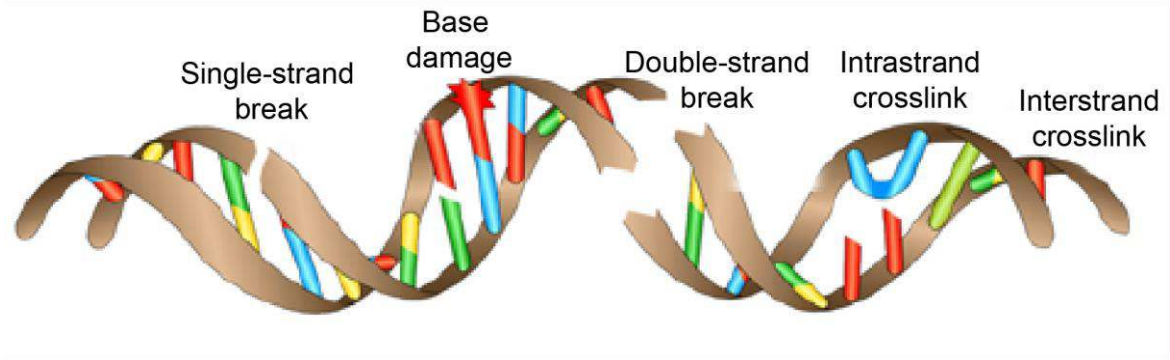
“Whole genome sequencing, mutational signatures & interventions in cancer therapy”



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Cancer genomes are complex

> 6,000 studies of whole genome sequencing analyses and cancers

Article

Pan-cancer whole-genome analyses of metastatic solid tumours

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Article

Pan-cancer analysis of whole genomes

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The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium

Cancer is driven by genetic change, and the advent of massively parallel sequencing has enabled systematic documentation of this variation at the whole-genome scale[1–3]. Here we report the integrative analysis of 2,658 whole-cancer genomes and their matching normal tissues across 38 tumour types from the Pan-Cancer Analysis of Whole Genomes

nature genetics

OPEN

Pan-cancer patterns of somatic copy number alteration

Travis I Zack[1–3,11], Steven E Schumacher[1,2,11], Scott L Carter[1], Andrew D Cherniack[1], Gordon Saksena[1], Barbara Tabak[1], Michael S Lawrence[1], Cheng-Zhong Zhang[1], Jeremiah Wala[1,2,4,5], Craig H Mermel[1], Carrie Sougnez[1], Stacey B Gabriel[1], Bryan Hernandez[1], Hui Shen[6], Peter W Laird[6], Gad Getz[1,12], Matthew Meyerson[1,7–9,12] & Rameen Beroukhim[1,2,7,8,10,12]

Mutational signatures
Germline + somatic driver mutations
(secondary mutations – treatment)

