Harnessing mutational signatures to pinpoint the development of chemoresistance in metastatic and relapsed osteosarcoma

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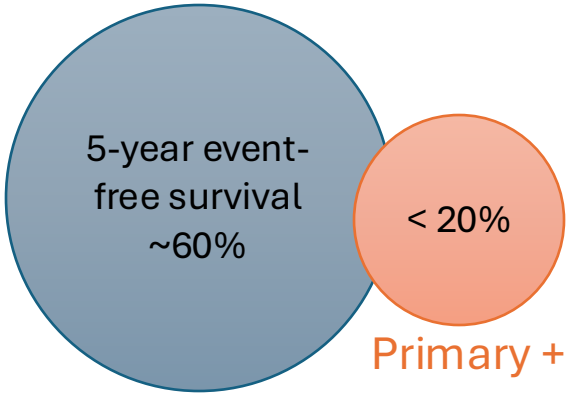
Laboratory Medicine & Pathobiology
UNIVERSITY OF TORONTO

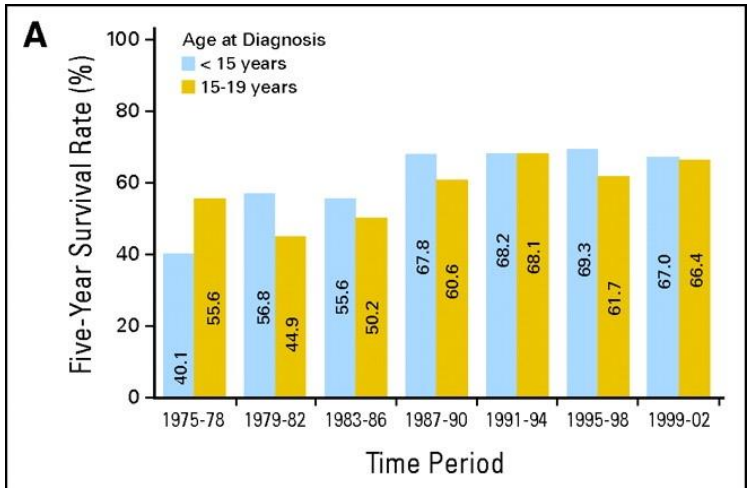
Nothing to disclose

Osteosarcoma remain difficult to treat

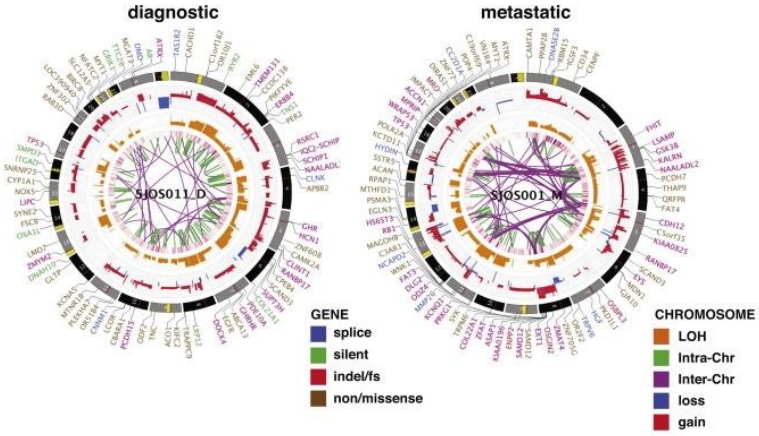
Localised disease

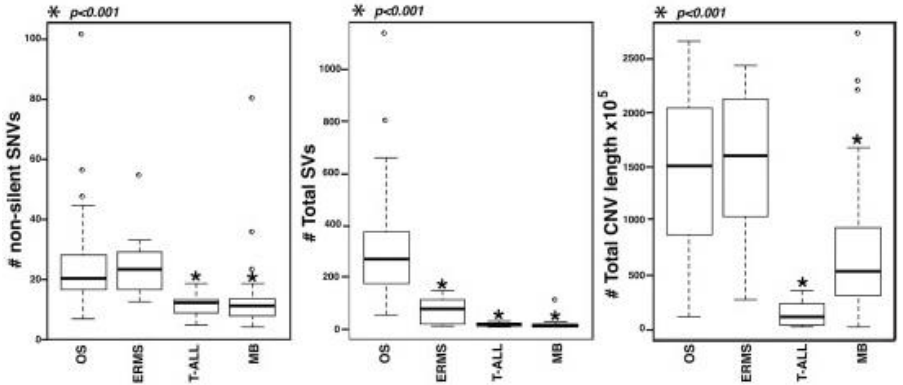


Primary + Metastases



Journal of clinical oncology 28.15 (2010): 2625-2634.

