Reconstructing the Starts of Human Tumors

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June 3, 2016

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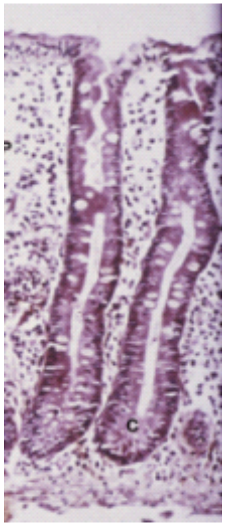
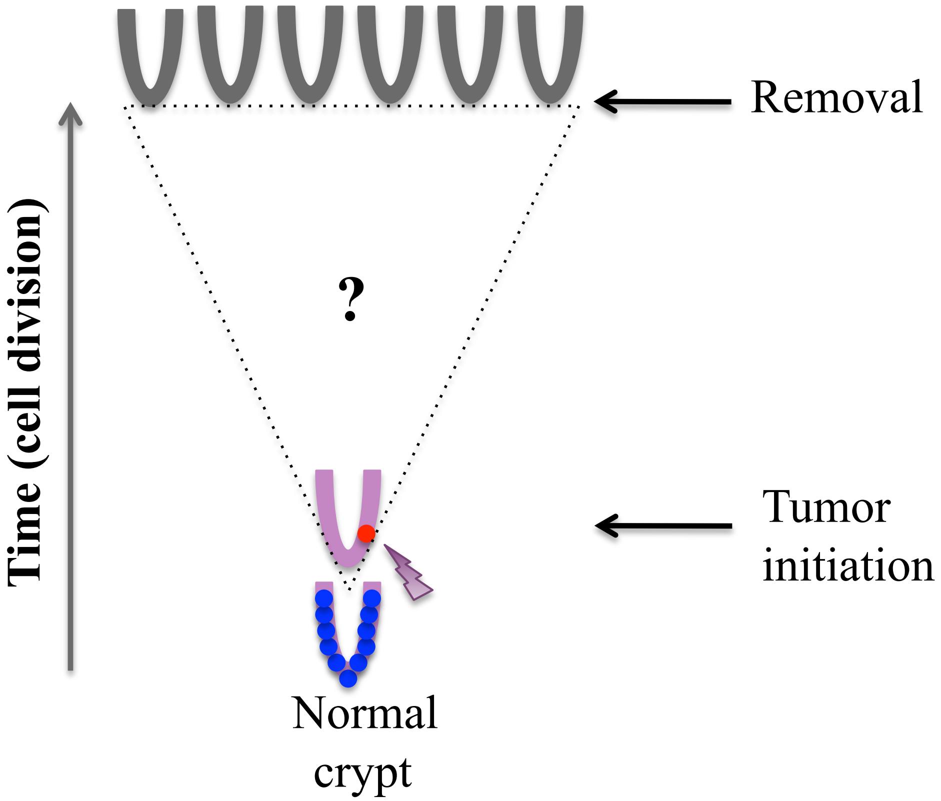
Cancer is a Clonal Expansion

Colon Crypt



Single crypt
~2,000 cells



Time (cell division)

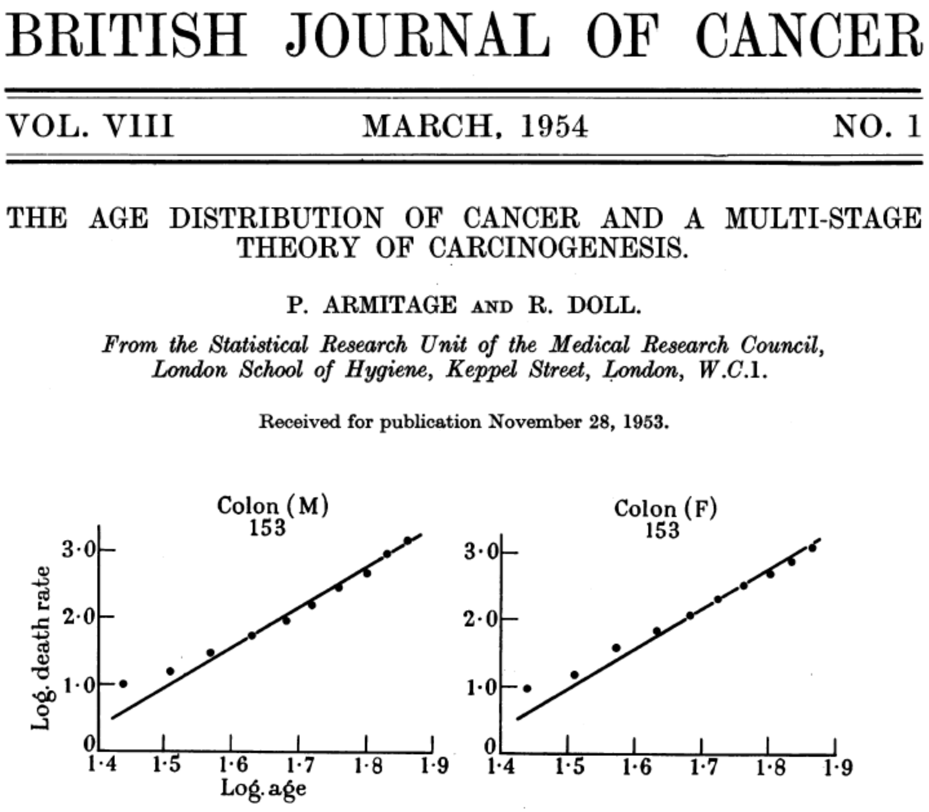
?

Removal

Tumor
initiation

Normal
crypt

Modeling Cancer Growth



BRITISH JOURNAL OF CANCER

VOL. VIII MARCH, 1954 NO. 1

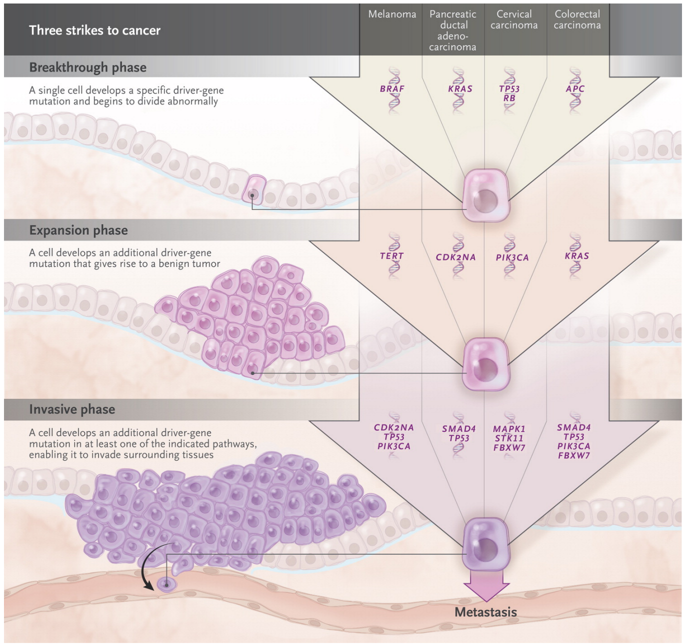
THE AGE DISTRIBUTION OF CANCER AND A MULTI-STAGE THEORY OF CARCINOGENESIS.

