

Genomic Evidence for Depolyploidization as a Stabilising Force in post-WGD Cancers

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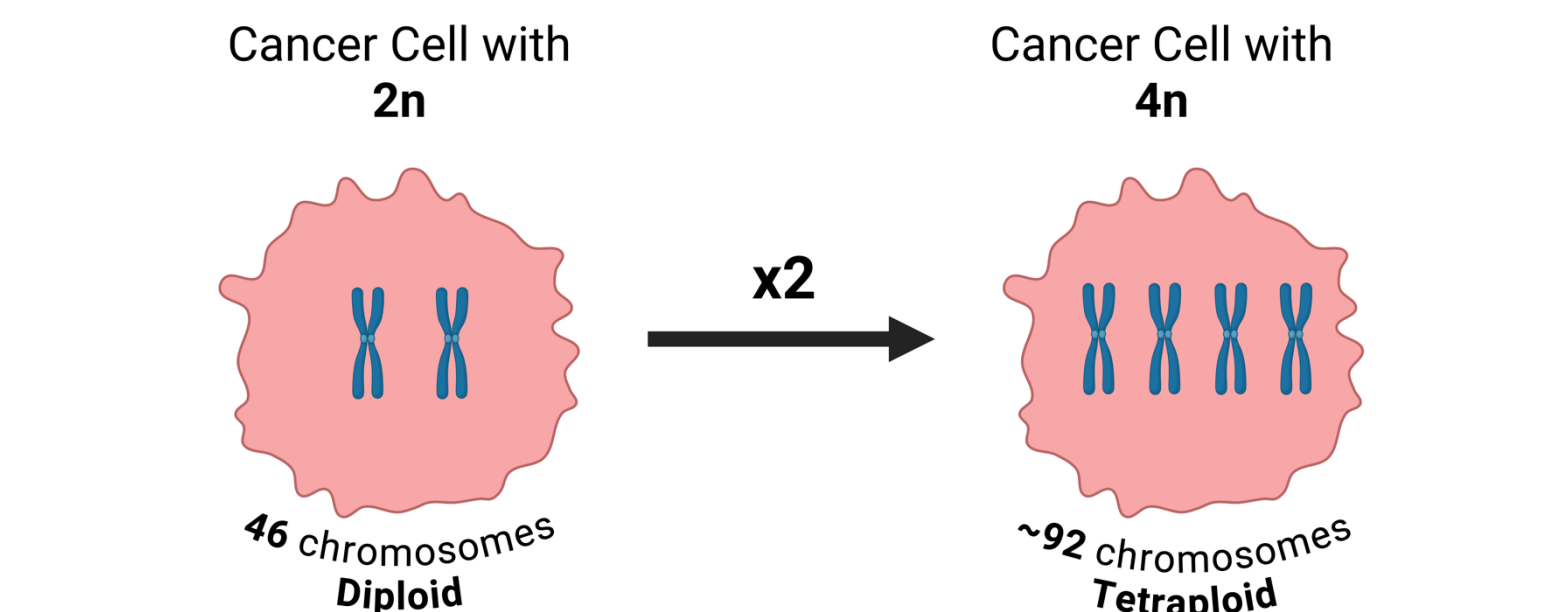


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Background

What is whole-genome duplication (WGD) and why does it matter in cancer?

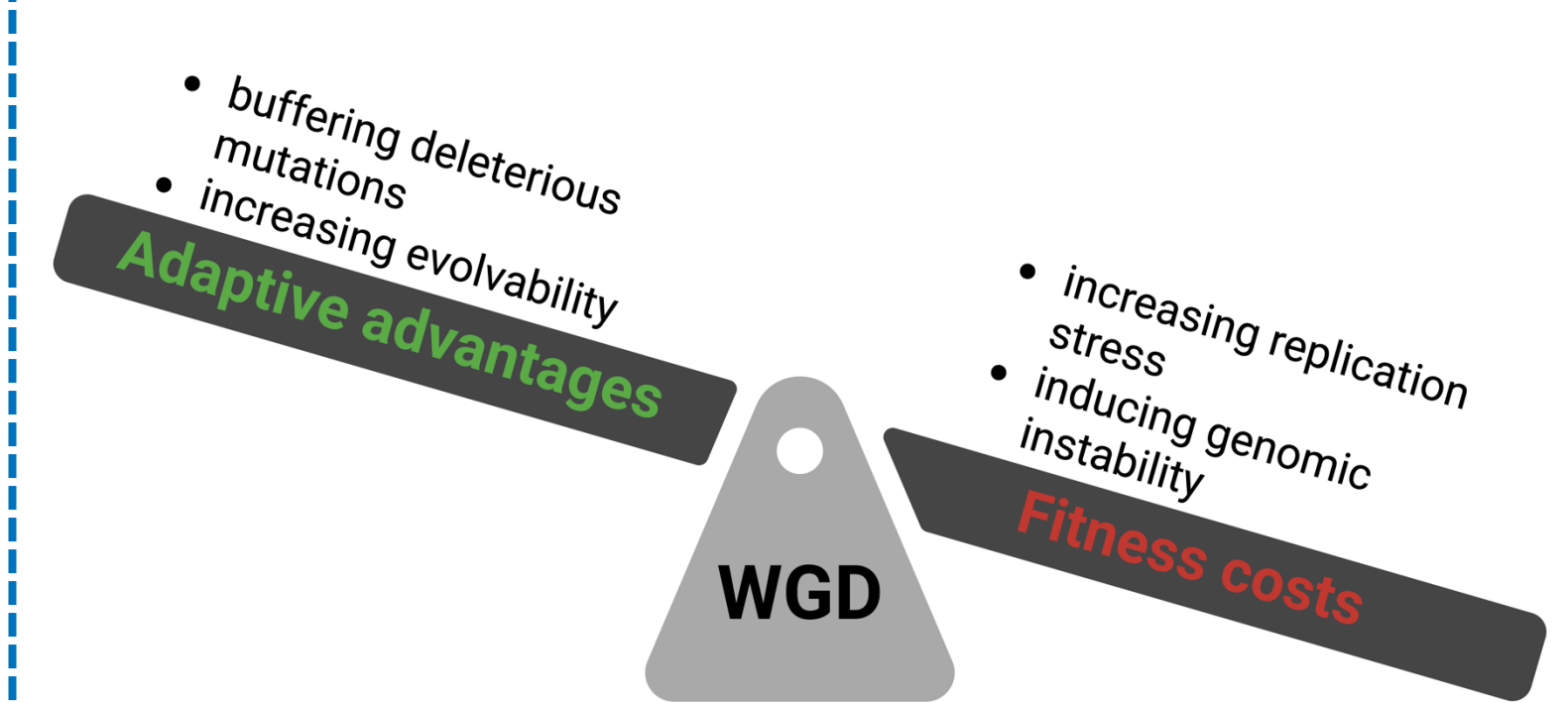
WGD is the duplication of a **complete set of chromosomes**