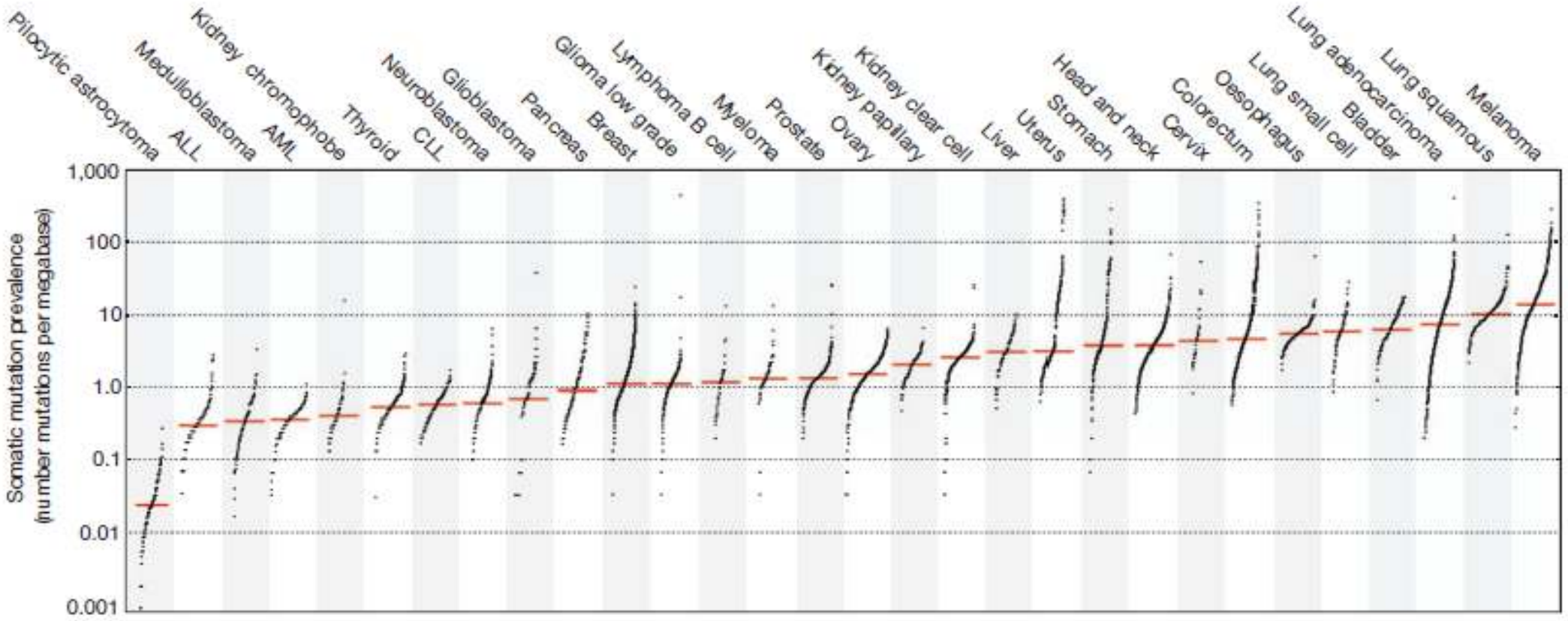
(Alexandrov *et al.*, Nature 500: 415-421, 2013)

(ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium, Nature 578: 82-93, 2020)

A compendium of mutational signatures of environmental agents (Kucab *et al.*, Cell 177: 821-836, 2019)

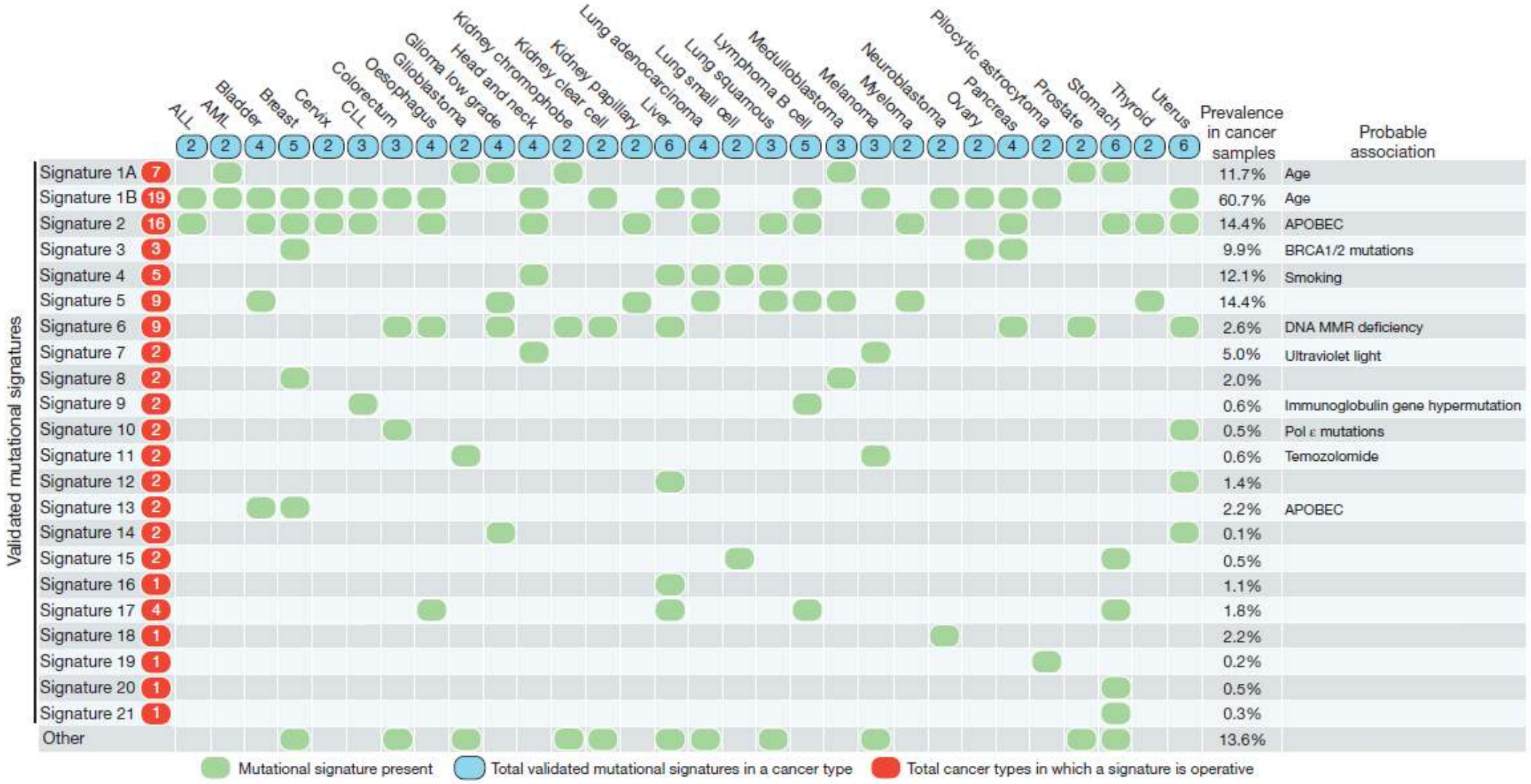
Pan-cancer whole genome analyses of metastatic solid tumours (PCAWG cohort)

