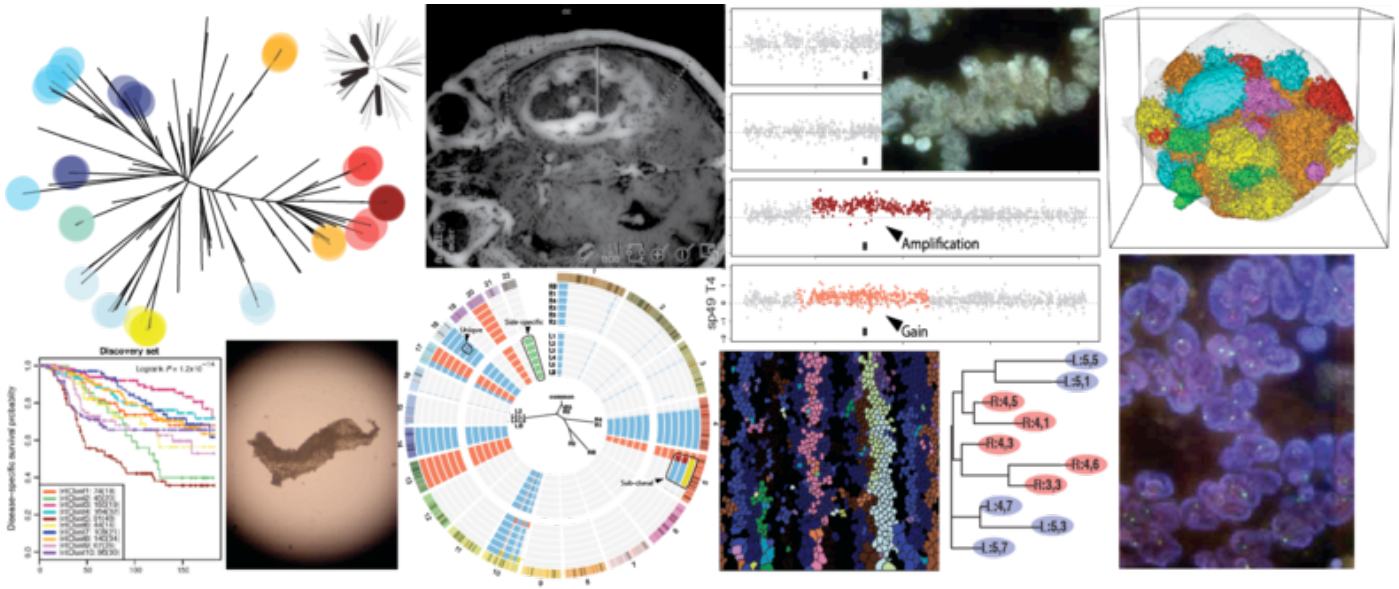
Delineating the mode and tempo of human tumor evolution



Christina Curtis
Departments of Medicine & Genetics
Stanford University
med.stanford.edu/curtislab

Stanford MEDICINE

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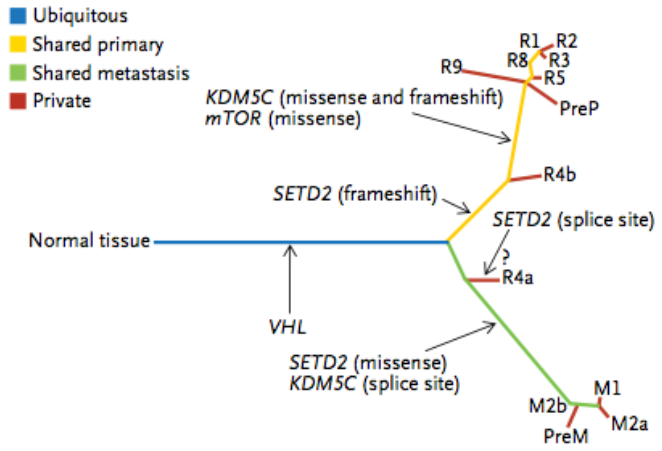
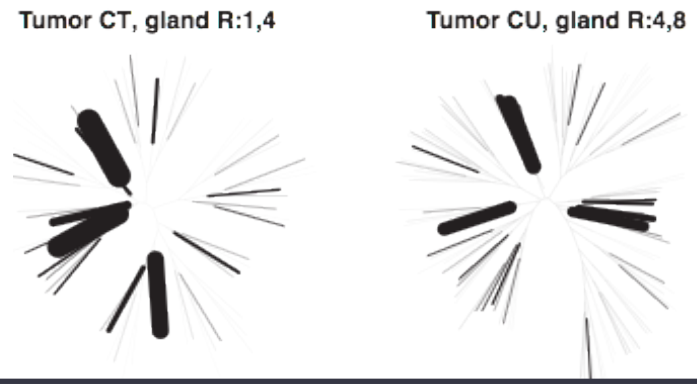
DIE LUFT DER FREIHEIT WEHT
1891

Intra-tumor heterogeneity is pervasive

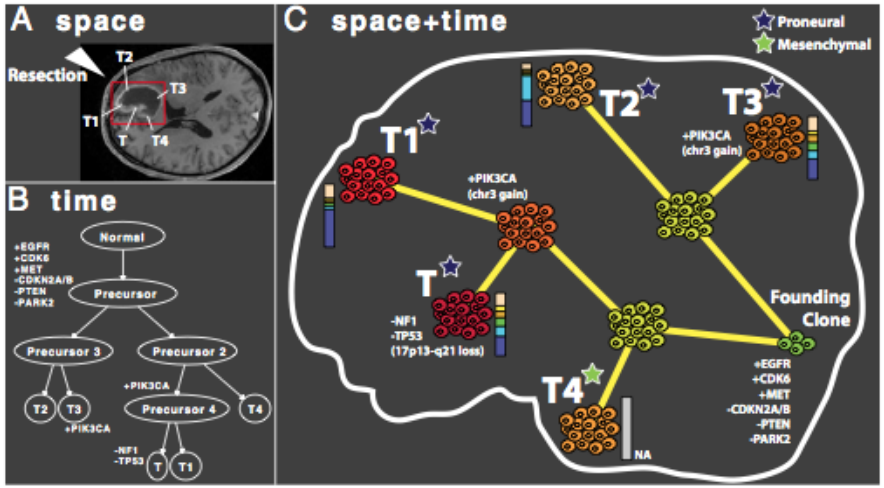
Renal Cell Carcinoma - Gerlinger *et al*. *NEJM* 2012



Colorectal cancer - Sottoriva *et al*. *Can Res* 2012



Glioblastoma - Sottoriva *et al*. *PNAS* 2013



Patient	Subtype
R4	Classical
sp57	Mesenchymal
sp41	Mesenchymal
sp50	Proneural
sp52	Classical, Neural
sp54	Mesenchymal, Proneural
sp55	Mesenchymal, Classical
sp42	Mesenchymal, Proneural
sp56	Classical, Mesenchymal, Neural
sp49	Classical, Proneural, Neural

Genetic reconstruction of individual colorectal tumor histories

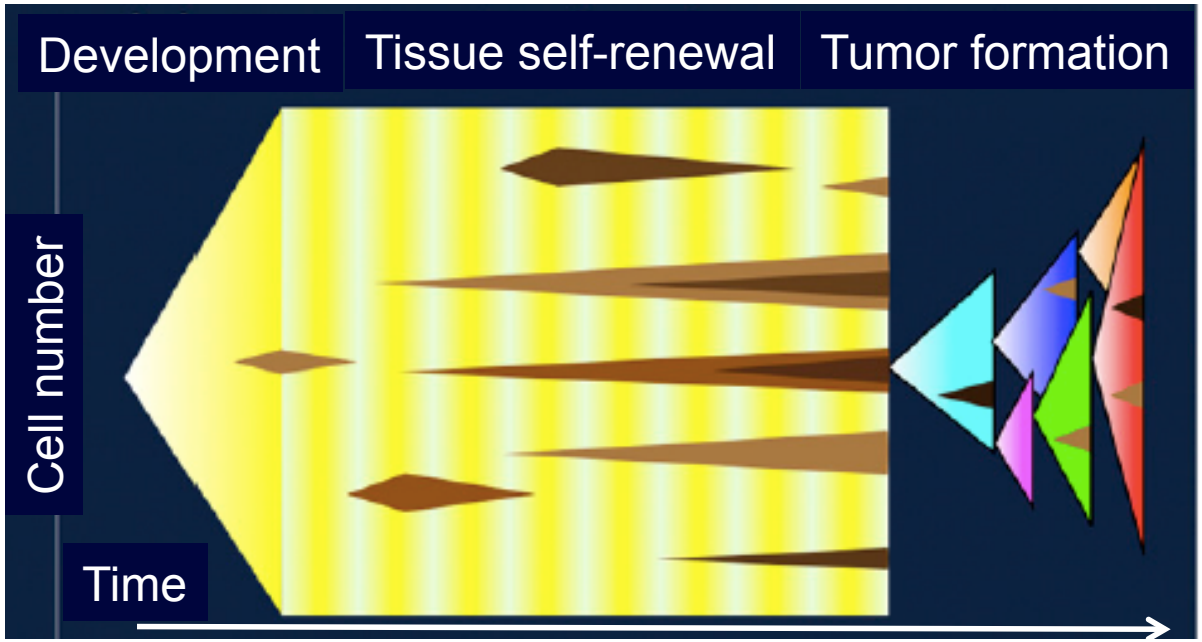
Jen-Lan Tsao[†], Yasushi Yatabe[†], Reijo Salovaara[‡§], Heikki J. Järvinen[¶], Jukka-Pekka Mecklin[‖], Lauri A. Aaltonen[§], Simon Tavaré[††], and Darryl Shibata[†,‡‡] Feb 1, 2000

[†]Department of Pathology, University of Southern California School of Medicine, Los Angeles, CA 90033; Departments of [‡]Pathology and [§]Medical Genetics, Haartman Institute, FIN-00014, University of Helsinki, Finland; [¶]Second Department of Surgery, Helsinki University Central Hospital, FIN-00029, Helsinki, Finland; [‖]Jyvaskyla Central Hospital, FIN-40620, Jyvaskyla, Finland; and [††]Departments of Biological Sciences, Mathematics, and Preventive Medicine, University of Southern California, Los Angeles, CA 90089

Half or more of the somatic mutations in cancers of self-renewing tissues originate prior to tumor initiation

Cristian Tomasetti[a,b,1], Bert Vogelstein[c,d,1], and Giovanni Parmigiani[a,b,1] Feb 5, 2013

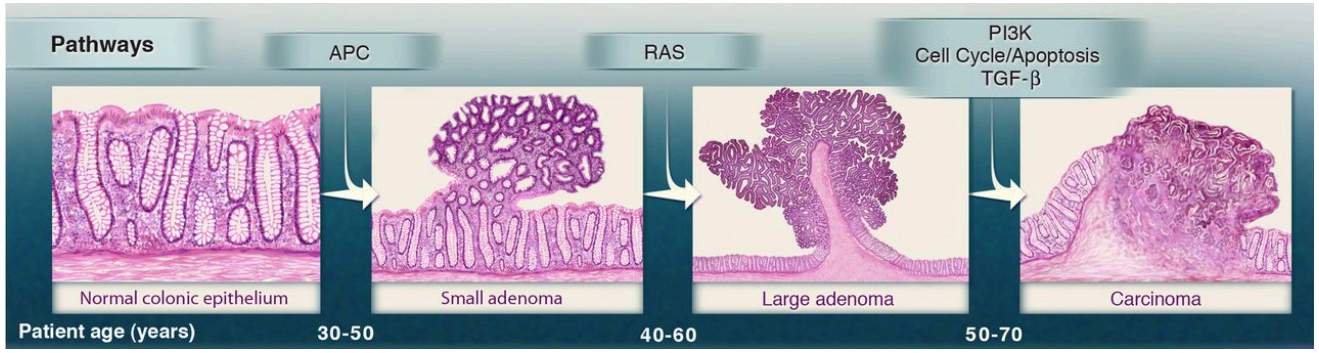
[a]Department of Biostatistics, Harvard School of Public Health, Boston, MA 02115; [b]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02115; and [c]Ludwig Center for Cancer Genetics and Therapeutics and [d]Howard Hughes Medical Institute, Johns Hopkins Kimmel Cancer Center, Baltimore, MD 21231



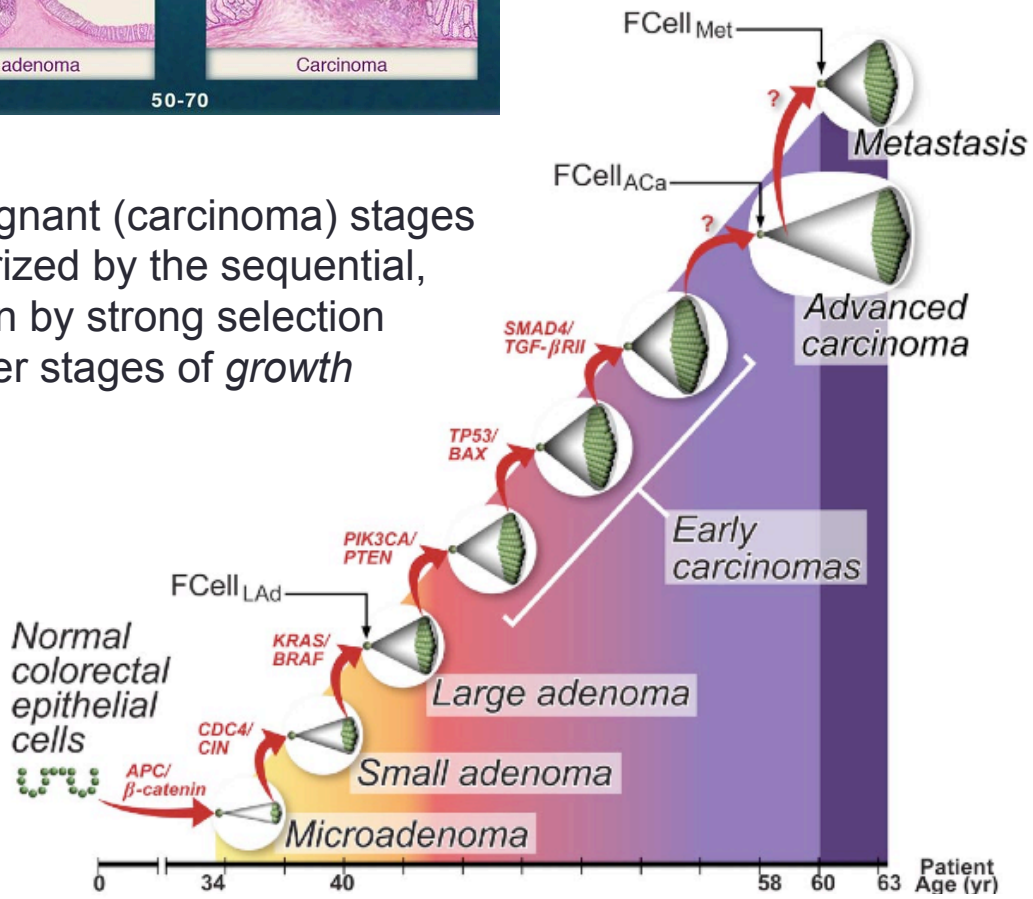
Inferring tumor dynamics

- Clonal diversification and selection are critical to tumor progression, but their ***dynamics*** are poorly understood
- What happens during the first cell divisions may provide clues as how to better detect and treat cancers
- While this process cannot be directly observed, patterns of somatic alterations faithfully report on tumor ancestry
- Interpretation of these processes has been hindered by the lack of a *quantitative evolutionary framework*

