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Evolution of the Genomic Landscape in NSCLC

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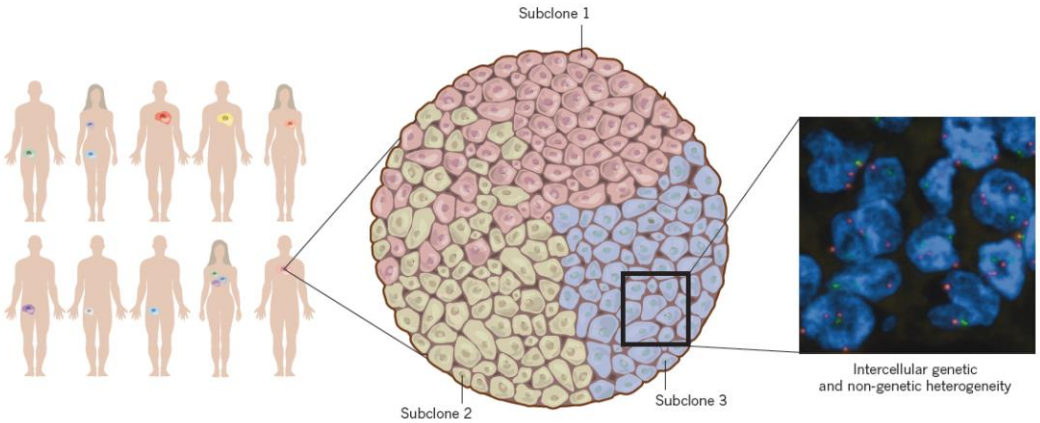
Disclosure Slide

- No conflict of interest to declare

Genomic Landscape of Lung Cancer

- Previous sequencing efforts in characterising lung cancer have demonstrated a complex and heterogeneous genomic landscape
- Few studies have commented on clonal architecture or evolution of lung tumours



Intertumour Heterogeneity

Intratumour Heterogeneity

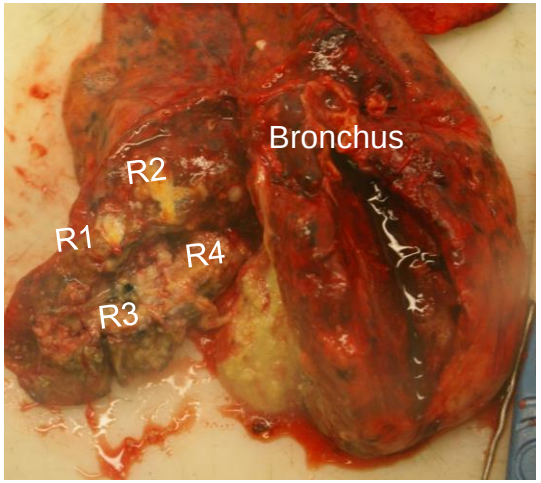
Intercellular Heterogeneity

Burrell et al, Nature 2013

- Tumours are composed of subclones with distinct, but clonally related, mutational patterns

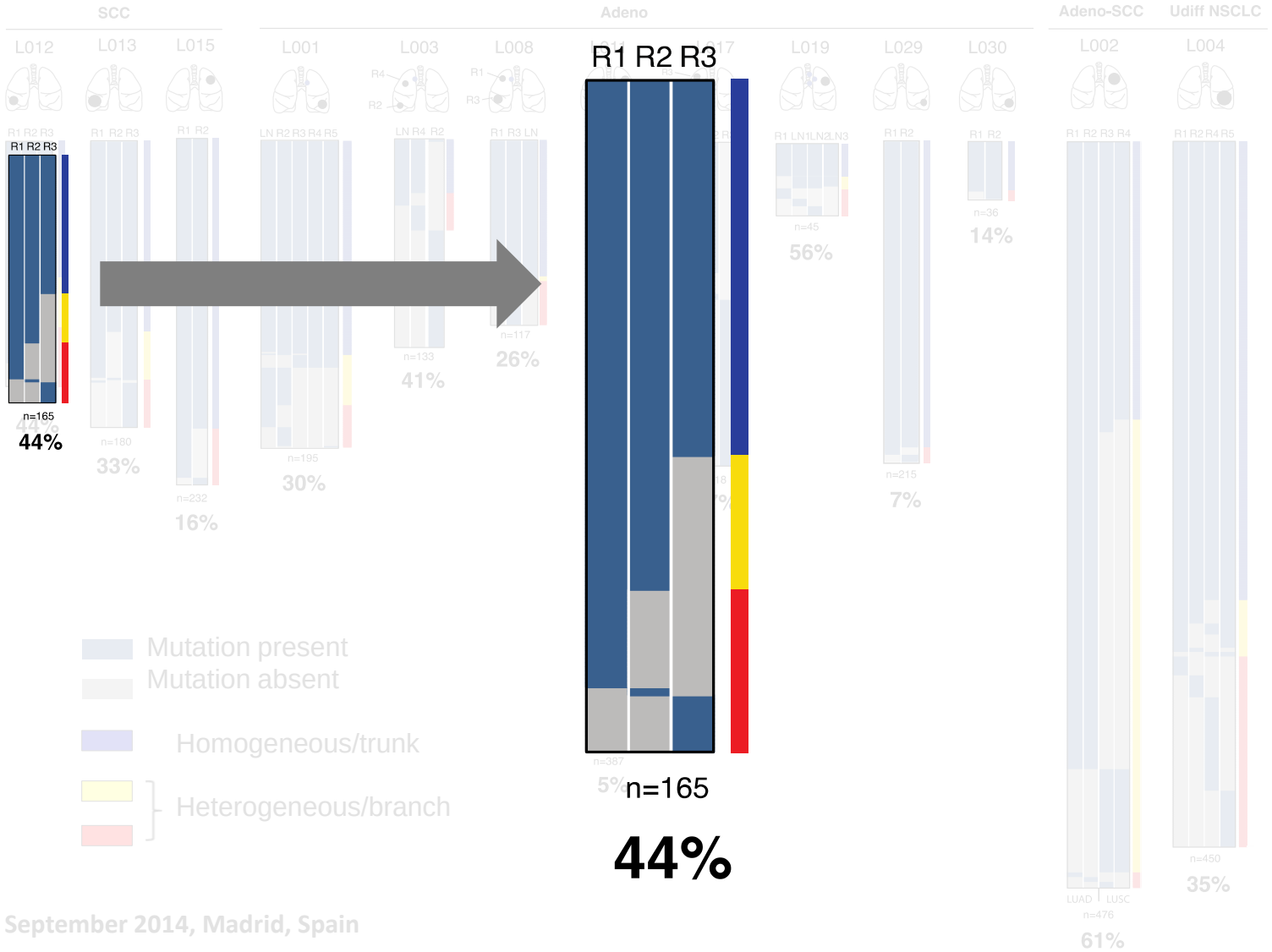
Multi-Region Sequencing of Primary NSCLC Tumours