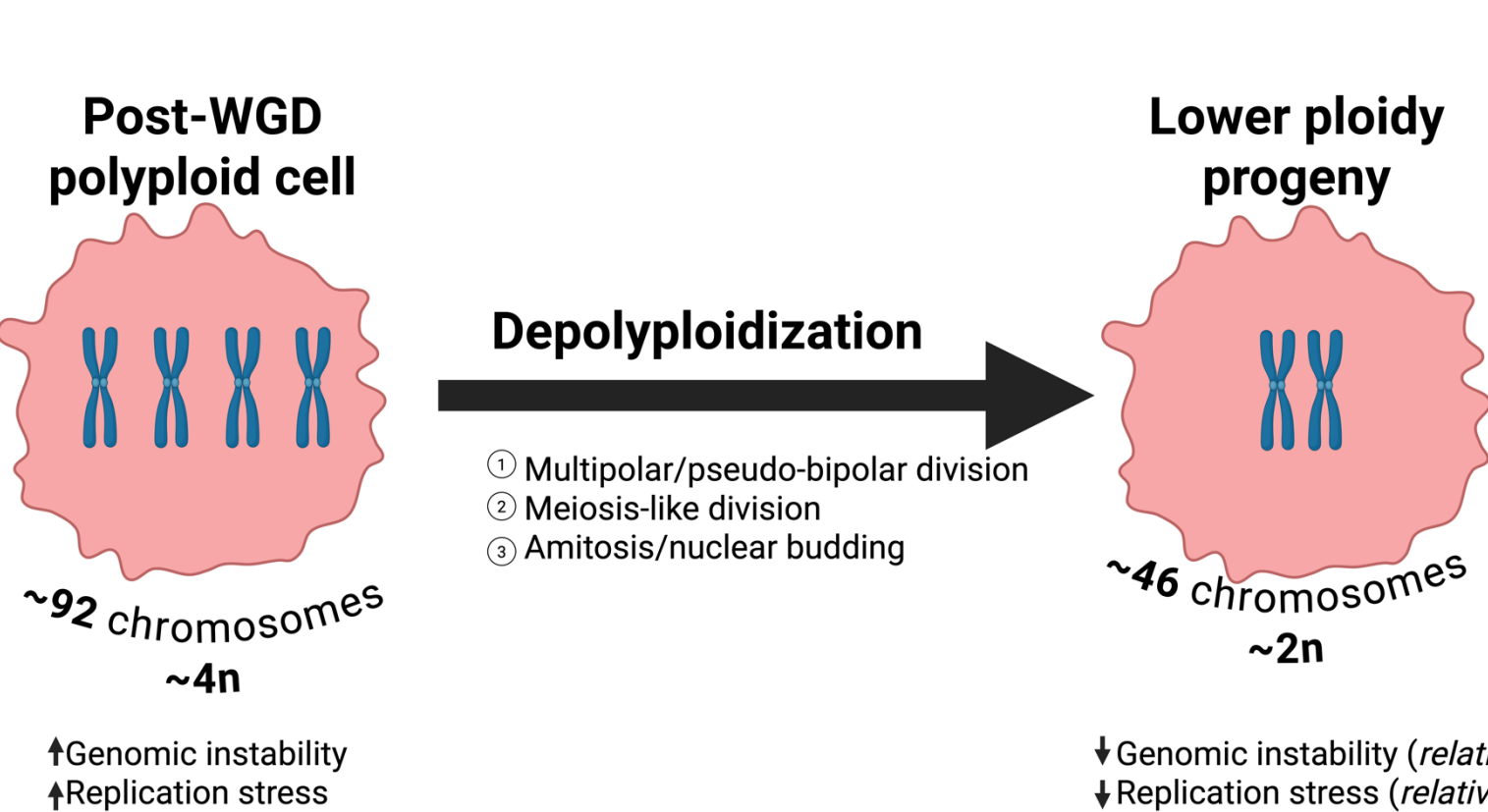
Occurs in **37%** of **primary** tumours and **58%** of **metastatic** tumours

What are the effects of WGD on tumours?

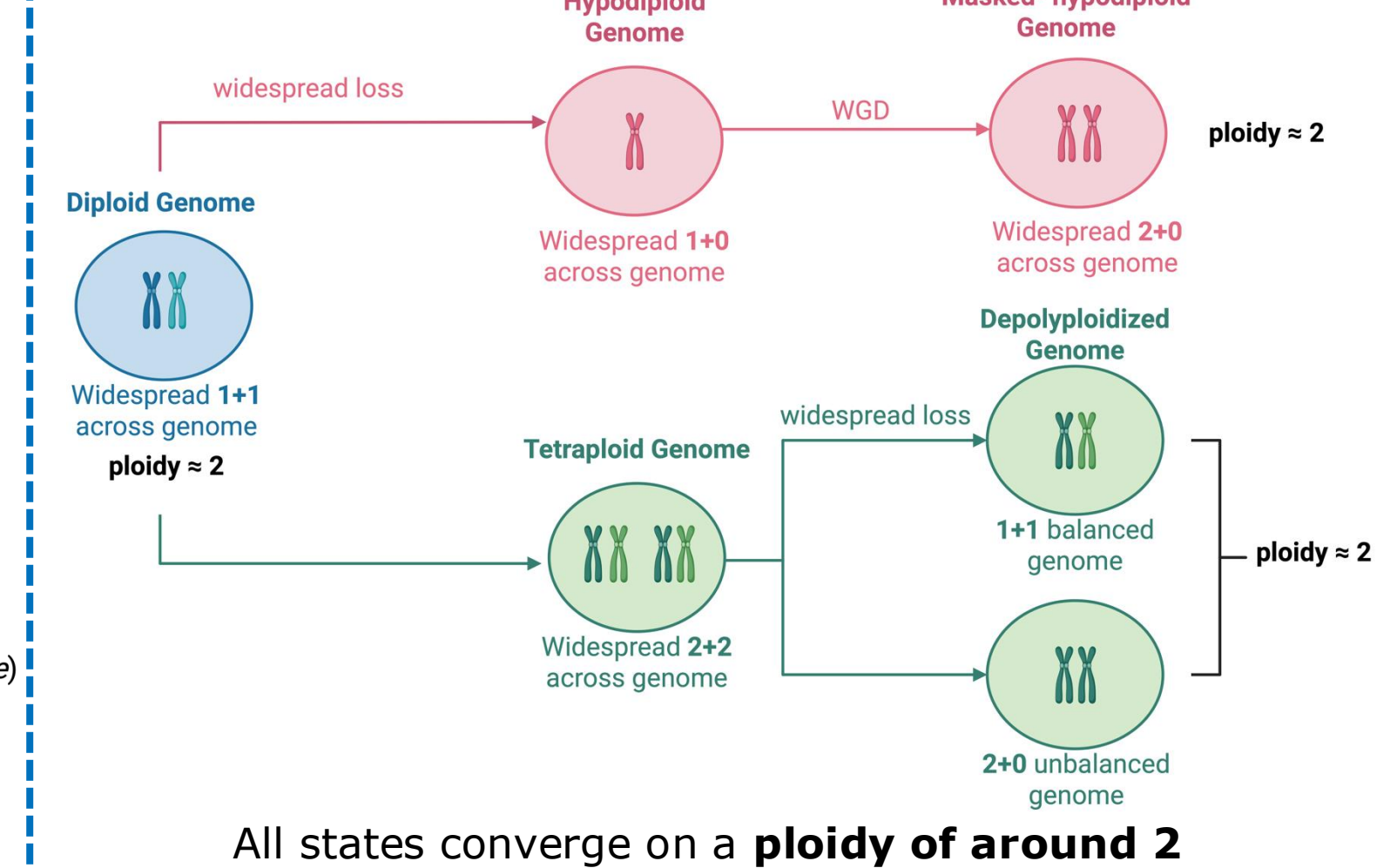
WGD is associated with **poorer prognosis, accelerated cancer genome evolution, increased tumour cell diversity** and **exhibits tissue specific patterns**.