Clonal evolution in the colon



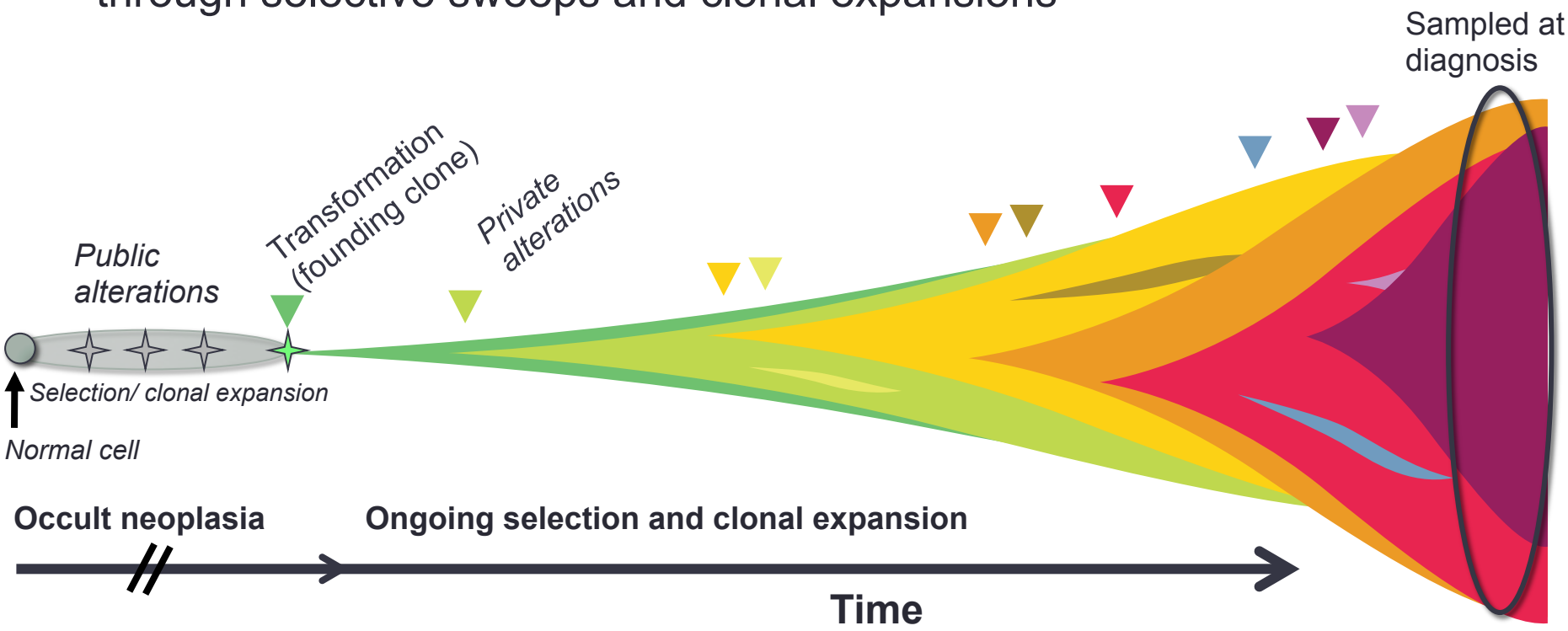
- Well defined benign (adenoma) and malignant (carcinoma) stages
- Tumor ***initiation*** in the colon is characterized by the sequential, step-wise acquisition of alterations driven by strong selection
- This has since been used to describe later stages of *growth*



Vogelstein *et al*. *Science* 2013
Jones *et al*. *PNAS* 2008
Fearon and Vogelstein, *Science* 1990

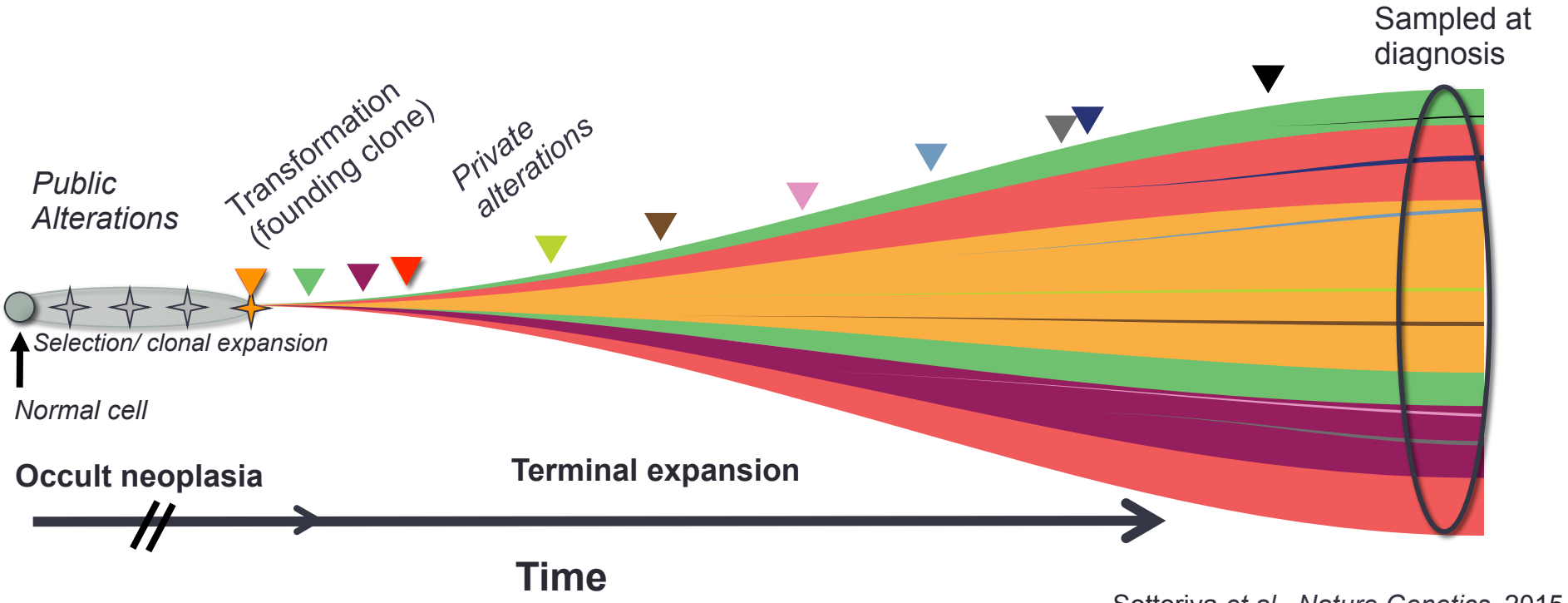
The sequential clonal expansion model

- The classic view of tumor progression involves the stepwise accumulation of alterations leading to the sequential expansion of cells (clones) with a growth advantage
- The fittest cells expand and come to dominate the tumor population through selective sweeps and clonal expansions



A Big Bang model of colorectal tumor growth

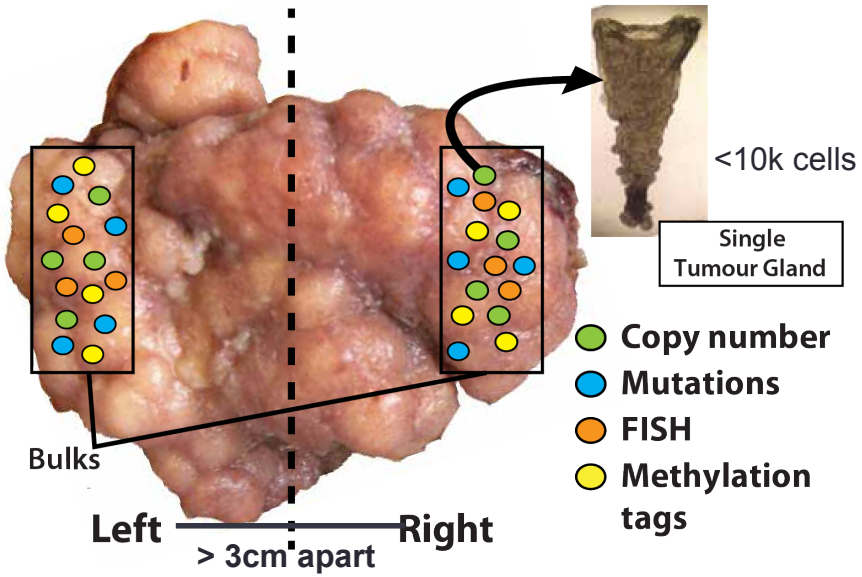
- Once the tumor is *established*, rapid growth occurs in the absence of *stringent* selection; compatible with effectively neutral evolution
- This *terminal* expansion is populated by many heterogeneous subclones
- The timing of a mutation is the primary determinant of its frequency
- Both public and the majority of *detectable* private alterations occur very early



Sottoriva *et al.*, *Nature Genetics*, 2015

Multi-region & multi-scale profiling of CRC

- Pure glands/crypts can readily be isolated from colorectal cancers (CRC)
- Gland fission most likely mechanism of expansion
- Facilitates inference of clonal dynamics
- A small *selective* advantage in a single cell should homogenize the gland population

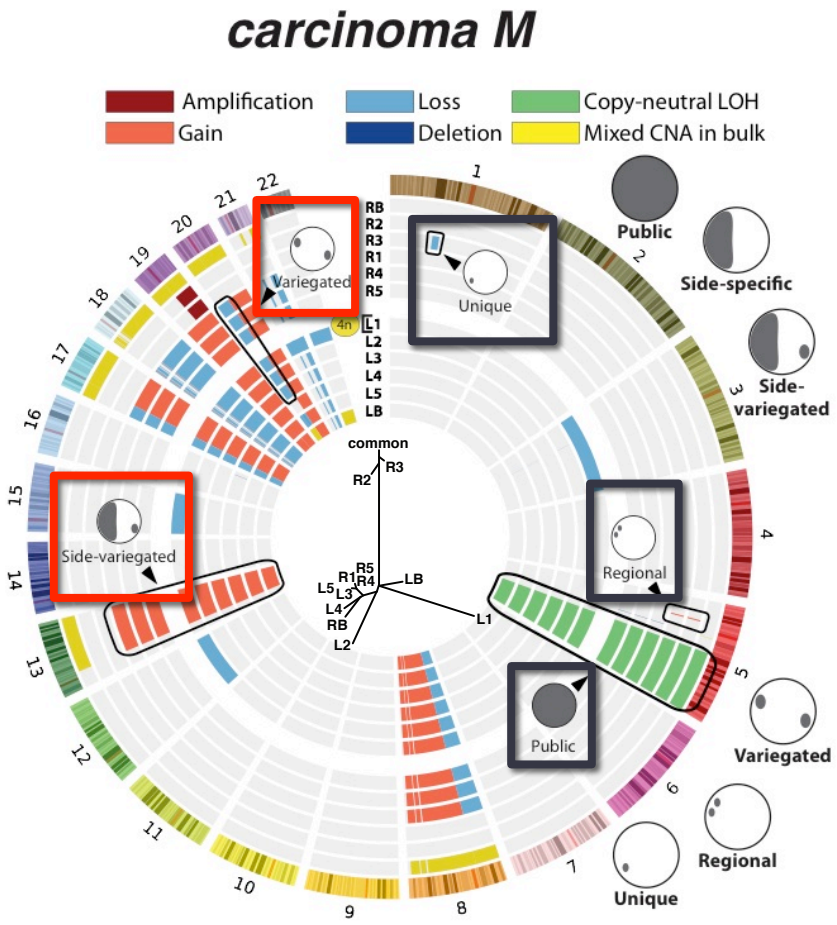


- Isolated ~350 *individual* glands, bulks, single cells and normal tissue from 11 carcinomas and 4 adenomas for multi-scale (epi)genomic profiling

- Characterized the phylogenetic relationship between glands & the topographical distribution of *public* and *private* alterations