P. ARMITAGE AND R. DOLL.

From the Statistical Research Unit of the Medical Research Council, London School of Hygiene, Keppel Street, London, W.C.1.

Received for publication November 28, 1953.

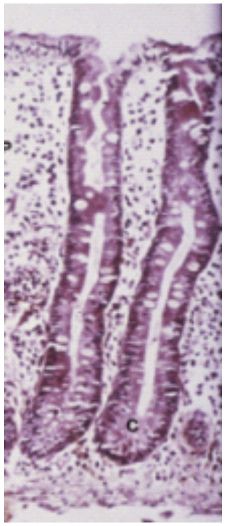
Three Strikes to Cancer



**Vogelstein B, Kinzler KW.
N Engl J Med (2015)**

Population Structure

Colon Crypt



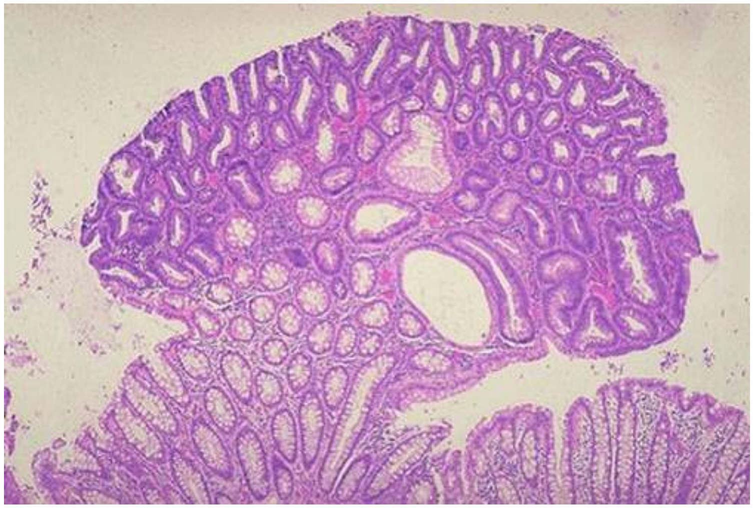
migration

Differentiated Cells

Stem cells

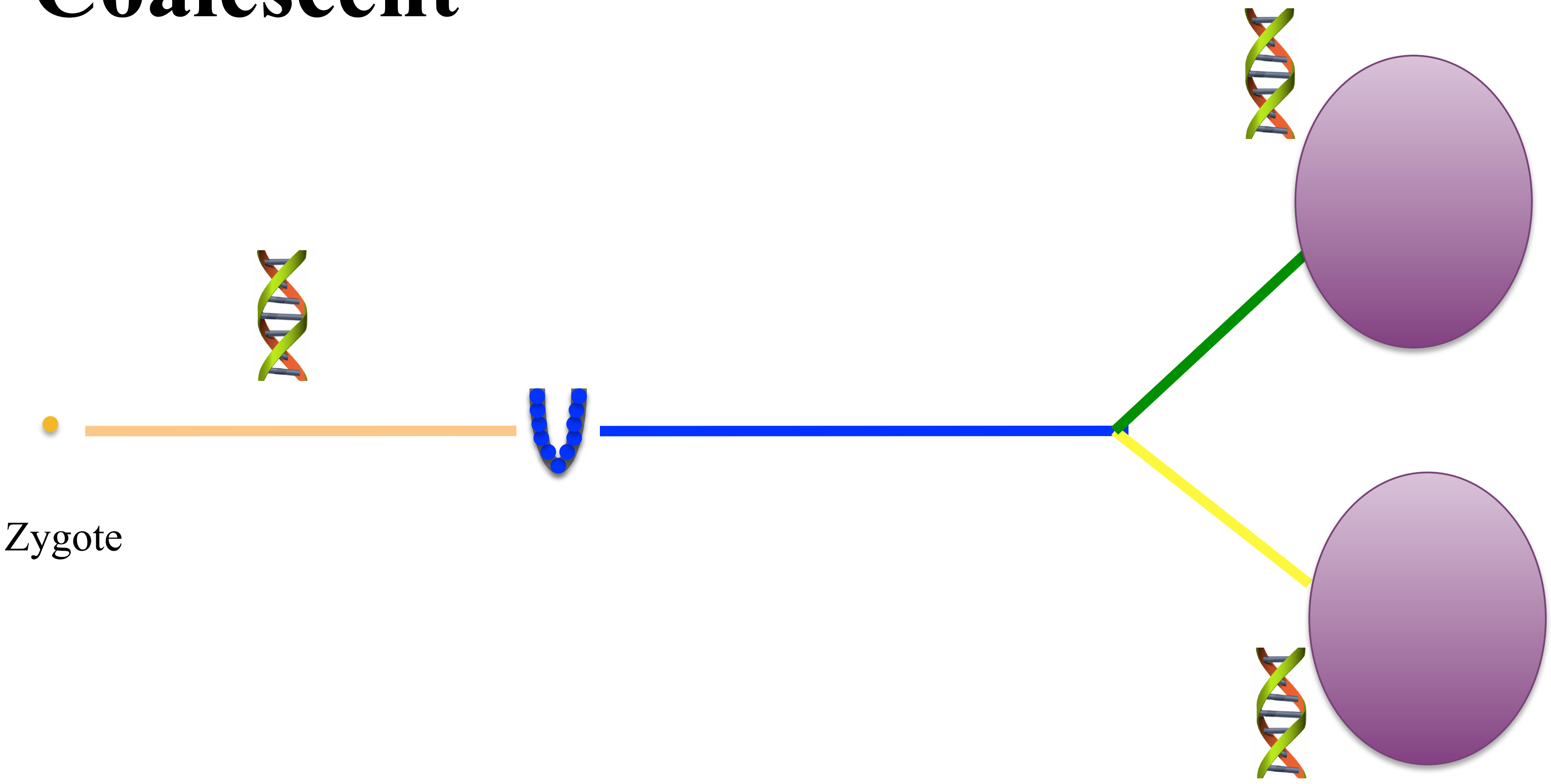
Single crypt
~2,000 cells

Colon tumor



Single cancer gland
~10,000 cells

Coalescent

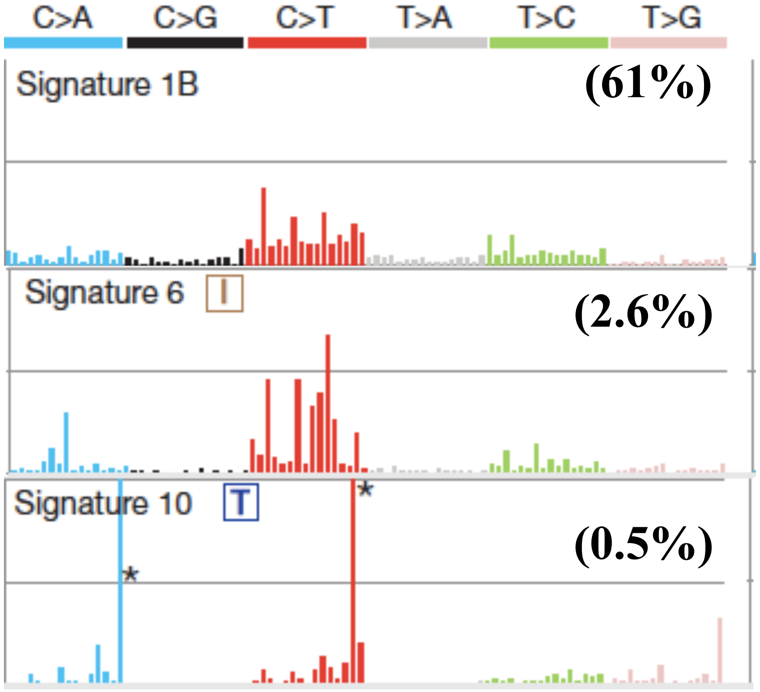


Signatures of mutational processes in human cancer

22 AUGUST 2013 | VOL 500 | NATURE | 415

- 7,032 cancers (30 classes)
- Found 20 mutational signatures
- Colorectal tumors (n~550) represented a mixture of 4 signatures

Colorectum



Age

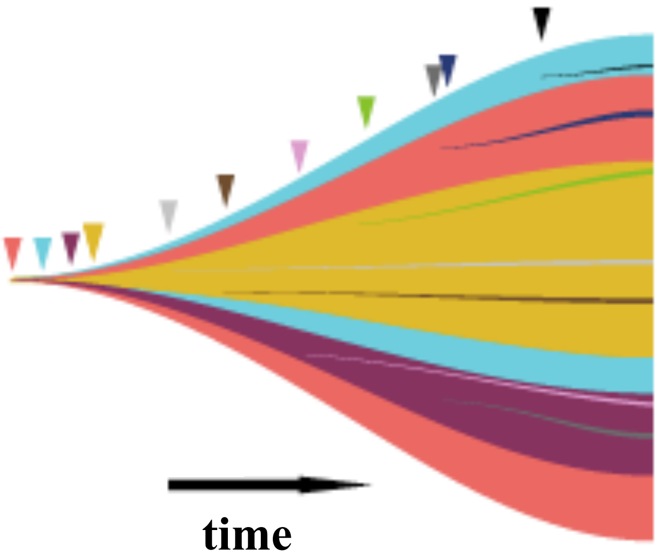
DNA MMR deficiency

Pol ε Mutations

Other (unspecified)

Big Bang Expansion

Sottoriva et al. Nature Genetics (2015)

