

Day 4. Cancer Genome Analysis - Latin America and the Caribbean Mutational Signatures and Clinical Examples



Contribution of the mutational signatures to CRC and how this contribute to the discovery of new candidate genes

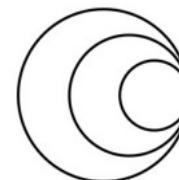
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Contributions of the mutational signatures to colorectal cancer

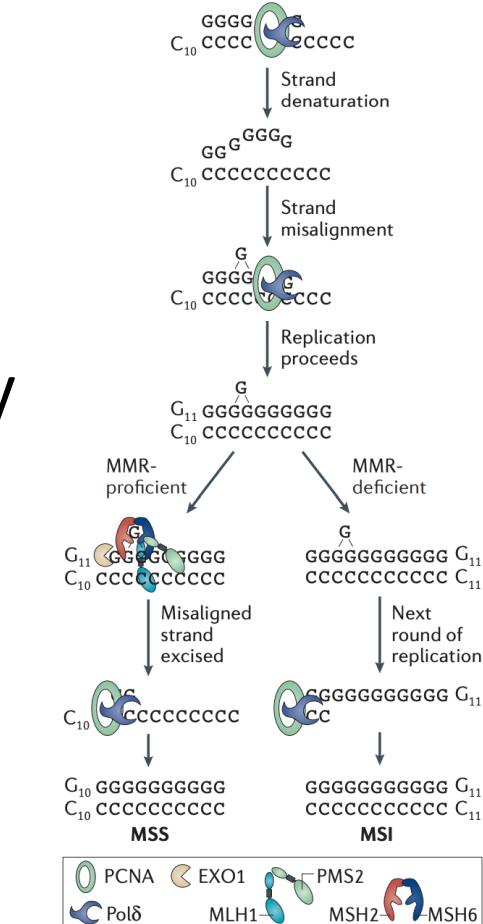
Mismatch repair deficiency – why is so important?

it is an agnostic predictive marker of response to immunotherapy

MSI-h tumors So much mutations So much neontigens So much TILs TILs express PD1

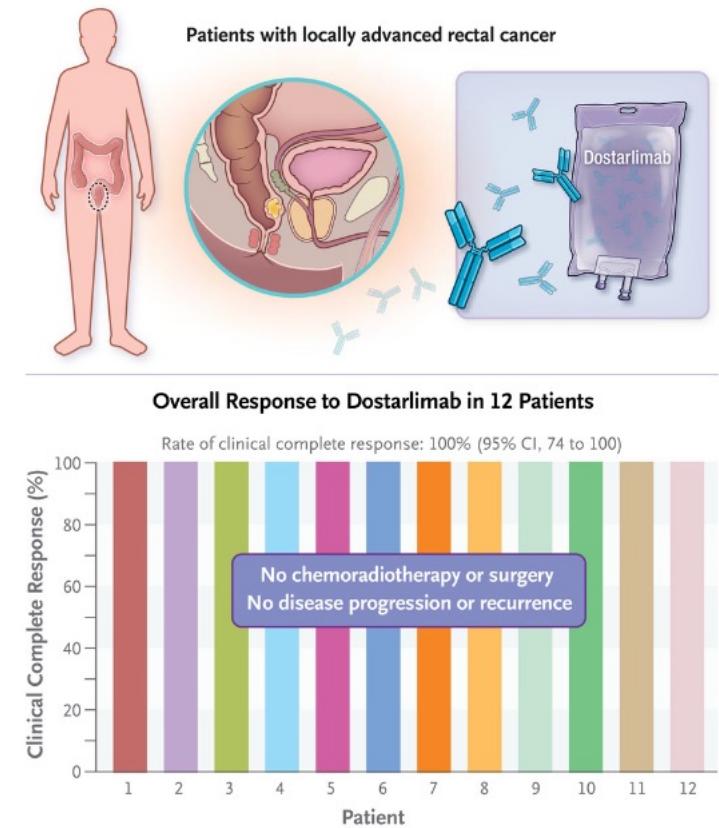
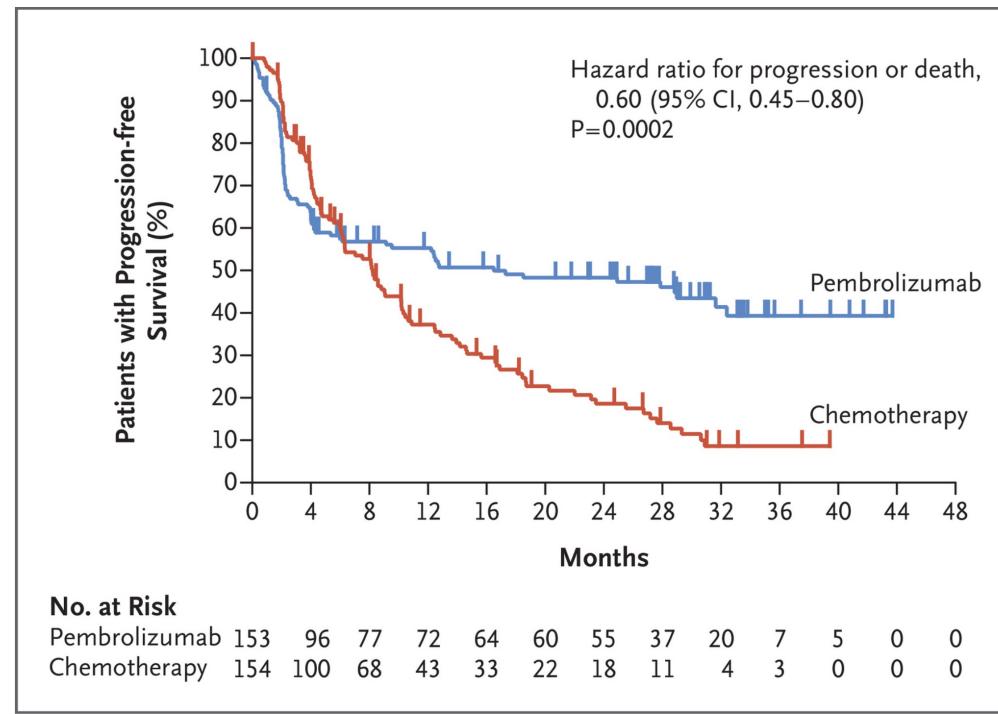
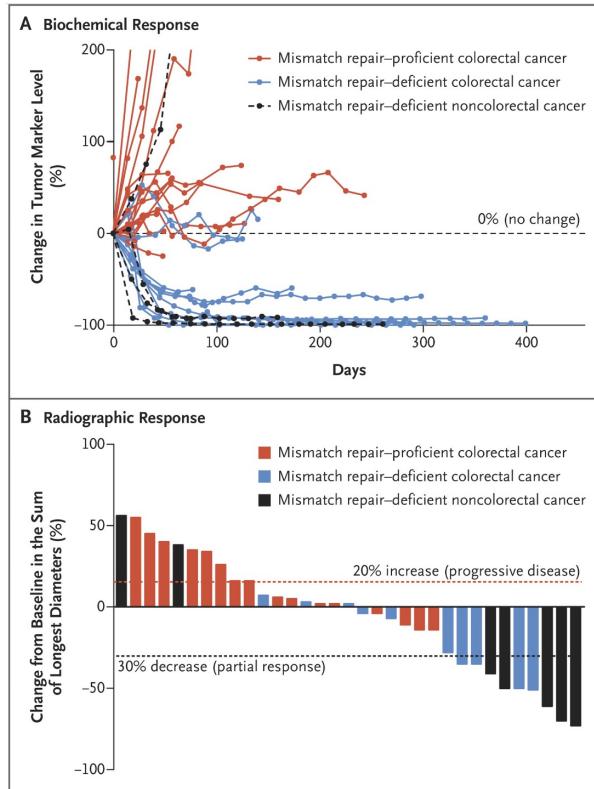
Anti-PD1 prevents this activation of immunotolerance