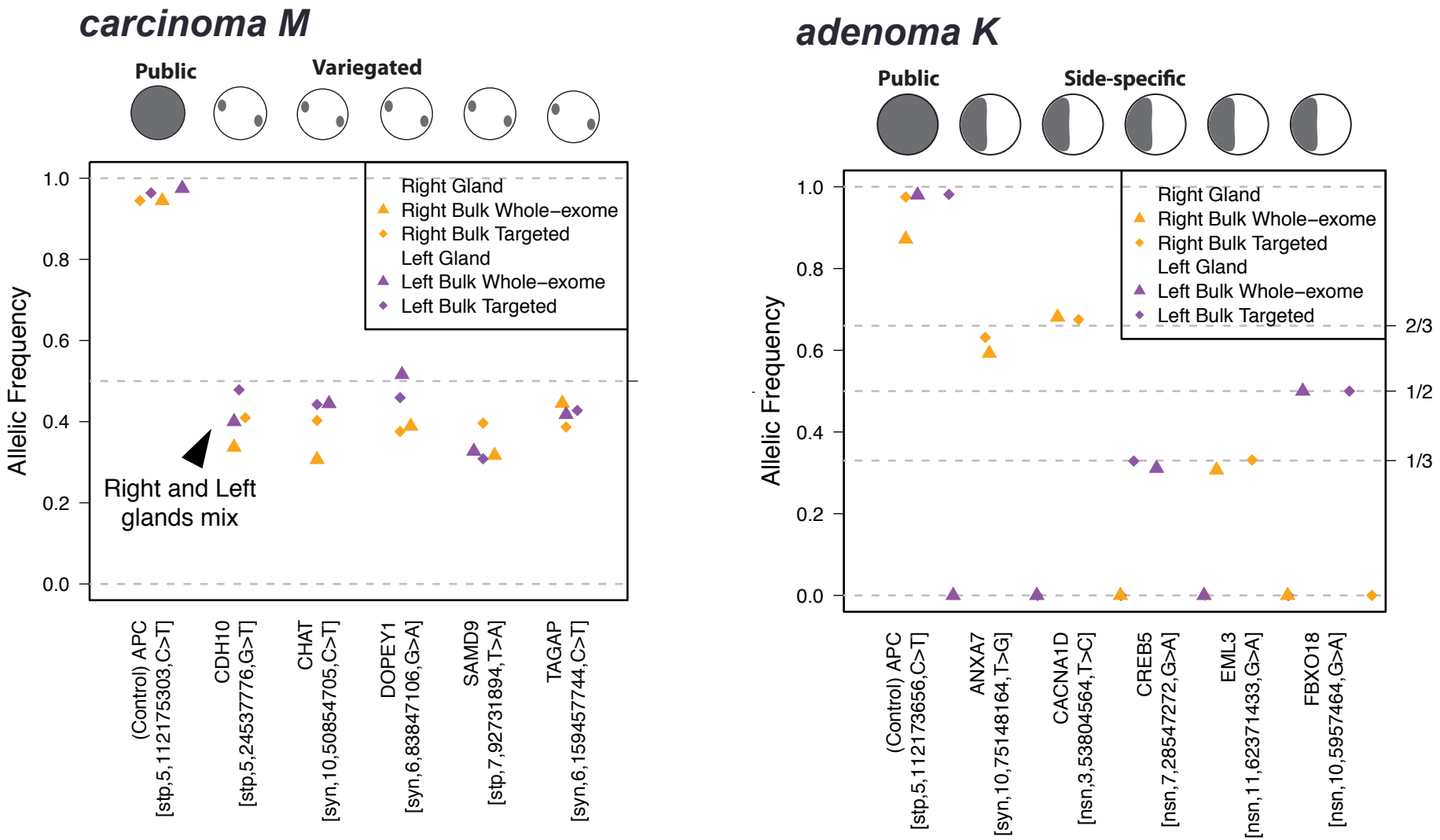
Sottoriva *et al.*, *Nature Genetics*, 2015

Single gland copy number profiling reveals variegation and sub-clone mixing

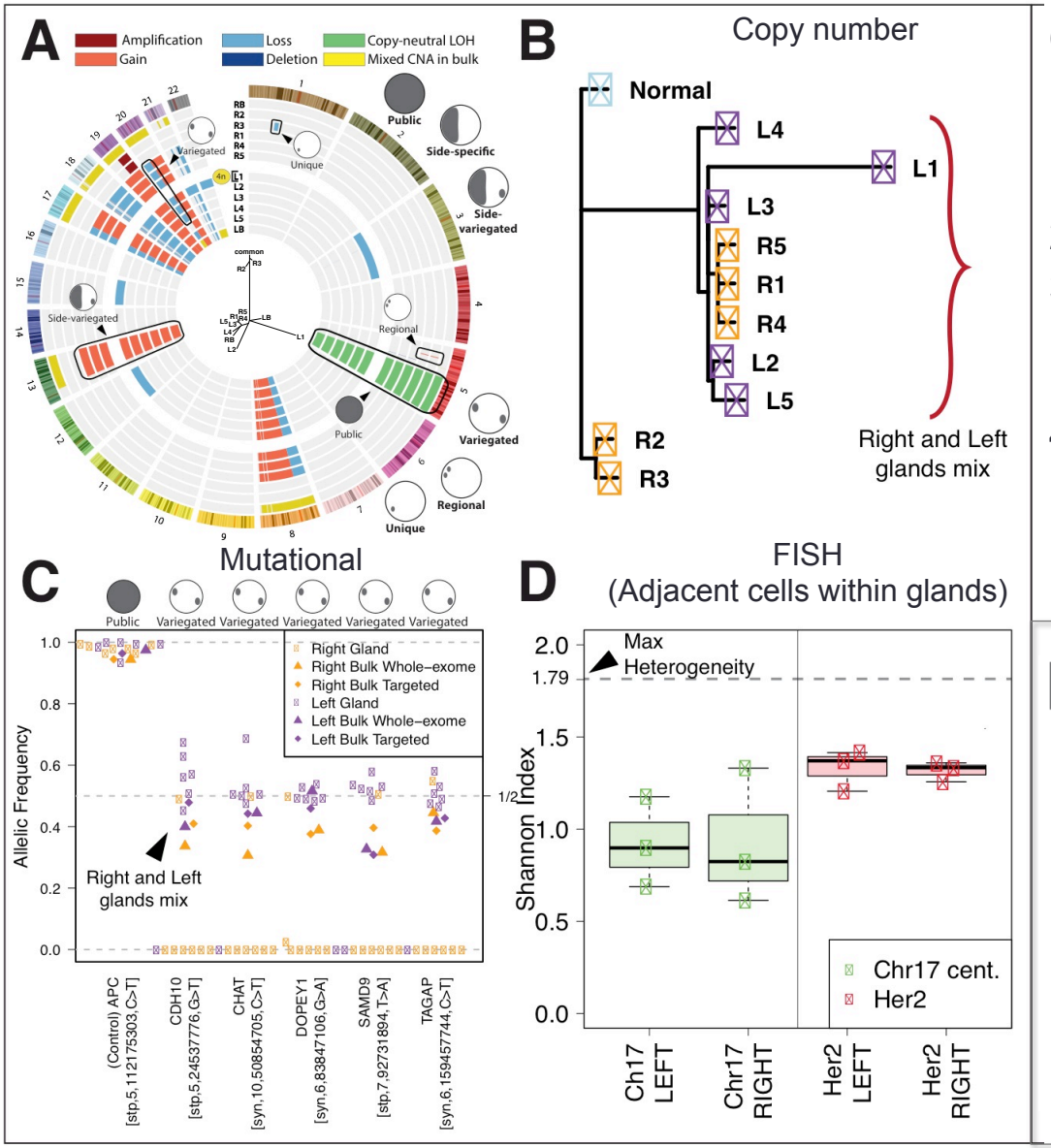


- **Public/clonal:** found in all glands
- **Side-specific:** found in all glands from one side only
- **Side-variegated:** found in all glands from one side and a subset from the opposite side
- **Variegated:** found in a subset of glands from one side and a subset from the opposite side
- **Regional:** found in a subset of glands from one side only
- **Unique:** found in only one gland

Single gland sequencing reveals sub-clone mixing in carcinomas but not adenomas

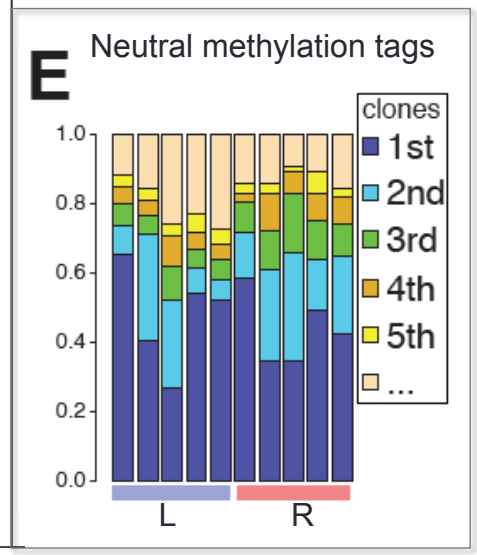


Genomic data summary



Observations:

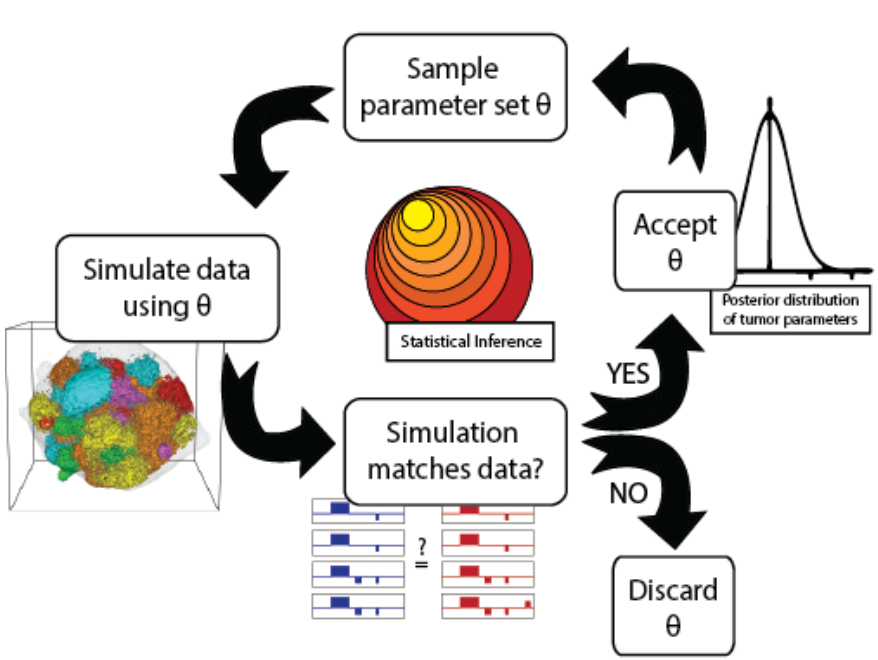
1. Extensive genetic variegation /sub-clone mixing between distant tumor regions (**A-C**)
2. Star-like phylogenies (**A, center**)
3. Uniformly high ITH at multiple scales; b*etween* glands (**A-C**) and *within* glands (**D, E**)
4. Private mutations are clonal within a gland (**C**)

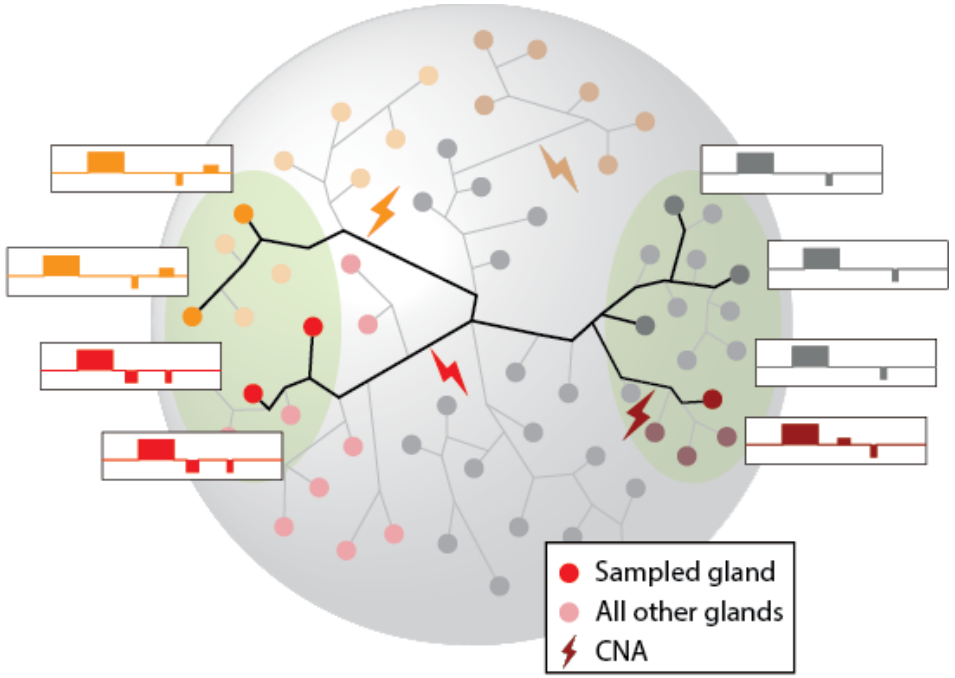


The genomic data are congruent with the predictions of the Big Bang model

- Uniformly high ITH at all scales implies the absence of a dominant population and that recent large-scale clonal expansions are rare
- Private mutations were clonal within the gland, reflecting their *early acquisition* and sufficient time for loss or fixation via turnover or neutral drift
- Molecular clock analysis similarly reveals a complex hierarchy of distinct clones within each gland; suggesting relatively old clonal expansions

Quantifying patient-specific tumor dynamics





Approximate Bayesian Computing (ABC)