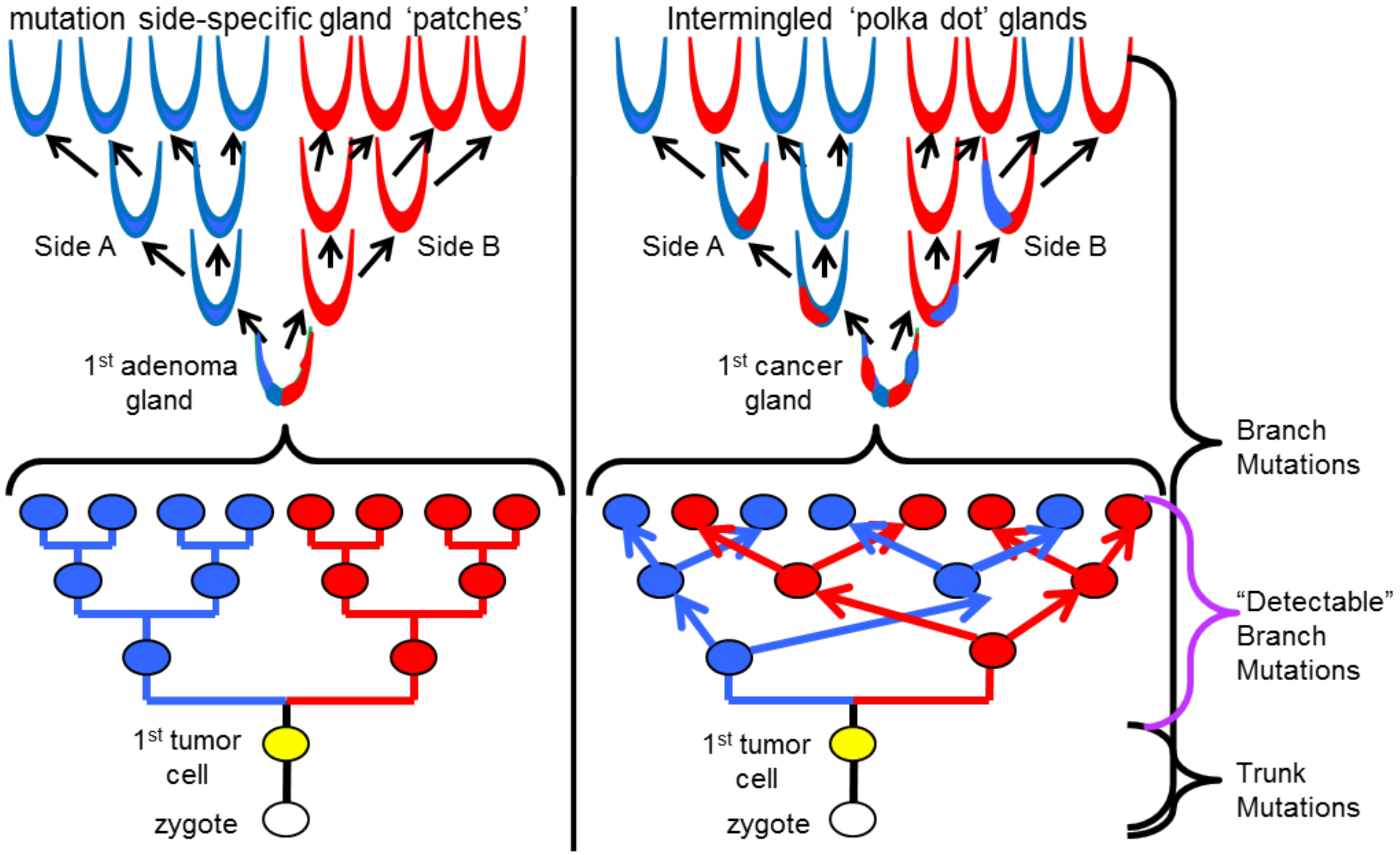


Division	# cells	SNV Frequency
0	1	50%
1	2	25%
2	4	12.5%
3	8	6.25%

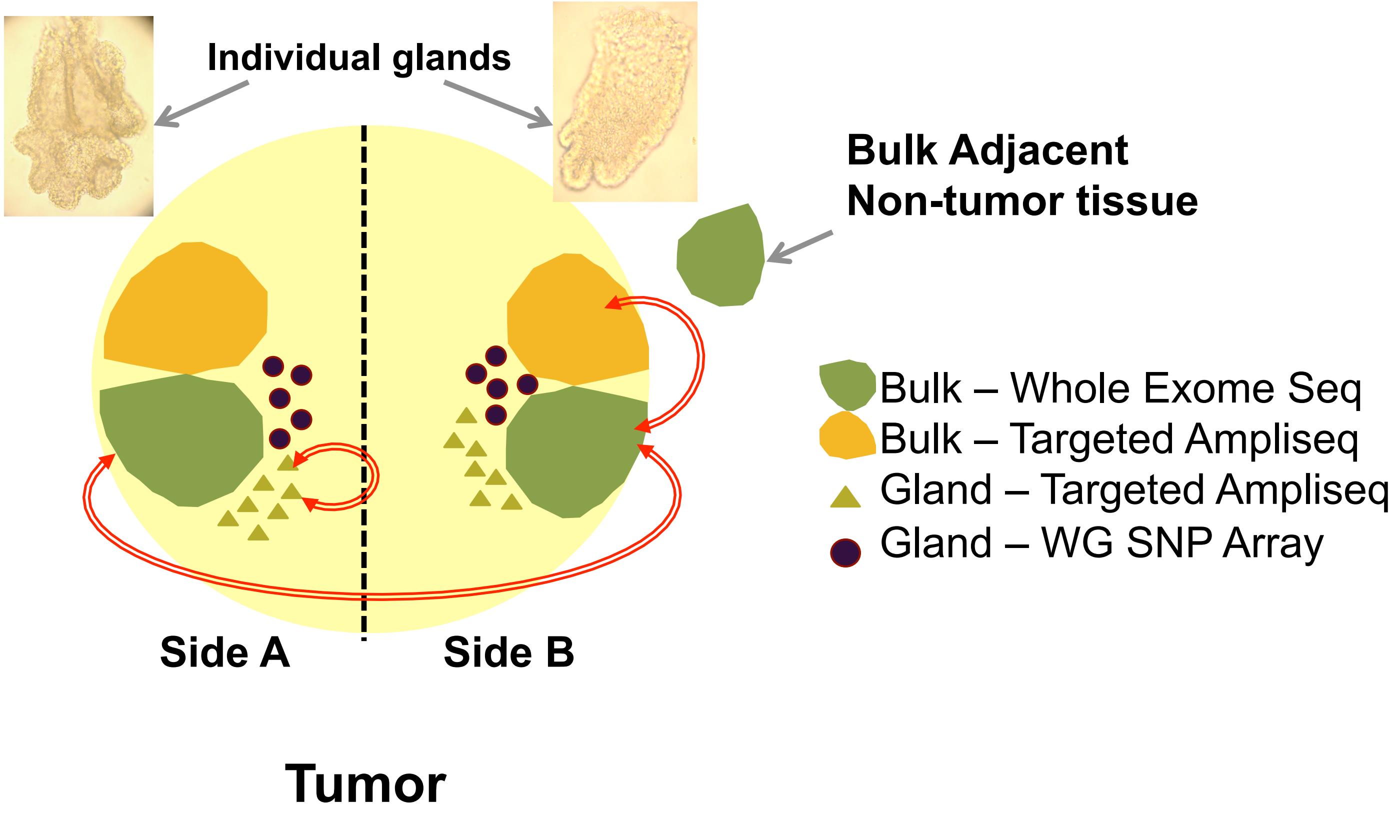
Mutation frequency is a function of time.