Precision medicine: mutational signatures as a marker for DNA repair activity



(Alexandrov *et al.*, Nature, 2013)

Precision medicine: mutational signatures in cancers

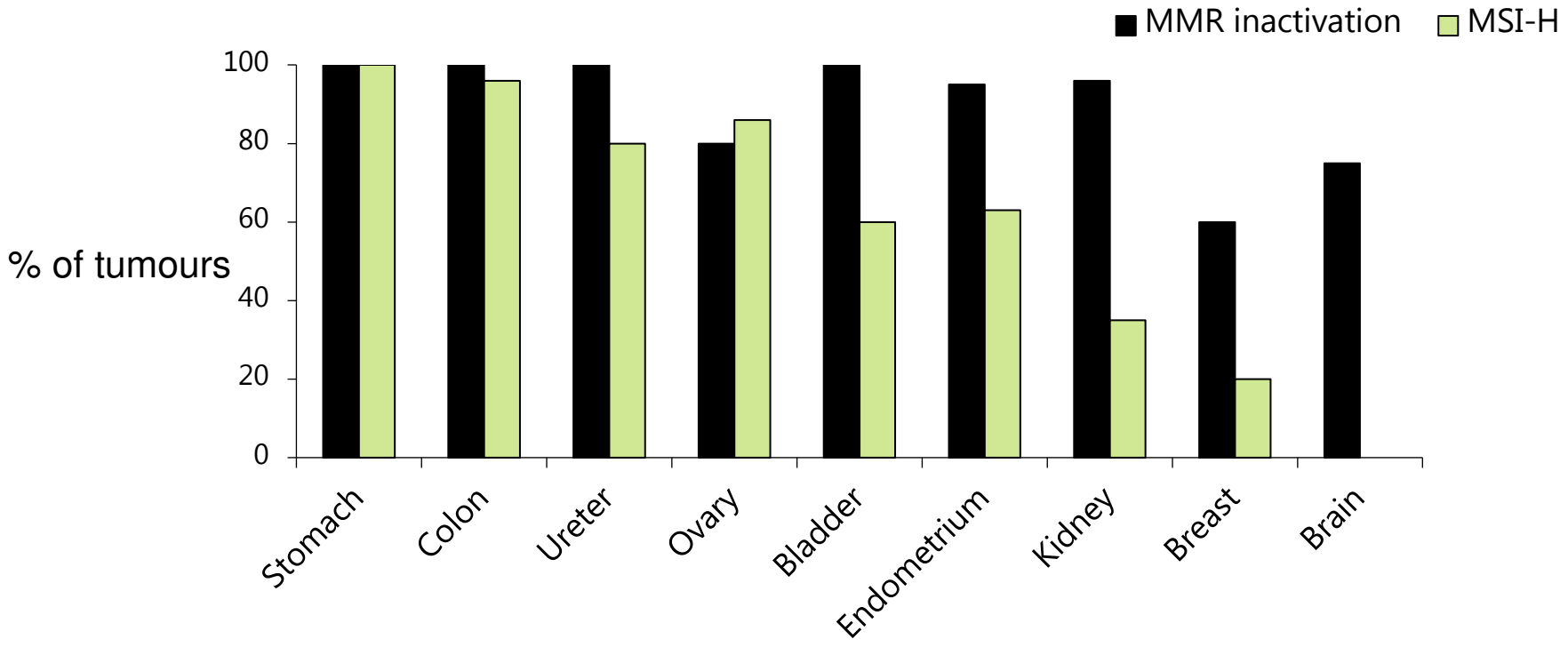


(Alexandrov *et al.*, Nature, 2013)

Current limitations to disease development & diagnosis – Lynch syndrome (HNPCC)

Tumour-specific pattern of MMR defects

Microsatellite instability (MSI) – Bethesda criteria (across 5 -12 markers)



(Peltomaki, 2016)

Current limitations to disease development & diagnosis – Lynch syndrome (HNPCC)