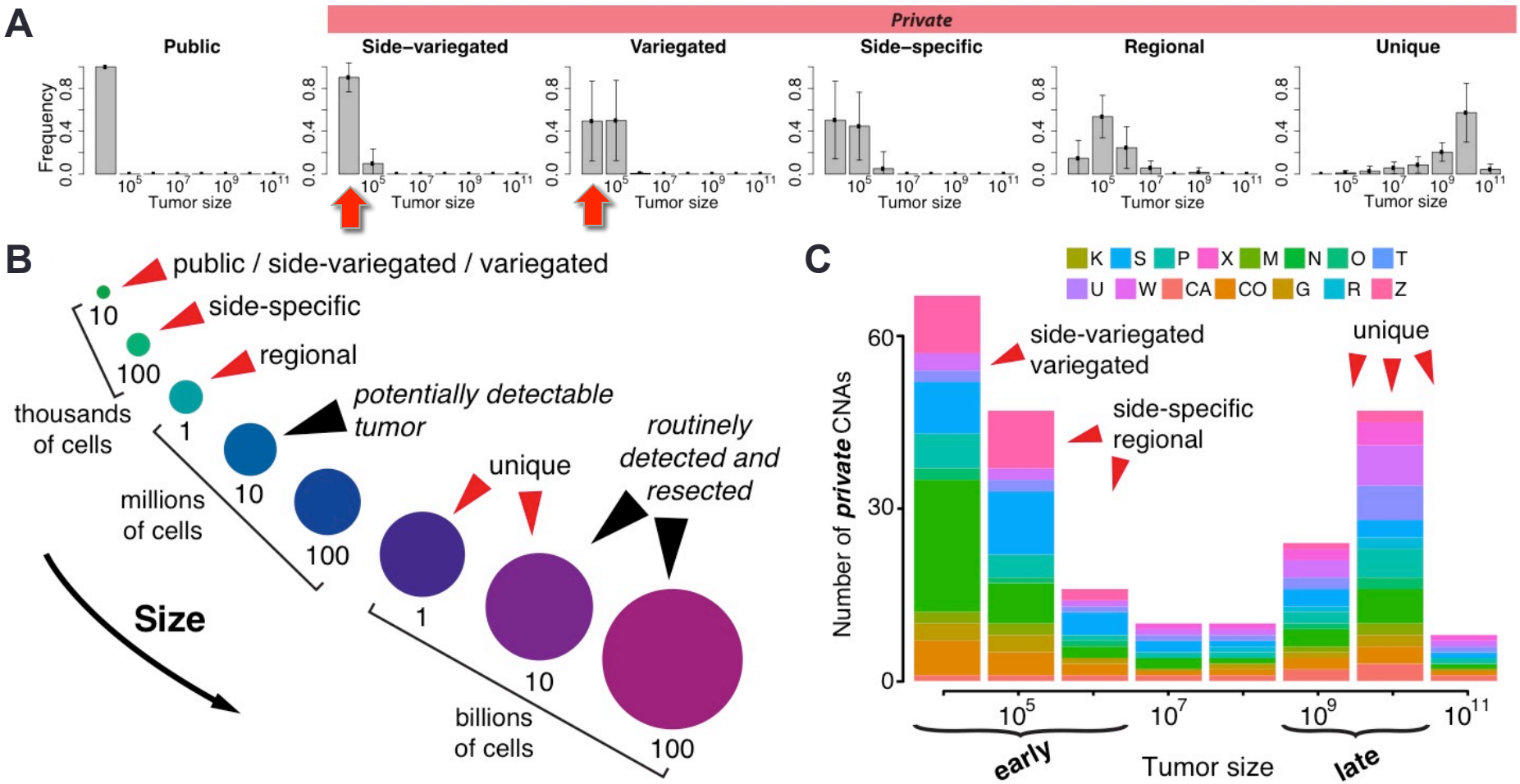
[Beaumont, 2002; Marjoram & Tavaré, 2006]

- Sample from approximation of $P(\theta|\rho(S(D),S(D')) < \varepsilon)$
- Obtain posterior probability estimates for mutation rate (μ), subclone fitness (σ), timeline (t) given the data and model of reference

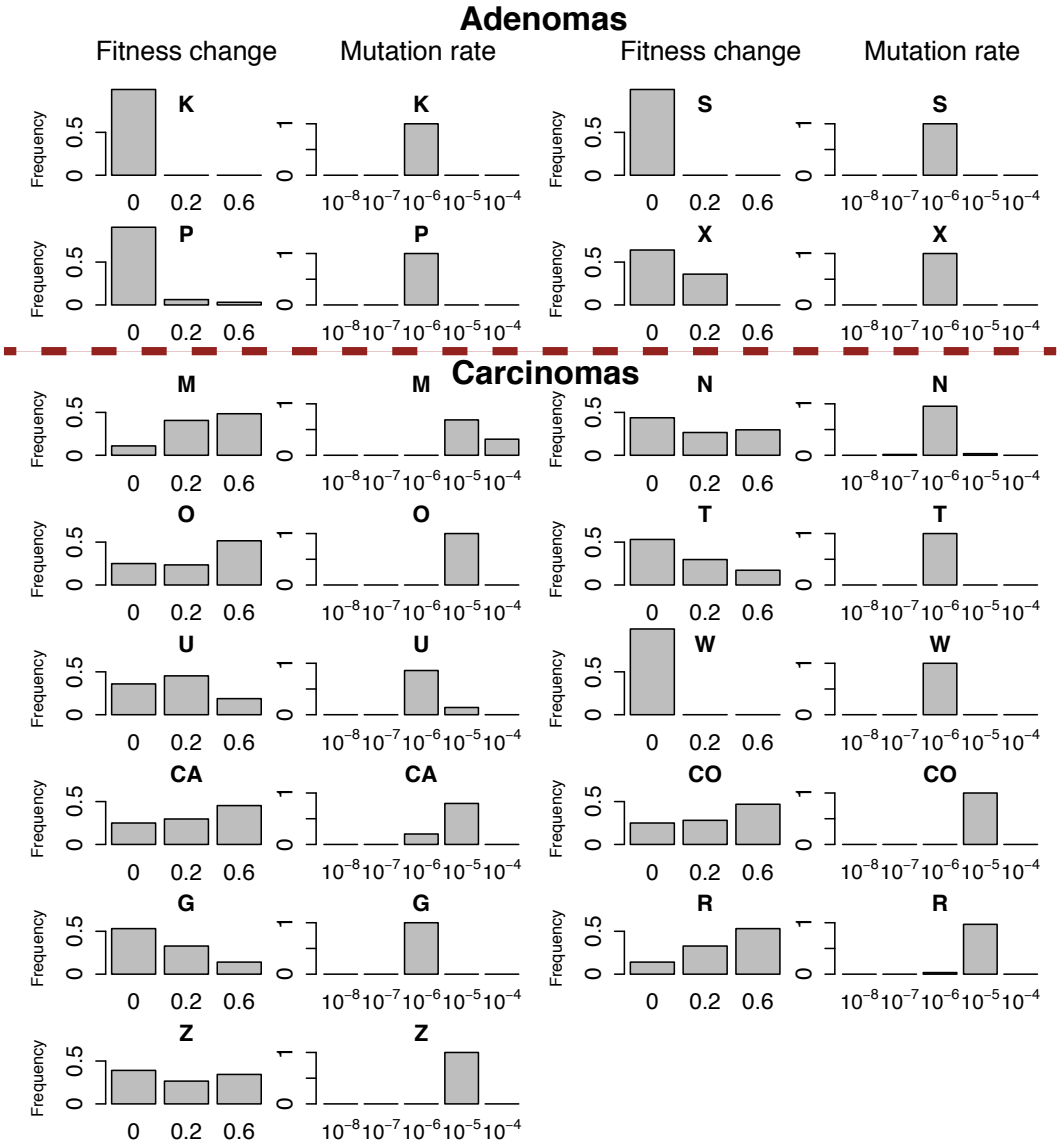
3-D model of tumor growth

- Spatial agent-based tumor model (8M glands)
- Simulate data D' from the computational model under $\theta'=(\mu, \sigma)$
- Generate virtual gland profiles

Most detectable ITH arises before the lesion is clinically evident



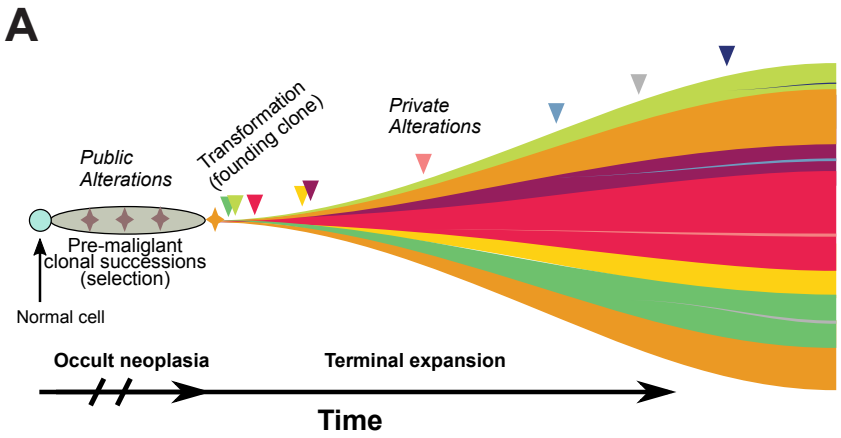
Signals of selection are detectable ...
but fail to alter subclonal architecture



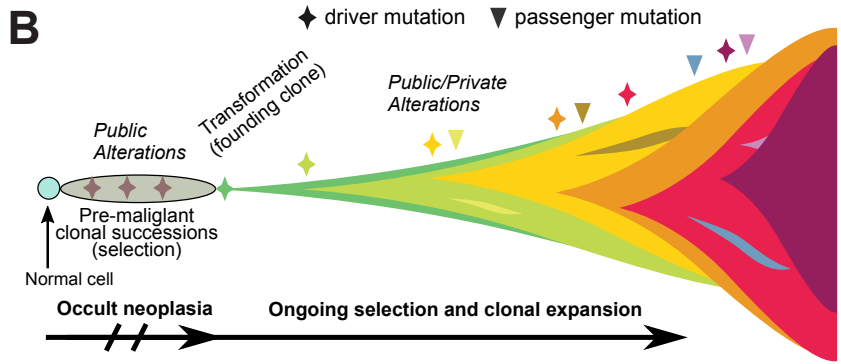
Carcinomas exhibit elevated subclone fitness differences and CNA rates, relative to adenomas

Implications of the Big Bang model

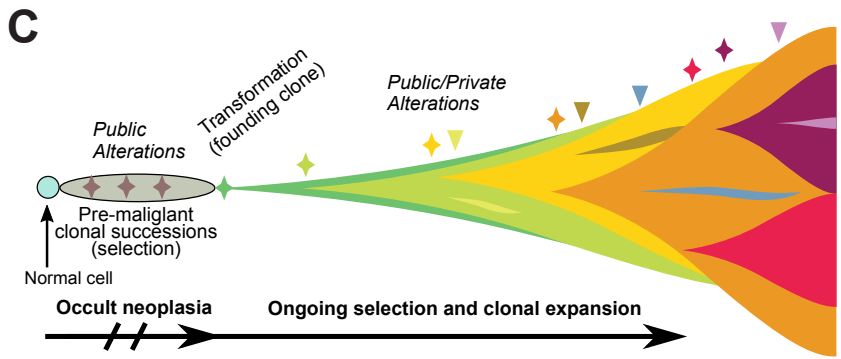
- In the Big Bang model, the tumor grows as a single terminal expansion, with selection uniformly conferred by drivers present in the first tumor cell
- Although selection is detectable, it is insufficient to alter subclonal architecture; compatible with *effectively neutral evolution*
- Most *detectable* ITH occurs early, whereas late arising, but potentially aggressive subclones may be undetected providing a heterogeneous substrate for resistance under treatment selective pressure
- Some tumors may be *born to be bad*, wherein invasive and metastatic potential is specified early; others may be evolutionarily stable



***Big Bang* model:**
Effectively neutral evolution
Terminal expansion



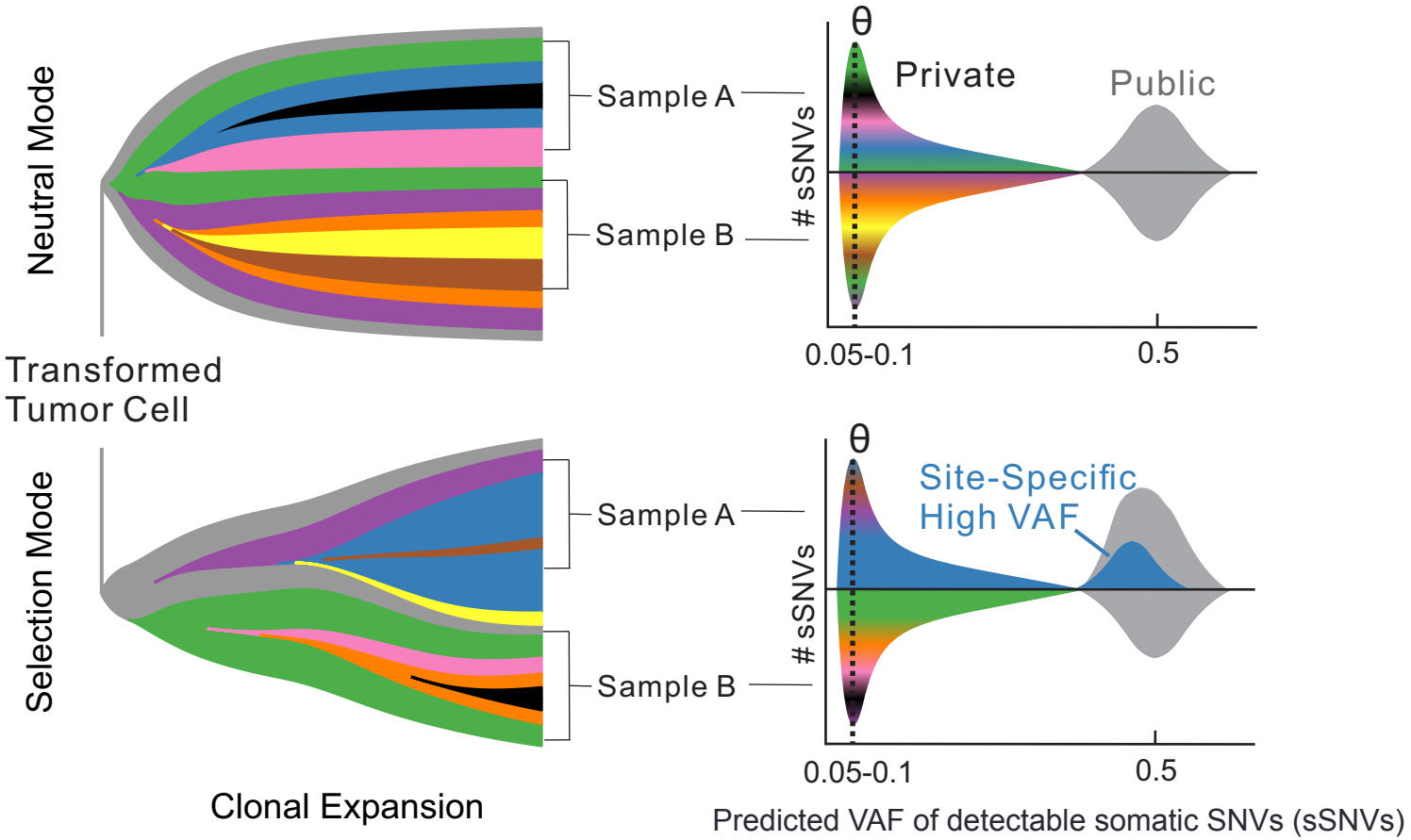
Linear evolution:
Ongoing selection
Successive clonal expansions



