Characterizing and forecasting tumour evolution

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Characterizing the mode of tumour evolution

Potential modes of tumour evolution

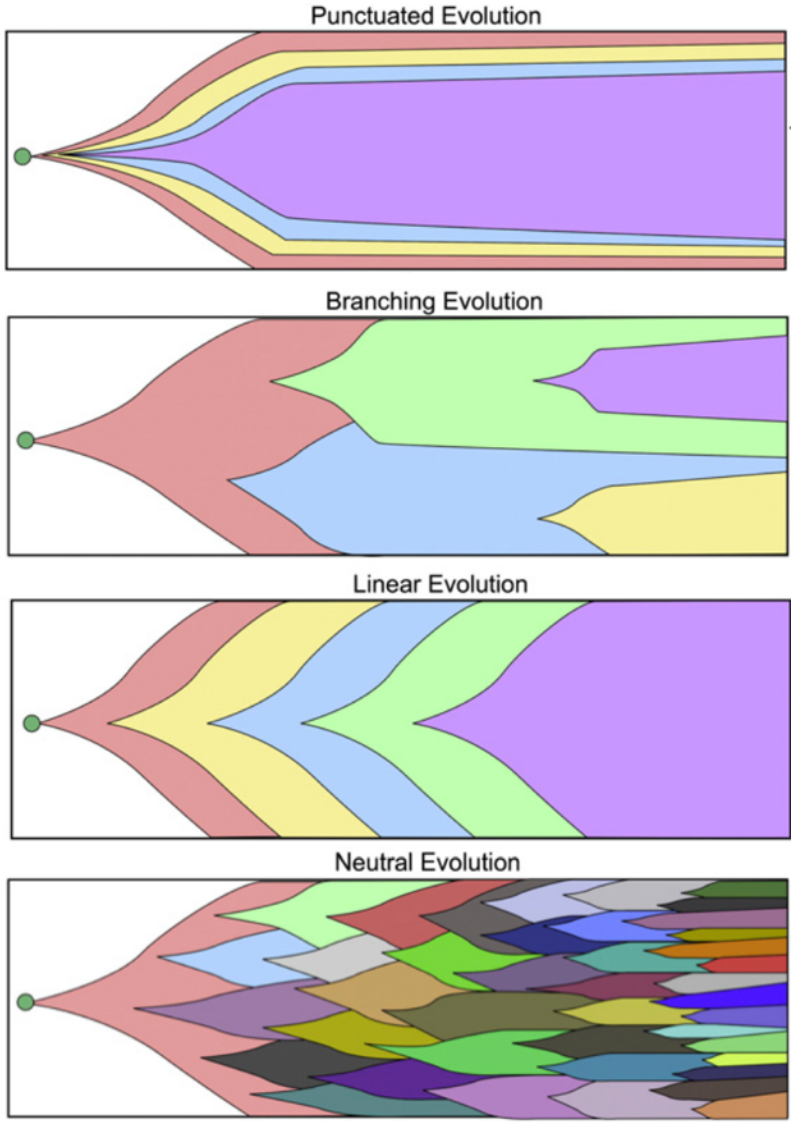


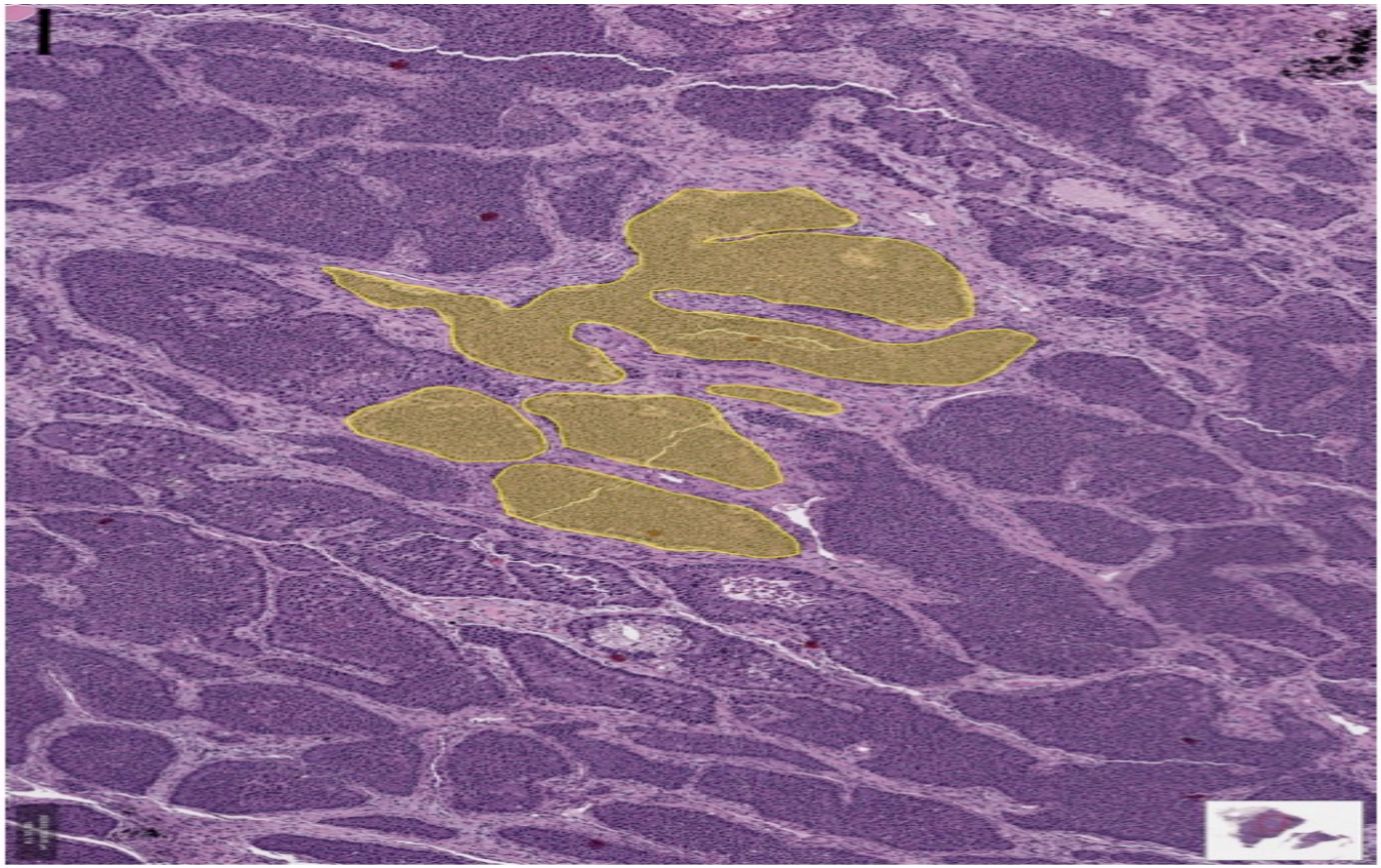
Figure adapted from Davis *et al. BBA Reviews on Cancer* (2017)

Modelling tumour evolution

- Stochastic, agent-based model
- Flexible spatial structure
- Either unconstrained growth or tissue invasion
- Evolution of cell division or dispersal rate
- Tracks all passenger mutations

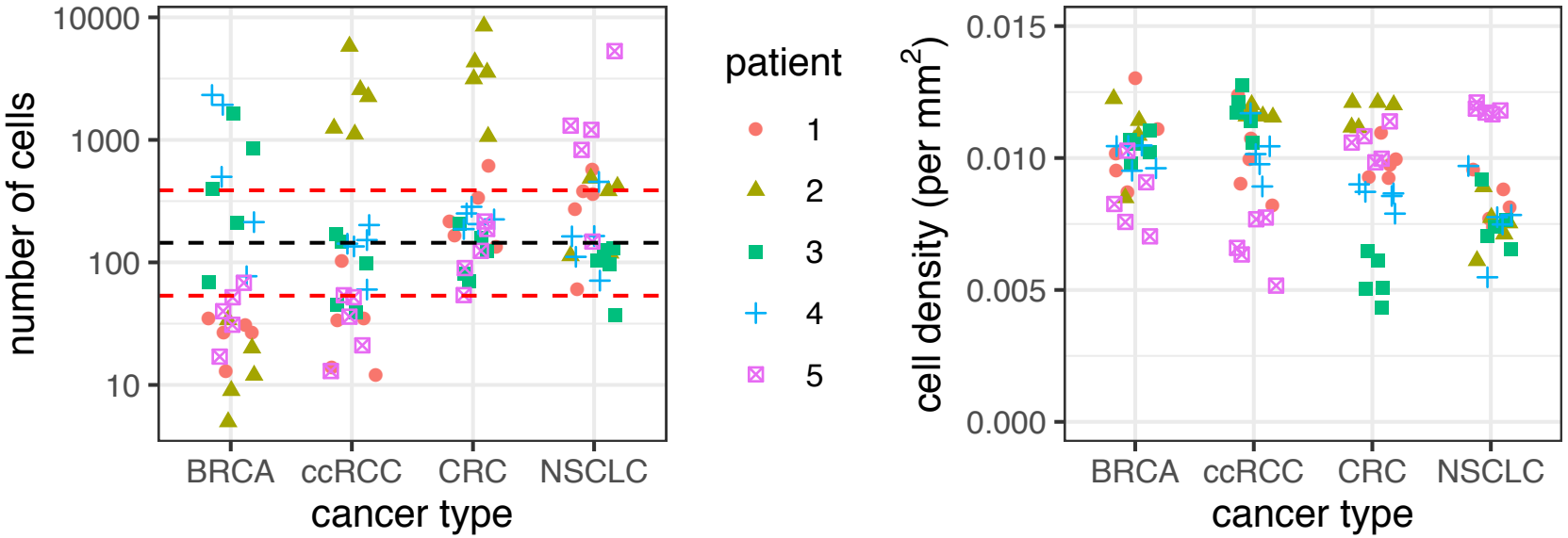
https://github.com/robjohnnoble/demon_model

Parametrization by histology image analysis



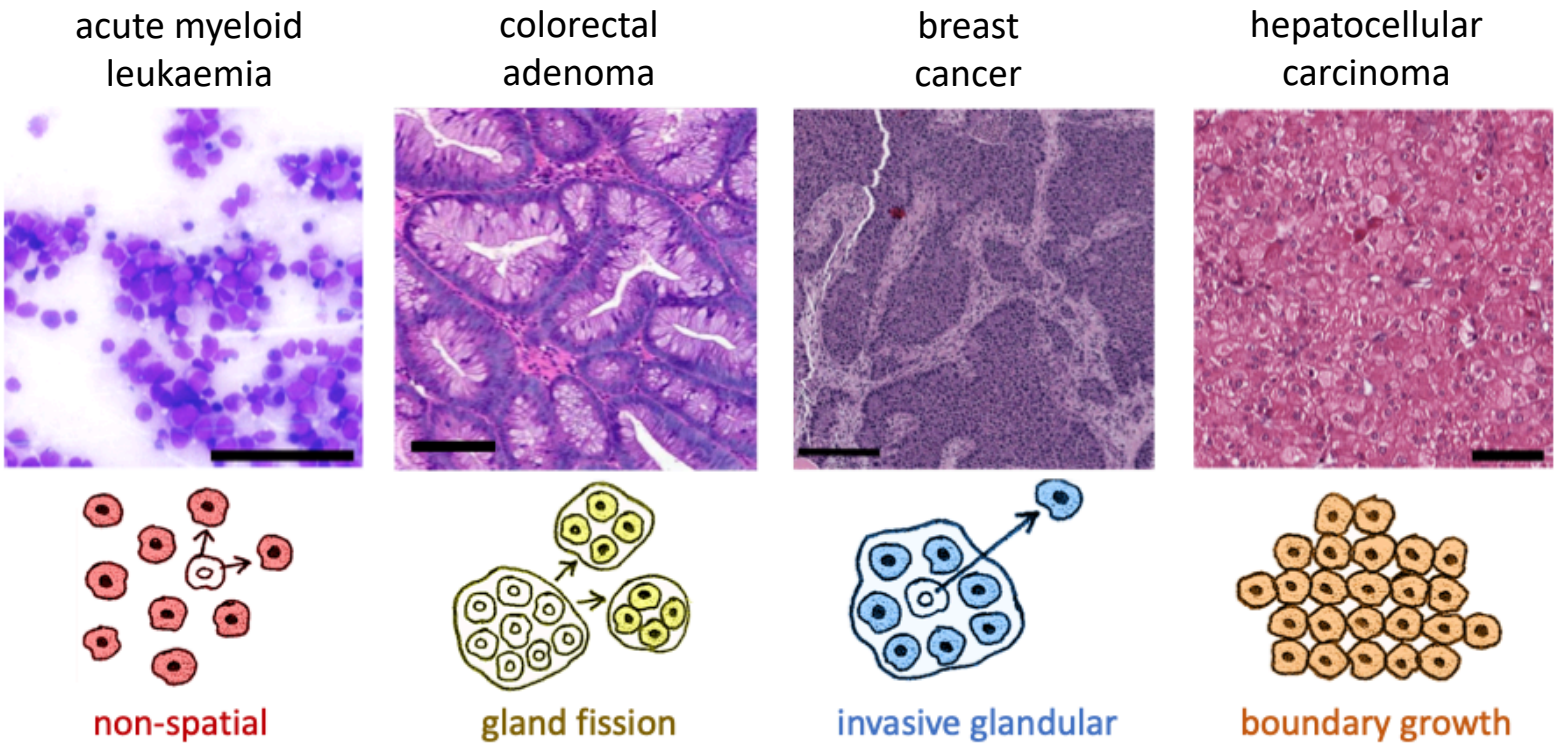
Jakob Kather
(University Hospital
RWTH Aachen)