Patient	Histology	Stage (I-IV)	Smoking Status (pack yrs)	Recurrence	Current Status	Overall Survival (mths)
L015	SCC	IA	Smoker (100)	No	Alive	26
L012	SCC	IB	Smoker (40)	No	RIP	2
L013	SCC	IB	Smoker (50)	No	Alive	27
L029	Adeno	IA	Ex (>40)	No	Alive	19
L030	Adeno	IA	Ex (40)	No	Alive	19
L017	Adeno	IIB	Smoker (48)	Yes	Alive	25
L019	Adeno	IIIA	Never	Yes	RIP	15
L011	Adeno	IB	Smoker (45)	Yes	RIP	19
L003	Adeno	IIIB	Never	No	Alive	28
L008	Adeno	IIIA	Ex (25)	Yes	Alive	27
L001	Adeno	IIA	Ex (10)	No	Alive	30
L002	Adeno-SCC	IIIA	Smoker (>50)	Yes	RIP	12
L004	Undiff NSCLC	IIB	Smoker (50)	Yes	RIP	23



- Patients with NSCLC eligible for curative resection
- Multi-region sampling from primary tumours +/- lymph nodes
- DNA extracted from fresh-frozen tissue
- Blood used for germ line DNA

Heterogeneity of Non-Silent Mutations



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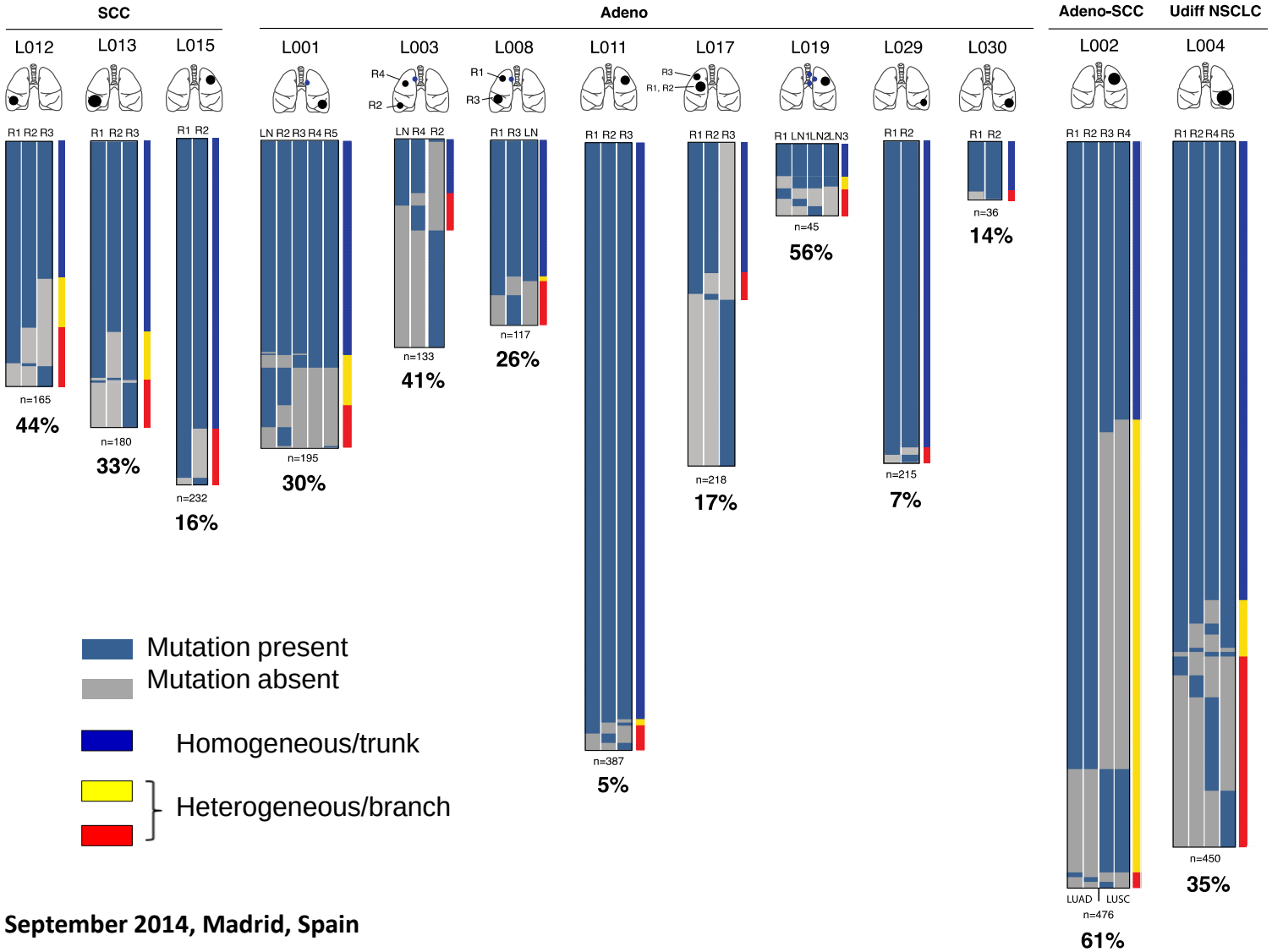
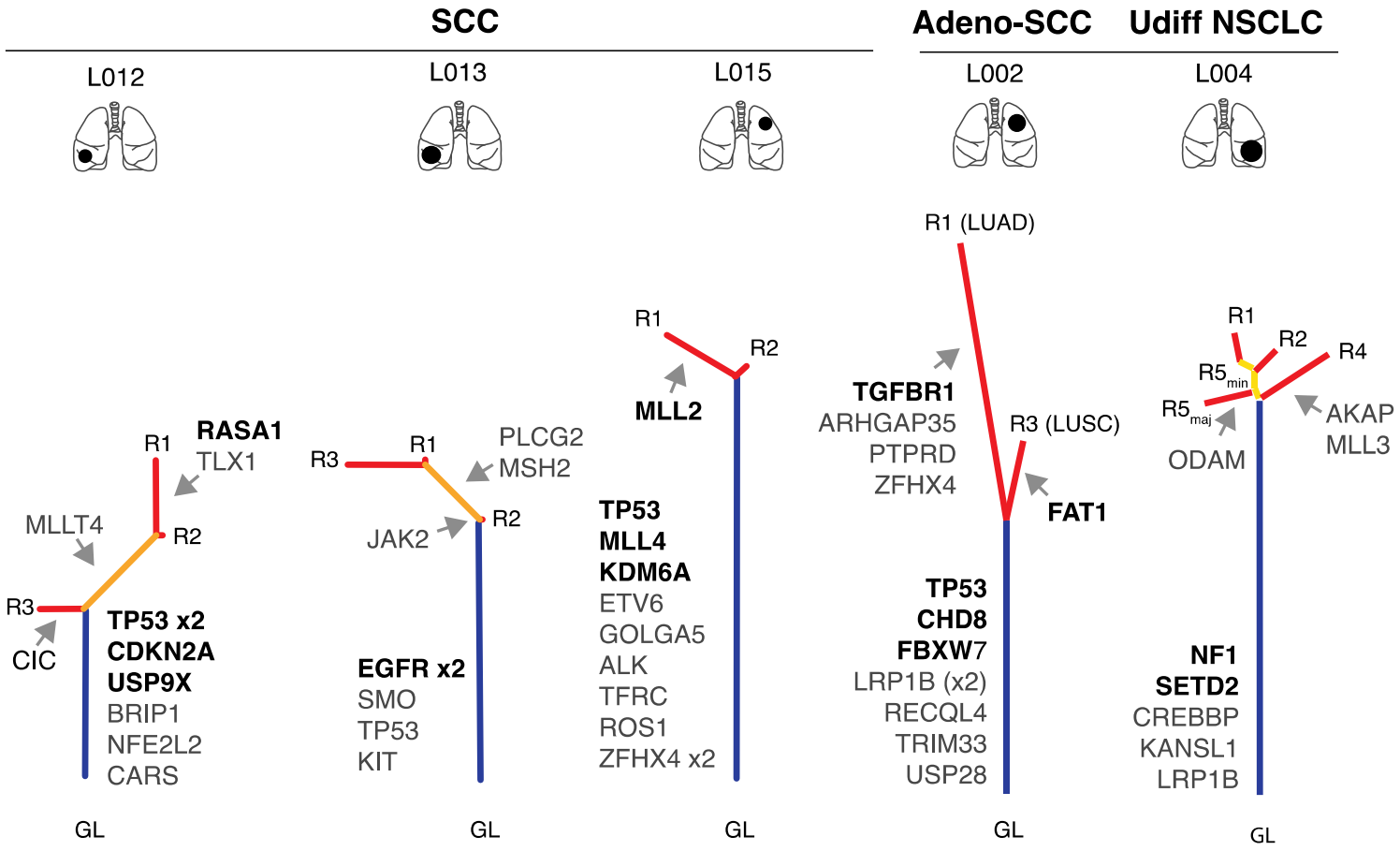
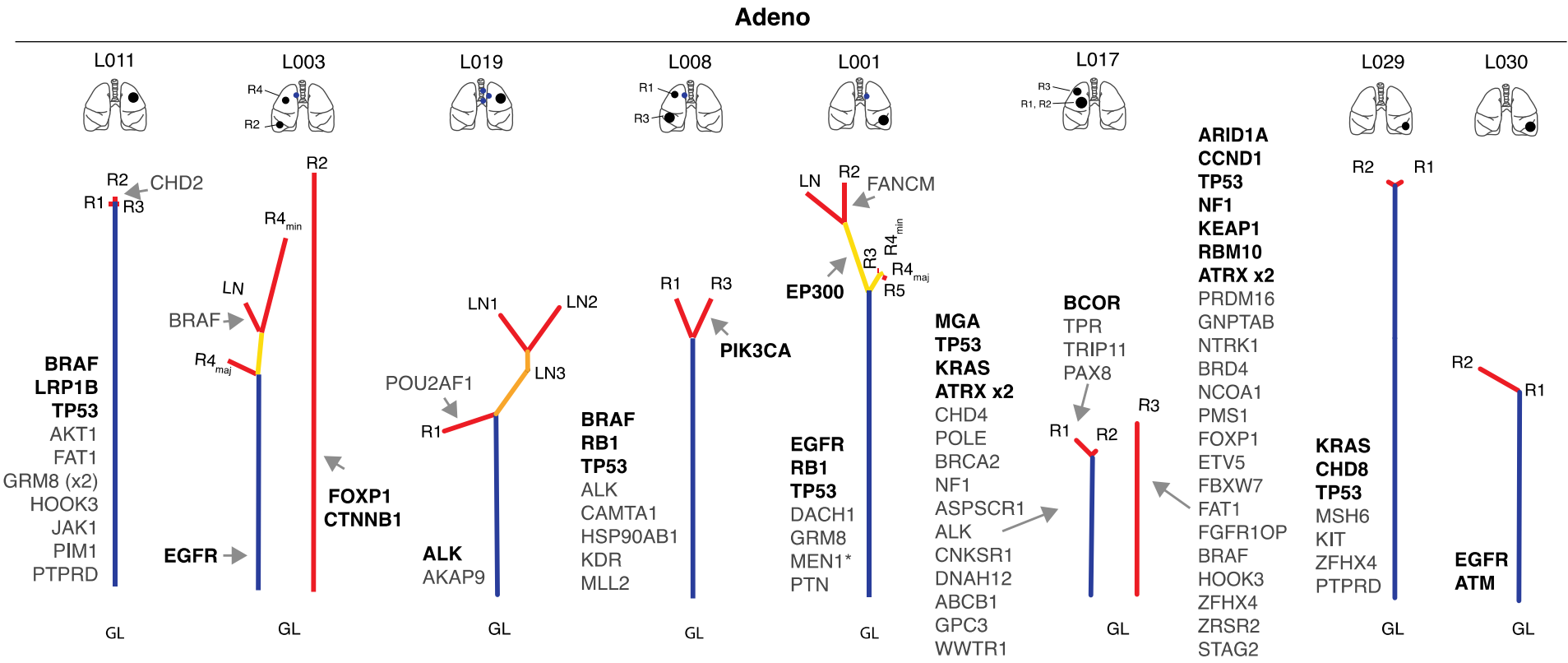


