colorectal cancer, CRC) and in female patients the uterus (endometrial cancer, EC).

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Microsatellite-unstable cancers

Microsatellite instability is caused by dysfunction of the cellular DNA mismatch repair (MMR)-system, which detects and repairs DNA base mismatches during DNA replication. Deficiency of the MMR system can occur sporadically, or in the context of Lynch syndrome, in both cases leading to accumulation of insertion and deletion mutations at repetitive sequence stretches, called microsatellites.

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Immunoediting in cancer evolution

Our antigen repertoire determines the recognition of our own cells by the immune system as "self". As soon as the antigen repertoire of a cell

Function and diversity of HLA molecules

Human leukocyte antigens (HLA) serve as recognition molecules, which allow our immune system to identify cells as part of the body. O...

www.indicate-lynch.org

Growing Network of INDICATE

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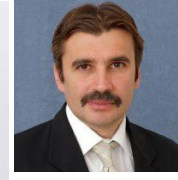
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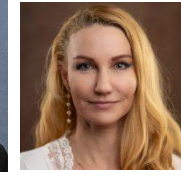
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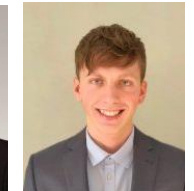
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