How do tumours resolve the costs of polyploidy?



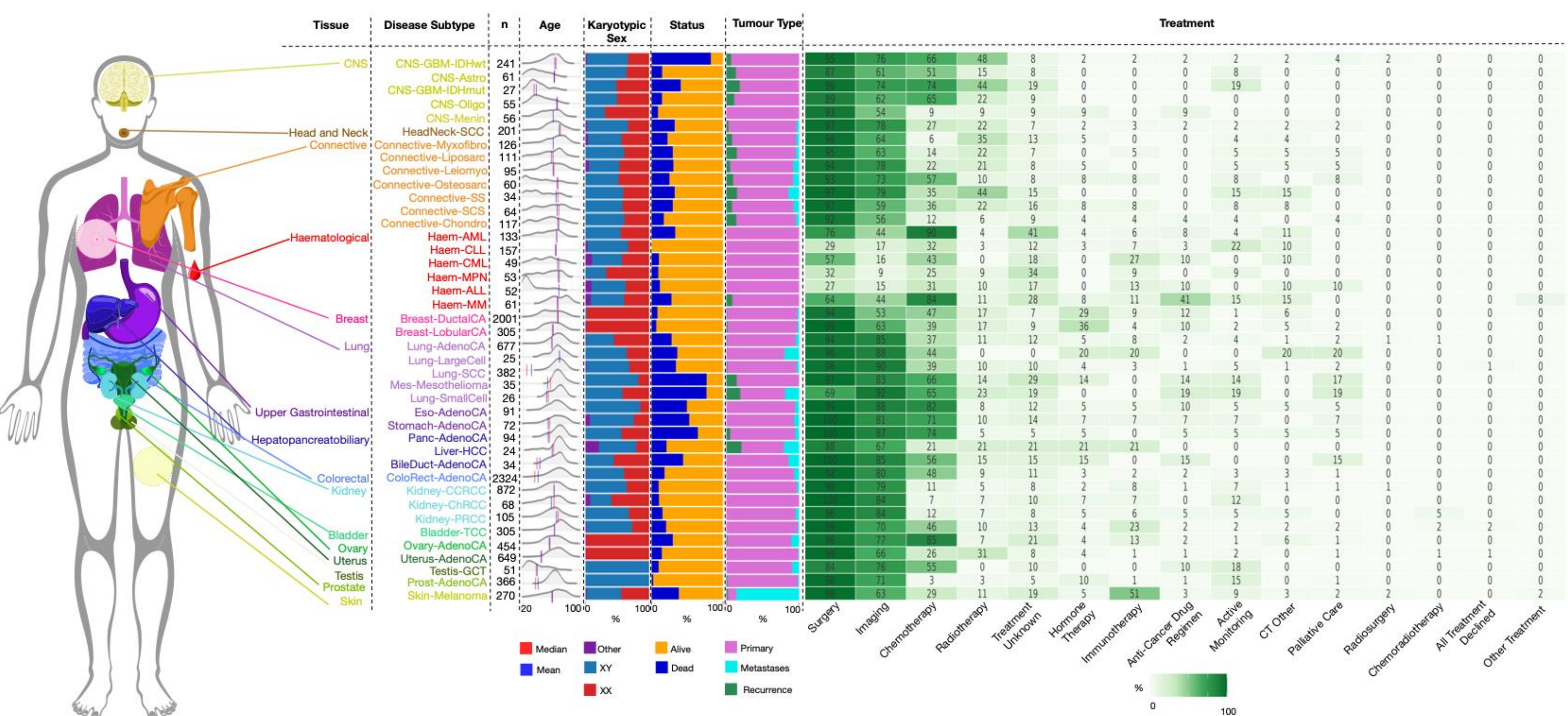
Why is depolyploidization hard to detect in cancer?



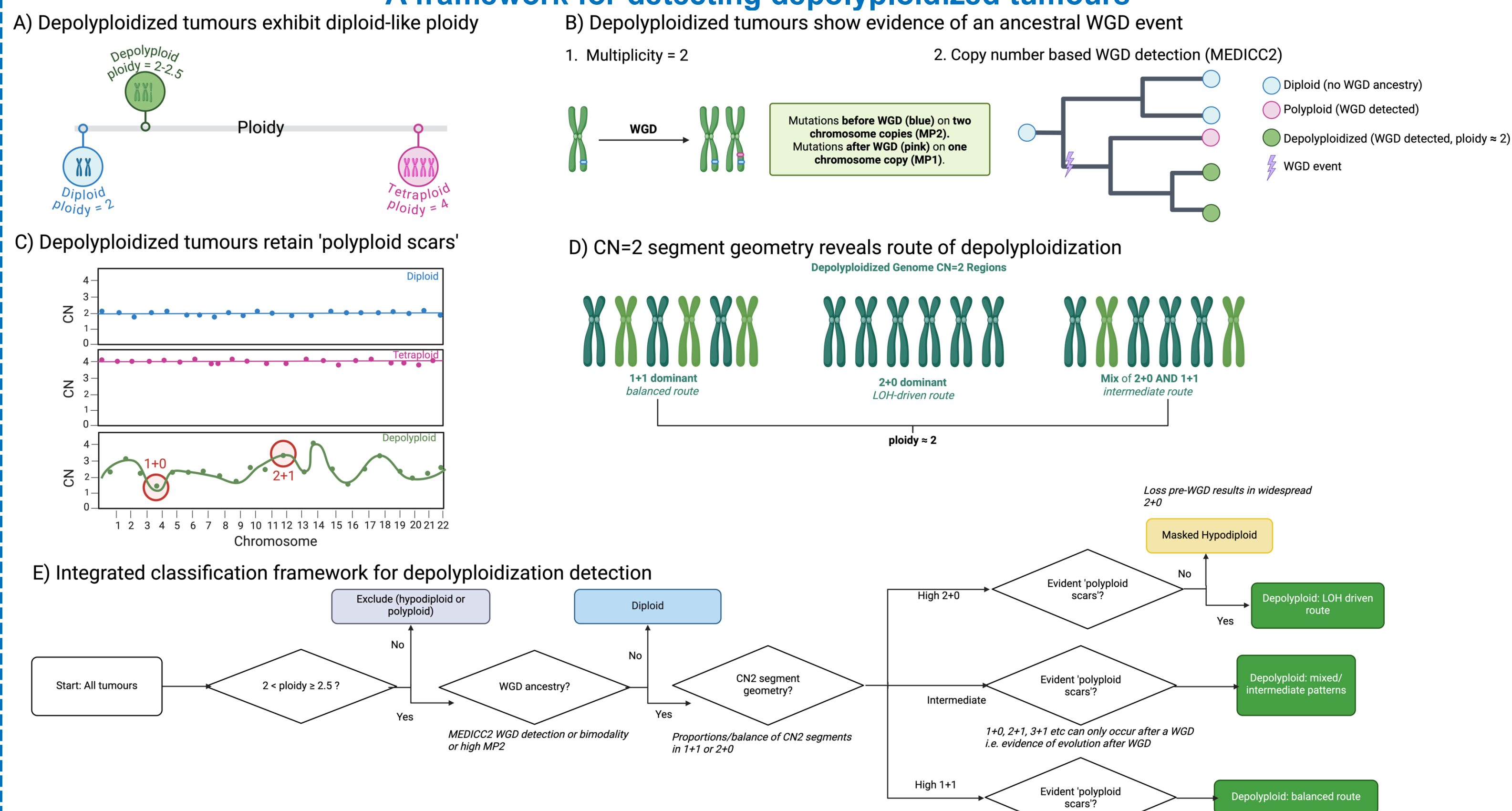
Methods

The 100,000 Genomes Project Cancer Cohort

- 10,983 tumour-normal sample pairs from 10,975 NHS cancer patients
- Genomes span 41 tumour types, consisting of 93% primary, 6% metastatic and 1% recurrent