It is a molecular somatic feature of patients with a suspected hereditary syndrome



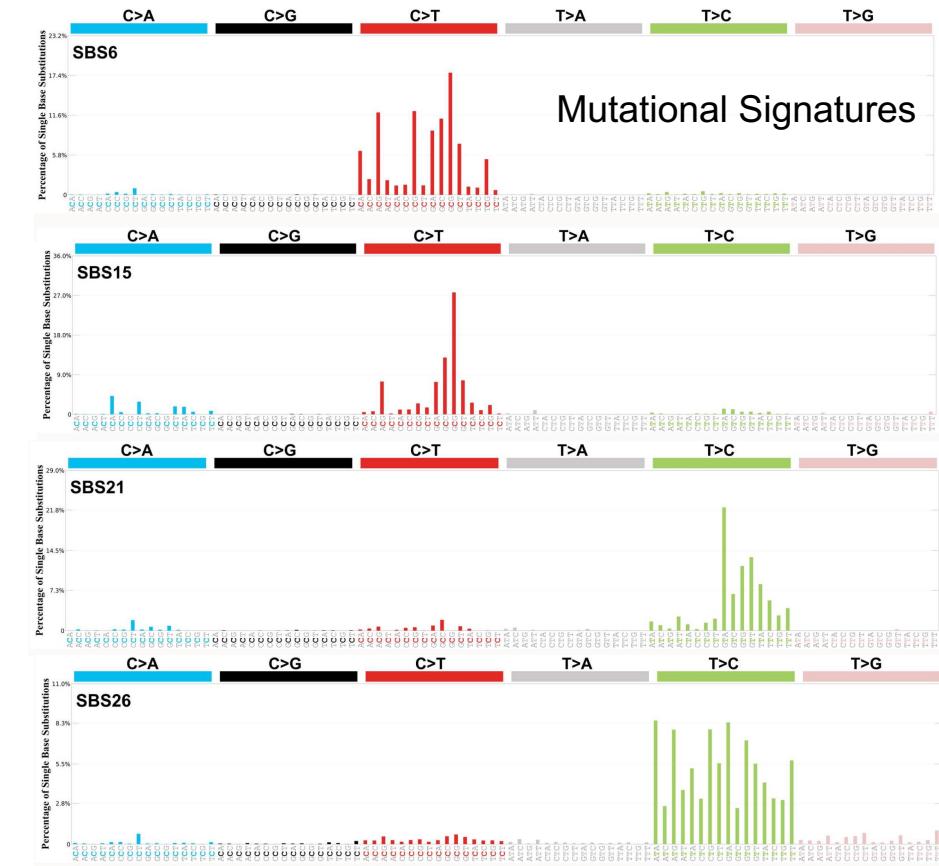
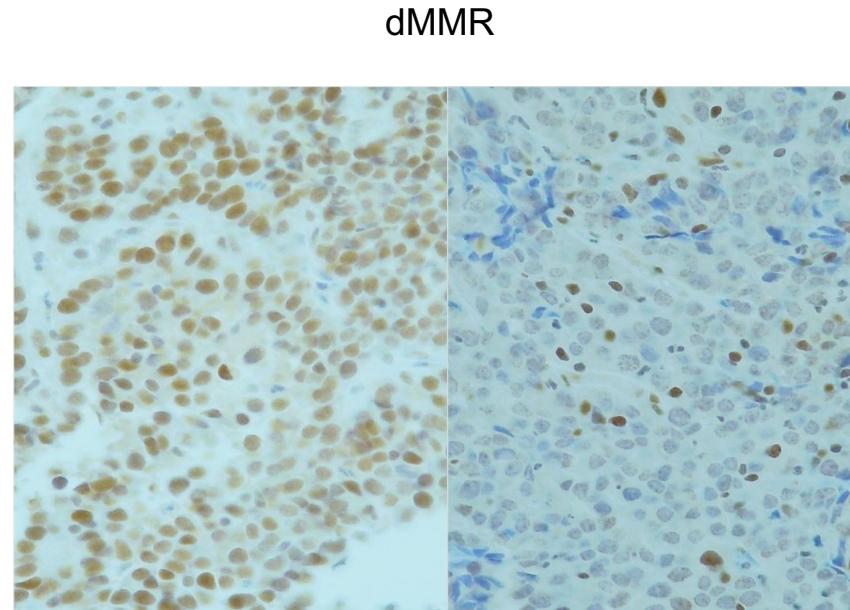
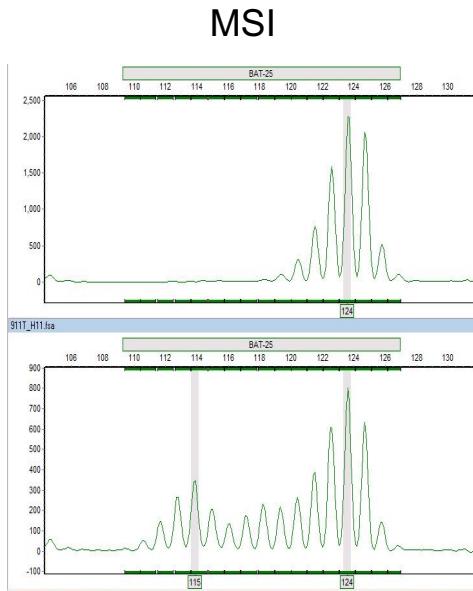
Contributions of the mutational signatures to colorectal cancer

Agnostic predictive marker of response to immunotherapy



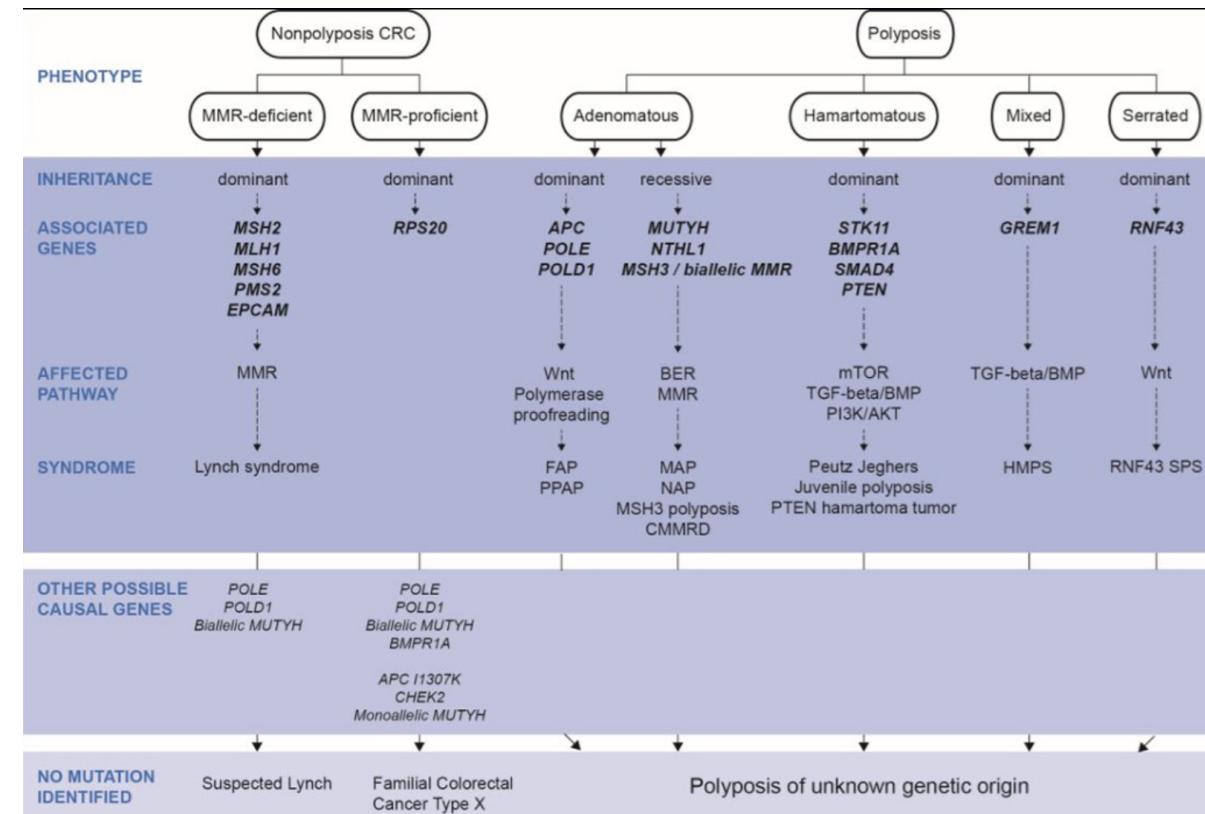
Contributions of the mutational signatures to colorectal cancer

Mismatch repair deficiency – what are the ways to measure it?