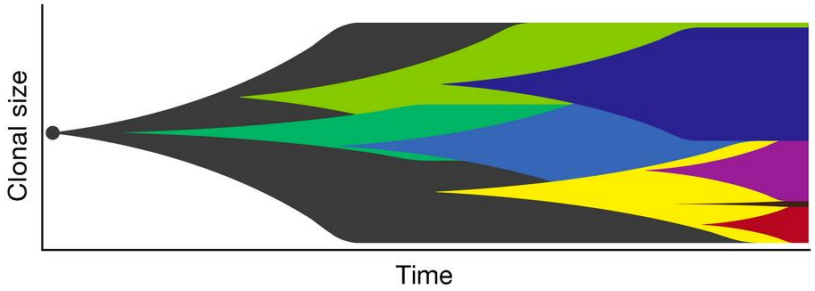


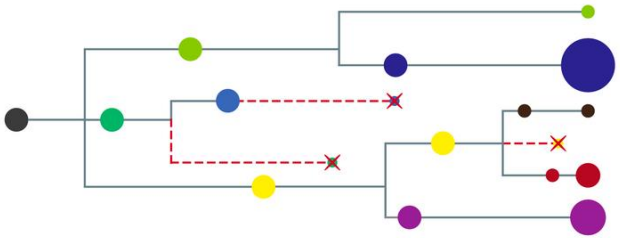


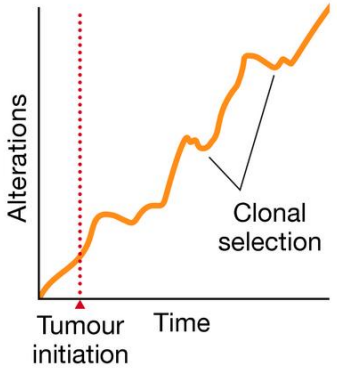
Osteosarcoma genomes are complex

Cell Reports (2014) 7104-112

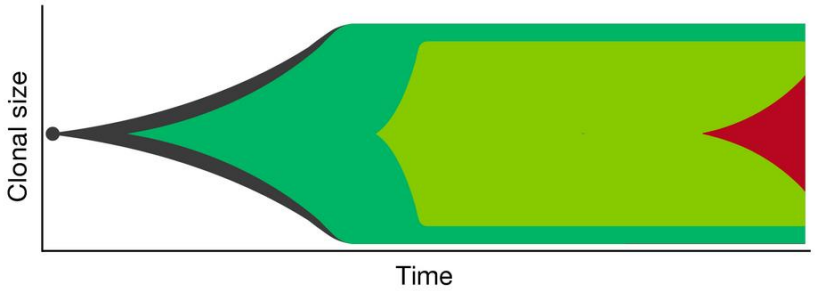
Model A: gradual branching

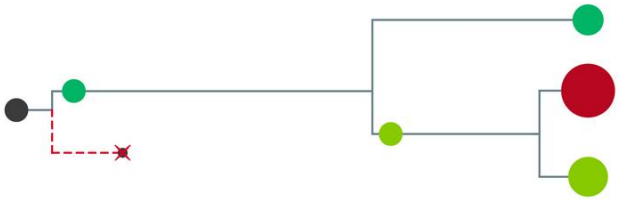


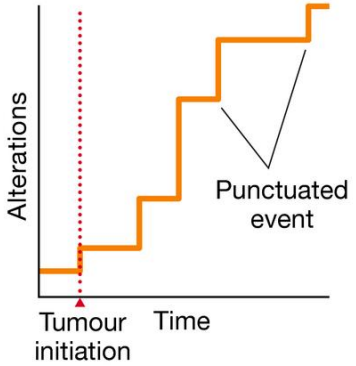




Model B: punctuated bursts







PRIMARY
Early events

Chemotherapy pressures

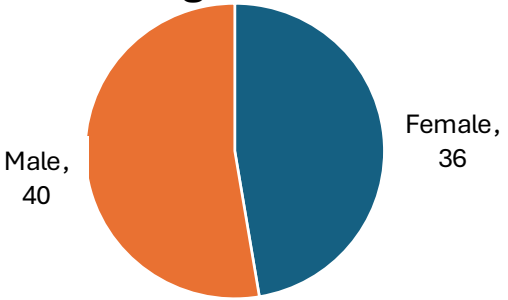
RELAPSE/MET
Expansion of post-treatment populations

Evolution of osteosarcoma: Pathway to chemoresistance

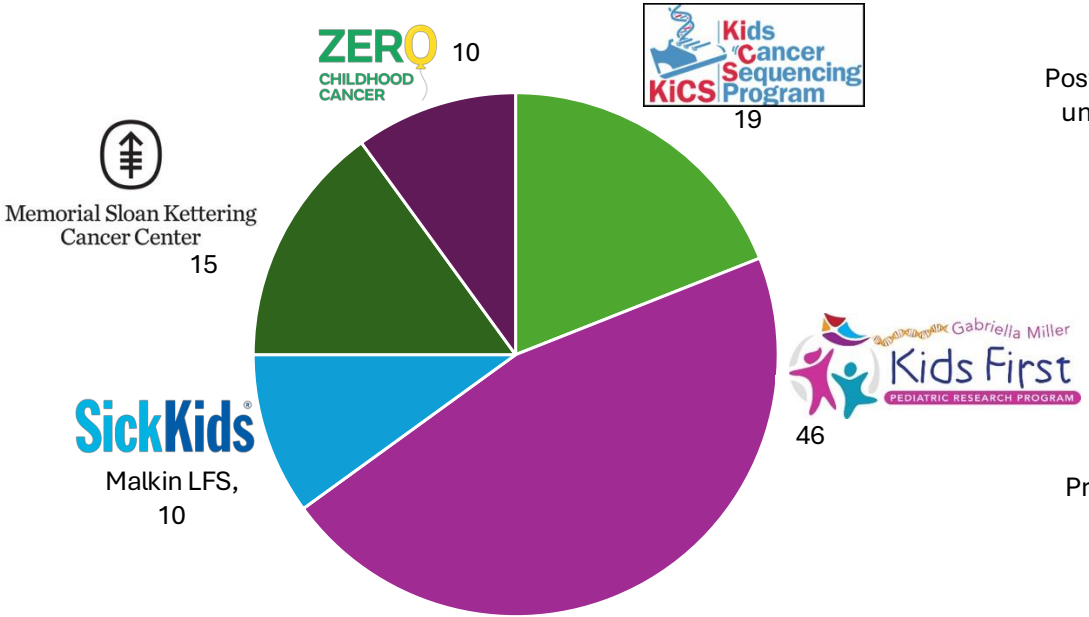
Vendramin, R., Litchfield, K., & Swanton, C. (2021). *The EMBO journal*, *40*(18), e108389.

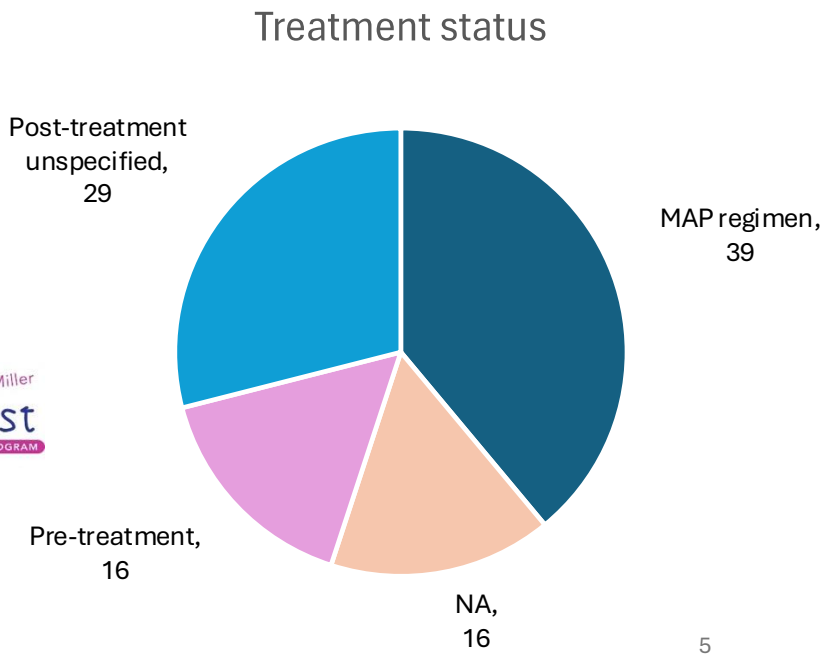
Curated large pediatric osteosarcoma WGS cohort