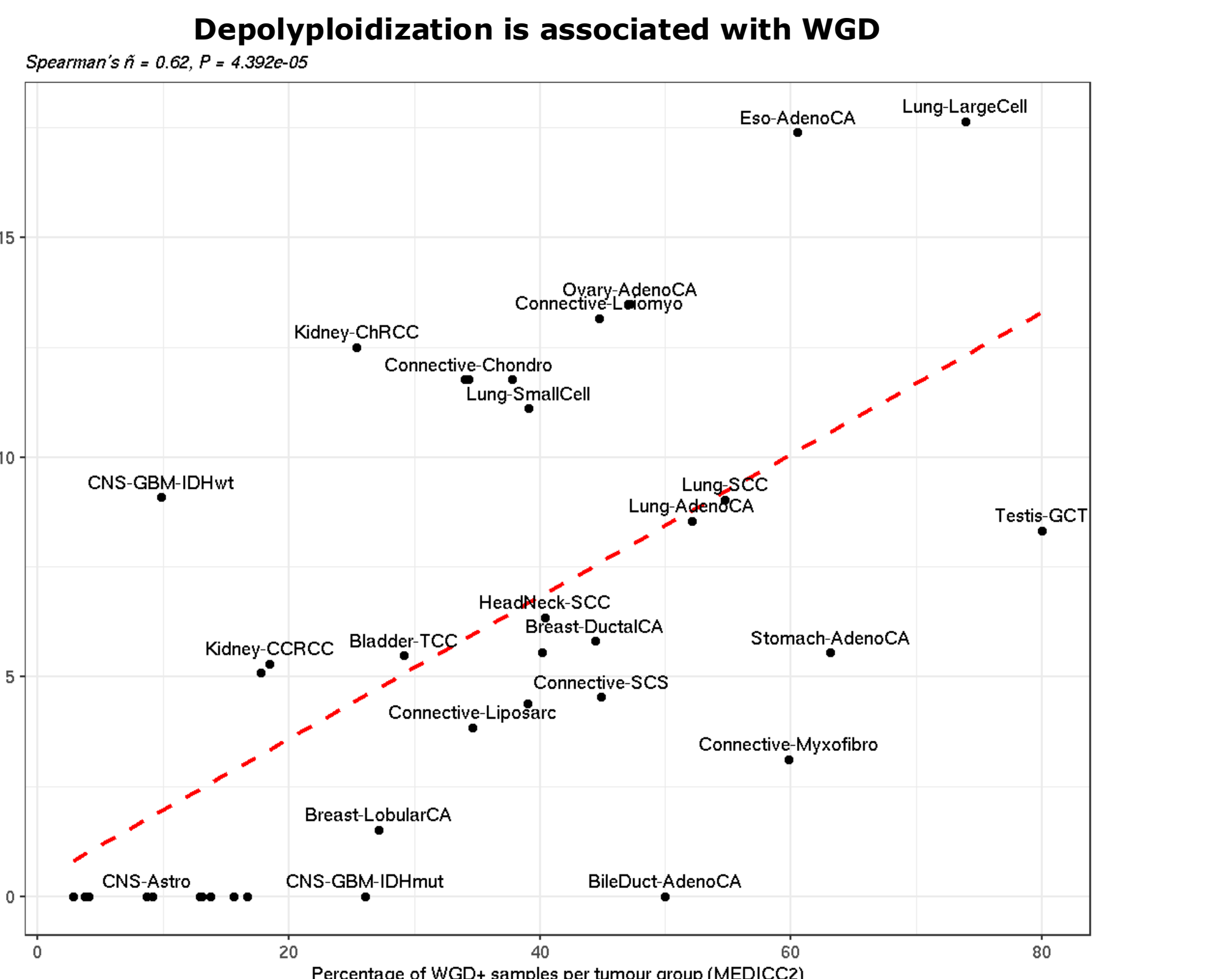
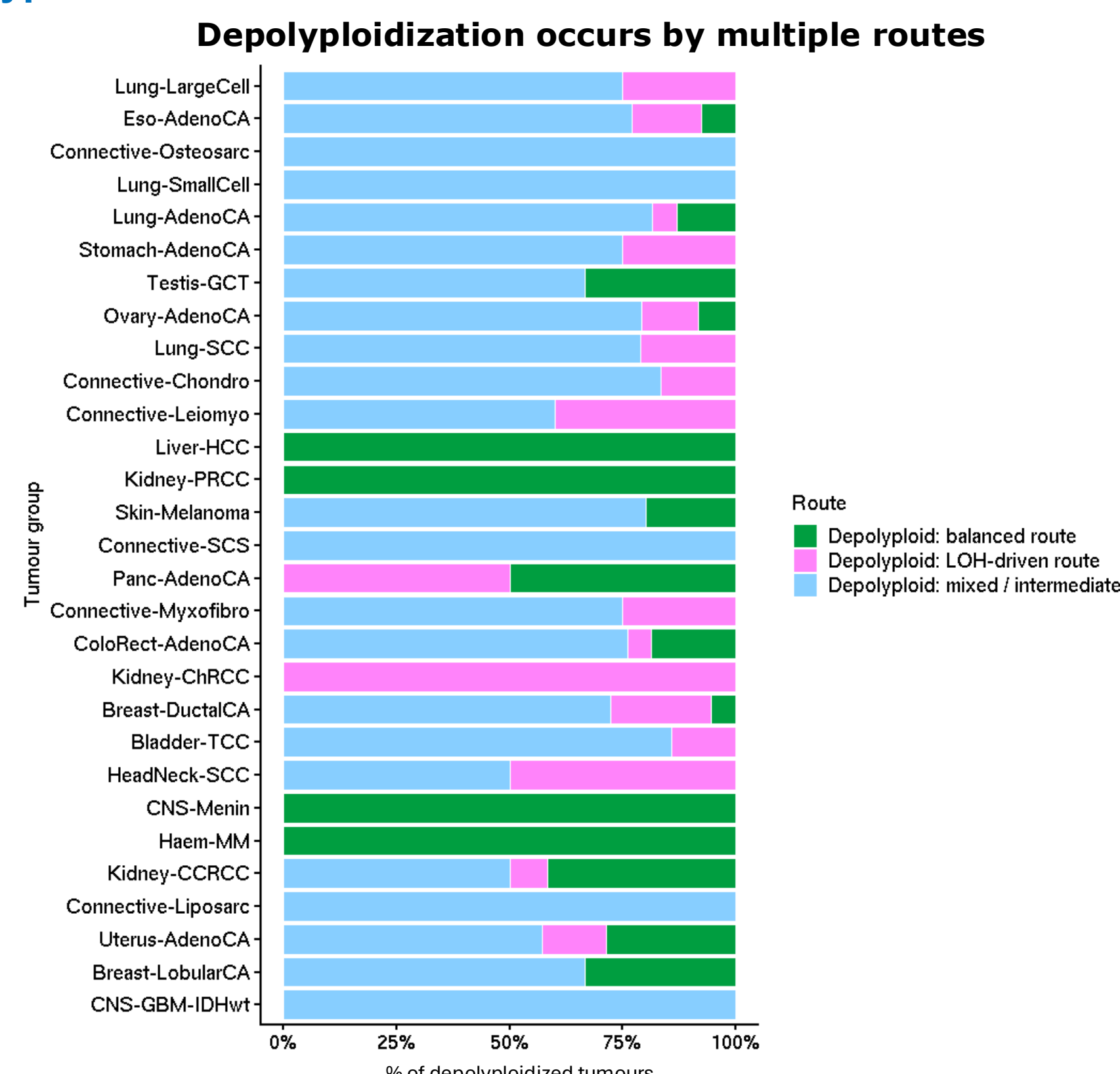
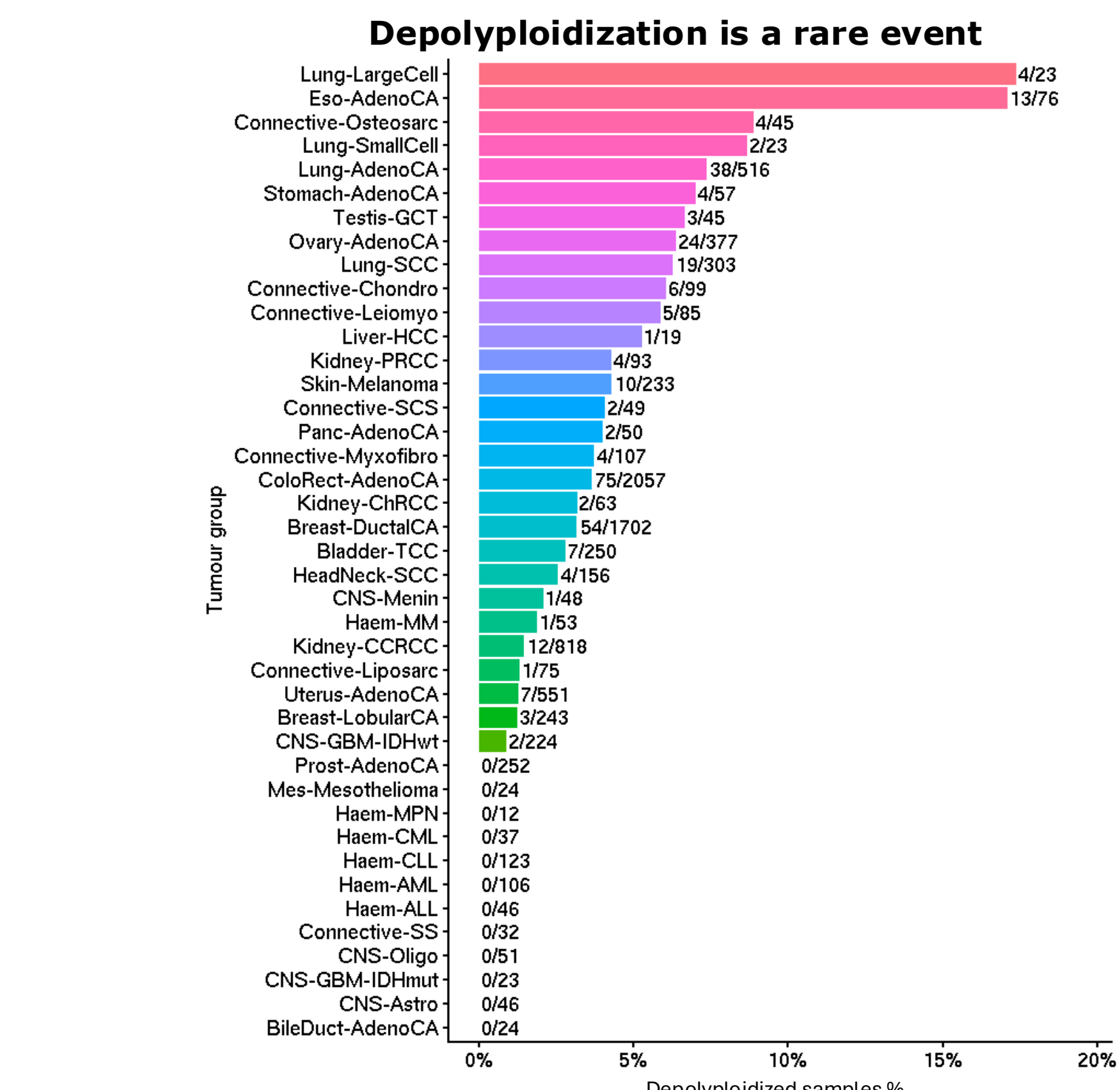


