Reconstructing Human Tumor Histories By Comparing Genomes From Different Parts of the Same Cancer

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Somatic Evolution in the Clinic

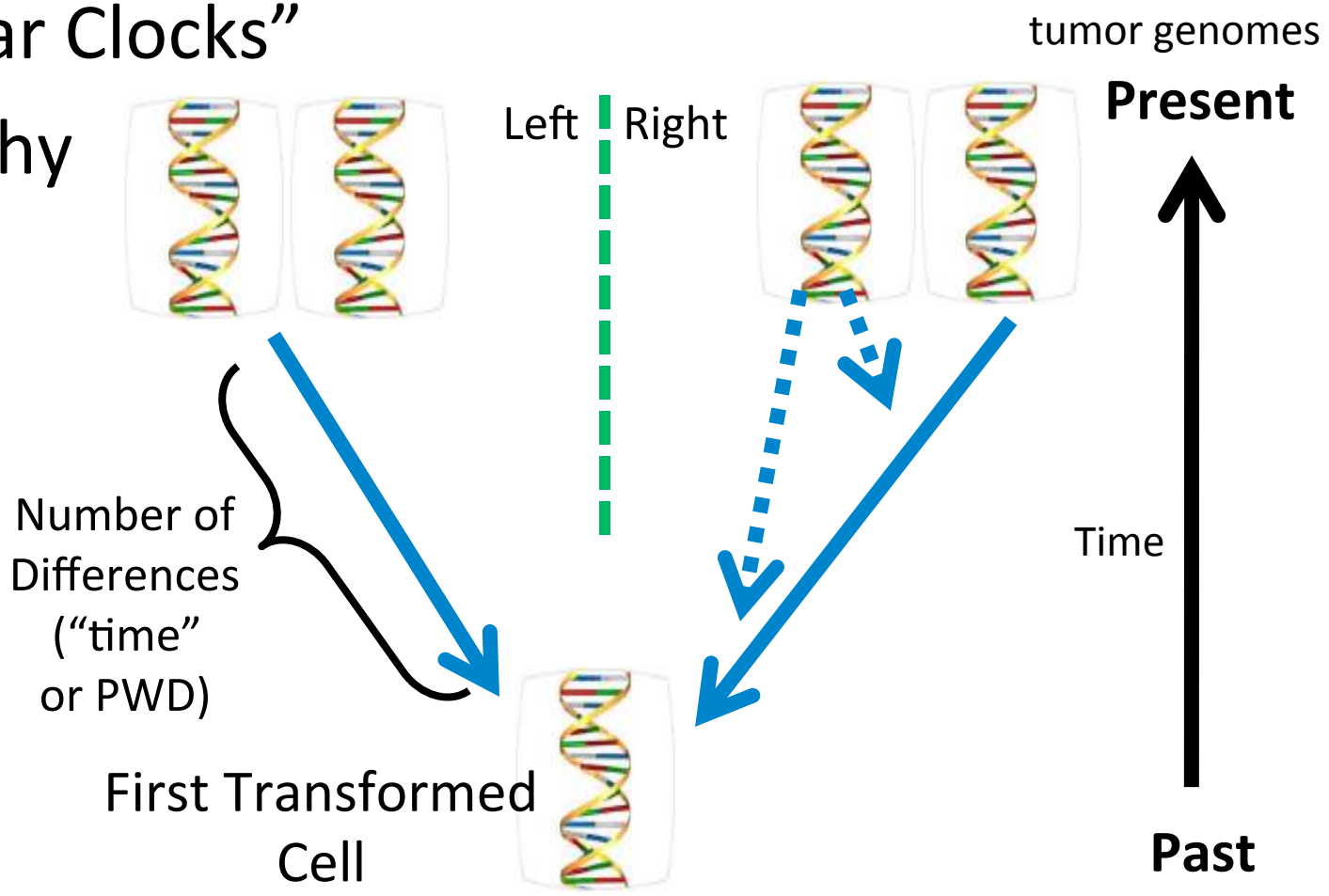
- Widely Accepted That Tumors Evolve
- Many Different Possible Pathways
- Serial Observations Impractical
- A Patient "Suddenly" Has Cancer
- Clinical Questions (Patient Specific):

  --- How Did This Tumor Evolve?

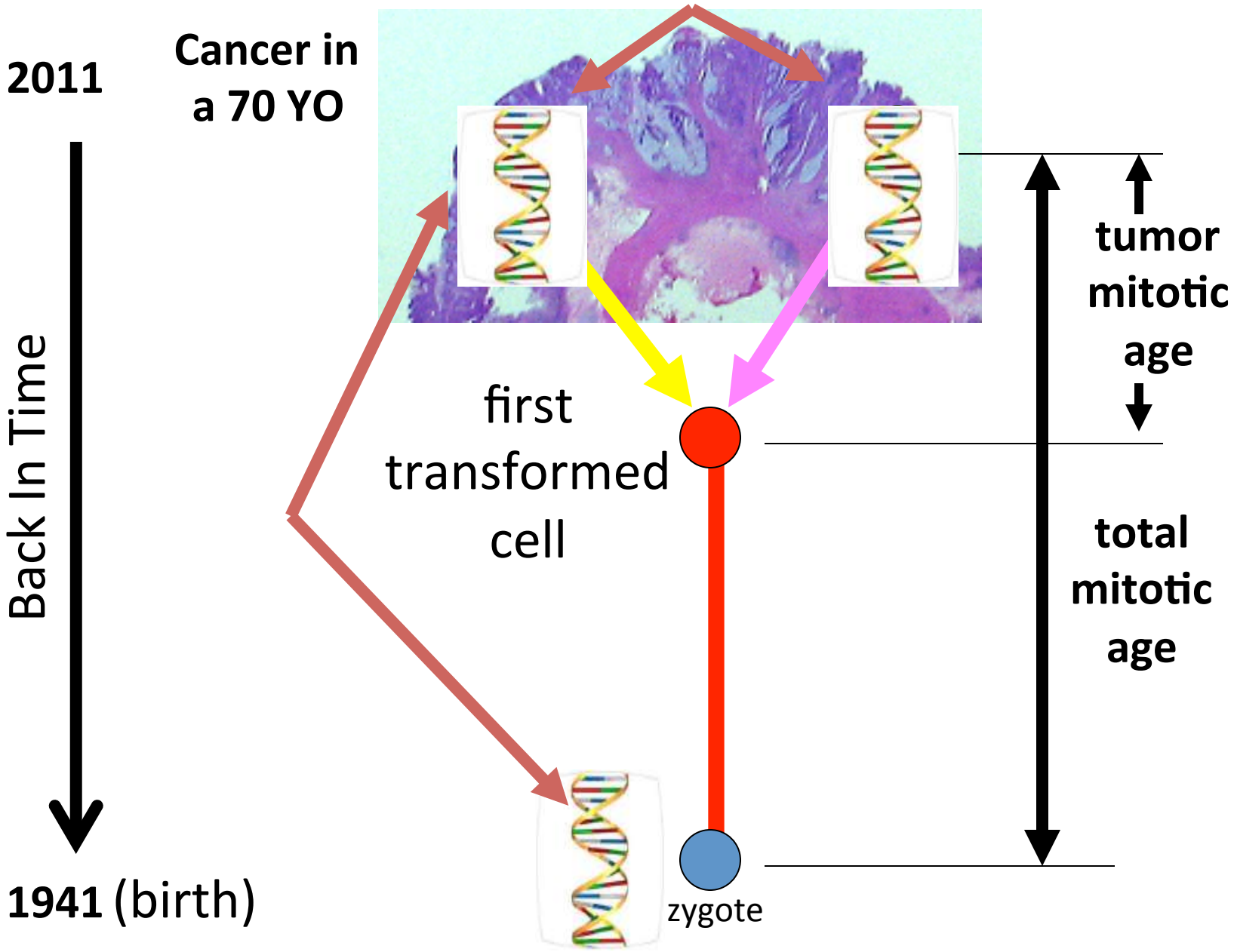
  --- Do Different Evolutionary Histories Matter?