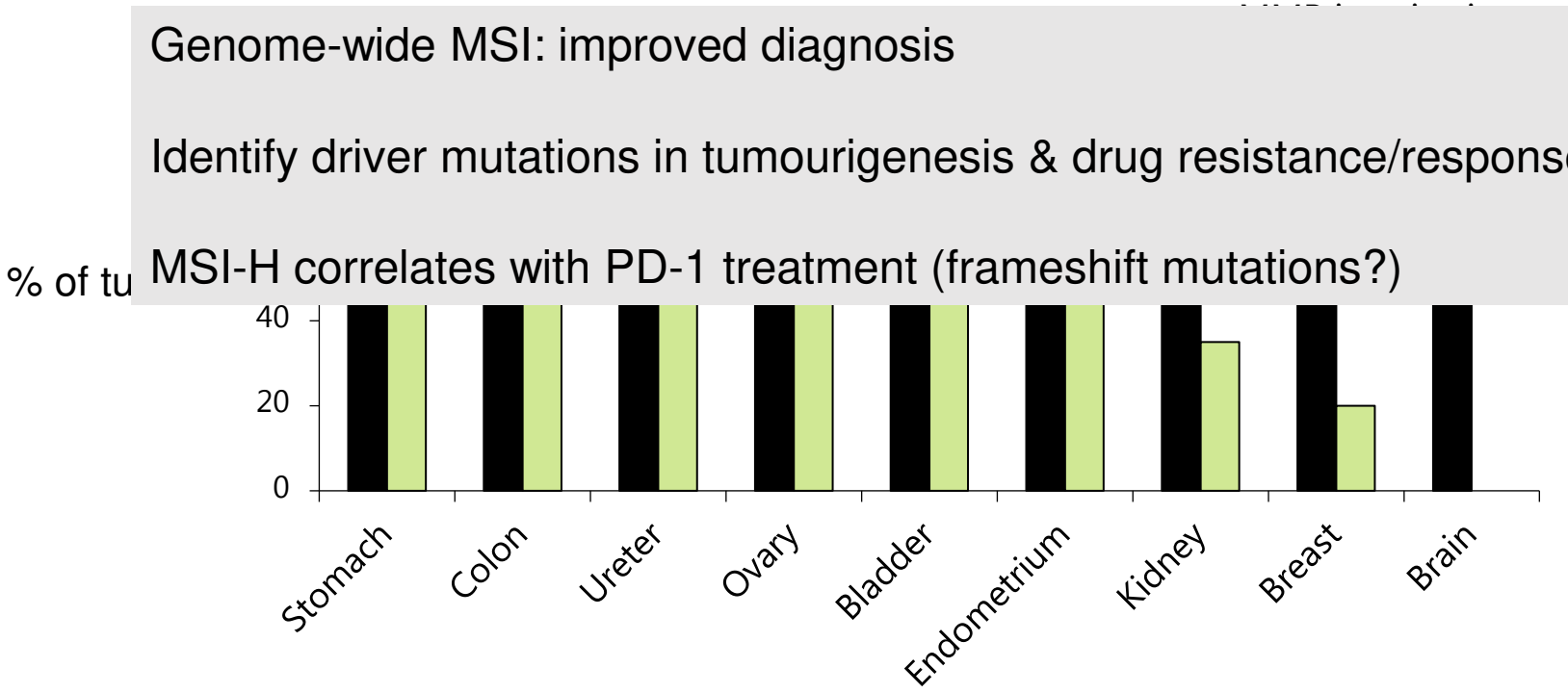
Tumour-specific pattern of MMR defects

Microsatellite instability (MSI) – Bethesda criteria (across 5 -12 markers)