Contributions of the mutational signatures to colorectal cancer – CRC germline landscape

It is a molecular somatic feature of patients with a suspected hereditary syndrome



MLH1/PMS2 MSH2/MSH6

POLE or POLD1 exonuclease domain

Sporadic MSI

Lynch

Sporadic High TMB
MSS

PPAP

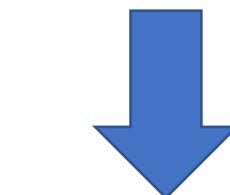


1st Hit Somatic

2nd Hit Somatic



dMMR/MSI



1st Hit Germline

2nd Hit Somatic



dMMR/MSI

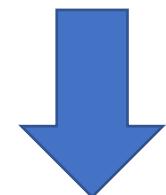


1st Hit Somatic

2nd Hit Somatic



pMMR/MSS or dMMR/MSI



1st Hit Germline

2nd Hit Somatic



High TMB

A blue wedge shape pointing upwards, labeled "High TMB" at its base.

MLH1/PMS2 MSH2/MSH6

POLE or POLD1 exonuclease domain

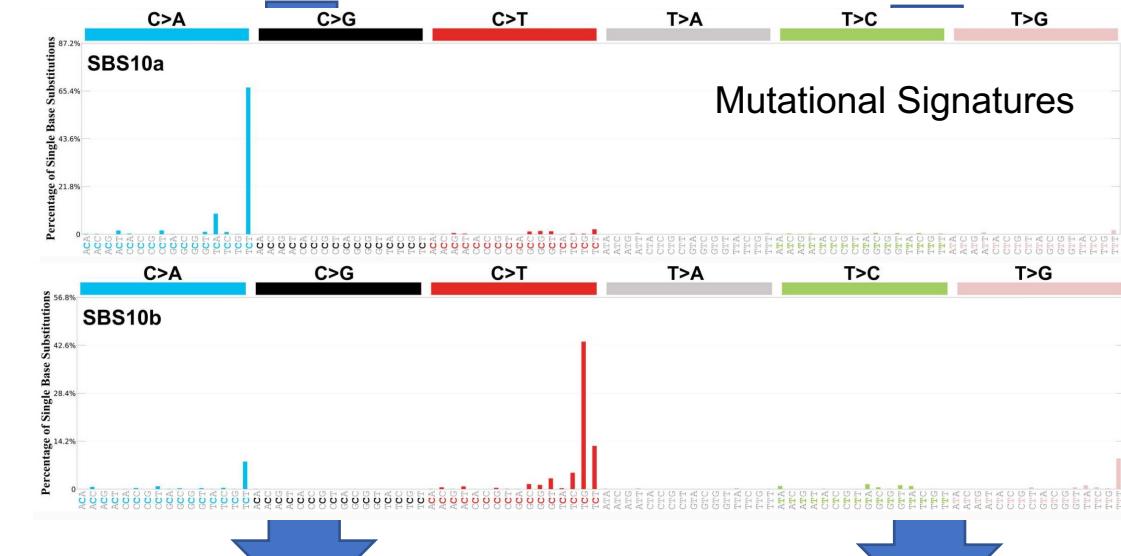
Sporadic MSI

Lynch



Sporadic High TMB MSS

PPAP



pMMR/MSS or dMMR/MSI

High TMB

Contributions of the mutational signatures to colorectal cancer

Lynch syndrome is caused by mutations in germline in genes responsible for DNA mismatch repair (MMR) *MLH1/MSH2/MSH6/PMS2*

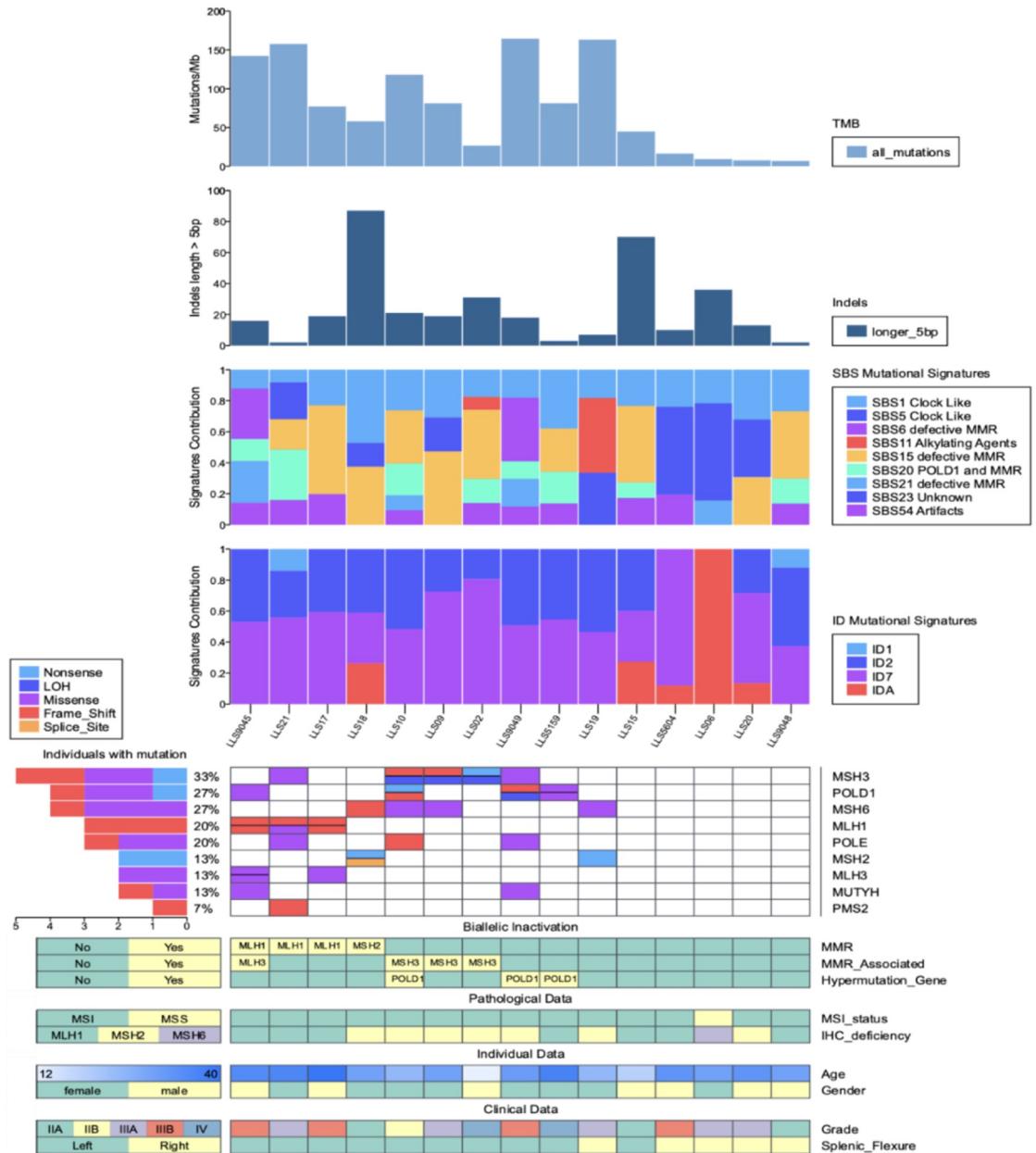
Sometimes, we have doubts about how to classify pathogenic variants in cancer.

