Personalized CRC Prevention: A case for Hereditary CRC Syndromes

Eduardo Vilar, MD, PhD
Associate Professor & Deputy Chair
Department of Clinical Cancer Prevention
The University of Texas MD Anderson Cancer Center
evilar@mdanderson.org

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Disclosure Information

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Eduardo Vilar, MD, PhD

Janssen Research & Development (Consulting)

PI on NCI U01 CA231425 ‘Neoantigen Vaccination for Lynch Syndrome Immuneprevention’: a Co-Investigator on this grant is an employee of NousCom, srl

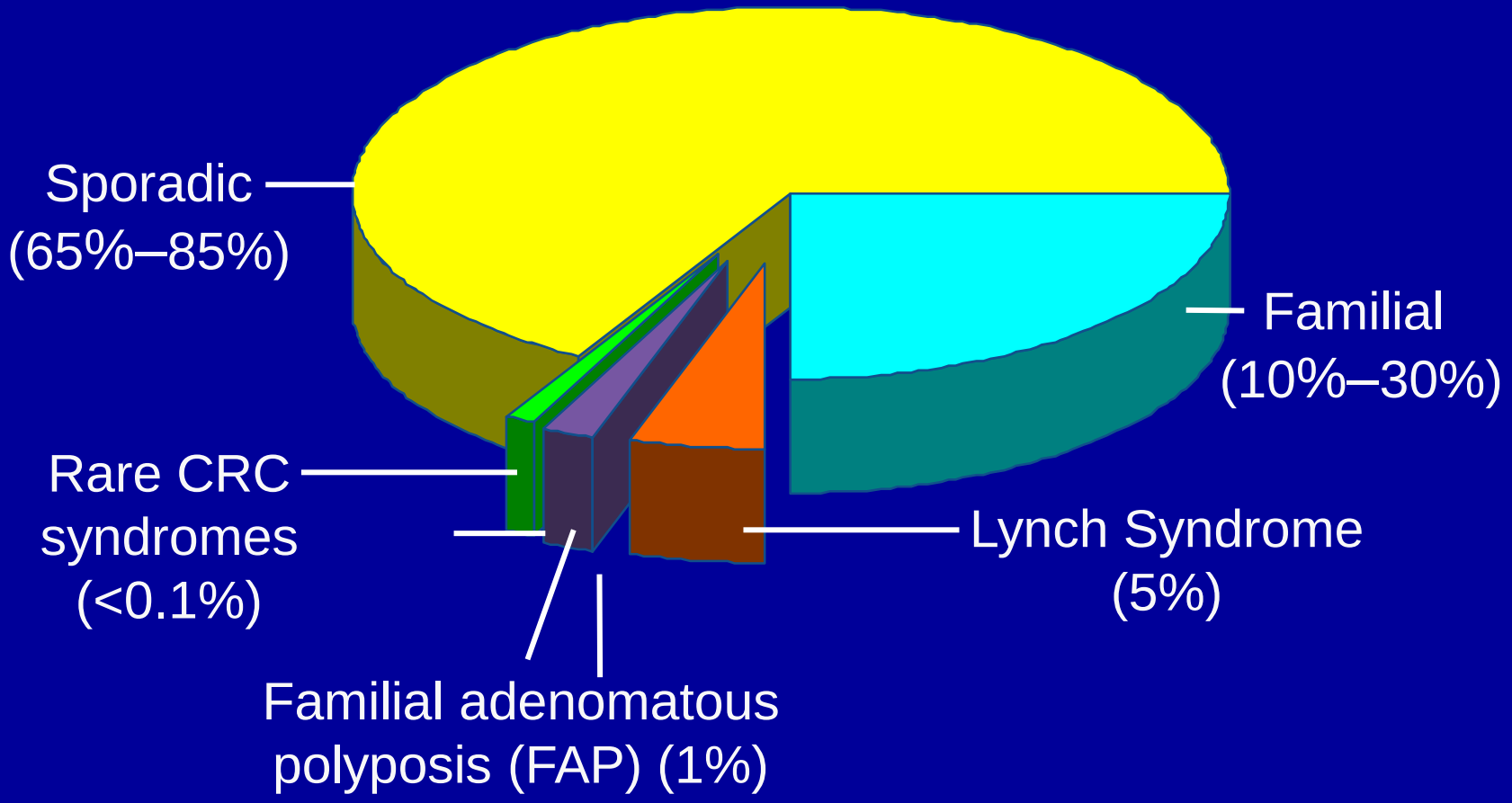
-and-

I will be discussing off label use of agents in this presentation

Outline

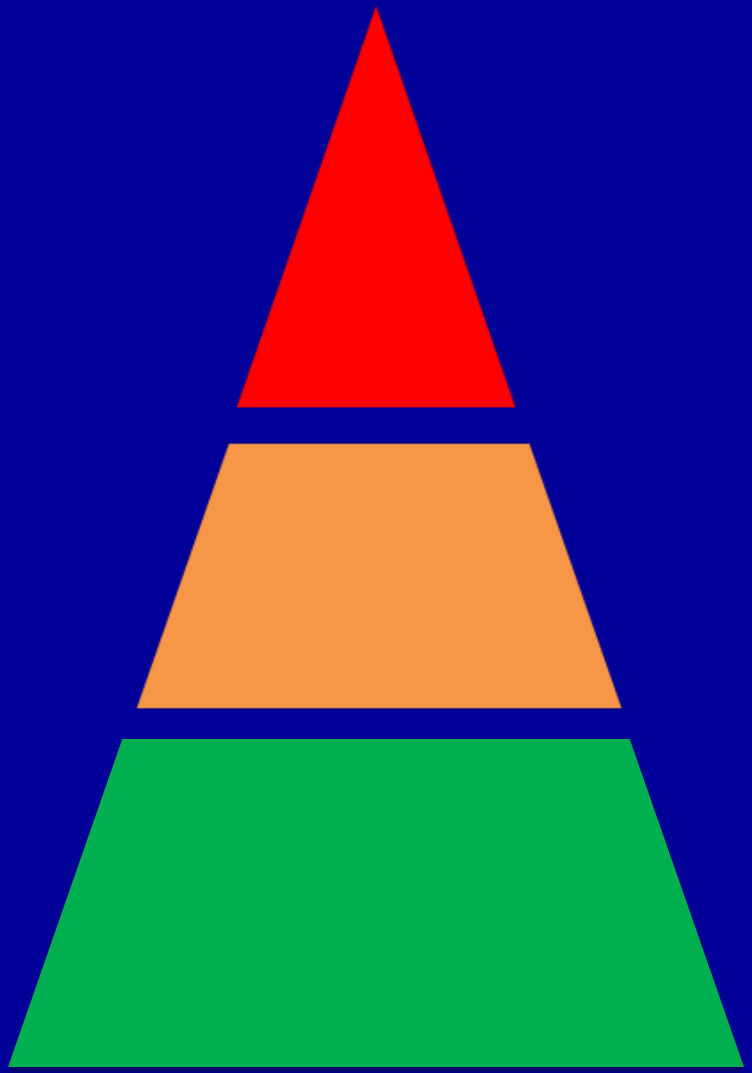
1. The importance of CRC High-risk Populations
2. Immuno-profiling of Lynch Syndrome Pre-Cancers
    - Lynch syndrome clinical trials
    - Lynch Syndrome vaccine development efforts
3. CMS application to Sporadic polyps
    - From Genetics to Sporadics

Causes of Hereditary Susceptibility to CRC



Adapted from Burt RW et al, *Prevention and Early Detection of CRC*, 1996

CRC Risk categories



High Risk

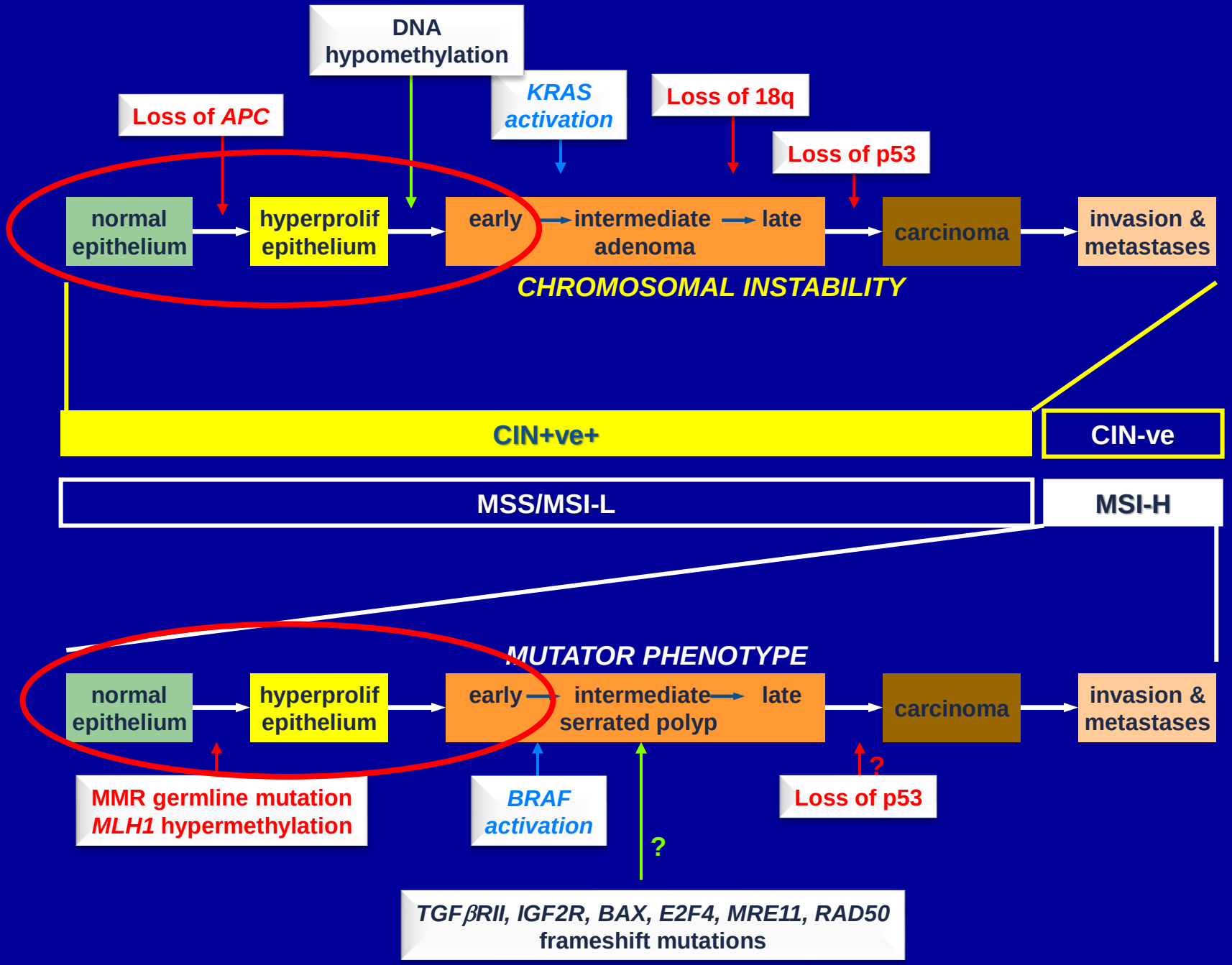
- ✓ Hereditary CRC Syndromes

Increased Risk

- ✓ Personal history of adenoma, SSP, CRC
- ✓ Inflammatory Bowel Disease (UC, CD)
- ✓ Positive family history

Average Risk

- ✓ Age ≥50 y
- ✓ No history of adenoma, SSP or CRC
- ✓ No history of IBD
- ✓ No Family History



Fearon and Volgelstein, *Cell* (1990); Vilar, *Nature Reviews Clinical Oncology* (2010)

Hereditary CRC Syndromes as Models for CRC Carcinogenesis

Polyposis Syndromes

Adenoma

…posis (*MUTYH*)

Hamartoma predominant

Peutz-Jeghers Sd (*LKB1*, *STK11*)

Juvenile polyposis Sd (*BMPR1A*, *DPC4*, *PTEN*)

Cowden Sd (*PTEN*)

Hyperpla…

…posis Sd

CIN +ve [Non-Hypermut]

CIMP-High [Methylators]

Non-polyposis Syndromes

…*PMS2*)

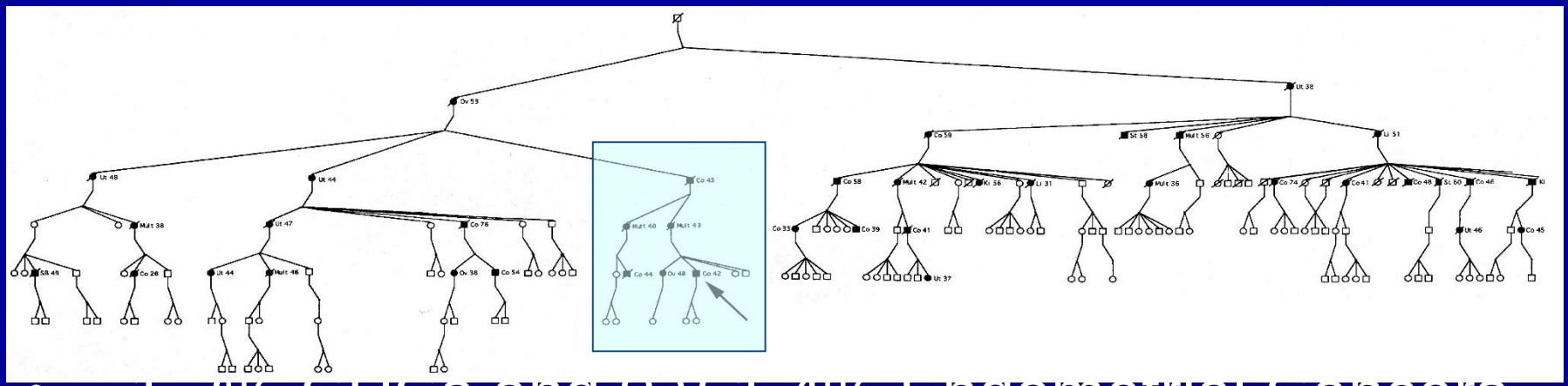
Mismatch repair proficient

Familial Colorectal Cancer Type X

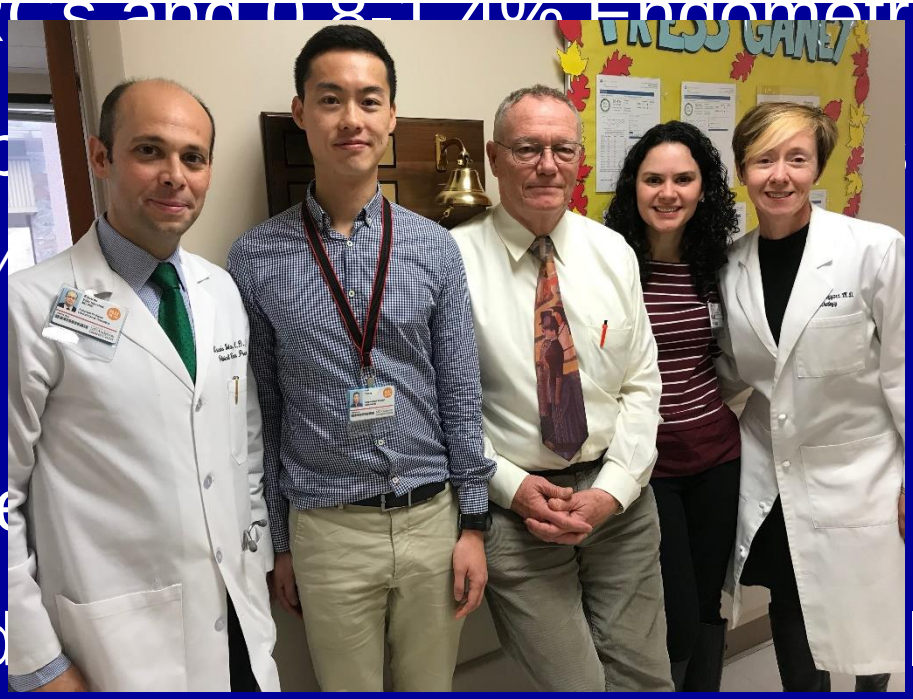
Other Syndromes

MSI-H [Hypermut]

Lynch Syndrome



- 1-3% CRC's and 1.8-4% Endometrial Cancers
- Caused b (*MLH1,*
  MSH2/EPCAM
- High but
- Variable e
- Tumors d lity



Hampel and de la Chapelle, *CAPR* (2011); Gruber, *GeneReviews* (2012)

Lynch Syndrome

LS-related tumors

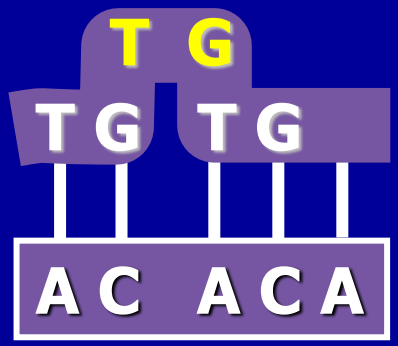
- ✓Colorectal Cancer (52-82%)
- ✓Endometrial Cancer (25-60%)
- ✓Ovarian Cancer (4-12%)
- ✓Urinary Tract Tumors (1-4%)
- ✓Gastric Cancer (6-13%)
- ✓Small Bowel (3-6%)
- ✓CNS – GBM (1-3%)
- ✓Prostate? Breast?