Semi-automated image analysis of invasive glandular tumours



50% of cases between 53 and 387 cells

Four types of spatial structure



Model parameters

Fixed:

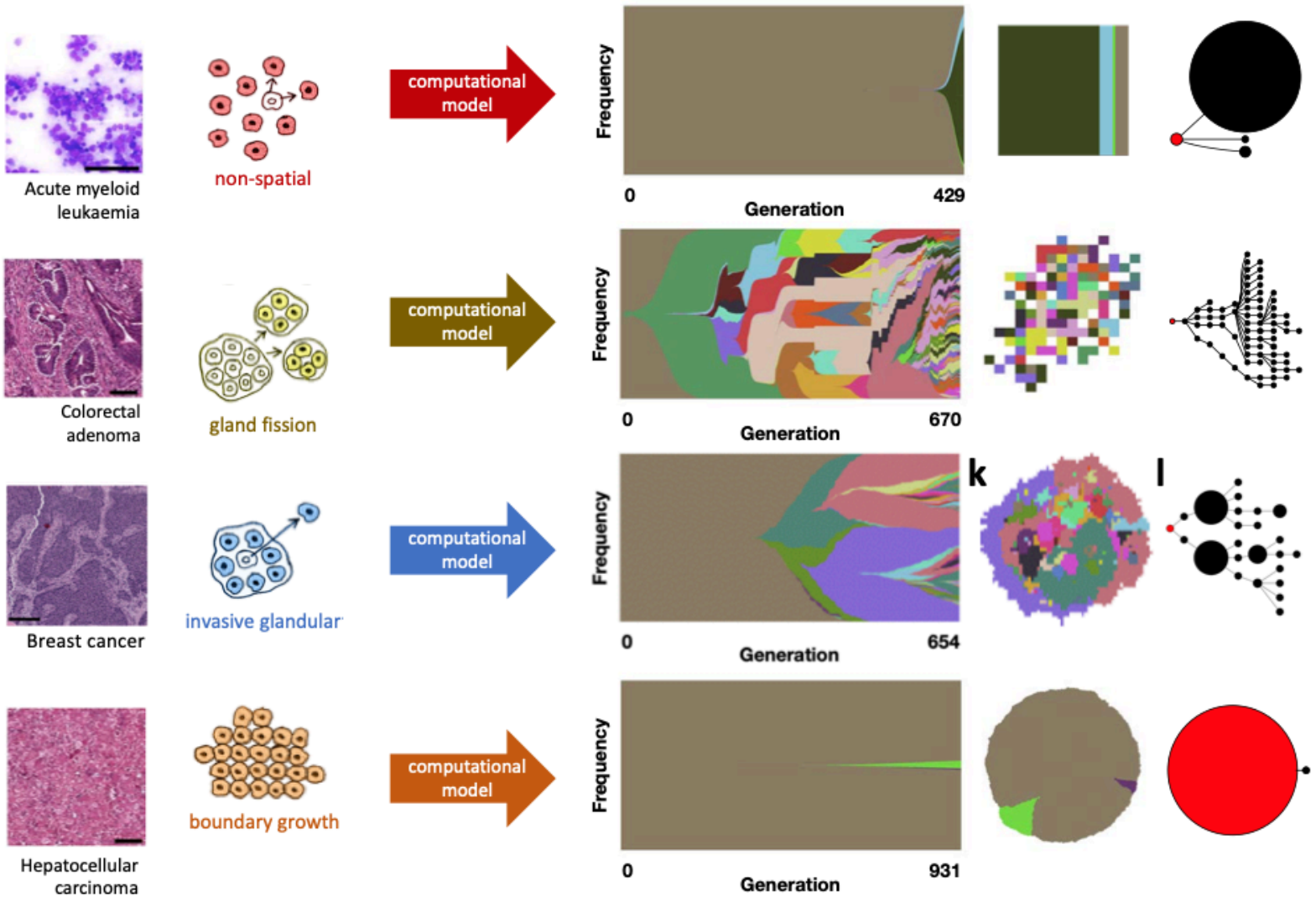
- Driver mutation rate (10^{-5} per division)
- Multiplicative driver fitness effect (mean 0.1)

Varied:

- Dispersal process (migration or deme fission)
- Deme carrying capacity

Dispersal rate adjusted for similar growth times

Four oncoevotypes

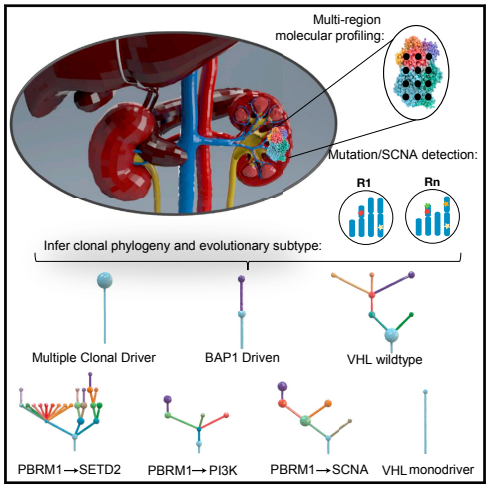


Plotting package: https://CRAN.R-project.org/package=ggmuller

Comparing to data

Deterministic Evolutionary Trajectories Influence Primary Tumor Growth: TRACERx Renal

Graphical Abstract



Authors

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In Brief

A multi-center prospective study on 101 patients with clear-cell renal cell carcinoma resolves the evolutionary features and subtypes underpinning the diverse clinical phenotypes of the disease and suggests these features as potential biomarkers for guiding intervention and surveillance.

Tracking the Evolution of Non–Small-Cell Lung Cancer

M. Jamal-Hanjani, G.A. Wilson, N. McGranahan, N.J. Birkbak, T.B.K. Watkins, S. Veeriah, S. Shafi, D.H. Johnson, R. Mitter, R. Rosenthal, M. Salm, S. Horswell, M. Escudero, N. Matthews, A. Rowan, T. Chambers, D.A. Moore, S. Turajlic, H. Xu, S.-M. Lee, M.D. Forster, T. Ahmad, C.T. Hiley, C. Abbosh, M. Falzon, E. Borg, T. Marafioti, D. Lawrence, M. Hayward, S. Kolvekar, N. Panagiotopoulos, S.M. Janes, R. Thakrar, A. Ahmed, F. Blackhall, Y. Summers, R. Shah, L. Joseph, A.M. Quinn, P.A. Crosbie, B. Naidu, G. Middleton, G. Langman, S. Trotter, M. Nicolson, H. Remmen, K. Kerr, M. Chetty, L. Gomersall, D.A. Fennell, A. Nakas, S. Rathinam, G. Anand, S. Khan, P. Russell, V. Ezhil, B. Ismail, M. Irvin-Sellers, V. Prakash, J.F. Lester, M. Kornaszewska, R. Attanoos, H. Adams, H. Davies, S. Dentro, P. Taniere, B. O'Sullivan, H.L. Lowe, J.A. Hartley, N. Iles, H. Bell, Y. Ngai, J.A. Shaw, J. Herrero, Z. Szallasi, R.F. Schwarz, A. Stewart, S.A. Quezada, J. Le Quesne, P. Van Loo, C. Dive, A. Hackshaw, and C. Swanton, for the TRACERx Consortium*

ABSTRACT

BACKGROUND

Among patients with non–small-cell lung cancer (NSCLC), data on intratumor heterogeneity and cancer genome evolution have been limited to small retrospective cohorts. We wanted to prospectively investigate intratumor heterogeneity in relation to clinical outcome and to determine the clonal nature of driver events and evolutionary processes in early-stage NSCLC.

Subclonal diversification of primary breast cancer revealed by multiregion sequencing

Lucy R Yates[1,2], Moritz Gerstung[1], Stian Knappskog[3,4], Christine Desmedt[5], Gunes Gundem[1], Peter Van Loo[1,6], Turid Aas[7], Ludmil B Alexandrov[1,8], Denis Larsimont[5], Helen Davies[1], Yilong Li[1], Young Seok Ju[1], Manasa Ramakrishna[1], Hans Kristian Haugland[9], Peer Kaare Lilleng[9,10], Serena Nik-Zainal[1], Stuart McLaren[1], Adam Butler[1], Sancha Martin[1], Dominic Glodzik[1], Andrew Menzies[1], Keiran Raine[1], Jonathan Hinton[1], David Jones[1], Laura J Mudie[1], Bing Jiang[11], Delphine Vincent[5], April Greene-Colozzi[11], Pierre-Yves Adnet[5], Aquila Fatima[11], Marion Maetens[5], Michail Ignatiadis[5], Michael R Stratton[1], Christos Sotiriou[5], Andrea L Richardson[11,12], Per Eystein Lønning[3,4], David C Wedge[1] & Peter J Campbell[1]