Why is so important to sequence tumors to make better decisions about the classification of suspected pathogenic variants

Contributions of the mutational signatures to colorectal cancer

But, what happens when there are early onset patients with CRC (under 40yo) that have MSI-high in their tumors but they don't have germline variants (WT for those genes in germline)?

Lynch-like Syndrome



Temozolamide treatment for an early lymphoma could inactivate with mutations the MMR genes and as consequence this patient have somatic MMR. (30yo patient with an MSI-h CCR tumor)

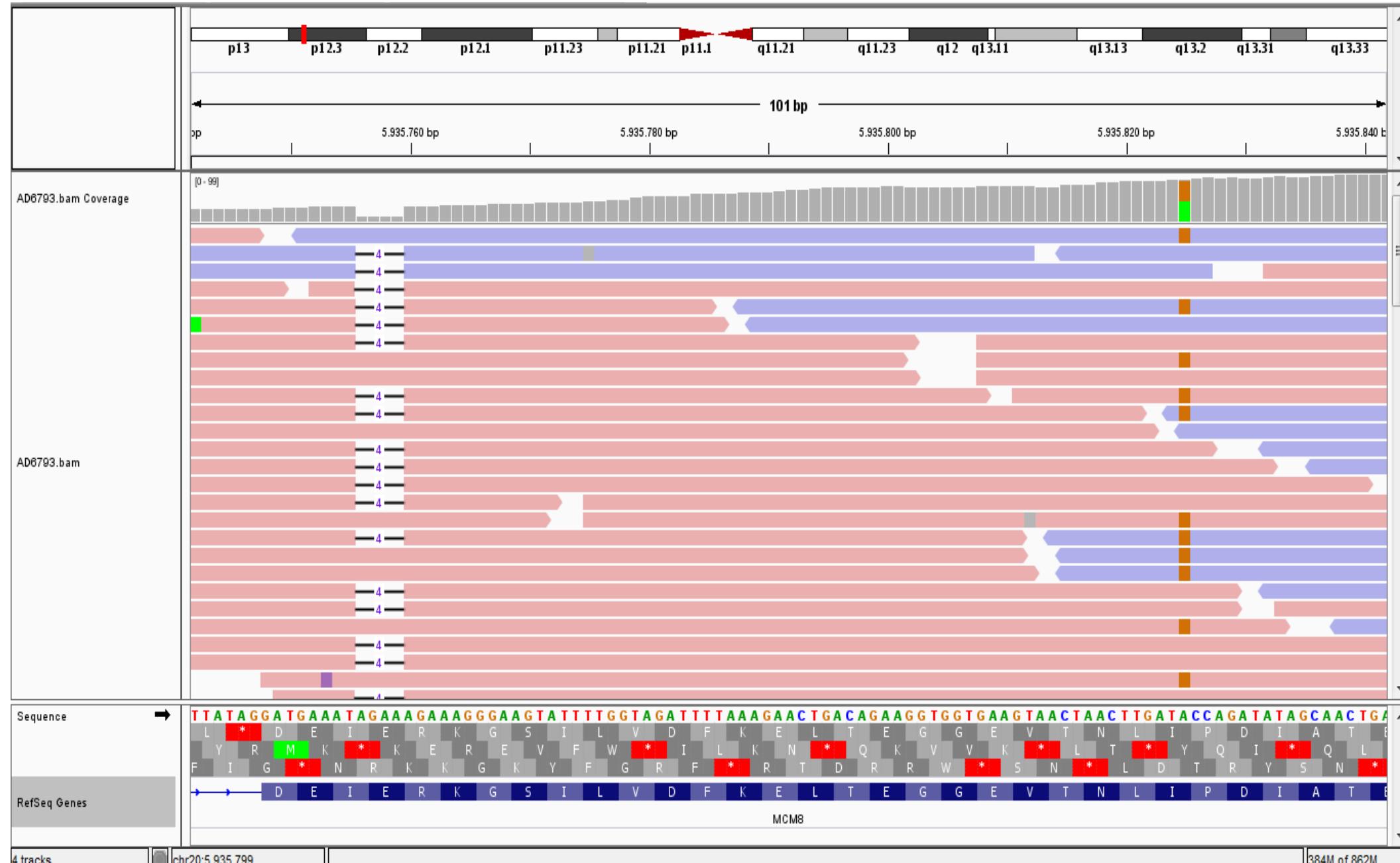
ORIGINAL REPORTS | Gastrointestinal Cancer

Treatment: TMZ followed by combination with low-dose ipilimumab and nivolumab.

Outcome: MSS CCR → MSI CCR

Can you imagine how these researchers are using mutational signatures in this study?

Golubicki et al, Cancers 2021; Morano F et al, JCO 2022.