Detectable mutations are old mutations

Tumor Growth Models

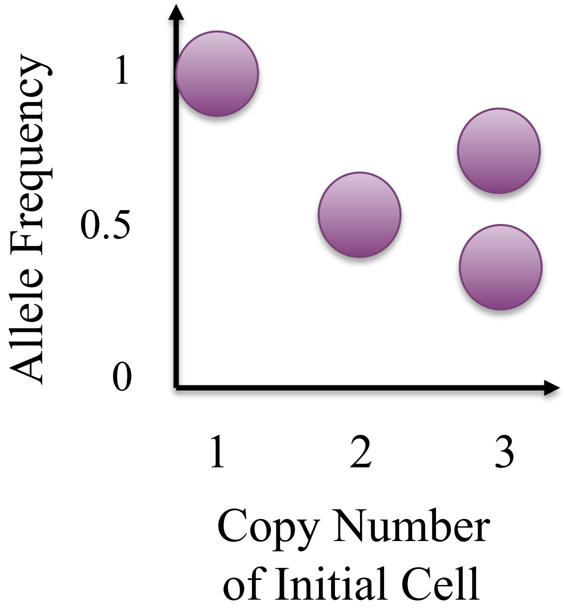


Tumor Sampling

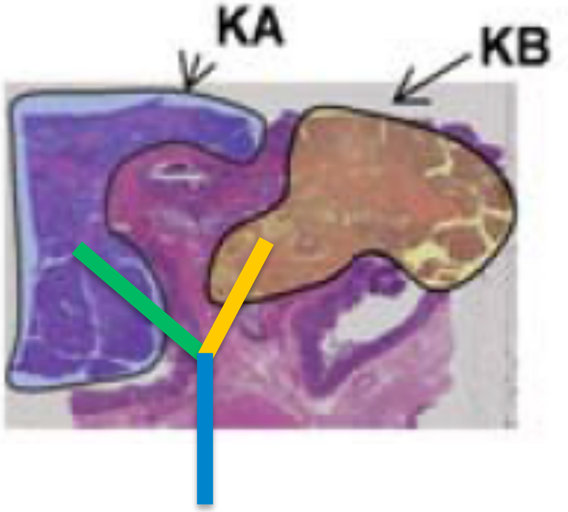


Identify Trunk Mutations

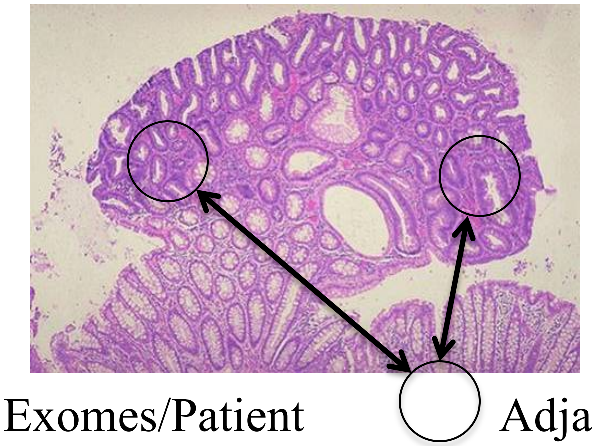
Single Sample



Multiple Samples



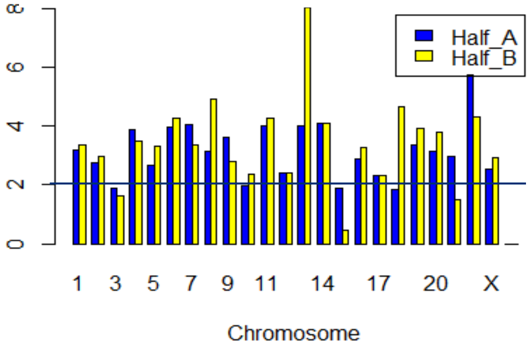
Whole Exome Sequencing



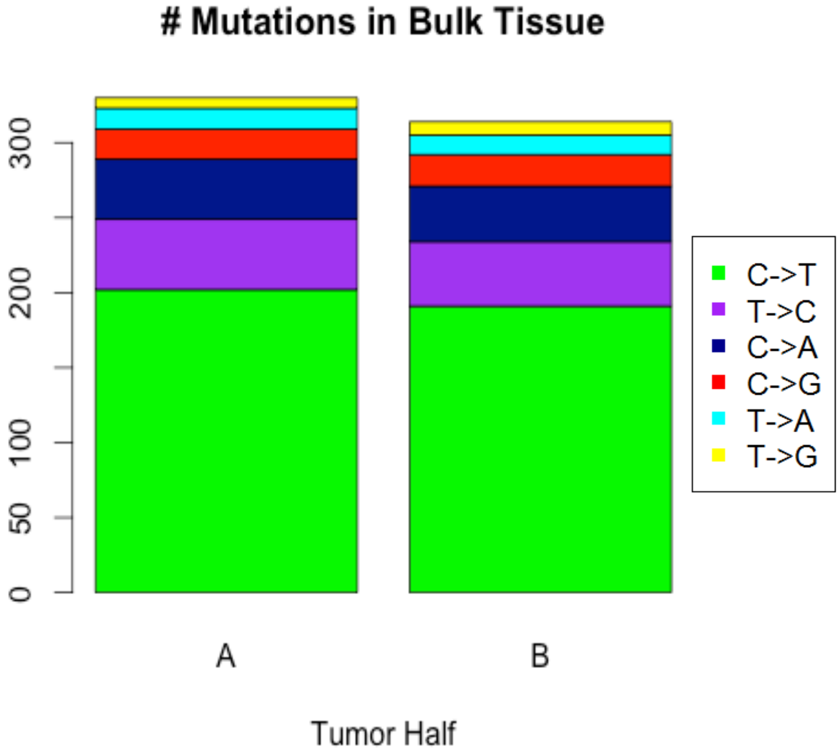
Colon
Cancer
(~30X)

3 Exomes/Patient

Adjacent
Normal (~15X)