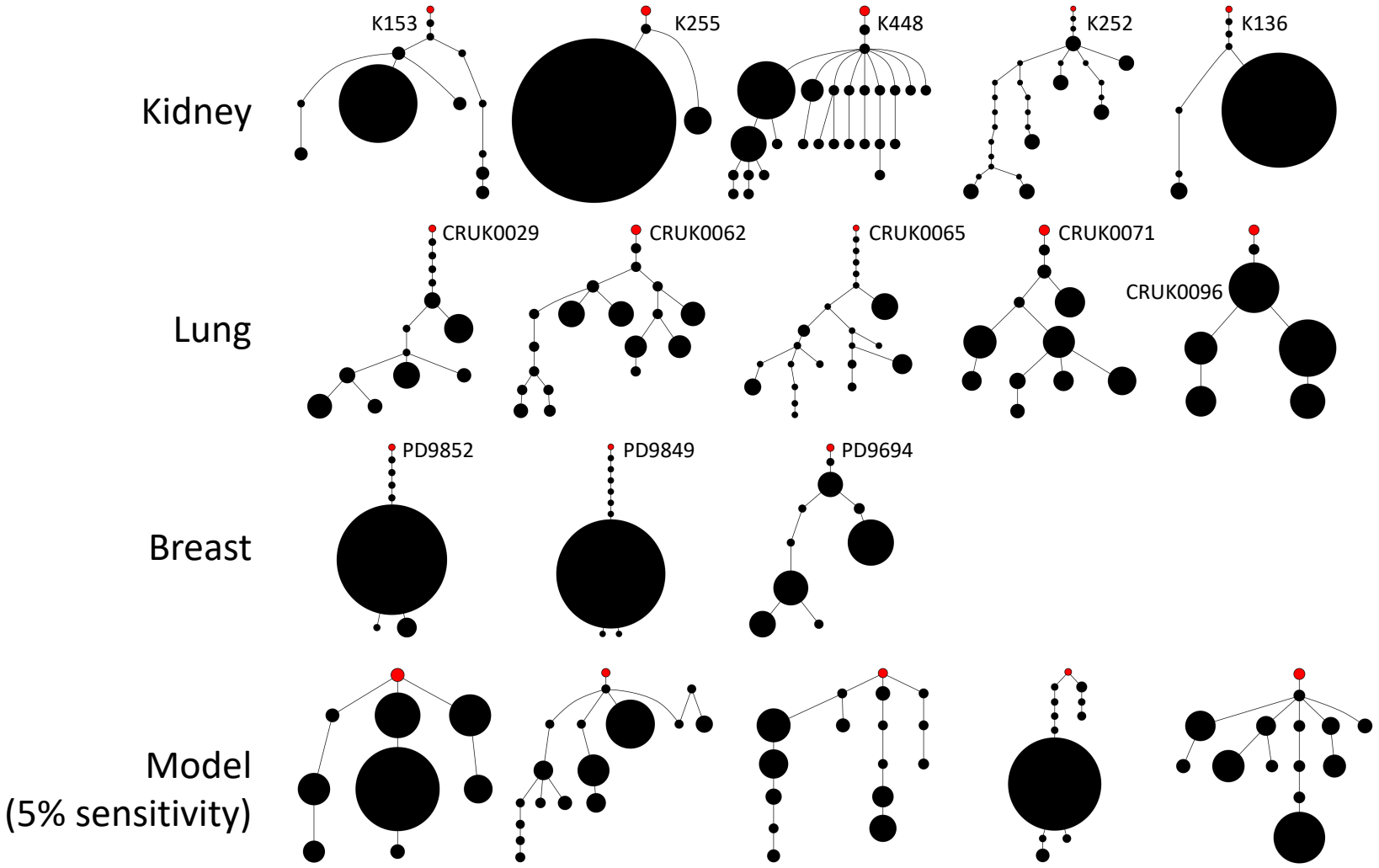
The sequencing of cancer genomes may enable tailoring of therapeutics to the underlying biological abnormalities driving a particular patient's tumor. However, sequencing-based strategies rely heavily on representative sampling of tumors. To understand the subclonal structure of primary breast cancer, we applied whole-genome and targeted sequencing to multiple samples from each of 50 patients' tumors (303 samples in total). The extent of subclonal diversification varied among cases and followed spatial patterns. No strict temporal order was evident, with point mutations and rearrangements affecting the most common breast cancer genes, including *PIK3CA*, *TP53*, *PTEN*, *BRCA2* and *MYC*, occurring early in some tumors and late in others. In 13 out of 50 cancers, potentially targetable mutations were subclonal. Landmarks of disease progression, such as resistance to chemotherapy and the acquisition of invasive or metastatic potential, arose within detectable subclones of antecedent lesions. These findings highlight the importance of including analyses of subclonal structure and tumor evolution in clinical trials of primary breast cancer.

Clonal Evolution of Acute Myeloid Leukemia Revealed by High-Throughput Single-Cell Genomics

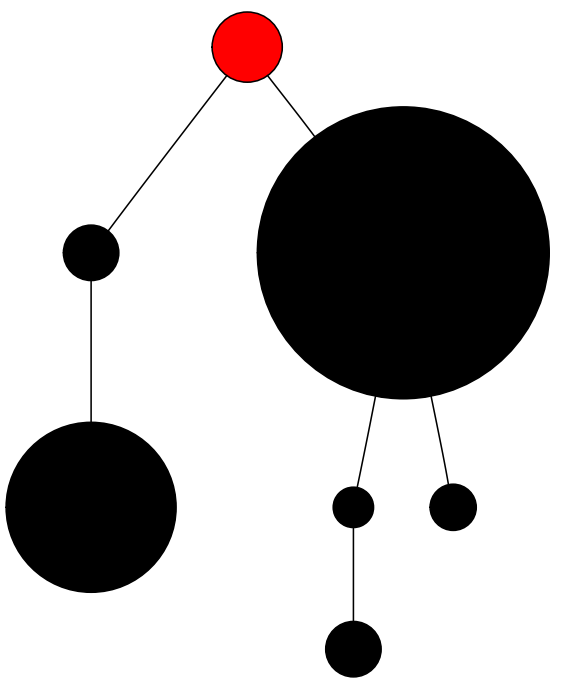
Kiyomi Morita, Feng Wang, Katharina Jahn, Jack Kuipers, Yuanqing Yan, Jairo Matthews, Latasha Little, Curtis Gumbs, Shujuan Chen, Jianhua Zhang, Xingzhi Song, Erika Thompson, Keyur Patel, Carlos Bueso-Ramos, Courtney D DiNardo, Farhad Ravandi, Elias Jabbour, Michael Andreeff, Jorge Cortes, Marina Konopleva, Kapil Bhalla, Guillermo Garcia-Manero, Hagop Kantarjian, Niko Beerenwinkel, Nicholas Navin, P Andrew Futreal, Koichi Takahashi

doi: https://doi.org/10.1101/2020.02.07.925743

Driver phylogenetic trees



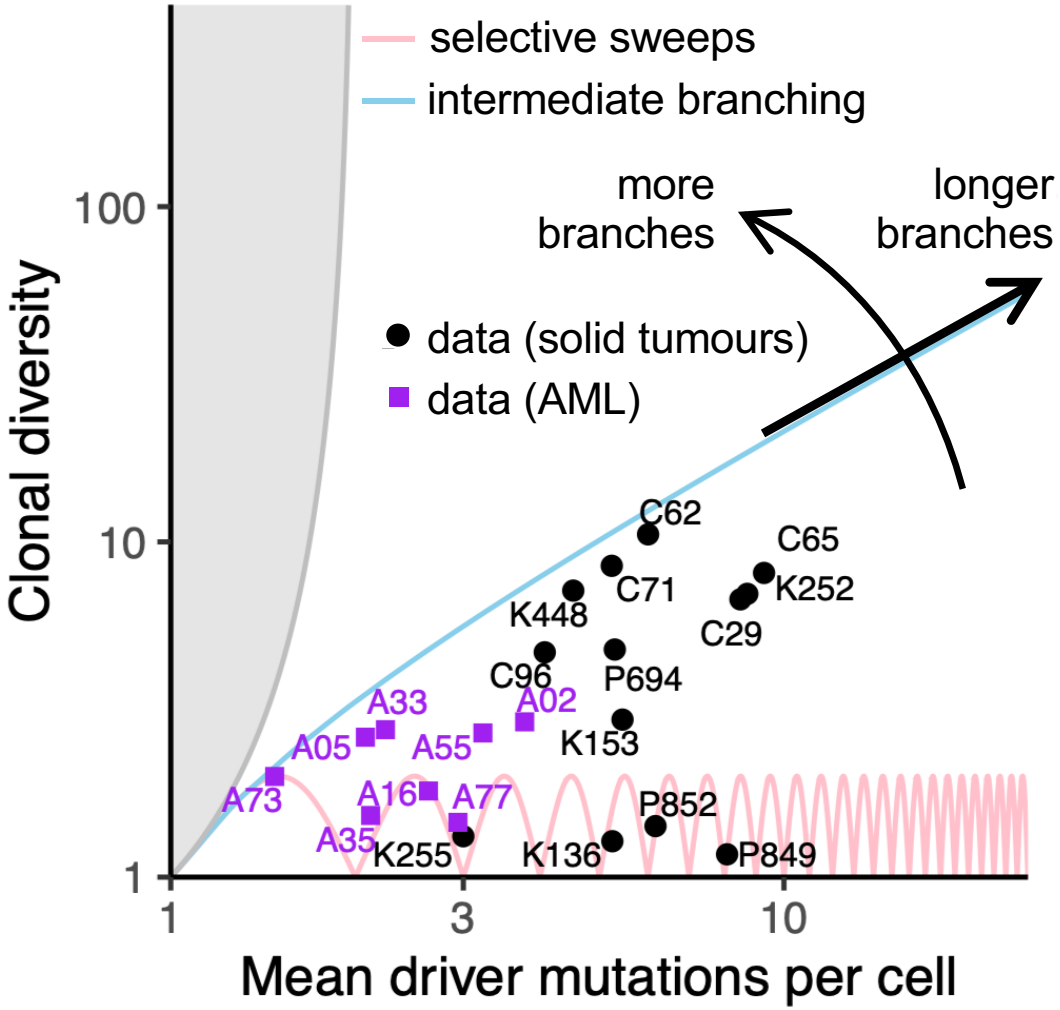
Summary evolutionary indices



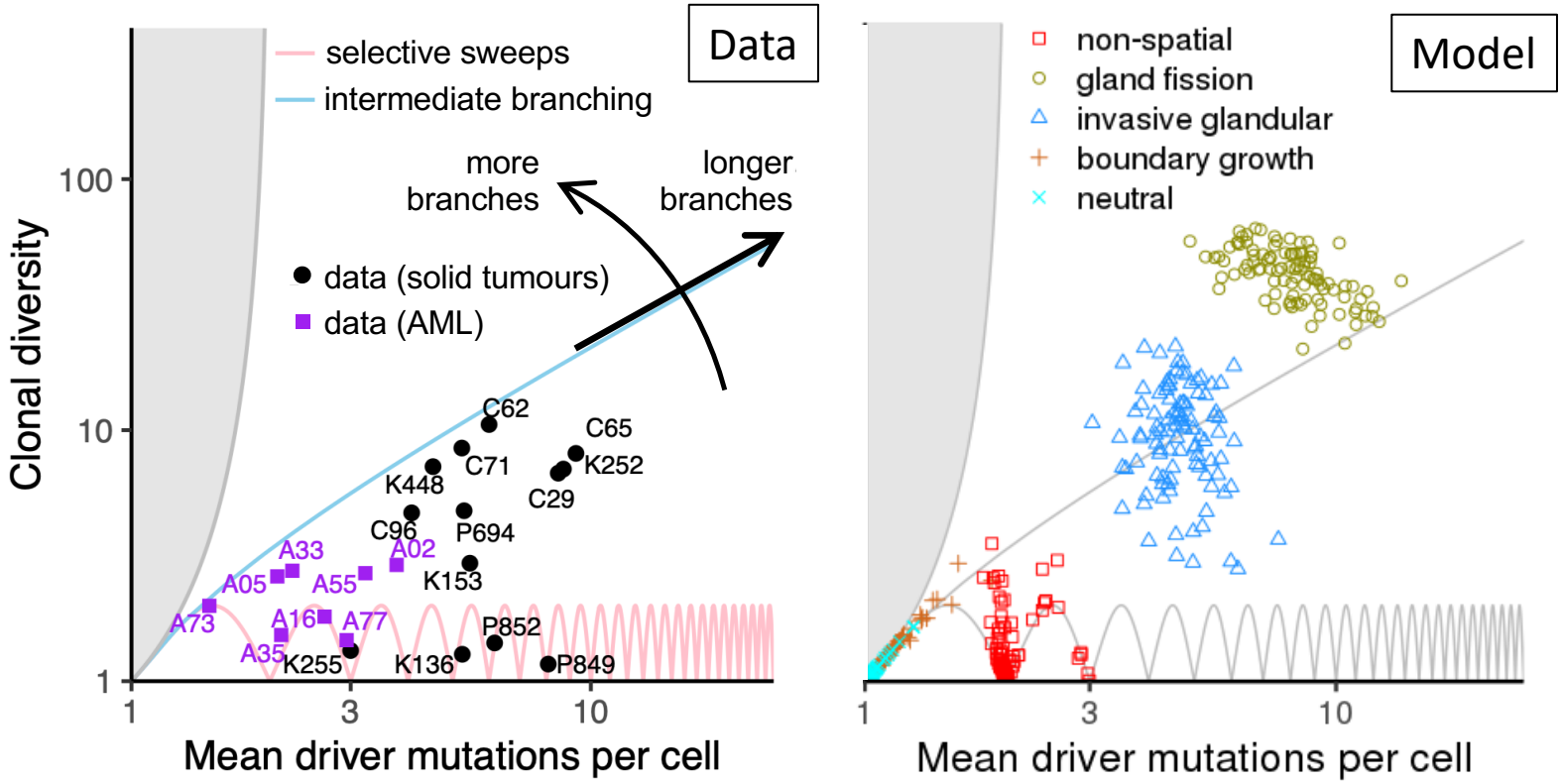
n = mean drivers per cell

D = diversity of driver combinations (inverse Simpson index)

