New Issues in Cancer Genomics for the Research and Treatment

~ PanCan analysis of MSI (microsatellite instability) and hypermutation of cancer genomes including breast cancers

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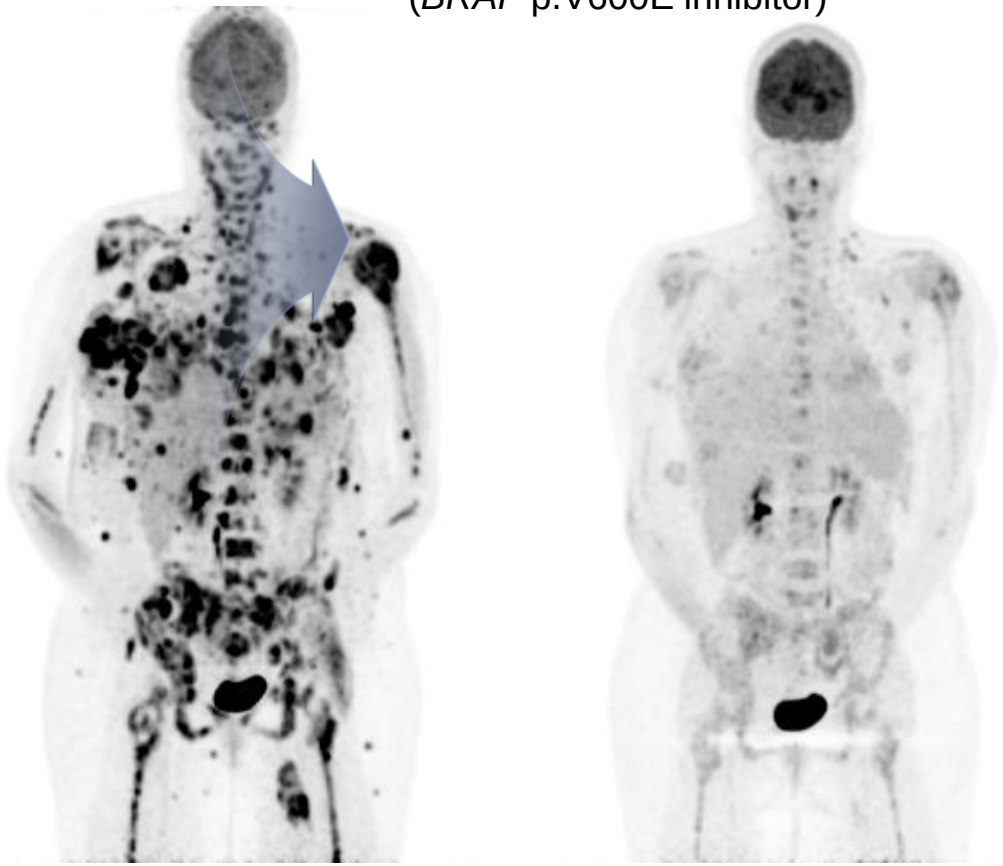
Dramatic responses compared to conventional chemotherapy

"Targeted cancer therapeutics"

Gleevec (2000)

Metastatic melanomas – Vemurafenib
(*BRAF* p.V600E inhibitor)



Two issues of targeted therapy

(1) “Responder-vs-nonresponder”

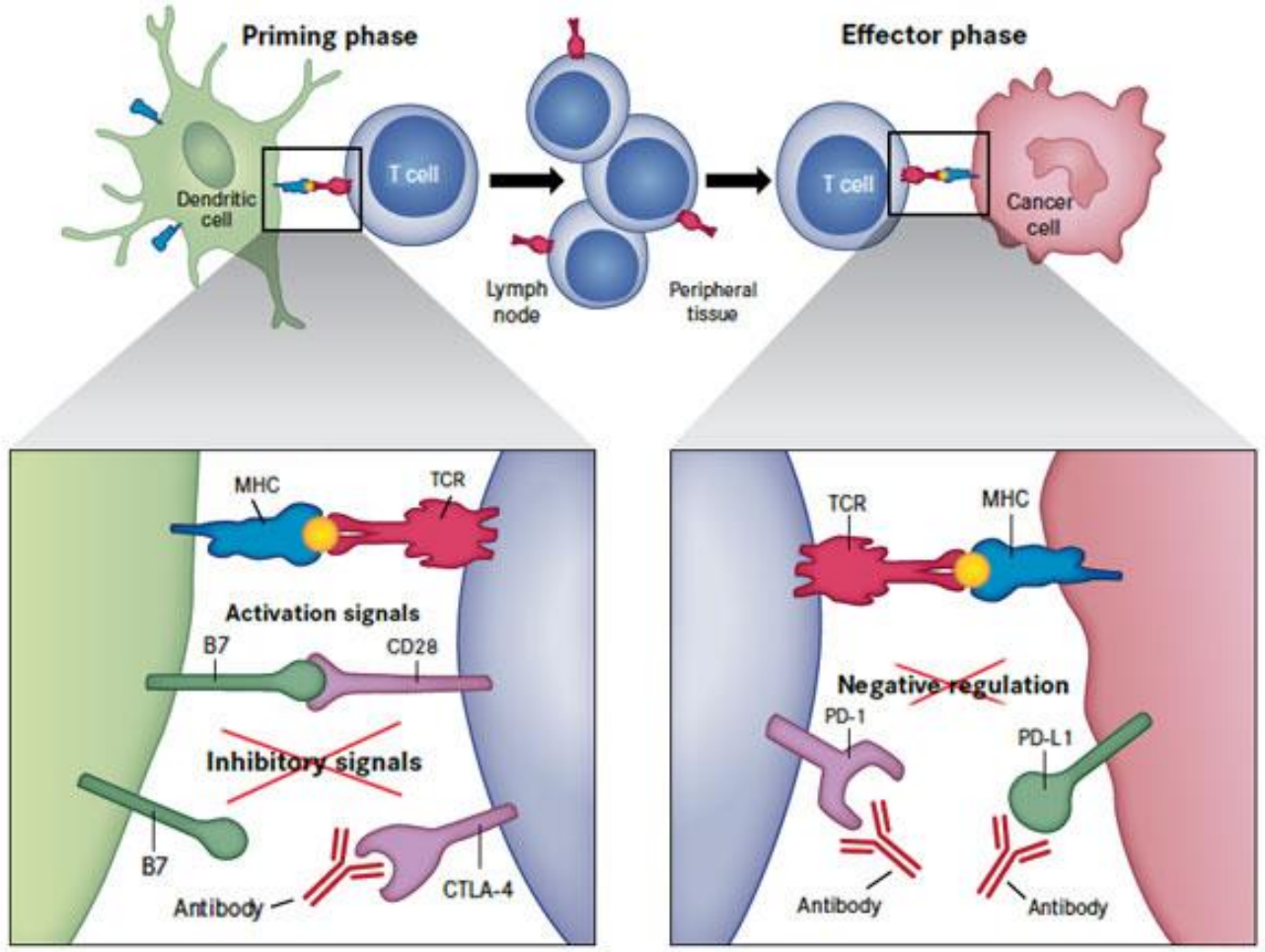
“Who will respond to the selected drugs?”

“What is predictive/prognostics biomarker”?