A framework for detecting depolyploidized tumours

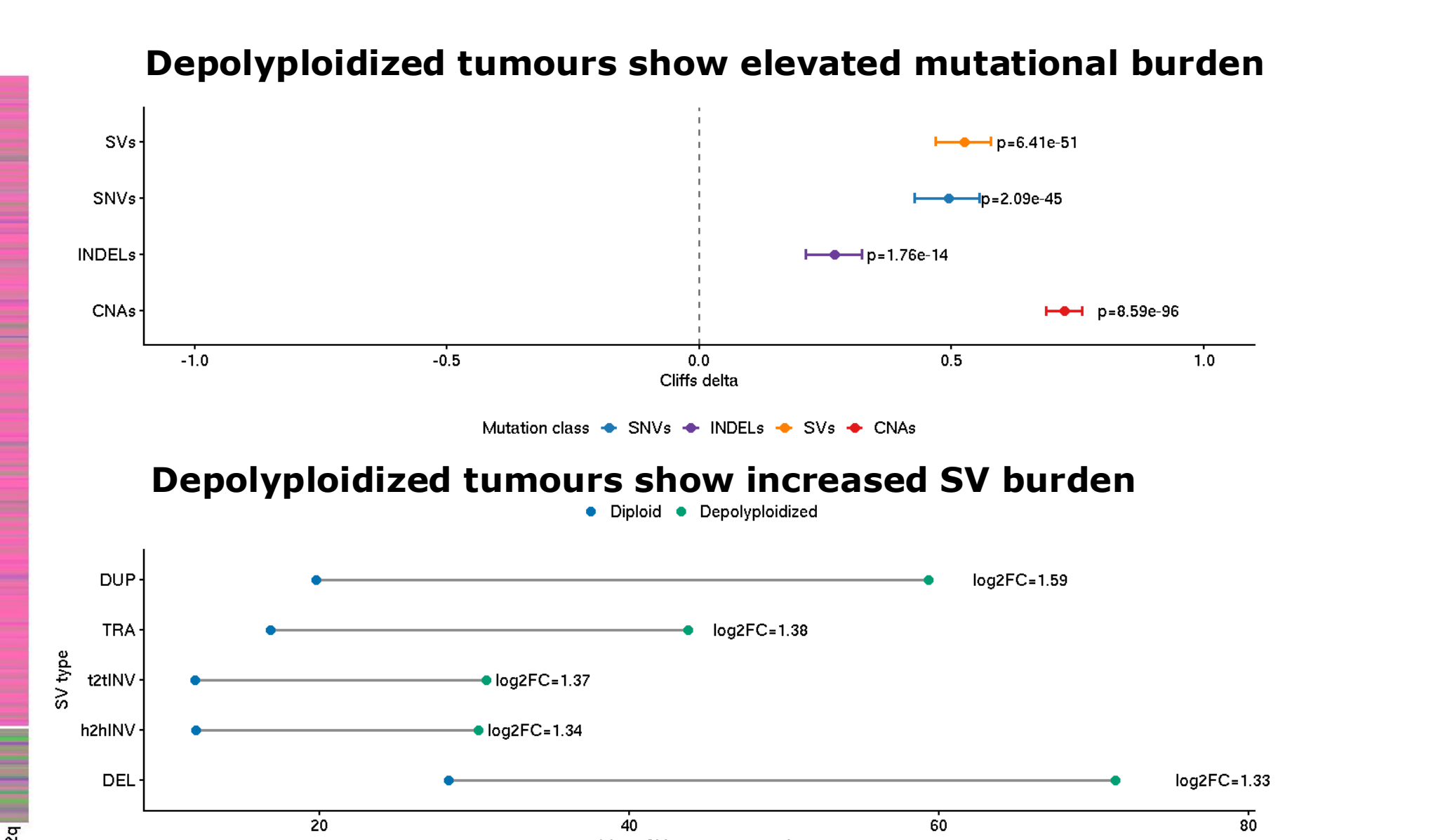