*Life-time risk

Gruber, *GeneReviews* (2012)

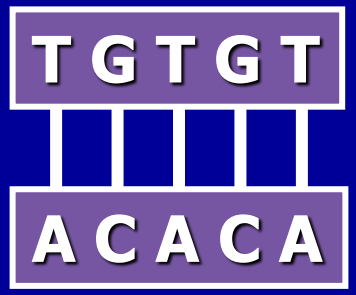
MSI is the molecular marker of Mismatch Repair deficiency

Ins/Del
Loop
Pol slippage

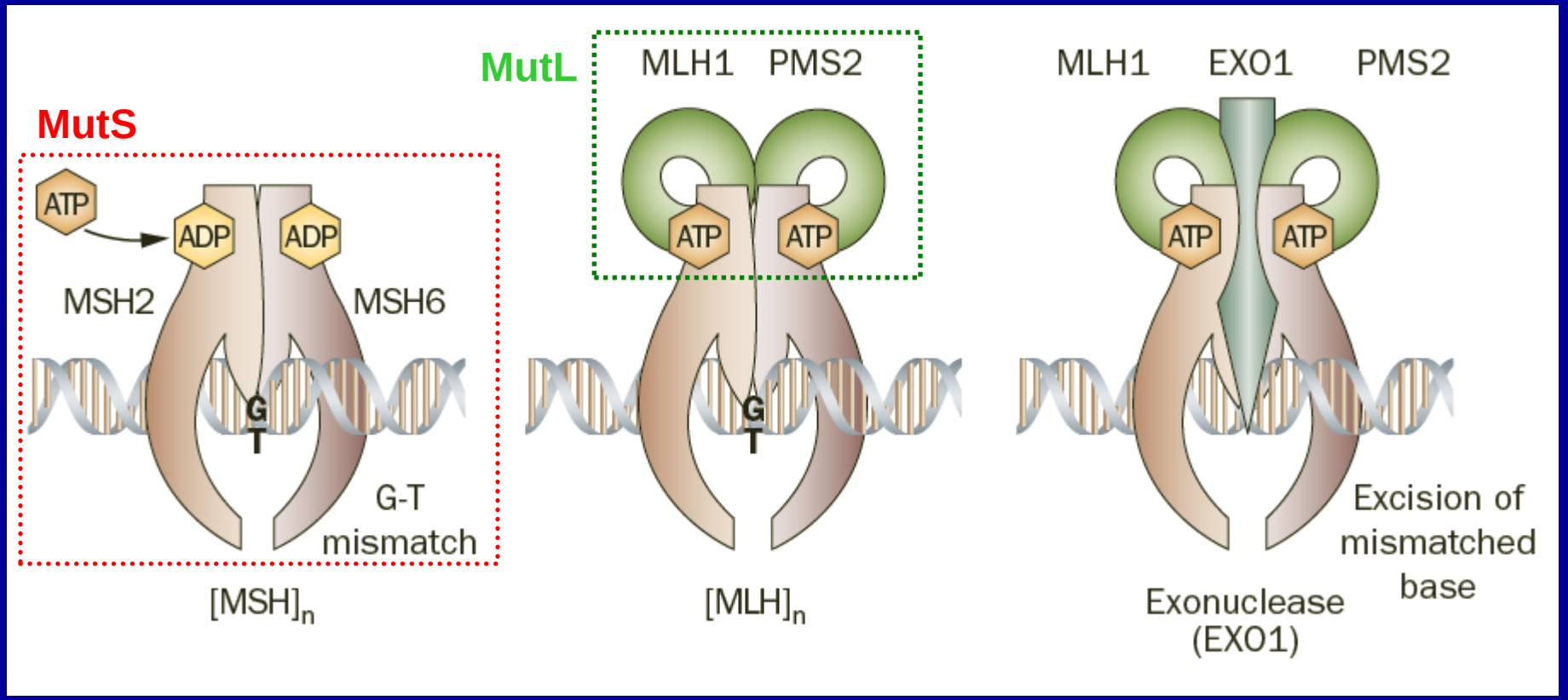


$(CA)_n$

Normal
DNA repair



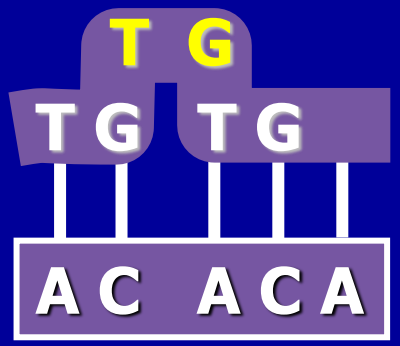
MMR System: MutS sliding clamp binds MutL to form a ternary complex



Vilar, *Nature Reviews Clinical Oncology* (2010)

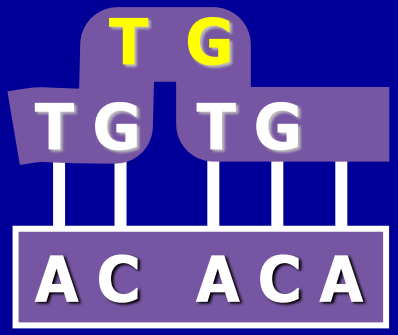
MSI is the molecular marker of Mismatch Repair deficiency

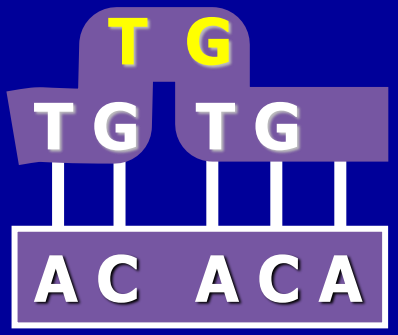
Ins/Del
Loop
Pol slippage



$(CA)_n$

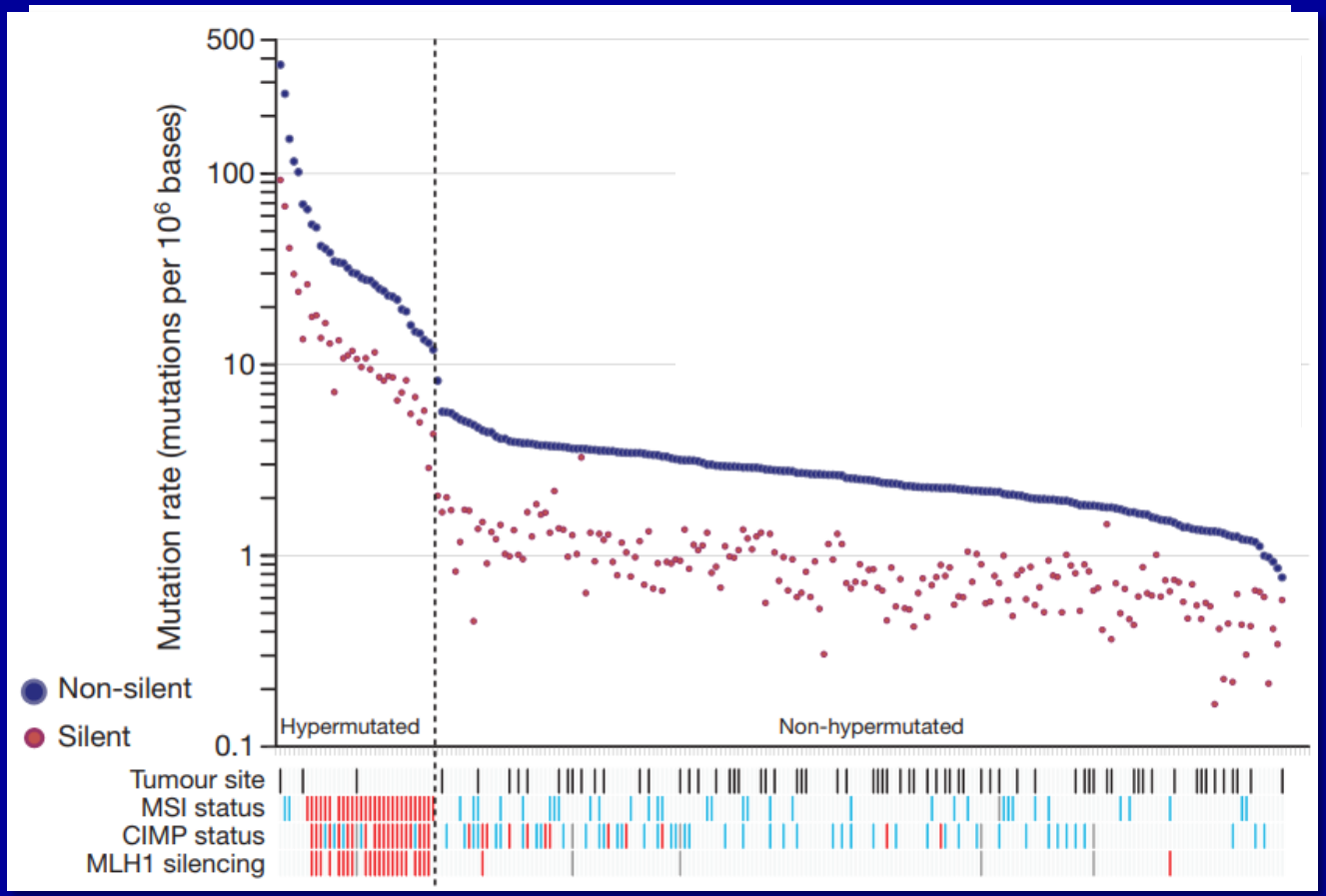
Defective
DNA repair
(dMMR)





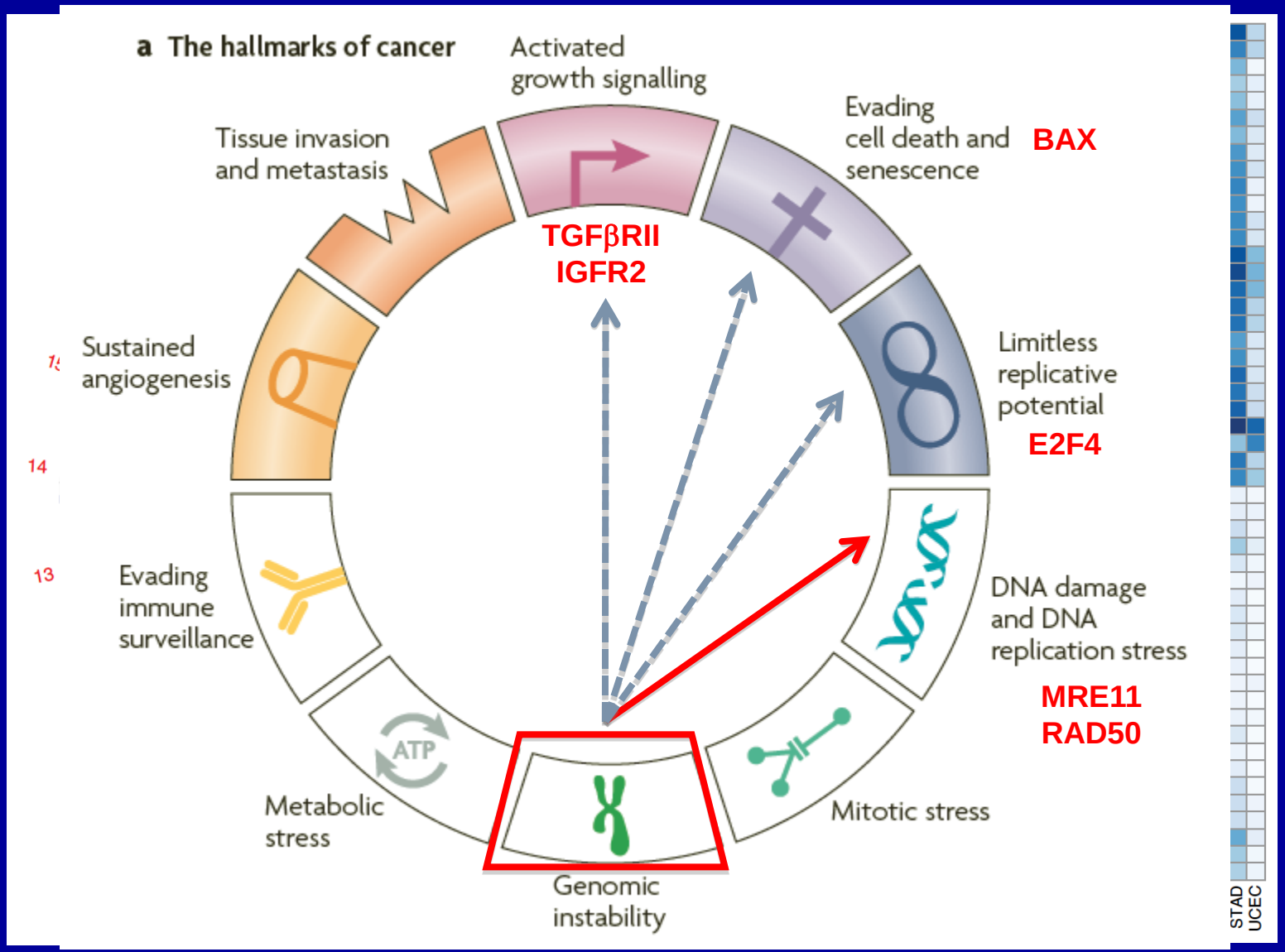
$(CA)_{n-2}$

MSI detection: multiple target microsatellites



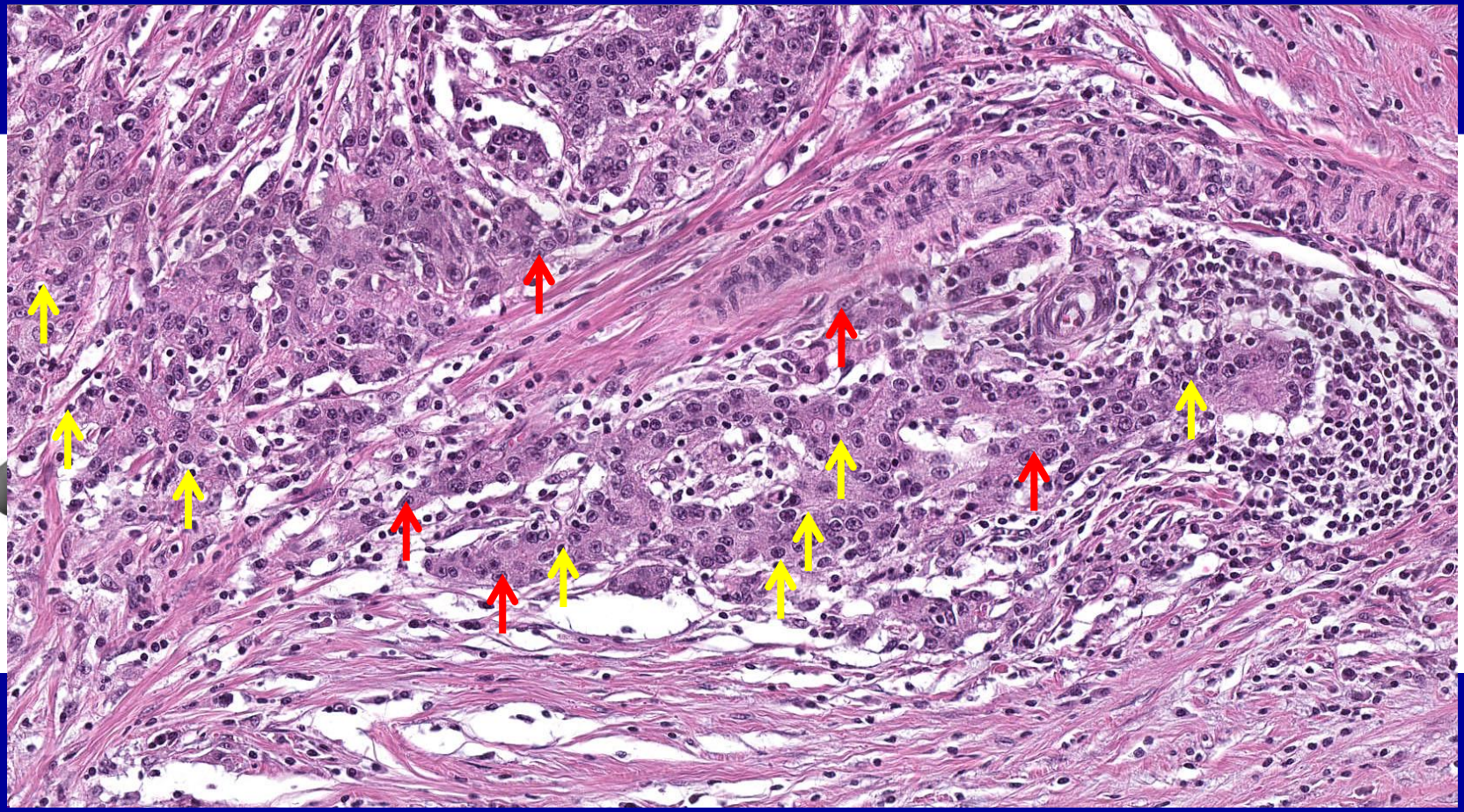
Gryfe, *NEJM* (2000); Vilar, *Nature Reviews Clinical Oncology* (2010); TCGA, *Nature* (2012)