Contributions of the mutational signatures to colorectal cancer

MCM8 gene

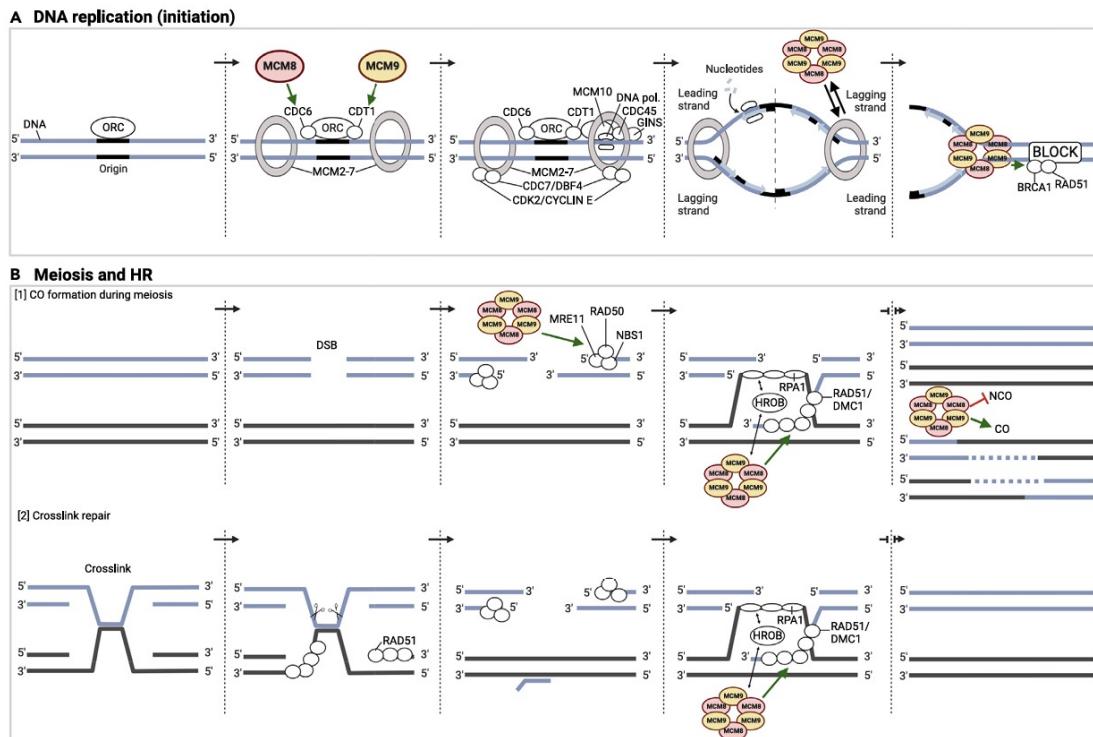
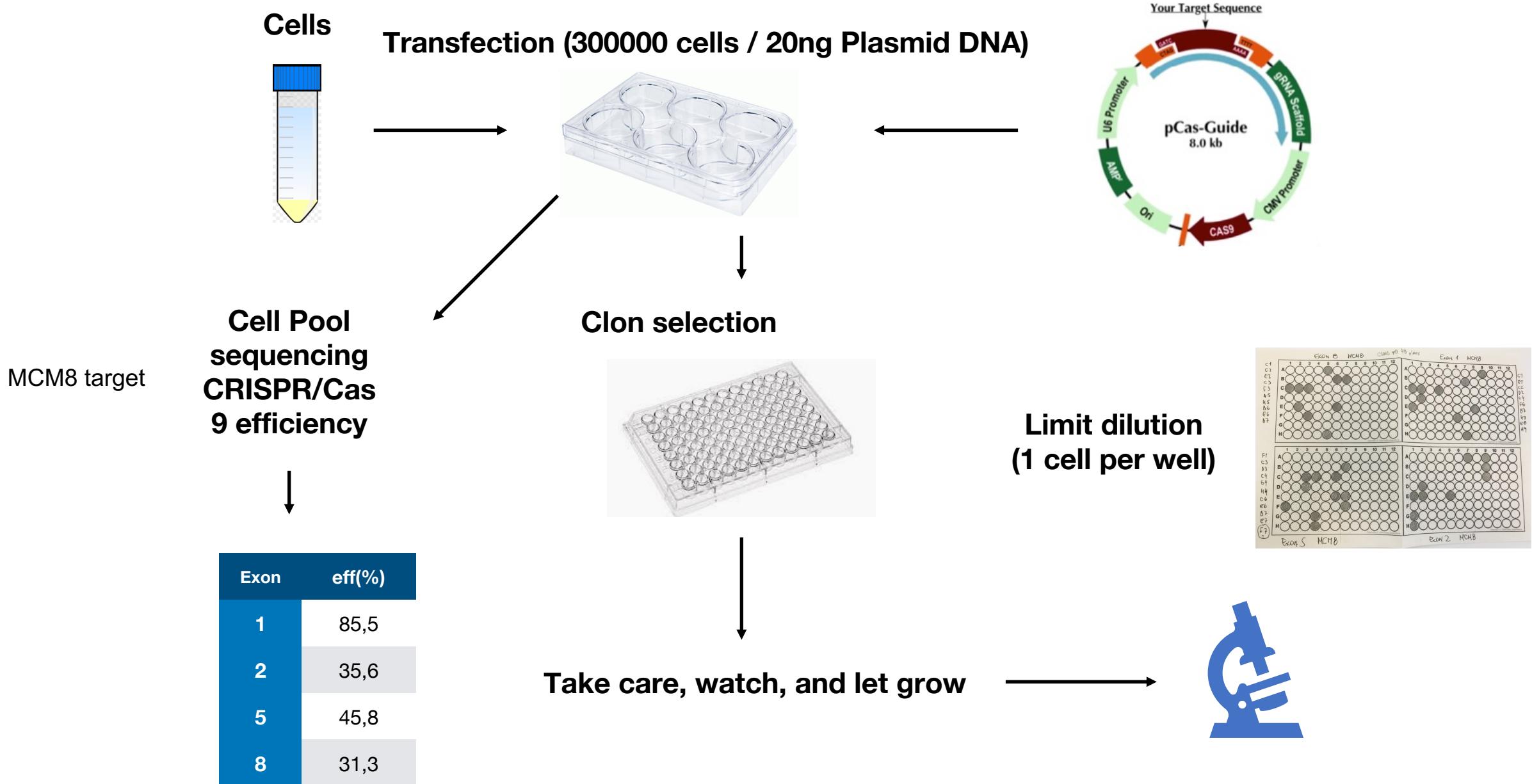
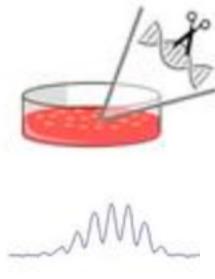


Table 1. Pathologies associated with MCM8/MCM9

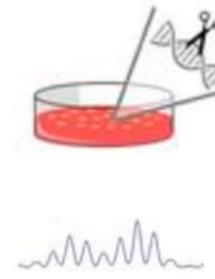
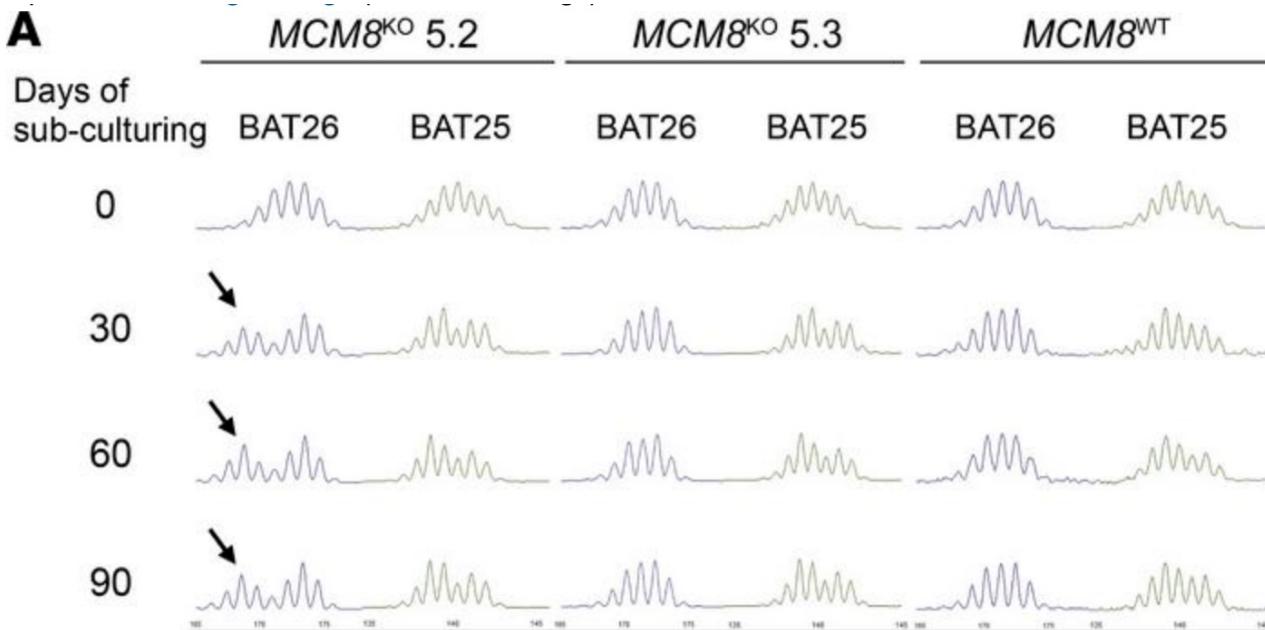
Pathology	MCM8	MCM9
Abnormal uterine bleeding	Shen et al. ⁷⁷	
Alzheimer disease	Ratnakumar et al. ⁷⁸	
Birth of child with Down syndrome		Pal et al. ⁷⁹
Infertility, female	AlAsiri et al., Tenenbaum-Rakover et al., Dou et al., Desai et al., Bouali et al., Zhang et al., Heddar et al., Wang et al., Jin et al., Tucker et al. ²⁴⁻³³	Desai et al., Alvarez-Mora et al., Fauchereau et al., França et al., Goldberg et al., Guo et al., Liu et al., Shen et al., Turkylmaz et al., Wood-Trageser et al., Yang et al., and Jolly et al. ^{27,34-36,38-44,80}
Born small for gestational age	Tenenbaum-Rakover et al., Heddar et al. ^{25,30}	Fauchereau et al., Turkylmaz et al., Wood-Trageser et al., Yang et al. ^{35,42-44}
Delayed puberty	AlAsiri et al., Tenenbaum-Rakover et al., Bouali et al., Heddar et al. ^{24,25,26,30}	
Facial naevi	Wang et al. ³¹	
Hearing loss	Tenenbaum-Rakover et al. ²⁵	
Hypothyroidism	AlAsiri et al. and Heddar et al. ^{24,30}	
Infantile uterus	AlAsiri et al., Tenenbaum-Rakover et al., Zhang et al. ^{24,25,29}	Fauchereau et al., Guo et al., Shen et al., Turkylmaz et al., Wood-Trageser et al., Yang et al. ^{35,39,41-44}
Invisible/small ovaries	AlAsiri et al., Tenenbaum-Rakover et al., Bouali et al., Zhang et al., Wang et al., Tucker et al. ^{24,25,28,29,31,33}	Fauchereau et al., Turkylmaz et al., Wood-Trageser et al., Yang et al. ^{35,42-44}
Kidney agenesis	Tenenbaum-Rakover et al. ²⁵	
Mental retardation	Tenenbaum-Rakover et al. ²⁵	
Osteoporosis/delayed bone age	Heddar et al. and Wang et al. ^{30,31}	Fauchereau et al., Wood-Trageser et al., Yang et al. ^{35,43,44}
Pectate chest	Wang et al. ³¹	
Pilomatricomas	Heddar et al. ³⁰	
Short stature	Wang et al. ³¹	França et al., Guo et al., Turkylmaz et al., Wood-Trageser et al. ^{36,39,42,43}

