Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Overview of dMMR/MSI, POLE mutations, and BRCA1/2 mutations

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Disclosures

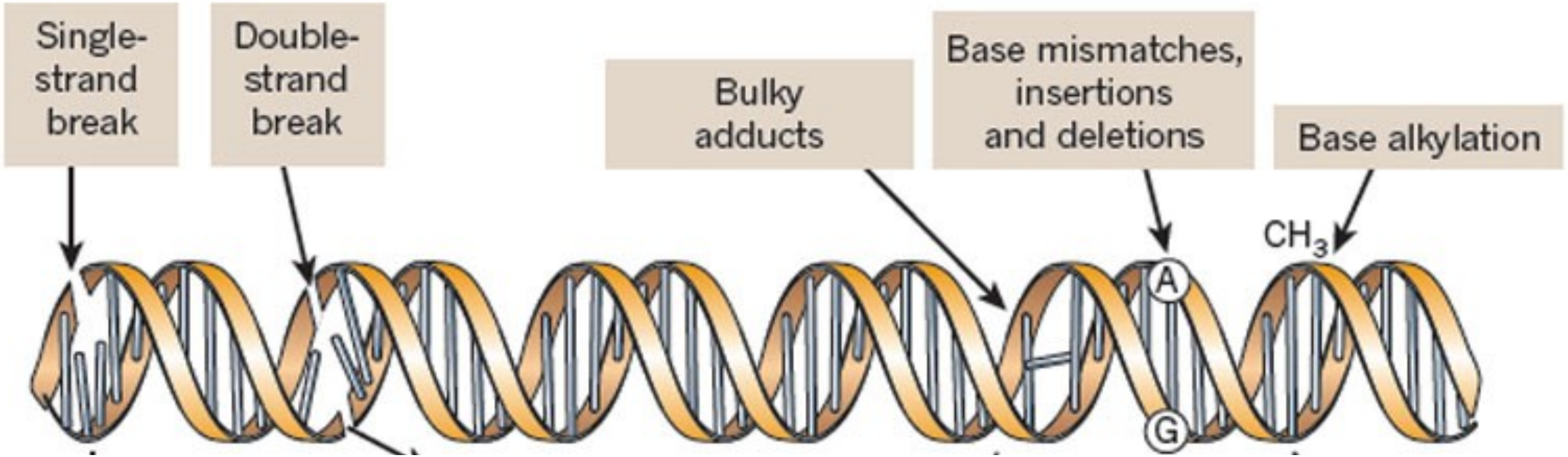
- No relevant disclosures

- I will be discussing non-FDA approved indications during my presentation.

Outline

- DNA Repair & Immunotherapy
- Microsatellite Instability
- POLE mutations
- BRCA1 and BRCA2 mutations
  (Homologous Recombination Repair Deficiency)

DNA Damage is Constant and Varied



The DNA damage response and cancer therapy
Nature. 2012 Jan 18;481(7381):287-94. PMID: 22258607

DNA Damage is Constant and Varied

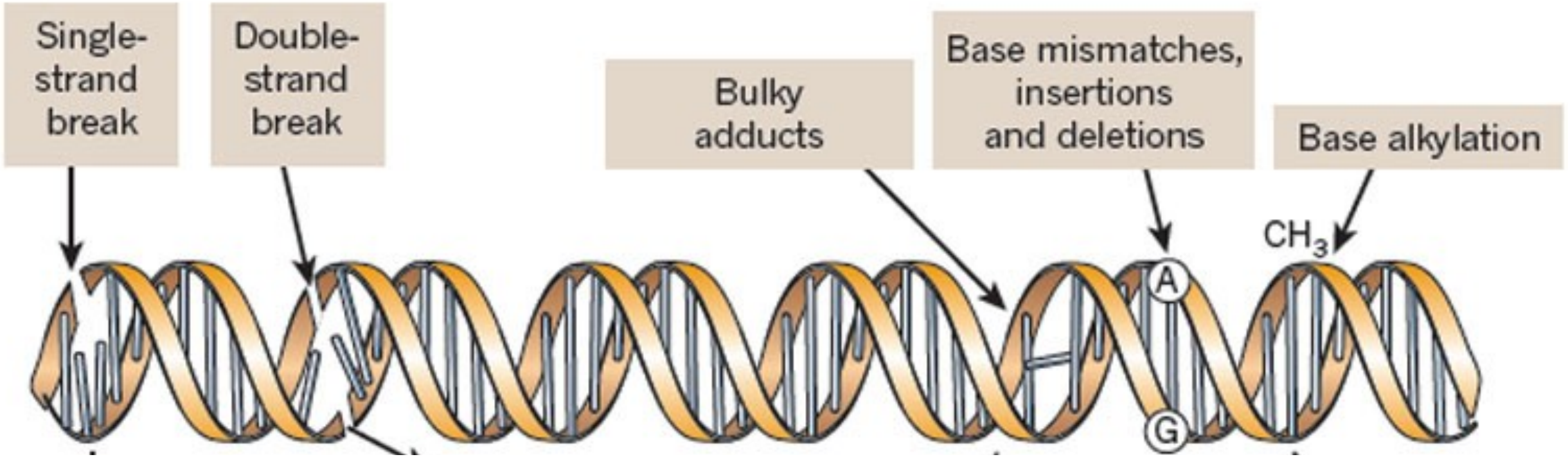
X-rays
Alkylating Agents

Ionizing
Radiation

UV Radiation
Hydrocarbons

Replication Errors

Tobacco
Environmental



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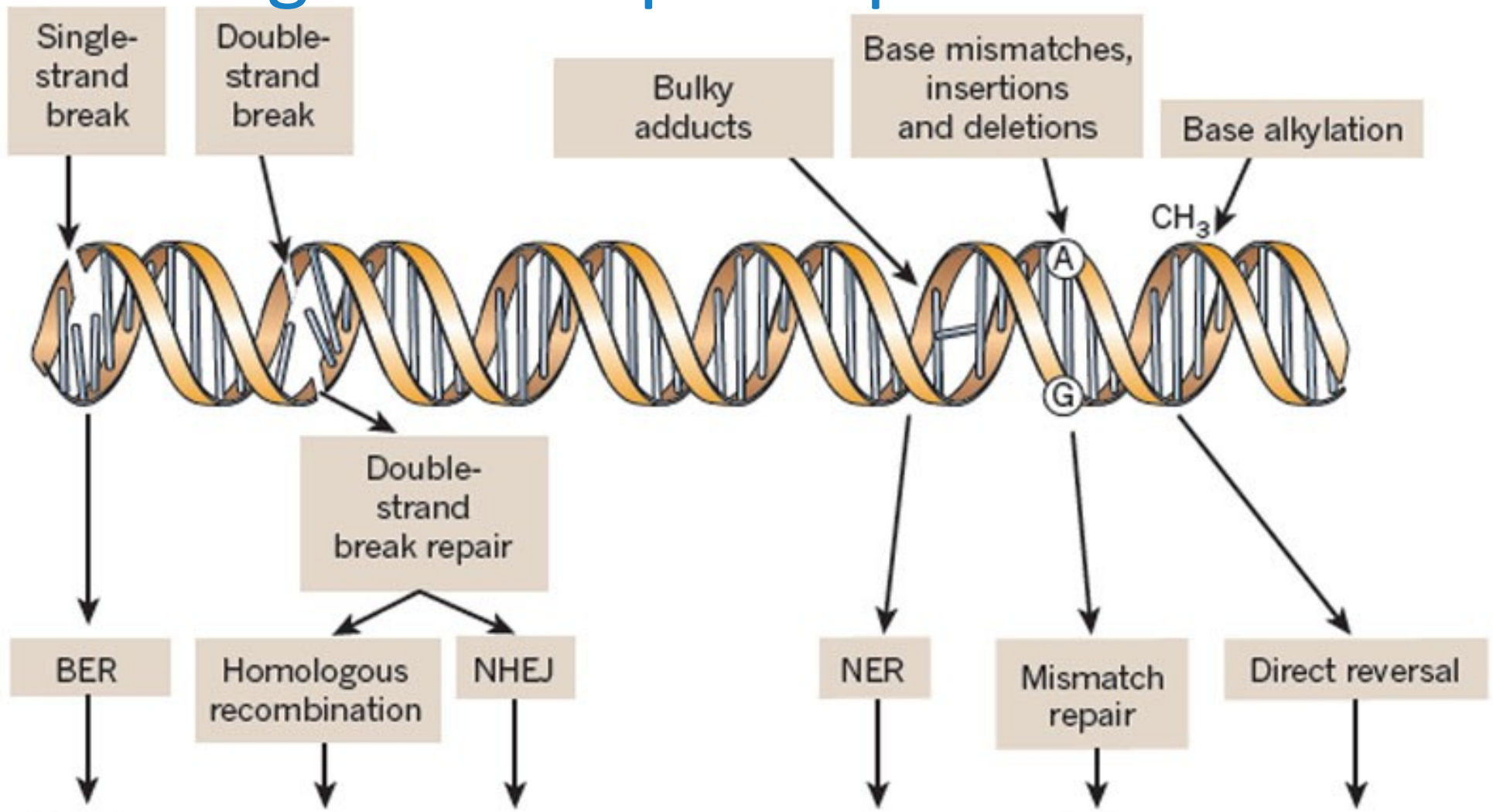
DNA Damage – Multiple Repair Mechanisms



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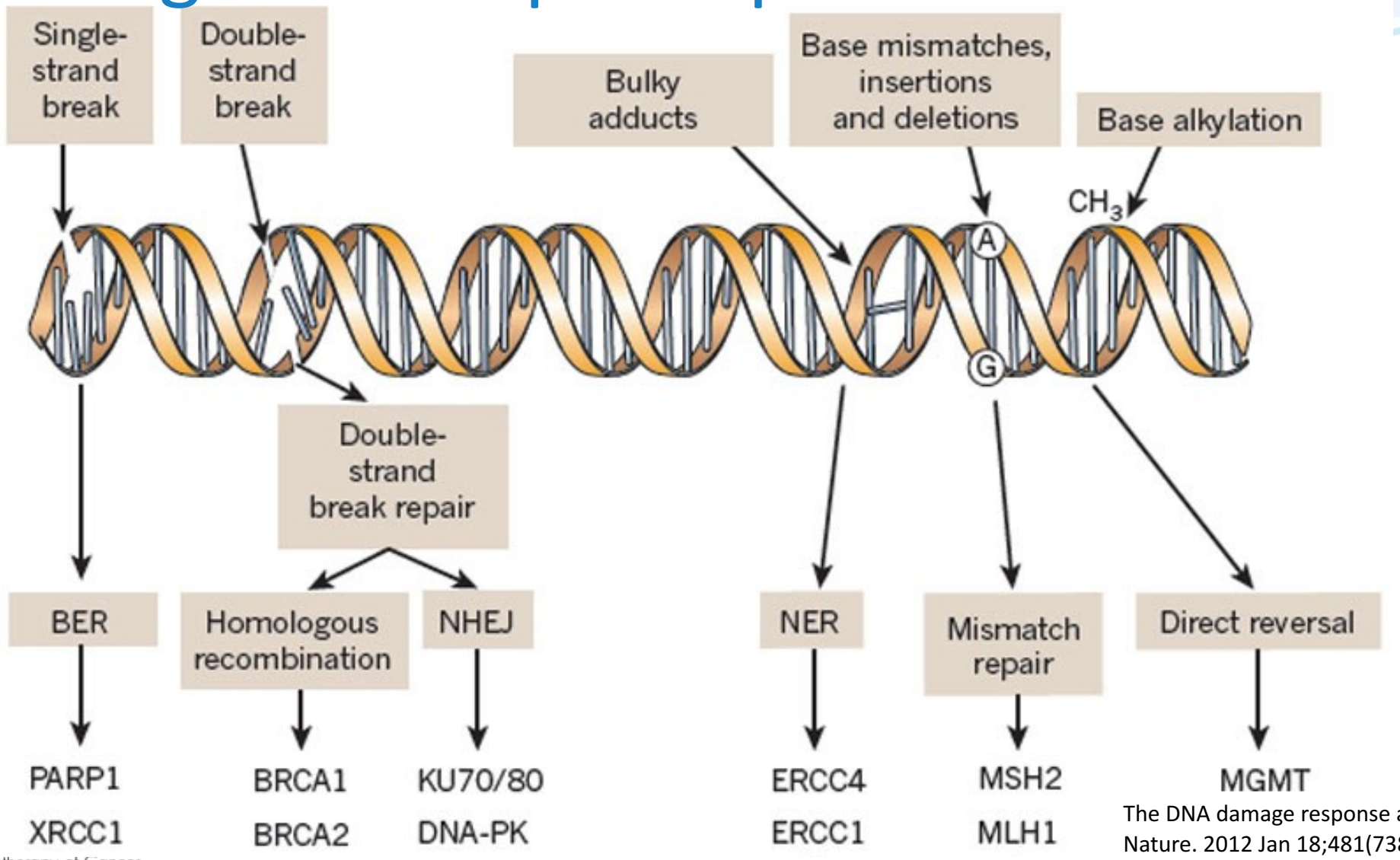