(2) *Most solid tumors will acquire ‘resistant mutations/clones’ and inevitably progress in a year….*

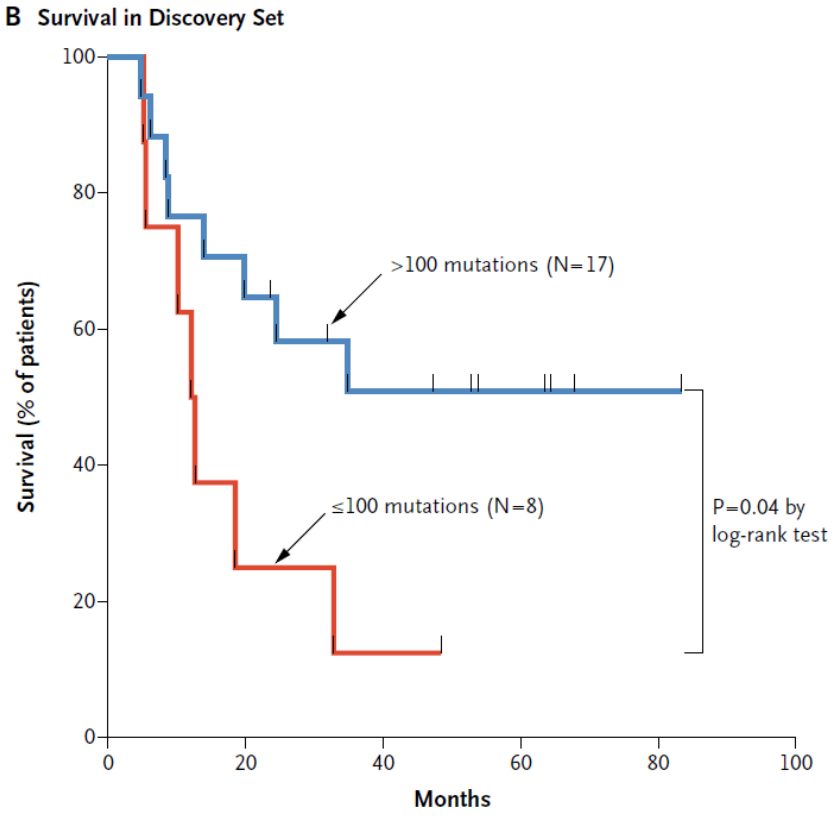
Disease progression

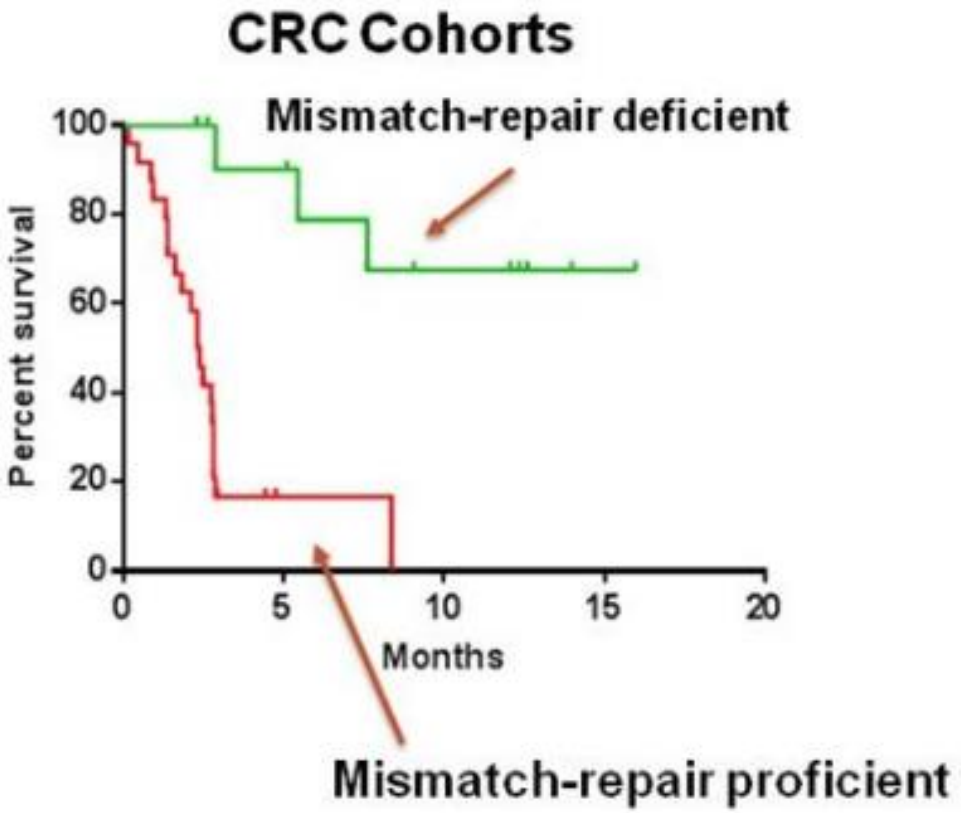
New strategy to treat the cancers "Immune checkpoint blockade treatment" targeting PD-1/PD-L1/CTLA-4



".. Objective, durable responses for a number of patients (responders).."

‘Mutation burden’ as predictive markers for immunotherapy

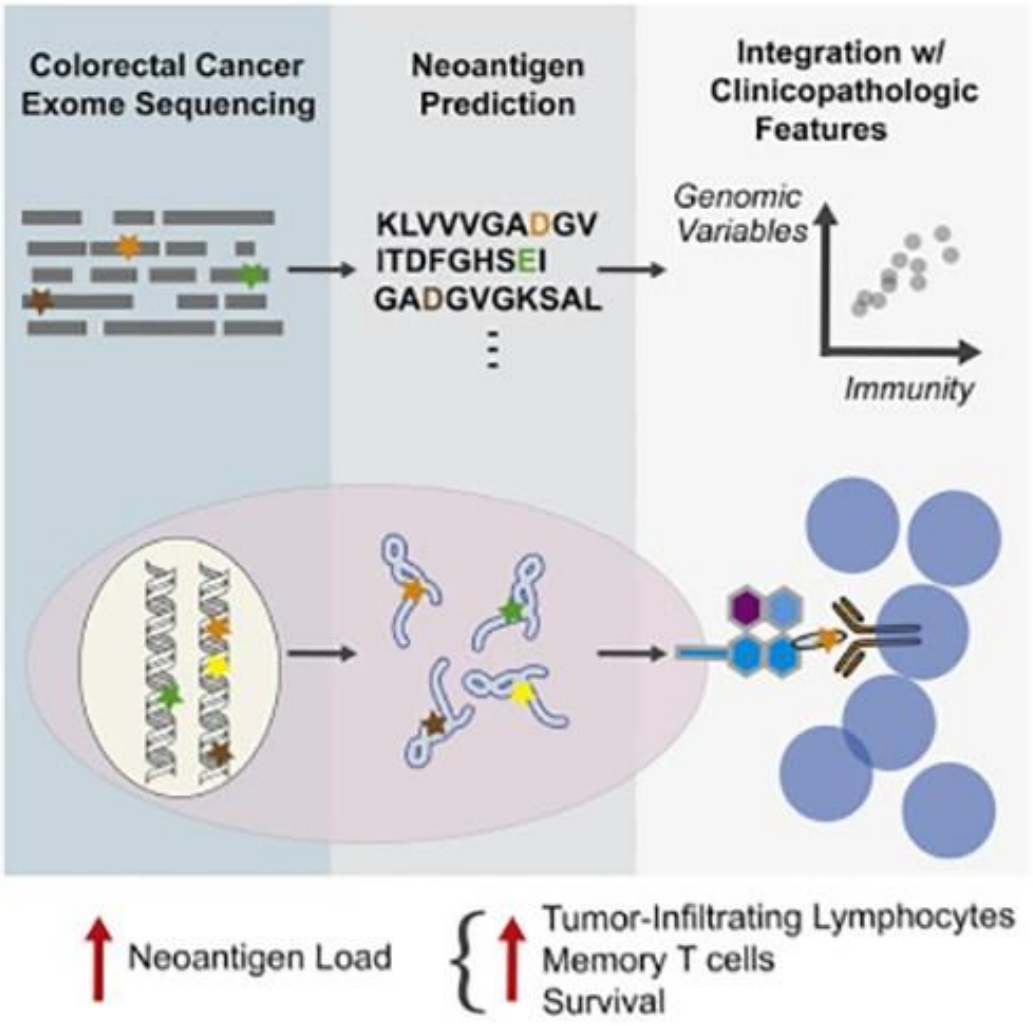




Increased mutation burden = increased efficacy of immune checkpoint blockade treatment (anti-CTLA4) of ‘melanoma’