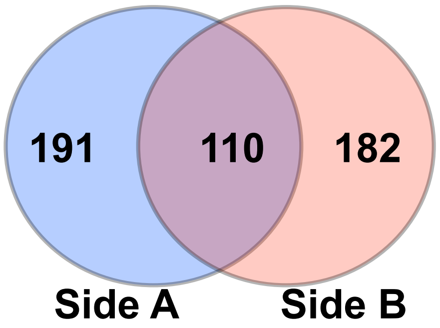


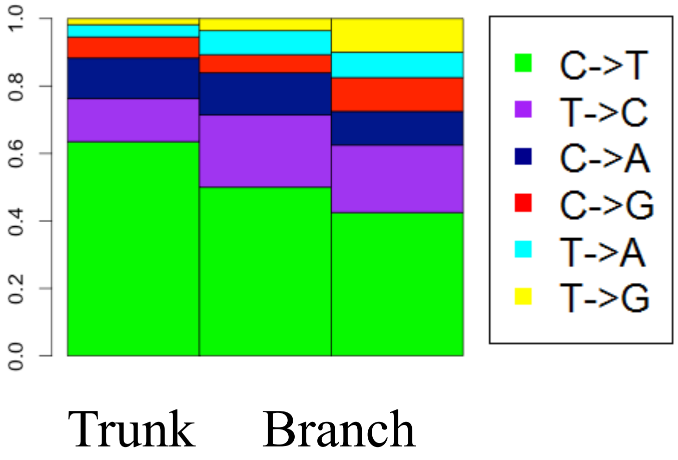
Average
3.1 sSNVs/Mb

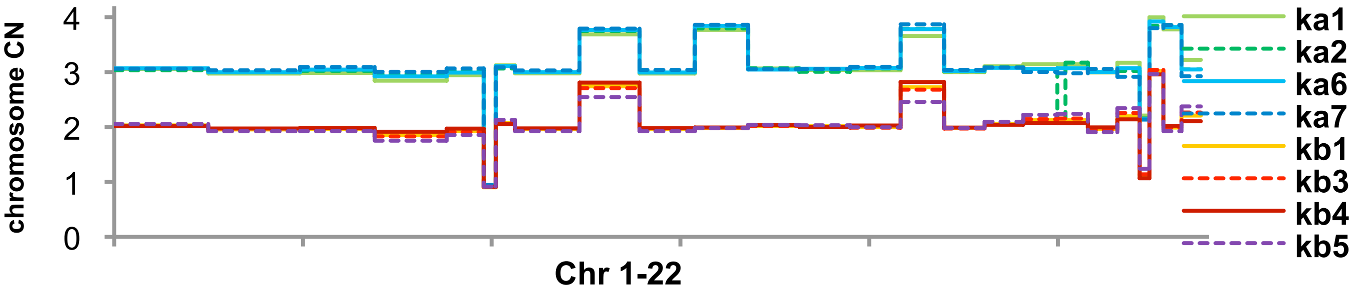


Somatic Mutations/ Copy Number Alterations

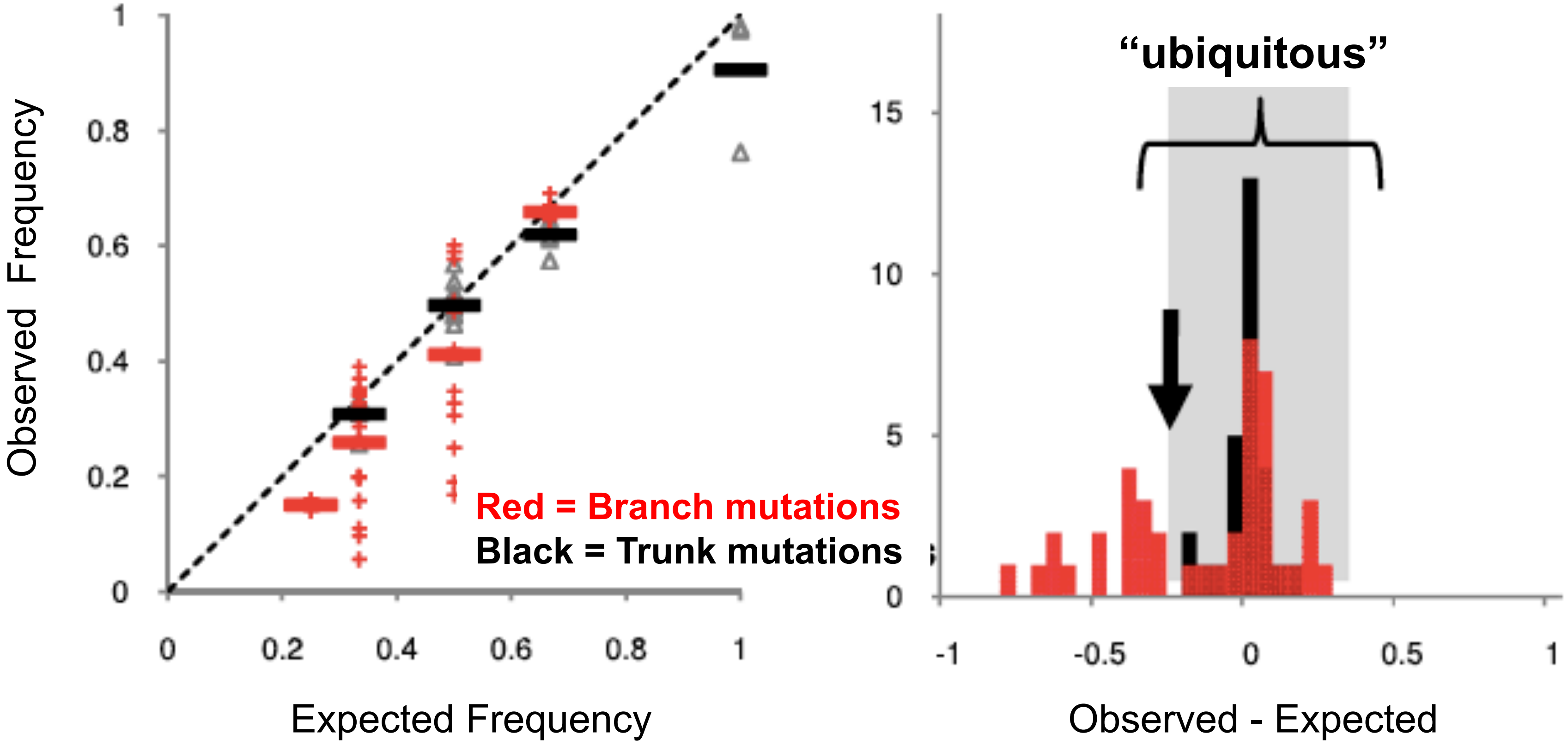