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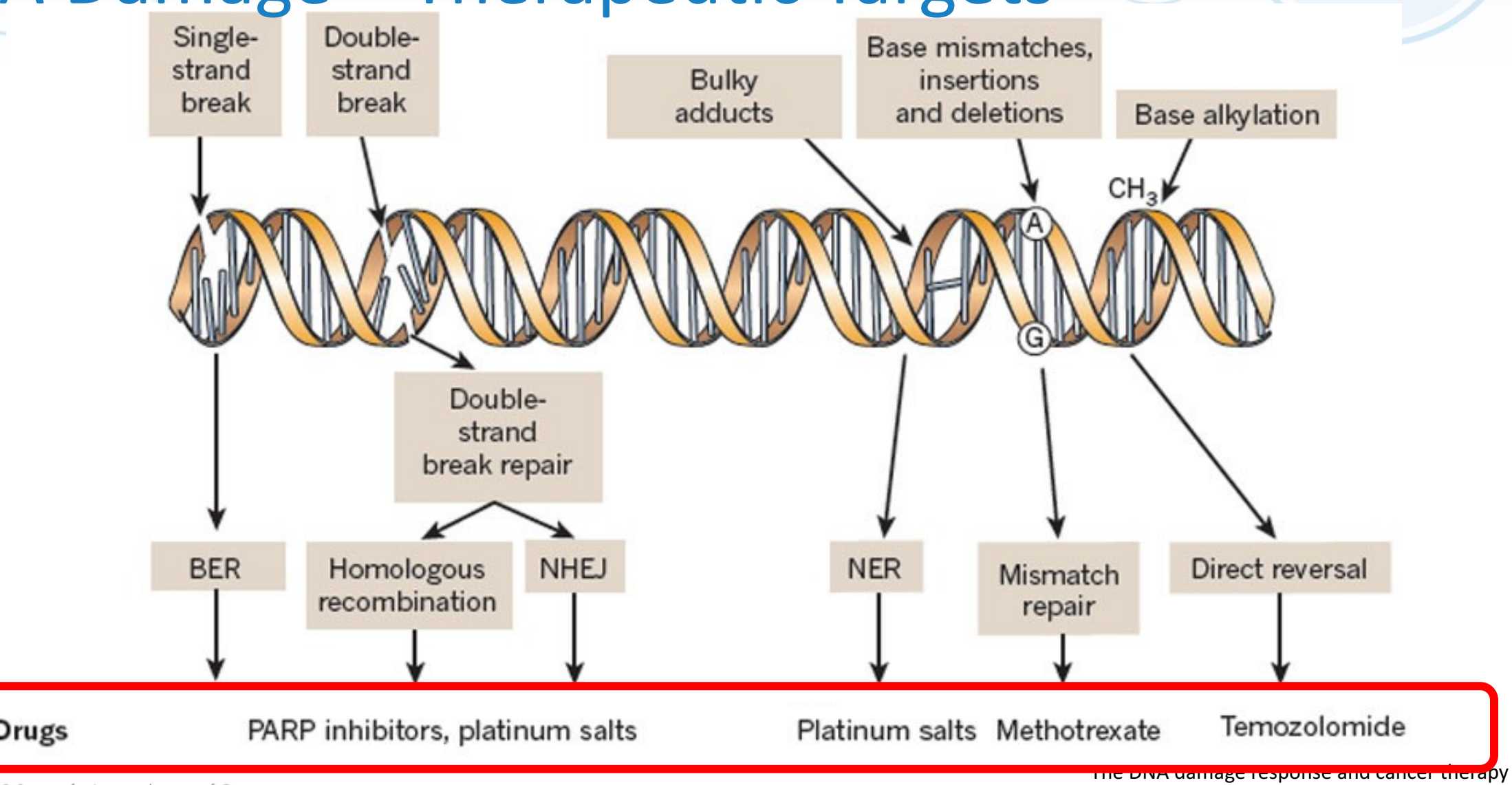
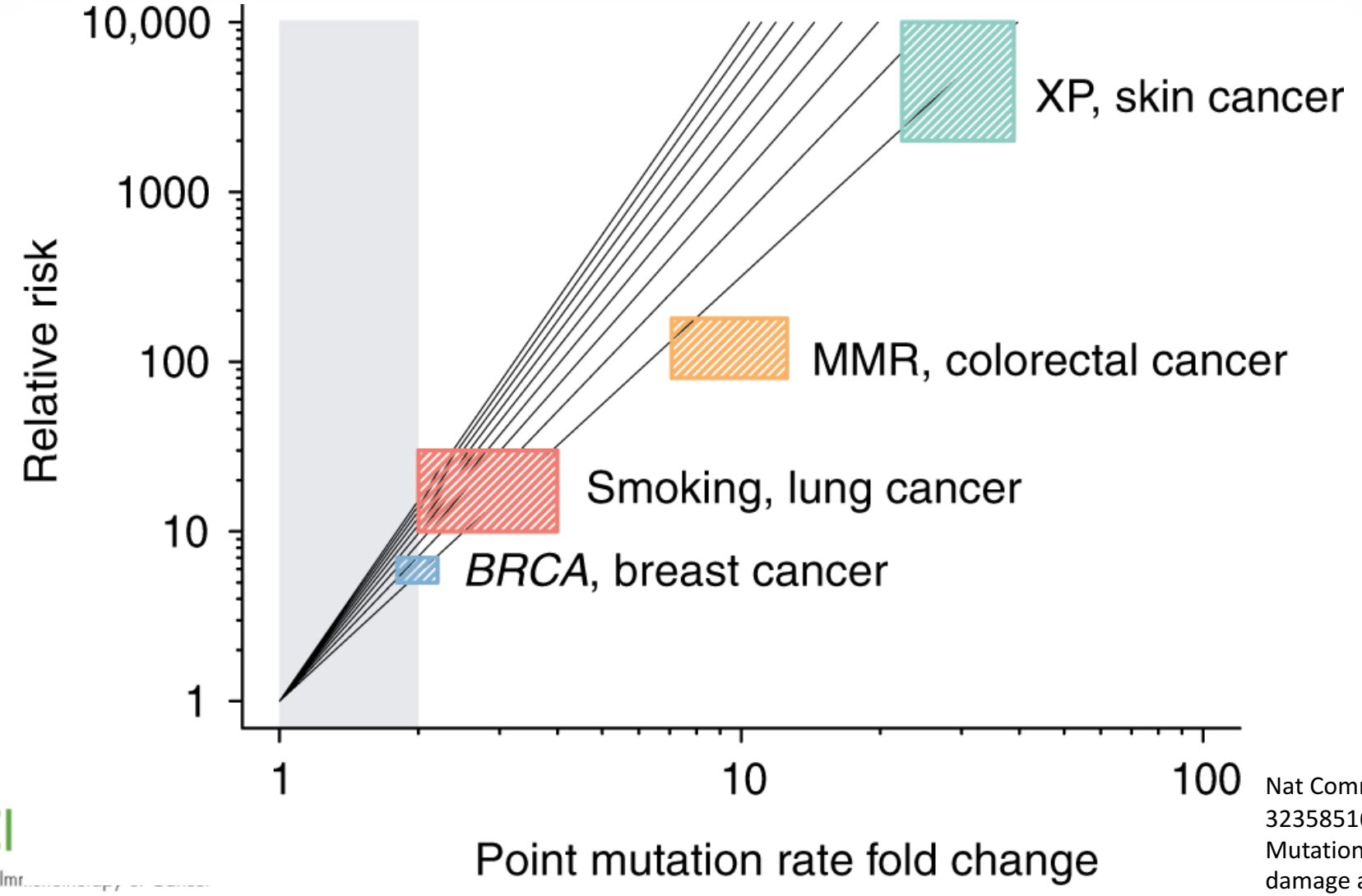
The DNA damage response and cancer therapy Nature. 2012 Jan 18;481(7381):287-94. PMID: 22258607

DNA Damage – Therapeutic Targets



The DNA damage response and cancer therapy
Nature. 2012 Jan 18;481(7381):287-94. PMID: 22258607

Hereditary Cancer risk & Mutation Rate

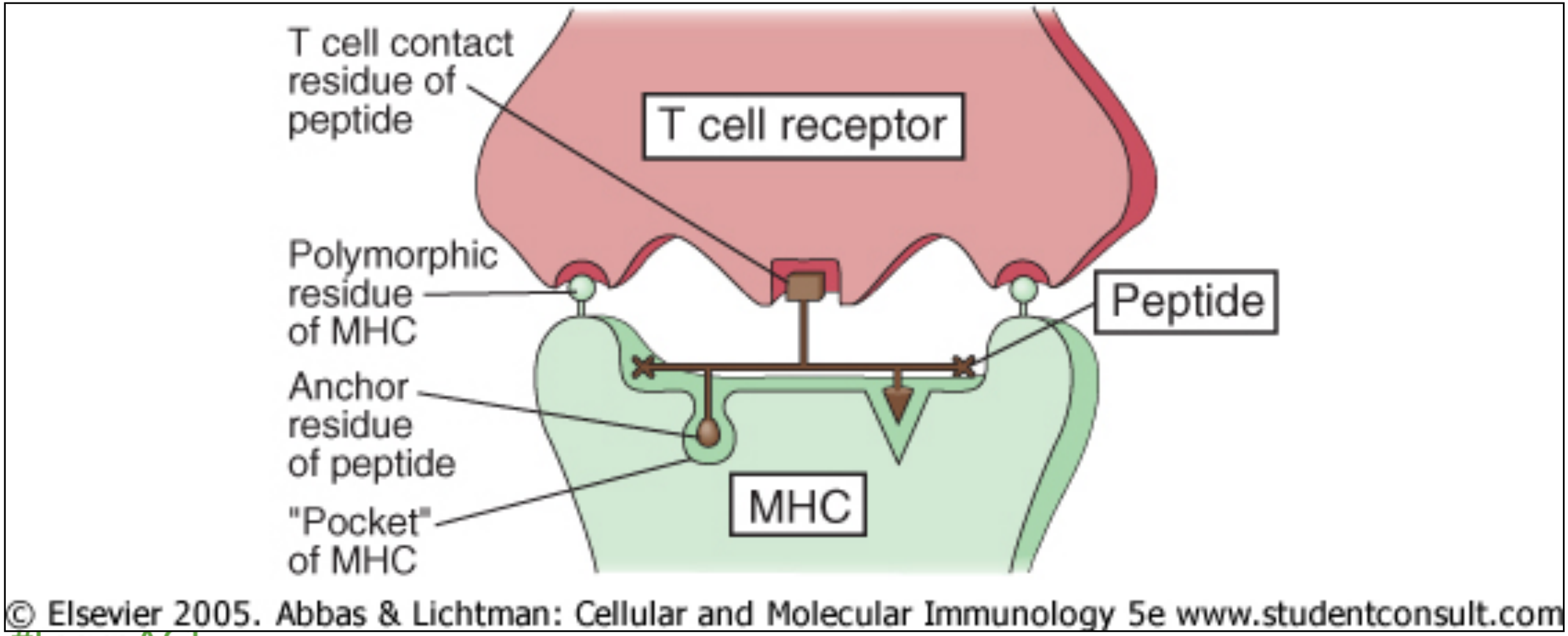


Nat Commun. 2020 May 1;11(1):2169. PMID: 32358516
Mutational signatures are jointly shaped by DNA damage and repair

DNA-Repair Defects & Immunotherapy

- Mutation profiles of cells with DNA repair defects?
- Rationale for potential efficacy of immunotherapy?
- Supporting Data?

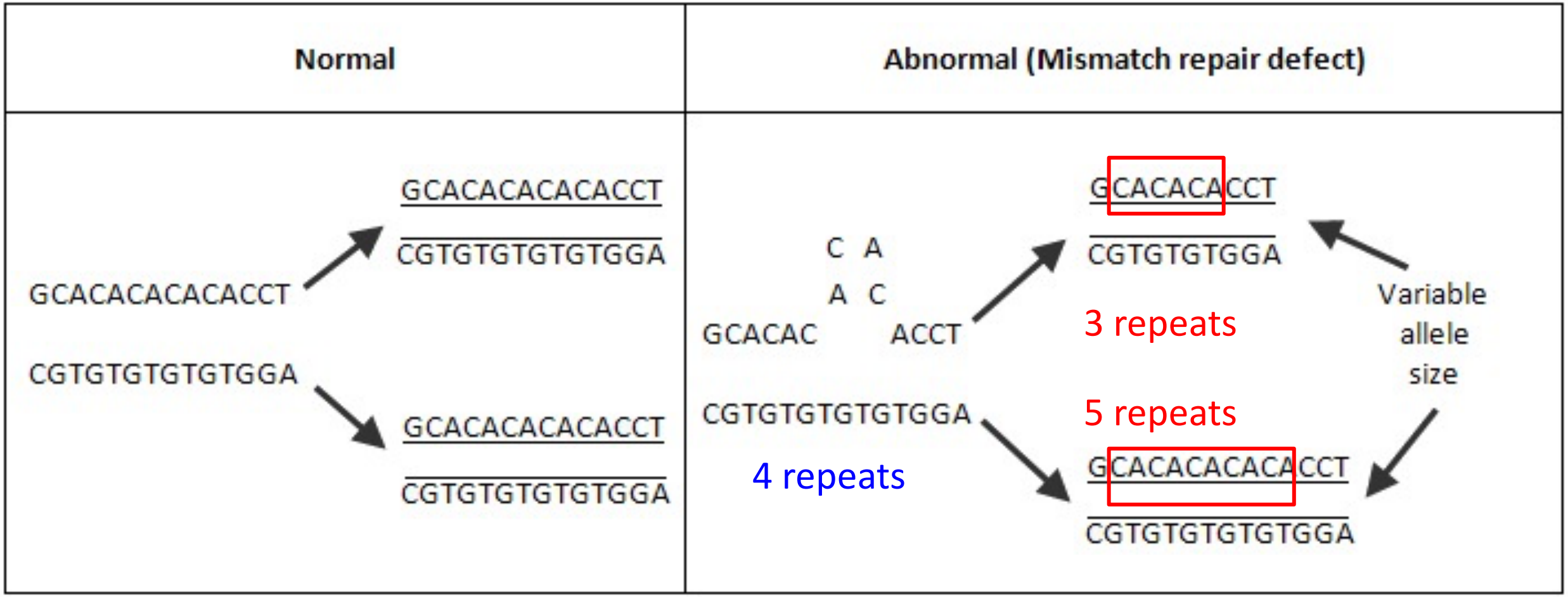
Immunotherapy: It's all about the TCR:Ag:MHC