An Approach To Patient Specific Tumor Histories

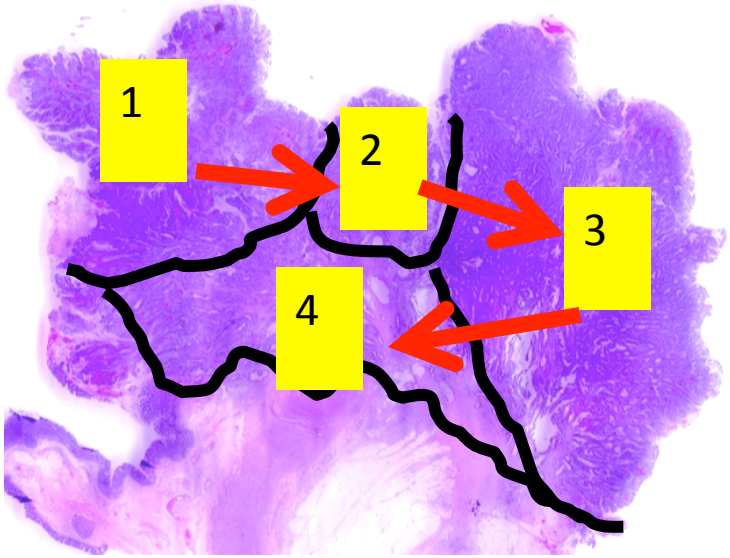
- Coalescent Theory
- "Molecular Clocks"
- Topography



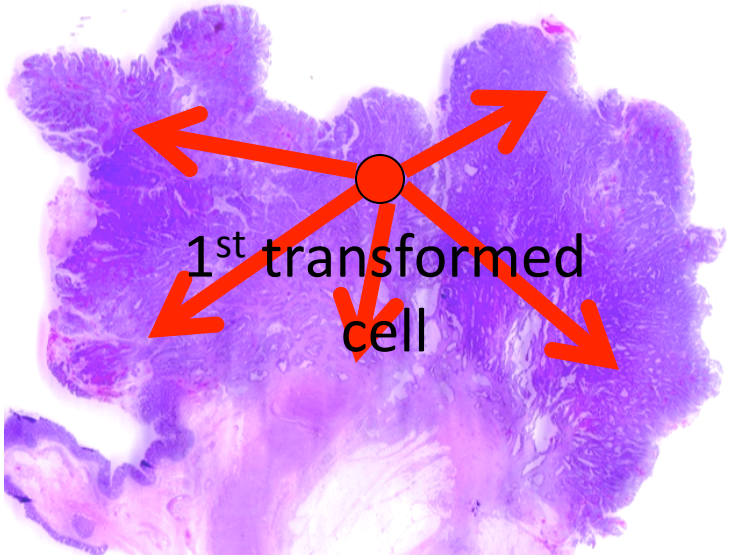
Basic Cancer Ancestry Reconstruction



A Problem: The Evolution of Any Individual Human Cancer is Unknown



Sequential or
Clonal Evolution



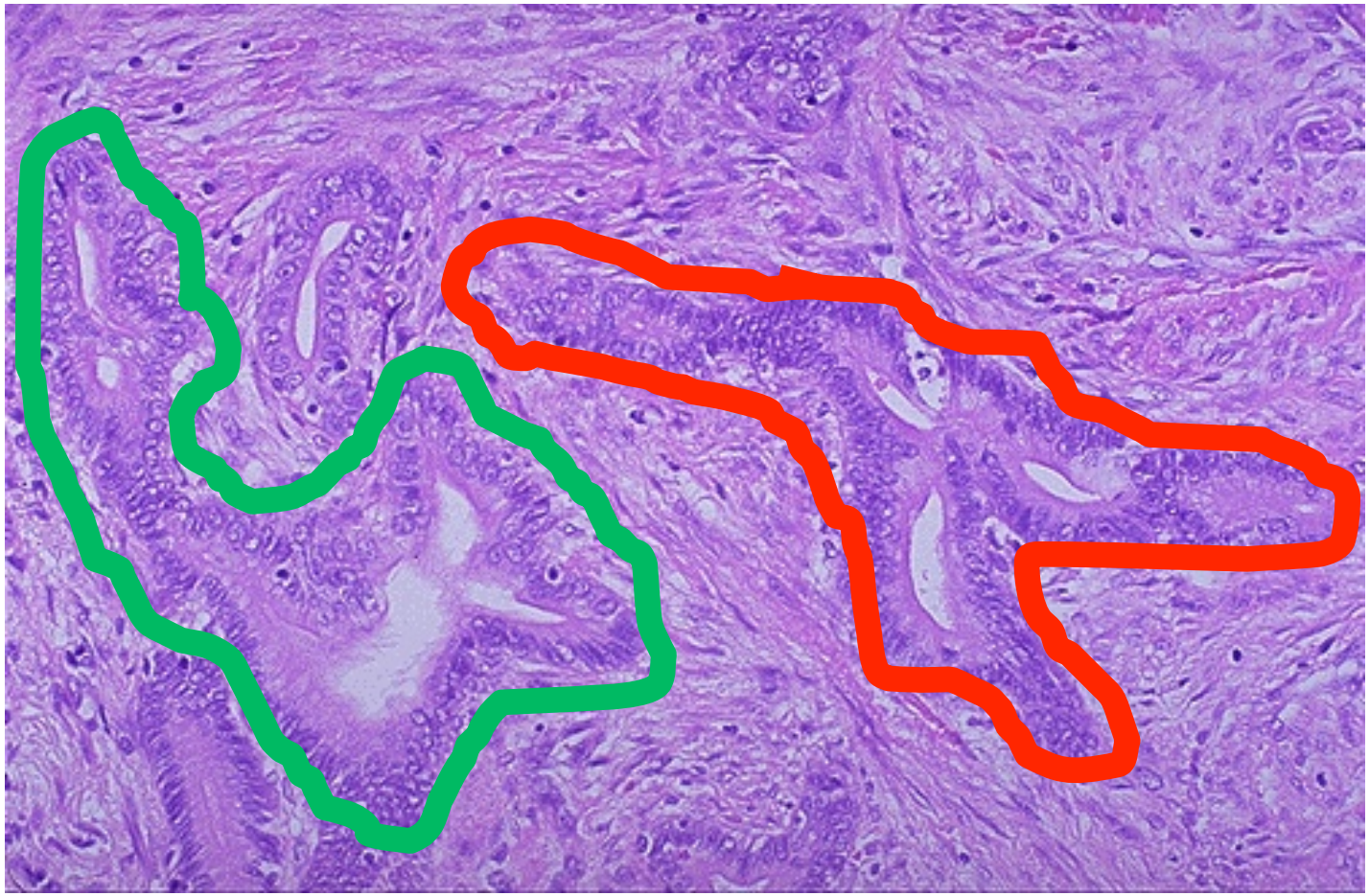
"Big Bang" (full malignant potential at transformation)