MSI and Secondary mutations



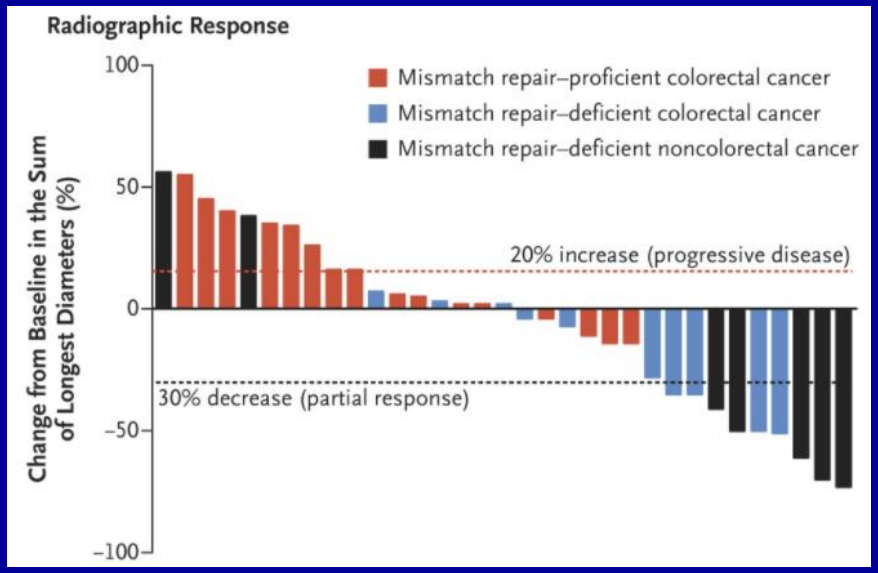
Hause, *Nature Medicine* (2016); Negrini, *Nature Reviews Molecular Cell Biology* (2010)

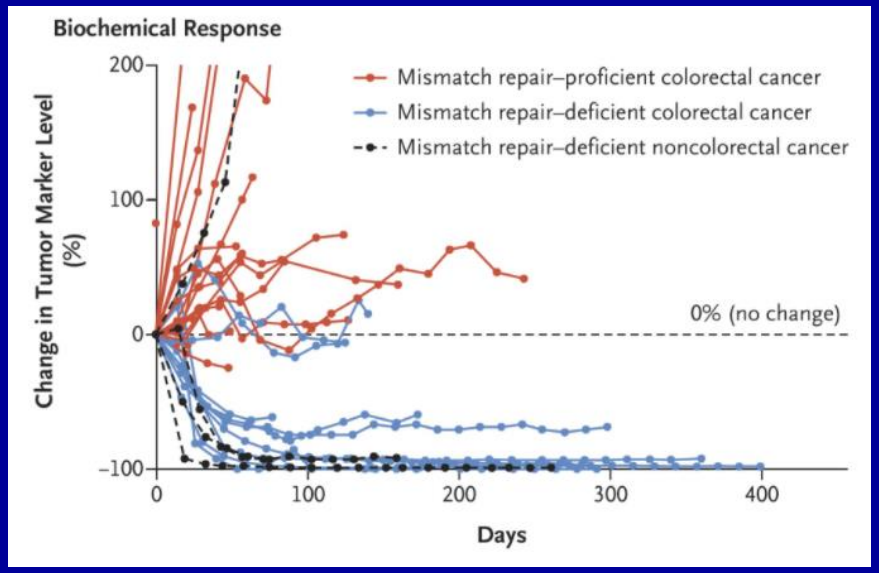
FSP and Tumor Infiltrating Lymphocytes



Slide courtesy of Melissa Taggart, MD – Neoantigen courtesy of Steve Lipkin, MD, PhD

Pembrolizumab in MSI-H CRC

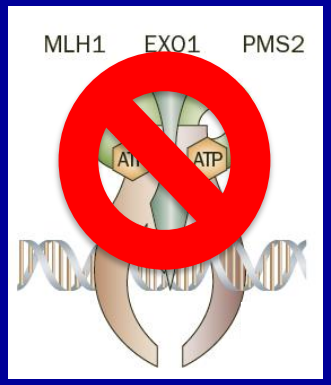


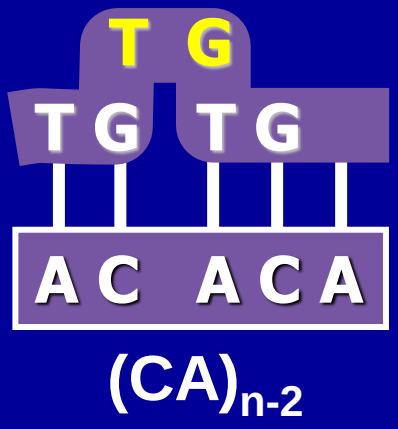


	MMR-deficient CRC N=28	MMR-proficient CRC N=28
Response Rate	57%	0%
Disease Control Rate	89%	16%

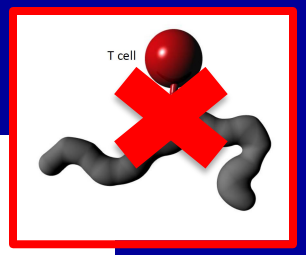
Le DT, *NEJM* (2015)

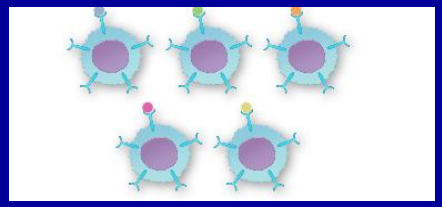
Lynch Syndrome

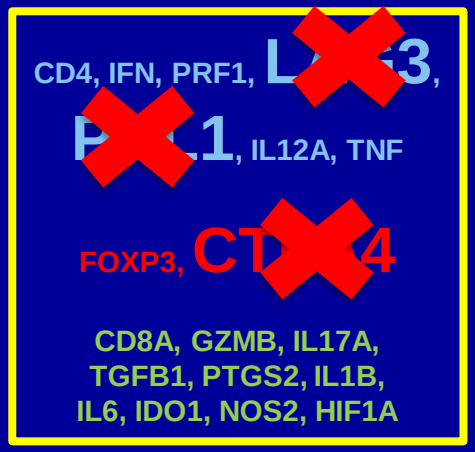




$(CA)_{n-2}$







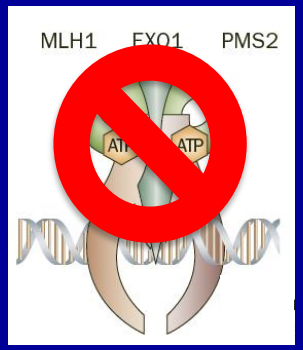
Interception in High-Risk Genetics

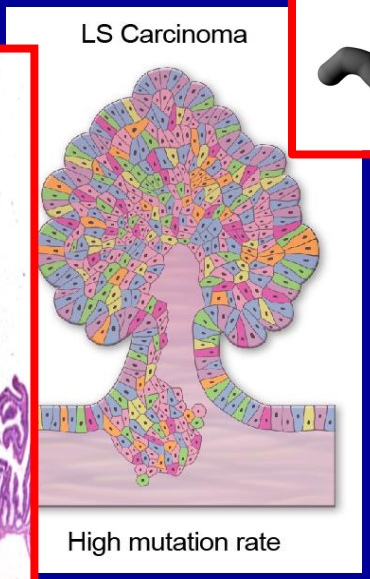
'Treatment without Prevention is simply unsustainable'

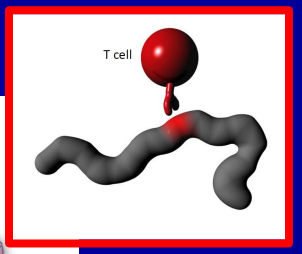
(Bill Gates)

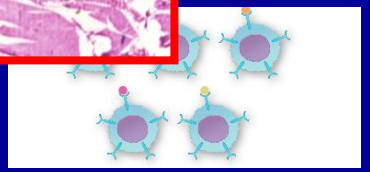
https://www.gatesfoundation.org/Media-Center/Press-Releases/2006/08/Putting-the-Power-of-HIV-Prevention-in-the-Hands-of-Women

Lynch Syndrome









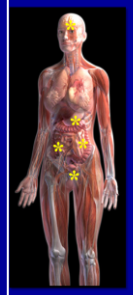
CD4, IFN, PRF

FOXP3, CT A4

CD8A, GZMB, IL17A,
TGFB1, PTGS2, IL1B,
IL6, IDO1, NOS2, HIF1A

Interception in High-Risk Genetics

14 LS



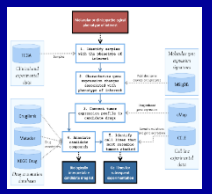
LS-related tumors
- ✓Colorectal Cancer (52-82%)
- ✓Endometrial Cancer (25-60%)
- ✓Ovarian Cancer (4-12%)
- ✓Urinary Tract Tumors (1-4%)
- ✓Gastric Cancer (6-13%)
- ✓Small Bowel (3-6%)
- ✓CNS – GBM (1-3%)
- ✓Prostate? Breast?
- *Life-time risk

Colon Polyps
Normal mucosa
Germline
Lynch Syndrome

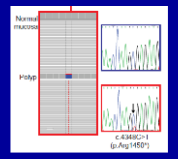
Pre-Cancers
Tumors
Normal

DNA & RNA

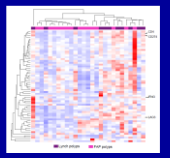
Next-Gen Seq
RNA-seq



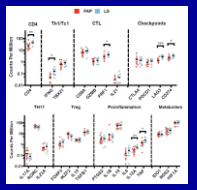
HLA & NeoAg



Mutations

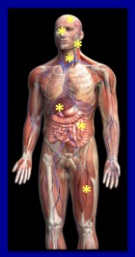


Expression



Immune Profile

Familial Adenomatous Polyposis



Extracolonic features
- ✓Duodenal Carcinoma (4-12%)*
- ✓Desmoid Tumors (15%)*
- ✓Thyroid Cancer - Papillary (2%)*
- ✓Medulloblastoma (2%)*
- ✓Hepatoblastoma (1.6%)*
- ✓Adrenal mases (7.4%)
- ✓Osteomas
- ✓CHRPE
- ✓Dental abnormalities (17%)
- ✓Benign cutaneous – Epidermoid cysts

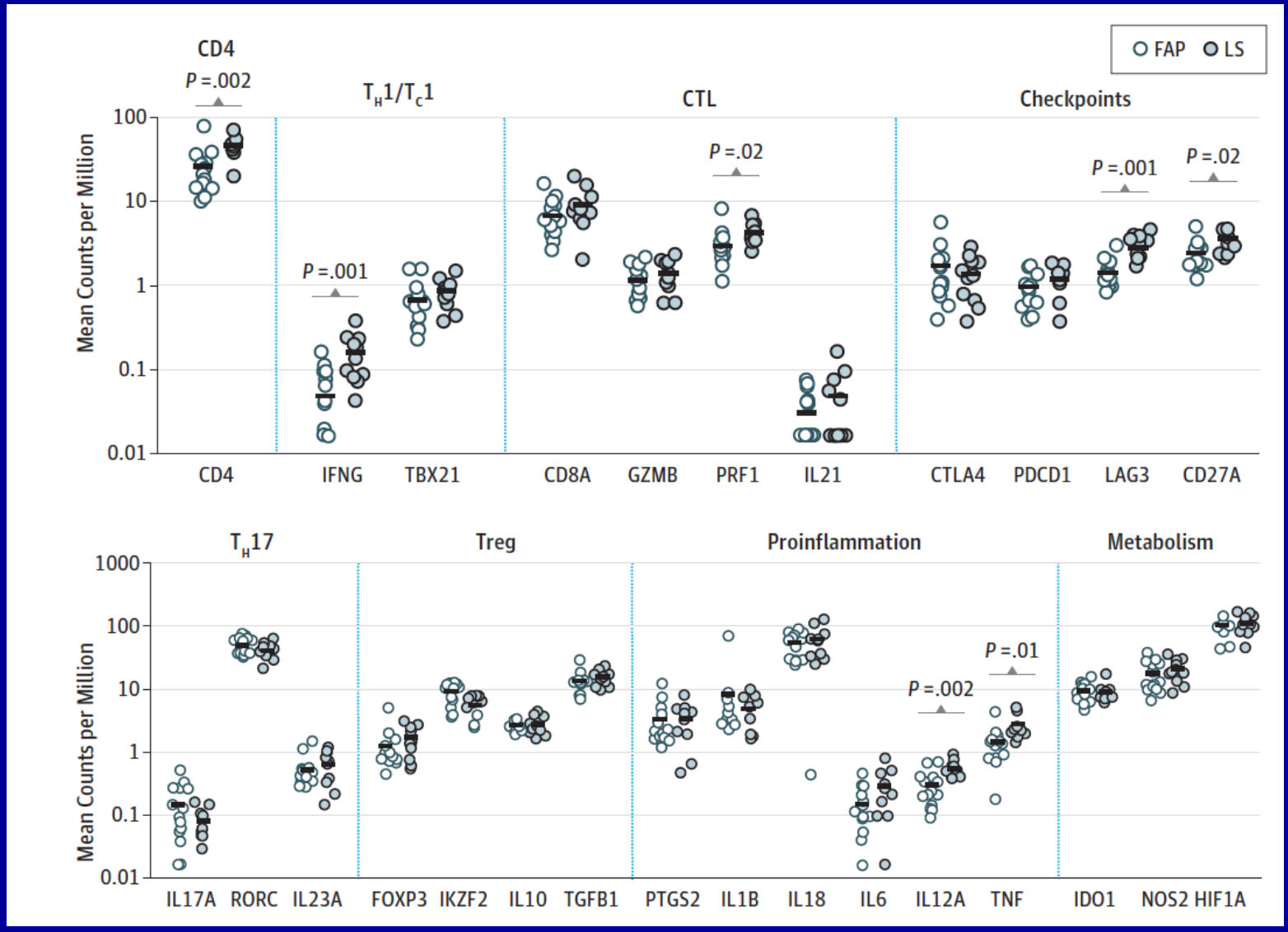
*Life-time risk

Galiatsatos, *Am J Gastroenterology* (2006); Jasperson, *GeneReviews* (2011)