Mismatch Repair Deficiency/ Microsatellite Instability (dMMR/MSI-High)

dMMR Pathophysiology

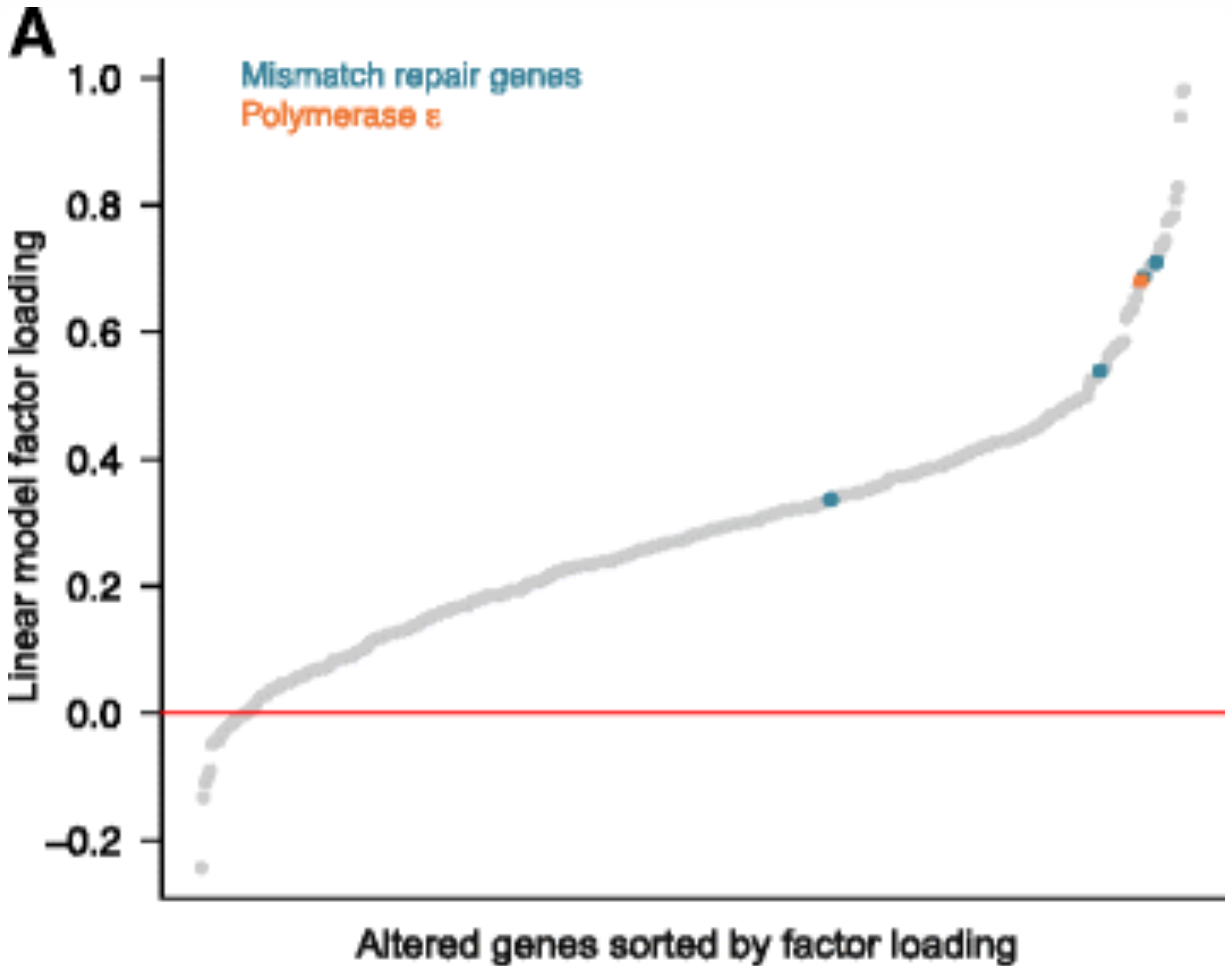
Microsatellite Replication

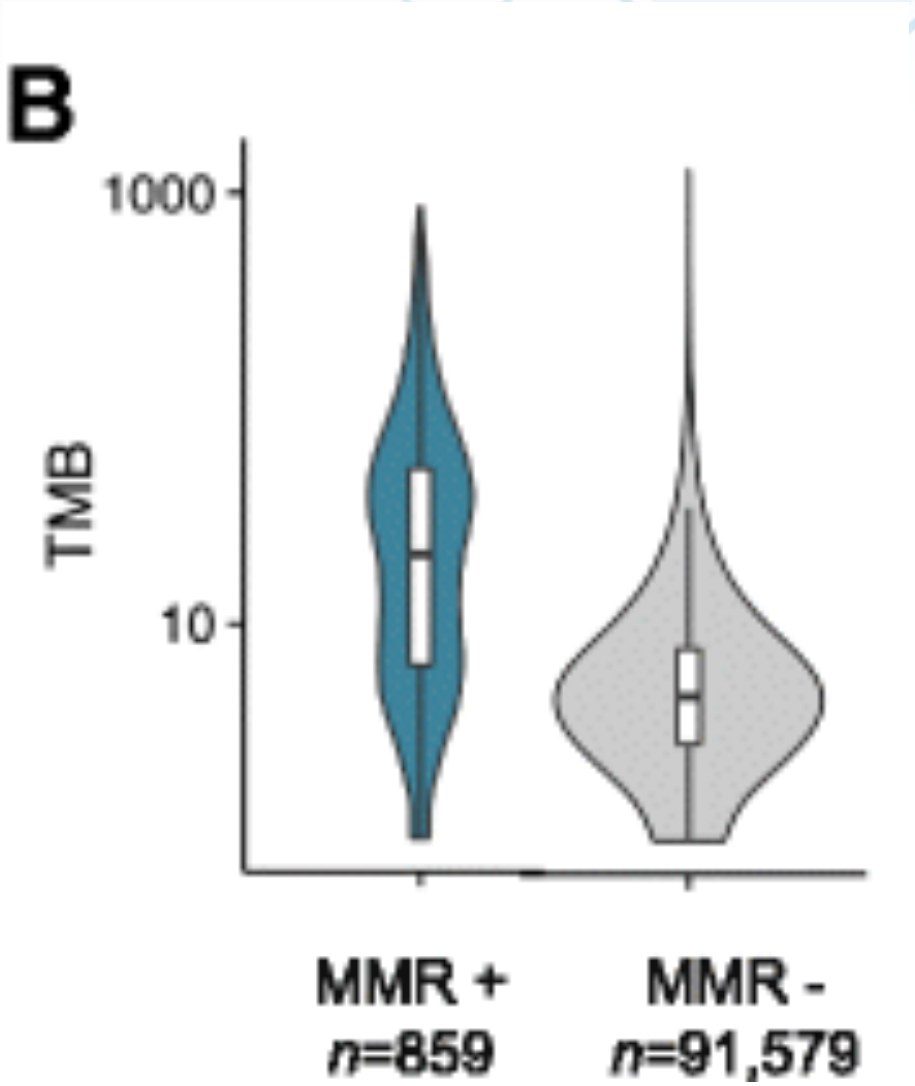


Result: Substitution & frameshift mutations

http://www.ncbi.nlm.nih.gov/books/NBK1211/

MSI-H Mutational Load





Genome Med. 2017 Apr 19;9(1):34. PMID: 28420421
Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden

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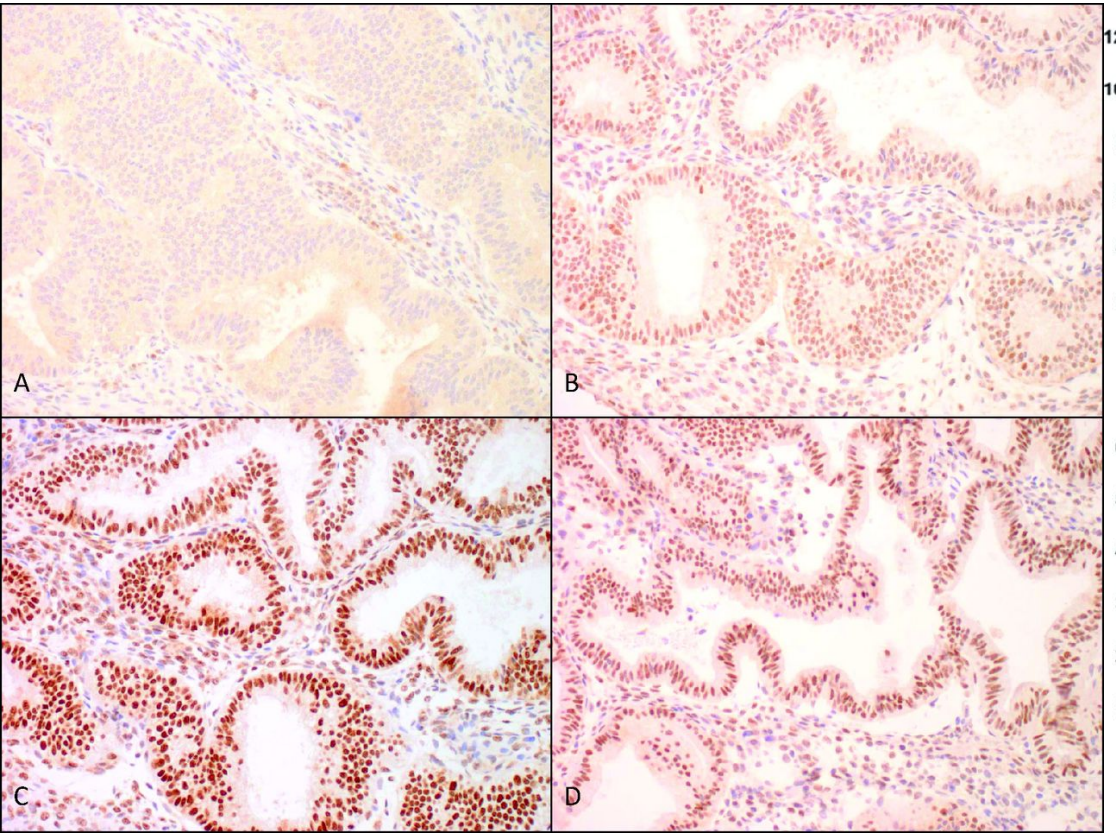
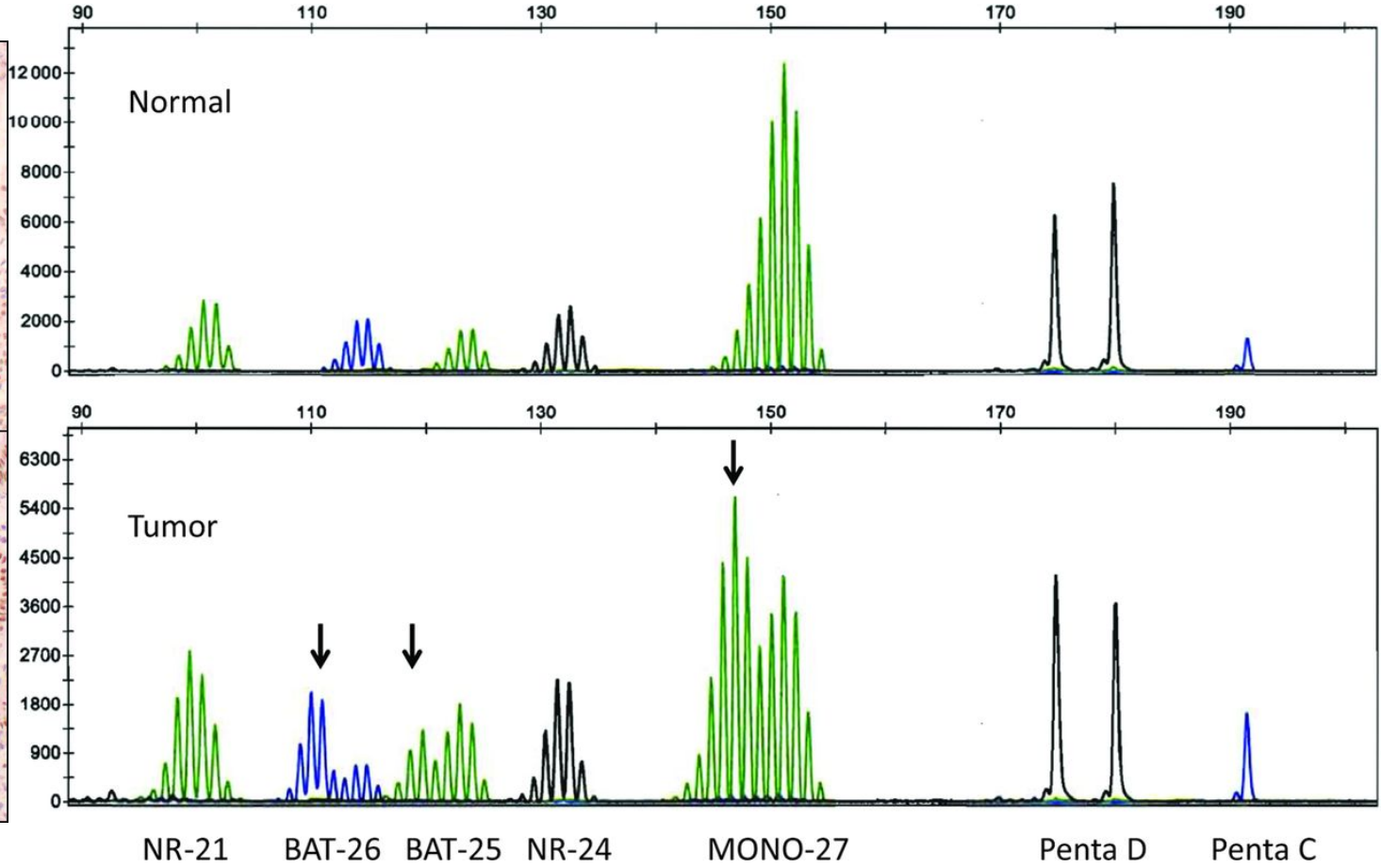
Laboratory Methods