Older Parts More Diverse

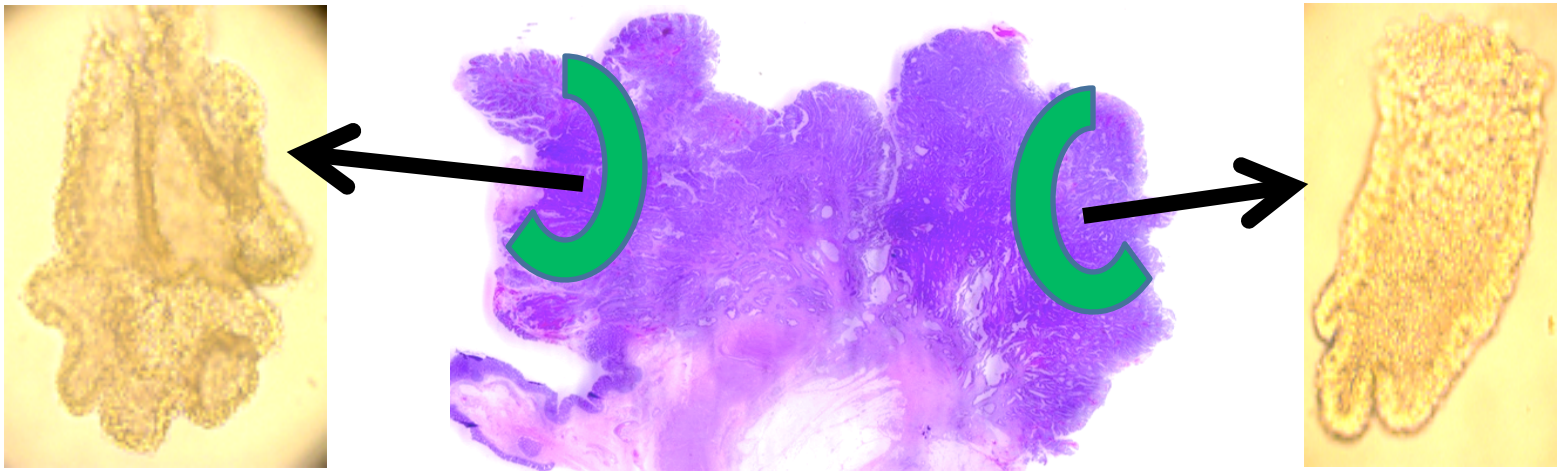
Uniform Diversity

Colorectal Cancer: Adenocarcinoma

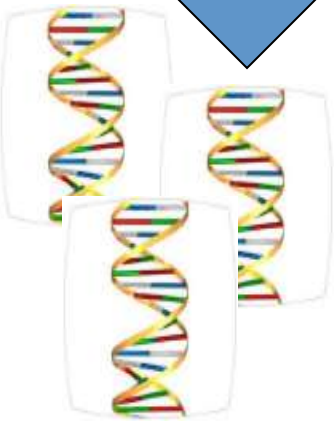
(small glands or populations or neighborhoods of adjacent cells)



How To Sample Tumor Diversity?



EDTA Washout: Single Cancer Glands



Isolate DNA

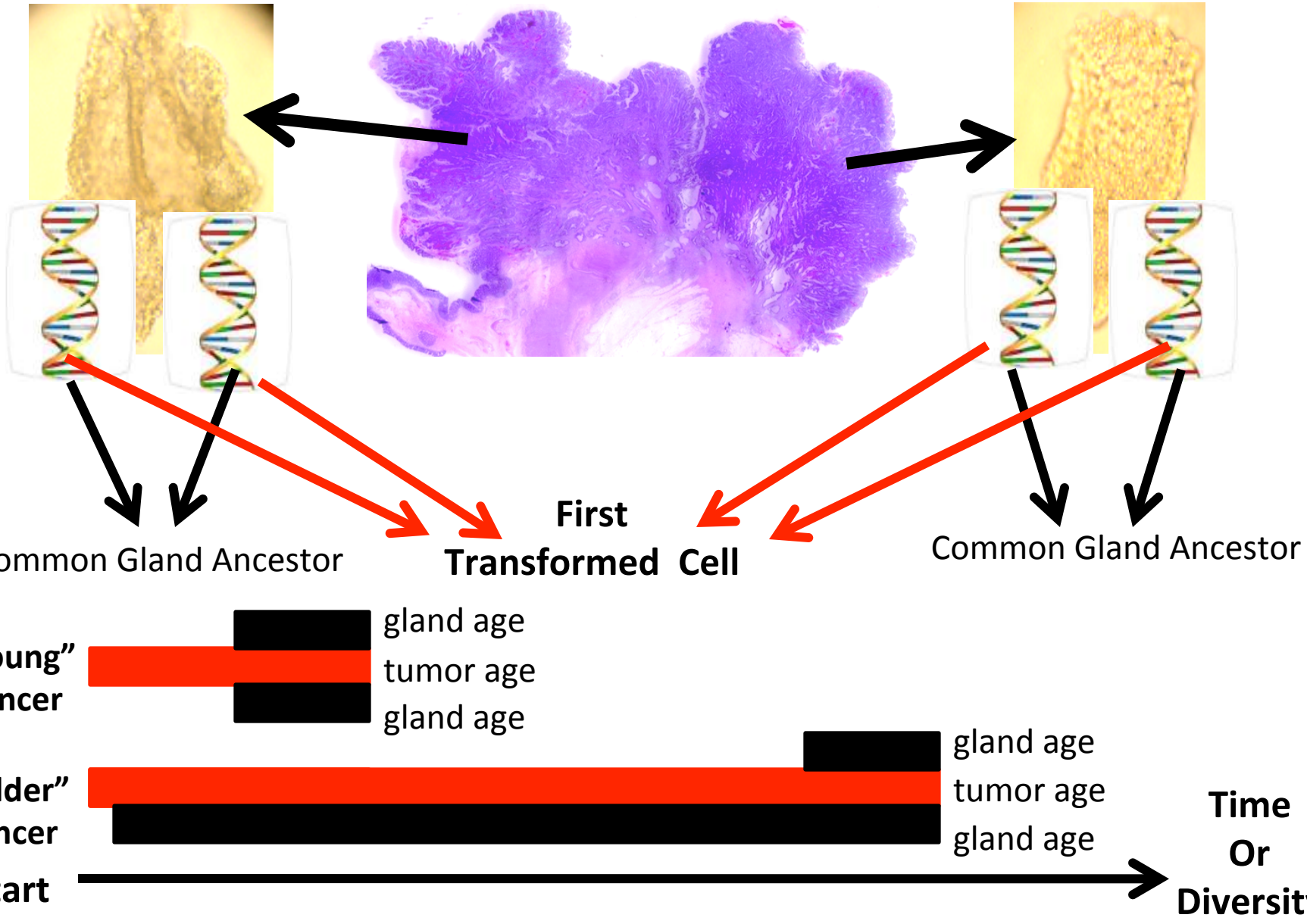
PCR clock locus

clone PCR products into bacteria

sequence individual clones

calculate PWD (pairwise distance)

How To Sample Tumor Diversity?