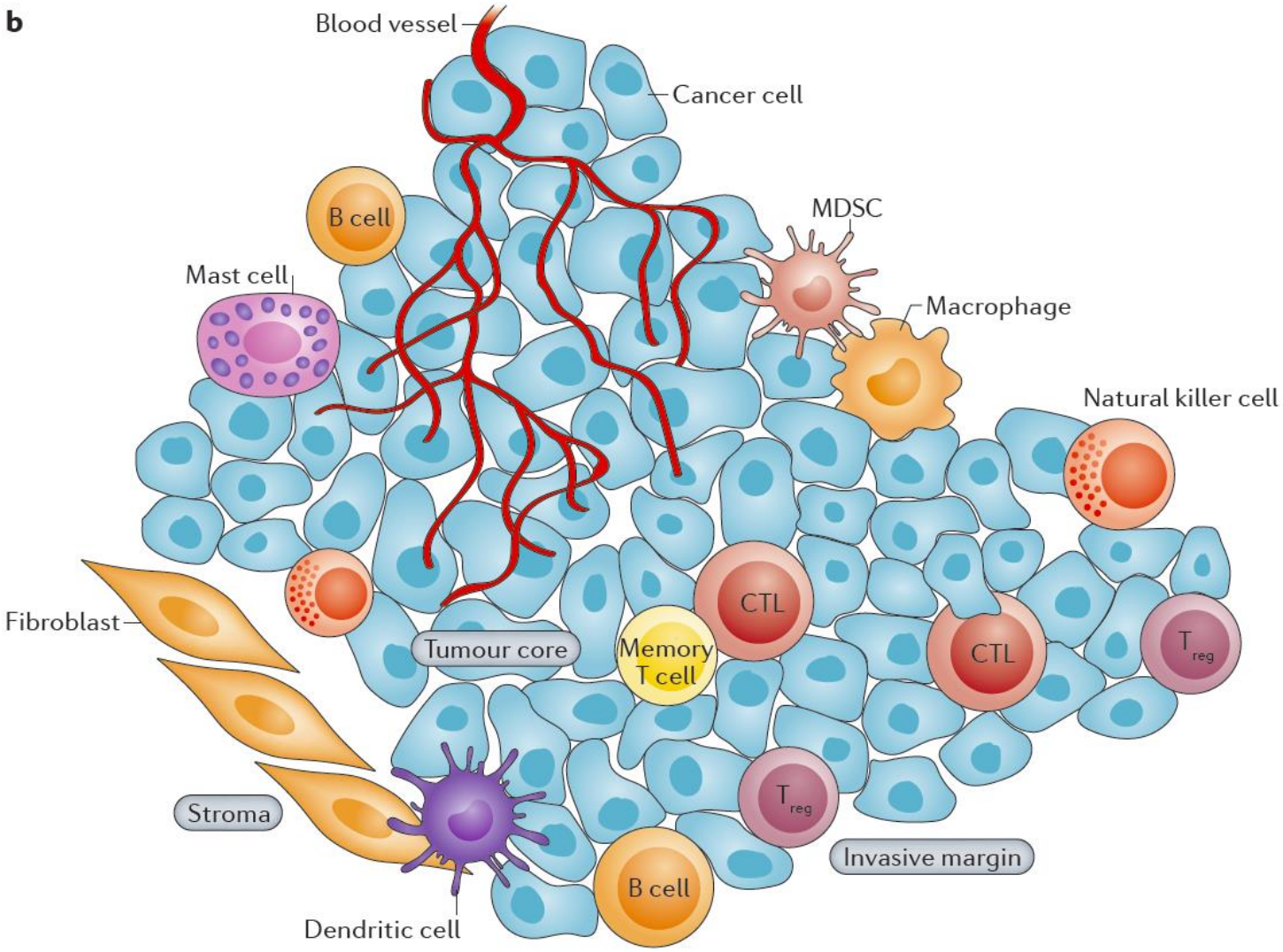
Mutator phenotype (=MSI-H) colorectal cancers will respond to anti-CTLA4 agents (>60%).

More somatic mutations, more neoantigens



Neoantigens are enriched in the *hypermutated* microsatellite-unstable phenotype tumors and rarely shared among patients → more neoantigens will lead to highly elevated cytotoxic T cell responses

Anti-cancer response in the complex millieu of tumor microenvironments…



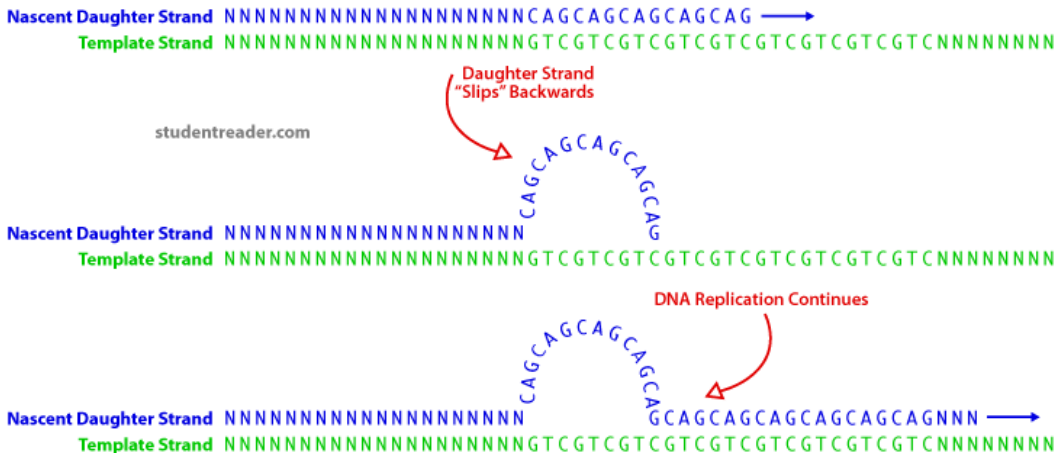
Pan-Cancer analysis of hypermutated genomes using TCGA data & signature analysis

MSI (Microsatellite Instability) with a MMR deficiency

Mononucleotide: $(A)_{13}$	AAAAAAAAAAAAA
Dinucleotide: $(GT)_8$	GTGTGTGTGTGTGTGT
Trinucleotide: $(GAT)_7$	GATGATGATGATGATGATGAT
Tetranucleotide: $(CTAG)_6$	CTAGCTAGCTAGCTAGCTAGCTAG
Pentanucleotide: $(CATTG)_5$	CATTGCATTGCATTGCATTGCATTG
Hexanucleotide: $(GGATCC)_4$	GGATCCGGATCCGGATCCGGATCC

… 8 millions 'short tandem repeats' in the human genome (~5% of total)

… DNA repair machineries to fix those errors (MLH1, MSH2/6, PMS1, PSM2, etc.)