10 FAP

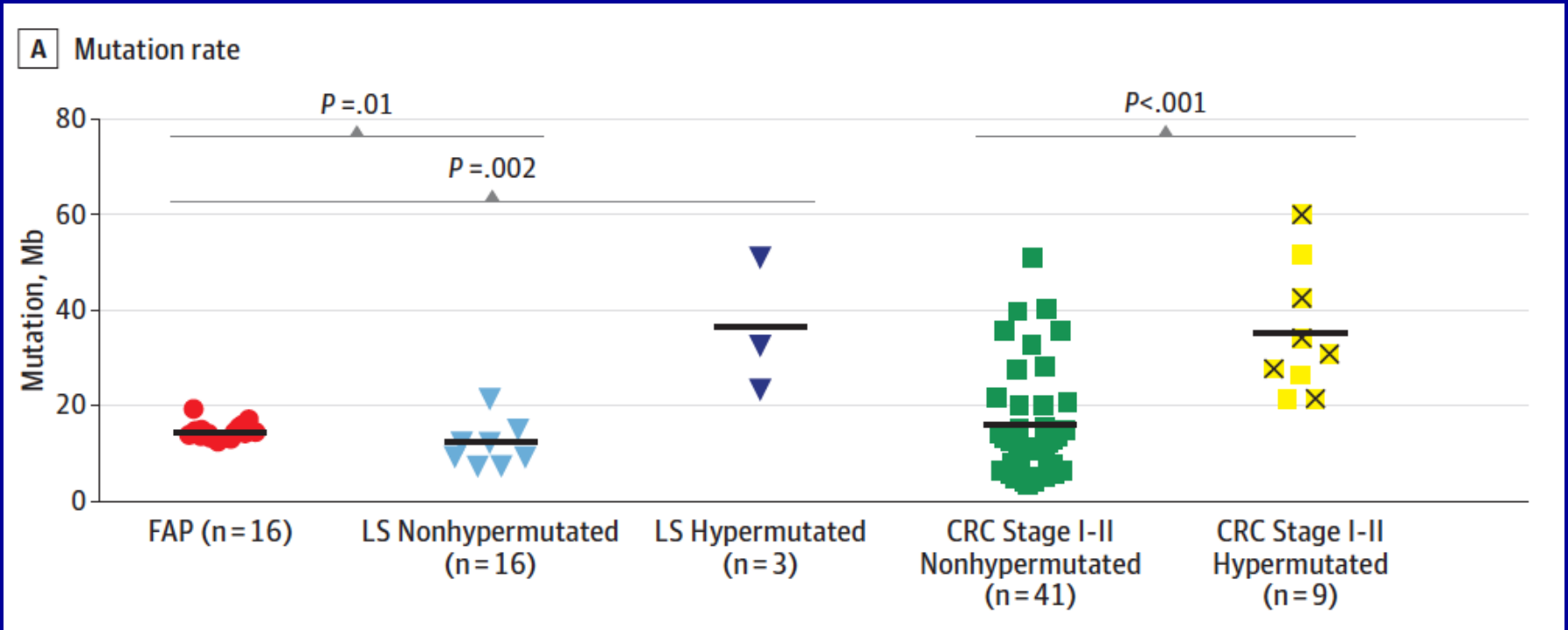
Protocol IRB# PA12-0327, *Kyera Evans, Laura Reyes, CCP Research Core*

Lynch Syndrome



Chang, *JAMA Oncology (2018)*

Lynch Syndrome



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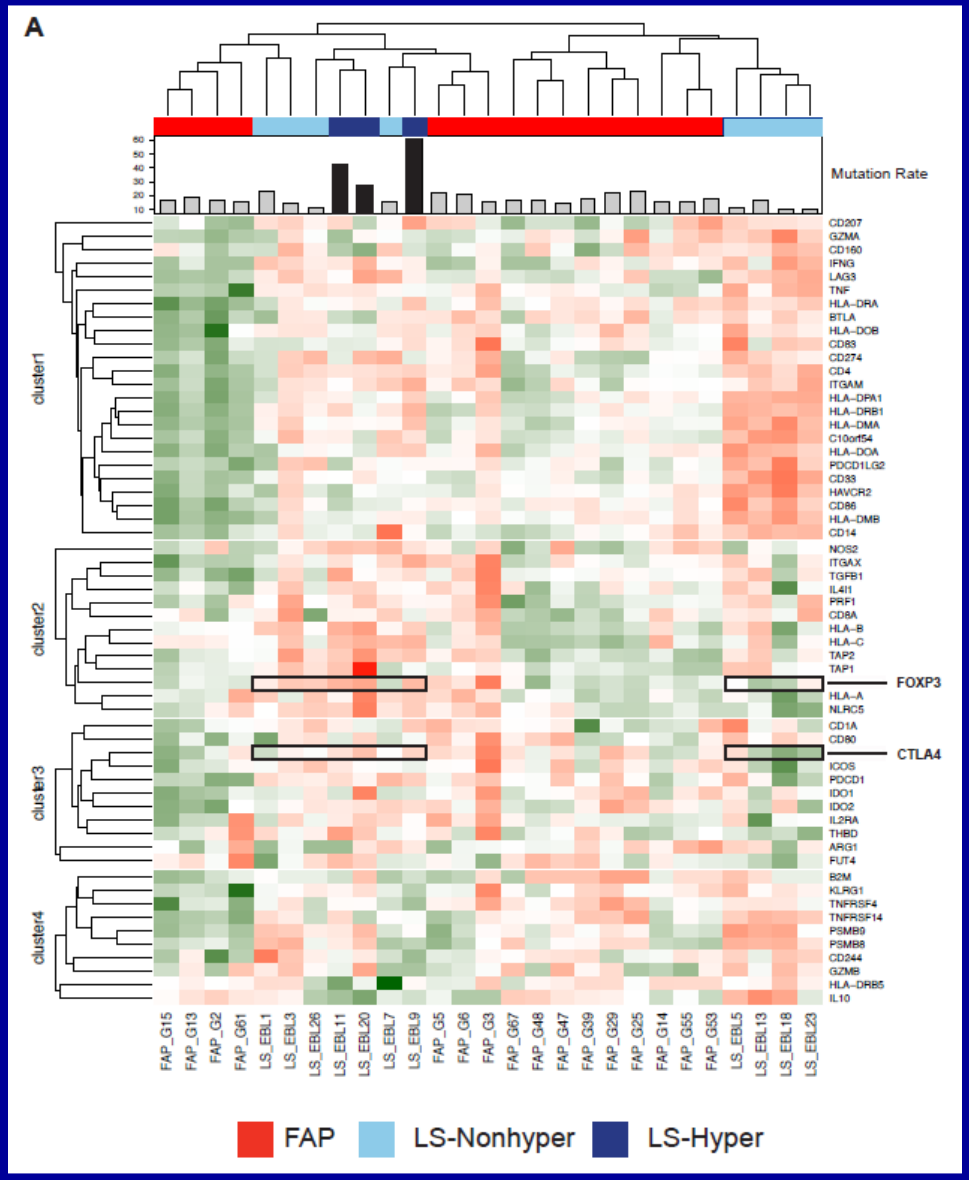

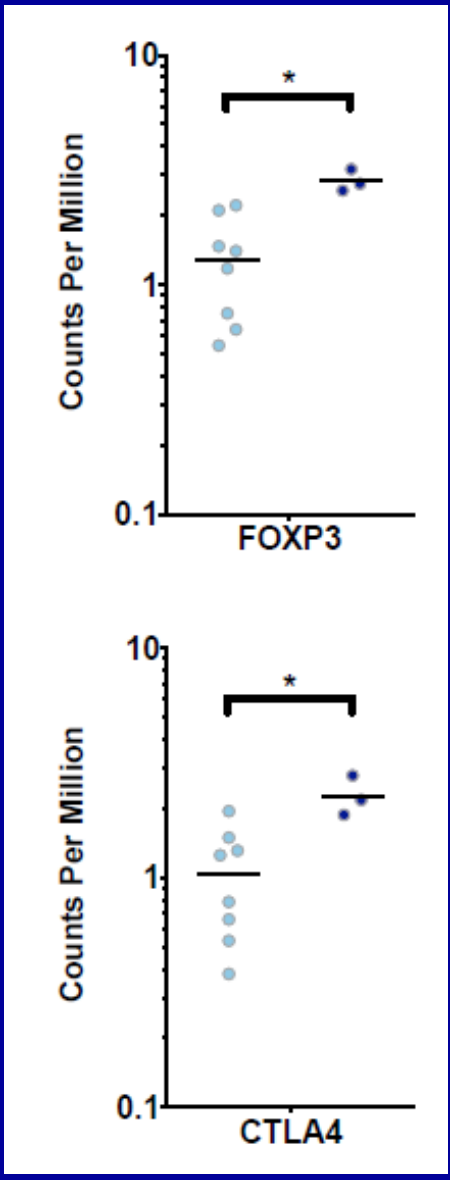

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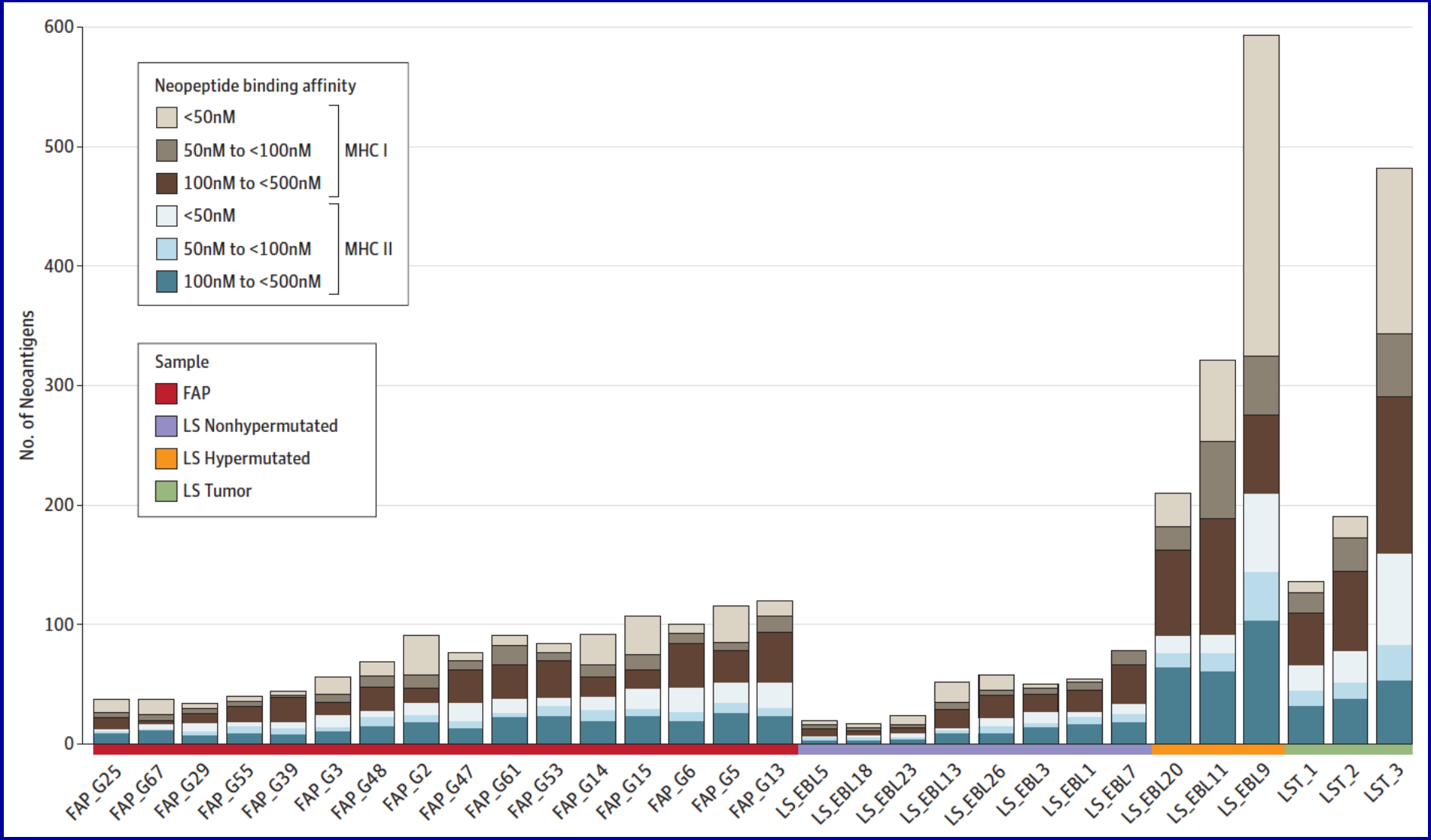

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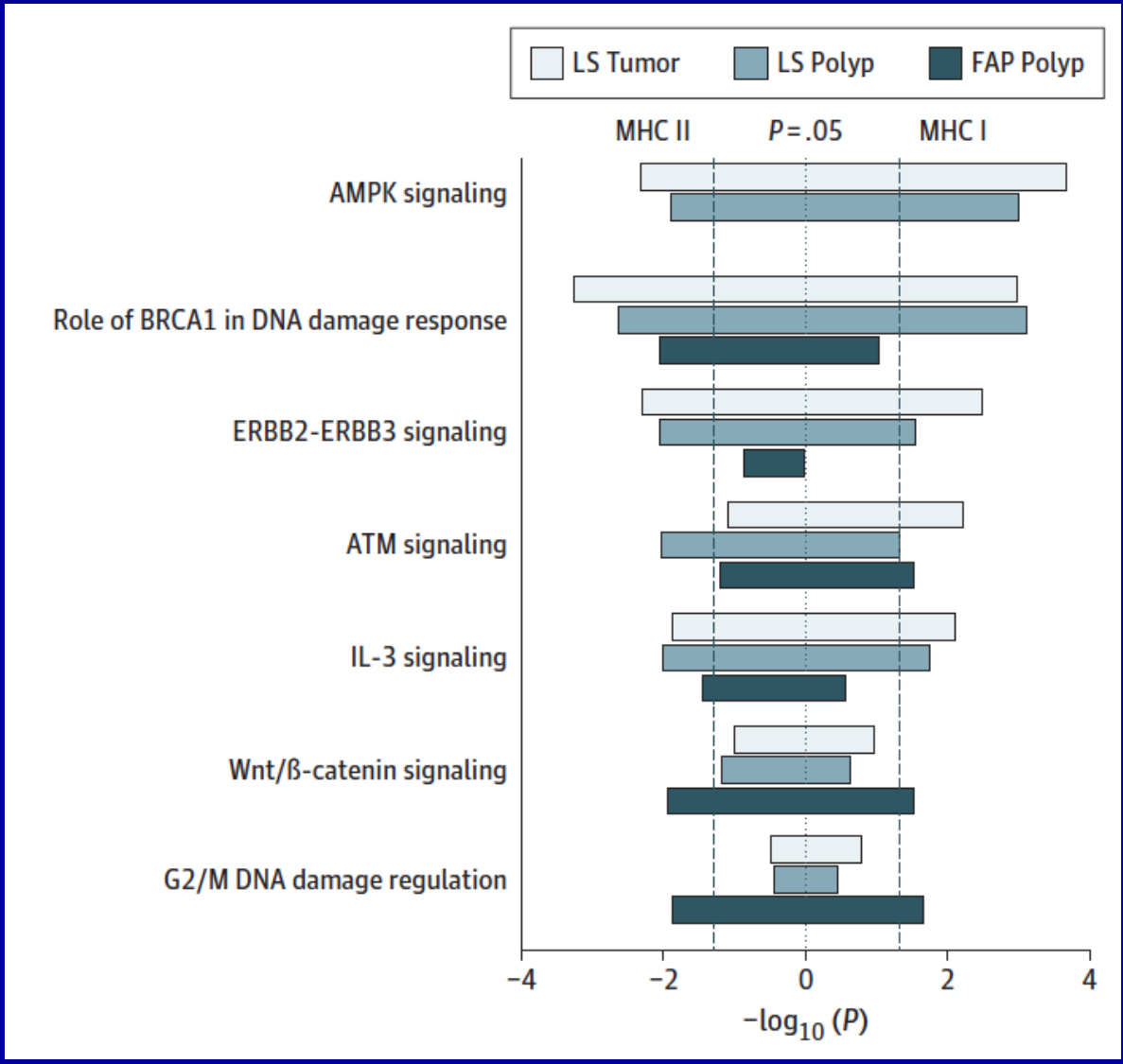
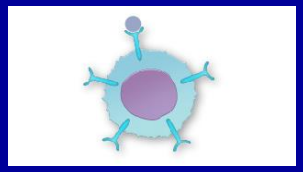


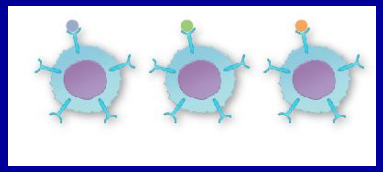
Chang, *JAMA Oncology (2018)*

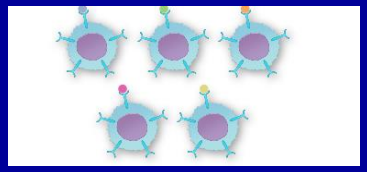
Lynch Syndrome

Epithelium

Neo-Antigens







Immune Signals (Activation)