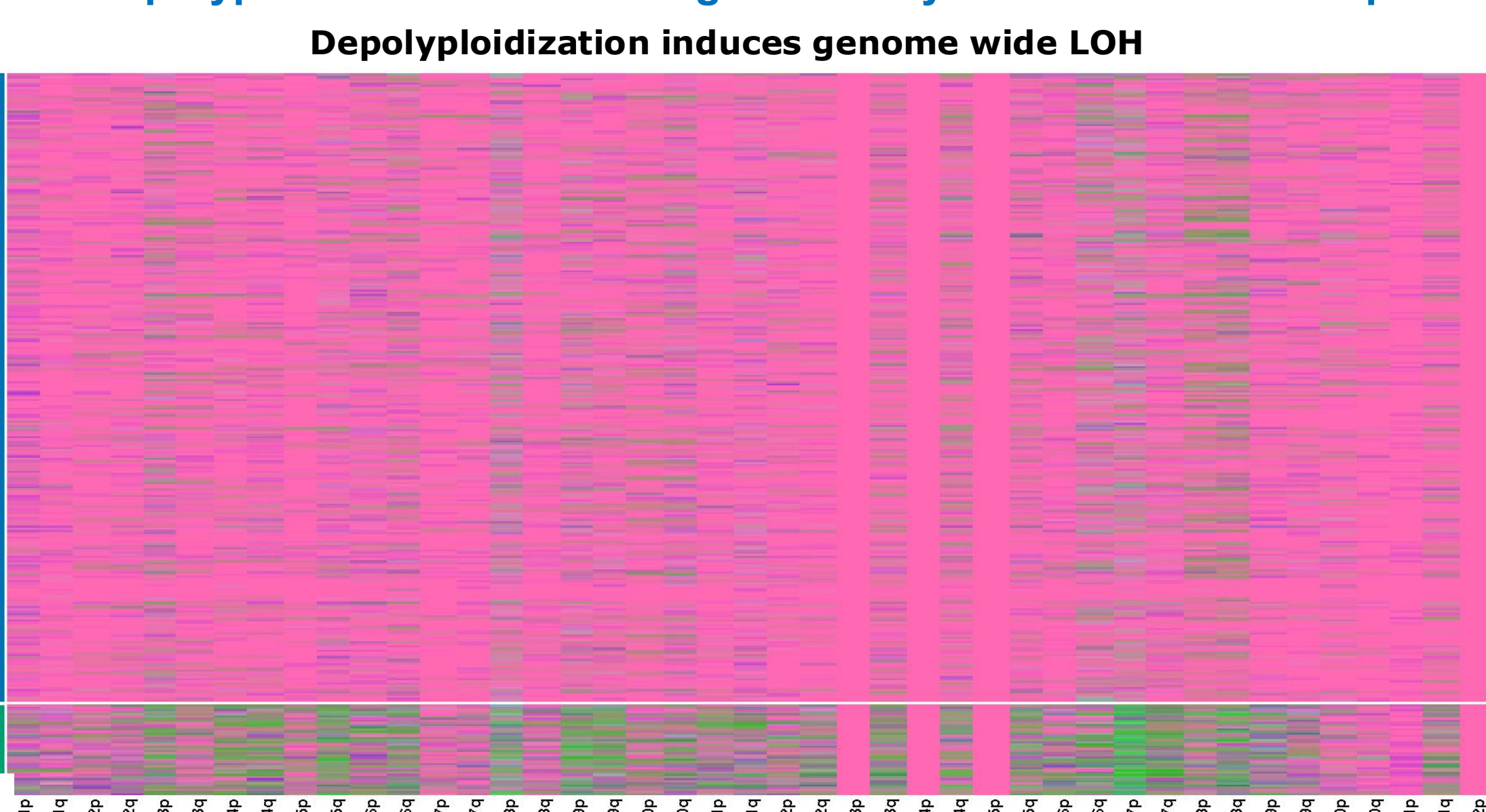
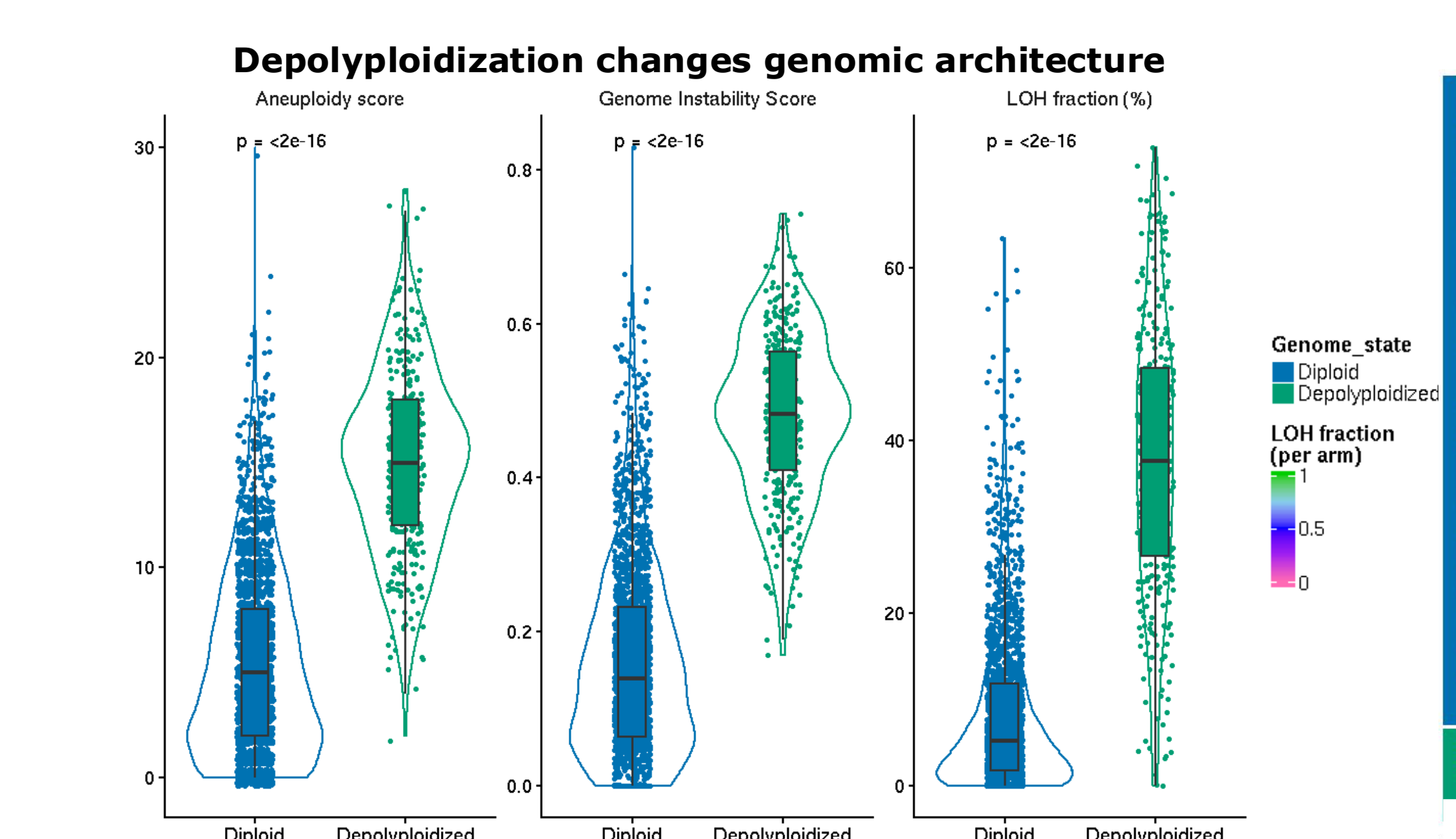