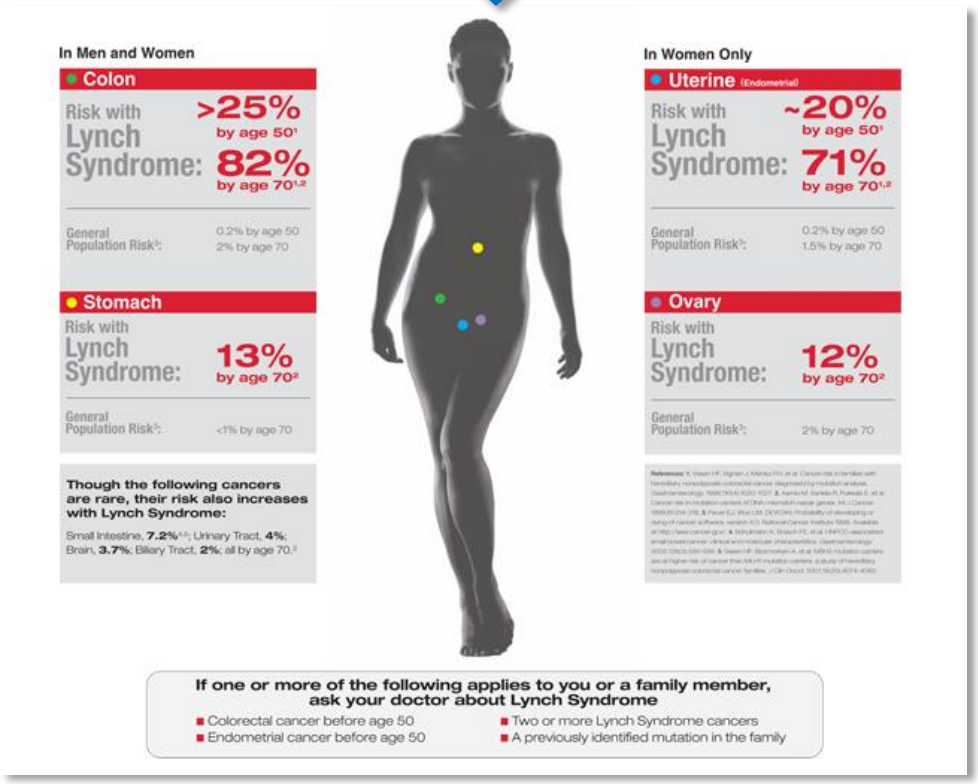


… DNA slippage errors during DNA replication can give 'length polymorphism' of microsatellite (10^{-2}~10^{-6} per generation in vivo)

Lynch Syndrome and MS-unstable Colorectal Cancers

Germline mutations of *MSH2, MSH6* *VS* **Promoter hypermethylation of *MLH1***

'Lynch syndrome'



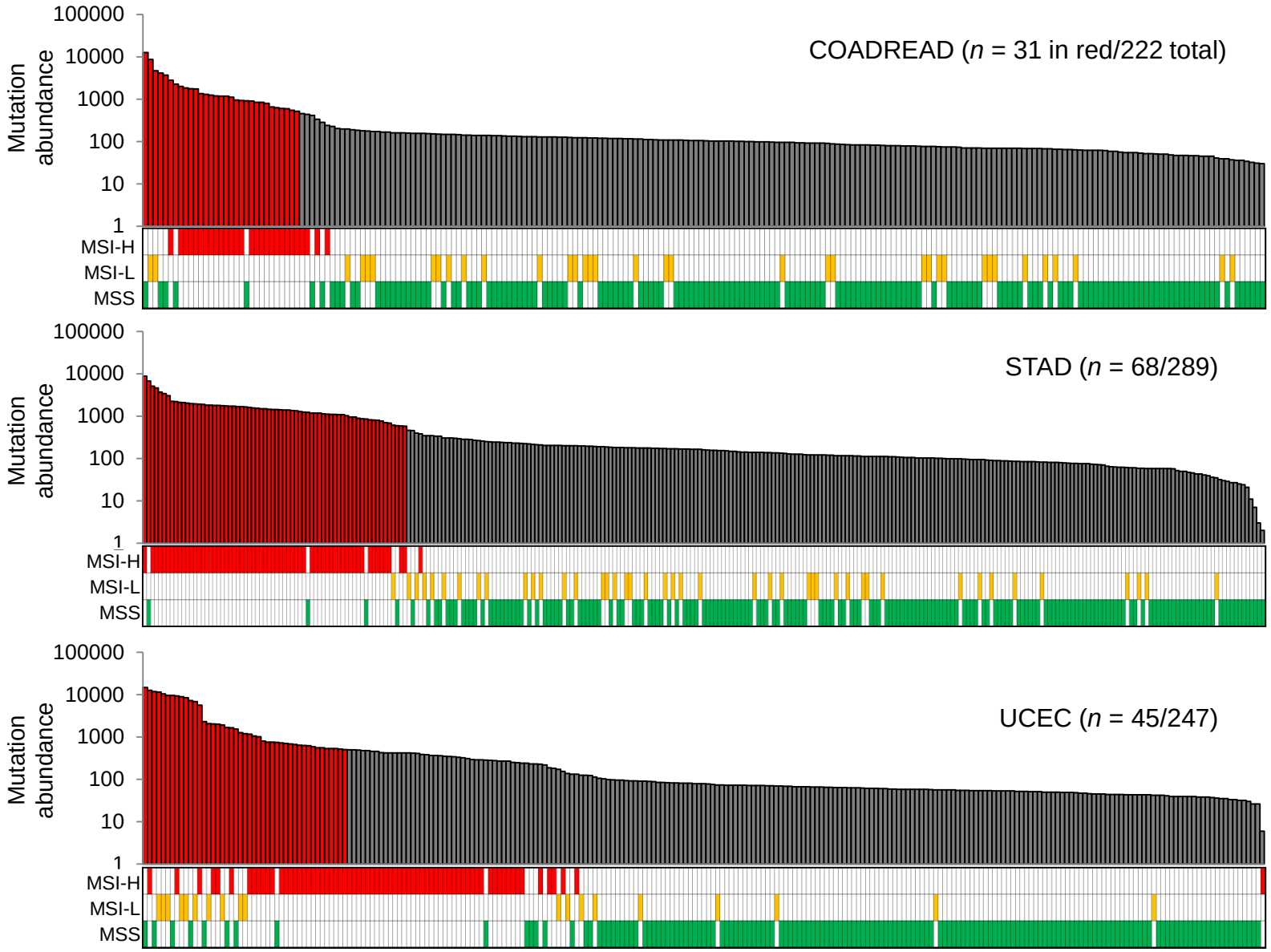
Cancer risk in Lynch syndrome

20% of sporadic CRC *VS* 80% of sporadic CRC

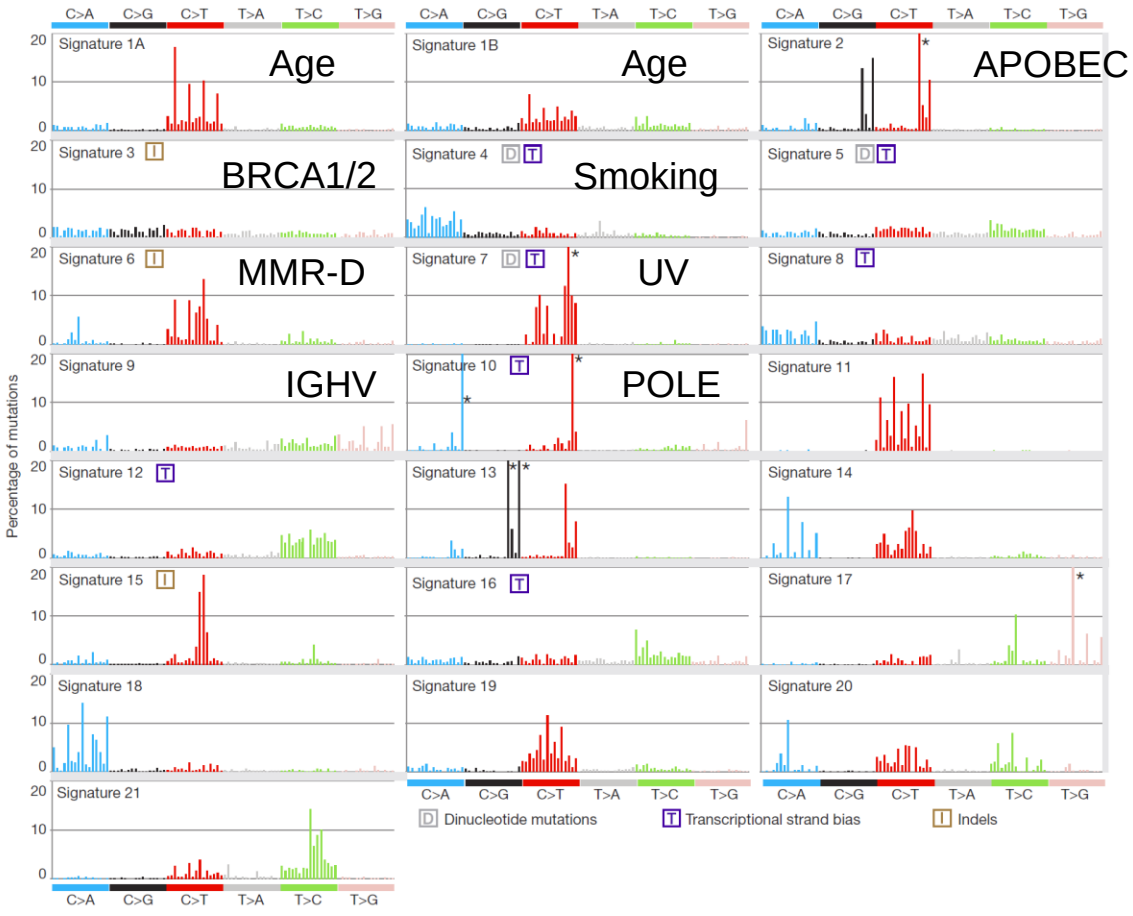
- MS-unstable (MSI-H) but CN-stable
- Hypermutation
- Old females
- Right-sided colon
- Better survival