CD4, IFN, PRF1, LAG3, PDL1, IL12A, TNF

CD4, IFN, PRF1, LAG3, PDL1, IL12A, TNF

FOXP3, CTLA4

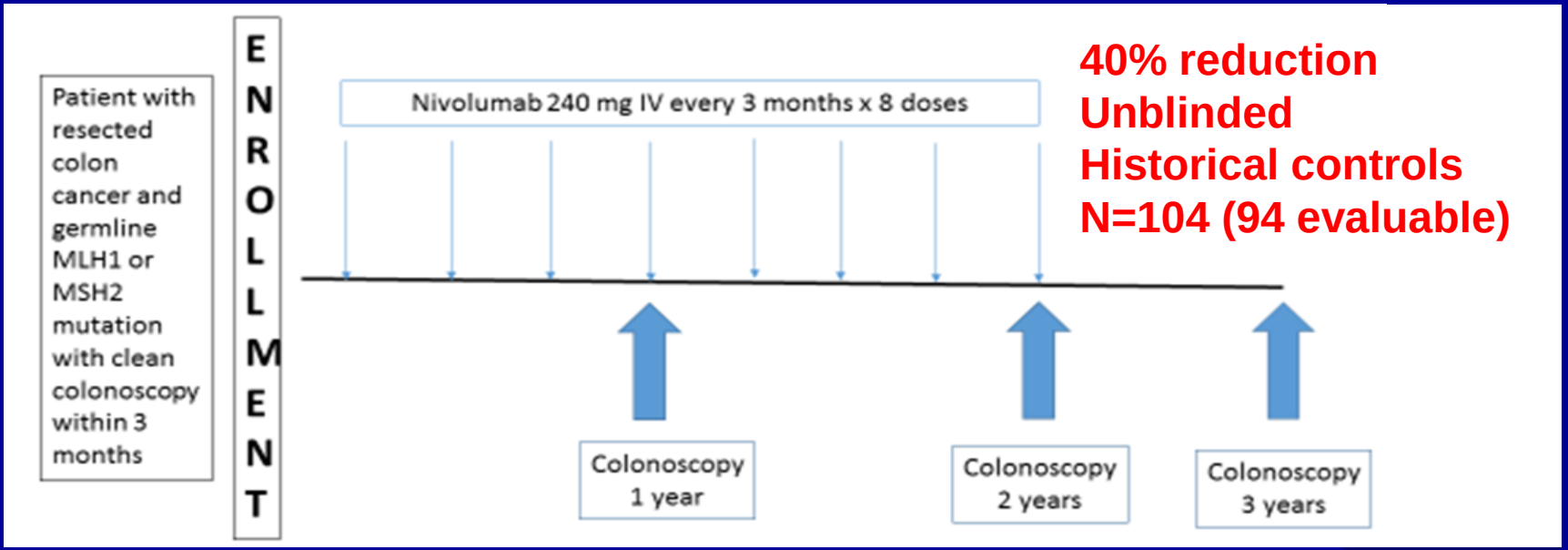
CD4, IFN, PRF1, LAG3, PDL1, IL12A, TNF

FOXP3, CTLA4

CD8A, GZMB, IL17A, TGFB1, PTGS2, IL1B, IL6, IDO1, NOS2, HIF1A

Willis, *CCR (2019)*; Chang, *JAMA Oncology (2018)*

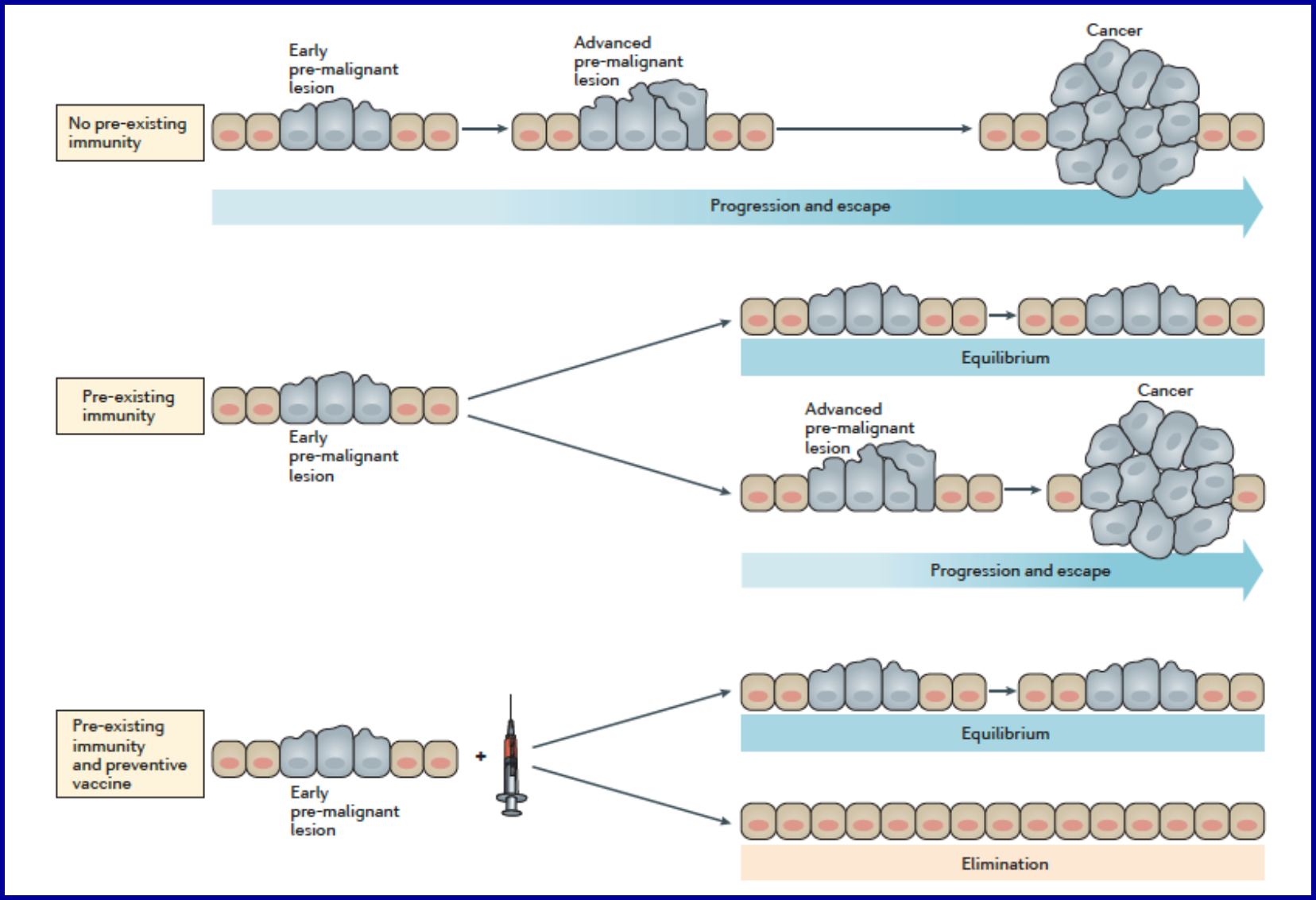
A Phase II Study of PD-1 Inhibition for the Prevention of Colon Adenomas in Patients With Lynch Syndrome and a History of Partial Colectomy



Primary Objective: Reduce incidence of adenomas
Others: Incidence of advanced adenomas, colon and other LS-related tumors, Safety, and Immunogenicity

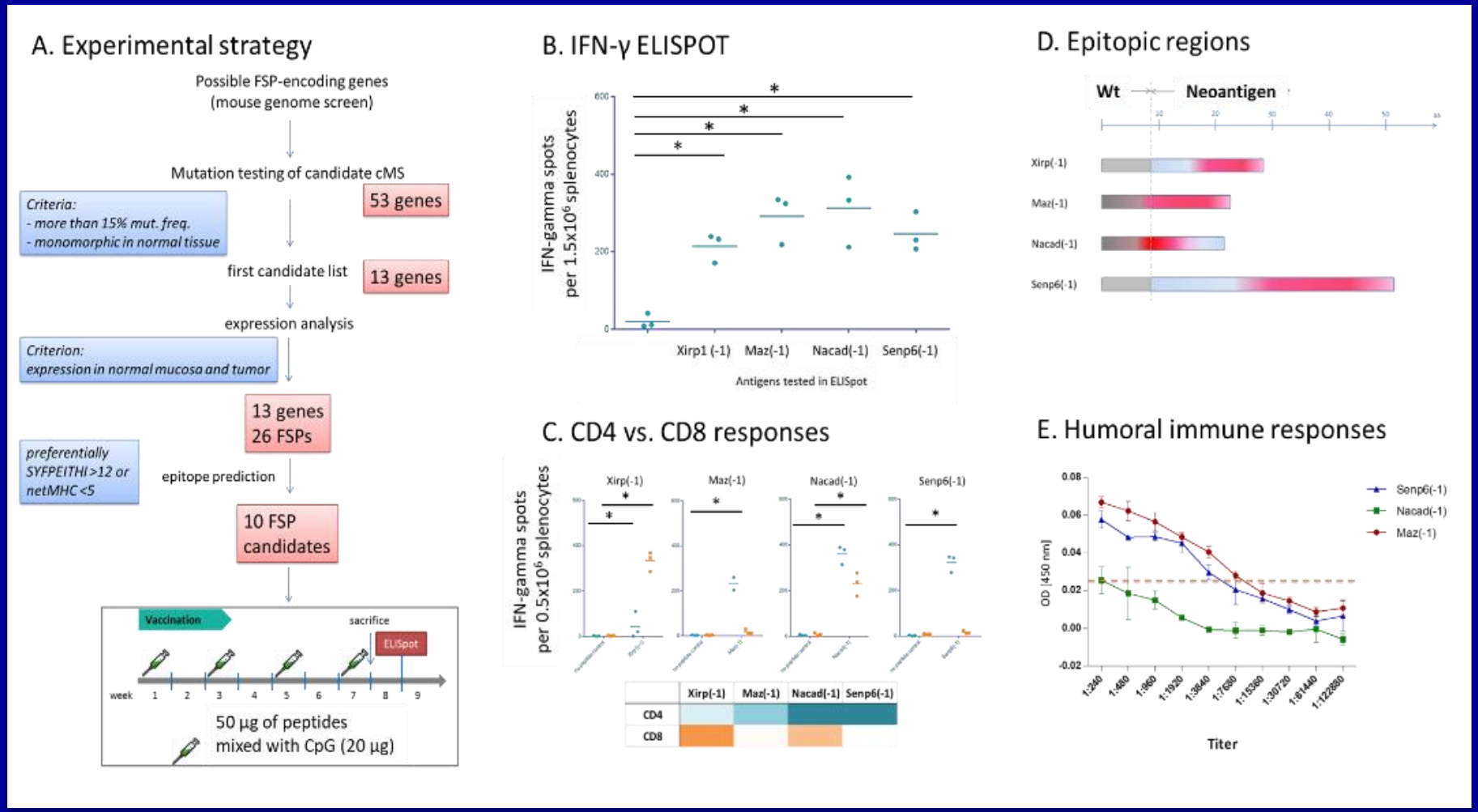
NCT03631641; Joanne Jeter, MD (PI) - OSCCC

Lynch Syndrome Vaccines



Finn, *Nature Review Immunology (2018)*

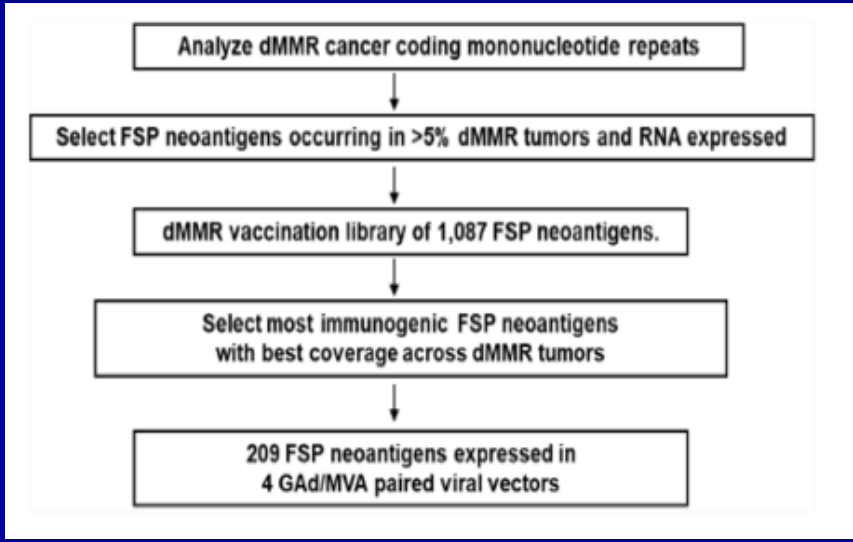
Frameshift Peptide Vaccine for prevention in LS mouse model

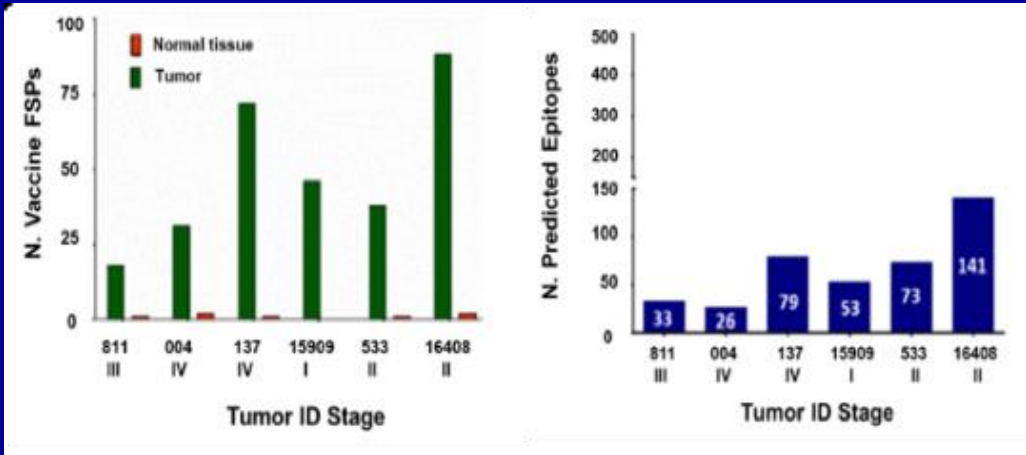


Slide courtesy of Steve Lipkin, MD, PhD;