76 pediatric patients
Mean age: 14.34

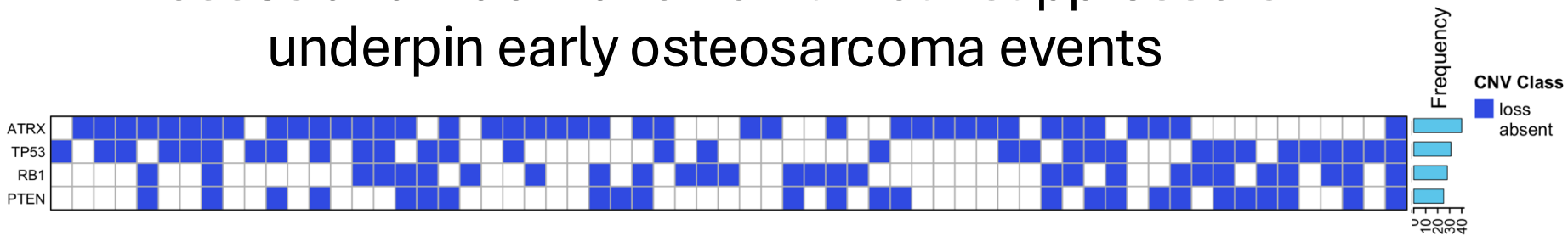


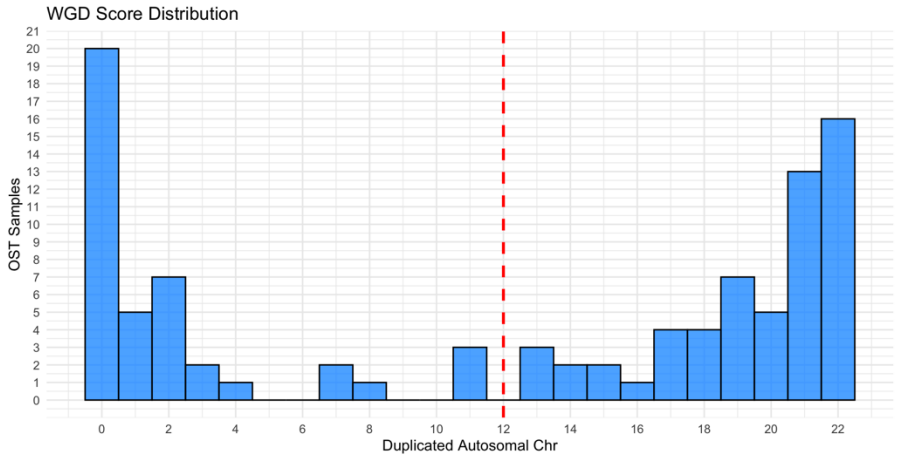
100 WGS tumour samples + matched germline





Whole genome duplication, widespread copy number losses and inactivation of tumour suppressors underpin early osteosarcoma events

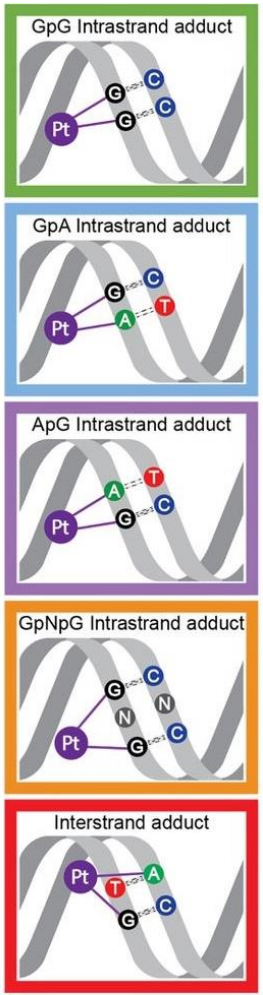




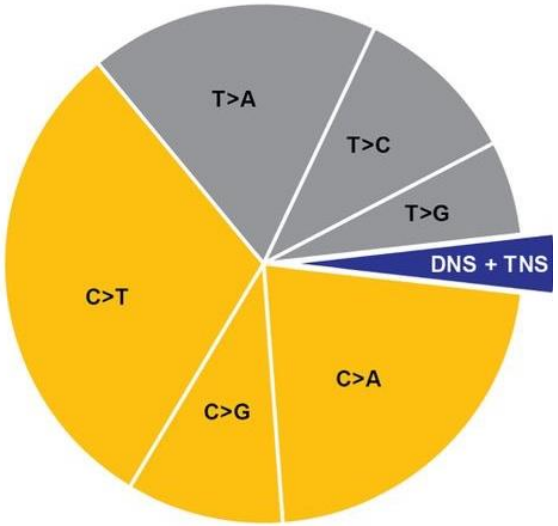
- Mean bulk ploidy: 2.86
- Tumour mutational burden (TMB):
  - 29 samples categorised hypermutant (TMB > 10 mut/Mb)
  - Mean primary TMB: 1.76 mut/Mb
  - Mean non-primary TMB: 3.21 mut/Mb

59% samples classified as whole genome duplicated:
51% of primary tumours, 69% of non-primary tumours