Genome-wide MSI: improved diagnosis

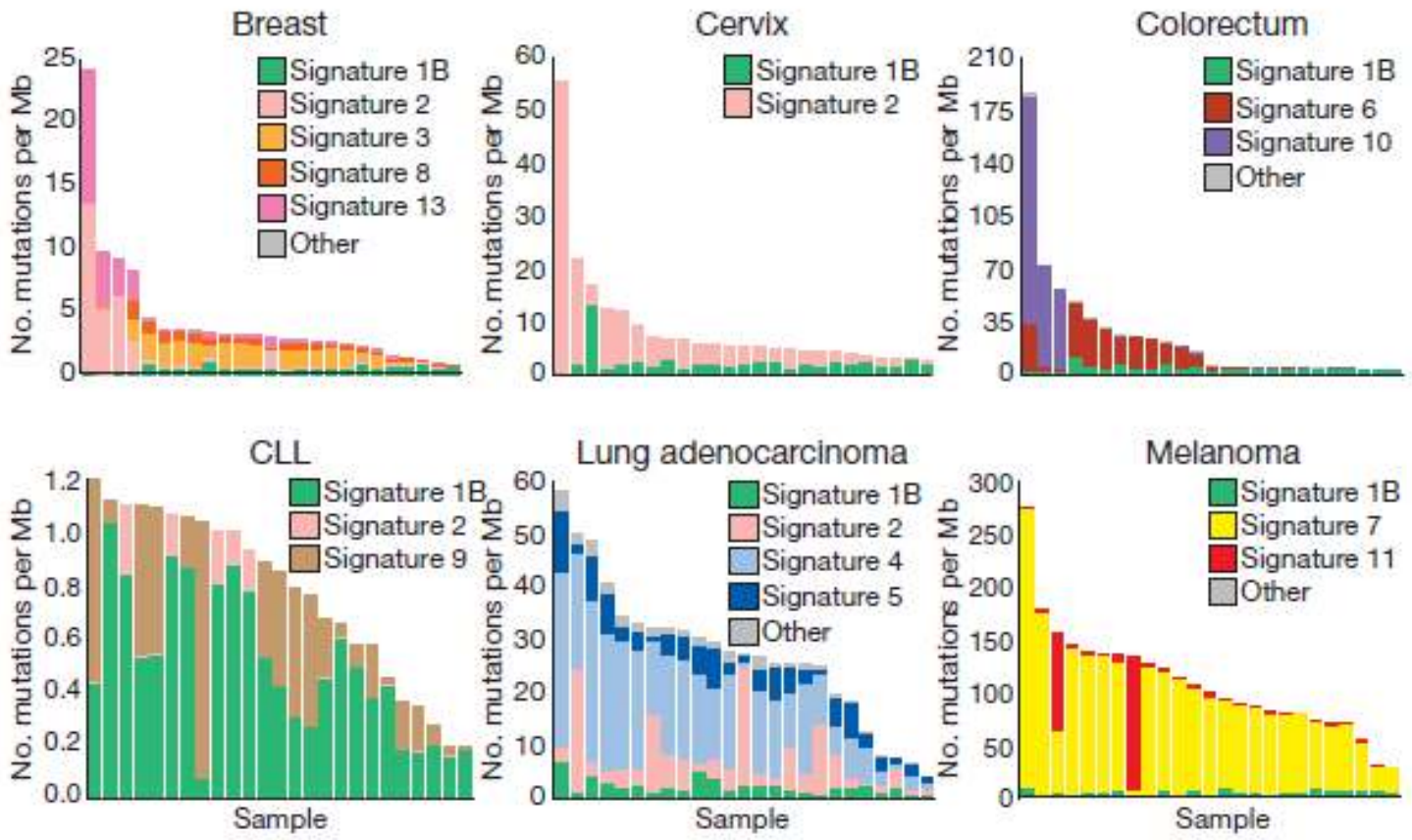
Identify driver mutations in tumourigenesis & drug resistance/response