Functional assay – MCM8 is also involved in DNA MMR?

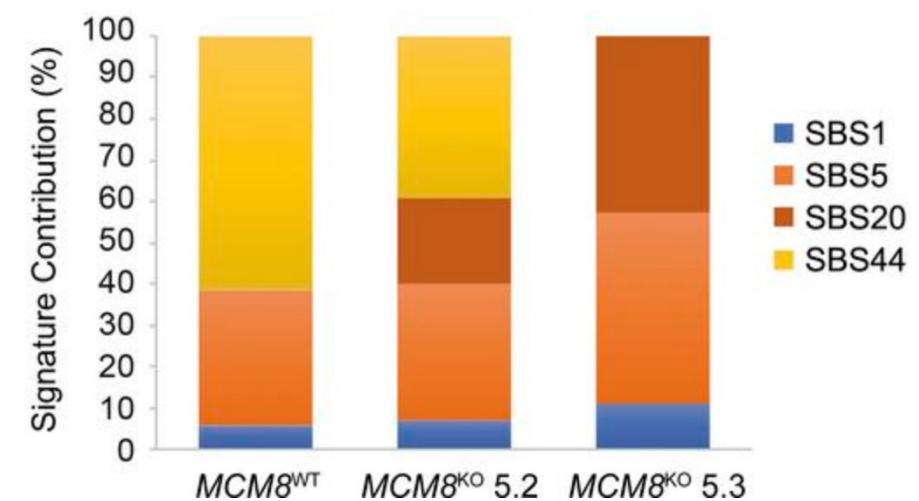


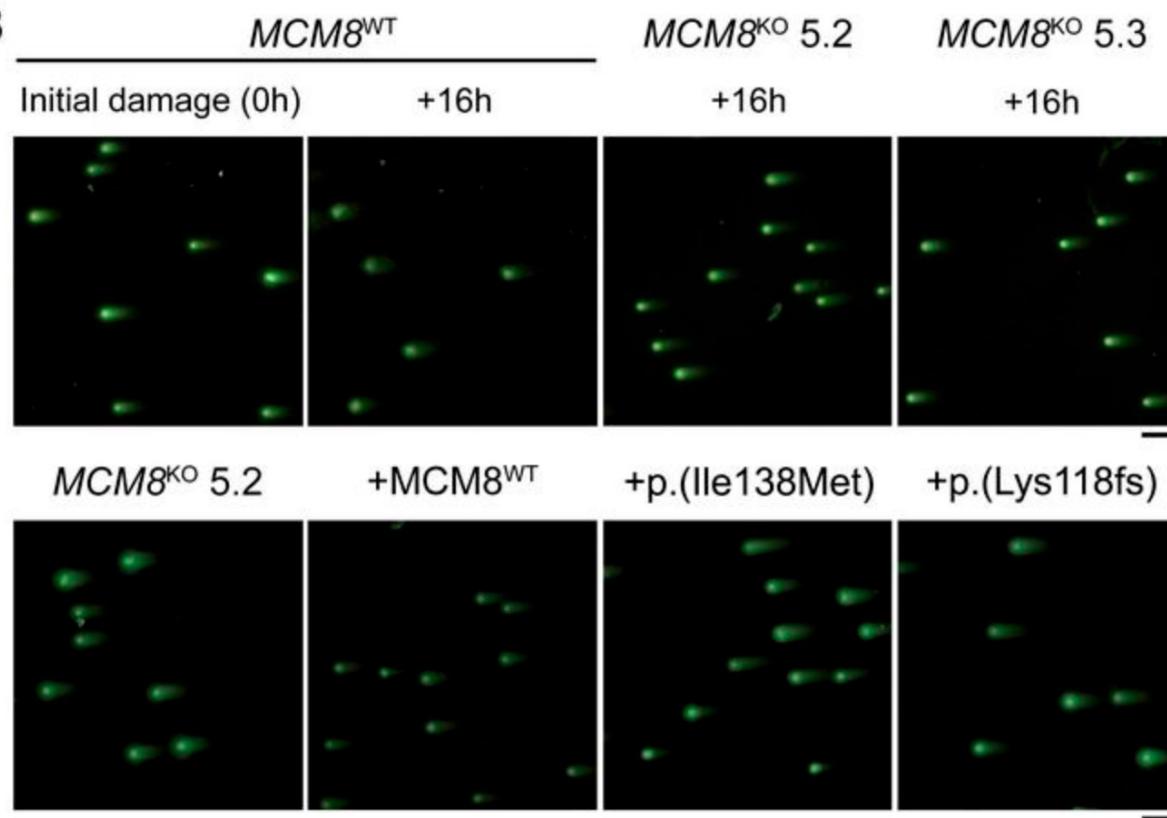
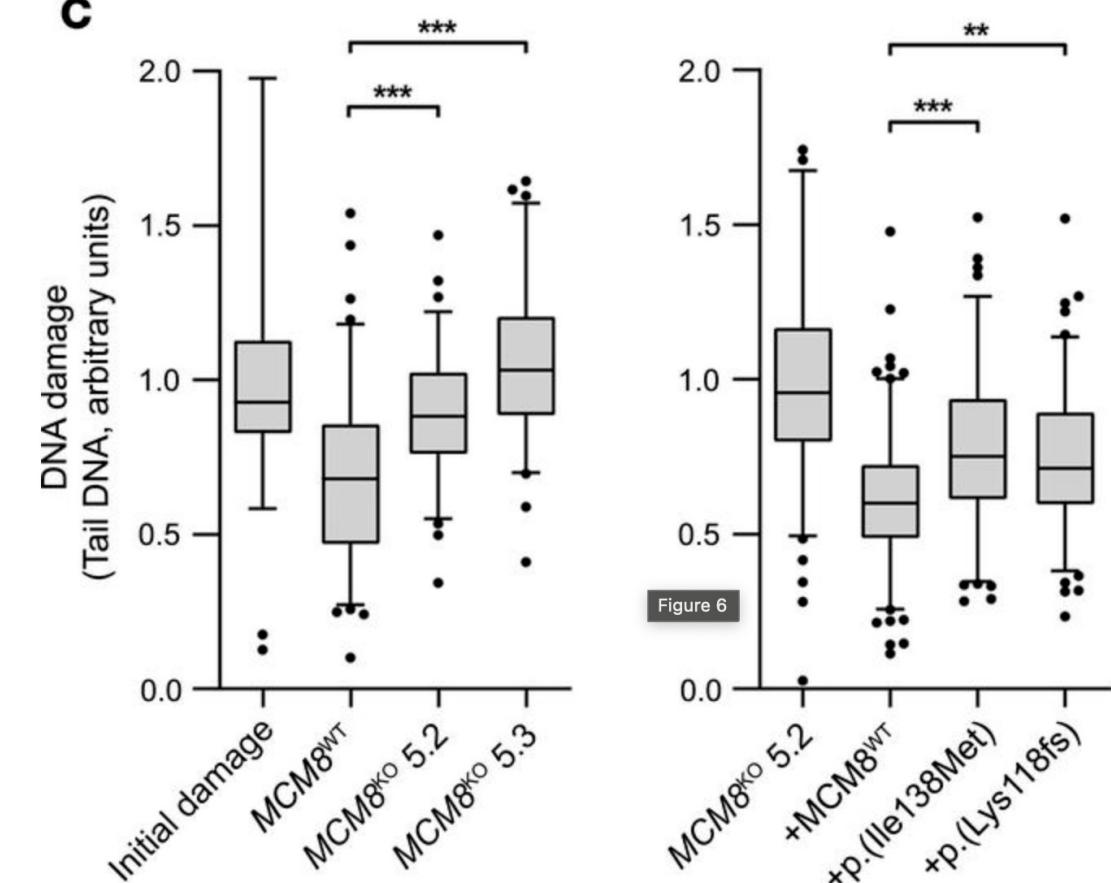