Somatic Cell Molecular Clock

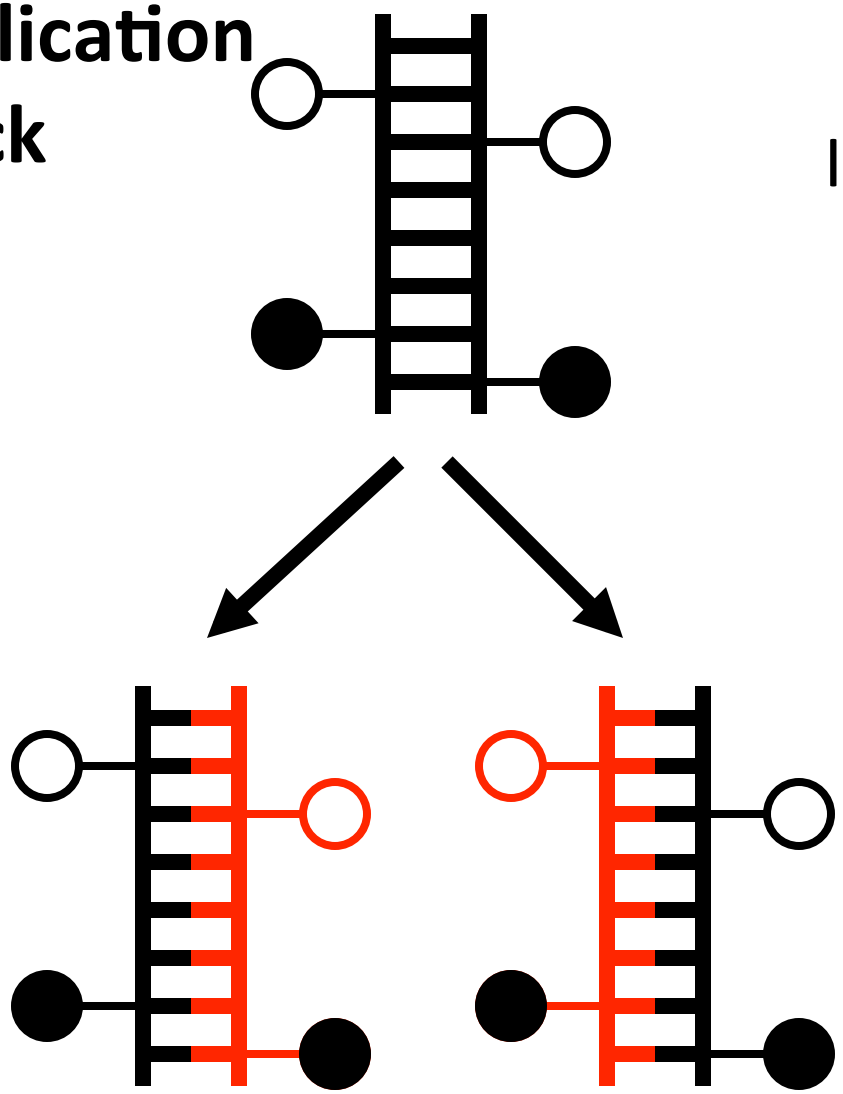
Problems:

--- Somatic Cell DNA Replication Fidelity
Too High!

Potential Solution: Epigenetic Molecular Clock

Substitute the 5’ to 3’ Order of Bases
With the 5’ to 3’ Order of CpG DNA Methylation

Replication Clock



Genome Replication

Molecular Clock:
Information Passed
From Cell to Cell

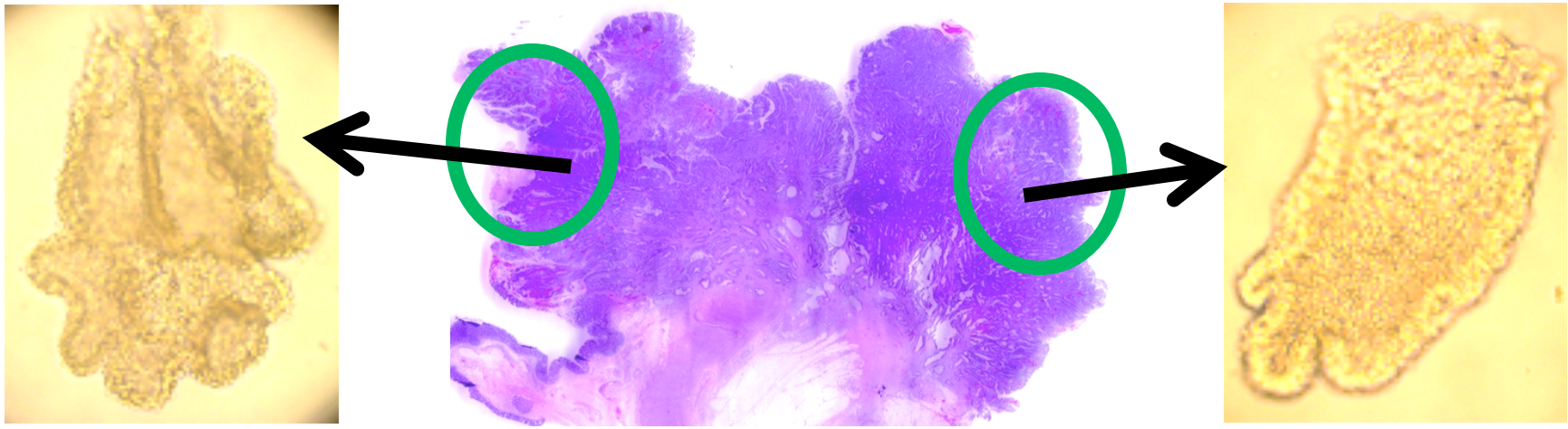
Epigenetic Fidelity
is less than
Genetic Fidelity