Results

Depolyploidization is a rare but recurrent outcome associated with WGD

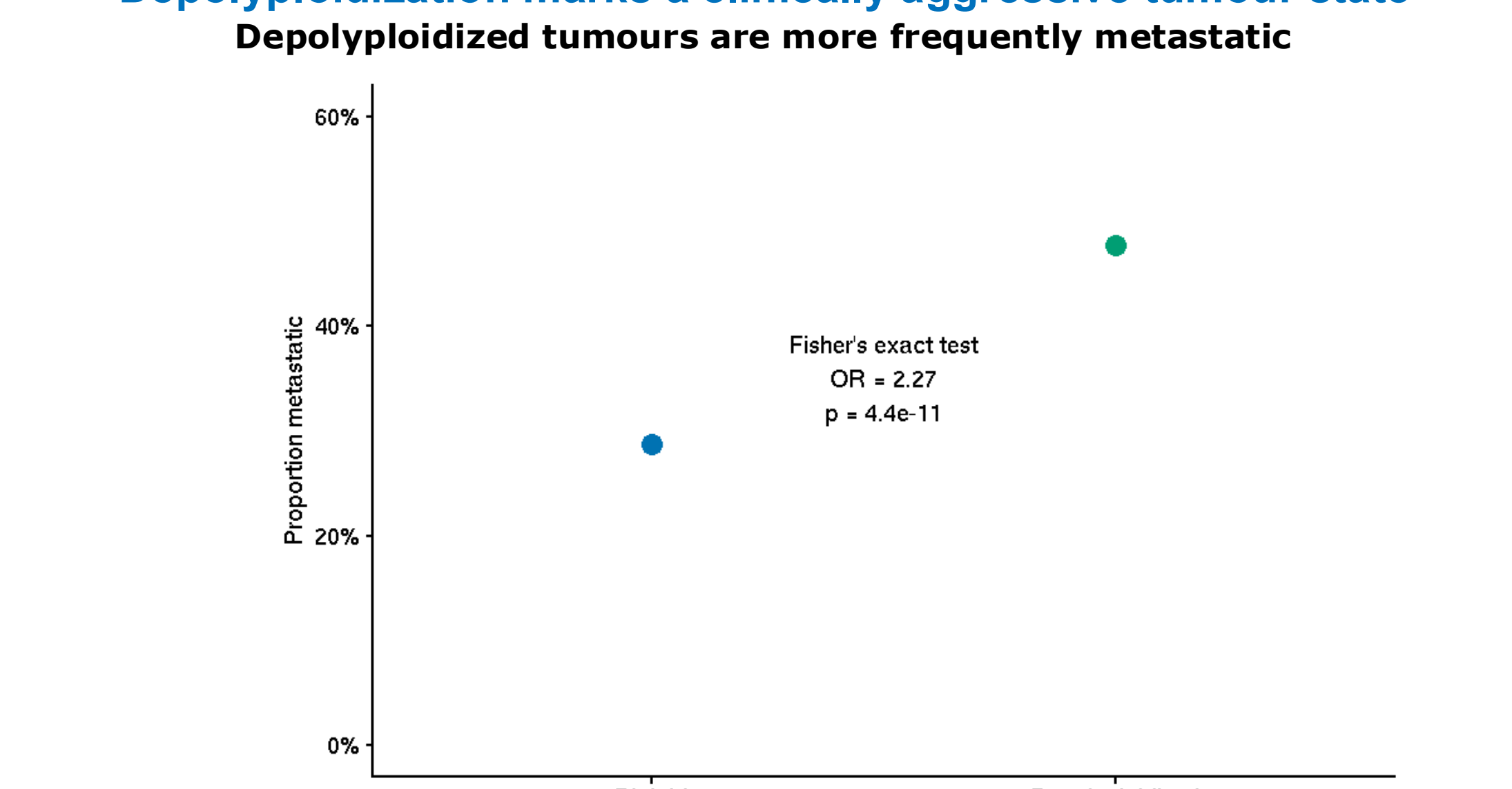
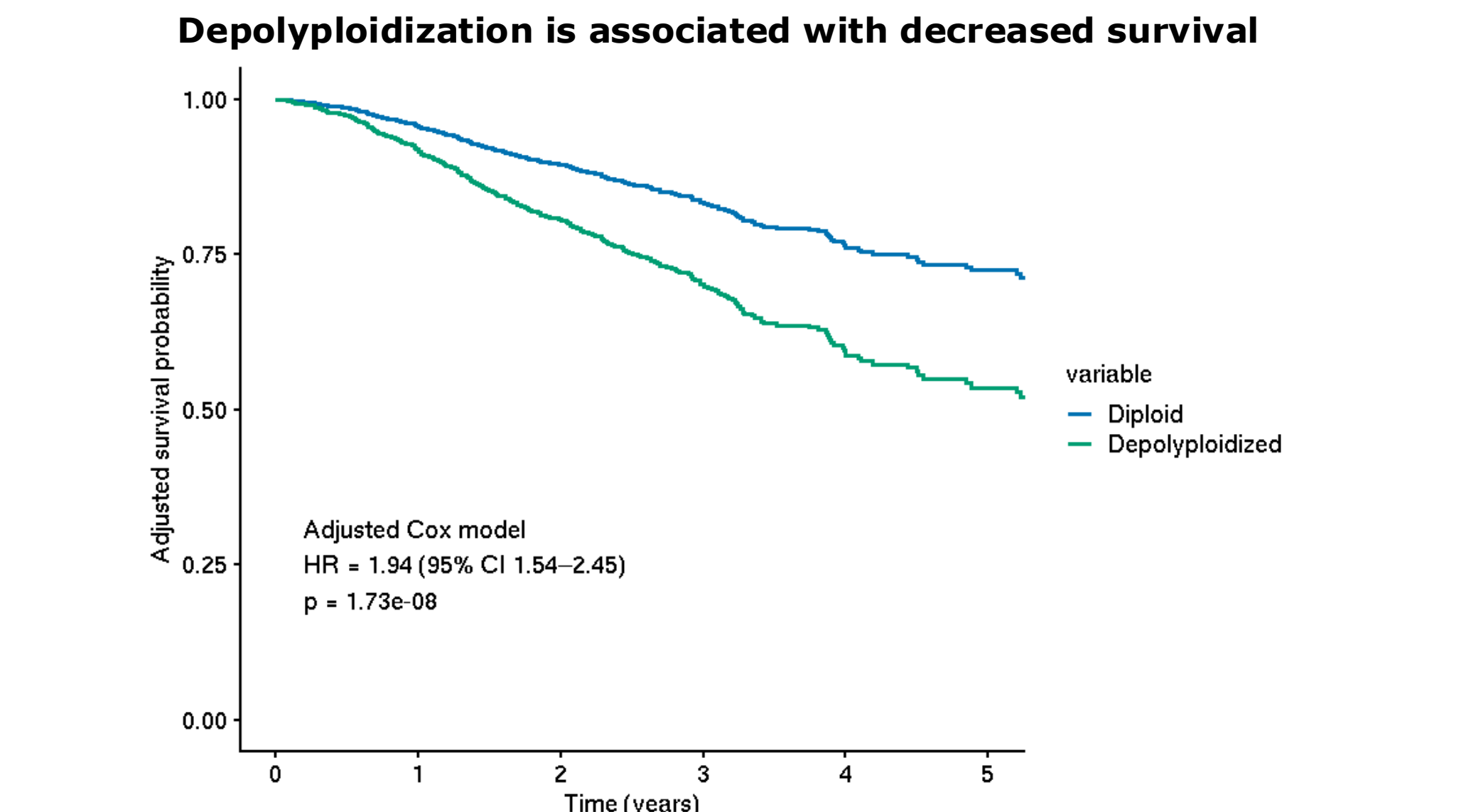