- MS-stable but CN-unstable

Hypermutation (>10 mutations/Mb or >500 exonic mutations; red) in three MSI-prone tumors (colorectal, stomach, endometial cancers)



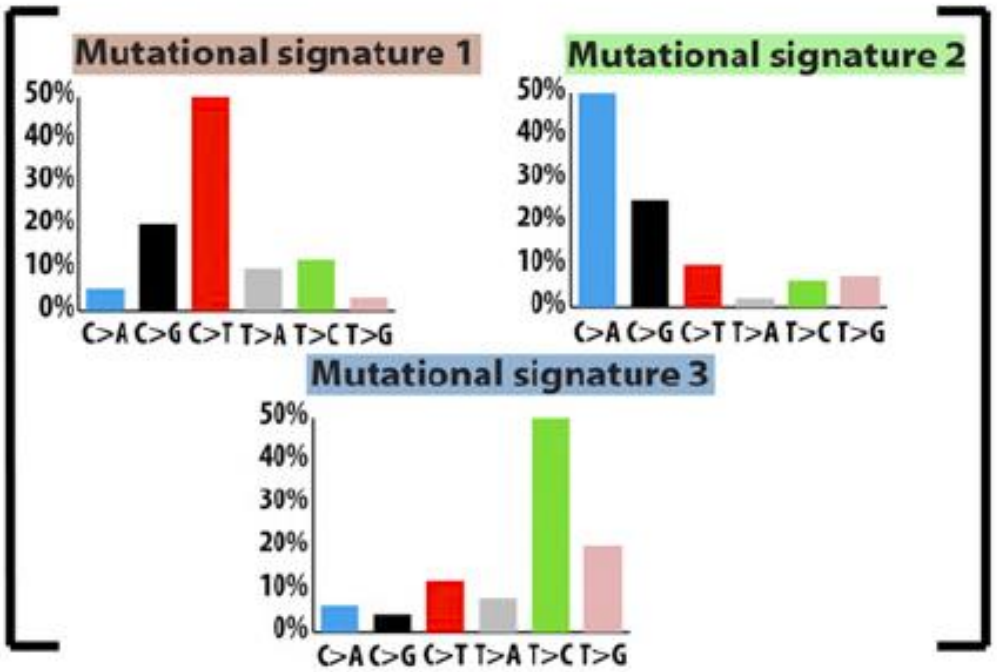
Extension of six-bar mutation spectra into 96 nucleotide-context ‘mutation spectrum’



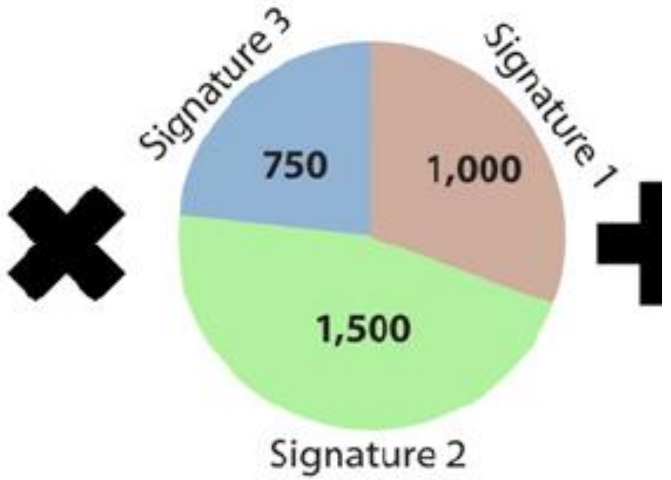
Variable types of mutation signature (with specific causes) are present in variable frequencies across turmor types

A collection of mutations in individual tumor genomes can be separated into a set of mutation signatures