Confidential – Unpublished Data – PLEASE DO NOT POST

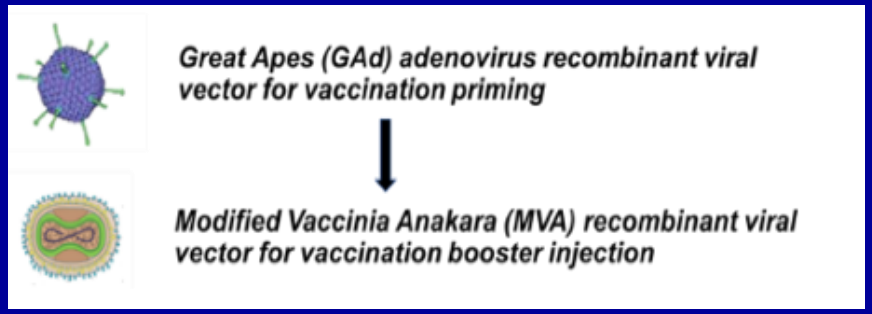
Lynch Syndrome Vaccines

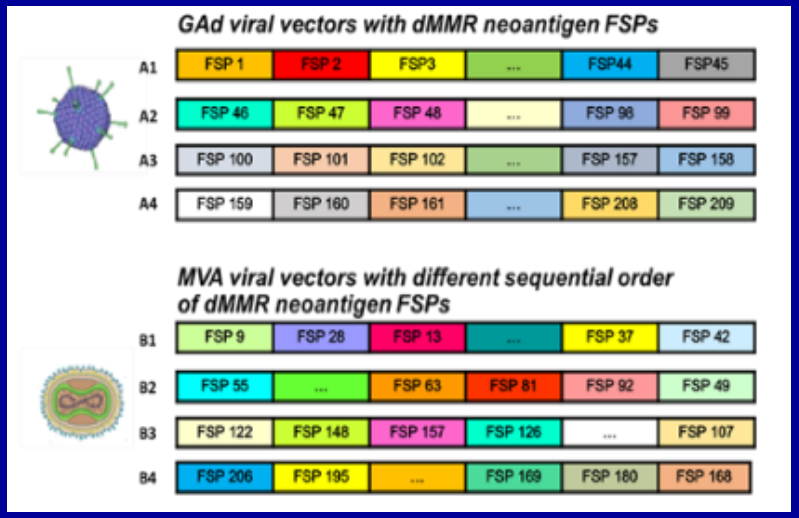


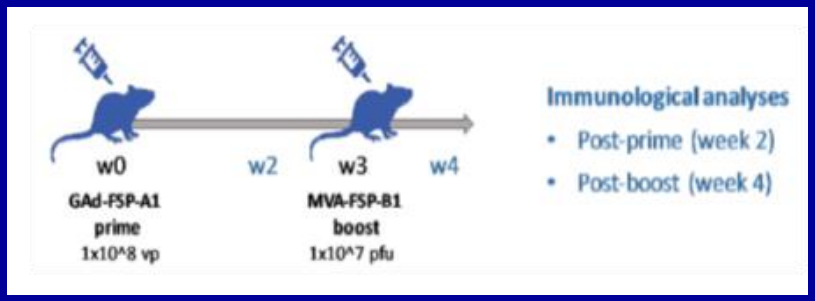


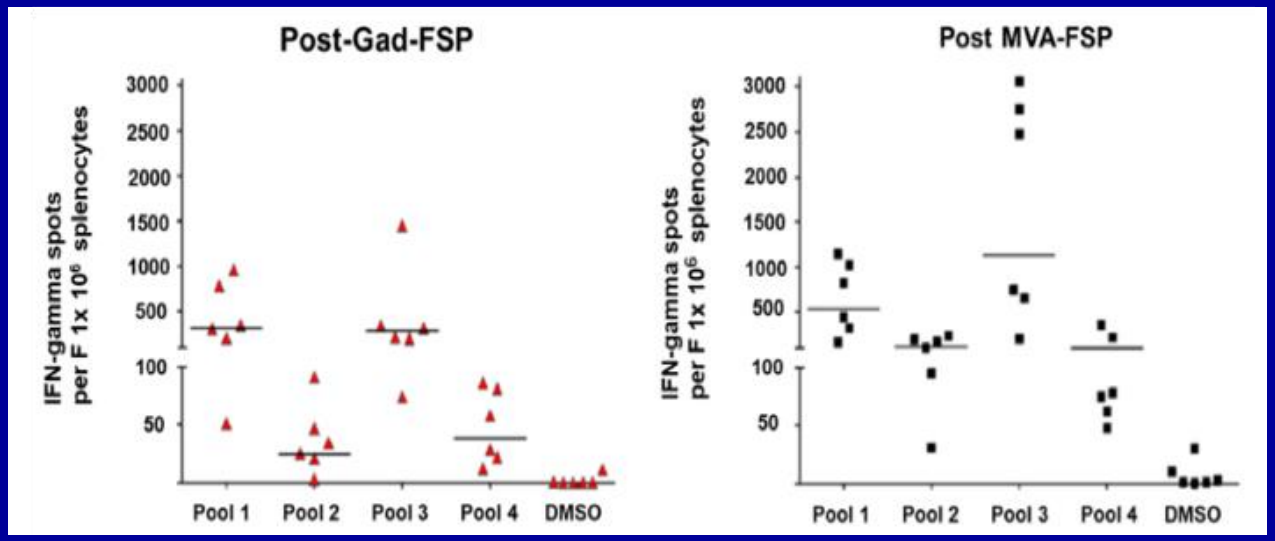
Scarselli, *STIC (2017)*

Lynch Syndrome Vaccines



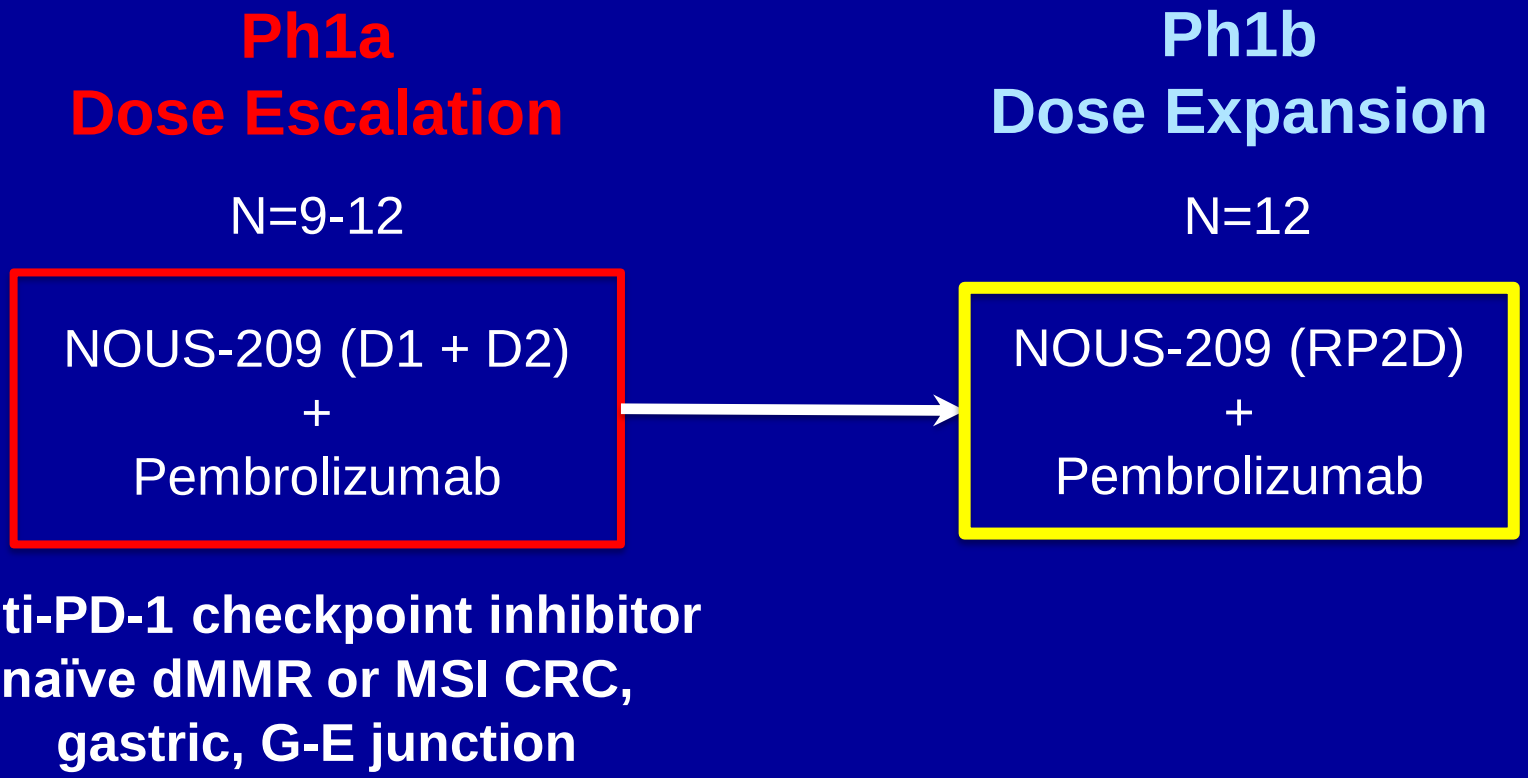






Scarselli, *STIC (2017)*

Lynch Syndrome Vaccines



Anti-PD-1 checkpoint inhibitor naïve dMMR or MSI CRC, gastric, G-E junction

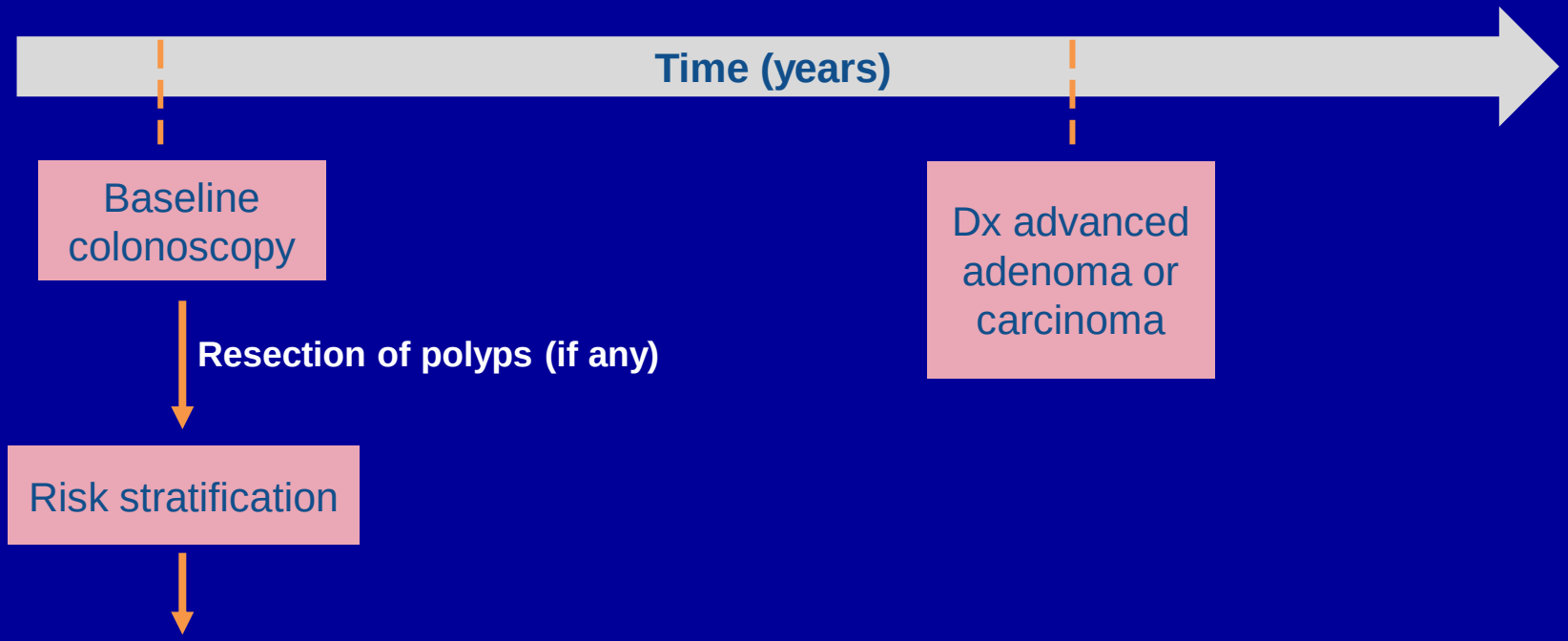
Estimated Start date: September 2019

Courtesy of Paola Antonini & Elisa Scarselli – NousCom – NCT 04041310

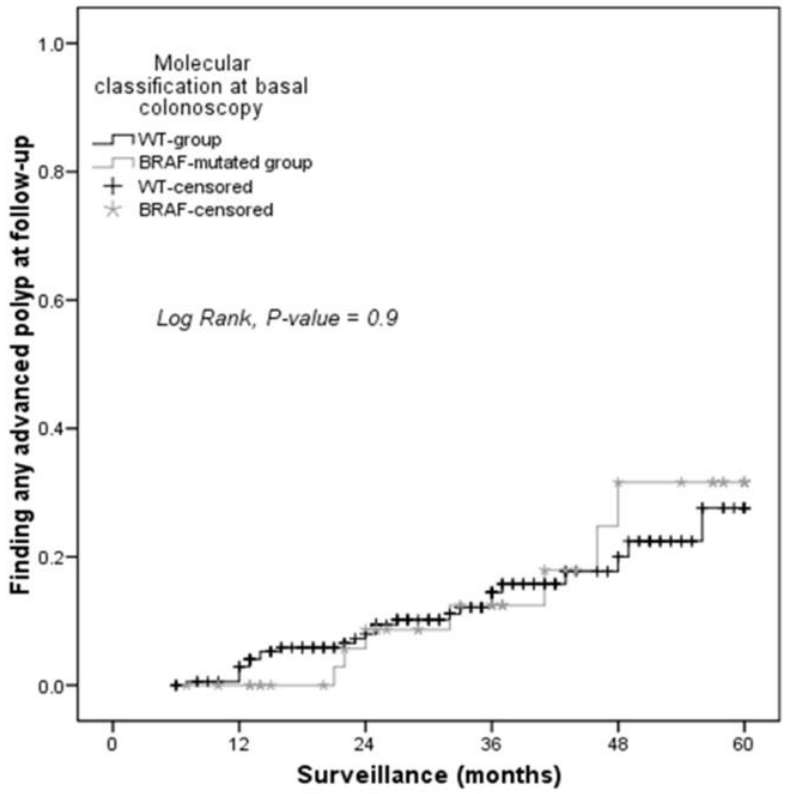
Conclusions

- LS polyps display a unique inmunoprofile with overexpression of immune checkpoints
- Activation of the immune system was independent of NeoAg and Mut rates
- Hypemut LS polyps display immune tolerance prior to carcinoma progression
- Neoantigens are involved in DNA repair mechanisms
- Potential use of CPI and vaccines in LS
- Clinical trials in ‘rare’ pops are feasible

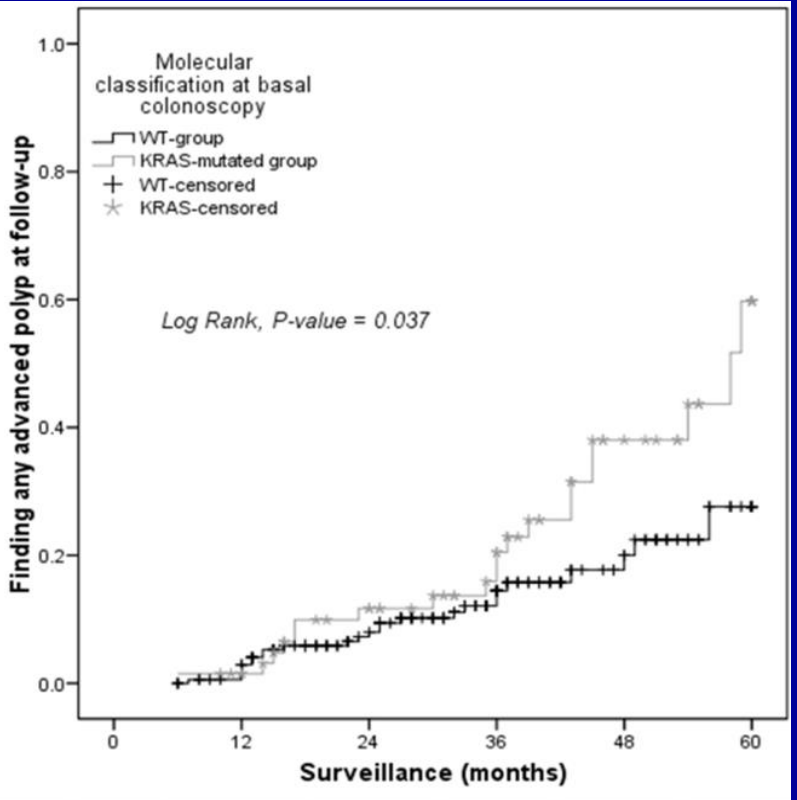
Refining CRC surveillance



Does the molecular profile of a polyp have prognostic significance?