MMR IHC

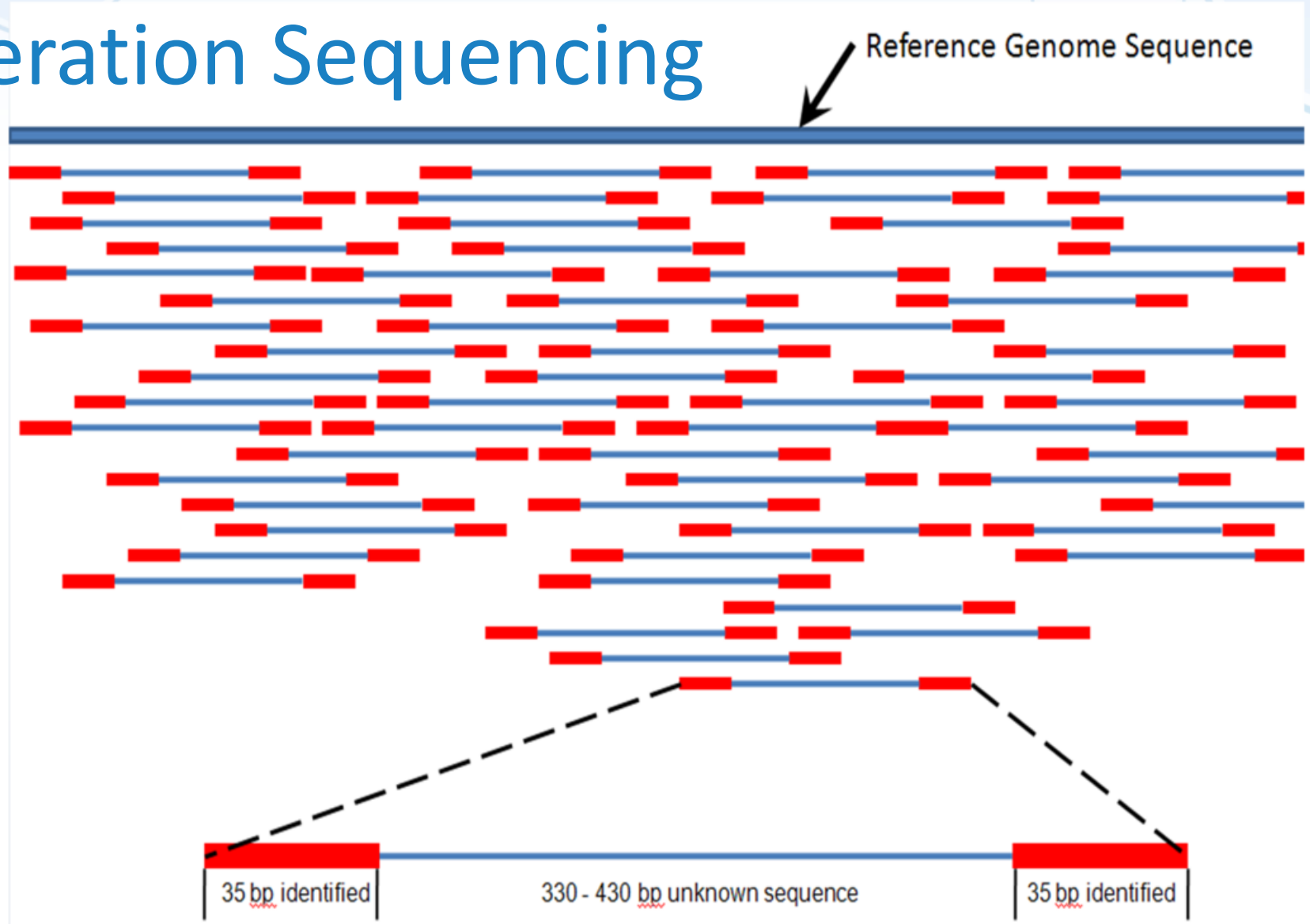


MSI PCR



http://www.ncbi.nlm.nih.gov/books/NBK1211/

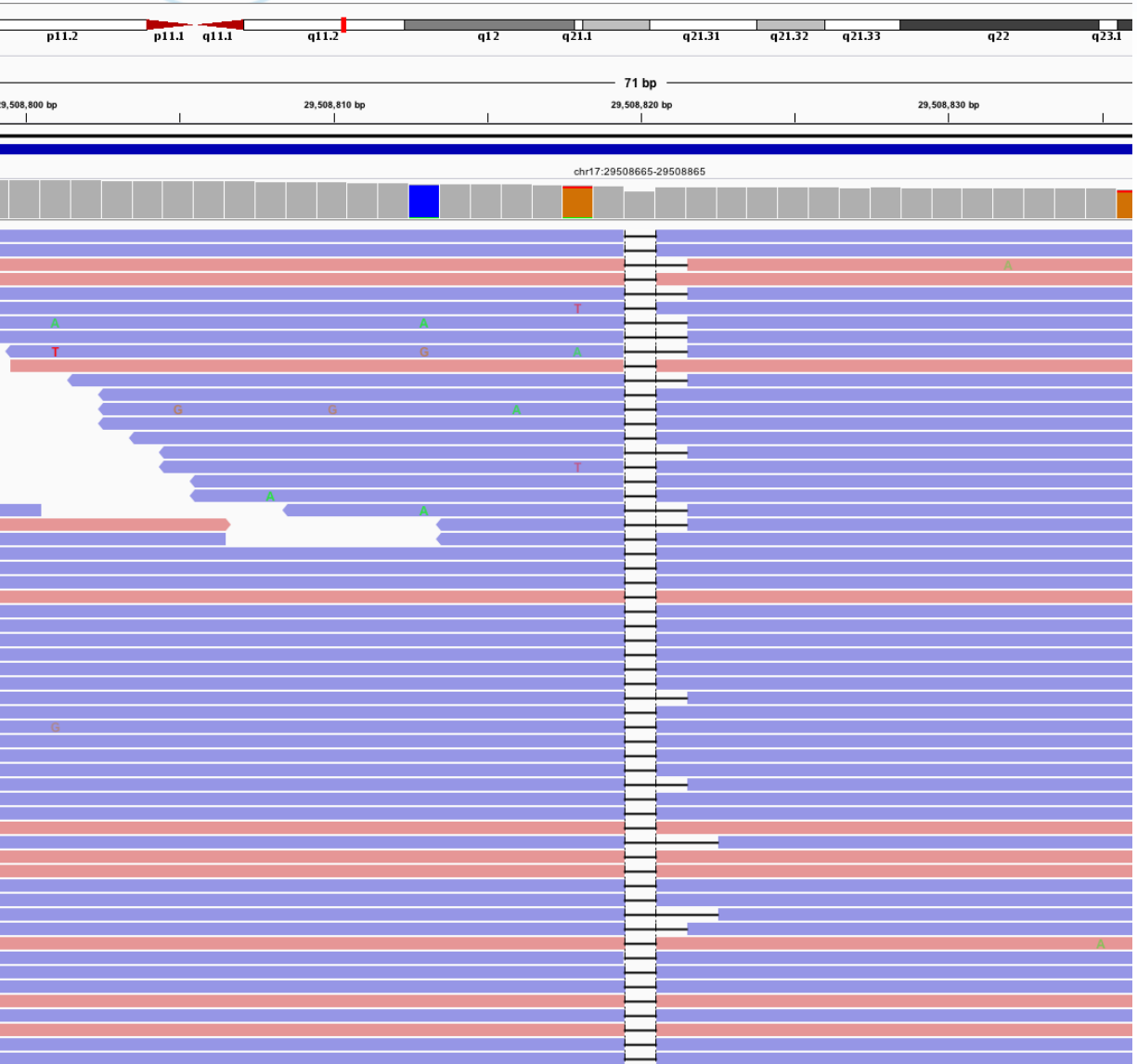
Next Generation Sequencing



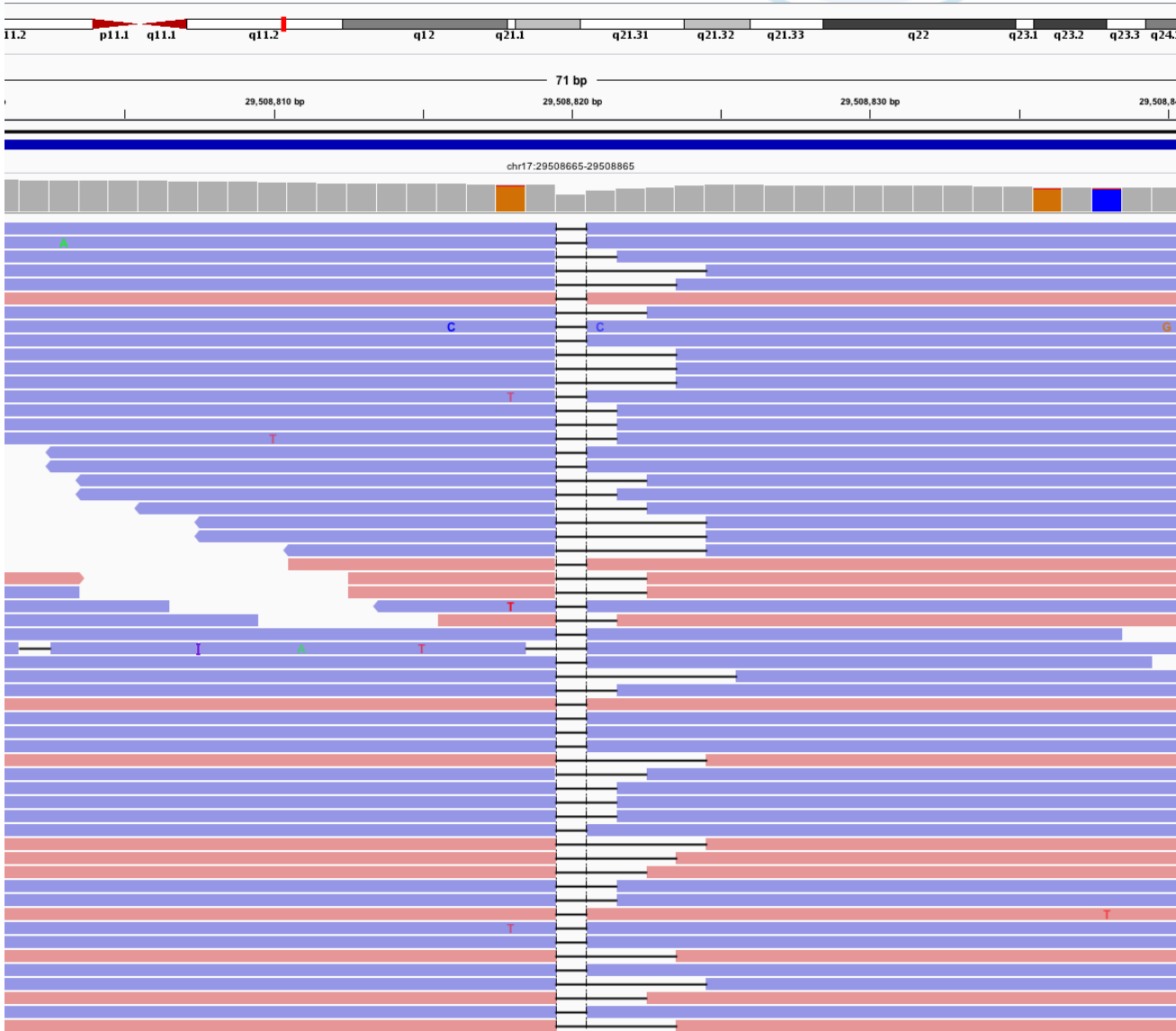
https://en.wikipedia.org/wiki/DNA_sequencing#/media/File:Mapping_Reads.png