Evolutionary Trees



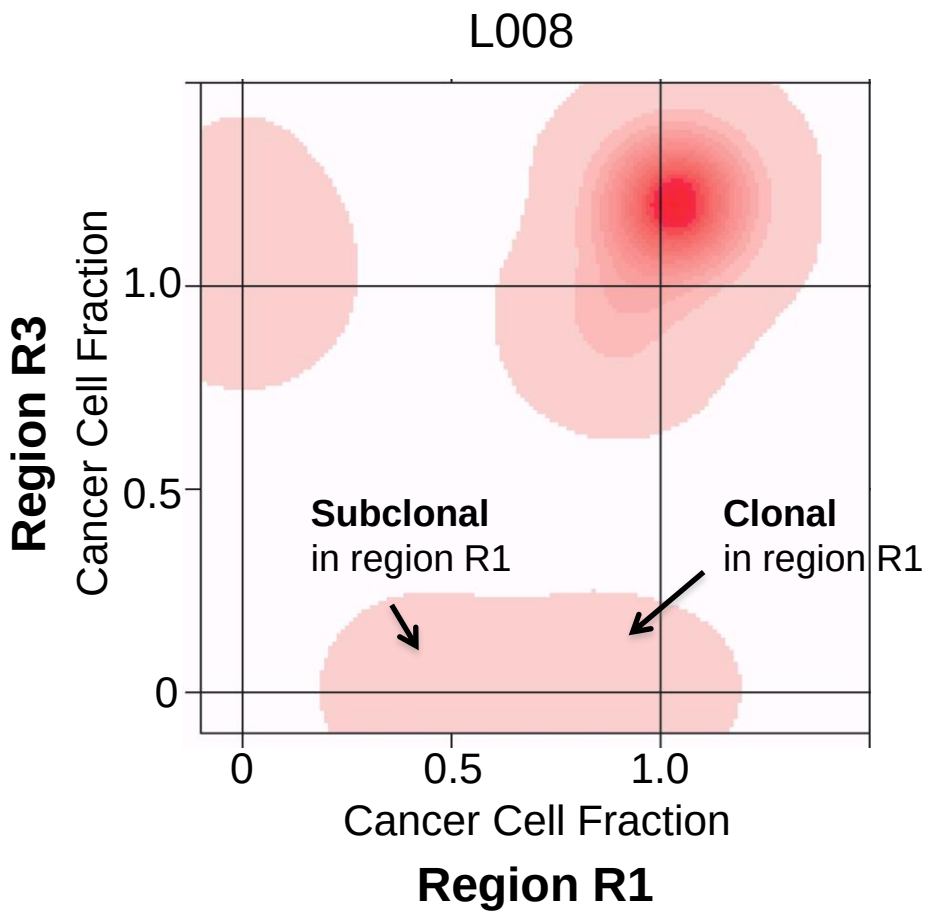
Driver genes - enriched on trunk & present on branches

Evolutionary Trees



The Illusion of Clonality in a Single Biopsy

(2D Dirichlet Density Plots)