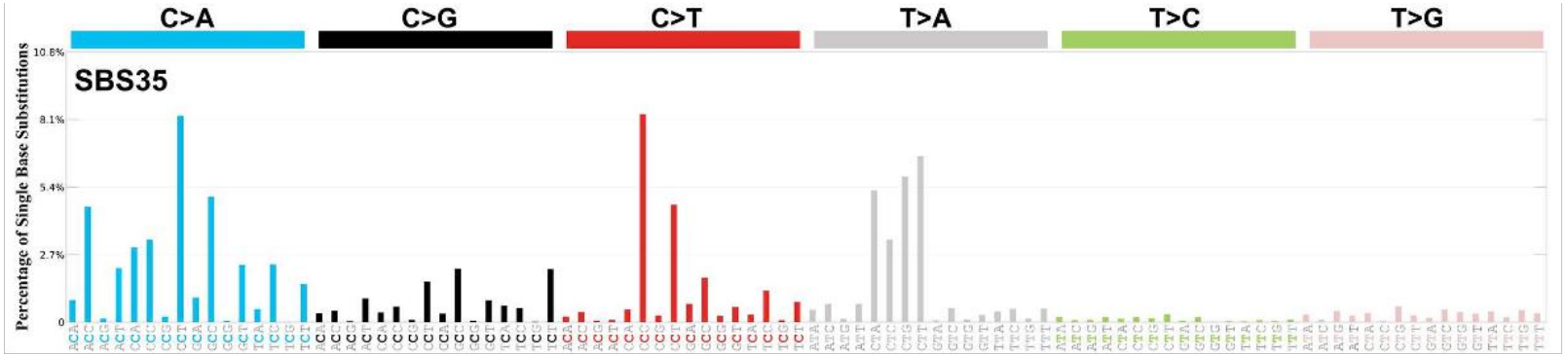
Cisplatin adduct types



Cisplatin induced base substitutions



Mutational signatures denote the effects of mutagenic processes



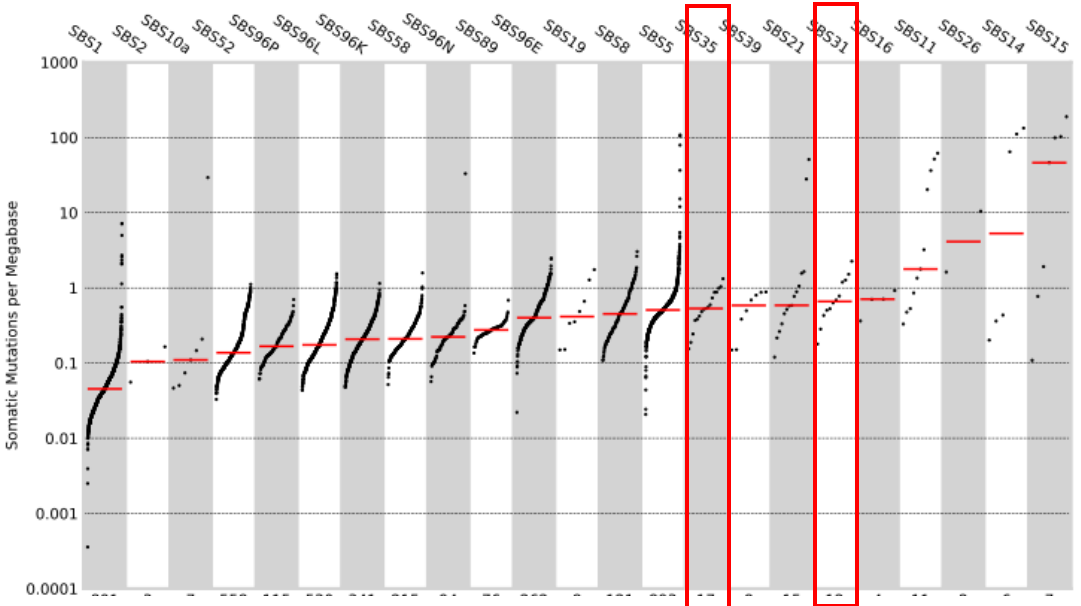
Arnoud Boot et al. Genome Res. 2018;28:654-665

Half of exposed osteosarcoma samples develop platinum sig

- 28/100 samples contained a platinum-associated mutational signature
  - 23 non-primary vs 5 primary samples
- A clinically-annotated subset of 33 samples with confirmed platinum exposure, 16 (48.5%) displayed a platinum-associated signature

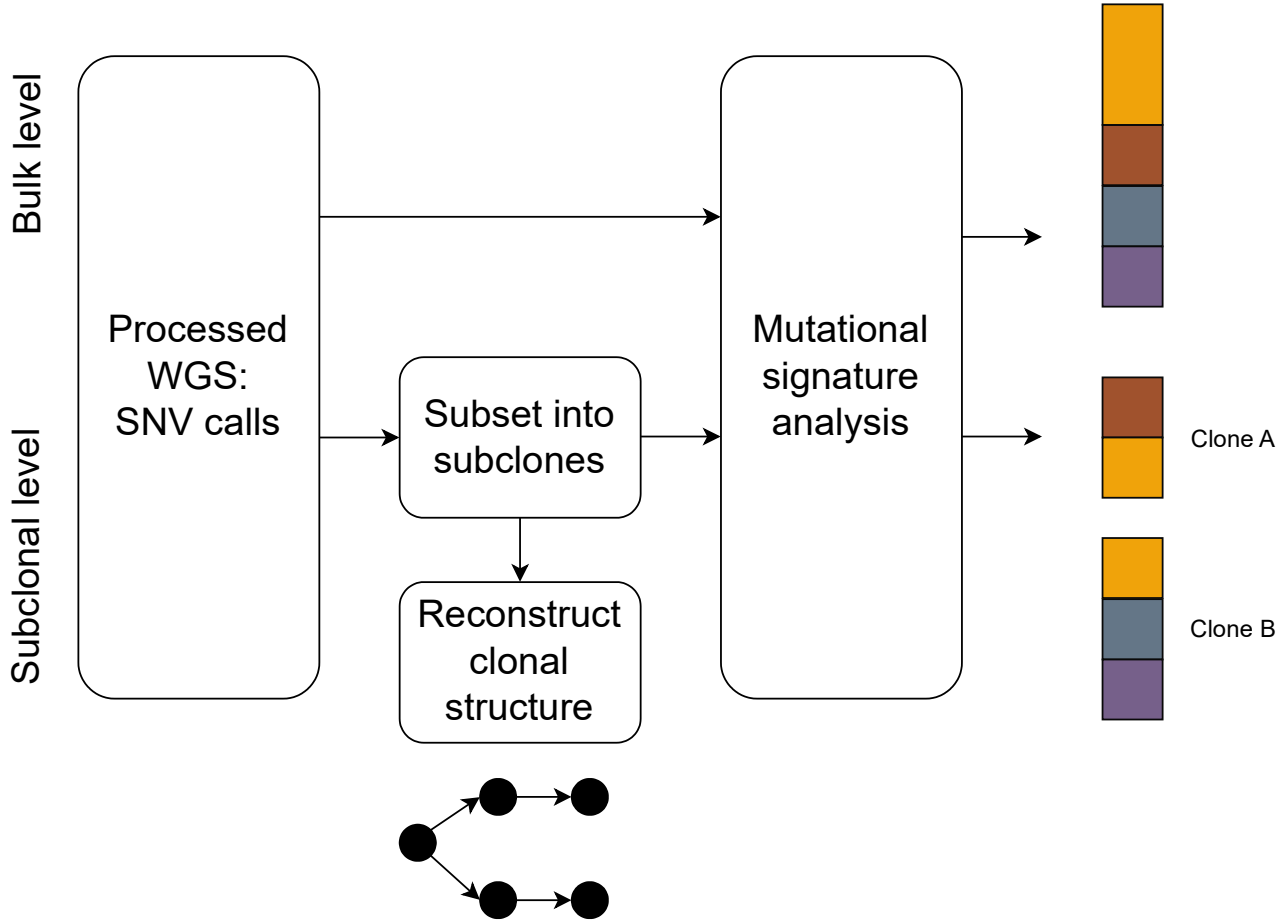
Platinum induces substantial mutational damage

- Mean 3,273 SNVs attributed to platinum damage
  - 30.3% of tumour mutational burden