Depolyploidized tumours are genomically distinct from true diploids

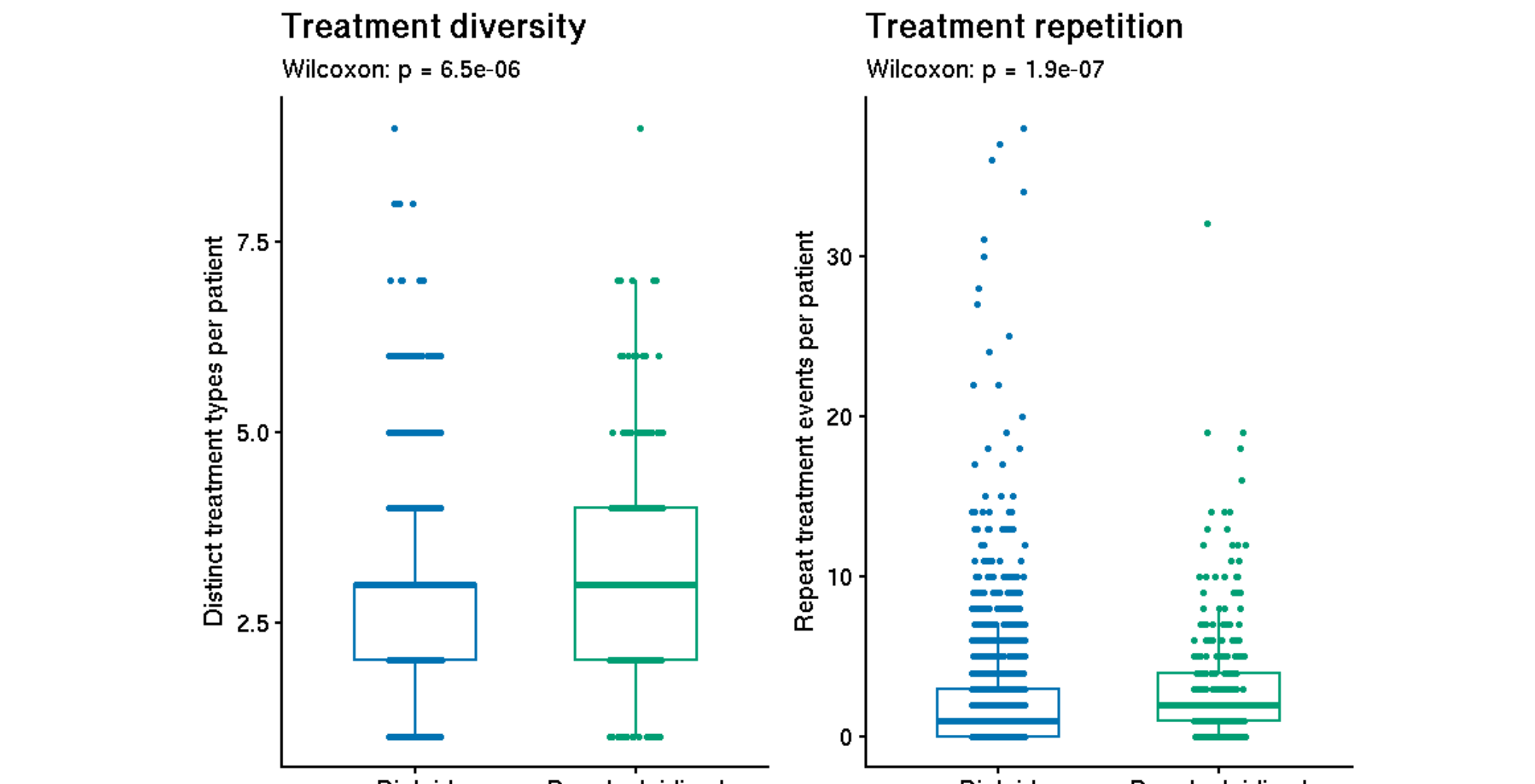


Depolyploidization marks a clinically aggressive tumour state

Depolyploidized tumours are more frequently metastatic



Depolyploidization is associated with greater treatment complexity



Conclusions and Implications

- Depolyploidization is **rare** but defines a **genomically distinct state** from true diploidy.
- Depolyploidization is associated with **more aggressive disease** and **poorer clinical outcomes**.
- Understanding depolyploidization may enable **improved patient stratification** and **identify new therapeutic vulnerabilities**.

Acknowledgements

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