10^{-9}

versus

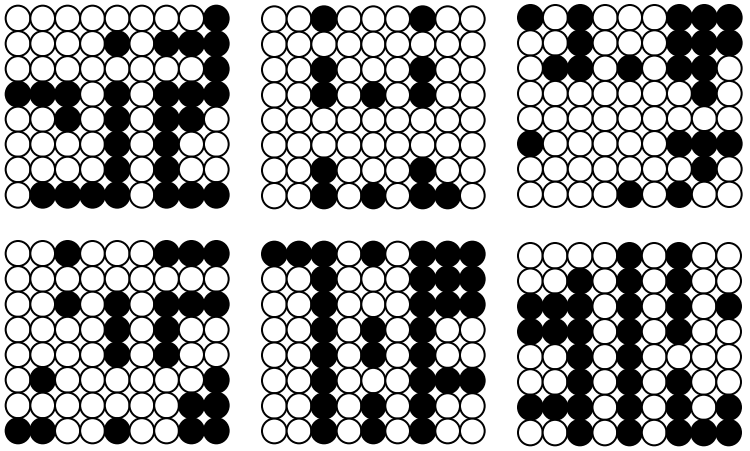
10^{-5}

Human Colorectal Cancer



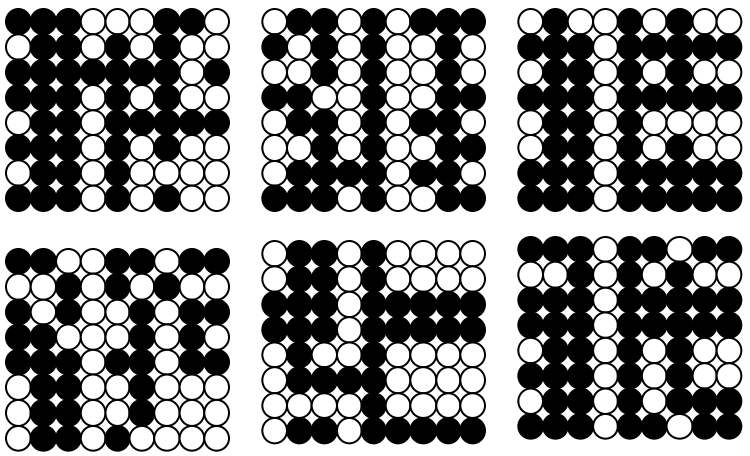
six cancer glands

left side

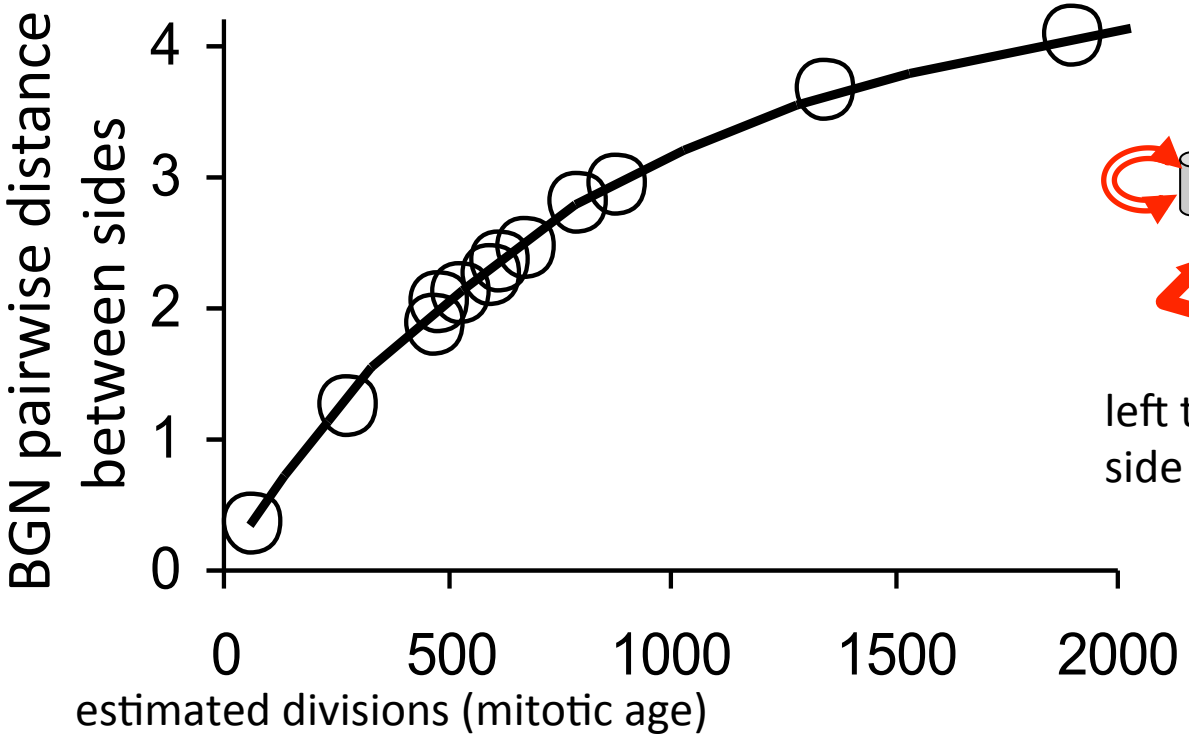


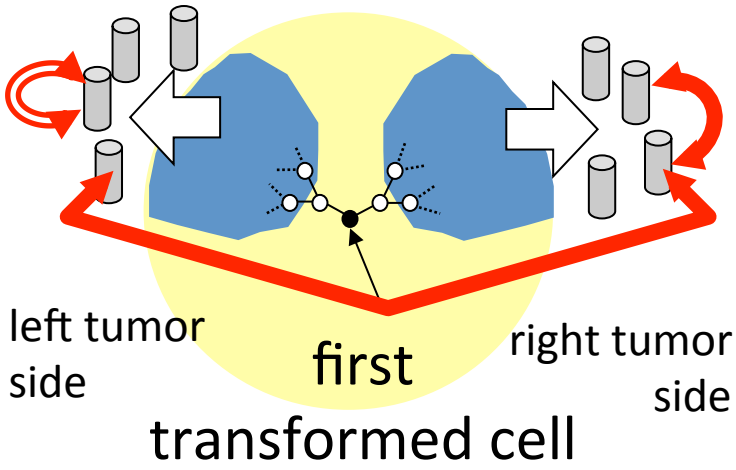
six cancer glands

right side



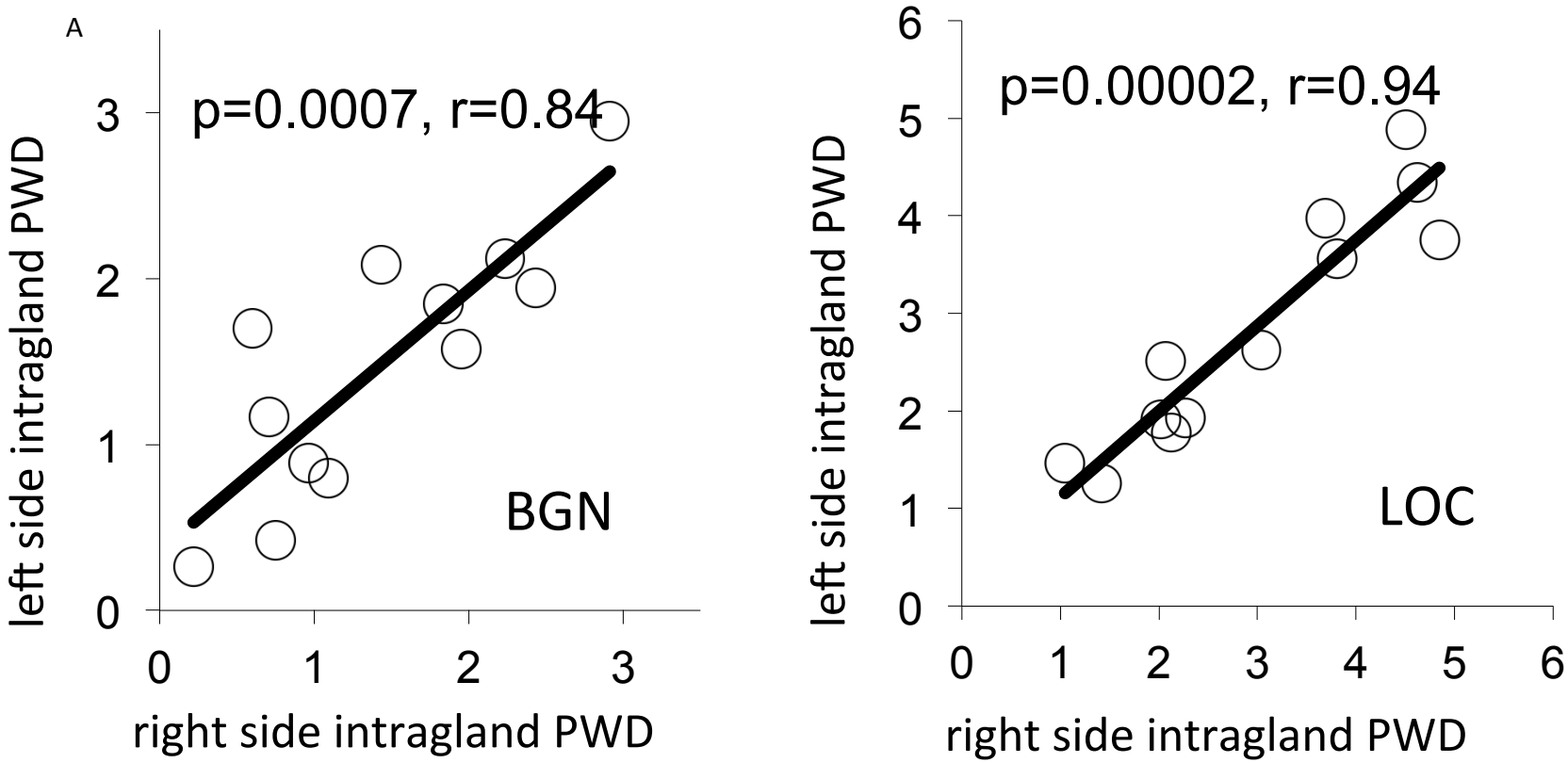
PWDs Between Cancer Sides Differ Between Cancers (N=12)