A list of somatic mutations (with sequence features) of a single cancer genome

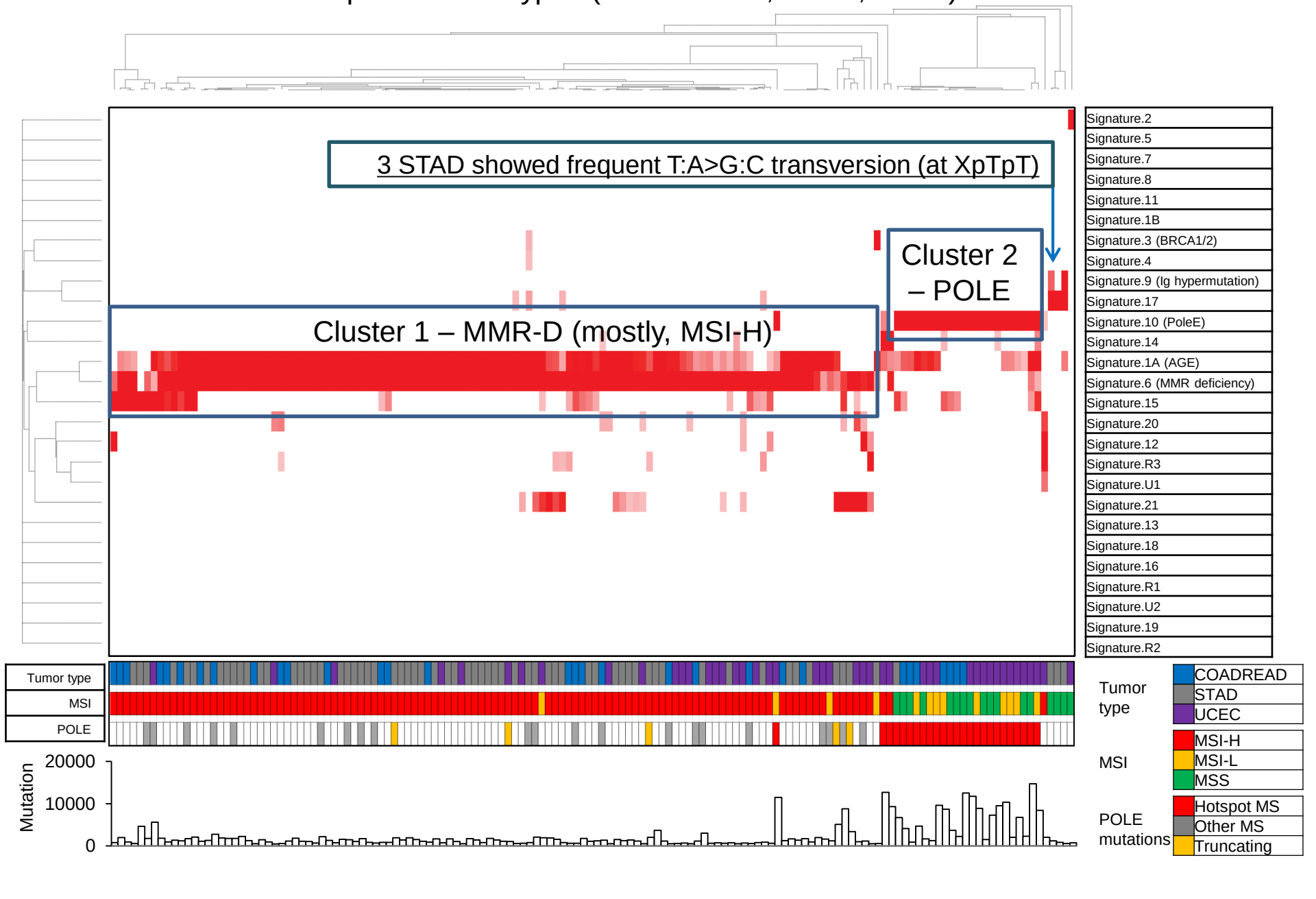


Signatures of mutational processes

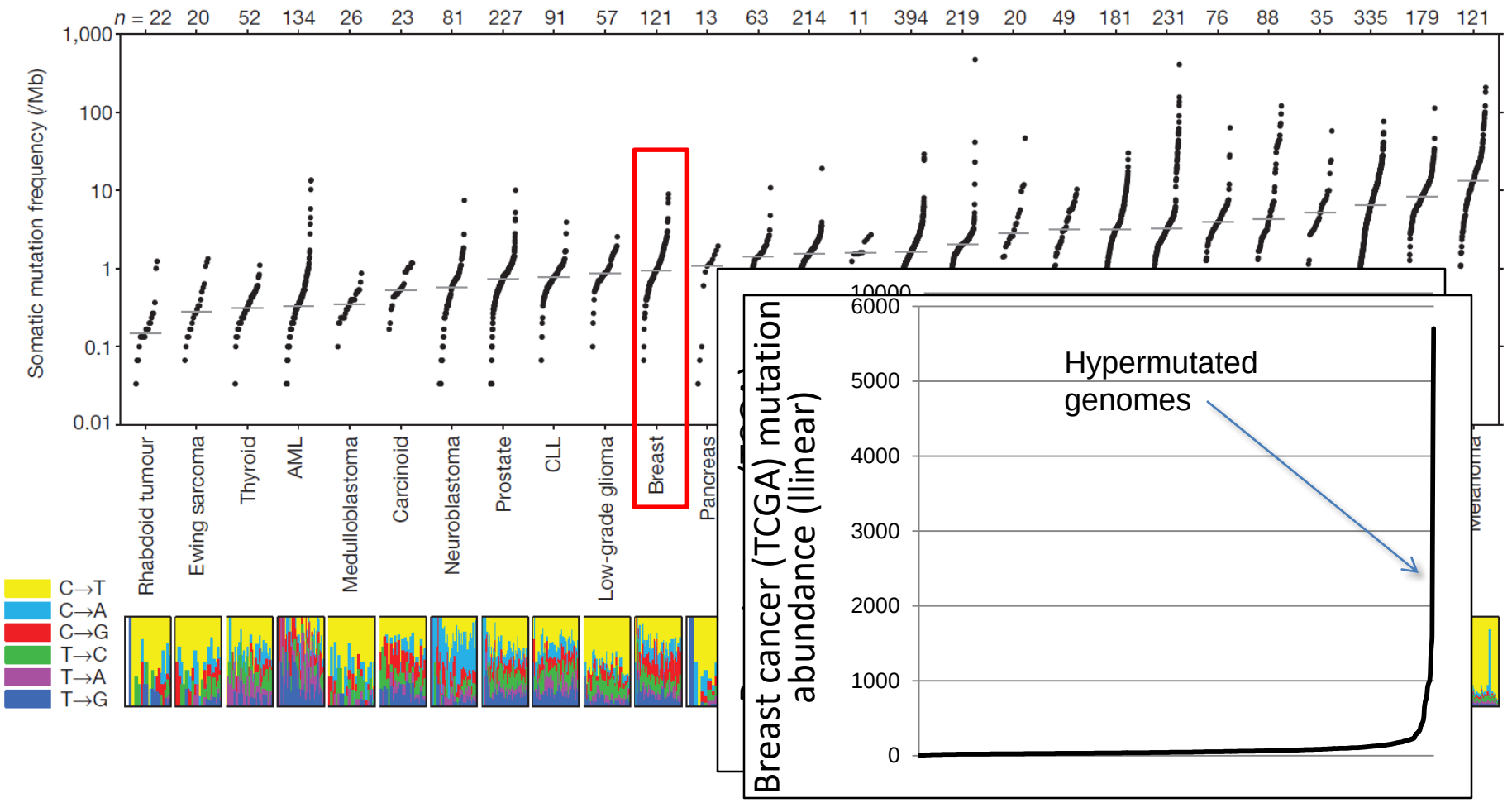


Number of mutations contributed by each signature

Mutation signature-based clustering analysis of 150 hypermutated genomes for 3 MSI-prone tumor types (COADREAD, STAD,UCEC)



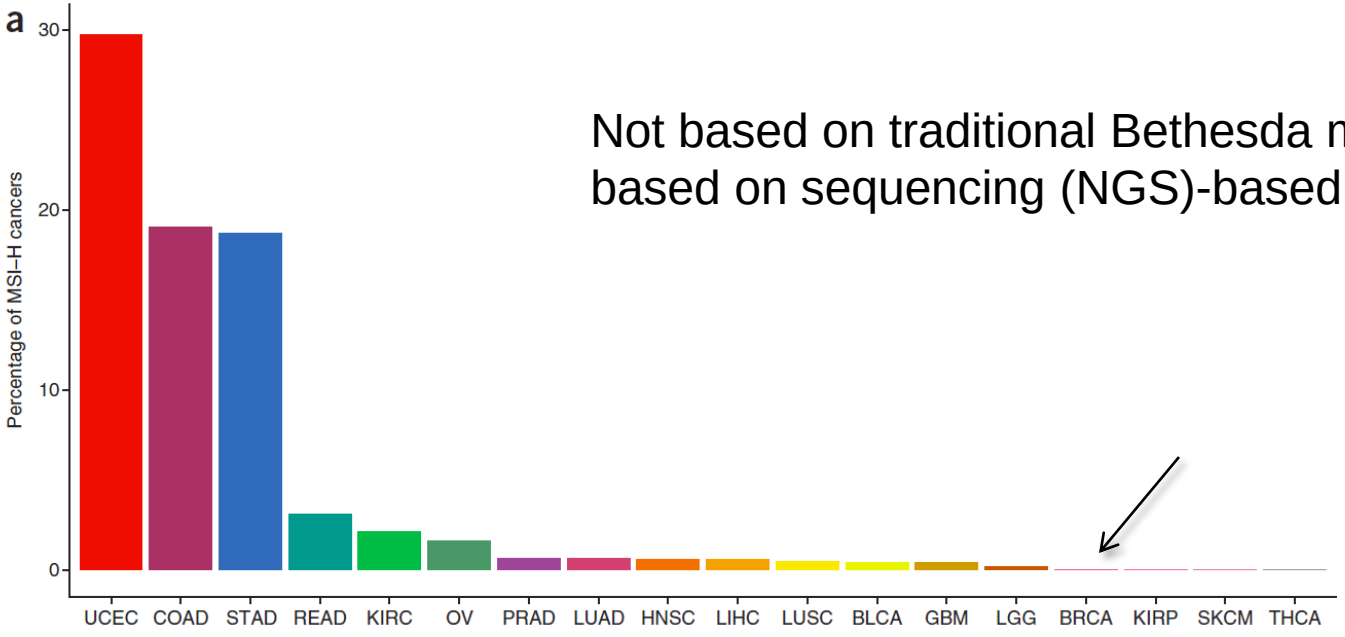
Mutation abundance/burden (i.e., the number of exonic mutations) is heterogeneous across tumor types



How many MSI-H and/or hypermutated genomes in BRCA?