MSI by NGS

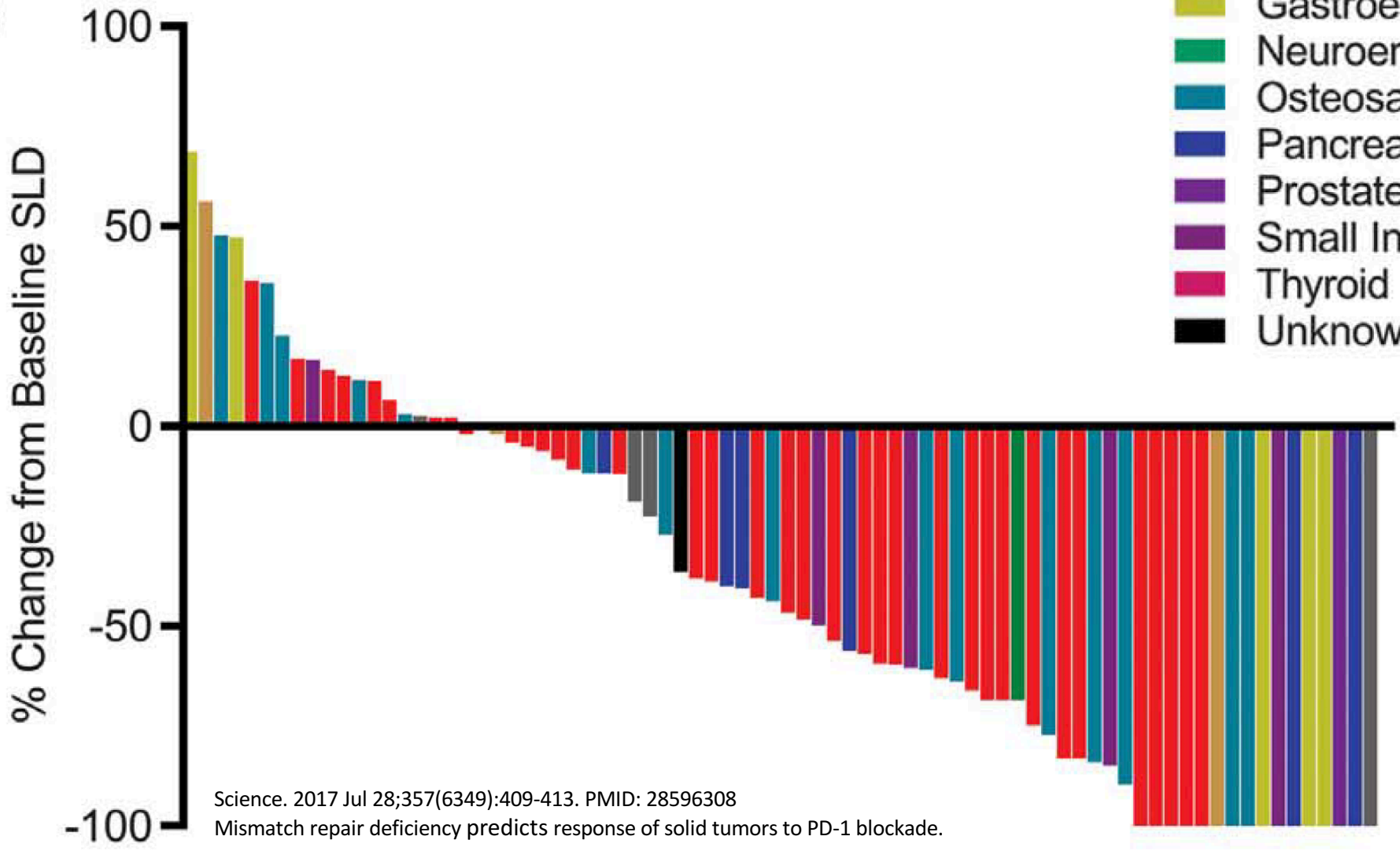
Blood



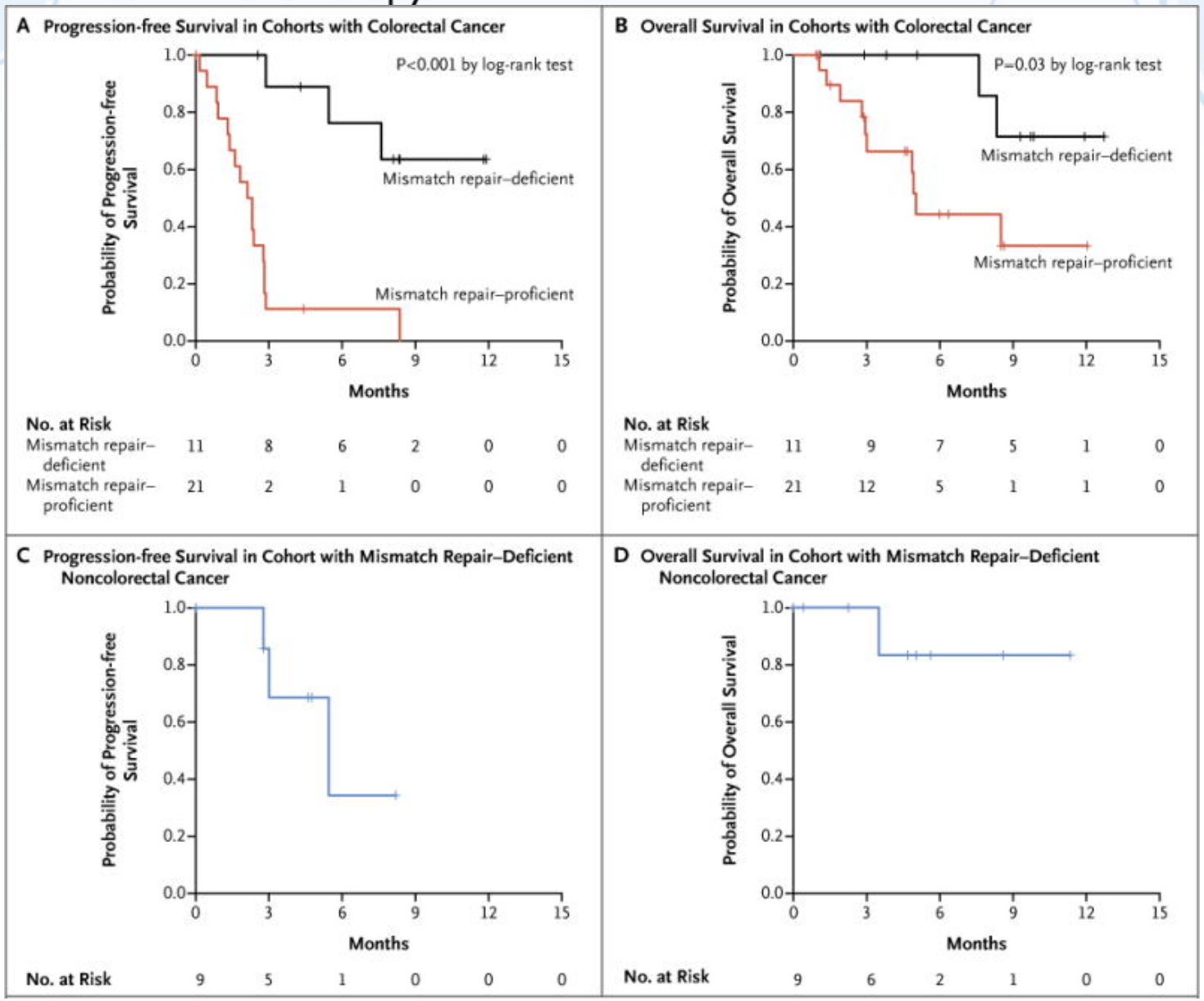
Neoplastic Tissue



dMMR Therapy Response



Science. 2017 Jul 28;357(6349):409-413. PMID: 28596308
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade.



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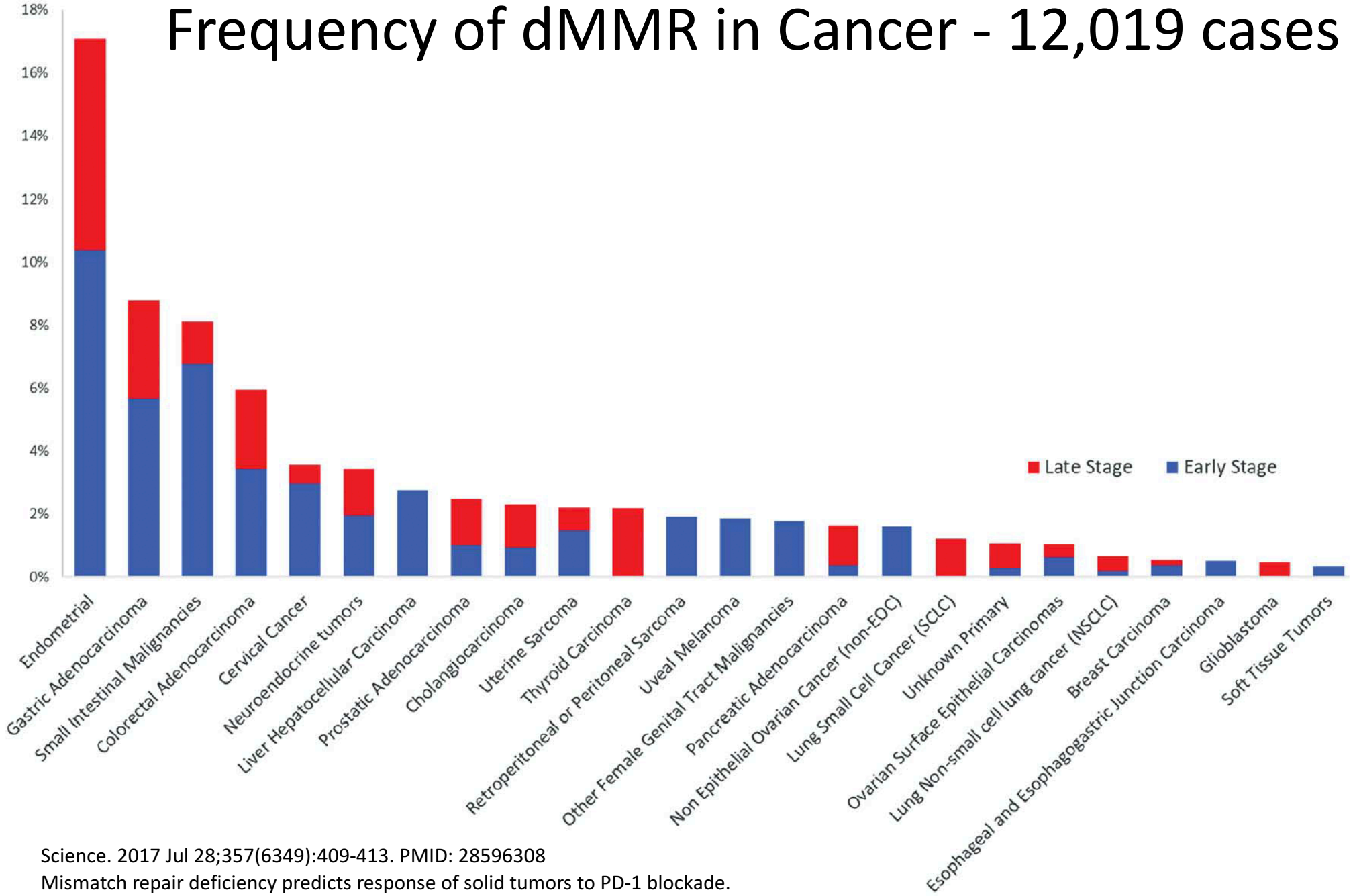
N Engl J Med. 2015 Jun 25;372(26):2509-20. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency
PMID: 26028255

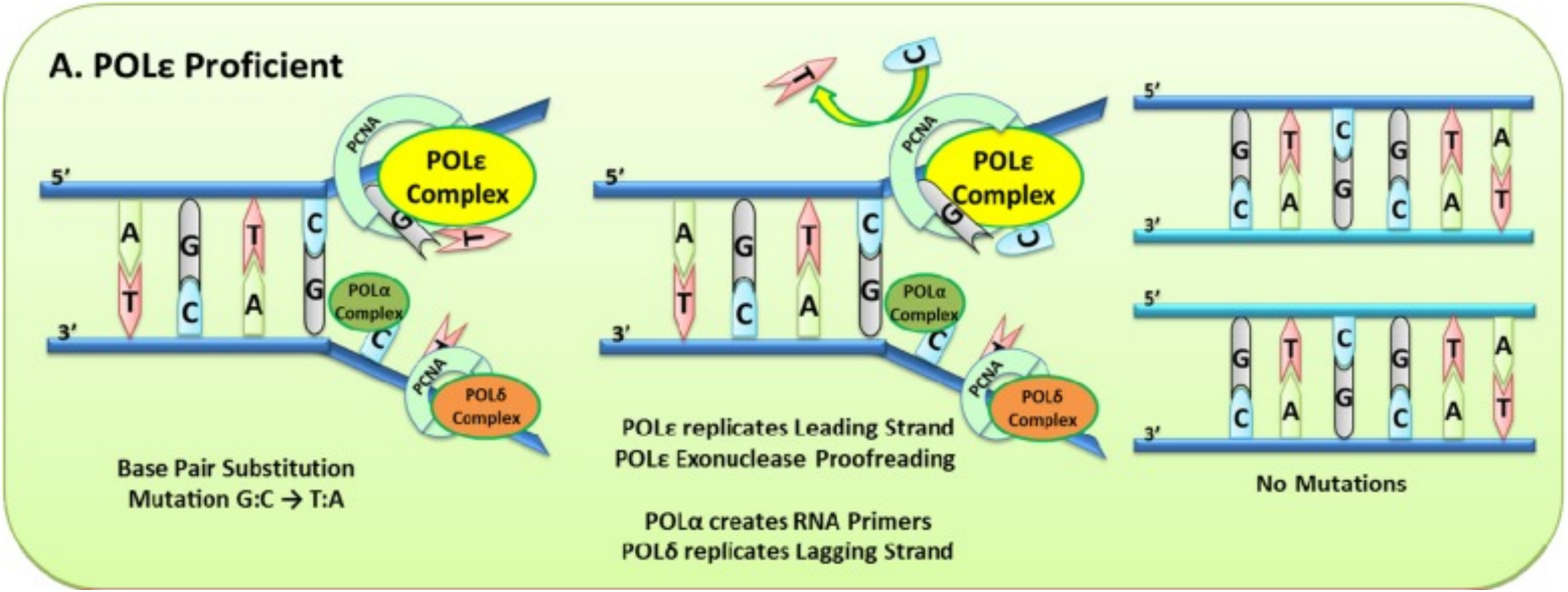
Frequency of dMMR in Cancer - 12,019 cases



Science. 2017 Jul 28;357(6349):409-413. PMID: 28596308
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade.

POLE Mutations

POLE Exonuclease Domain Mutations



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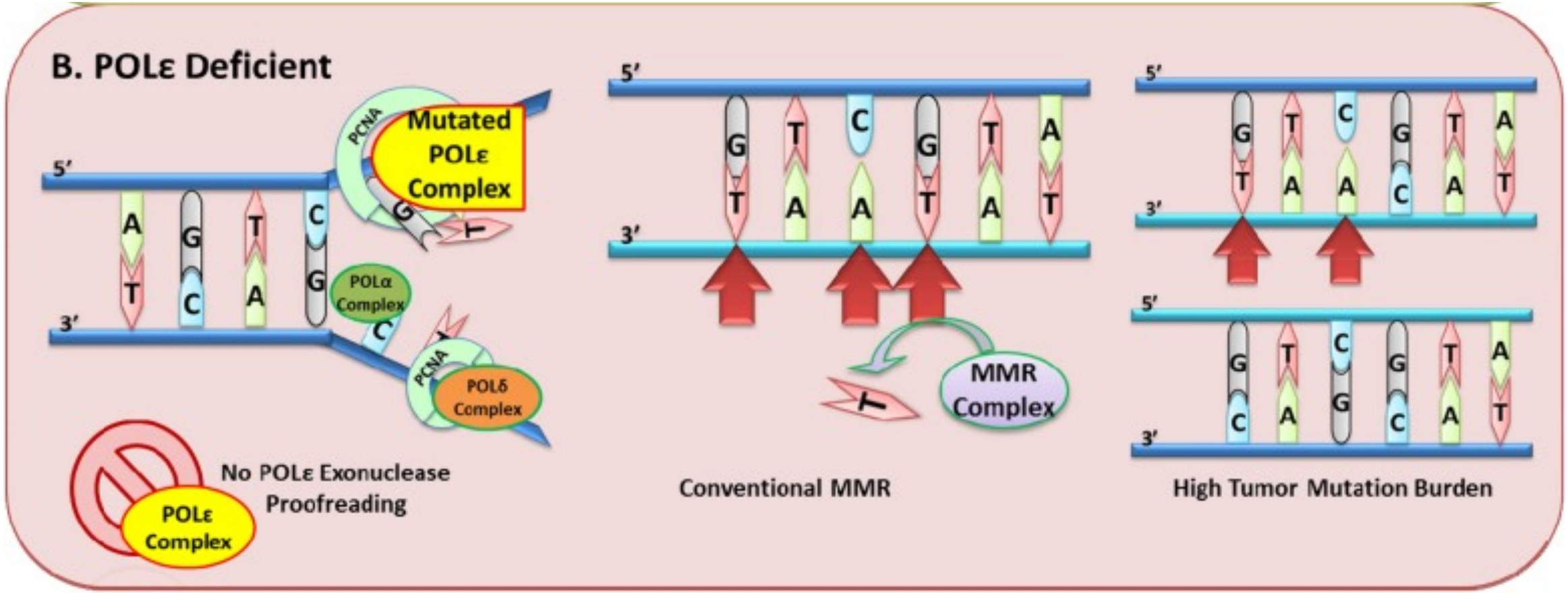
DNA Polymerase ε Deficiency Leading to an Ultramutator Phenotype: A Novel Clinically Relevant Entity. The Oncologist, 02 May 2017, 22(5):497-502 PMID: 28465371