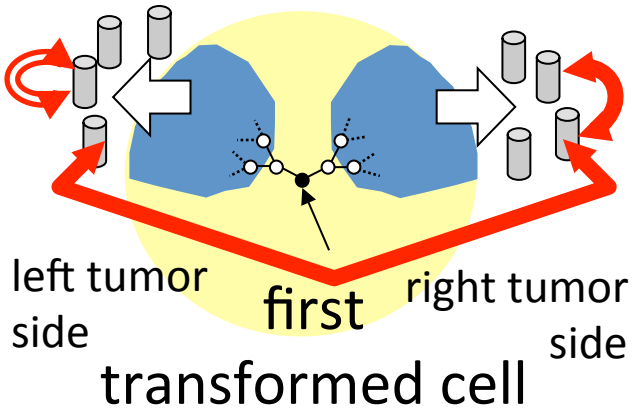


Different human cancers have different ages

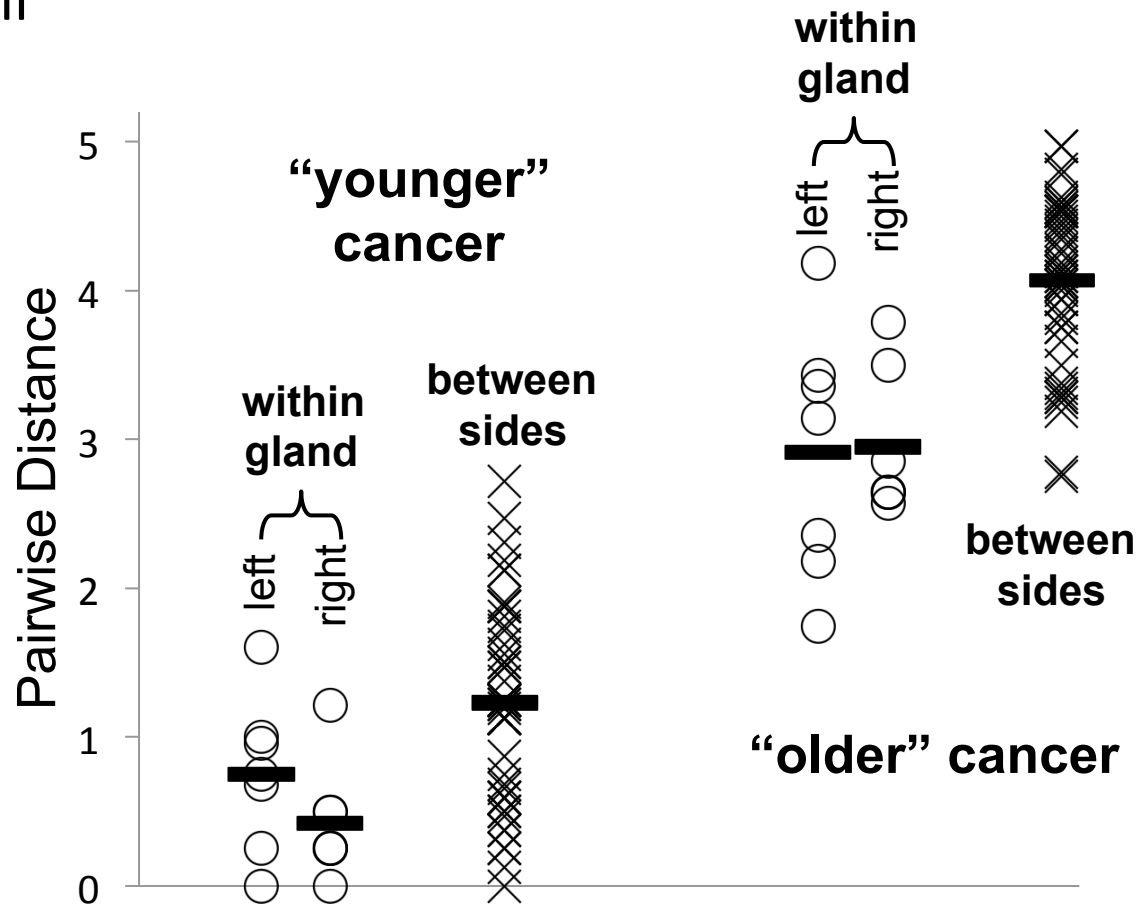
Cancer Glands From Left and Right Sides Are Similar For The 12 Human CRCs



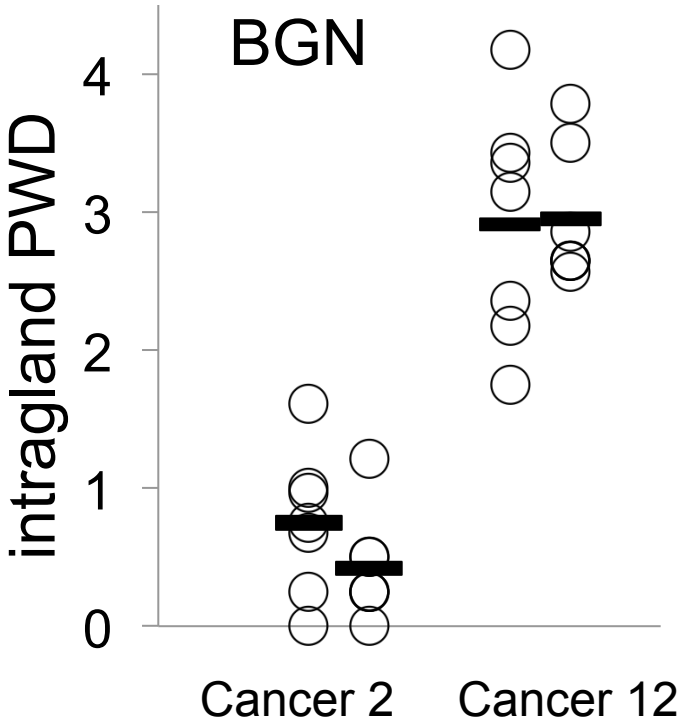
Glands Within A Cancer Have Similar Ages