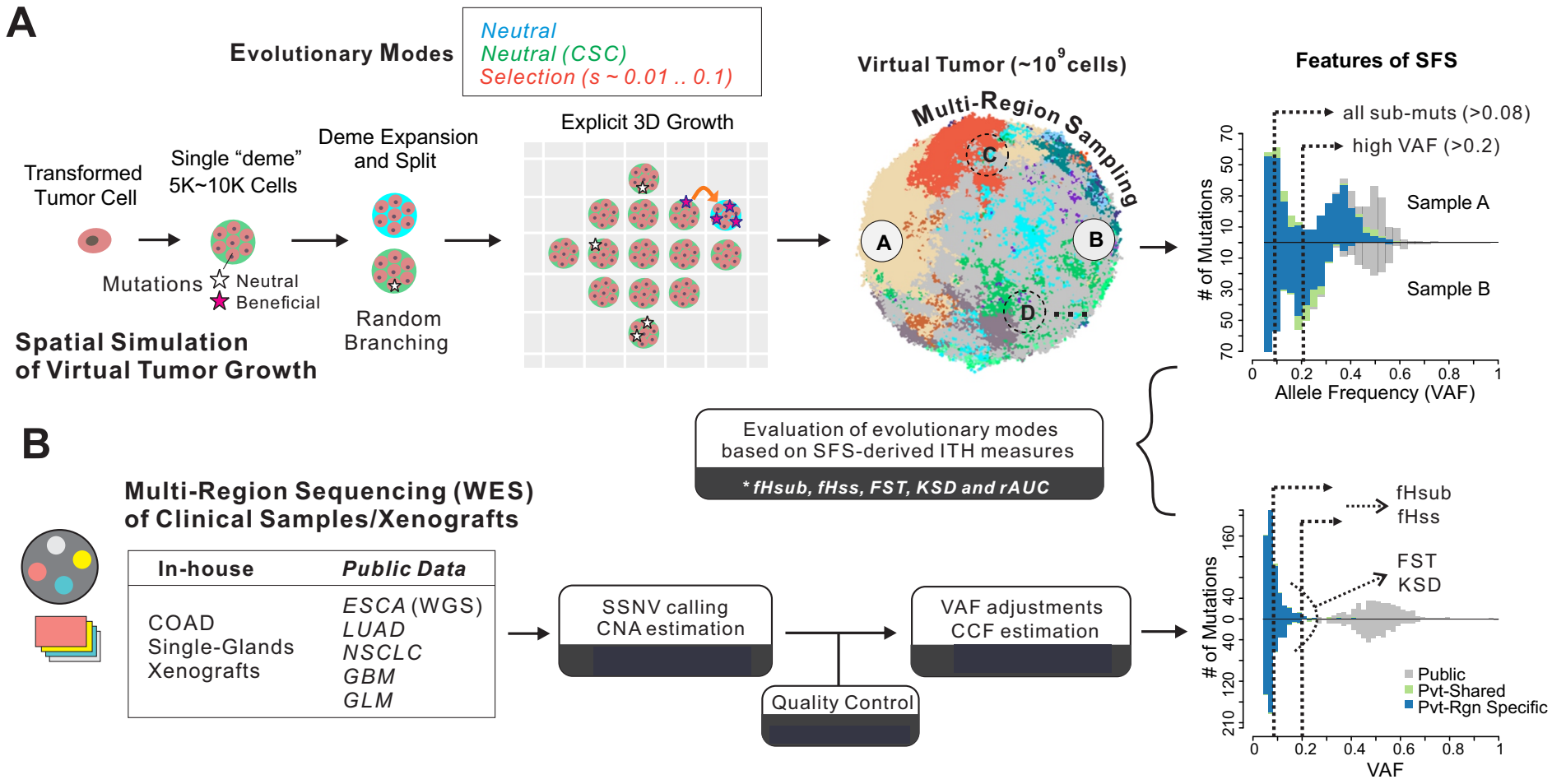
Branched evolution:
Ongoing selection
Co-occurring clonal expansions

Hu *et al.*, BBA Rev in Cancer 2017

Predicted variant allele frequency (VAF) distribution under effective neutrality vs. positive selection

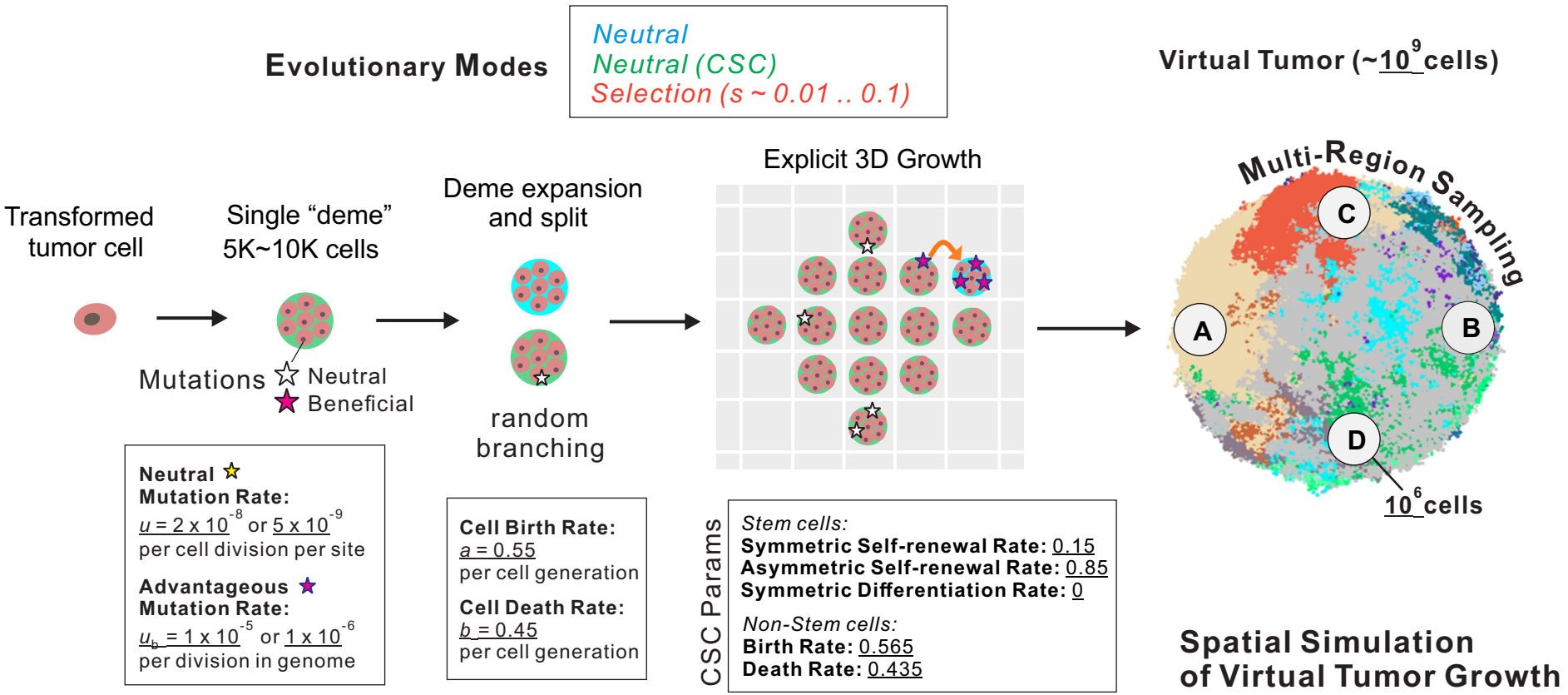


An extensible framework to simulate spatial tumor growth under different modes of evolution



https://github.com/cancersysbio/VirtualTumorEvolution
https://github.com/cancersysbio/VAP

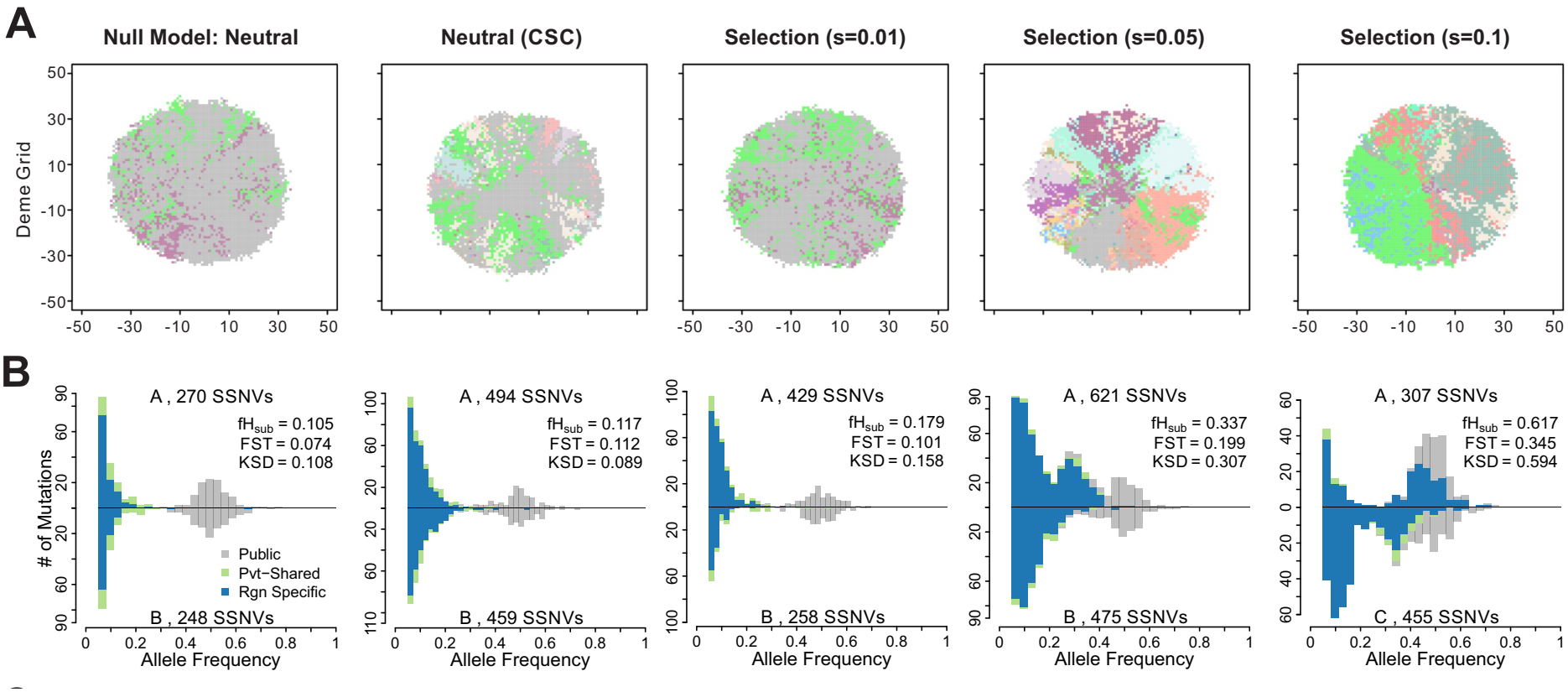
Spatial tumor growth model overview



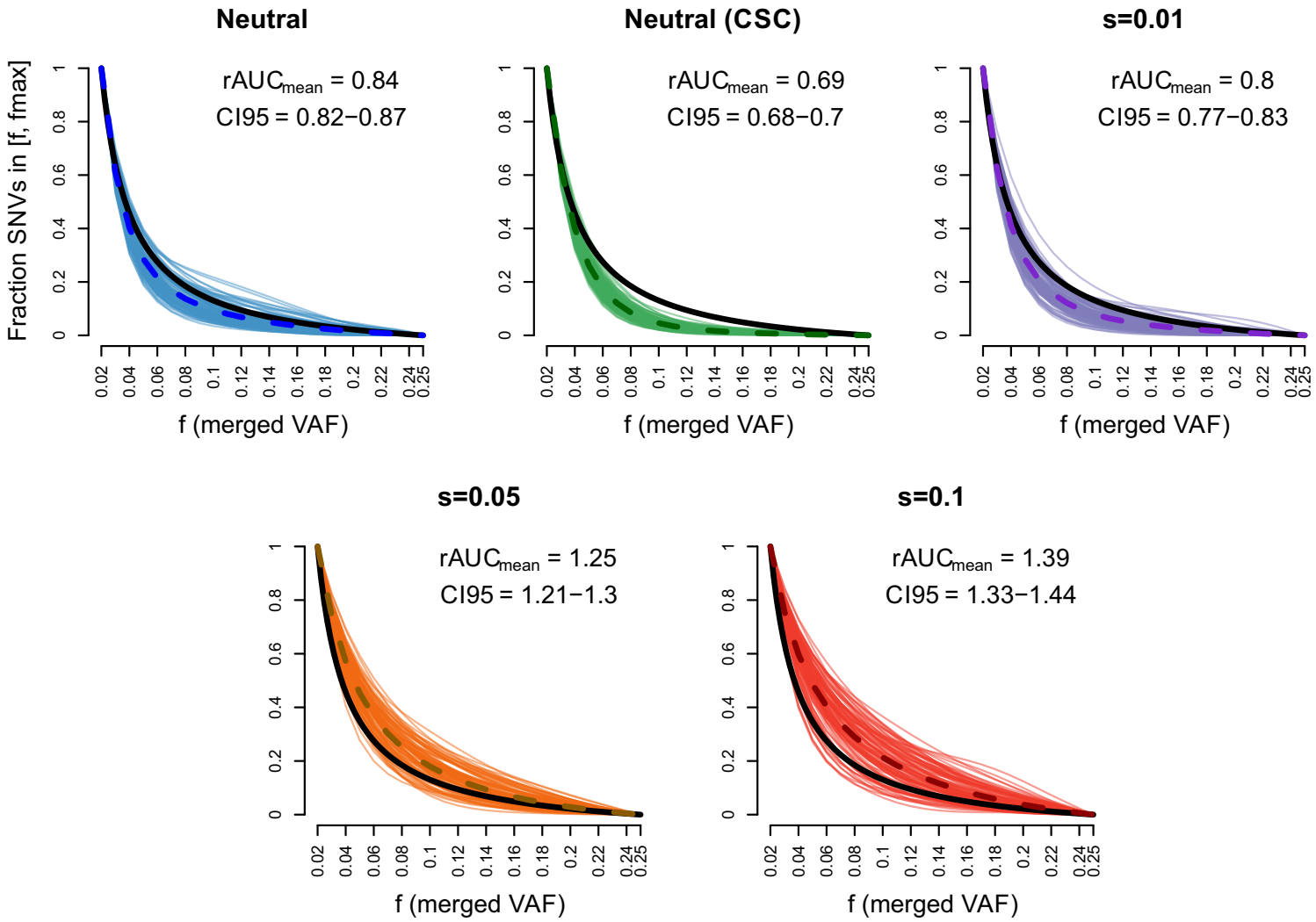
ITH metrics

- fHrs – fraction of high frequency (VAF>0.2) region-specific subclonal SSNVs out of all region-specific subclonal SSNVs (VAF>0.08)
- fHsub – fraction of subclonal SSNVs (VAF>0.08) with high frequency (VAF>0.2)
- FST (Fixation index) – a measure of genetic divergence between regions
- KSD (Kolmogorov-Smirnov distance) – dissimilarity of the SFS between regions
- rAUC ratio ofthe area under the cumulative SFS (pooled cumulative SFS for multiple regions) to the area under the theoretical neutral SFS