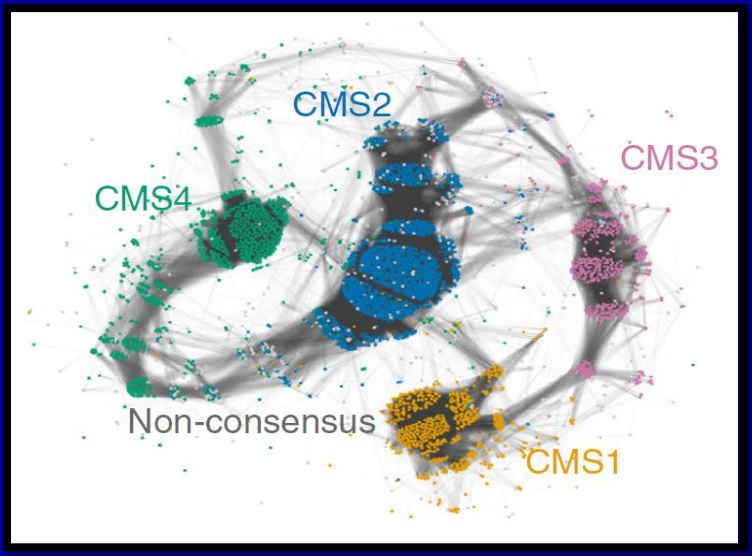
Wild-Type group	180	171	129	74	35	8
***BRAF*-mutated group**	43	43	31	21	10	3



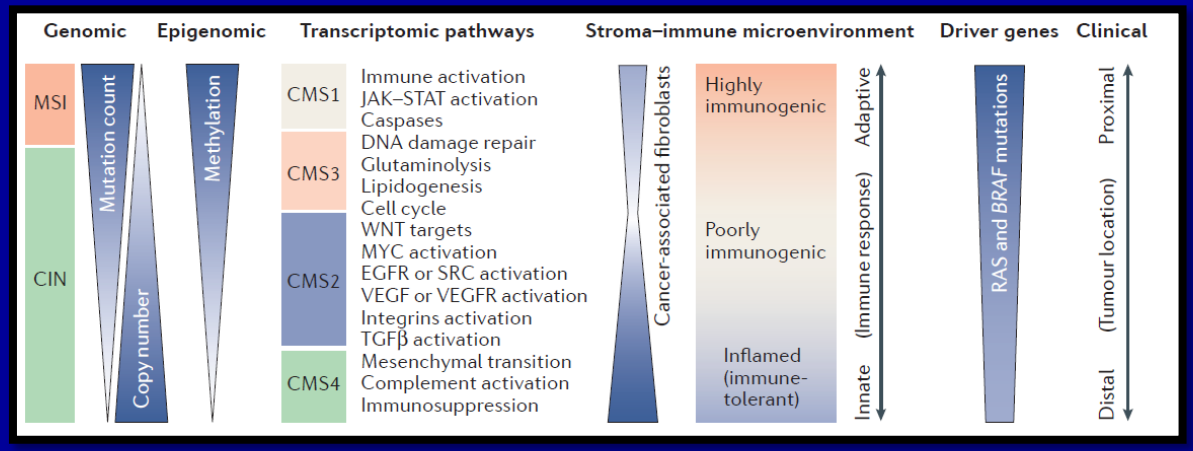
Wild-Type group	180	171	129	74	35	8
***KRAS*-mutated group**	66	62	48	36	15	4

Miriam, *Plos One* (2017)

Adenoma CMS subtypes

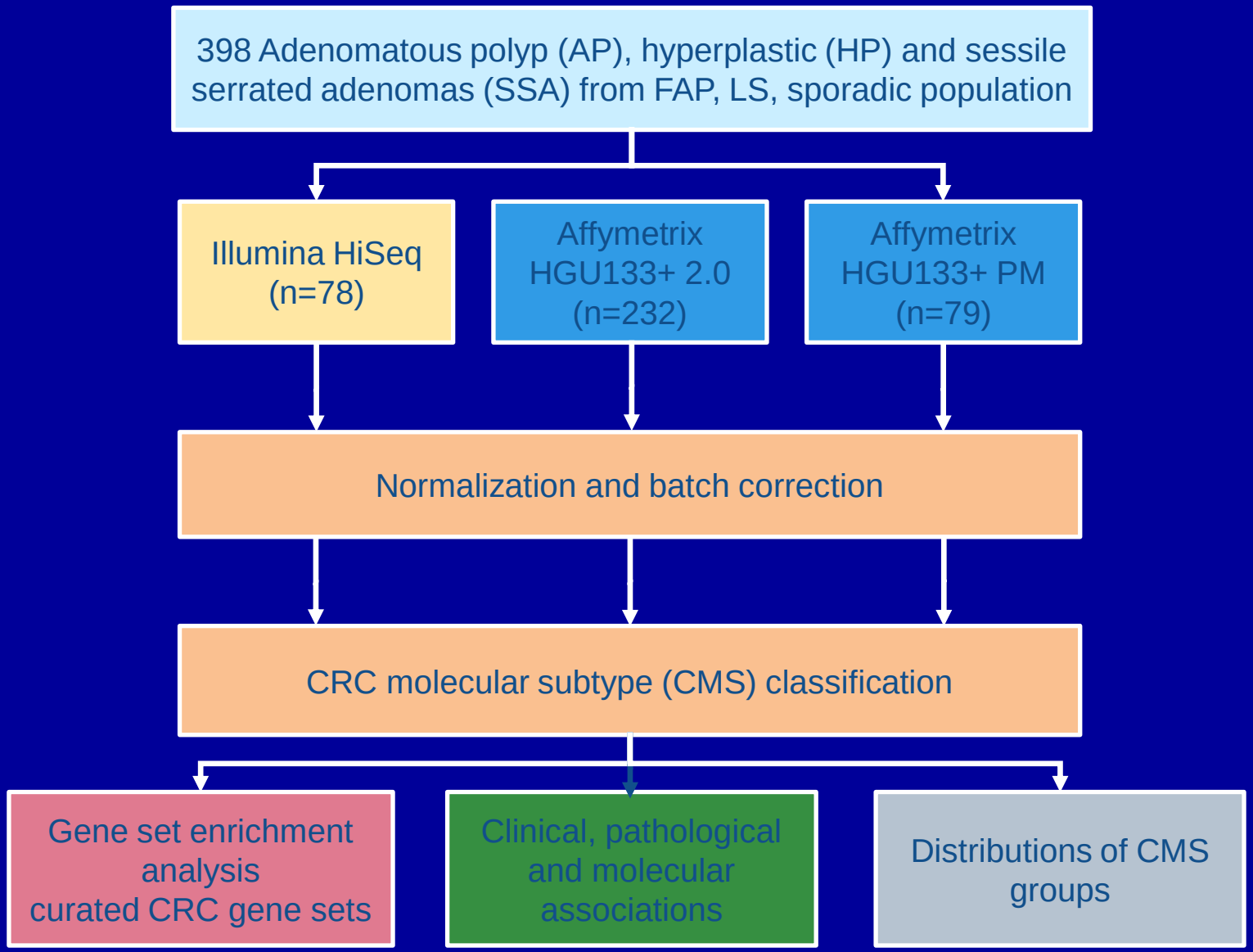


CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

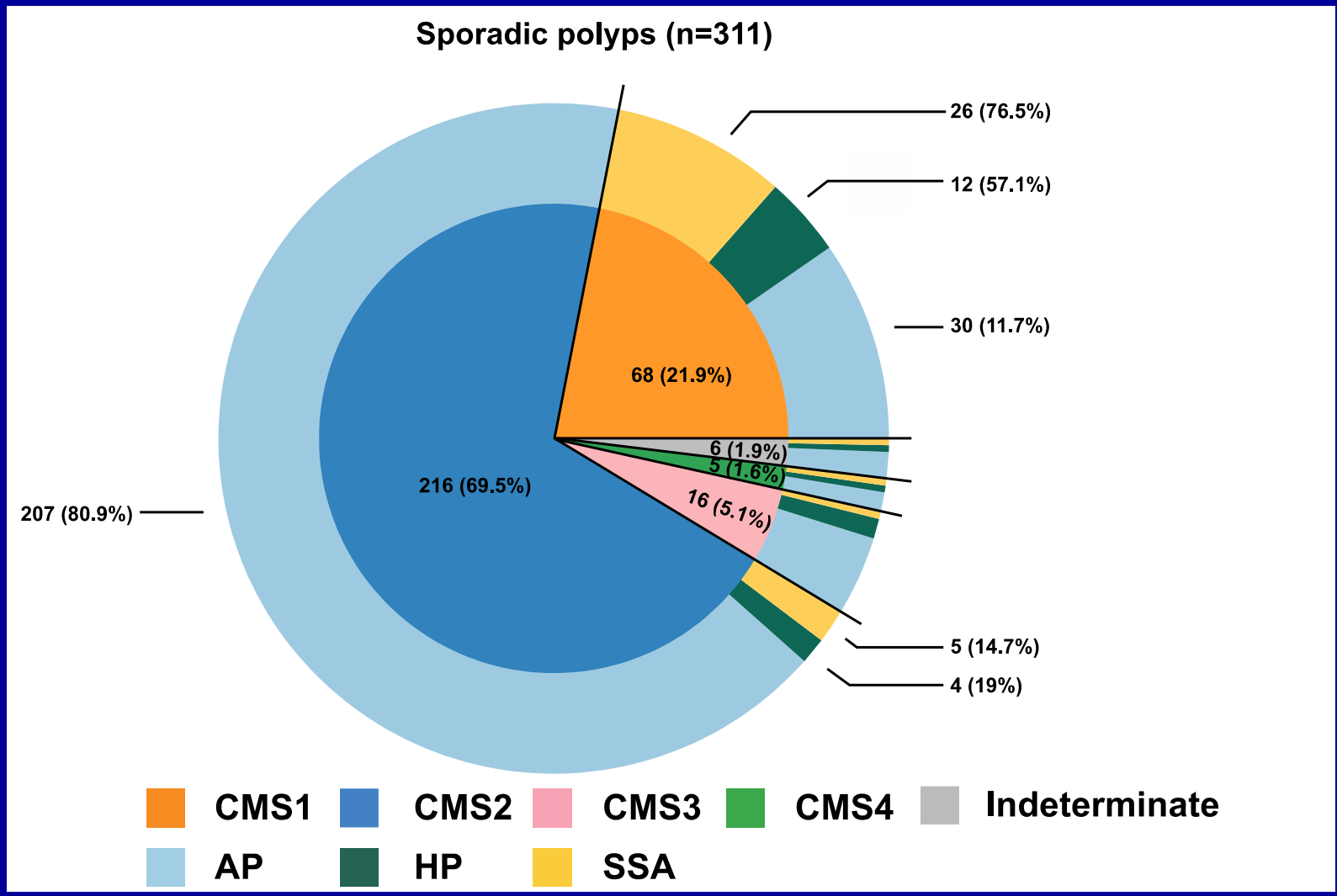


Guinney, *Nature Medicine* (2015); Dienstmann, *Nature Reviews Cancer* (2017)

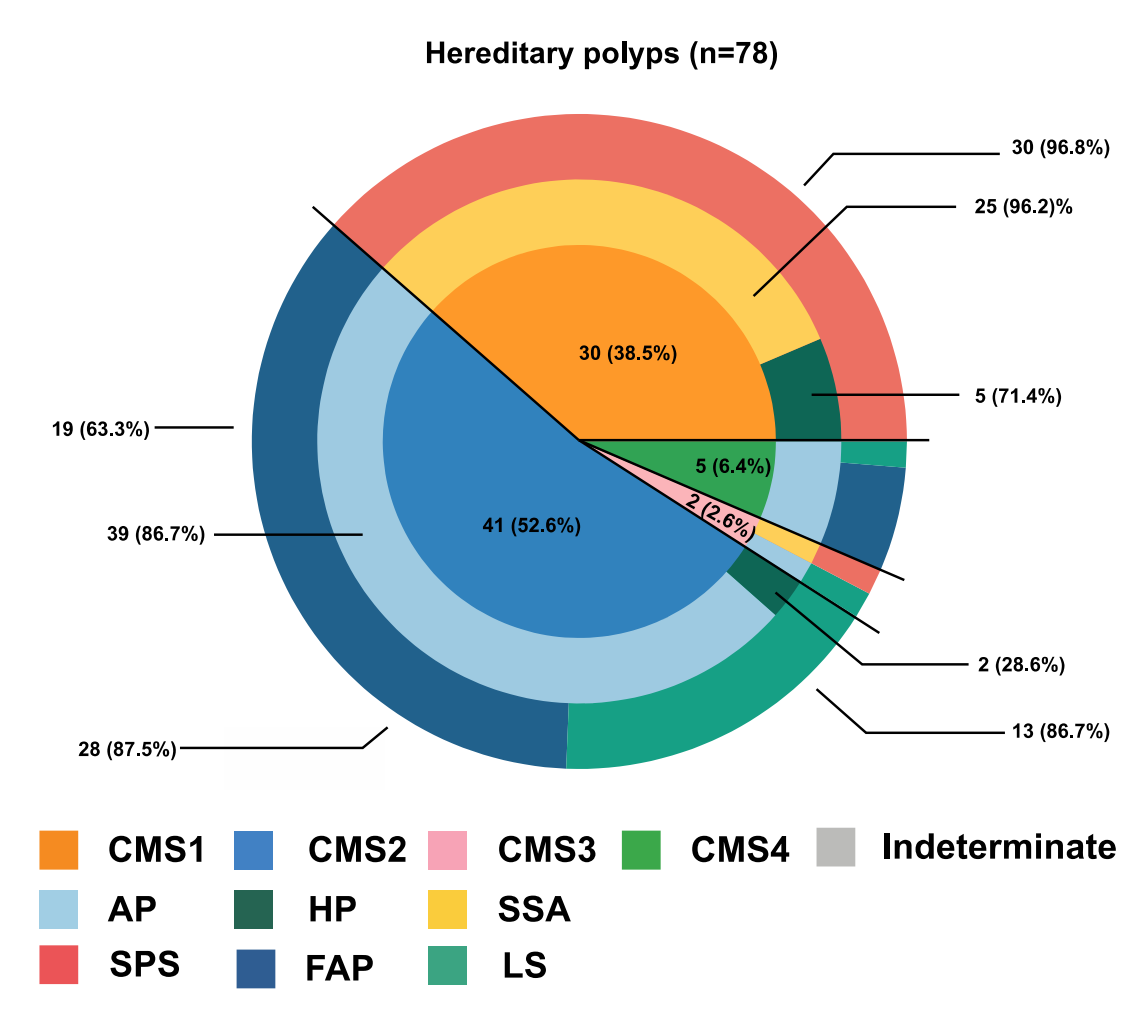
Analysis workflow



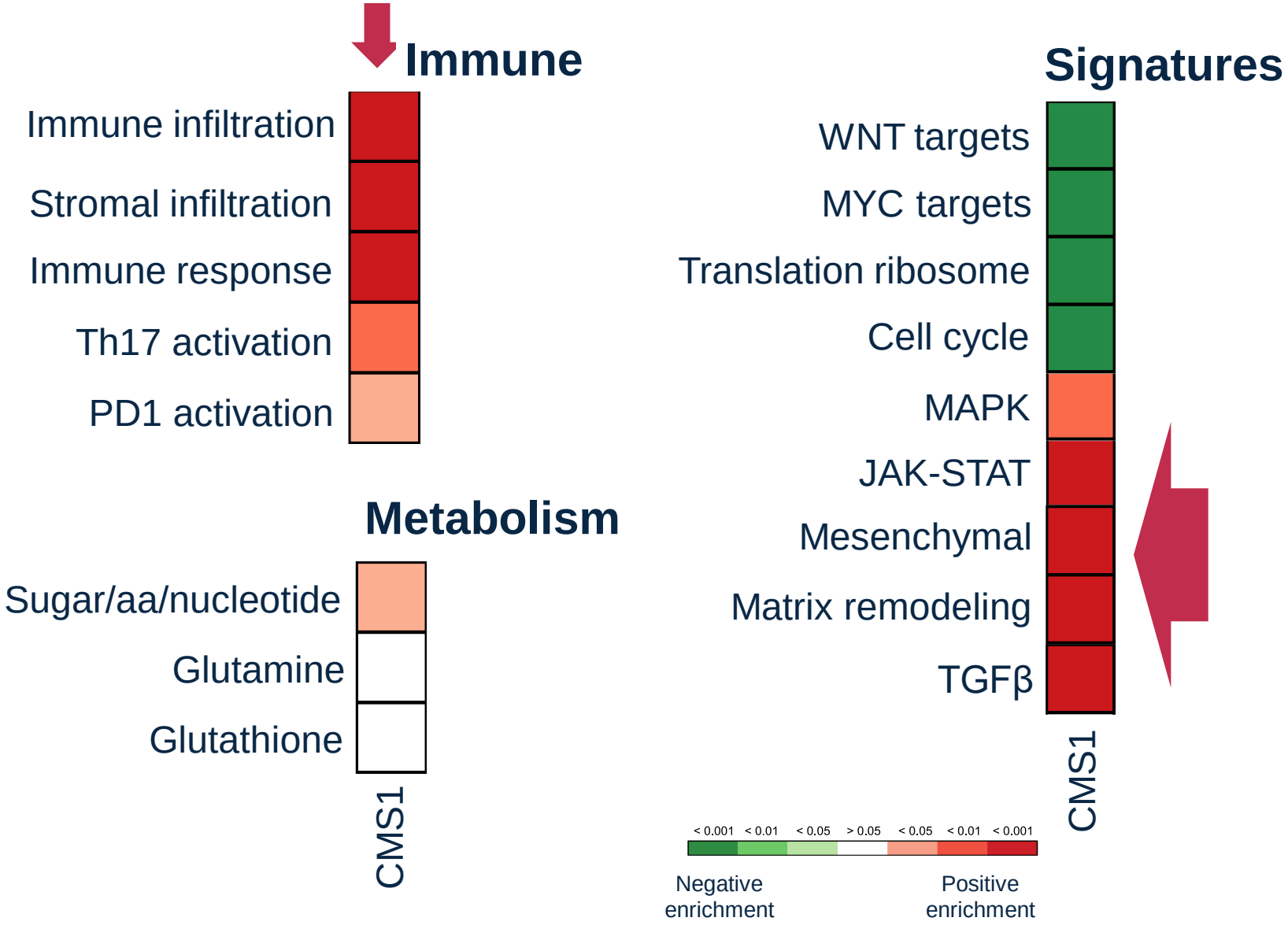
CMS1 and CMS2 are major subtypes in premalignancy