Classification and characterization of microsatellite instability across 18 cancer types

Ronald J Hause[1], Colin C Pritchard[2], Jay Shendure[1,3] & Stephen J Salipante[2]



Not based on traditional Bethesda markers, but based on sequencing (NGS)-based analysis!

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A molecular portrait of microsatellite instability across multiple cancers

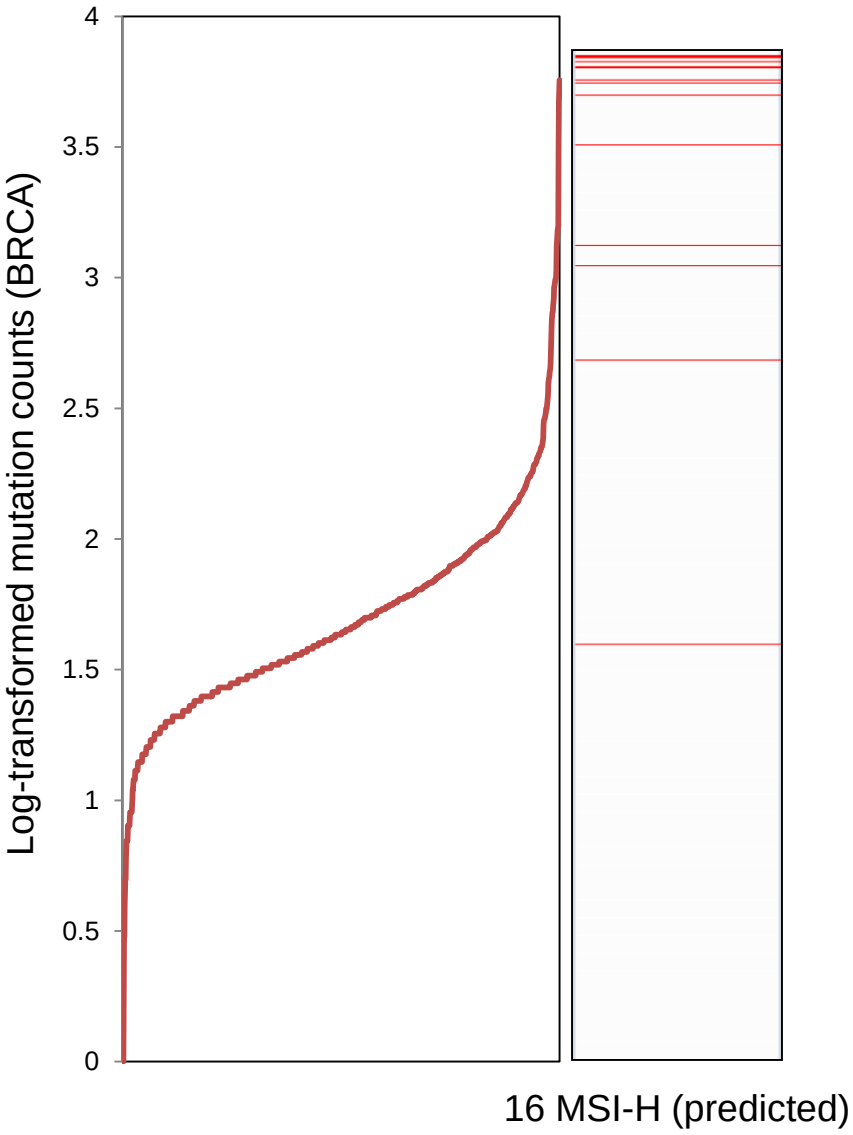
Isidro Cortes-Ciriano[1,2,*], Sejoon Lee[3,*], Woong-Yang Park[3], Tae-Min Kim[4] & Peter J. Park[1,2]

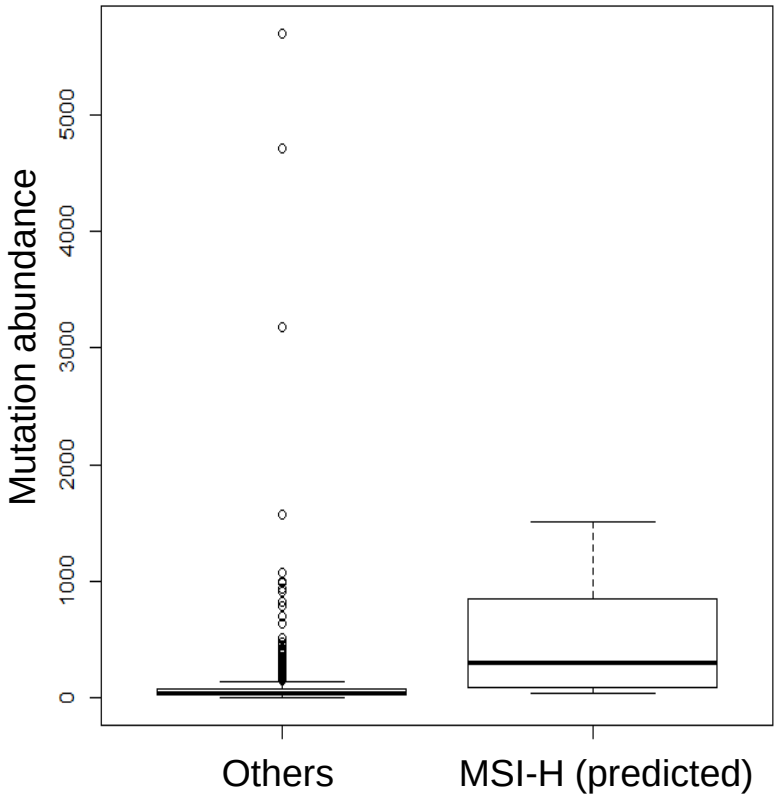
Table 1 | Tumour samples utilized to profile MSI.

Tumour type	Abbreviation	Samples	MSI-Hs (frequency)
Uterine corpus endometrial carcinoma	UCEC	265	75 (28.3%)
Stomach adenocarcinoma	STAD	292	64 (21.9%)
Colon adenocarcinoma	COAD	271	45 (16.6%)
Rectal adenocarcinoma	READ	76	3; 4* (9.2%)
Adrenal cortical carcinoma	ACC	92	5* (5.4%)
Oesophageal carcinoma	ESCA	183	3* (1.6%)
Cervical squamous cell carcinoma	CESC	305	7* (2.3%)
Ovarian cancer	OV	436	14* (3.2%)
Breast cancer	BRCA	922	16* (1.7%)
Cutaneous melanoma	SKCM	109	0* (0%)
Head and neck squamous cell carcinoma	HNSC	505	6* (1.2%)
Glioblastoma multiforme	GBM	316	4* (1.3%)
Urothelial bladder cancer	BLCA	368	2* (0.8%)
Liver hepatocellular carcinoma	LIHC	375	11* (2.9%)
Kidney renal clear cell carcinoma	KIRC	377	4* (1.1%)
Lung adenocarcinoma	LUAD	482	1* (0.2%)
Lung squamous cell carcinoma	LUSC	407	5* (1.2%)
Prostate adenocarcinoma	PRAD	497	3* (0.6%)
Pancreatic cancer	PAC	171	2* (1.1%)
Low grade glioma	LGG	514	3* (0.6%)
Papillary kidney carcinoma	KIRP	286	2* (0.7%)
Thyroid cancer	THCA	493	0* (0%)
Pheochromocytoma and paraganglioma	PHCA	176	0* (0%)
Total		7,919	281