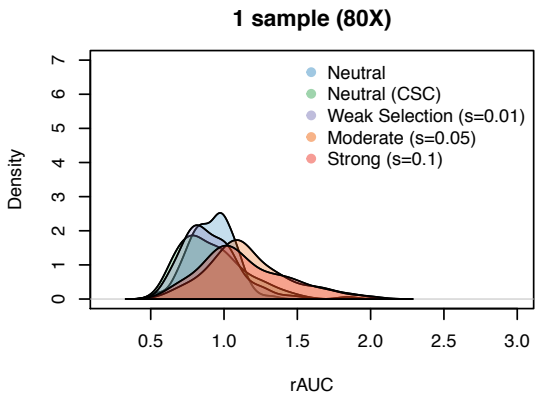
Patterns of subclonal diversity under different evolutionary modes

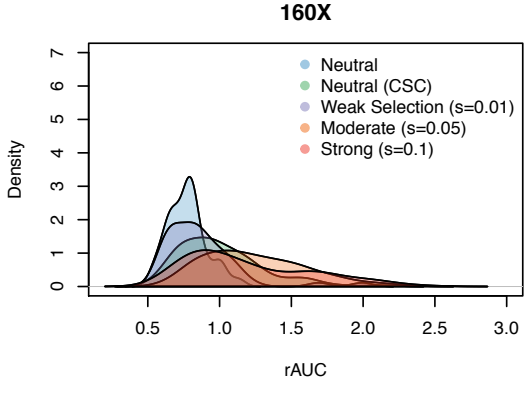


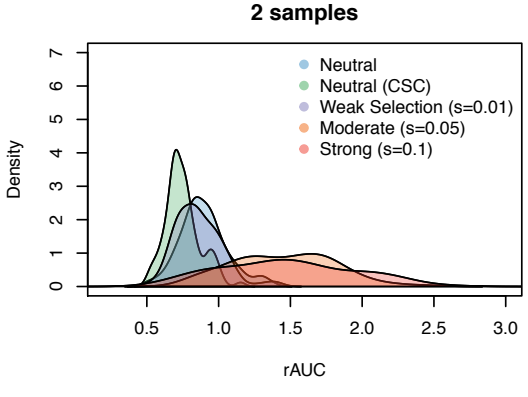
SFS under different evolutionary modes



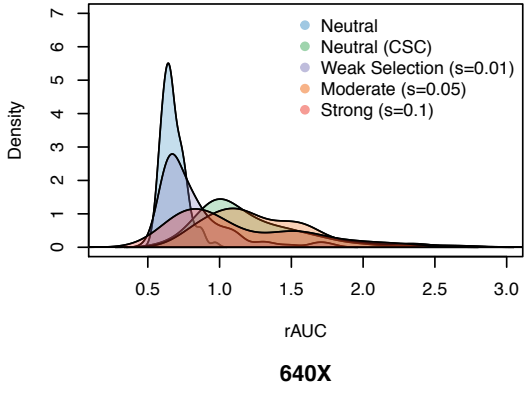
Distinguishing alternate models from the theoretical neutral model

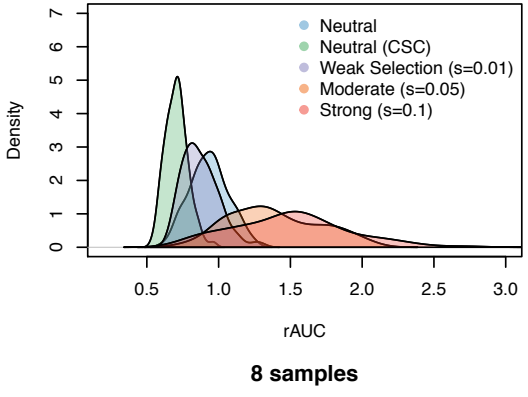


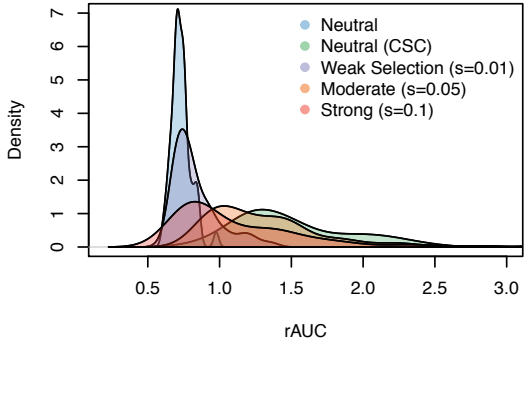


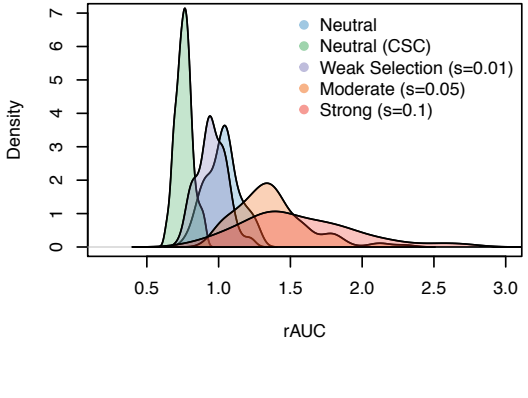


rAUC - ratio between the AUC in the simulated SFS vs theoretical neutral SFS

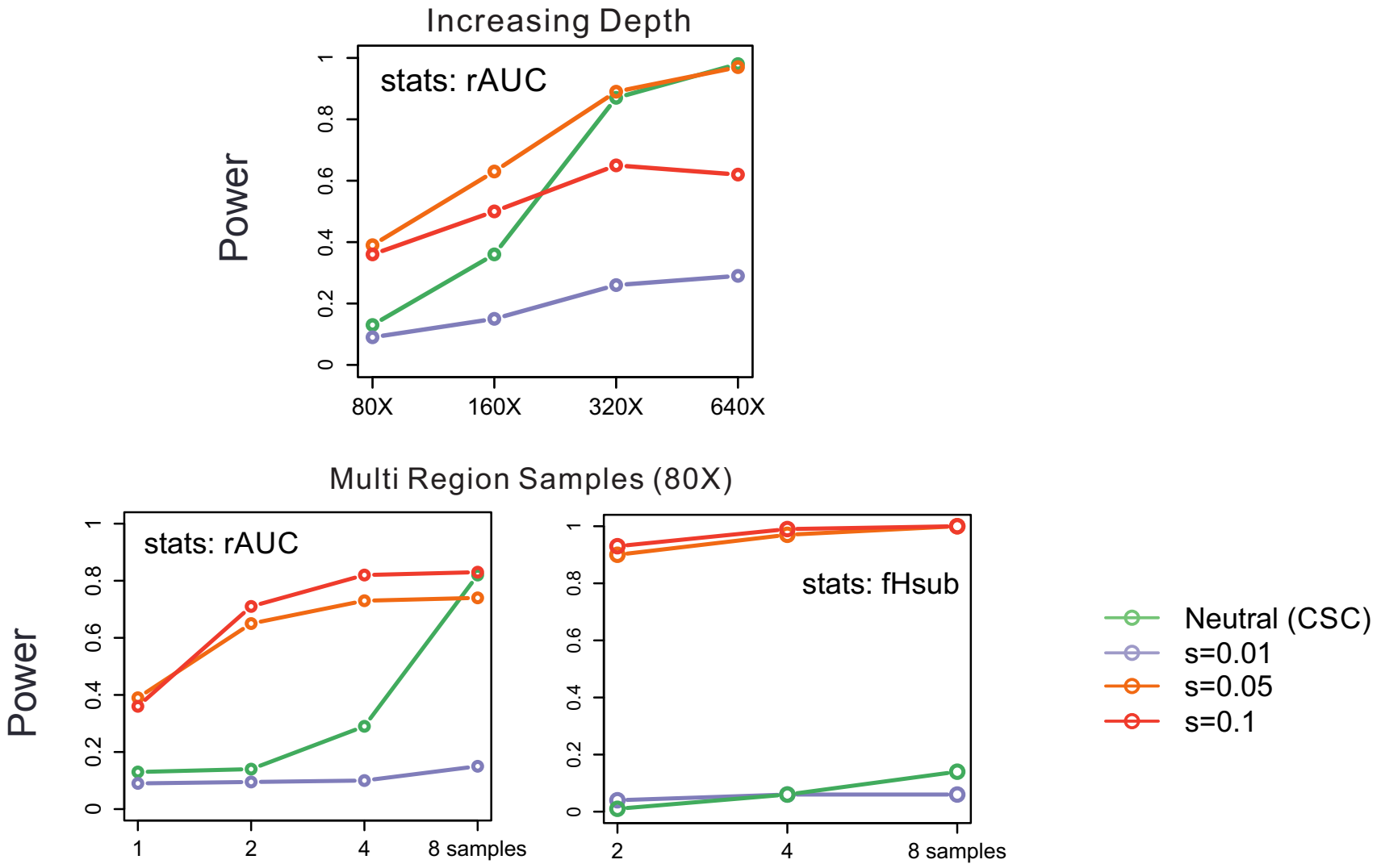




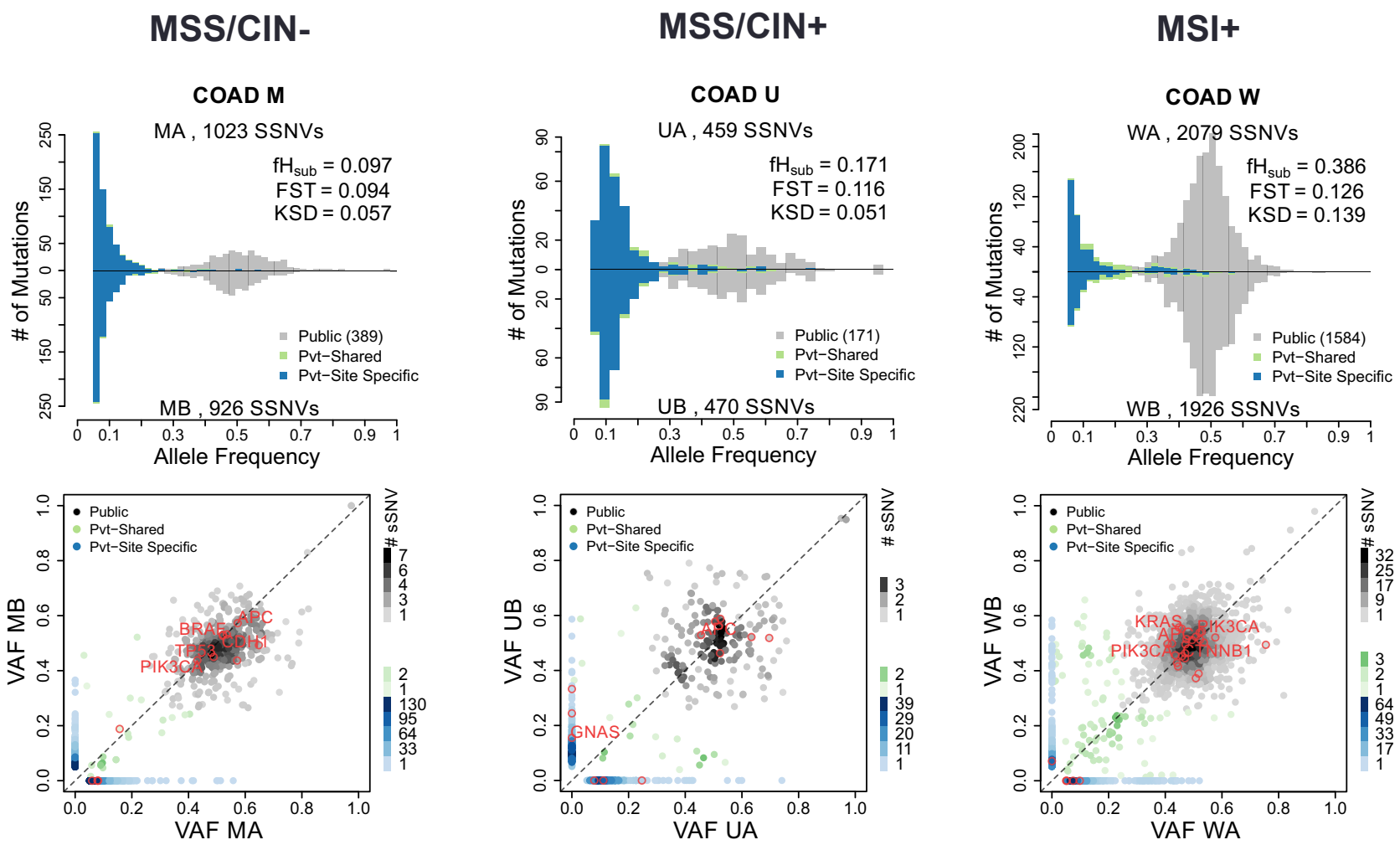




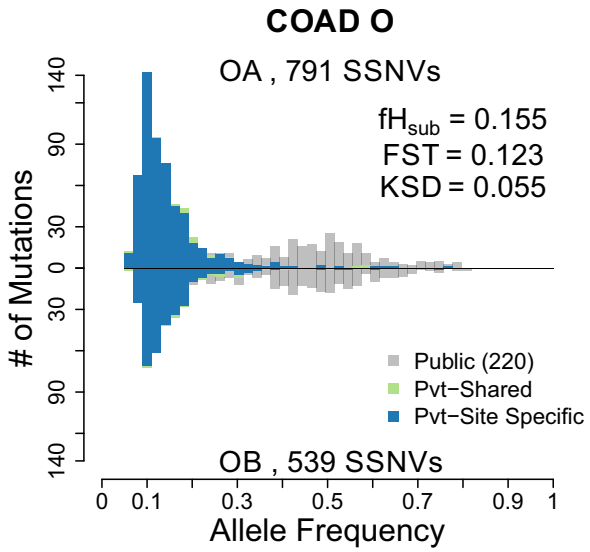
Distinguishing alternate models from the simulated neutral