POLE Exonuclease Domain Mutations



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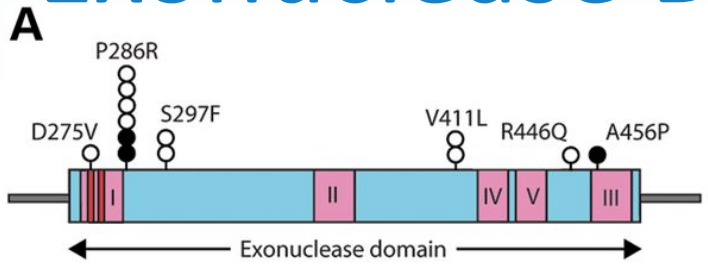
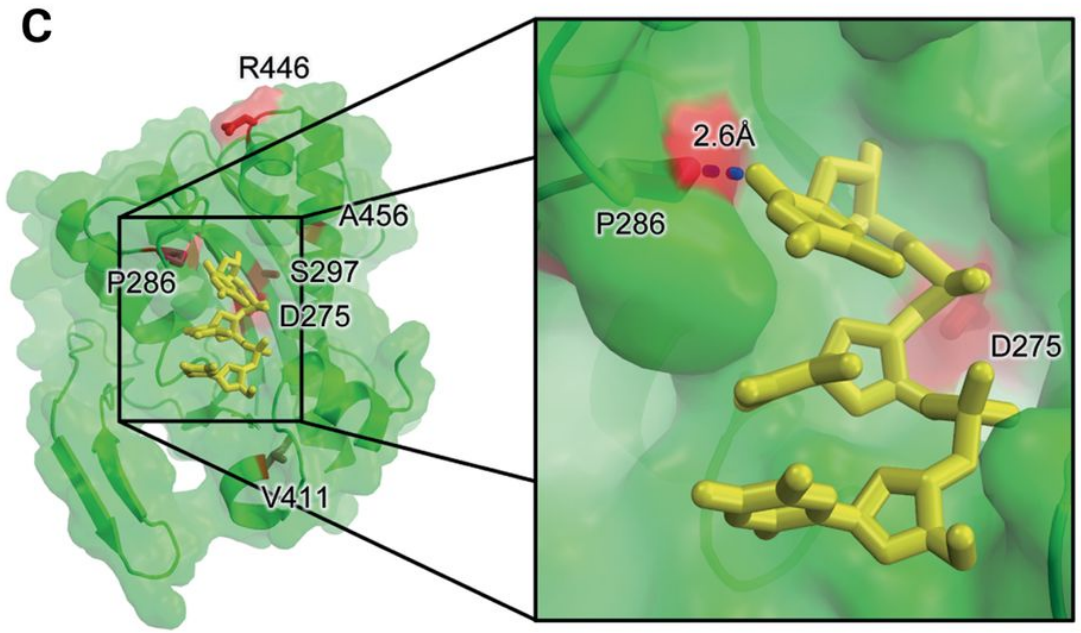
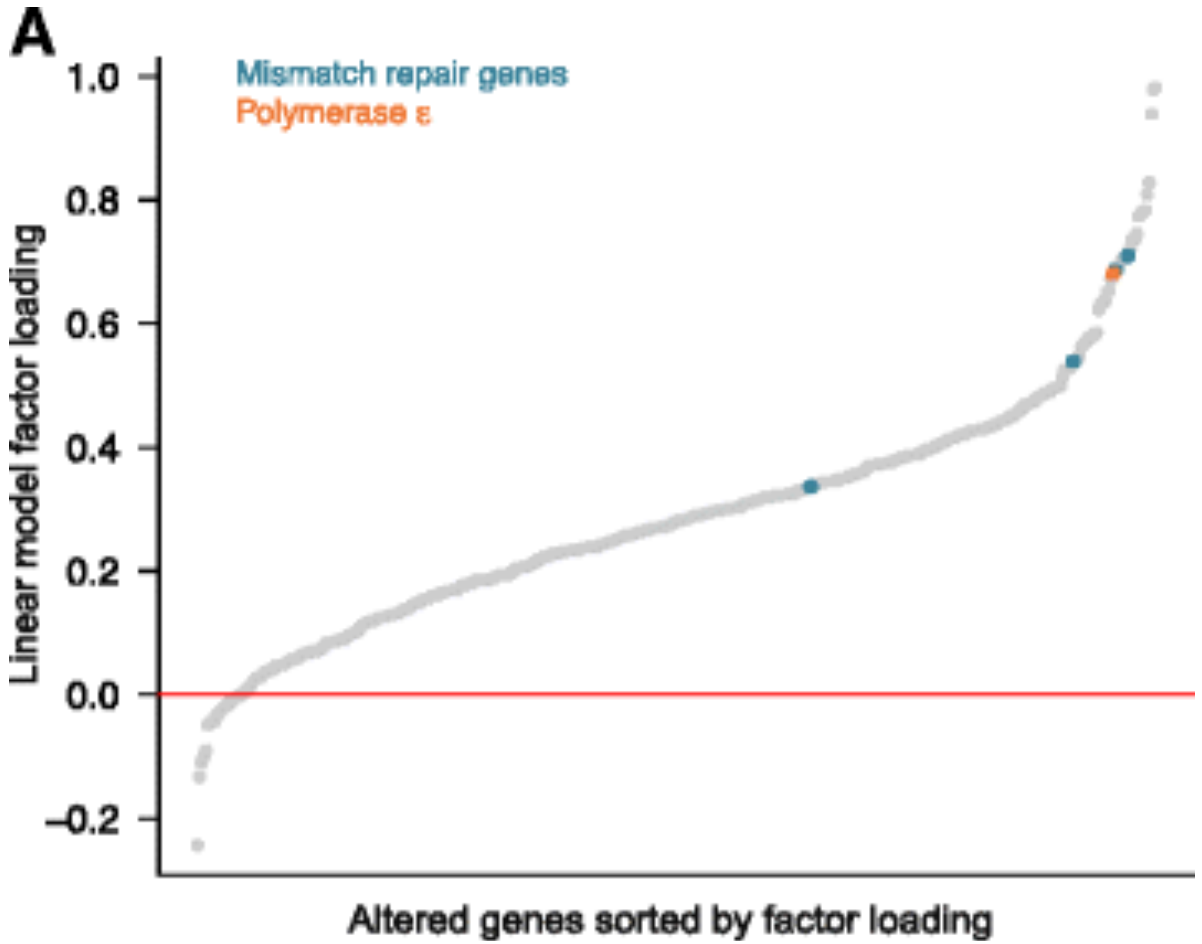
POLE – Exonuclease Domain Mutations

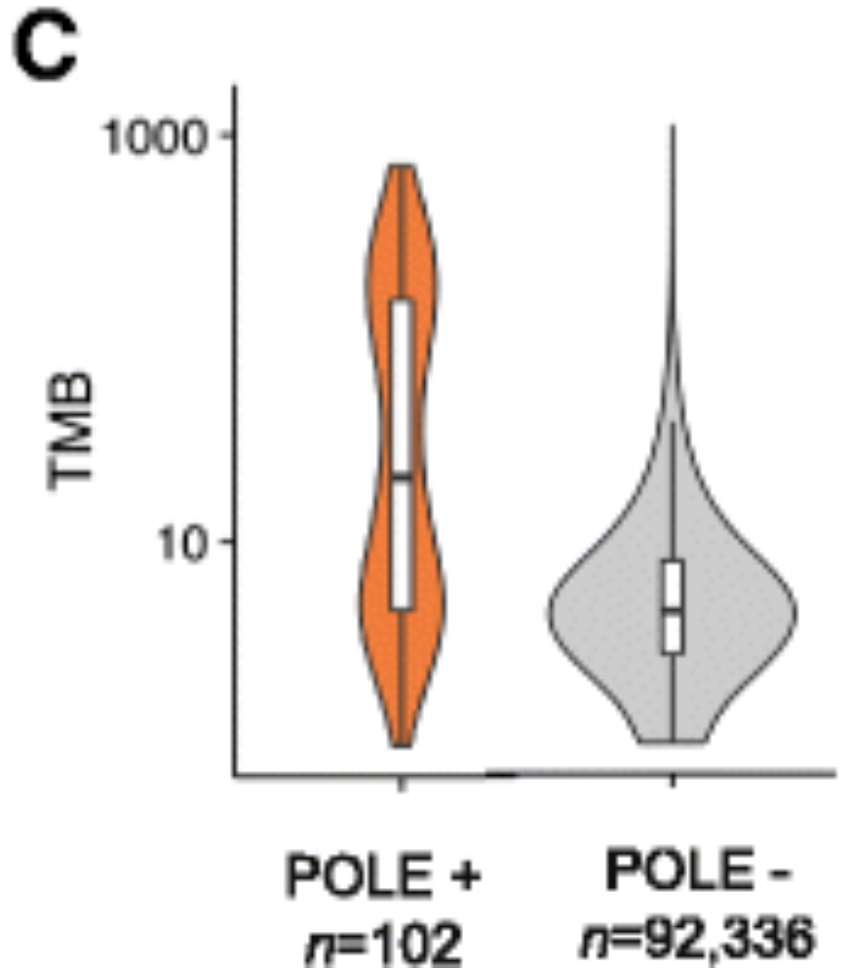




Hum Mol Genet. 2013 Jul 15;22(14):2820-8. PMID: 23528559
DNA polymerase ε and δ exonuclease domain mutations in endometrial cancer

POLE -Mutational Load





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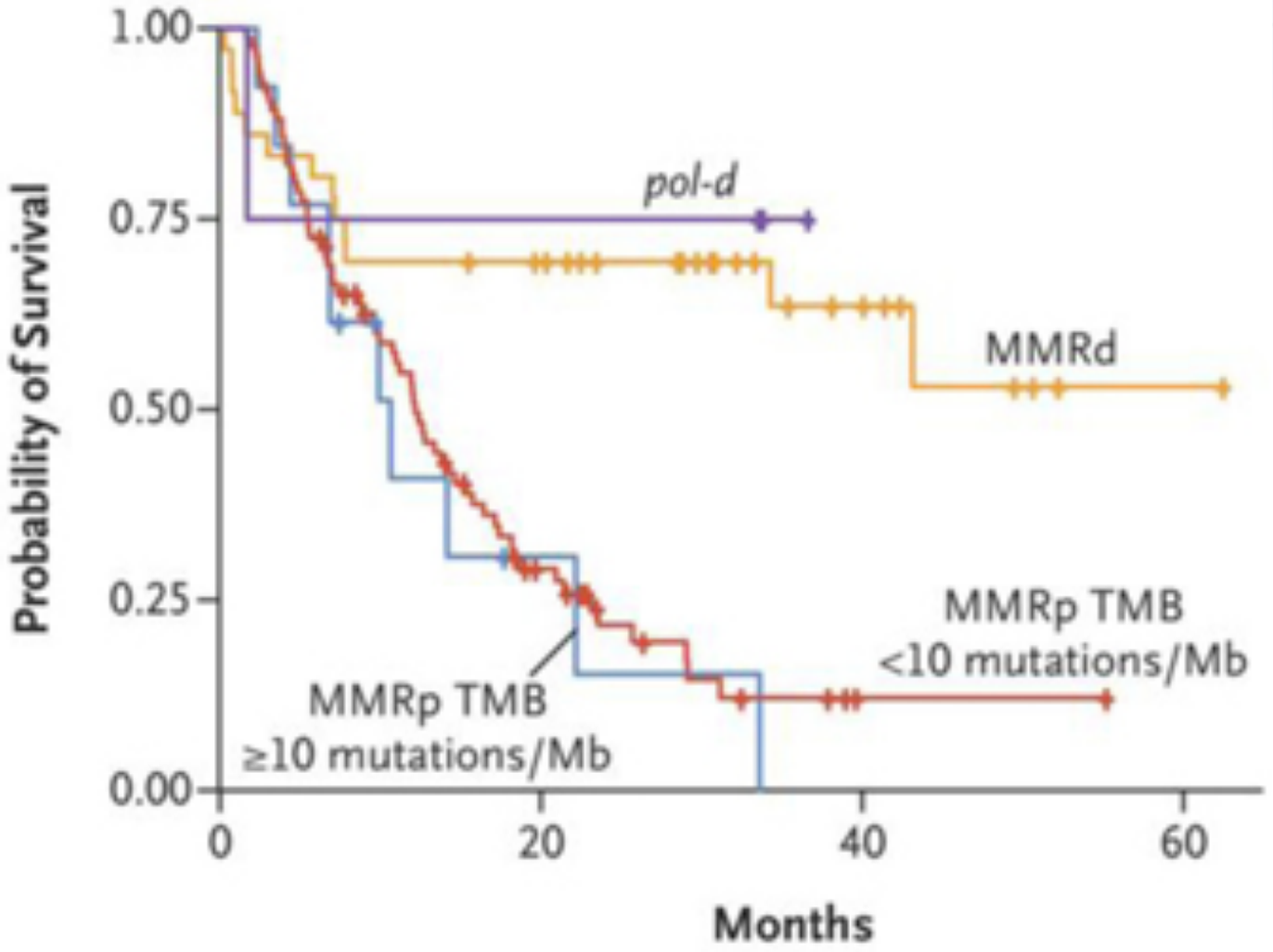
Genome Med. 2017 Apr 19;9(1):34. PMID: 28420421
Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden

B Overall Survival, by DNA-Repair Status



pol-d	4	3	0	0
MMRd	36	23	9	1
MMRp TMB <10 mutations/Mb	84	18	1	0
MMRp TMB ≥10 mutations/Mb	13	2	0	0

DNA-Repair Status	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
pol-d	1/4	NR (1.68–NE)
MMRd	13/36	NR (34.28–NE)
MMRp TMB <10 mutations/Mb	64/84	12.1 (9.61–15.3)
MMRp TMB ≥10 mutations/Mb	10/13	10.6 (4.41–22.2)