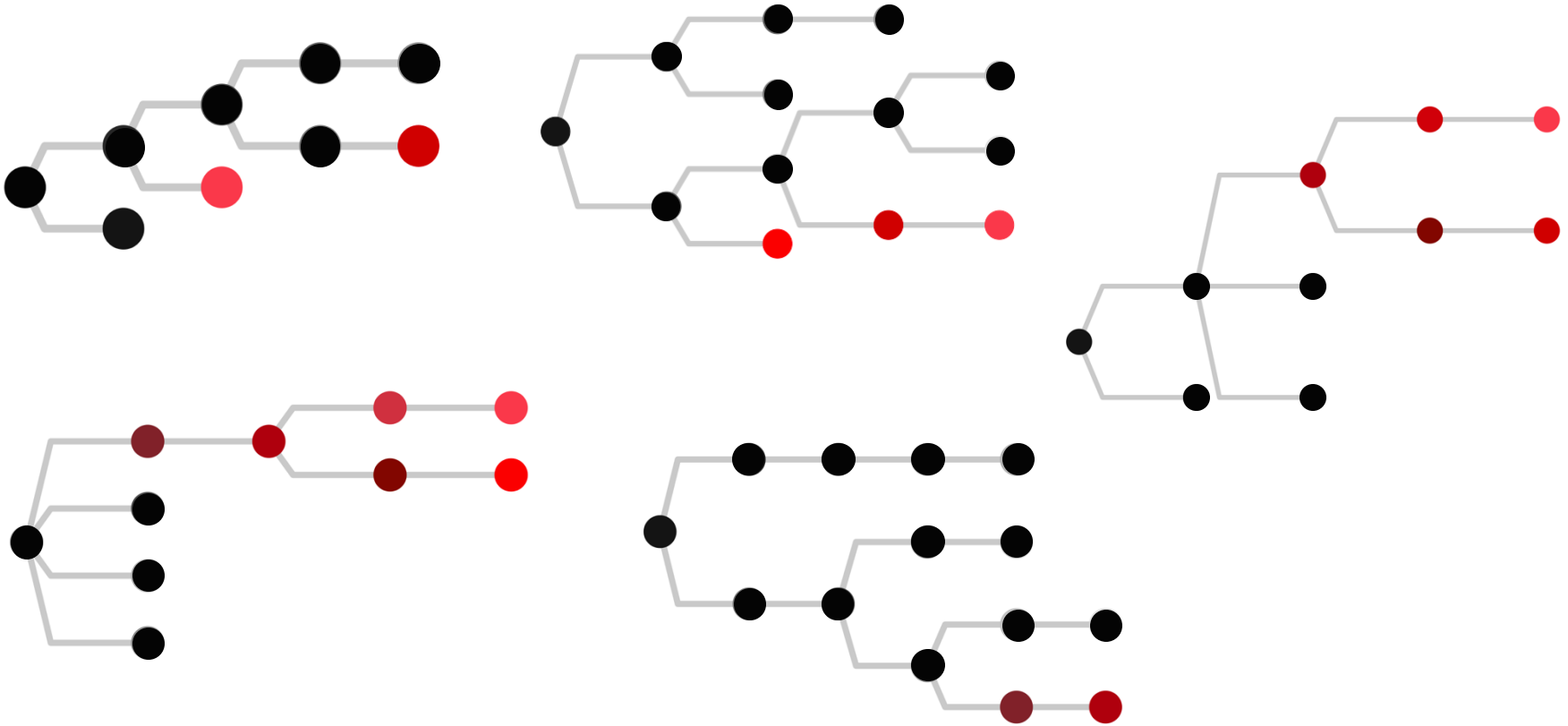
Methods

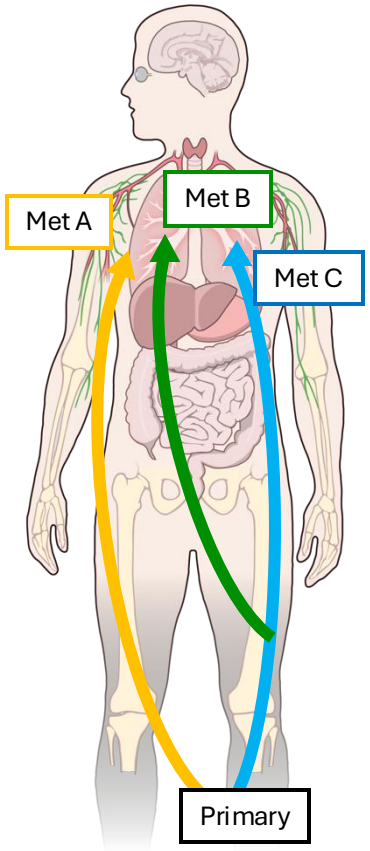
Extracting mutational signature at the subclonal level elucidates temporal and spatial changes in mutational processes



Pyclone-VI: Gillis, S., Roth, A. *BMC Bioinformatics* 21, 571 (2020).
SigProfileExtractor: Islam, S.M. A.*, et al. Cell genomics* 2.11 (2022).

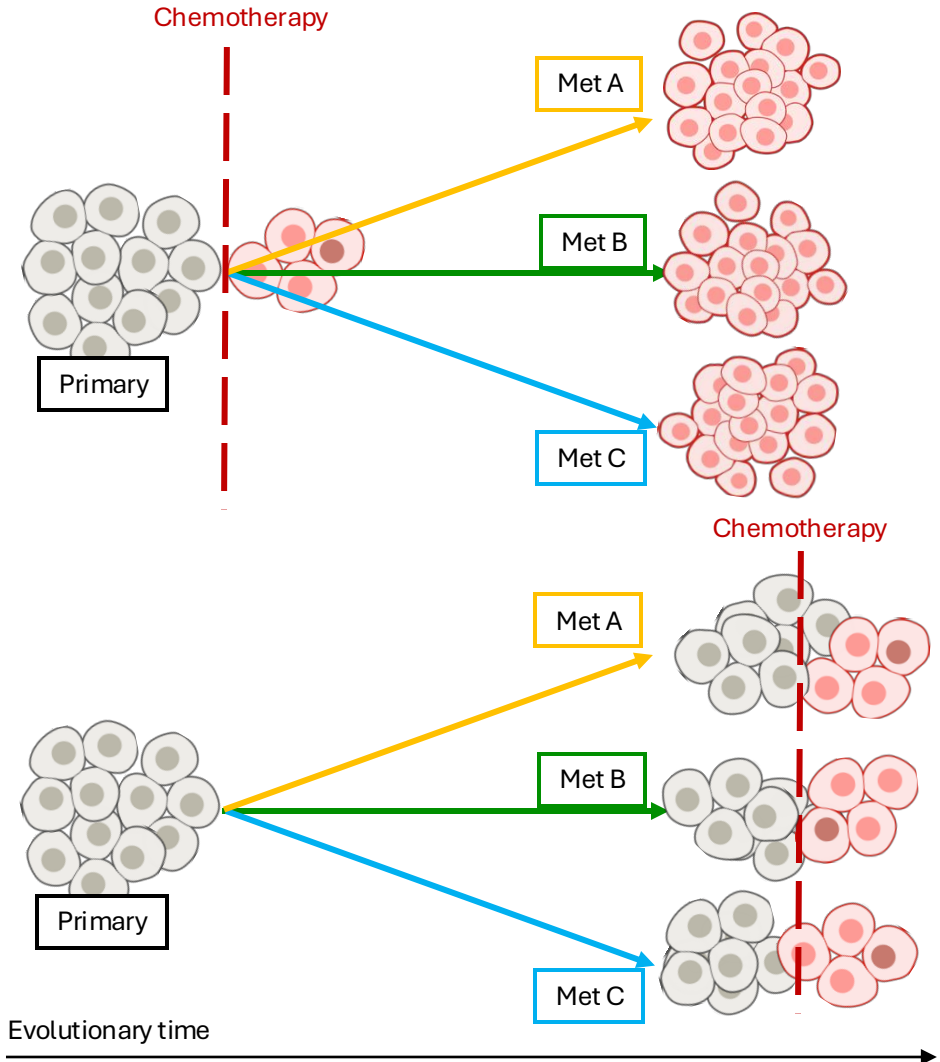
Mutational signatures can pinpoint resistant subpopulations