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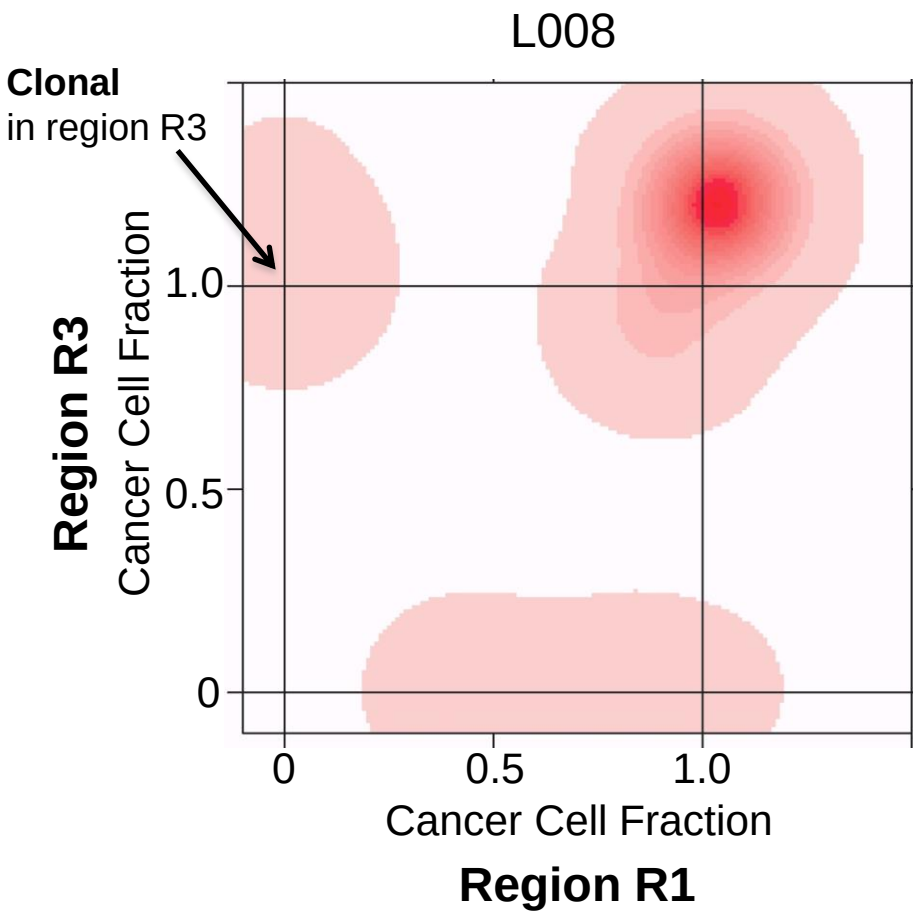

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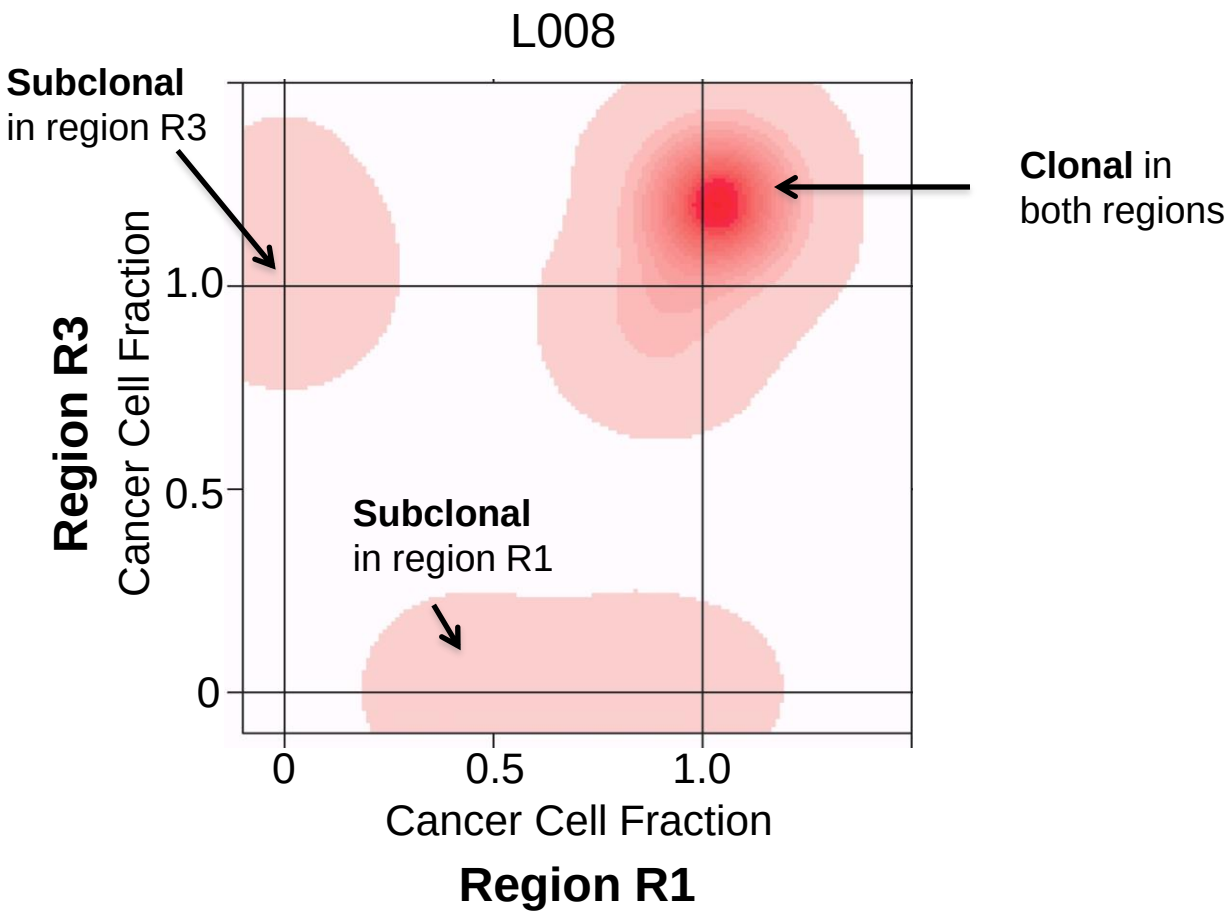
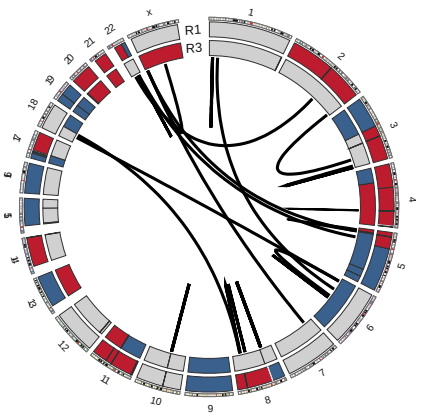
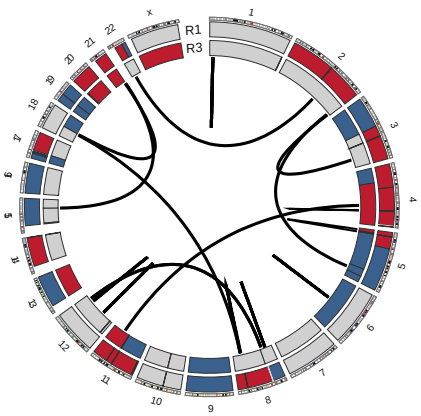