time

**A**

Single Base Substitution Signature Contribution - SigProfiler



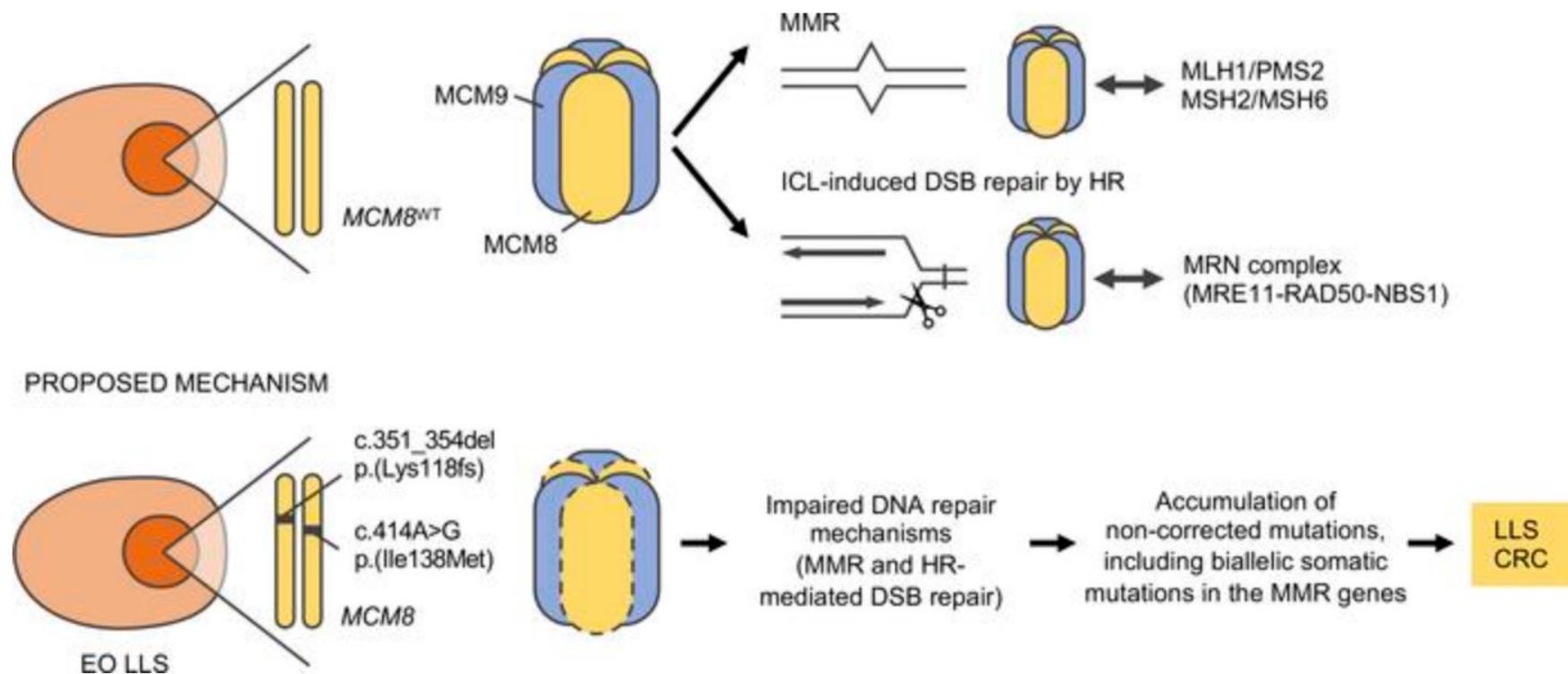
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Screening of the candidate gene variants in an independent cohort

Table 1. Variants in *MCM8* and *MCM9* detected in 131 Dutch patients with cancer

Patient	Cohort	Chrom	Position	Ref	Alt	Gene	DNA	Protein	GnomAD (exome) AF	CADD
<i>MCM8</i> biallelic carrier										
SX548	Breast cancer	20	5939275	T	A	<i>MCM8</i>	c.692T>A	p.(Ile231Lys)	0	23.6
SX548		20	5948200	A	G	<i>MCM8</i>	c.994A>G	p.(Thr332Ala)	0.00000398	23.3
<i>MCM8</i> monoallelic carriers										
DDPOL6309	Colonic polyposis	20	5966763	A	G	<i>MCM8</i>	c.2149A>G	p.(Ile717Val)	0.00757	22.9
DDPOL6367	Colonic polyposis	20	5935825	A	G	<i>MCM8</i>	c.414A>G	p.(Ile138Met)	0.0062	12.5
DDPOL6171	Colonic polyposis	20	5965579	A	G	<i>MCM8</i>	c.1886A>G	p.(Asn629Ser)	0.00000398	0.017
MSS2-1941	MMR-proficient familial CRC	20	5943962	C	T	<i>MCM8</i>	c.832C>T	p.(Arg278Cys)	0.000374	16.74
MSS2-1939	MMR-proficient familial CRC	20	5967973	G	A	<i>MCM8</i>	c.2209G>A	p.(Ala737Thr)	0.000768	29.1
<i>MCM9</i> biallelic carriers										
O11-69294-1	Lynch-like syndrome	6	119149180	G	A	<i>MCM9</i>	c.1642C>T	p.(Arg548Trp)	0.00000665	31
O11-69294-1		6	119252737	T	A	<i>MCM9</i>	c.152A>T	p.(Asn51Ile)	0.0000199	28.2
MSS13-1961	MMR-proficient familial CRC	6	119135994	T	C	<i>MCM9</i>	c.3425A>G	p.(Lys1142Arg)	0.000234	23.1
MSS13-1961		6	119149182	A	G	<i>MCM9</i>	c.1640T>C	p.(Leu547Pro)	0.0000532	24.5
<i>MCM9</i> monoallelic carriers										
O30-53743-1	Lynch-like syndrome	6	119136133	T	C	<i>MCM9</i>	c.3286A>G	p.(Met1096Val)	0.00239	0.078
DDCRC2261	MMR-proficient familial CRC	6	119136133	T	C	<i>MCM9</i>	c.3286A>G	p.(Met1096Val)	0.00239	0.078
O15-61771-1	Lynch-like syndrome	6	119137445	C	A	<i>MCM9</i>	c.1974G>T	p.(Gln658His)	0.00801	22.2
F69245	CRC family	6	119137445	C	A	<i>MCM9</i>	c.1974G>T	p.(Gln658His)	0.00801	22.2
024-58940-1	Lynch-like syndrome	6	119136385	C	G	<i>MCM9</i>	c.3034G>C	p.(Glu1012Gln)	0.000107	11.96
025-50293-1	Lynch-like syndrome	6	119150218	T	A	<i>MCM9</i>	c.1521A>T	p.(Glu507Asp)	0.00992	24.2
018-64293-1	Lynch-like syndrome	6	119137275	T	A	<i>MCM9</i>	c.2144A>T	p.(Asp715Val)	0.00137	11.8
MSS2-1941	MMR-proficient familial CRC	6	119135994	T	C	<i>MCM9</i>	c.3425A>G	p.(Lys1142Arg)	0.000234	23.1
NA41-1	MMR-proficient familial CRC	6	119137432	-	T	<i>MCM9</i>	c.1987dupT	p.(Ser663PhefsTer36)	0	-
NA96-14	MMR-proficient familial CRC	6	119147356	G	C	<i>MCM9</i>	c.1915C>G	p.(Leu639Val)	0.000625	25.4
MSS6-1938	MMR-proficient familial CRC	6	119234579	T	C	<i>MCM9</i>	c.911A>G	p.(Asn304Ser)	0.00357	26.1
NA209-15	MMR-proficient familial CRC	6	119137275	T	A	<i>MCM9</i>	c.2144A>T	p.(Asp715Val)	0.00137	11.8
All variants have allele frequency less than 0.01 in the gnomAD database. Potentially pathogenic genetic variants (CADD >15) are highlighted in bold. Chrom, chromosome; Ref, reference; Alt, alternative; gnomAD, the Genome Aggregation Database (https://gnomad.broadinstitute.org/); AF, allelic frequency; CADD, Combined Annotation Dependent Depletion (https://cadd.gs.washington.edu/); MMR, mismatch repair; CRC, colorectal cancer.										