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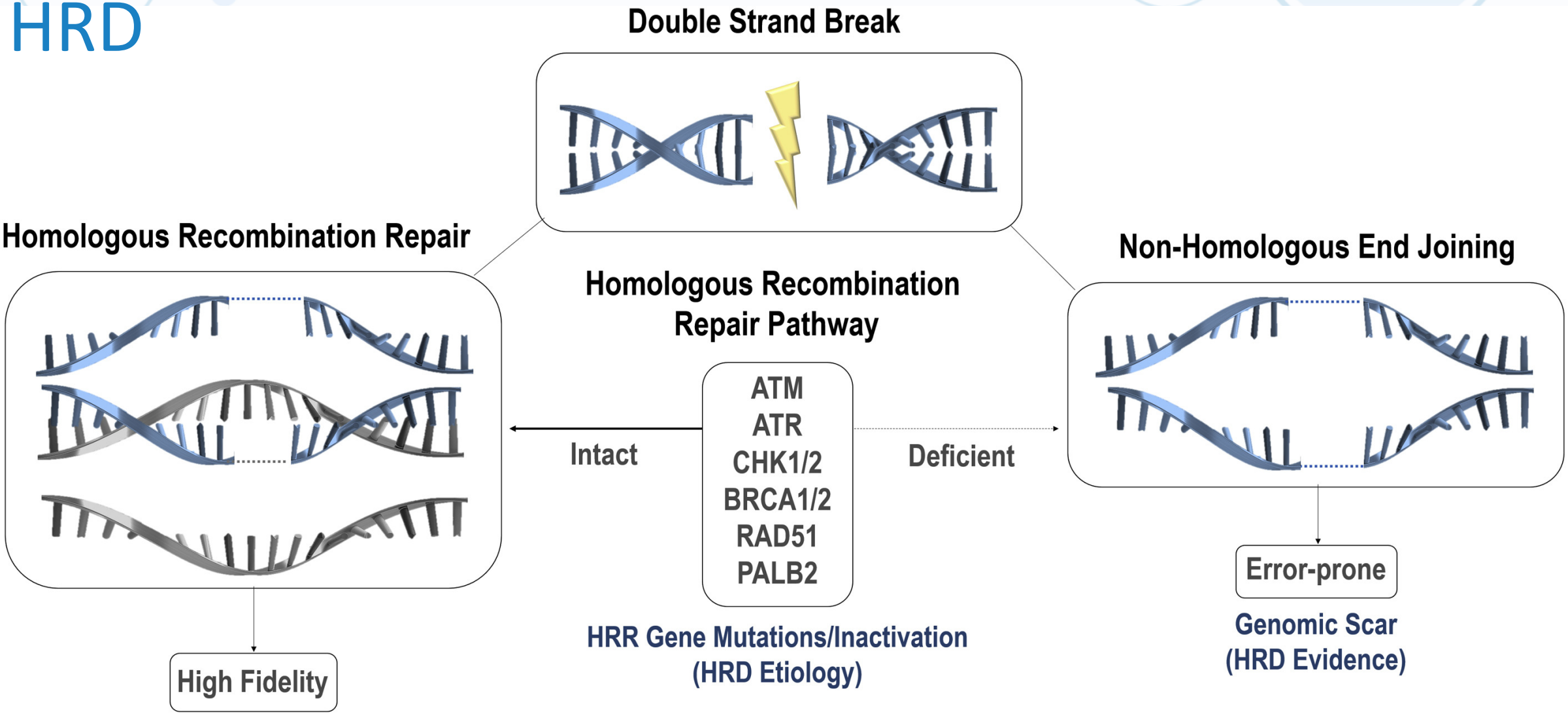
N Engl J Med. 2021 Mar 25;384(12):1168-1170. PMID: 33761214
The Spectrum of Benefit from Checkpoint Blockade in Hypermutated Tumors

BRCA1/BRCA2 (Homologous recombination Repair Deficiency - HRD)

HRD



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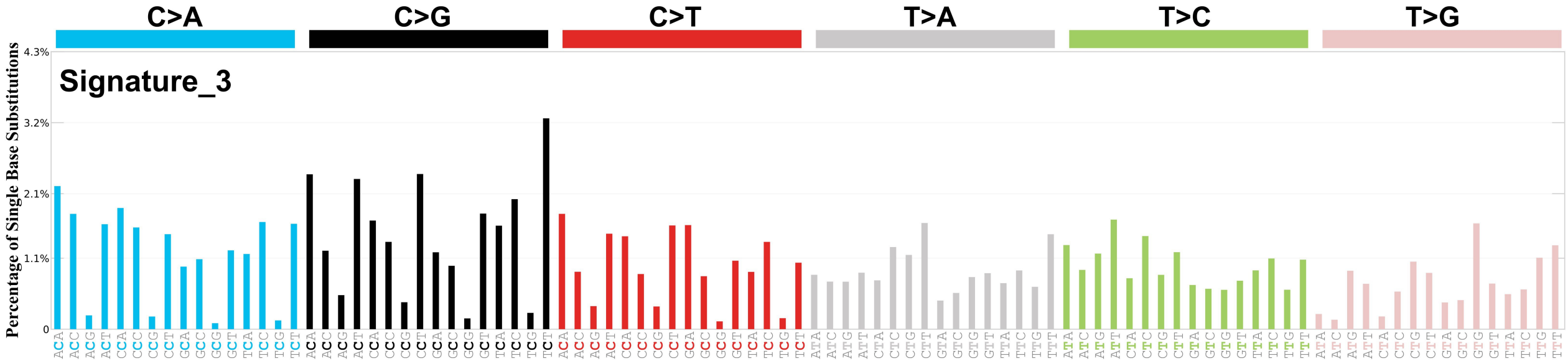
Surg Pathol Clin. 2021 Sep;14(3):415-428. MID: 34373093
Molecular Pathology of Ovarian Epithelial Neoplasms: Predictive, Prognostic, and Emerging Biomarkers

HRD Mutations

- Small indels and genome rearrangements
- Base substitutions (signature 3)



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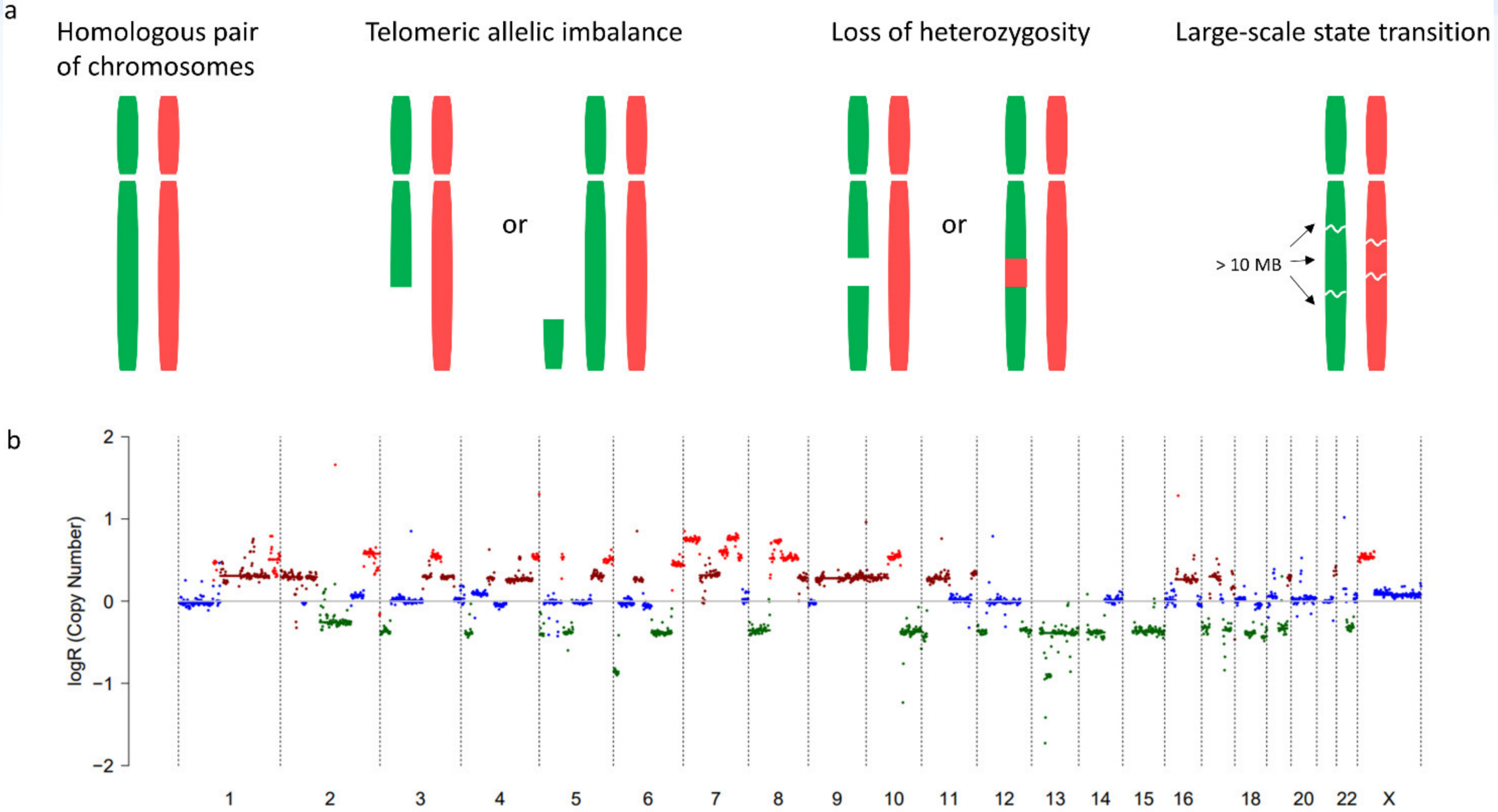
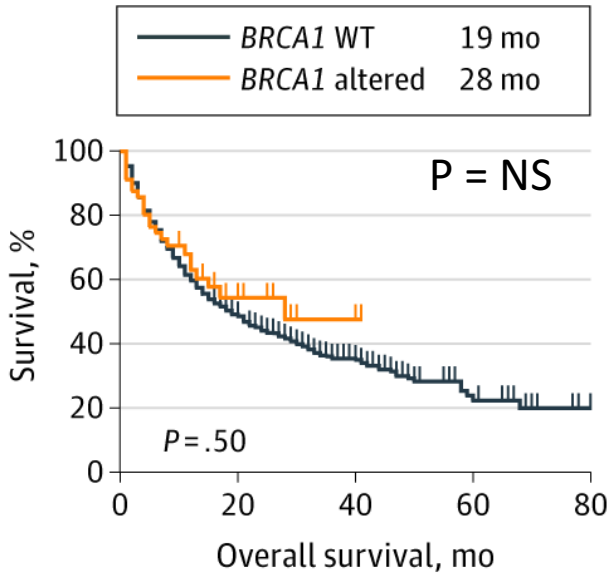
https://cog.sanger.ac.uk/cosmic-signatures-production/images/v3.2_SBS3_DIFFERENCE_GA_GRCh37.original.jpg



Cancers (Basel). 2021 May 7;13(9):2249. PMID: 34067105
Homologous Recombination Repair Deficiency and Implications for Tumor Immunogenicity

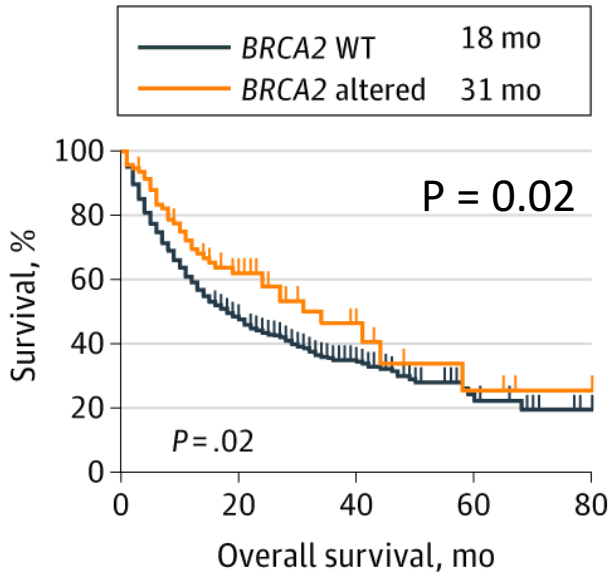
HRD and Immunotherapy

A Overall survival in MSKCC cohort of patients with or without *BRCA1* alteration



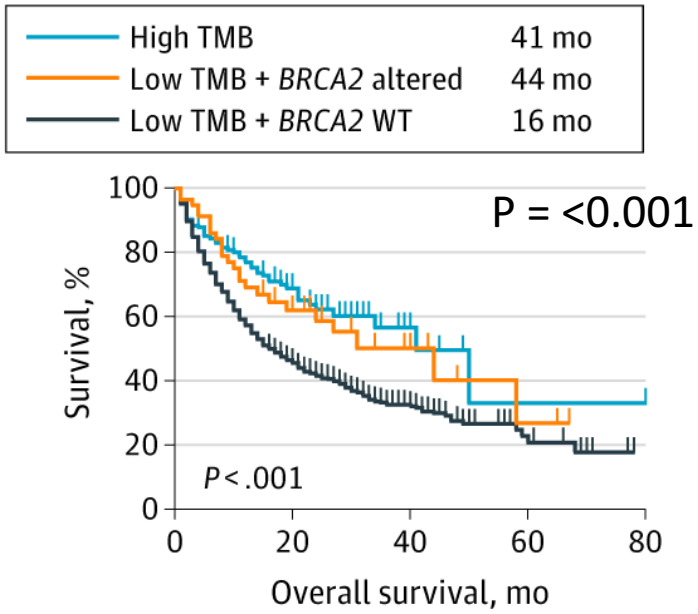
No. at risk					
BRCA1 WT	1604	416	82	15	2
BRCA1 altered	57	13	2	0	0

B Overall survival in MSKCC cohort of patients with or without *BRCA2* alteration



No. at risk					
BRCA2 WT	1565	393	74	12	1
BRCA2 altered	96	36	10	3	1

C Overall survival in MSKCC cohort of patients stratified by TMB and *BRCA2* status



No. at risk					
High TMB	170	59	9	2	2
Low TMB + *BRCA2* altered	58	24	7	2	0
Low TMB + *BRCA2* WT	1433	346	68	11	0