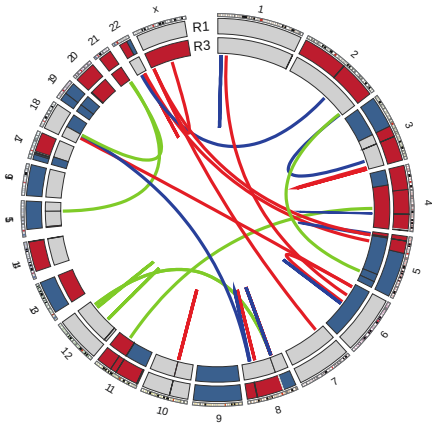
Heterogeneity of Structural Variations

R1 - Adeno



R3 - SCC

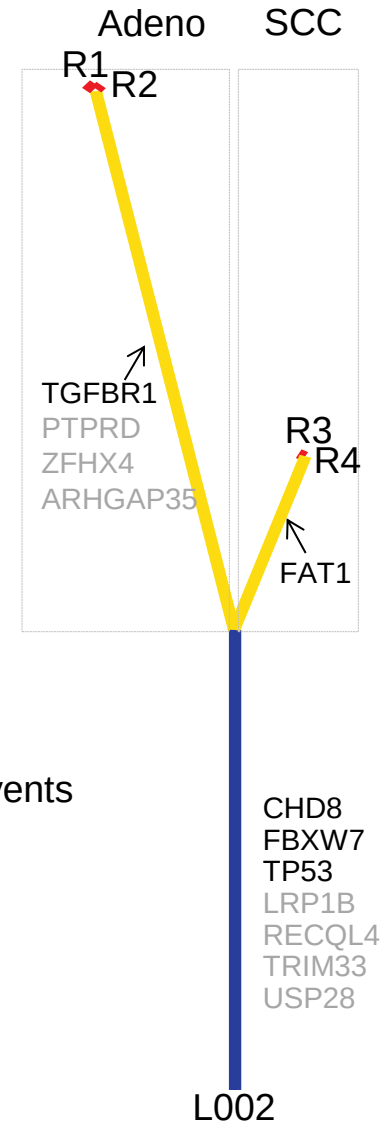




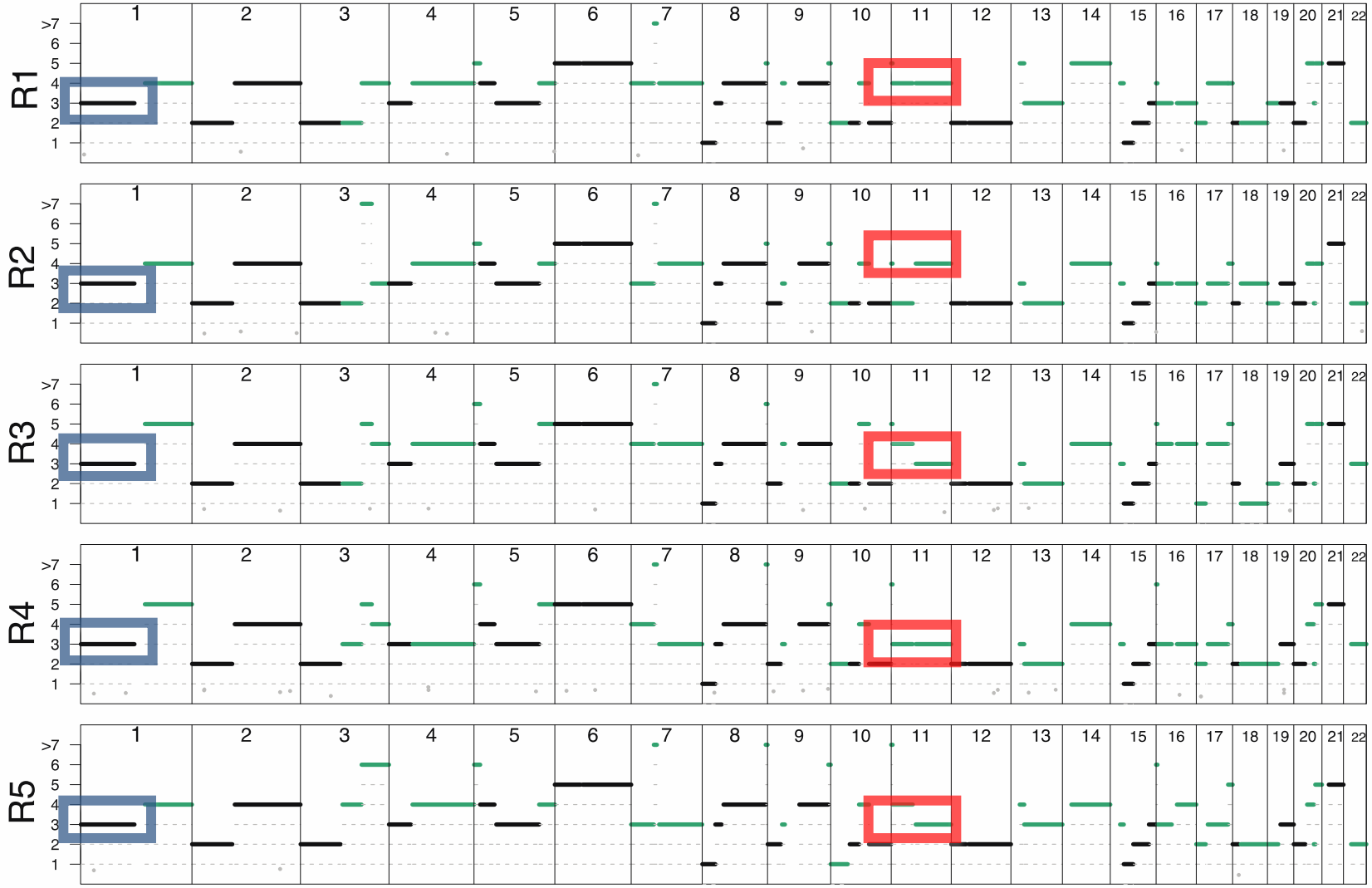
Shared = early events

R1 = late events

R3 = late events