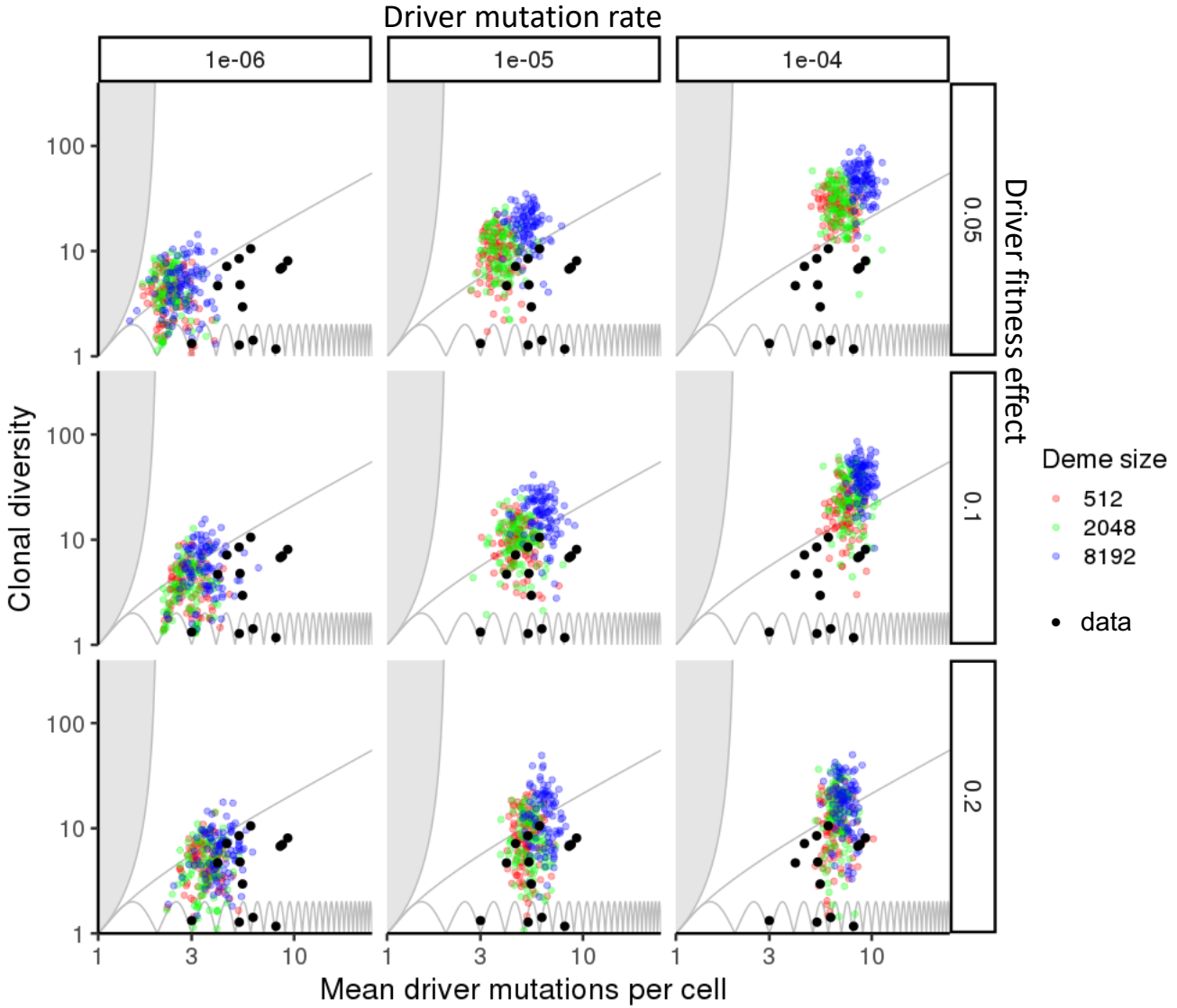
Defining oncoevotypes



Spatial structure governs oncoevotype



Invasive glandular model versus data



Multi-region bulk sequencing fails to detect rare subclonal drivers

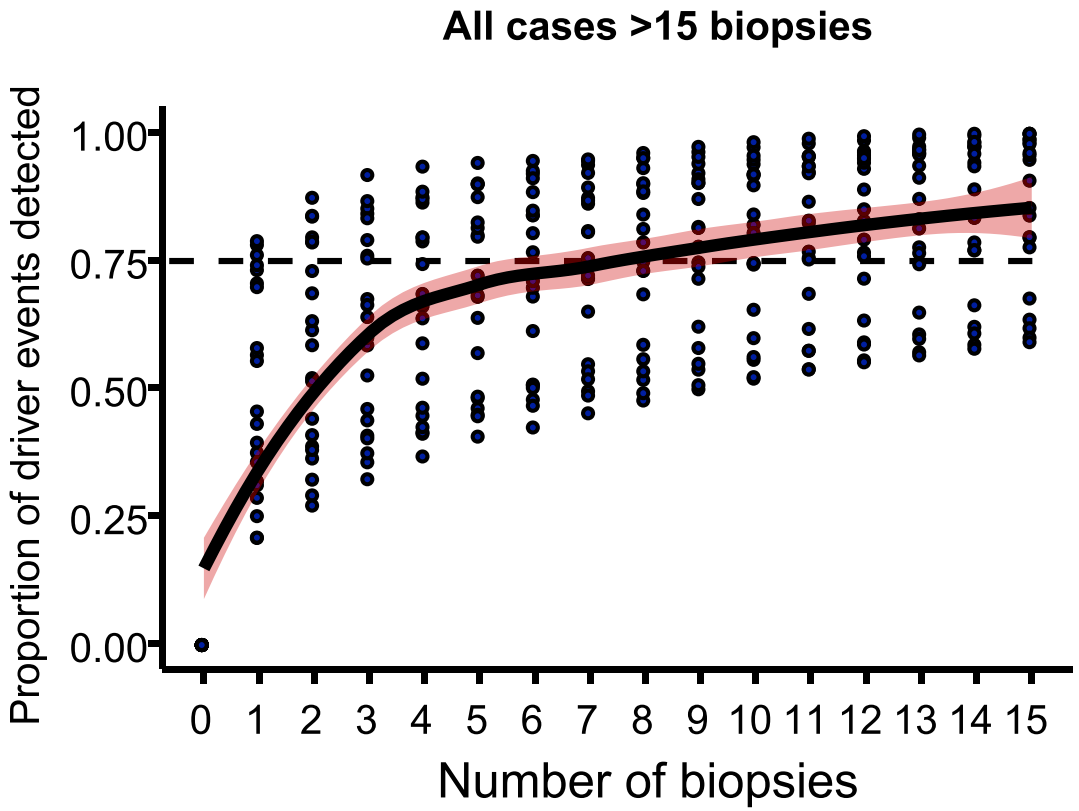
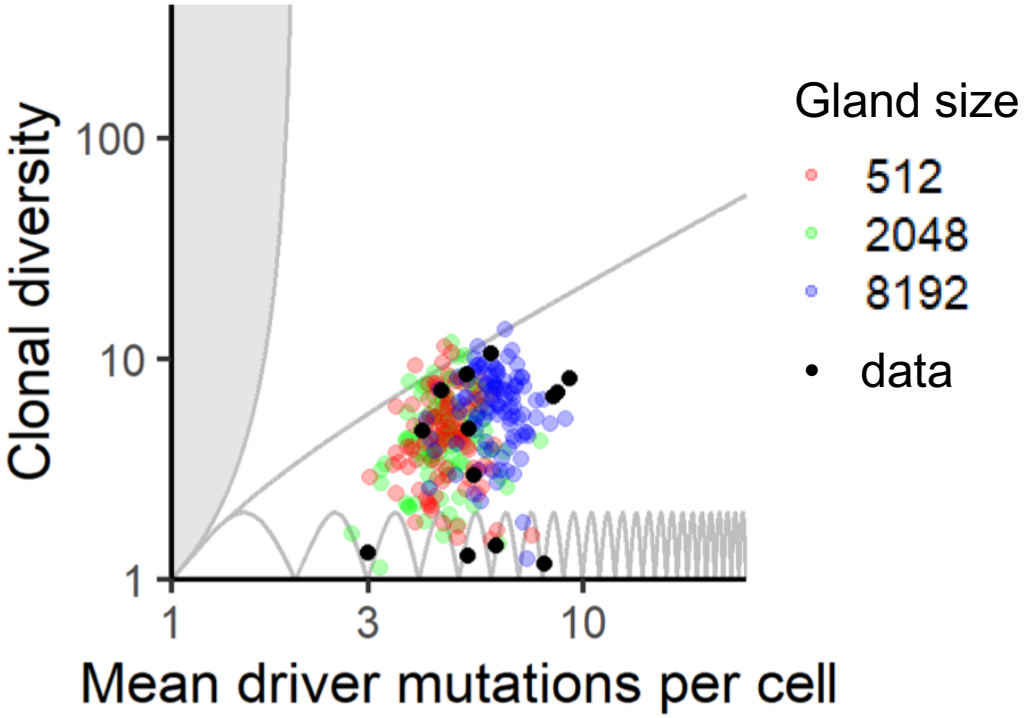
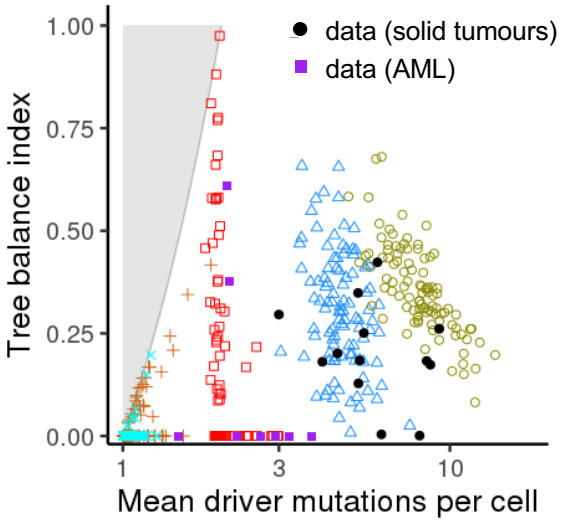


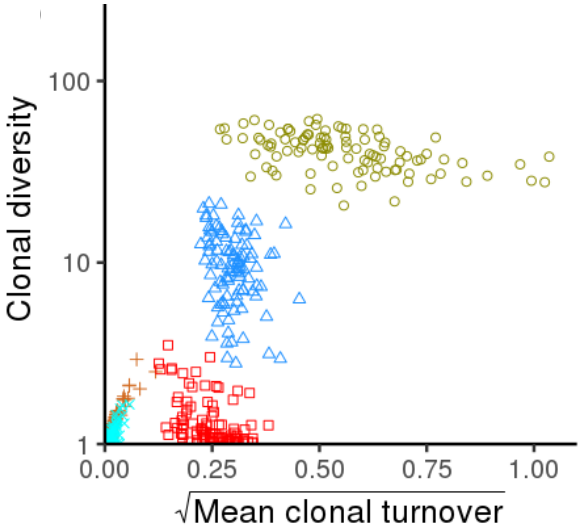
Figure adapted from Turajlic *et al. Cell* (2018)

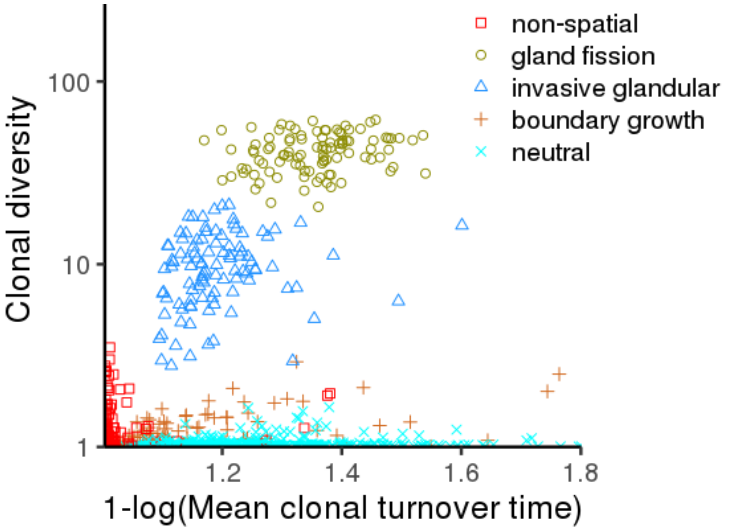
Invasive glandular model (5% sensitivity) versus data