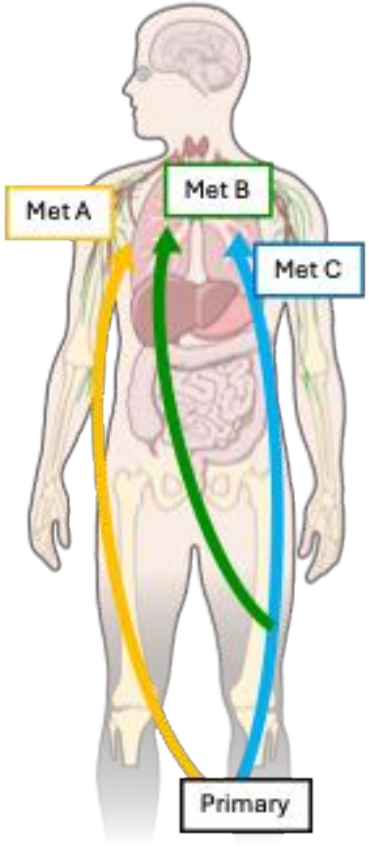


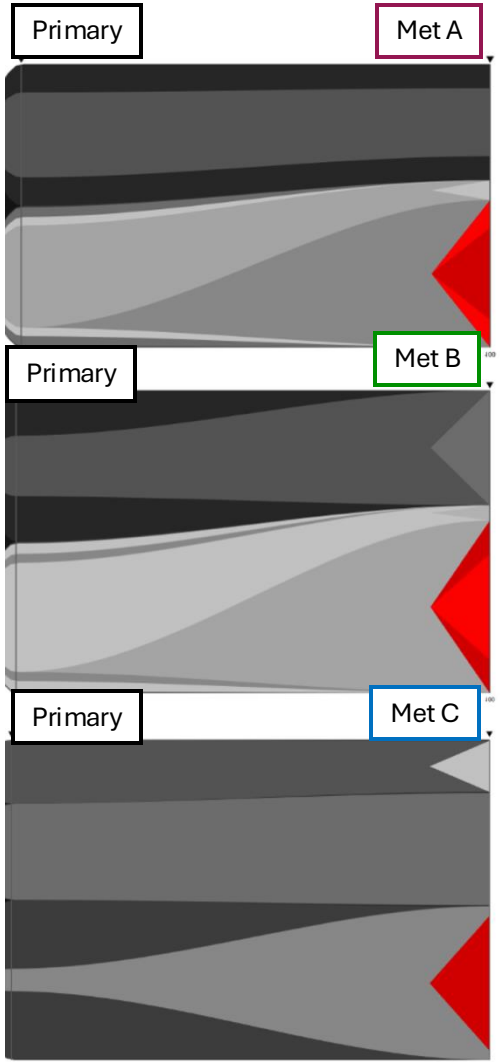
SBS31/35-

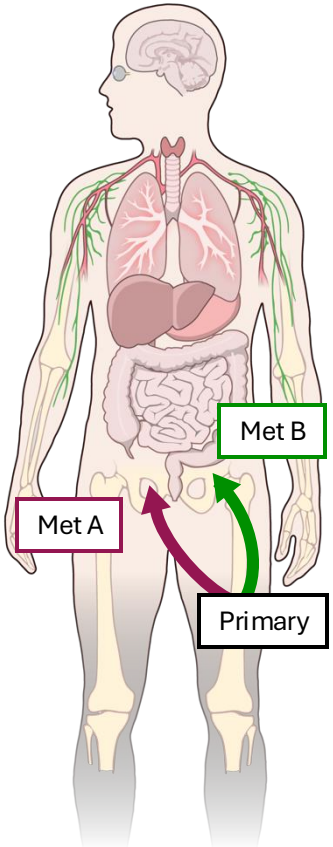
SBS31/35+

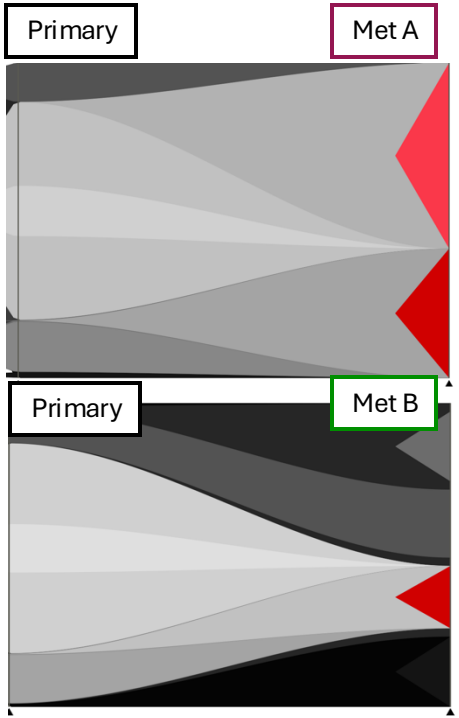


Timing metastatic bifurcation vs emergence of platinum-associated signatures