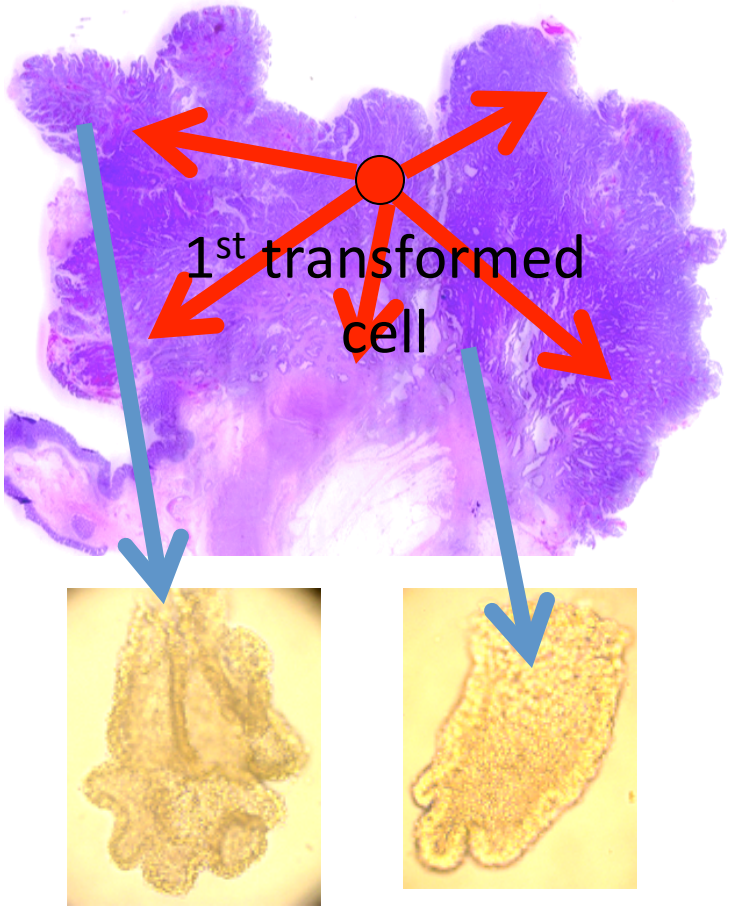


Older Cancers Have "older" Glands

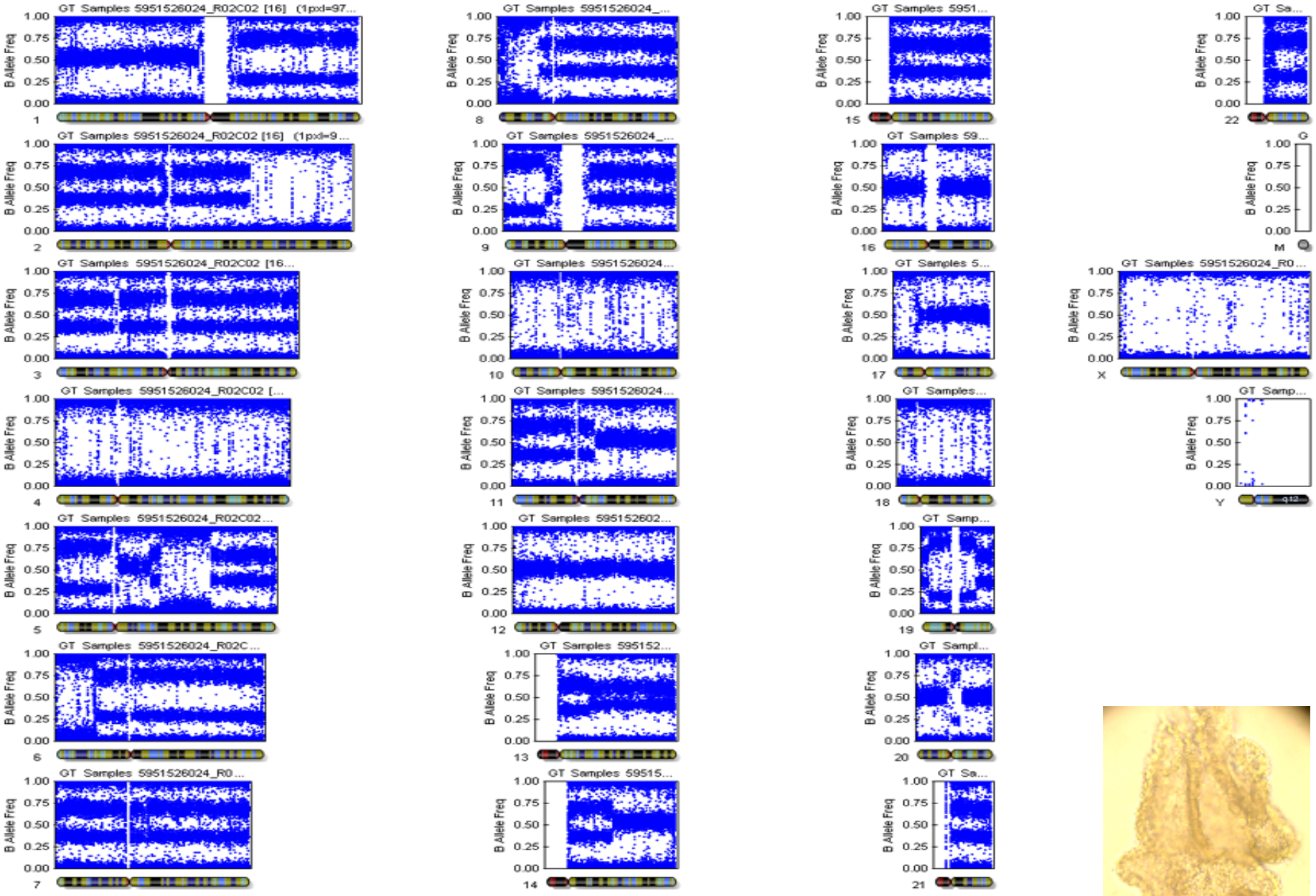


Simple Models of Tumor Growth





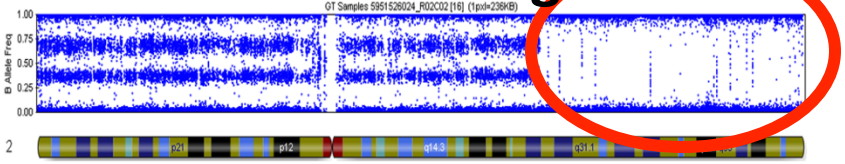
glands have similar ages or PWDs

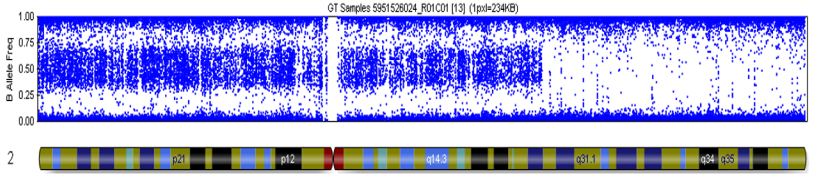


Illumina 660 SNP Microarray

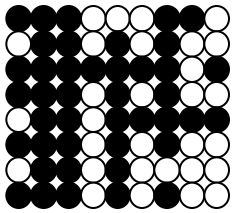
Chromosomal Changes

LOH



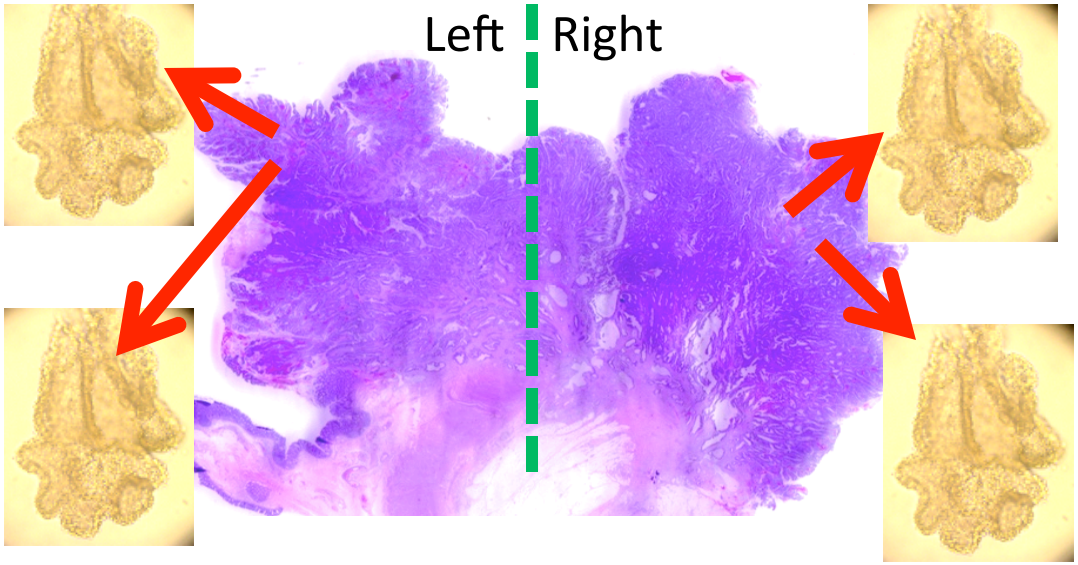


5’ 3’



.....AGCTCGCA
TCTTCAAGCCT
ACCATTAAT....

Left Right



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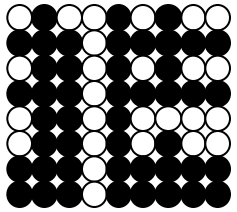

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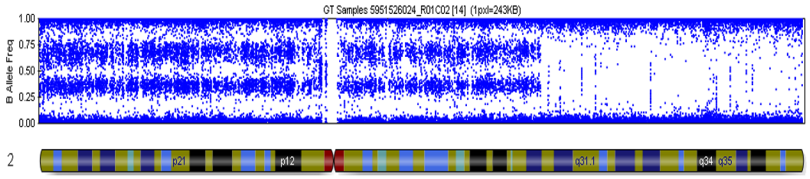