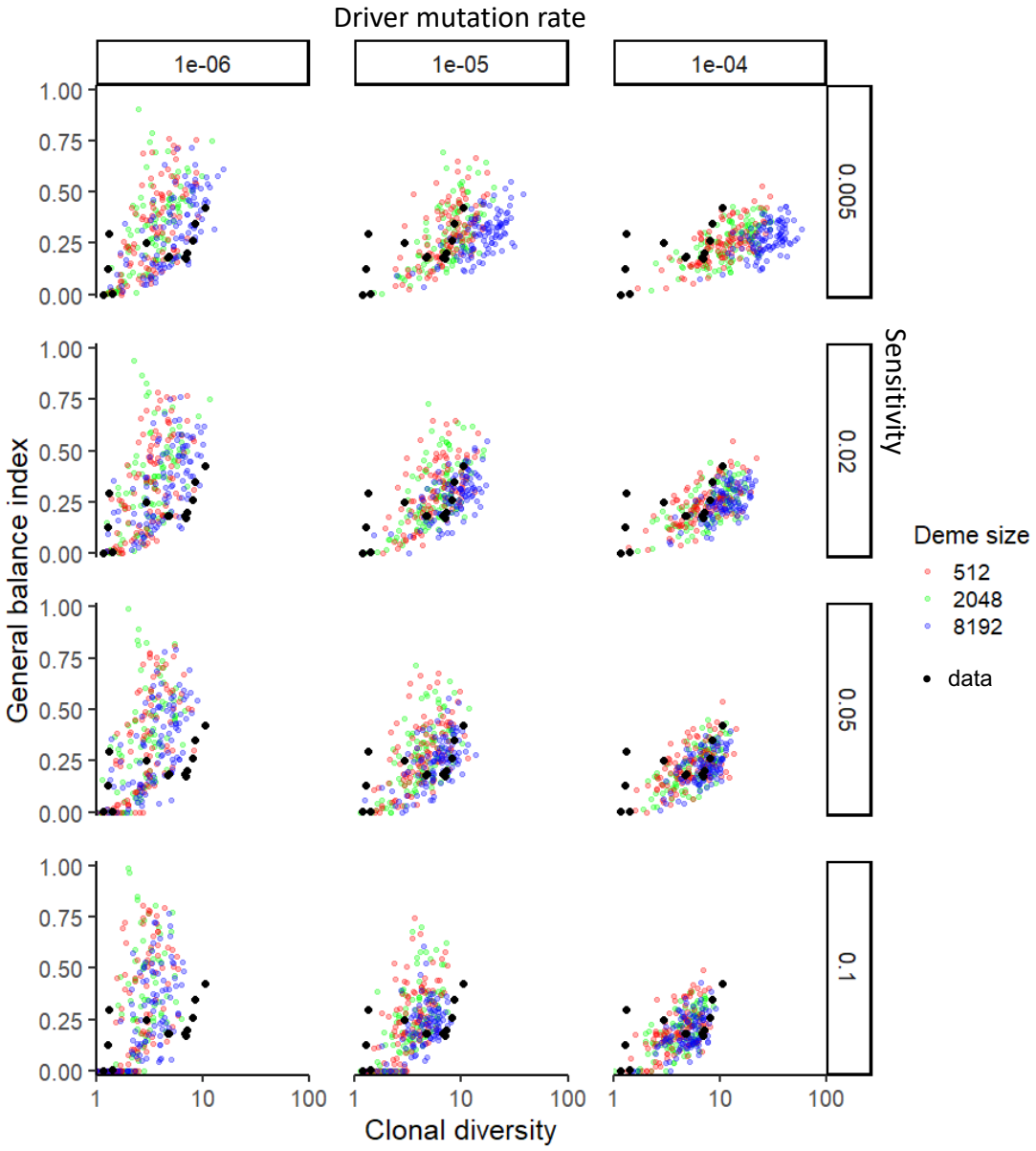
Alternative evolutionary indices







Invasive glandular model versus data



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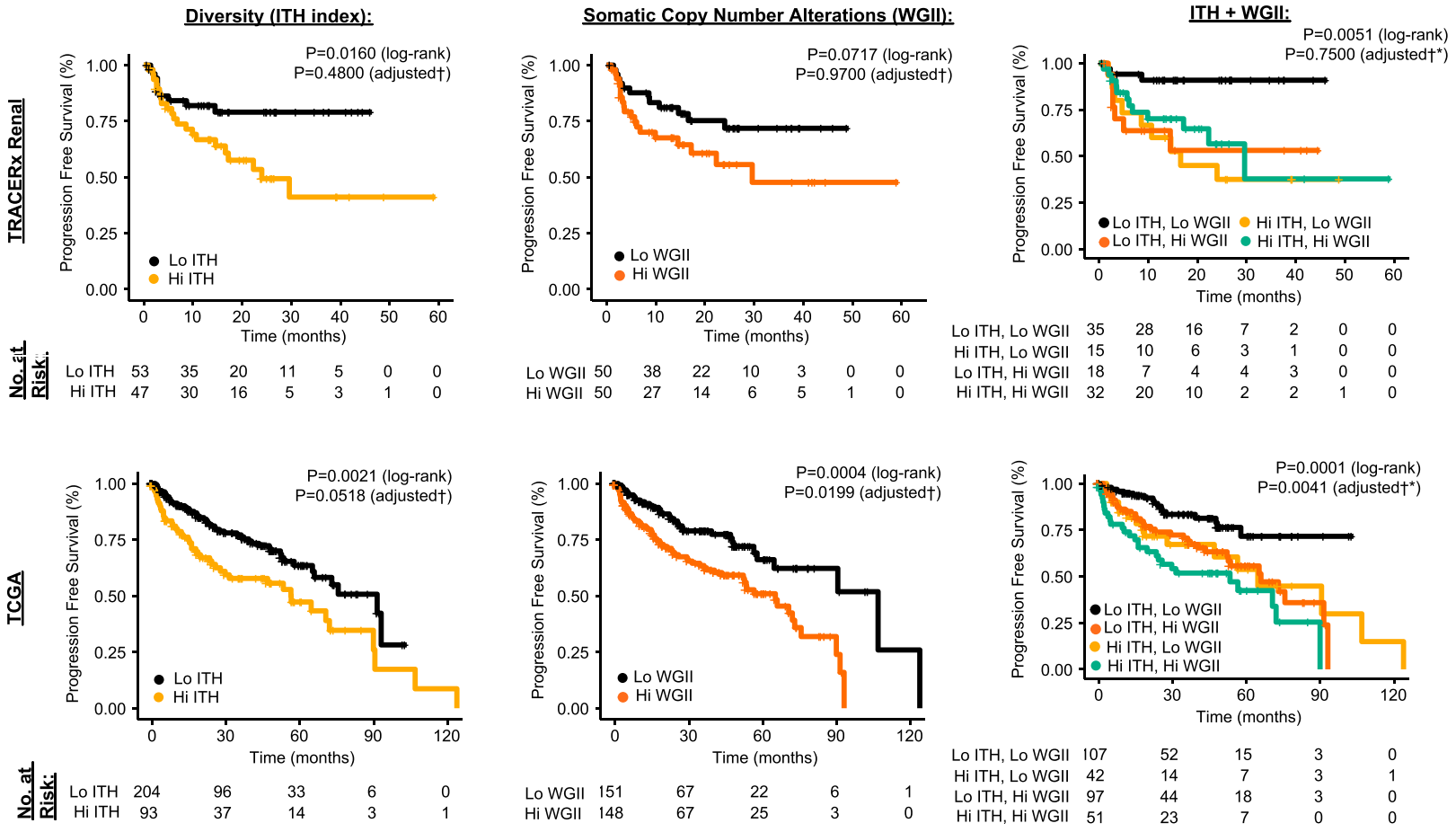
Forecasting tumour evolution

TRACERx Renal: Using ITH and GI to predict survival

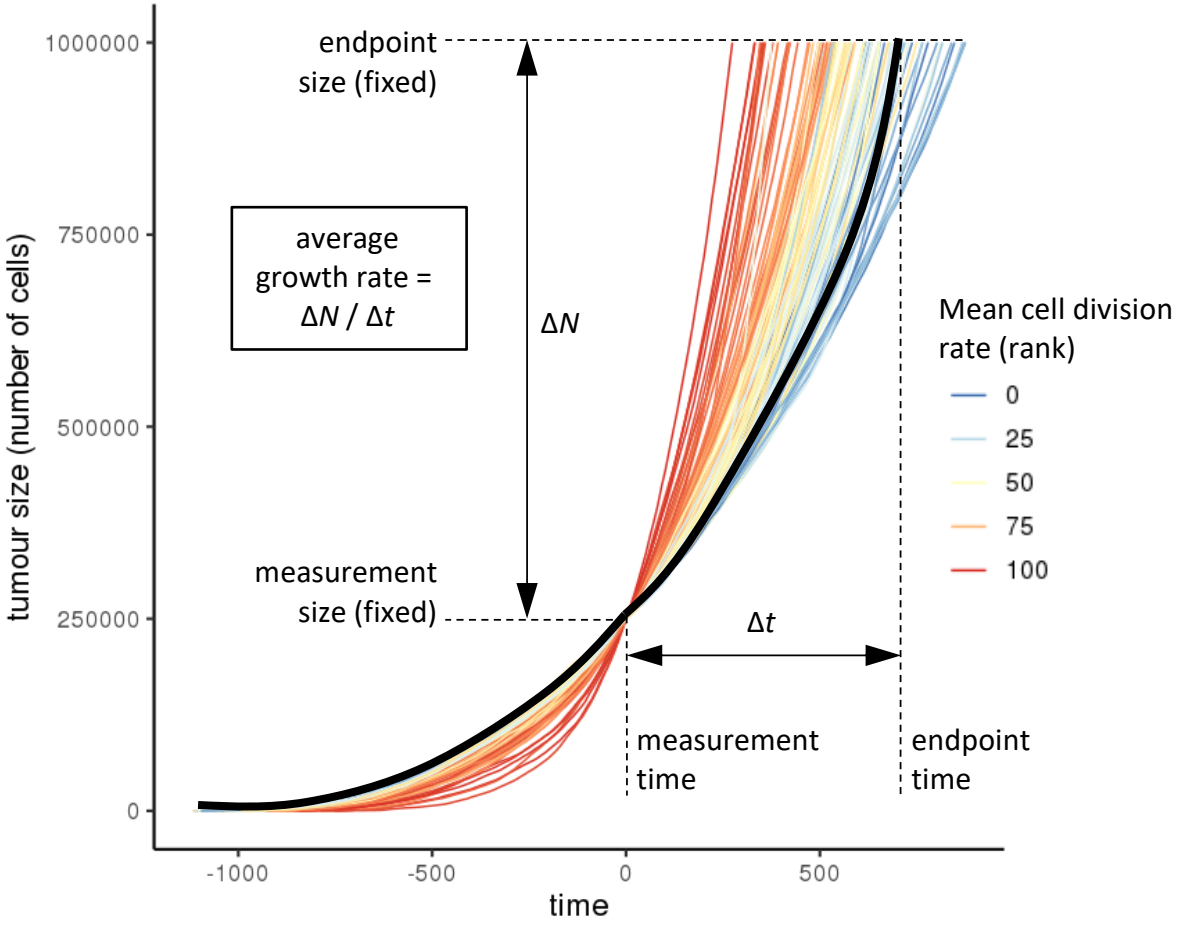


† All adjusted values are derived using a Cox proportional hazard model, including stage + grade as covariates