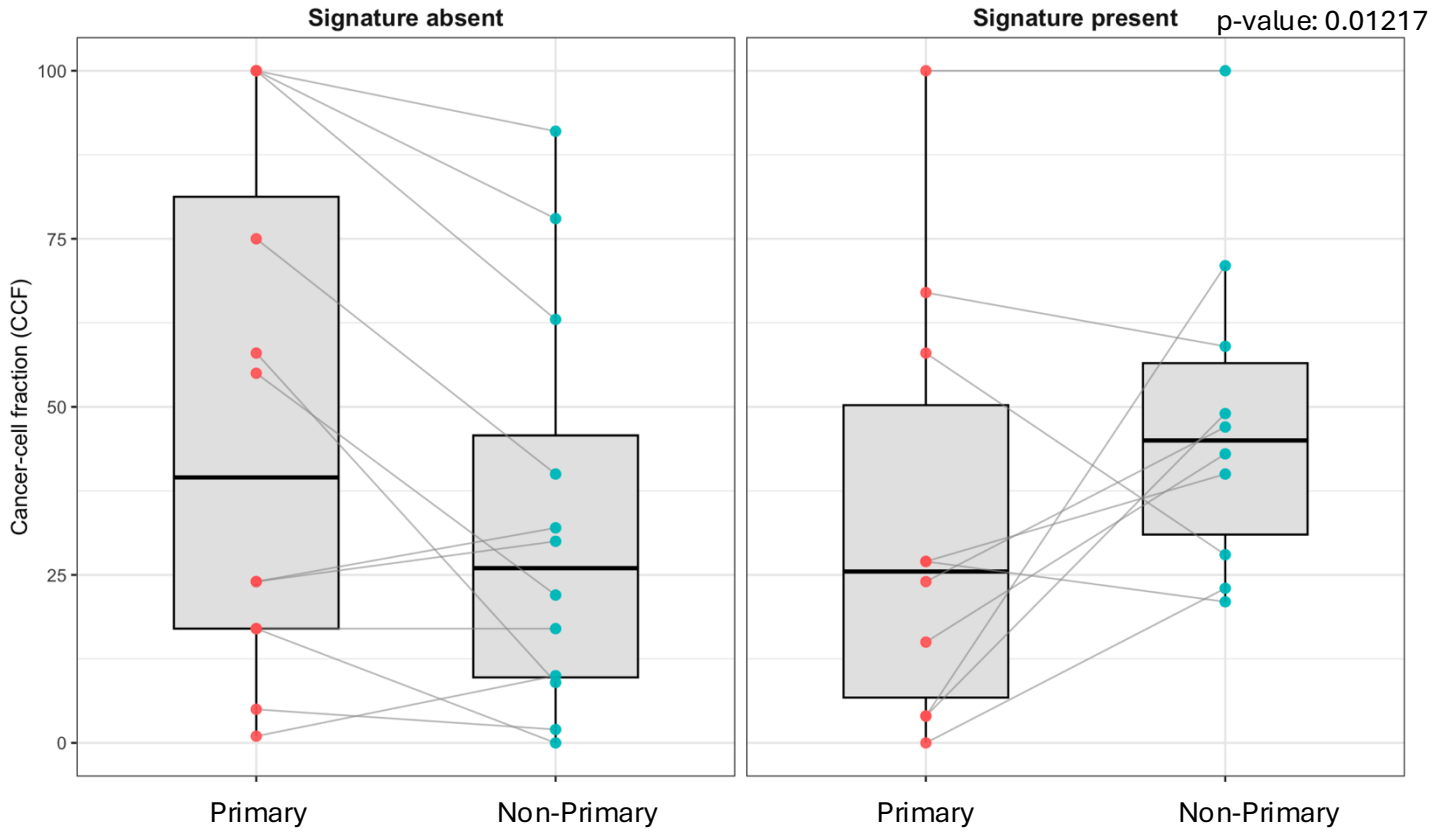


SBS31/35-

SBS31/35+

Metastatic bifurcation precedes the effects of therapy

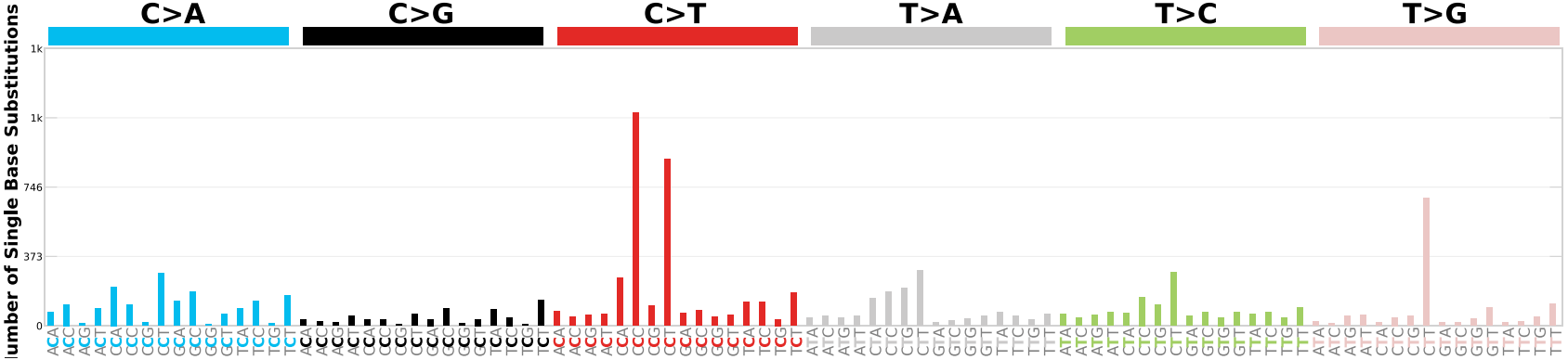
Chemoresistant clones enriched over time



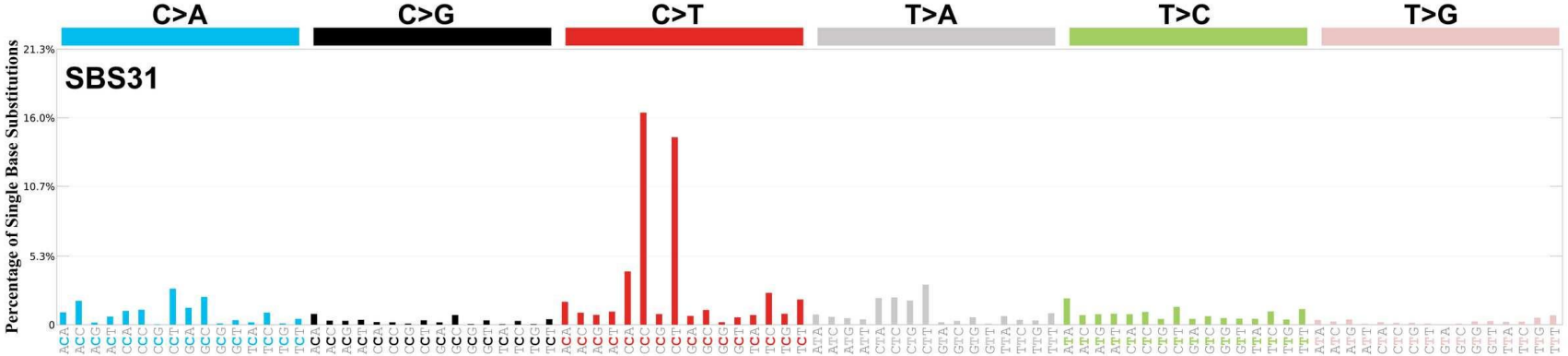
n = 11 pairs primary + non-primary tumours