Copy Number Events in L001



Shared copy number
Heterogenous copy number

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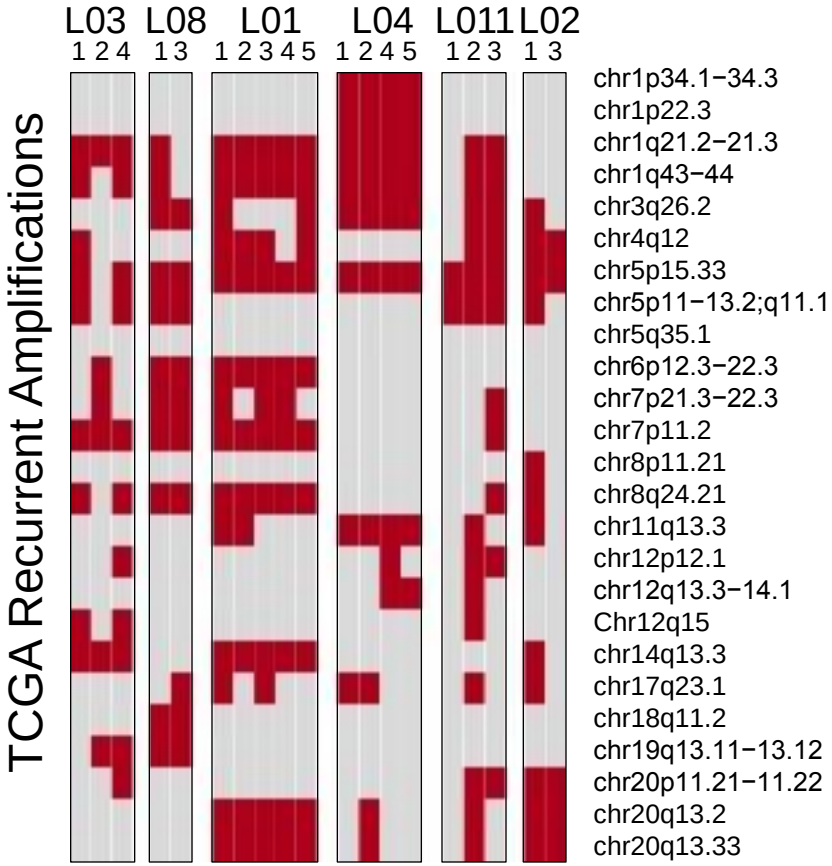
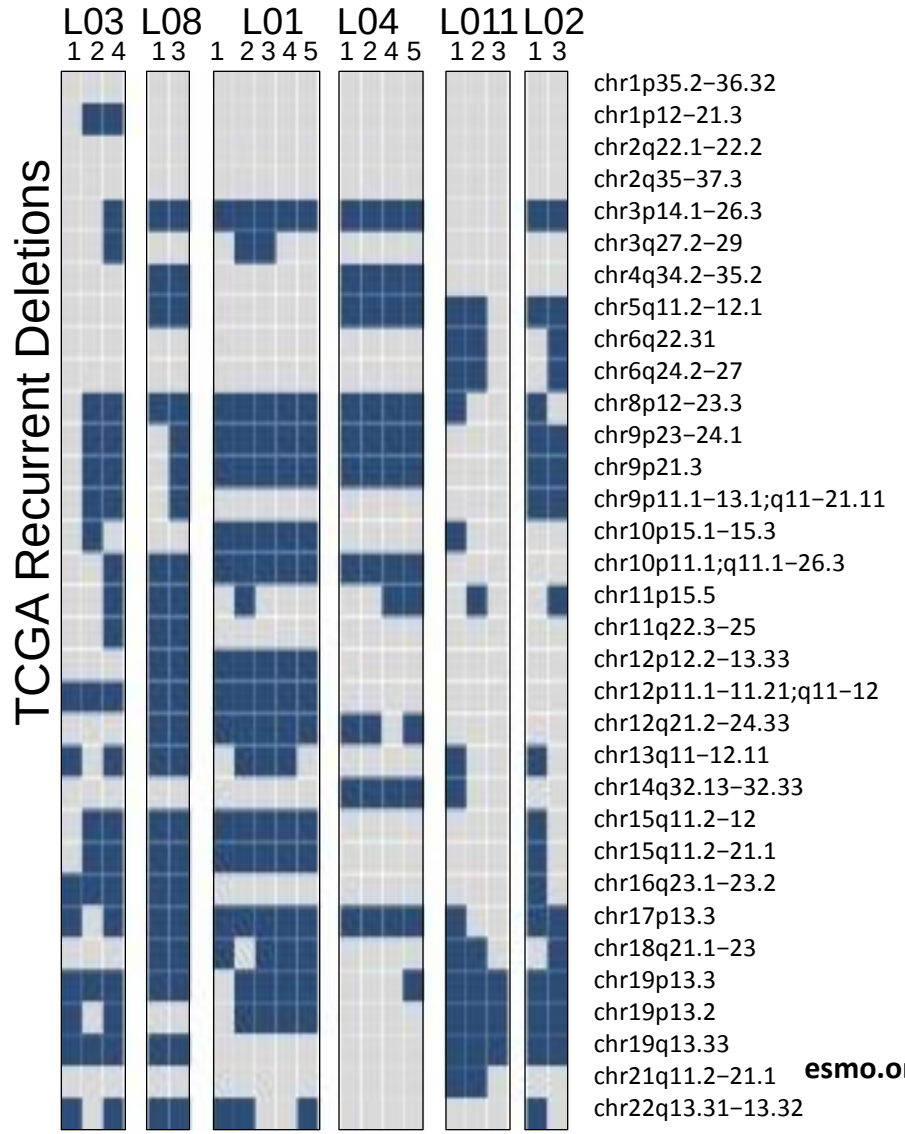
Spatial Heterogeneity of Recurrent Copy Number Alterations