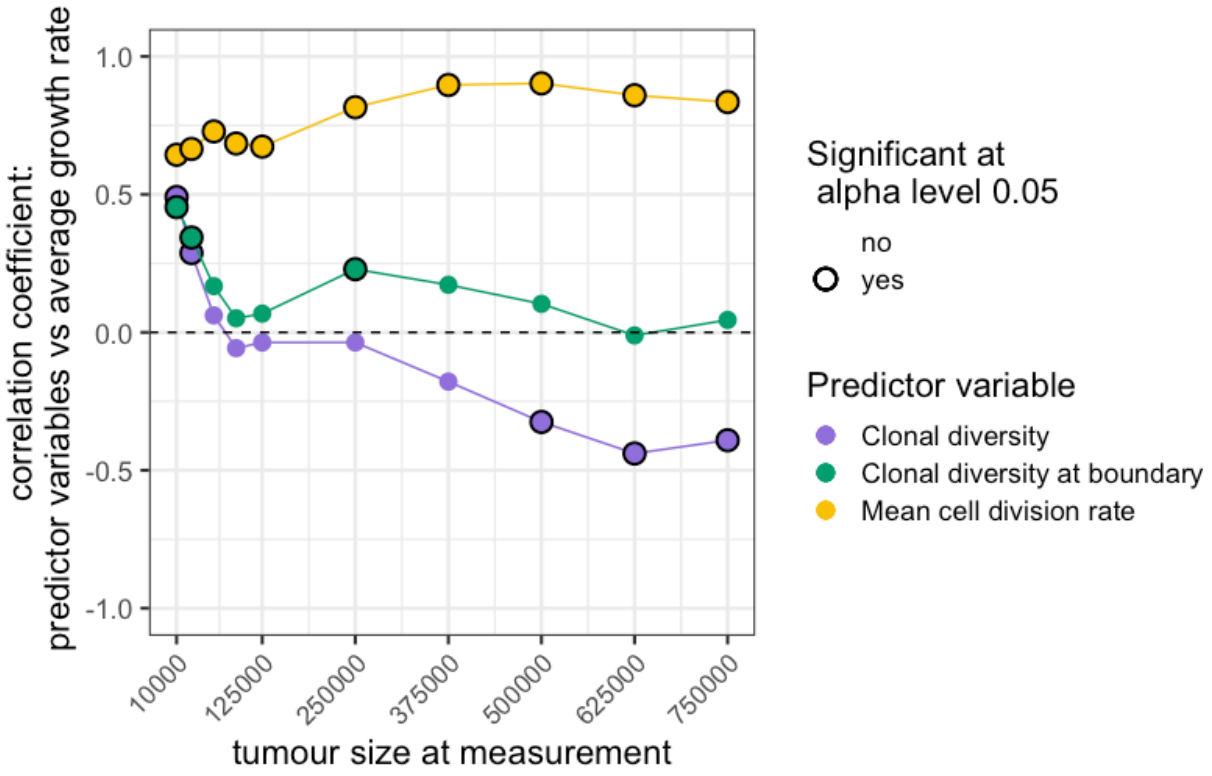
* P value for "Hi ITH, Hi WGII" vs "Lo ITH, Lo WGII" (the most significantly different groups for PFS in adjusted analysis)

Figure adapted from Turajlic *et al. Cell* (2018)

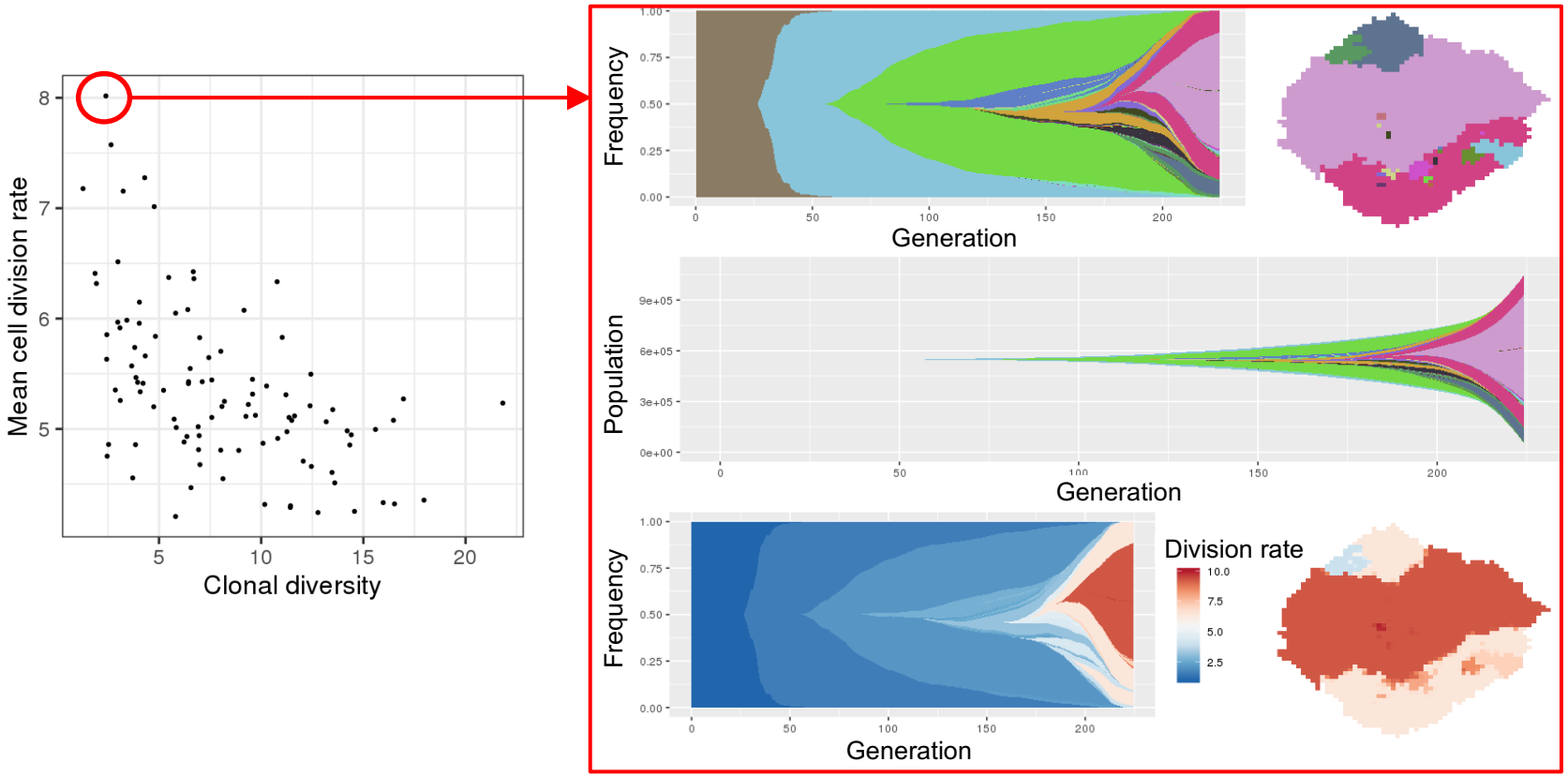
Clonal diversity as a predictor of future tumour growth rate



Clonal diversity as a predictor in cohorts with identical parameter values: UNRELIABLE



Higher diversity can correlate with slower tumour growth



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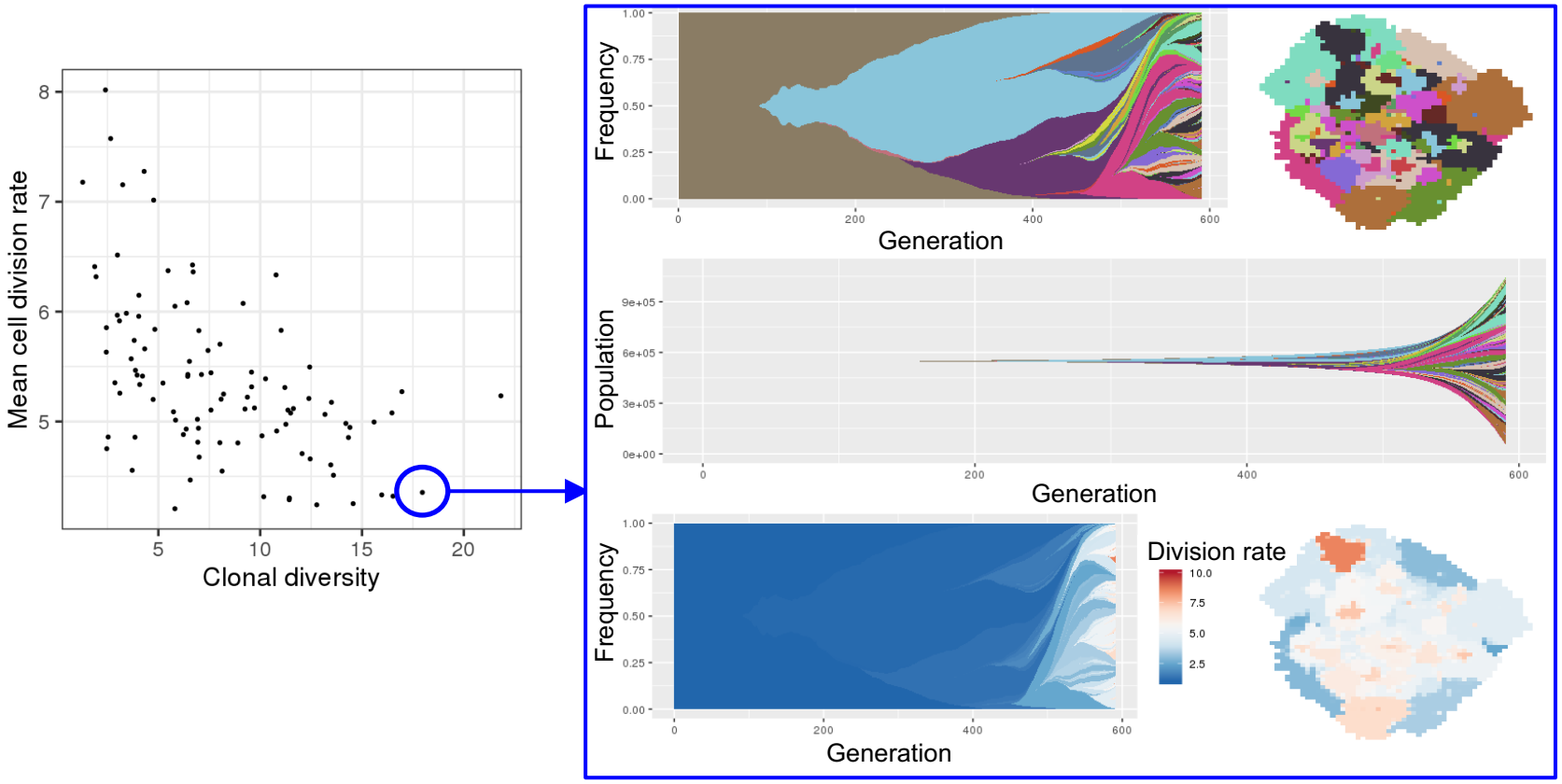