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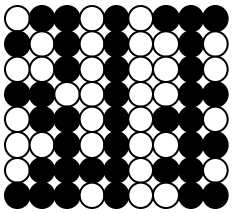

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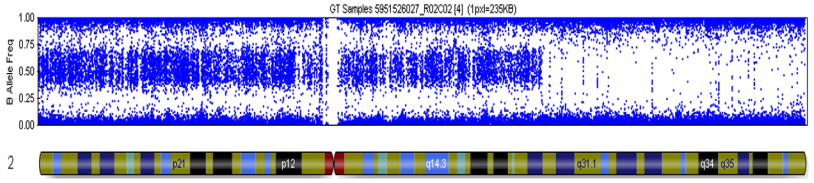

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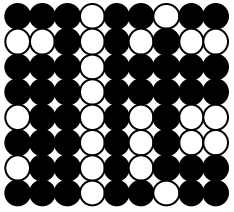

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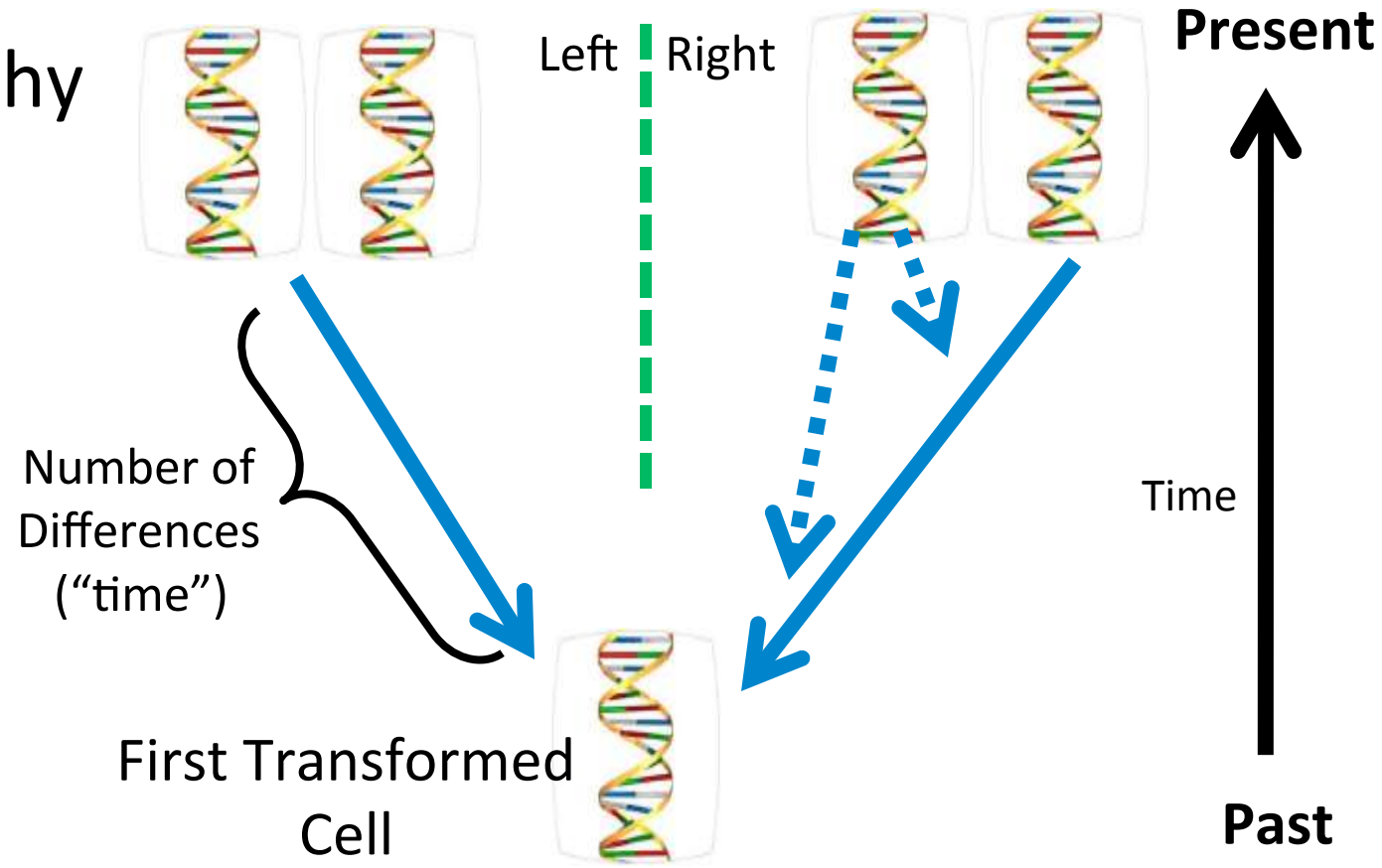

Genomes Are “Historical” Documents (almost perfect copies of copies)

zygote (start)

cancer cell (present day)

Acknowledgements

- Yasushi Yatabe
- Kyoung-Mee Kim
- Jung Yeon Kim
- Peter Calabrese
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