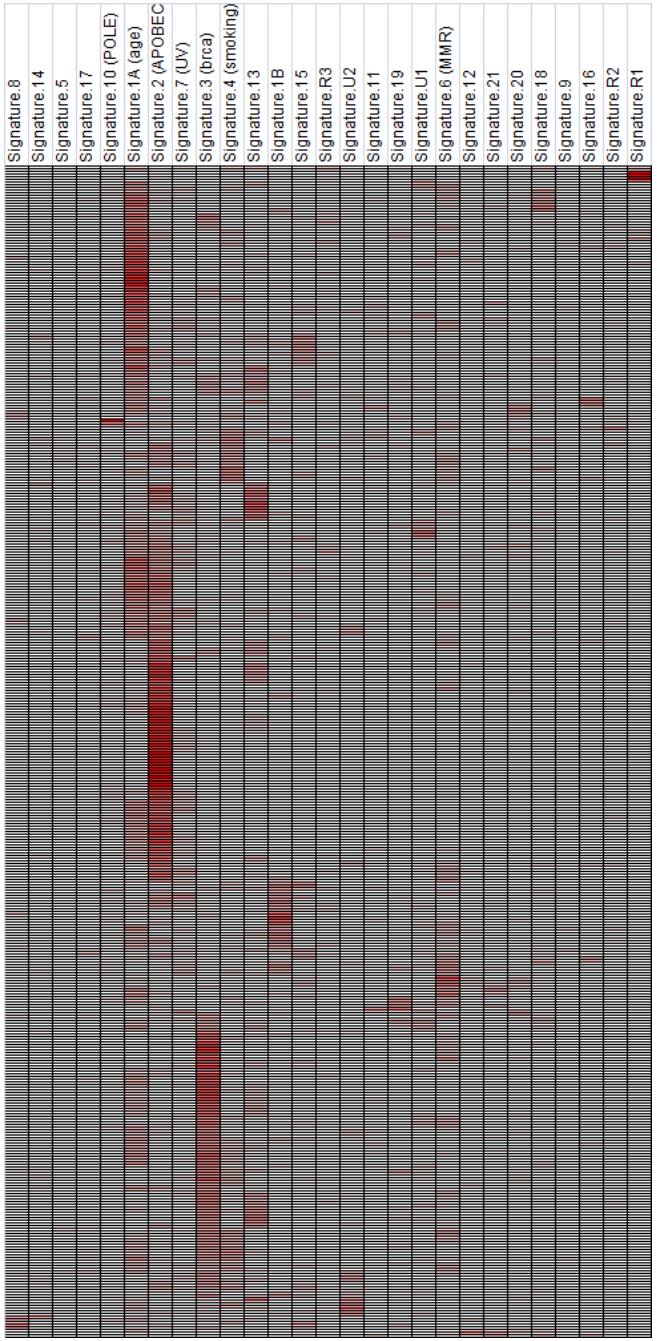
Cortes-Ciriano et al. In press

Predicted ‘MSI-H’ 16 BRCA genomes/exomes

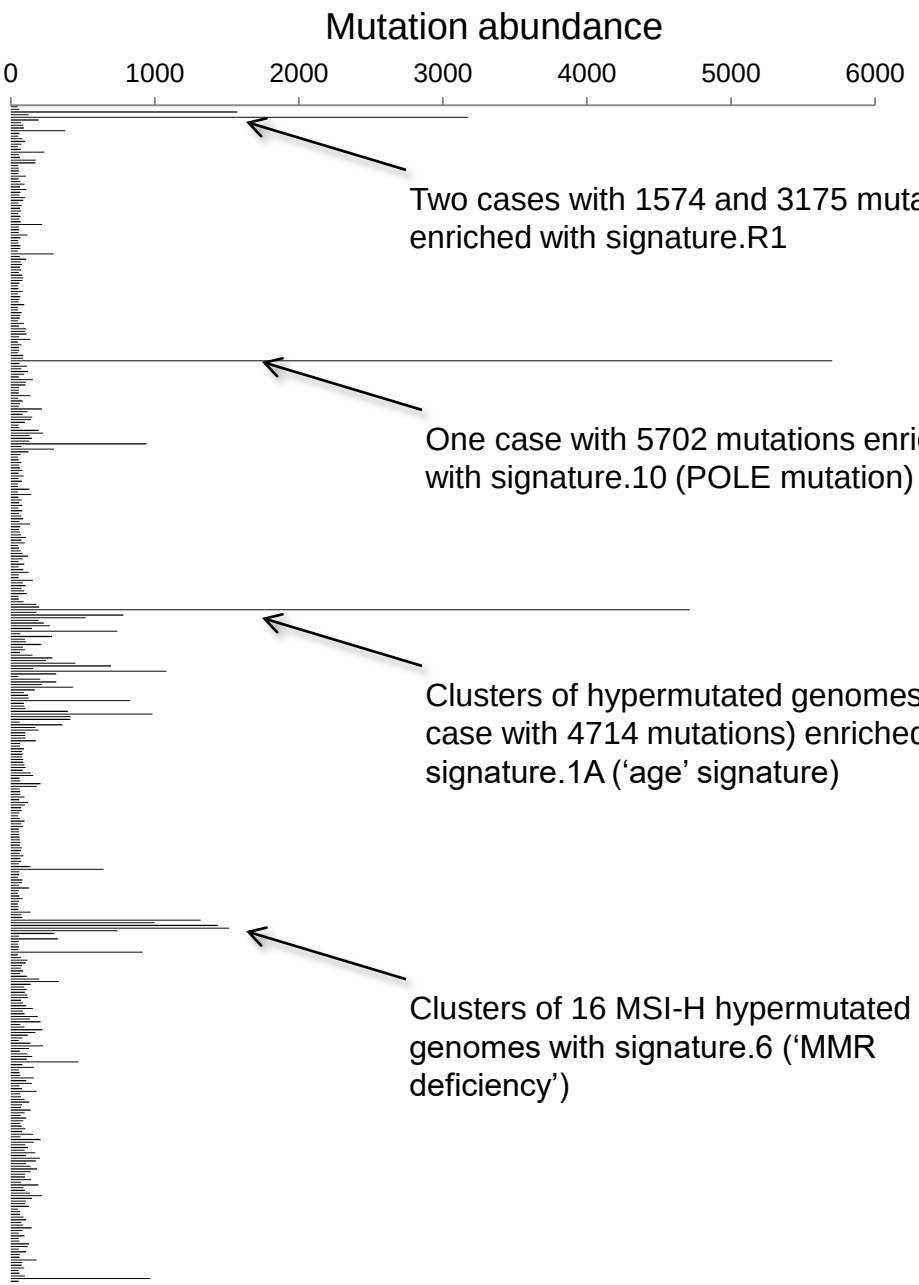




Mutation signature clustering-based analysis of BRCA



Mutation signature abundance



Two cases with 1574 and 3175 mutations enriched with signature.R1

One case with 5702 mutations enriched with signature.10 (POLE mutation)

Clusters of hypermutated genomes (one case with 4714 mutations) enriched with signature.1A (‘age’ signature)

Clusters of 16 MSI-H hypermutated genomes with signature.6 (‘MMR deficiency’)

Summary

• Tumor with an elevated mutation rate (‘mutator phenotype’) will respond better to immune checkpoint blockade treatment

• Hypermutation of MSI-prone tumors (colorectal, stomach and endometrial cancers) are mainly attributed to (i) MMR deficiency and (ii) POLE (hotspot) mutations

• Although the MSI-H fraction is low (2%) in breast cancers, MMR deficiency may induce hypermutation in breast cancers along with other causal events (POLE, age-related mutations, etc.)