Proposed mechanism – MCM8 is involved in HRR and MMR



MCM8 and MCM9 as predisposing genes for early-onset cancer, polyposis and primary ovarian insufficiency

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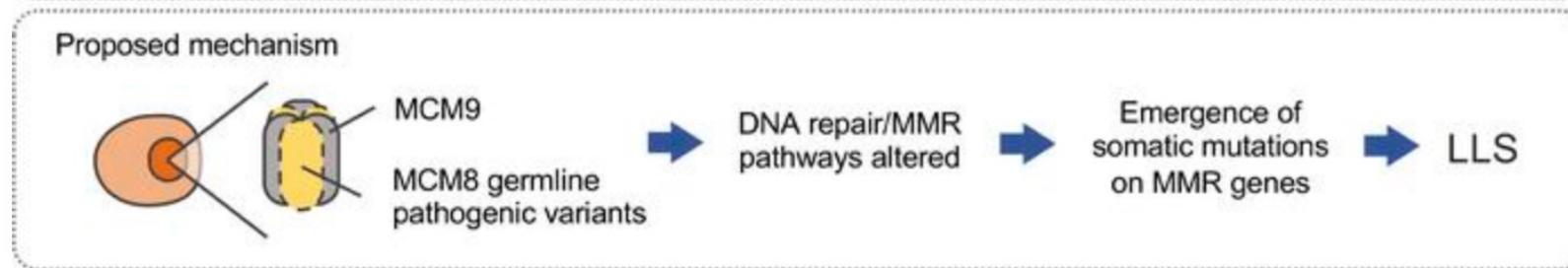
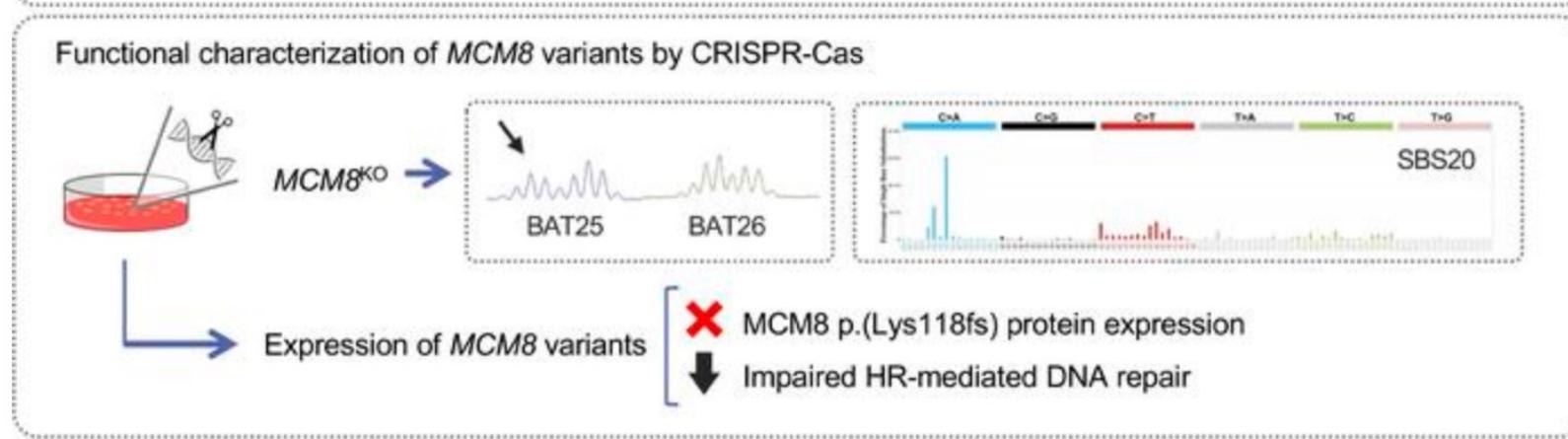
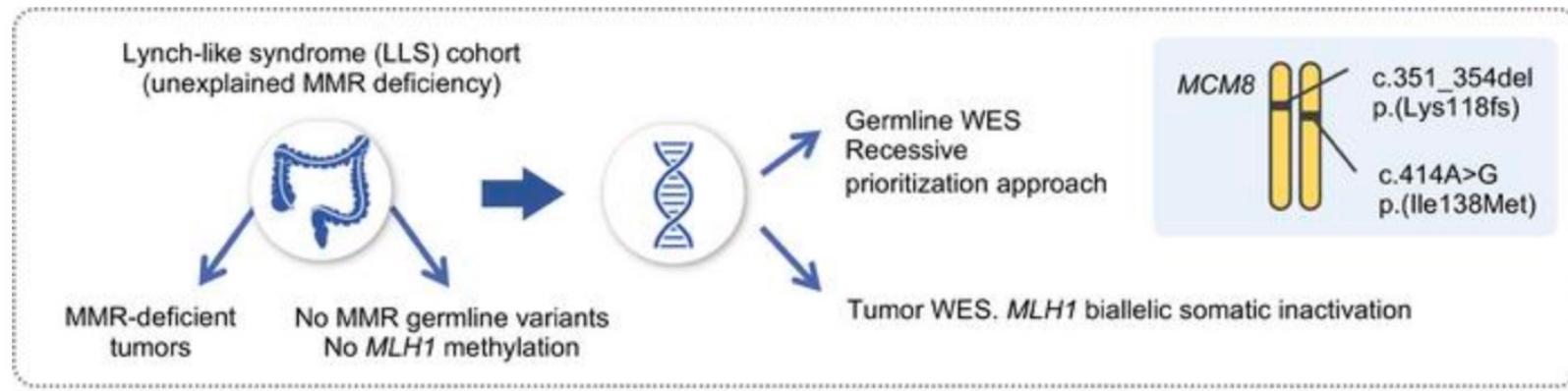


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More data is coming...



thanks for staying tuned!

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