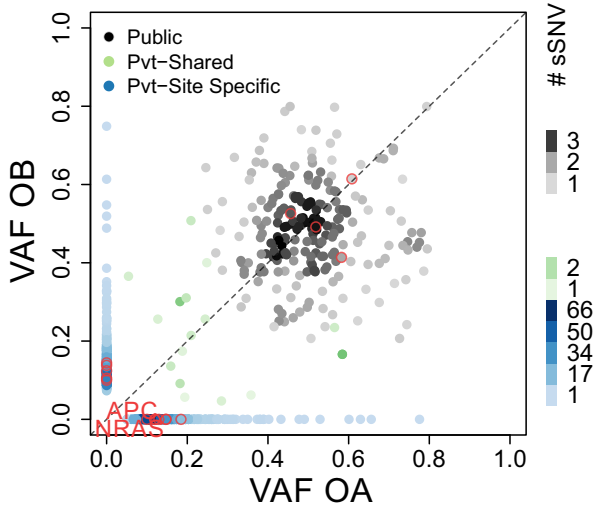


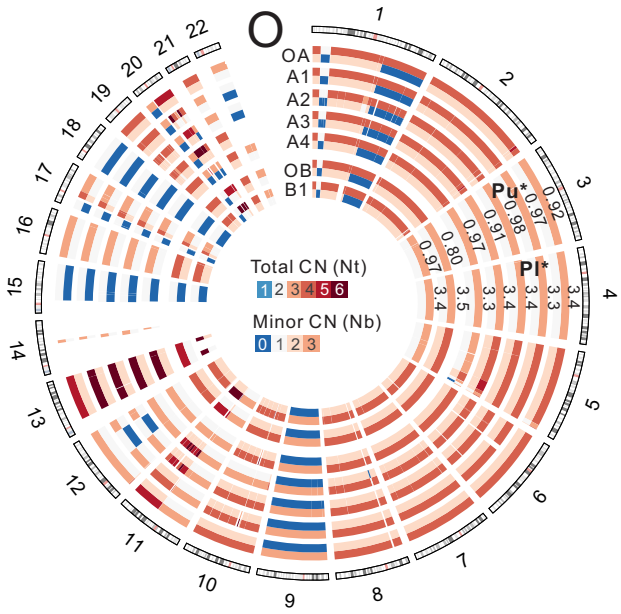
The SFS reflects tumor dynamics



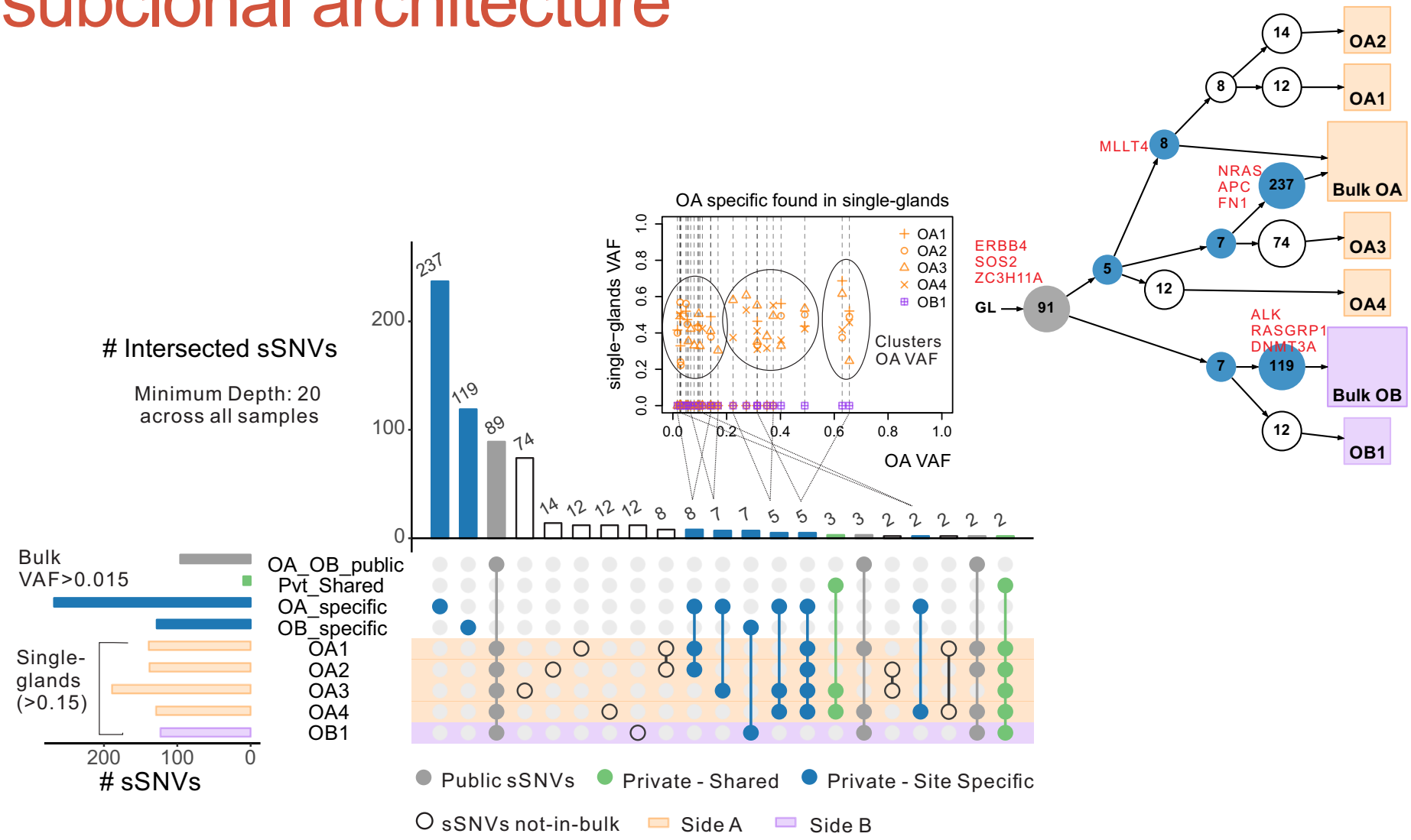
The SFS reflects tumor dynamics



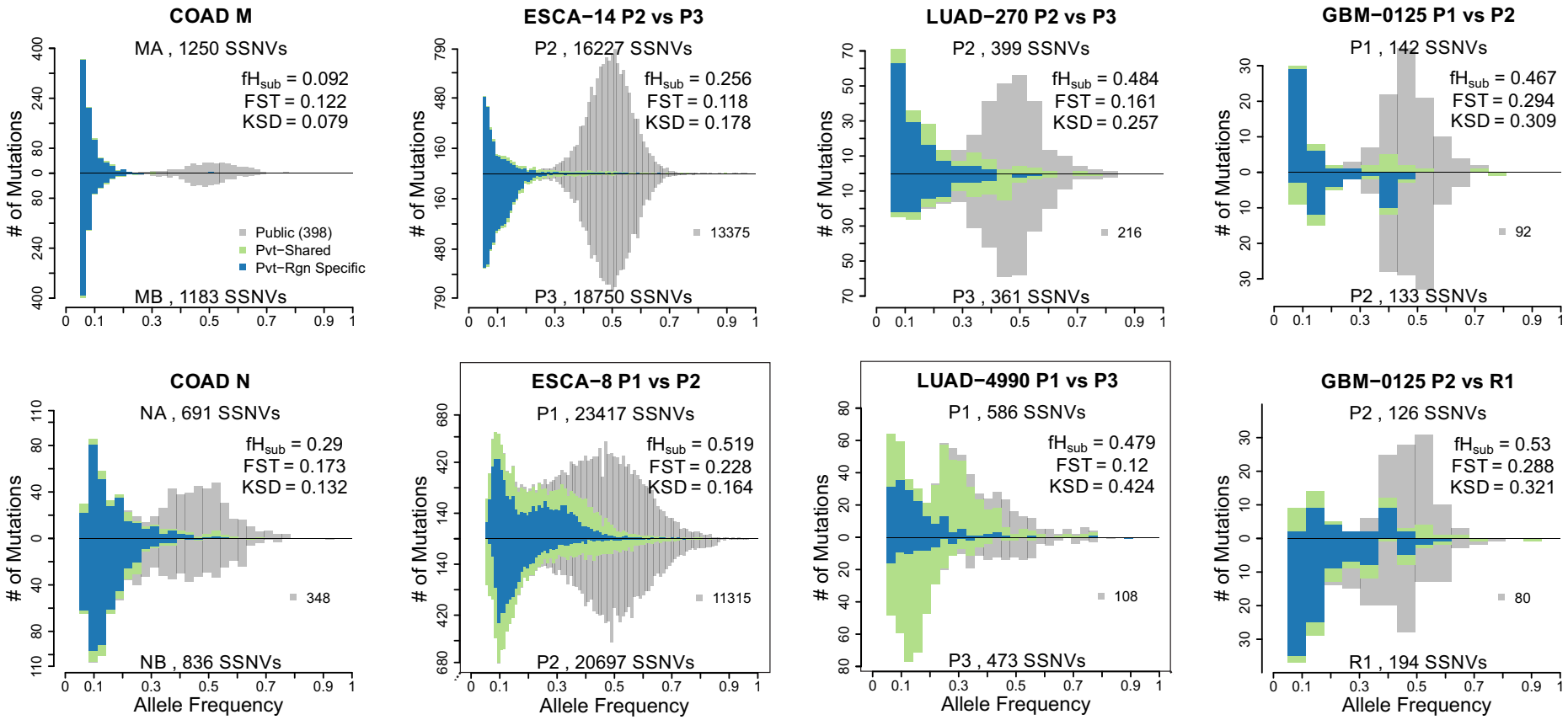




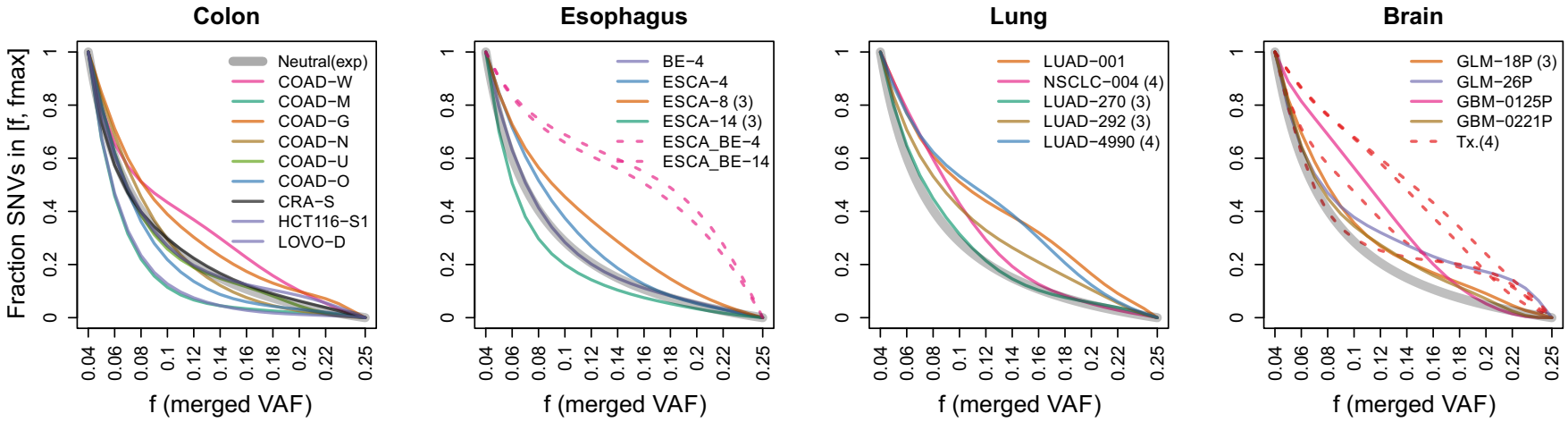
Single gland sequencing reveals complex subclonal architecture