Trunk and Branch mutations





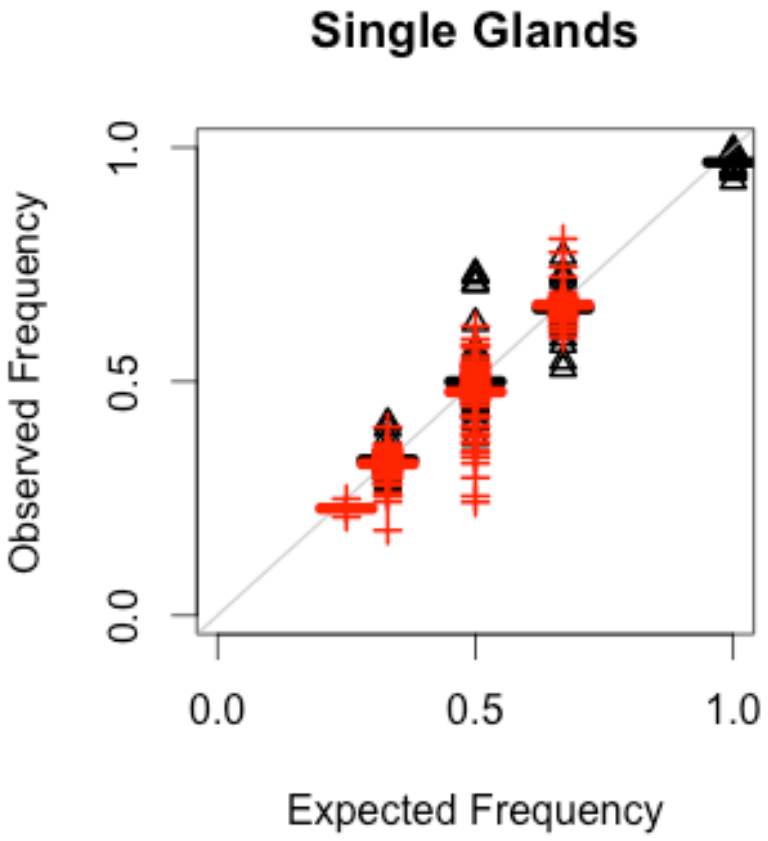


Trunk Mutations Overcalled in Single Samples



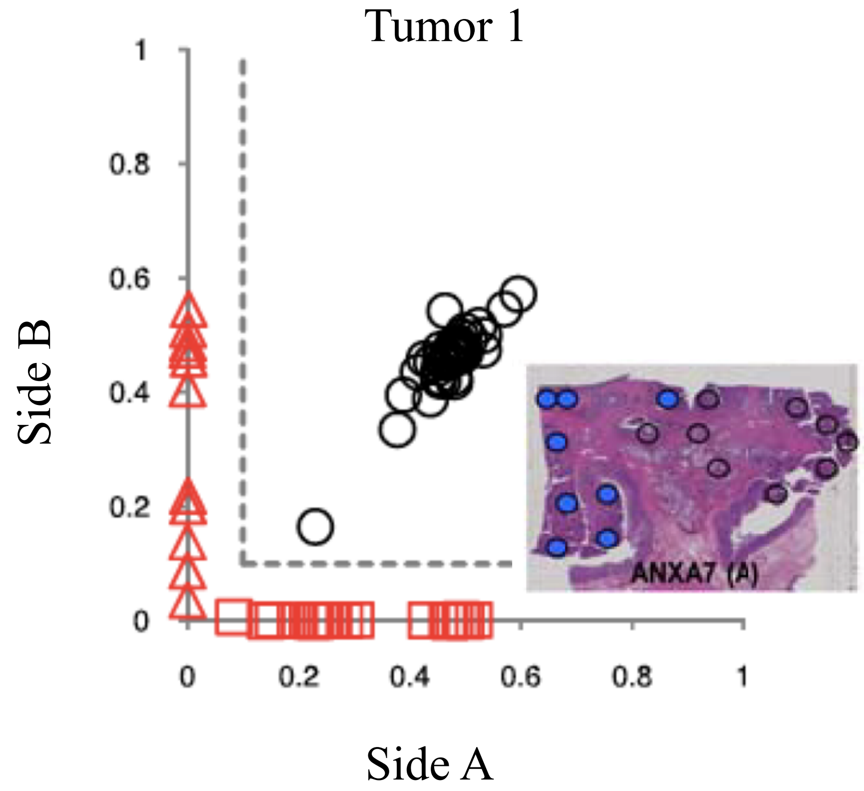
Red = Branch mutations
Black = Trunk mutations