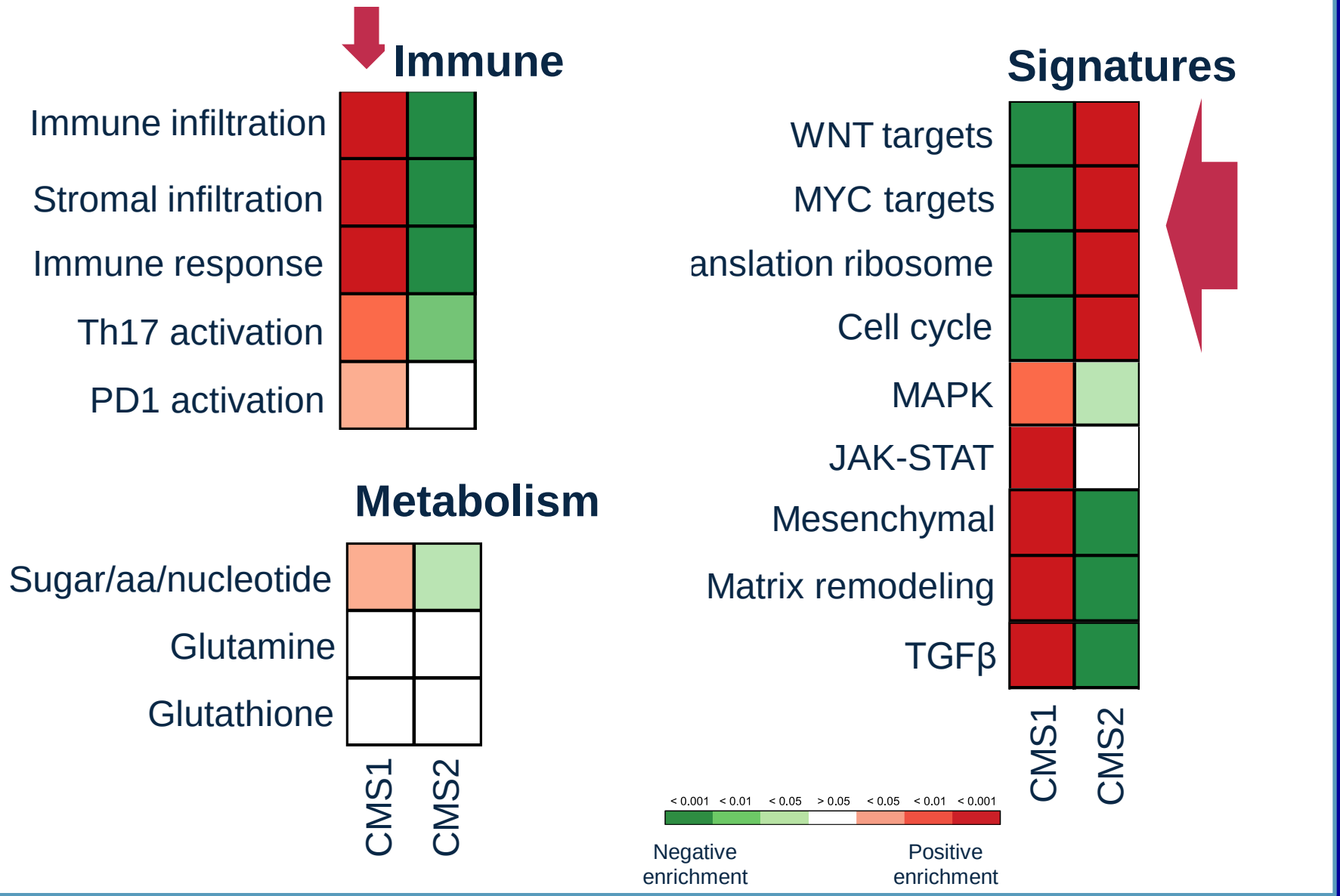
CMS1 and CMS2 are major subtypes in premalignancy



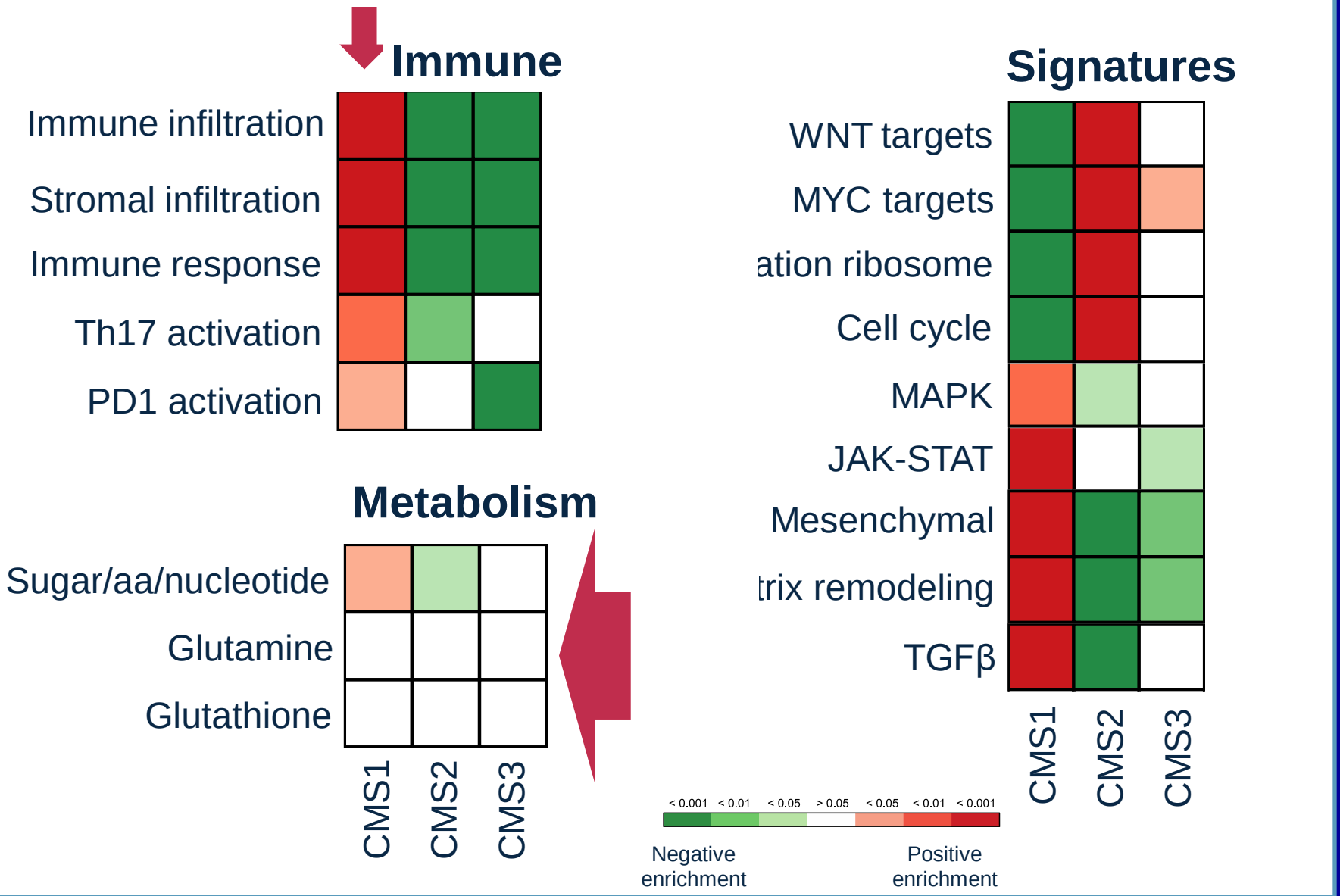
Pathway enrichment analysis



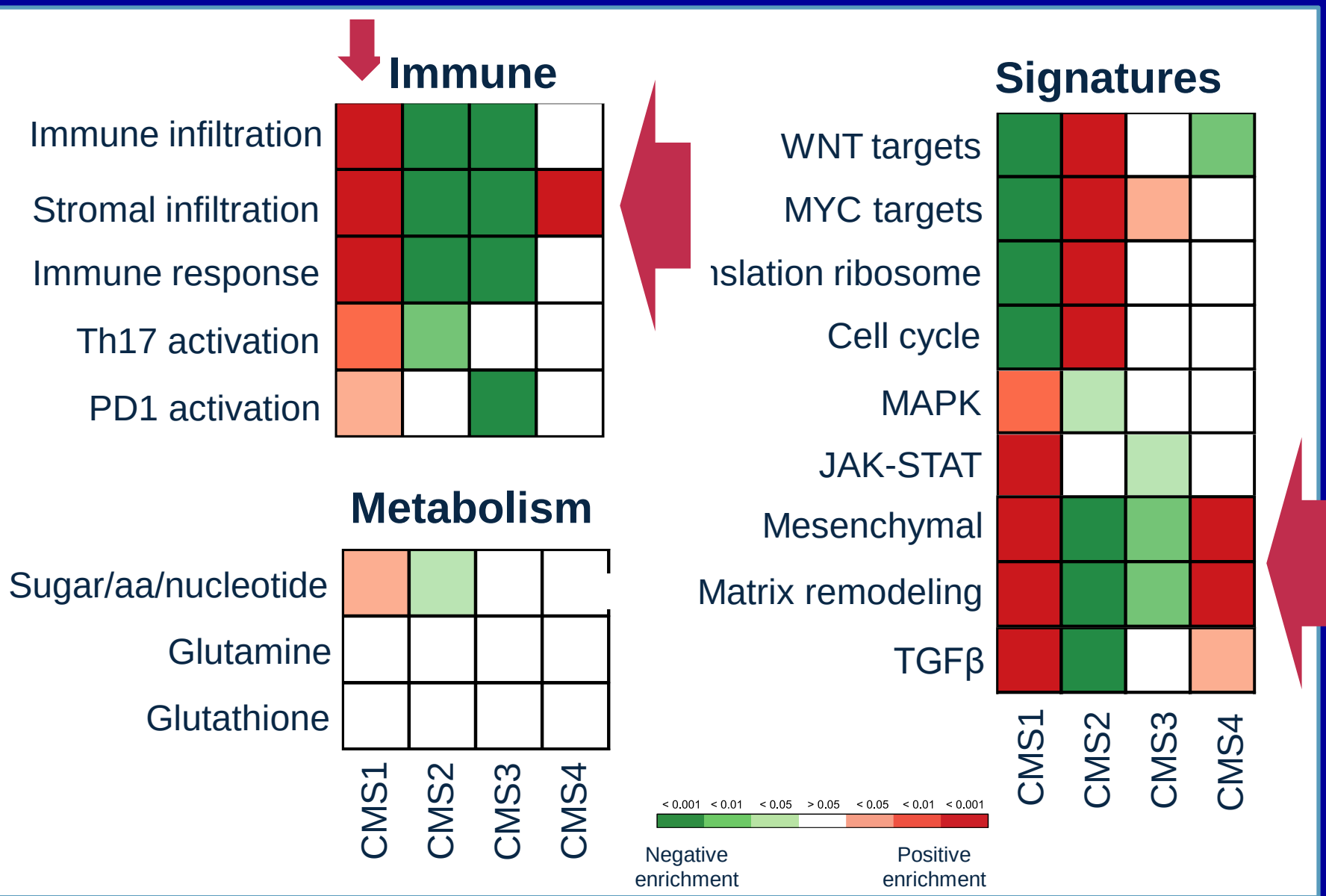
Pathway enrichment analysis



Pathway enrichment analysis



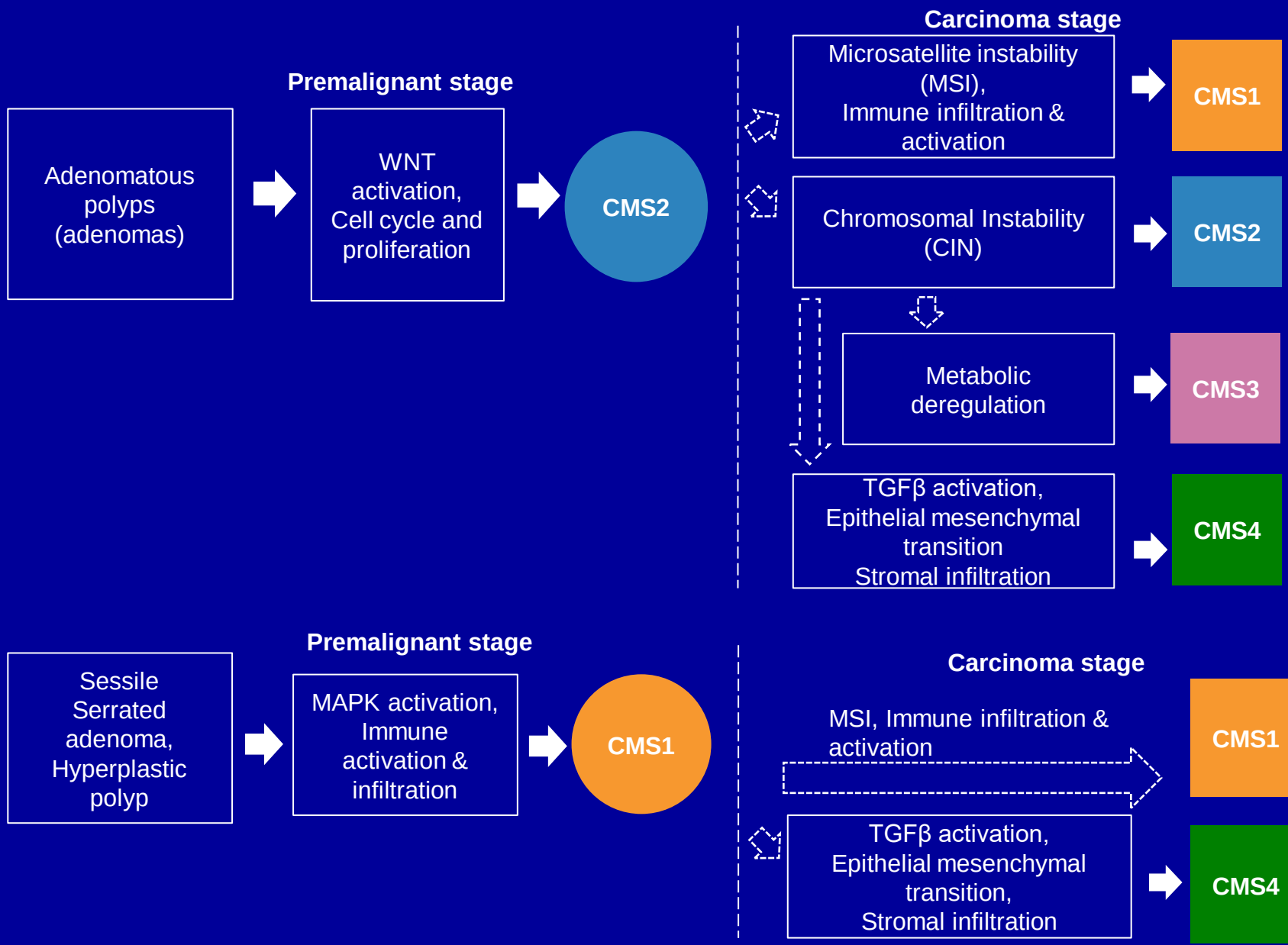
Pathway enrichment analysis



Clinical and pathological associations

Characteristics		CMS1	CMS2	CMS3	CMS4
Gender	n	57	218	12	7
	female	54%	47%	17%	57%
	male	46%	53%	83%	43%
	p-value	2.41E-01	7.91E-01	3.80E-02	7.11E-01
Presence of high-grade dysplasia (HGD)	n	30	246	13	8
	AP	60%	76%	85%	100%
	AP with HGD	40%	24%	15%	0%
	p-value	4.57E-02	5.95E-01	7.42E-01	2.07E-01
Location	n	59	210	11	7
	left	32%	66%	27%	86%
	right	68%	34%	73%	14%
	p-value	1.28E-05	1.27E-05	5.79E-02	2.45E-01
BRAF V600E	n	63	164	8	1
	Mutant	24%	2%	0	0
	Wildtype	76%	98%	100%	100%
	p-value	9.95E-07	7.73E-06	1.00E+00	1.00E+00
***KRAS* codon 12 and 13**	n	51	164	7	1
	Mutant	2%	13%	14%	0
	Wildtype	98%	87%	86%	100%
	p-value	1.94E-02	4.70E-02	5.55E-01	1.00E+00

Pathway activation driving CMS



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MDA GI SPORE – Project #2

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