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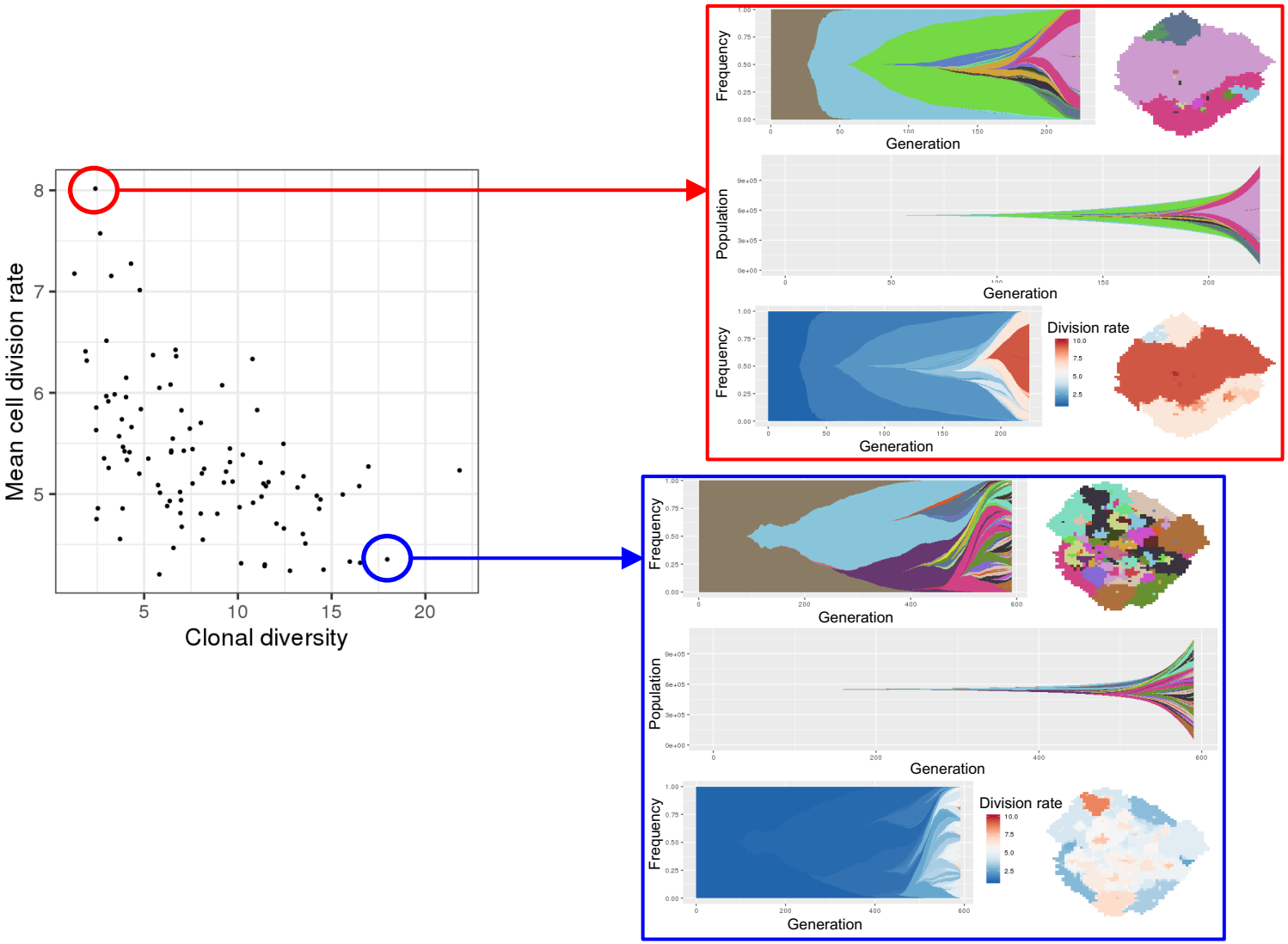

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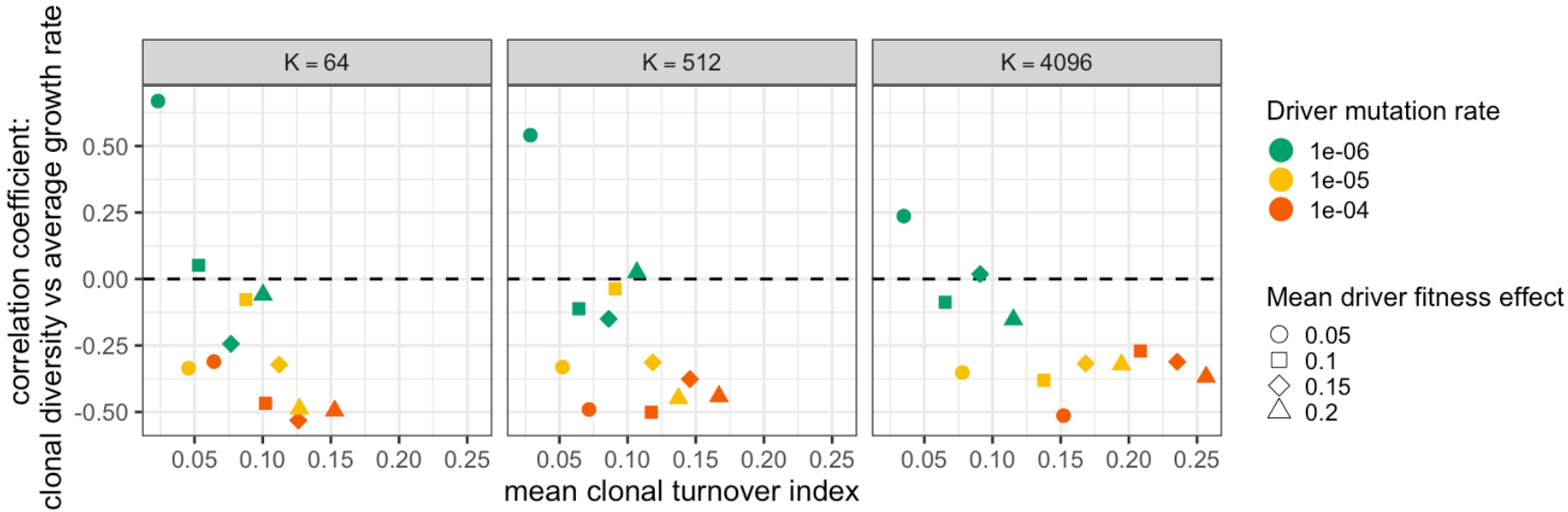
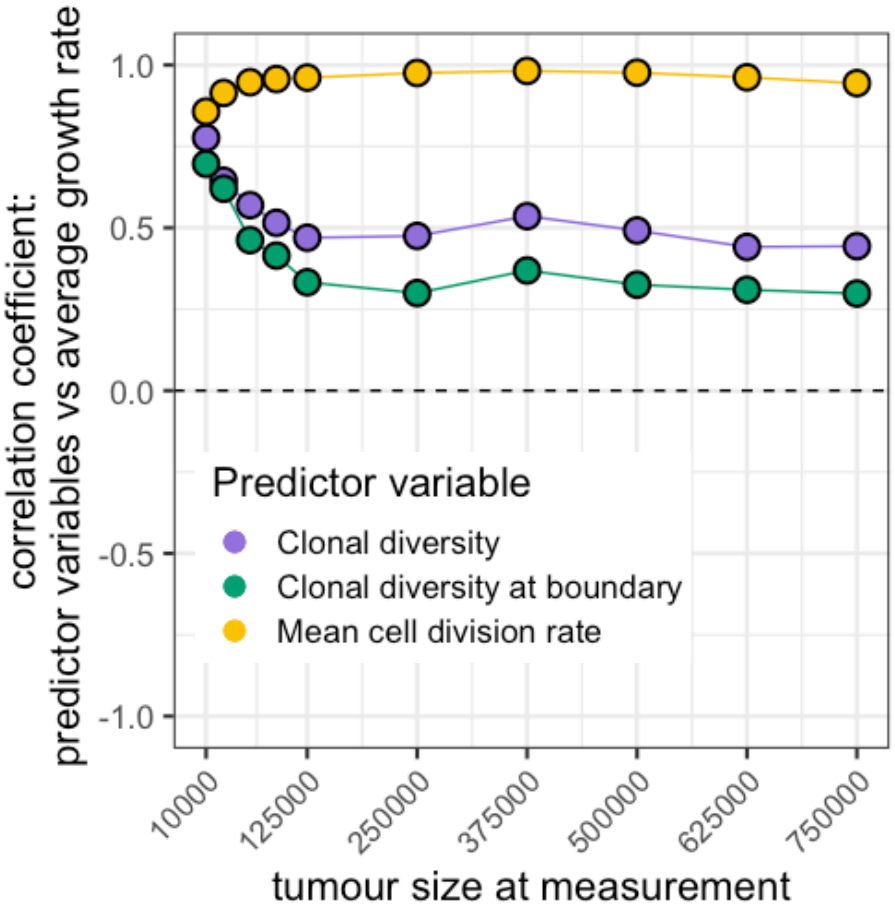


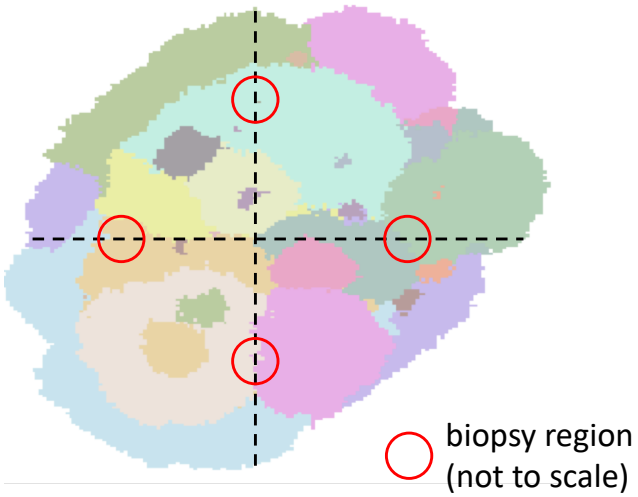
Accounting for biological variation

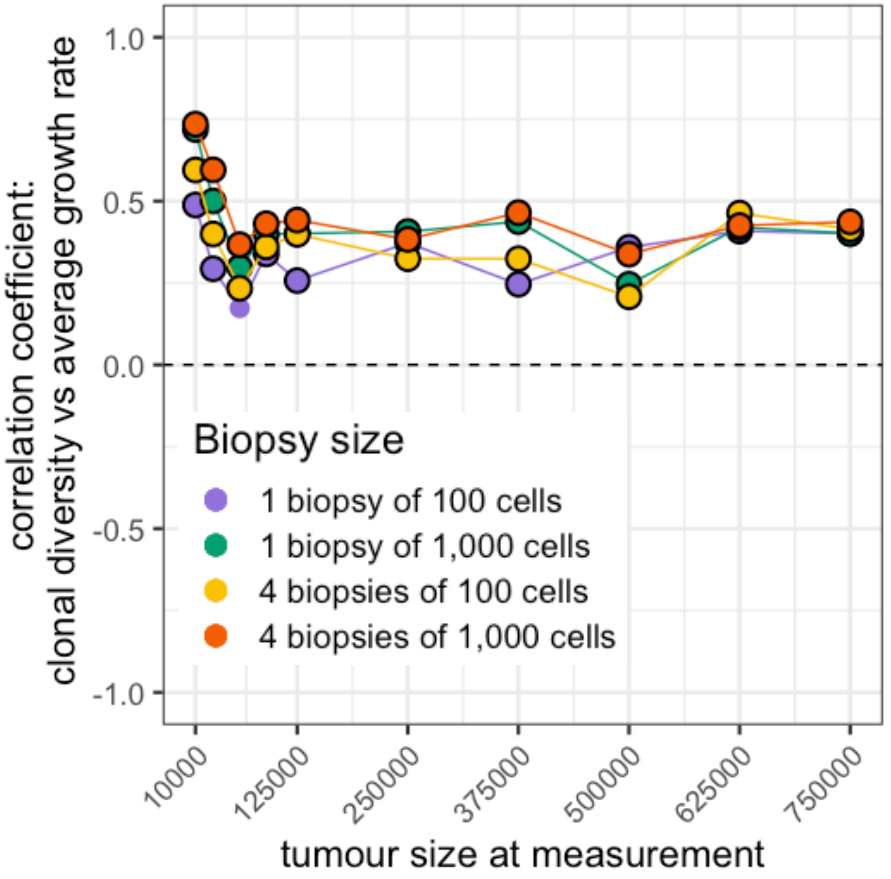
- In reality, even tumours of the same size and type vary in biological parameters because of intrinsic and microenvironmental factors
- Genomic instability and mutation burden are especially variable within cancer types
- Therefore simulate cohorts of tumours with differing driver mutation rates

Clonal diversity as a predictor in cohorts with diverse mutation rates: RELIABLE

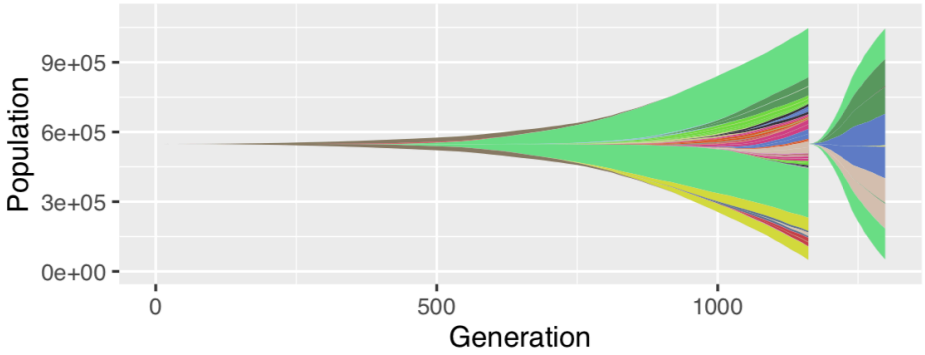


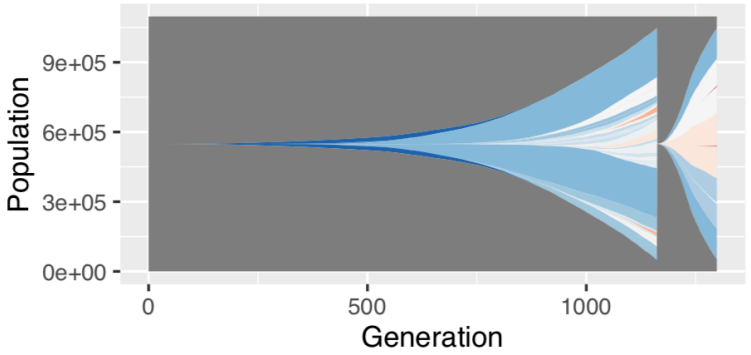
The predictive value of clonal diversity is robust to biopsy sampling error