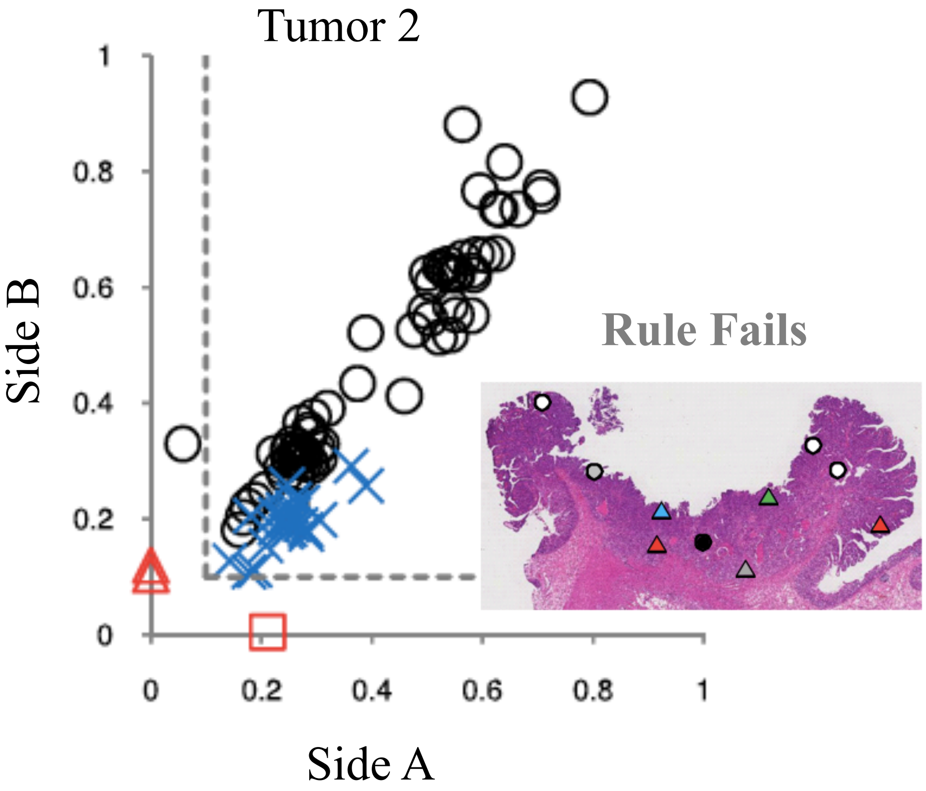
Glands are Clonal Populations



Mutation Classification

RULE: < 10% frequency on one side identifies branch mutations





Rule Fails

What happens at the start?

- Distinguish Trunk & Branch mutations

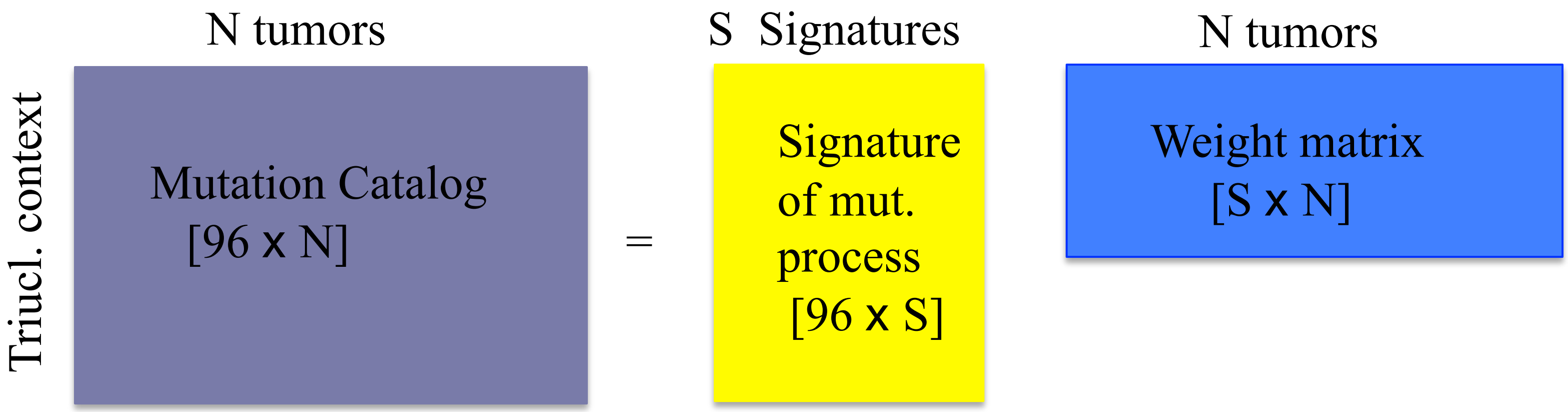
Tumor Type	#Trunk	#Branch
Adenoma	110	373
Adenoma	180	282
Adenoma	122	203
Adenoma	84	129

Tumor Type	#Trunk	#Branch
MSI	1134	237
MSS	128	122
MSS	129	326
MSS	129	112

- Are the mutational signatures different before and after tumor initiation?

Mutation Catalogs

- Accumulation of mutations from different mutational processes
- Use Non-negative Matrix Factorization to deconvolute individual mutational signatures



N tumors

Triucl. context

Mutation Catalog [96 x N]