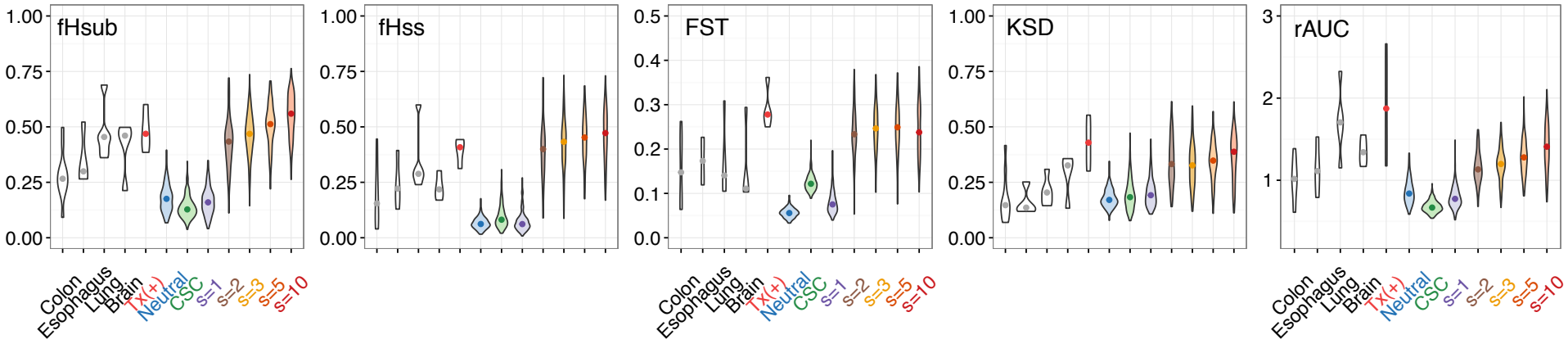


Variable modes of evolution in solid tumors

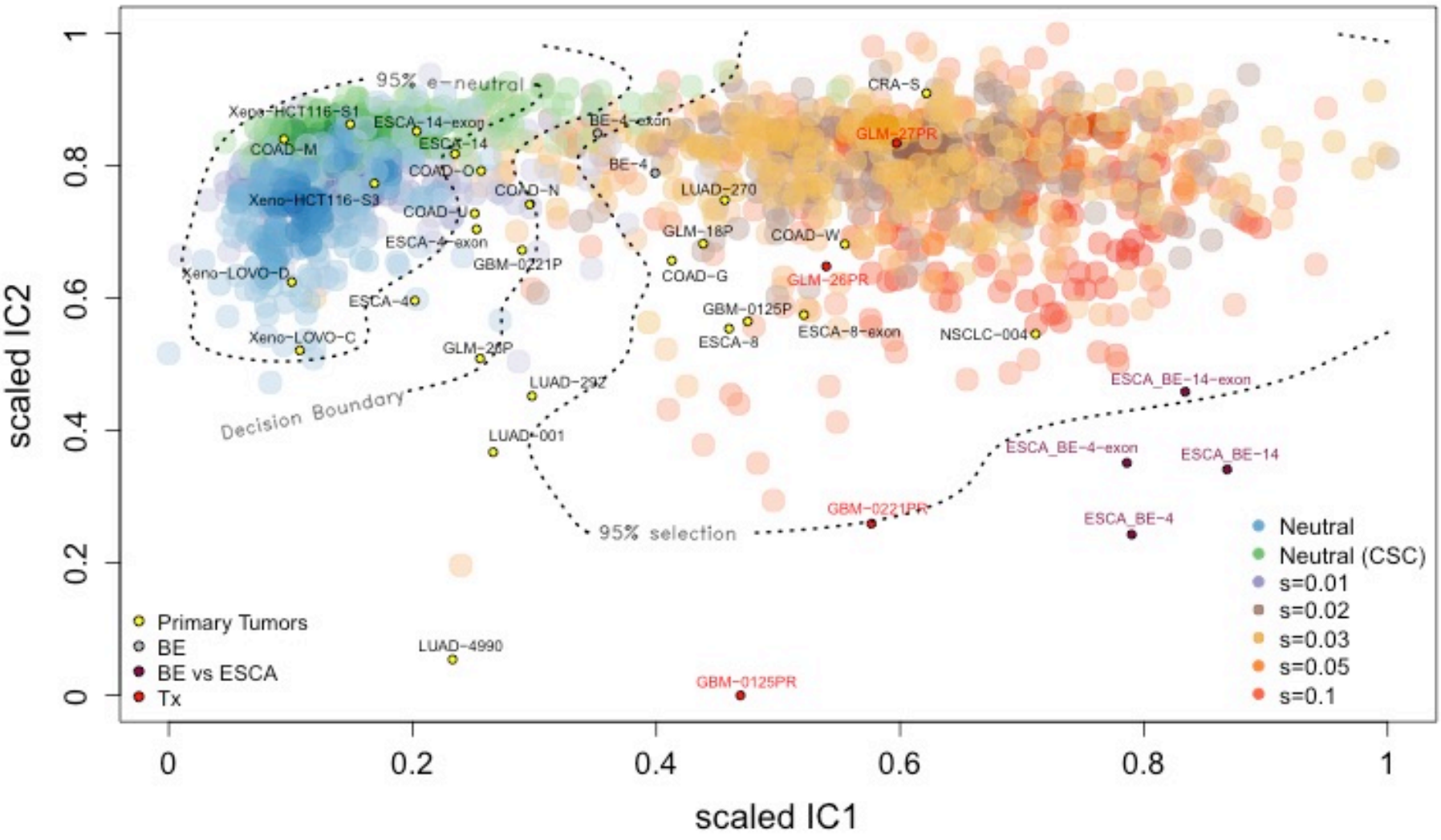


Variable modes of evolution in solid tumors

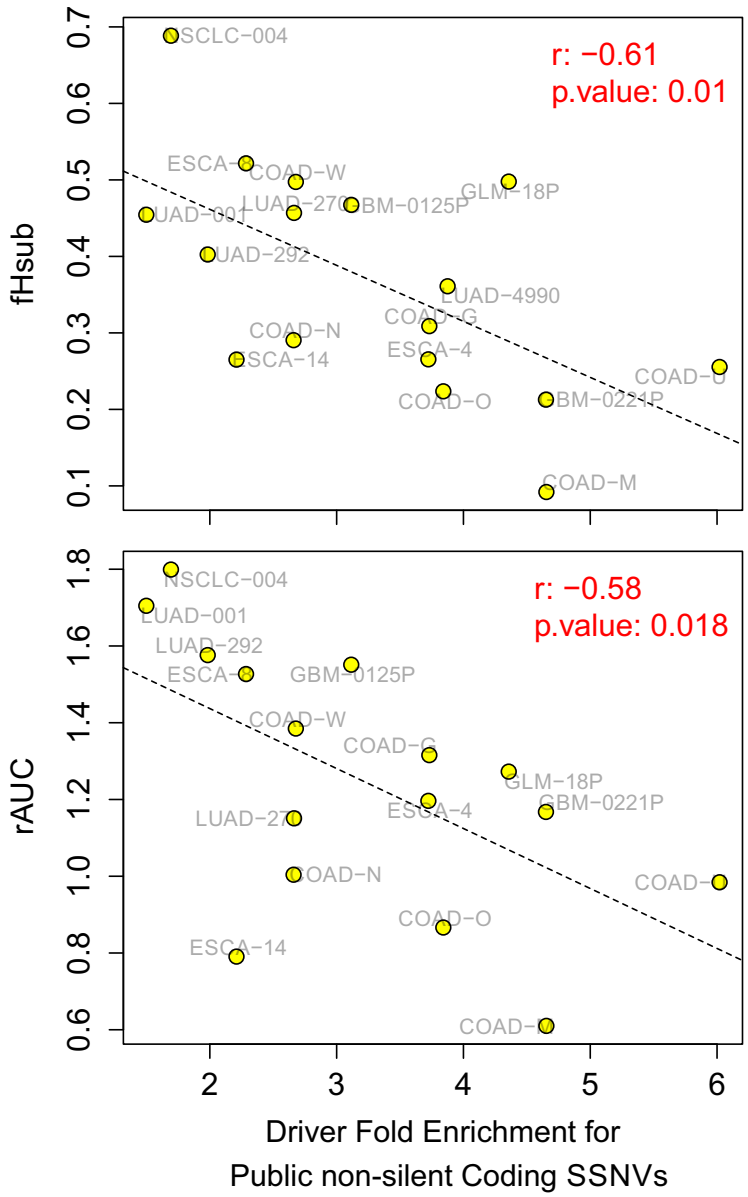


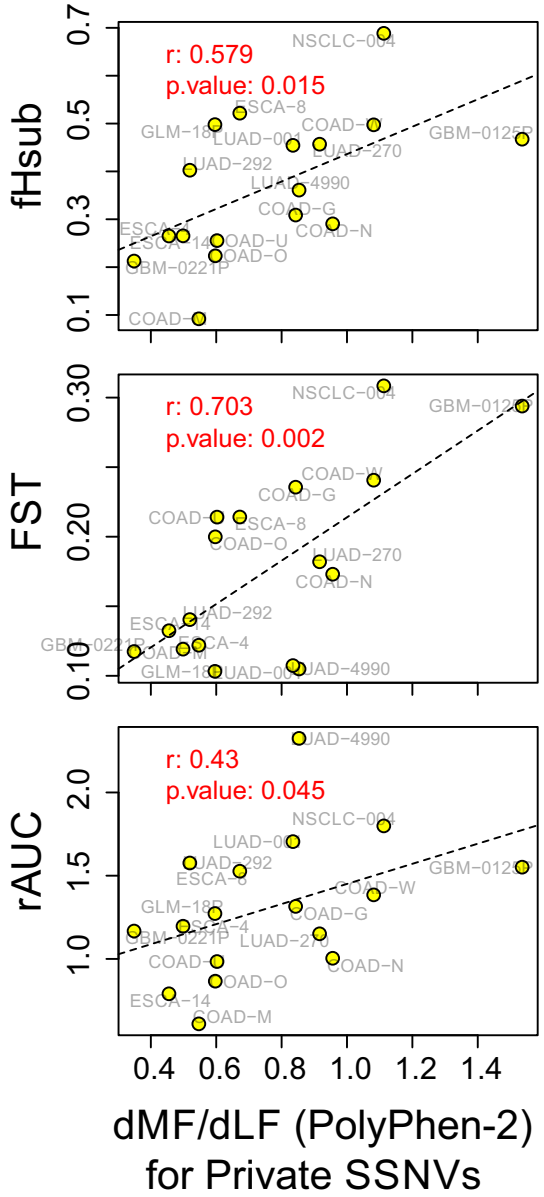


Distinguishing neutrality vs. positive selection



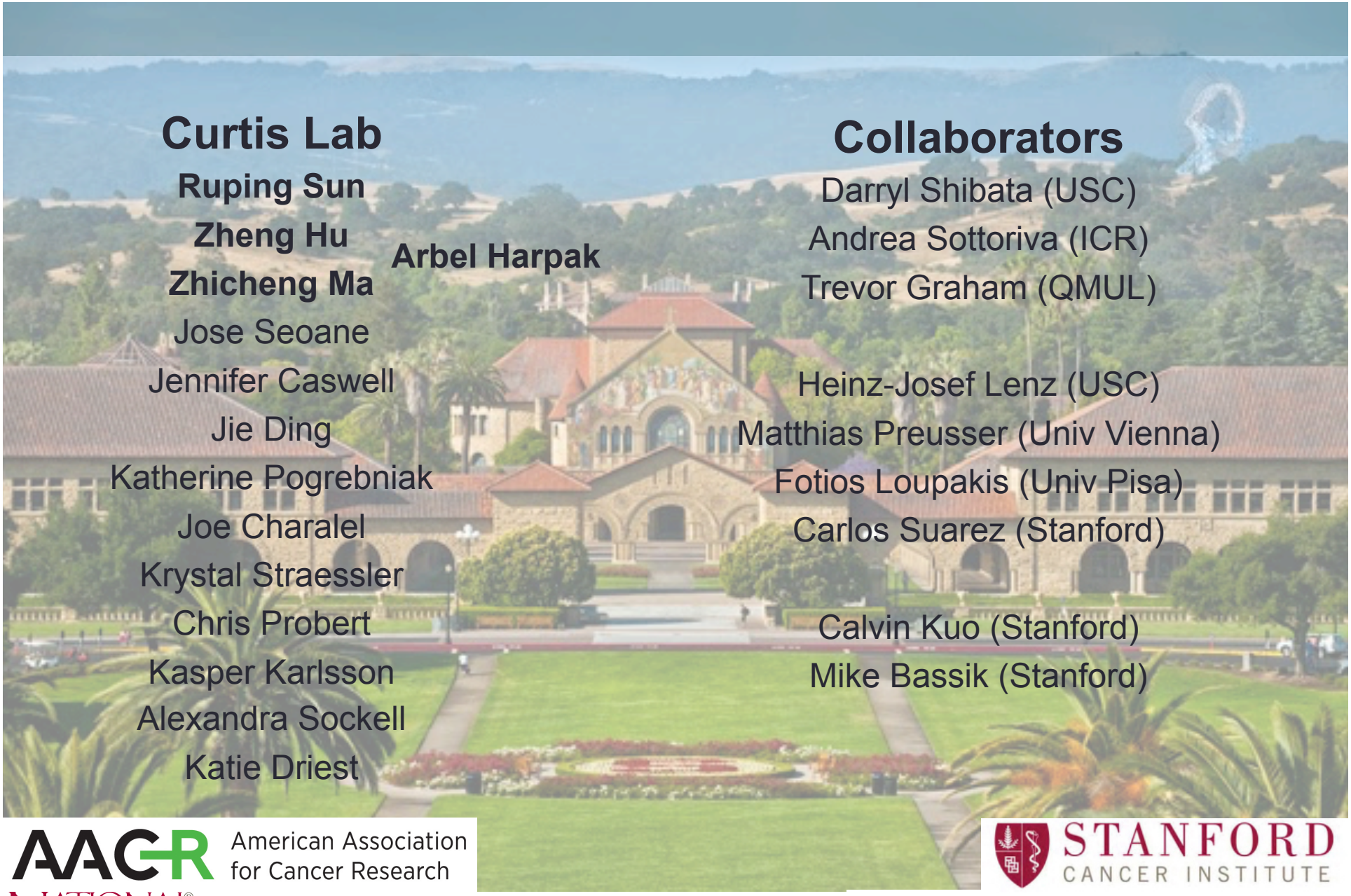
The mode of tumor growth informs ‘drivers’





Towards predictive models and forecasting tumor trajectories

- Tumors are governed by evolutionary principles such that patterns of adaptation may be ‘learned’ and potentially exploited therapeutically
- The ‘mode’ of primary tumor evolution has implications for delineating the ‘drivers’ of progression and its future trajectory
- It is instructive to consider a ‘null’ (neutral) model which generates testable predictions; selection is more complex and its signal can be dampened
- Ongoing efforts are focused on developing predictive models informed by evolutionary dynamics and longitudinal ‘omic’ measurements



Curtis Lab

Ruping Sun

Zheng Hu

Zhicheng Ma

Jose Seoane

Jennifer Caswell

Jie Ding

Katherine Pogrebniak

Joe Charalel

Krystal Straessler

Chris Probert

Kasper Karlsson

Alexandra Sockell

Katie Driest

Arbel Harpak

Collaborators

Darryl Shibata (USC)

Andrea Sottoriva (ICR)

Trevor Graham (QMUL)

Heinz-Josef Lenz (USC)

Matthias Preusser (Univ Vienna)

Fotios Loupakis (Univ Pisa)

Carlos Suarez (Stanford)

Calvin Kuo (Stanford)

Mike Bassik (Stanford)

AACR American Association for Cancer Research

NATIONAL CANCER INSTITUTE

susan g. komen FOR THE cure

THE V FOUNDATION for Cancer Research

The Breast Cancer Research Foundation

STANFORD CANCER INSTITUTE

Congressionally Directed Medical Research Programs CDMRP Department of Defense