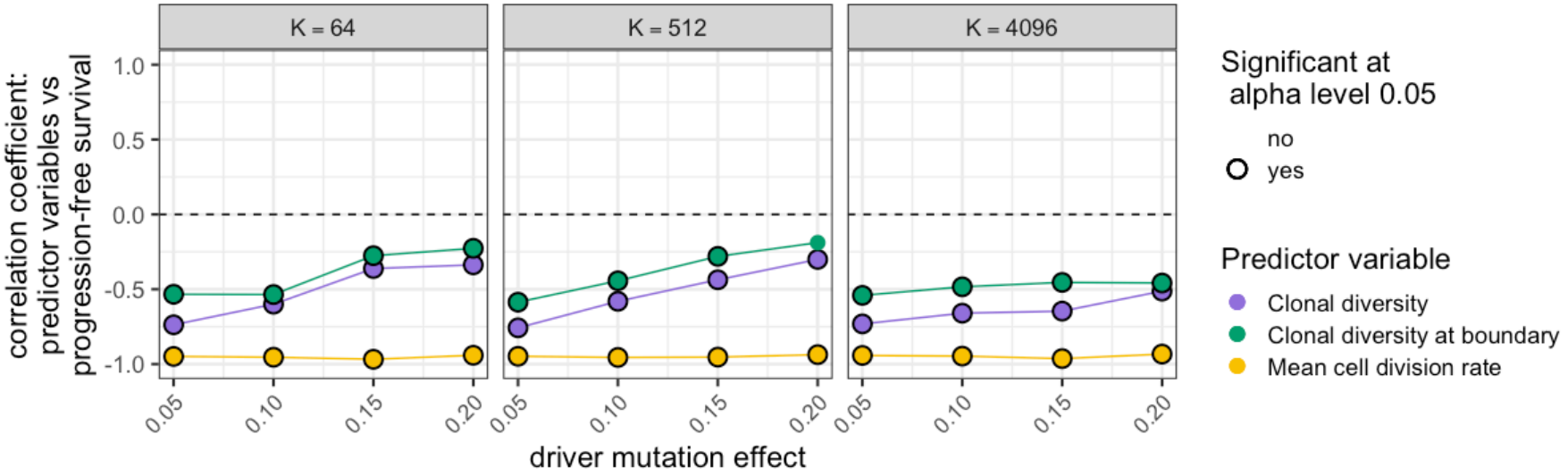




Forecasting progression-free survival

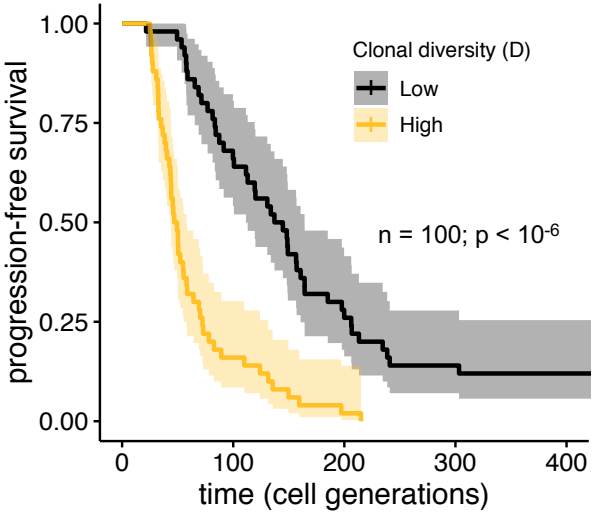


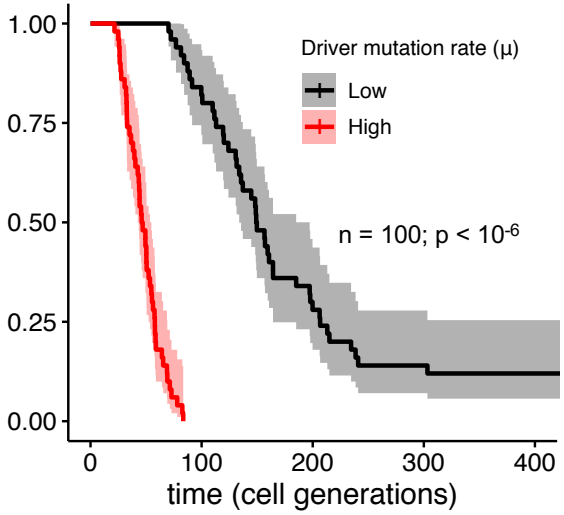


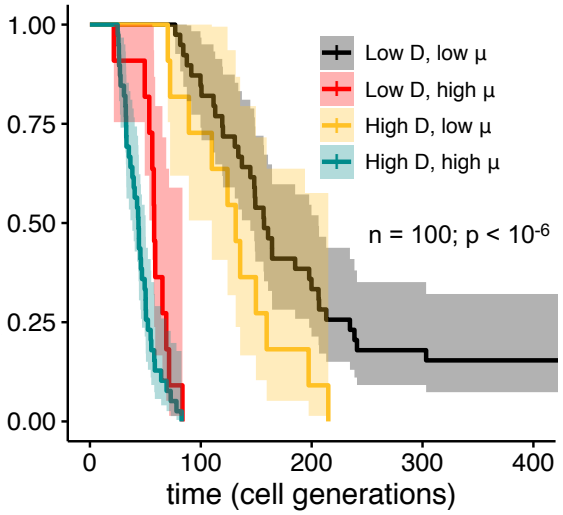


Forecasting progression-free survival

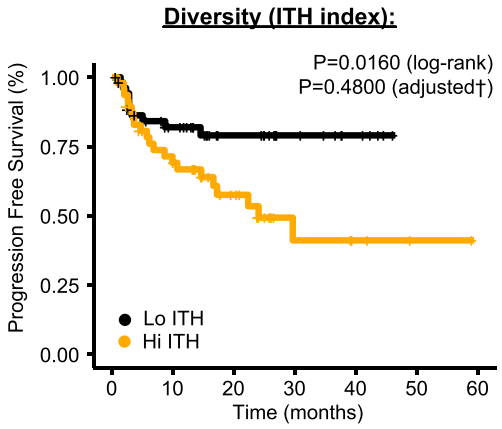
Model

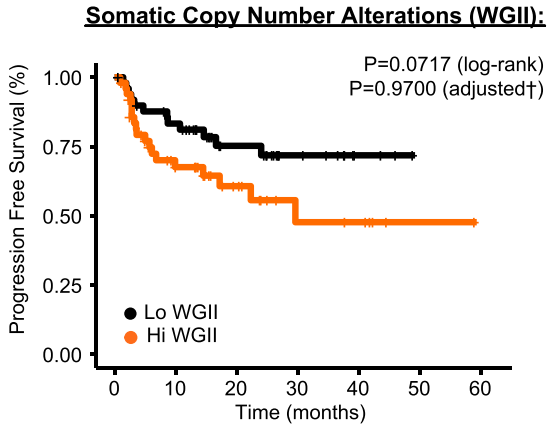


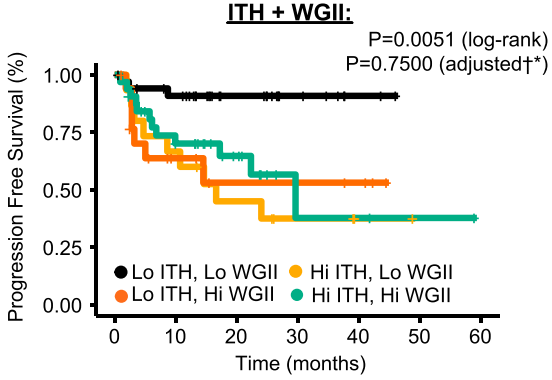




TRACERx Renal

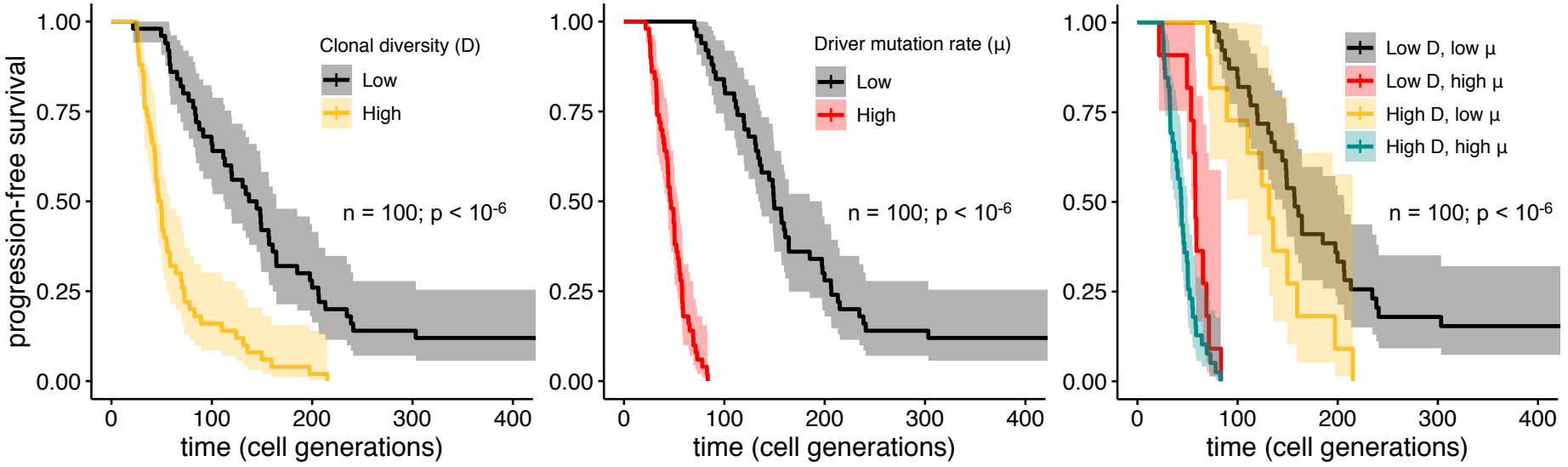






Second row adapted from Turajlic *et al. Cell* (2018)

Forecasting progression-free survival



term	estimate	std. error	z	p. value
$\log_{10}(D)$	3.81	0.467	8.16	$<10^{-6}$

term	estimate	std. error	z	p. value
$\log_{10}(D)$	-0.0392	0.477	-0.0822	0.935
$\log_{10}(\mu)$	35.7	6.58	5.42	$<10^{-6}$
$\log_{10}(\mu) \times \log_{10}(t + 10)$	-14	3.11	-4.52	$<10^{-5}$

Cox proportional hazards model
D = clonal diversity; μ = driver mutation rate; t = time (cell generations)
Green rows contain terms with significant effects ($p < 0.05$)

Summary

- Four oncoevotypes determined by mode of cell dispersal and range of cell-cell interaction
- Simple, mechanistic explanation for observations across human tumour types
- Appropriate modelling of spatial structure is essential for characterizing, forecasting and controlling tumour evolution
- Eco-evo prognostic biomarkers show promise but demand careful interpretation

Preprints on bioRxiv; in press or in revision for publication

Thank you

Niko Beerenwinkel
(ETH Zurich)

Dominik Burri
(ETH Zurich; Uni Basel)

Cécile Le Sueur
Jeanne Lemant
(ETH Zurich)

Michael Hochberg
(ISEM; Sante Fe Institute)

John Burley
(MEME master programme;
Brown University)

Jakob Kather
(University
Hospital
RWTH Aachen)

Yannick Viossat
(Université
Paris-Dauphine)

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