Positive control

Shared mutations

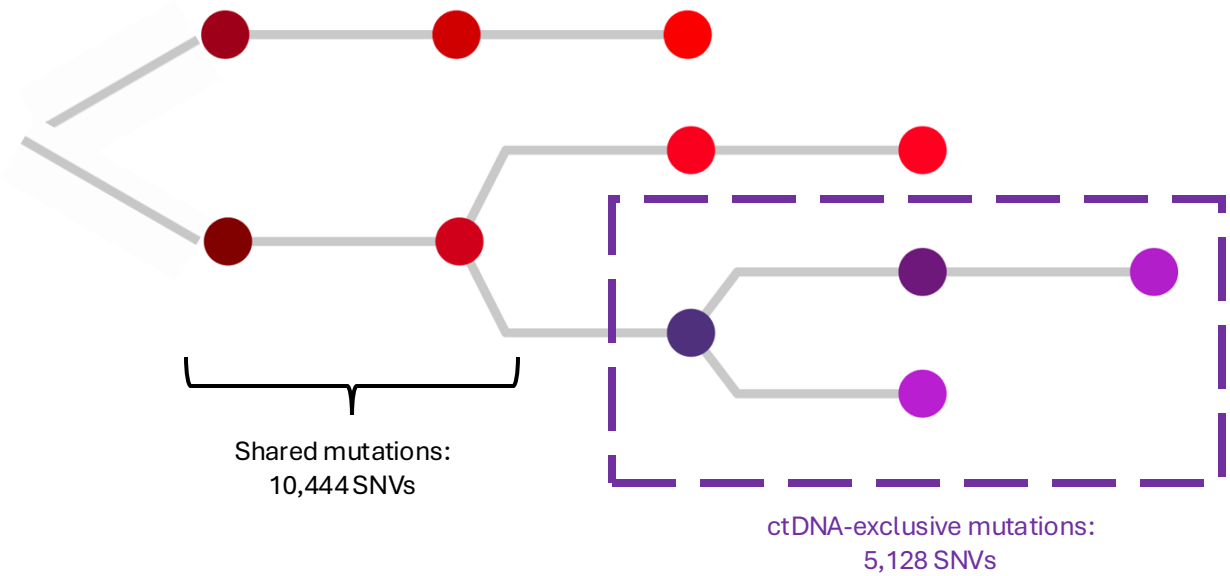


COSMIC reference catalogue

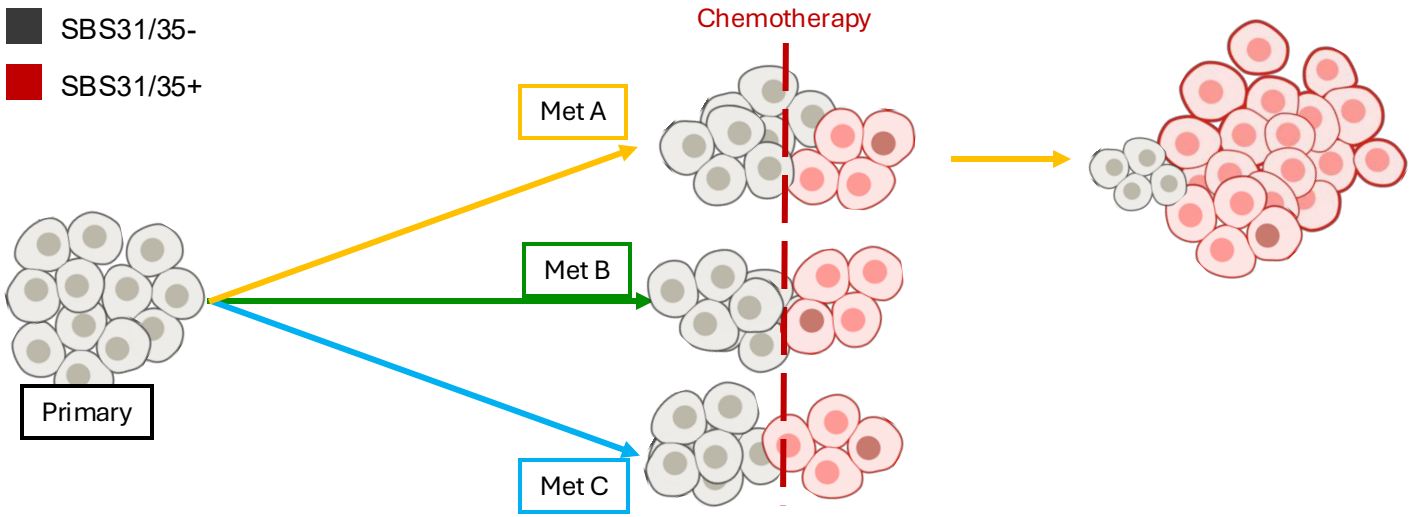


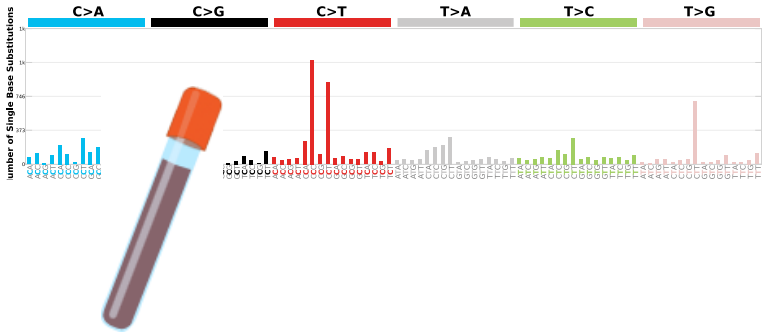
The same platinum-induced mutations found in bulk tumour and ctDNA

ctDNA captures subpopulations missed by bulk tumour WGS



Next steps: emergence/disappearance of signature in serial samples





Evolution of osteosarcoma: Pathway to chemoresistance

Acknowledgements

Shlien Lab Members

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- Rupal Hatkar
- Sarah Cohen-Gogo
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