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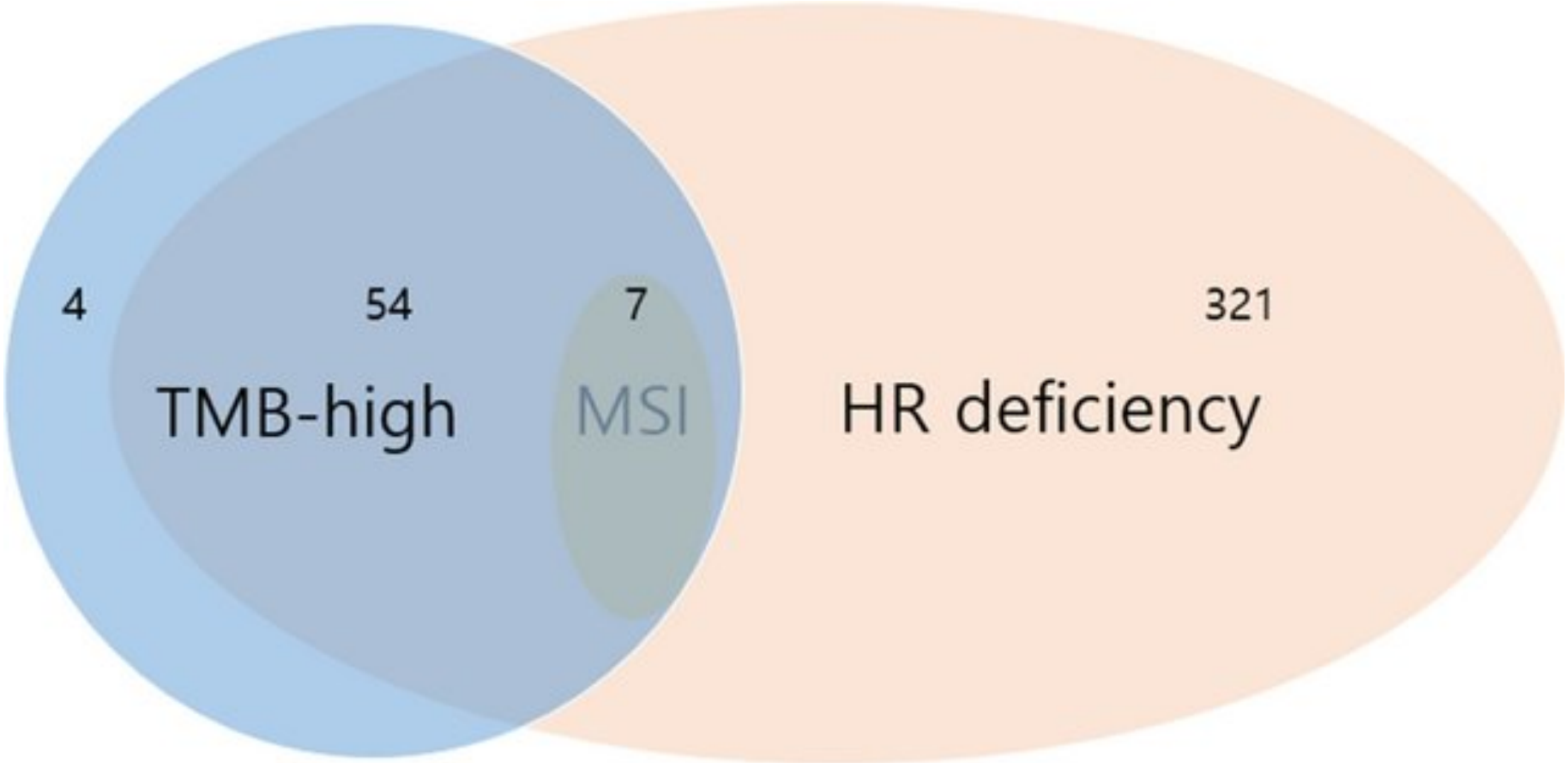
JAMA Netw Open. 2021 May 3;4(5):e217728. PMID: 33961040
Evaluation of BRCA1 and BRCA2 as Indicators of Response to Immune Checkpoint Inhibitors

Overlap of Signatures



J Cancer Res Clin Oncol. 2021 Sep 12. PMID: 34510272

The prevalence of homologous recombination deficiency (HRD) in various solid tumors and the role of HRD as a single biomarker to immune checkpoint inhibitors

Summary

- Different DNA-repair defects have different mutational impacts
- MSI & *POLE* mutations appear to predict checkpoint inhibitor response
- *BRCA1/BRCA2* (HRD) may predict checkpoint inhibitor response
- Mutations and mutation signatures are overlapping

THE OHIO STATE UNIVERSITY

- Heather Hampel
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- Rachel Pearlman
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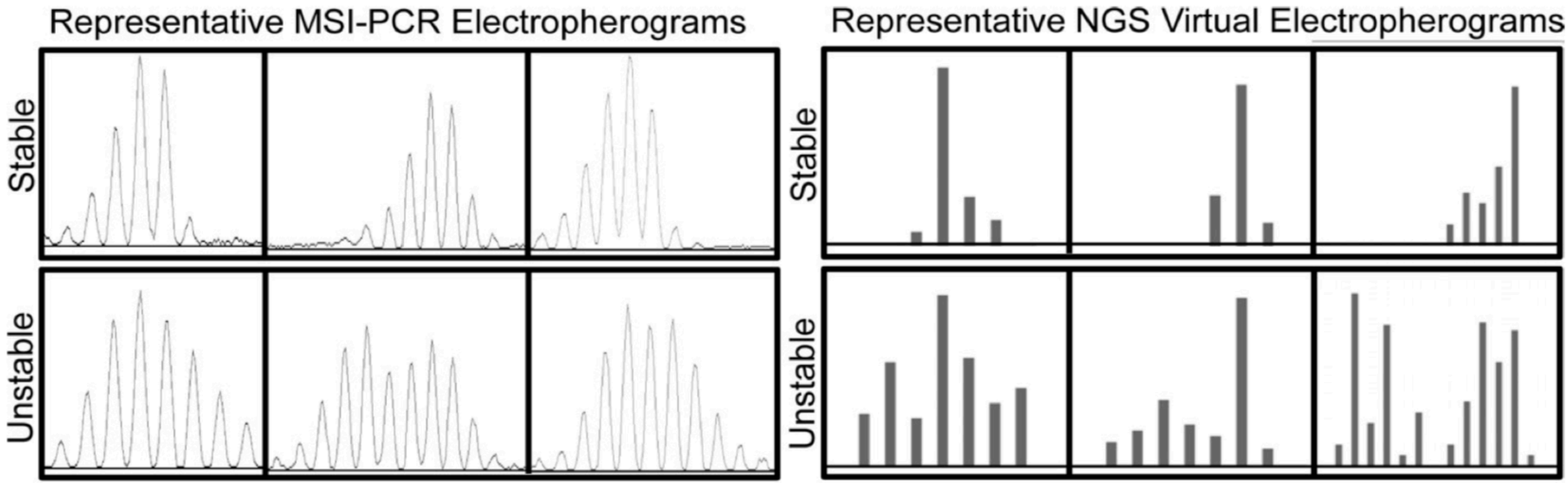
- Noah Hoffman
- Andrew McFaddin*
- Lauren Garrett*
- Tina Lockwood
- David Wu
- Vera Paulson

Clinical Chemistry 60:9
1192–1199 (2014)

Microsatellite Instability Detection by Next Generation Sequencing

Stephen J. Salipante,[1] Sheena M. Scroggins,[1] Heather L. Hampel,[2] Emily H. Turner,[1] and Colin C. Pritchard[1*]



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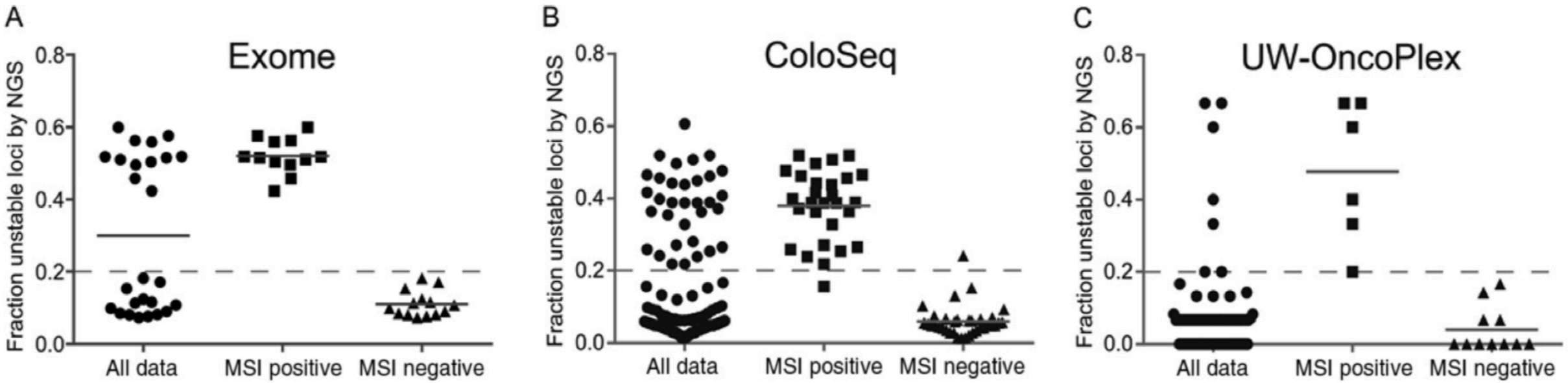

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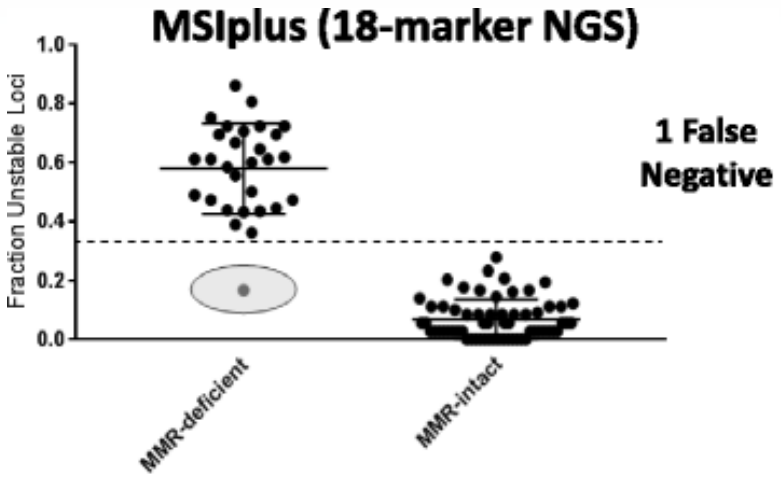
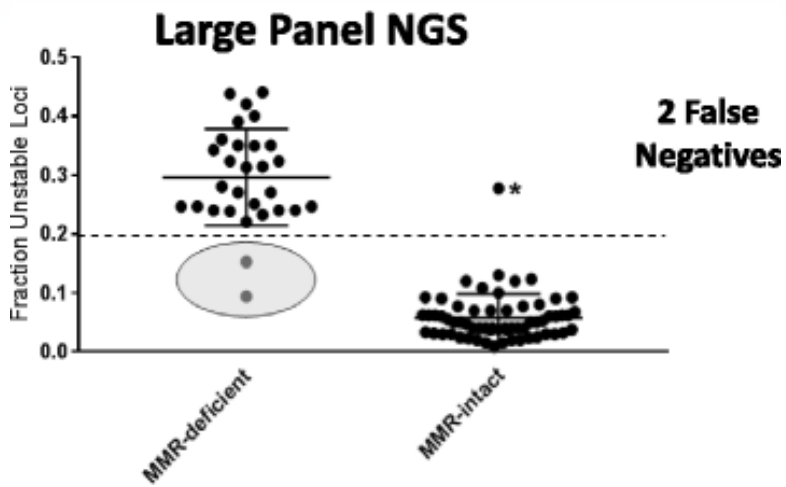
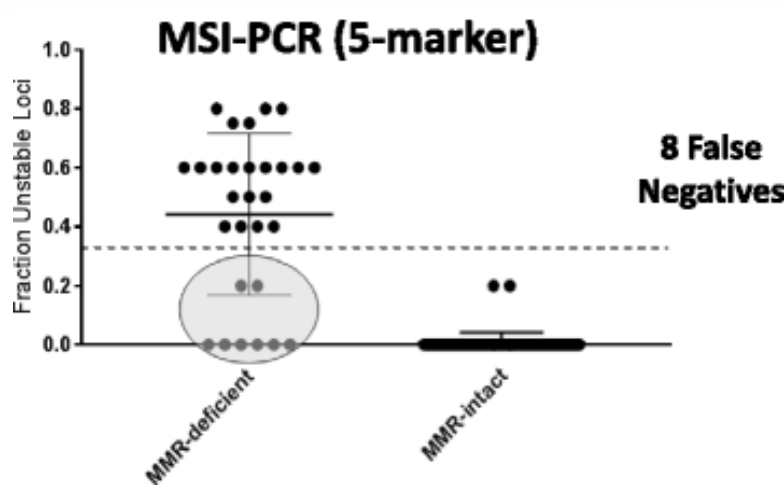
NGS vs PCR? (Prostate Cancer)







Assay	Sensitivity [95% CI]	Specificity[95% CI]
MSIplus (amplicon)	96.6% [80.4%-99.8%]	100% [92.7%-100%]
UW-OncoPlex	93.1% [75.8%-98.8]	98.4% [90.2%-99.9]
MSI PCR	72.4% [52.5%-86.3%]	100% [92.7-100%]

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Microsatellite instability in prostate cancer by PCR or next-generation sequencing.
J Immunother Cancer. 2018 Apr 17;6(1):29. PMID: 29665853

Advances in Cancer Immunotherapy™

A Focus on Biomarkers

Thursday, March 24, 2022 | 4–7:50 p.m. PDT
Hosted Virtually on Zoom Webinar

SITC's ACIs are FREE for all healthcare professionals in the clinical setting, students and patient advocates!

Highlighted Sessions Include:

An Overview of PD-L1
Allen Gown, MD – *University of British Columbia*

An Overview of TMB
Andrew Coveler, MD – *University of Washington/Fred Hutchinson Cancer Research Center*

An Overview of MMR, MSI, POLE mutations, BRCA mutations
Eric Konnick, MD, MS – *University of Washington*

TIL as a Biomarker
Shailender Bhatia, MD – *University of Washington*

Emerging Immune Biomarkers
Mary L. (Nora) Disis, MD, FACP – *University of Washington*

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