MSI-H correlates with PD-1 treatment (frameshift mutations?)



(Peltomaki, 2016)

Cell type-specific DNA damage and repair



(Alexandrov *et al.*, Nature, 2013)

Precision medicine: mutational drivers & tumour evolution

DNA damage response & repair

Synthetic sickness & lethality (SSL)

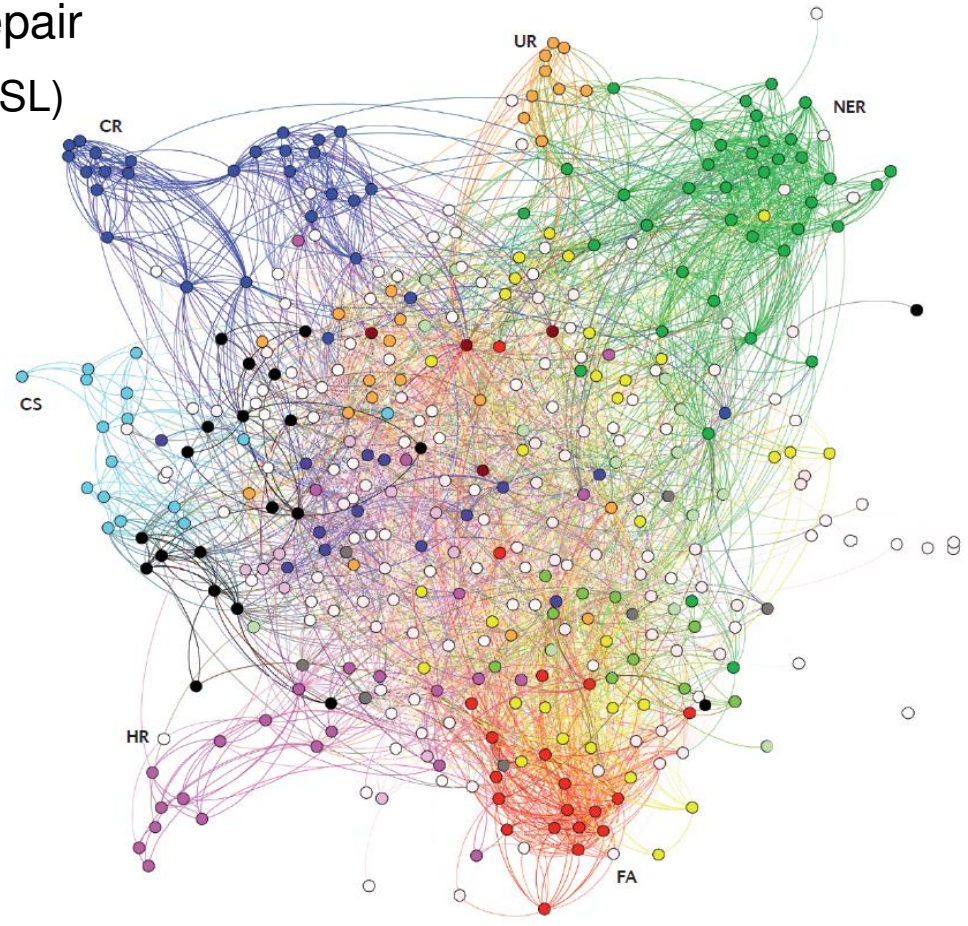


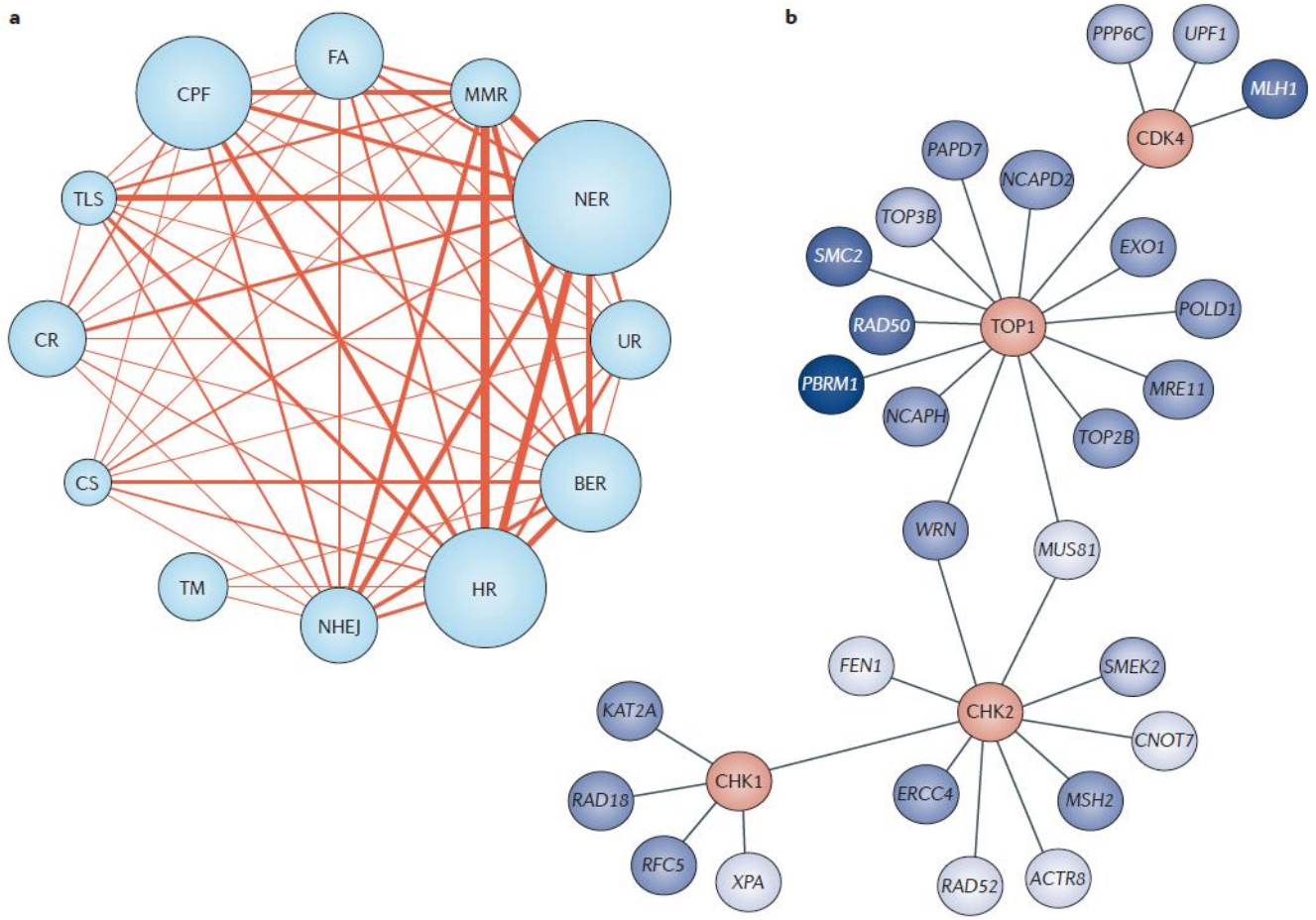
Figure 2 | **A network view of the DNA damage response.** A protein interaction network of the DNA damage response

Therapeutic opportunities within the DNA damage response

Laurence H. Pearl[1], Amanda C. Schierz[2,3], Simon E. Ward[4], Bissan Al-Lazikani[2] and Frances M. G. Pearl[2,4]

Pearl *et al.*, *Nat Rev Cancer*, 2015
Jeggo *et al.*, *Nat Rev Cancer,* 2016

Precision medicine: synthetic lethalities within the DNA damage response



Pearl *et al.*, *Nat Rev Cancer*, 2015
Jeggo *et al.*, *Nat Rev Cancer,* 2016

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