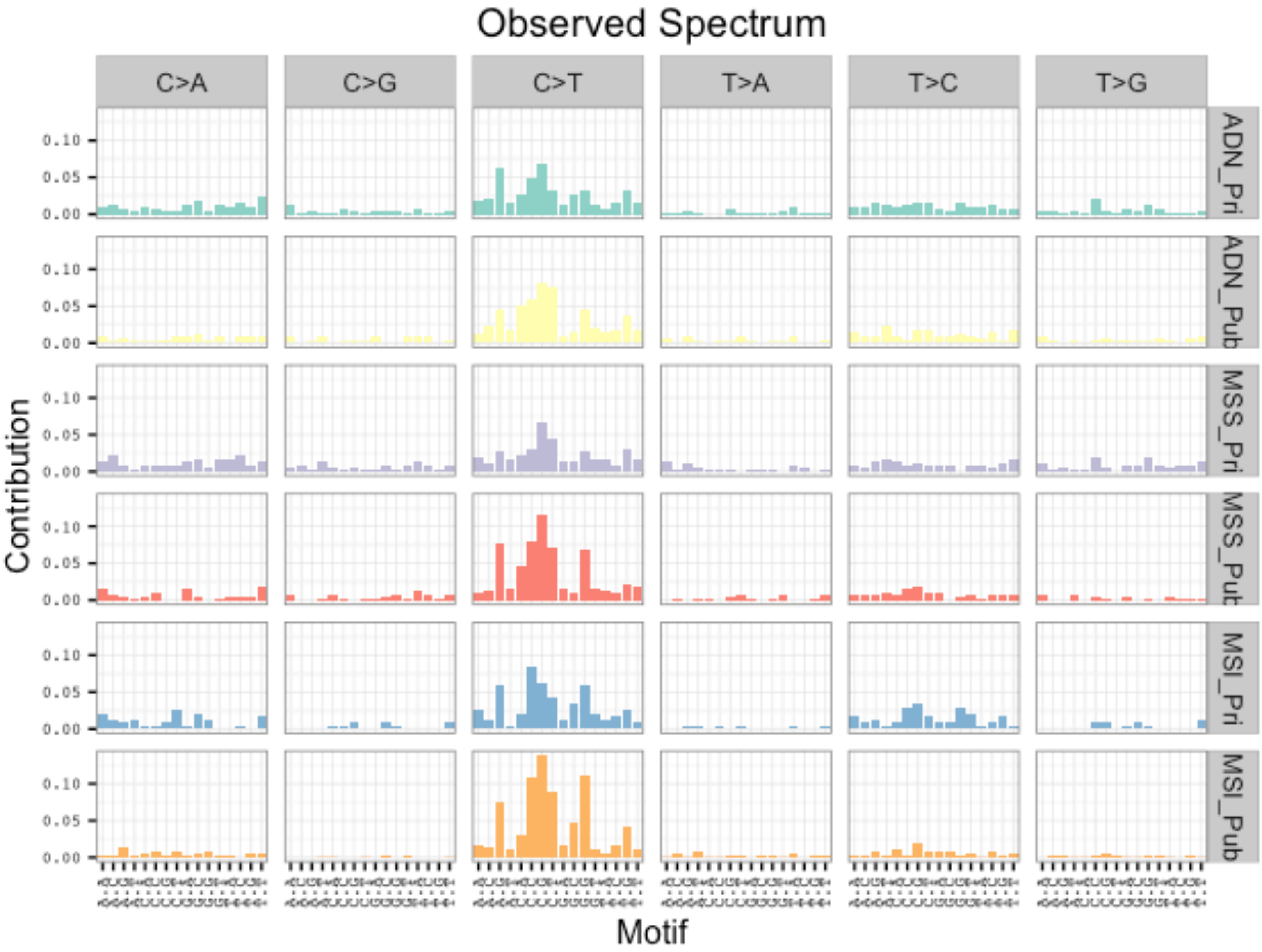
=

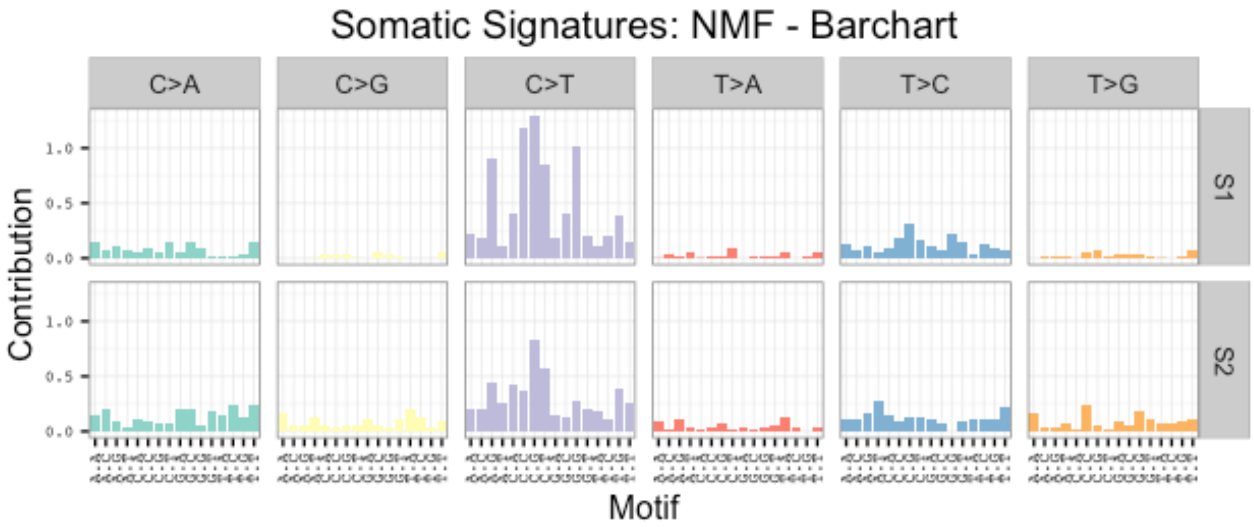
S Signatures

Signature of mut. process [96 x S]

N tumors

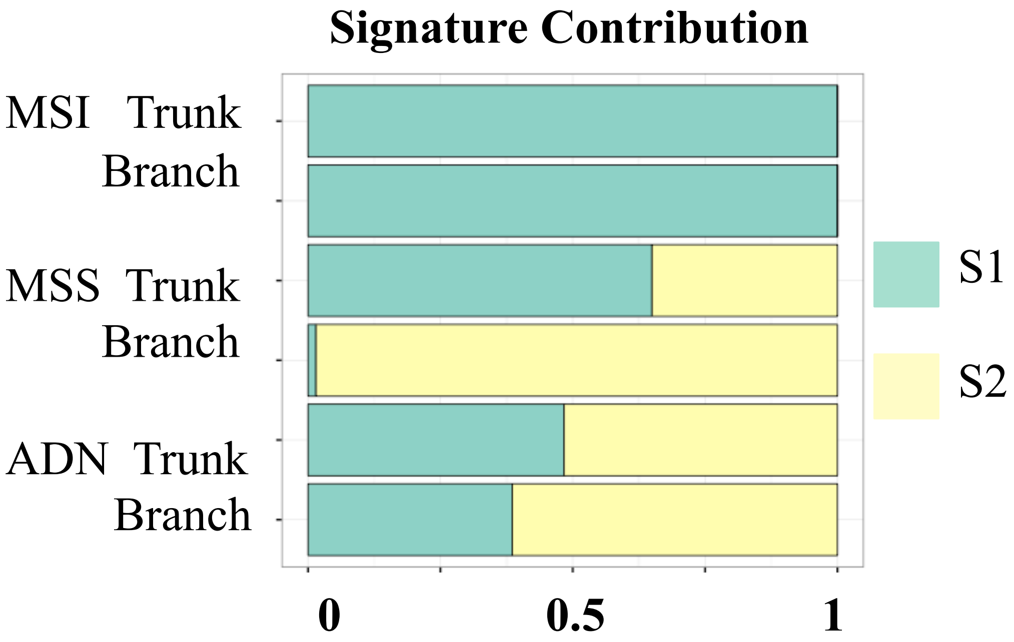
Weight matrix [S x N]


Observed Spectrum
C>A
C>G
C>T
T>A
T>C
T>G
ADN_Pri
ADN_Pub
MSS_Pri
MSS_Pub
MSI_Pri
MSI_Pub
Contribution
0.10
0.05
0.00
Motif



Counts of Variants by Tumor Type

Type (n)	#Trunk	#Branch
MSI (1)	1134	237
MSS (3)	386	560
Adenoma (4)	496	987



Summary

- Mutational signatures during tumor growth are not different than during normal evolution in
  - MSI tumors
  - benign adenomas

- Mutational signature during tumor growth appears to be different in MSS tumors

Conclusions

- Tumor initiation provides a unique bottleneck, when passenger somatic variants are easily fixed
- Mutations that we “see” are from before tumor is clinically detectable (only ~8-16 cells)
- Inference based on 1 sample is susceptible to overcalling trunk mutations due to spatial structure

Acknowledgements

University of So. California

Department of Pathology

Darryl Shibata

Department of Preventive Medicine
Paul Marjoram

Department of Computational Biology

Junsong Zhao

Matt Salomon

Stanford University

Christina Curtis

University College London

Andrea Sottoriva