Above mean ploidy
Below mean ploidy

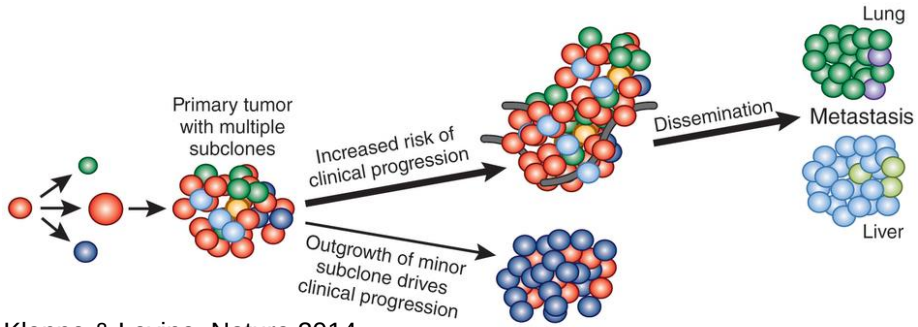
Clinical Implications of Intratumour Heterogeneity

- Sampling bias
  - May limit ability to predict therapeutic response
  - Biomarker validation
- Therapeutic resistance & failure
  - Selection of resistant subclones under selection pressures
  - NSCLC
    - T790M mutations & poor PFS
    - ALK mutations & drug resistance
- The challenge is to determine the relevance of intratumour heterogeneity
  - Clinical outcome
  - Response to specific therapies

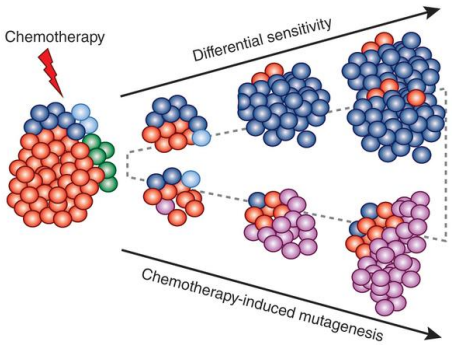
TRACERx

TRAcking non-small cell lung Cancer Evolution through therapy (Rx)

- UK-wide study of NSCLC from diagnosis to relapse in 850 patients
  - Patients eligible for curative resection
  - Track clonal evolution of tumours from diagnosis to relapse
  - Sample circulating biomarkers longitudinally
  - Establish the impact of intratumour heterogeneity on host immunity
  - Identify actionable mutations –> treatment stratification



Kleppe & Levine, Nature 2014



What is the role of clonal heterogeneity in cancer progression and clinical outcome?

Is clonal heterogeneity relevant to therapeutic response?

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Acknowledgements

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Rosetrees Trust
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CANCER RESEARCH UK
London Research Institute
The LRI will become part of the new Francis Crick Institute opening in 2015

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Cancer Research UK & UCL Cancer Trials Centre

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National Cancer Research Institute