The First Three Cancer Cell Divisions (Human Cancer Creation)

A Physical Sciences-Oncology Perspective

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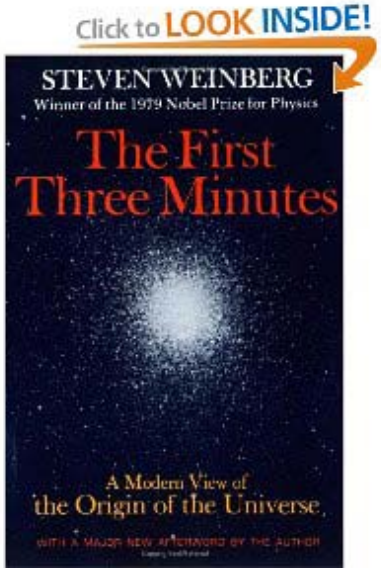
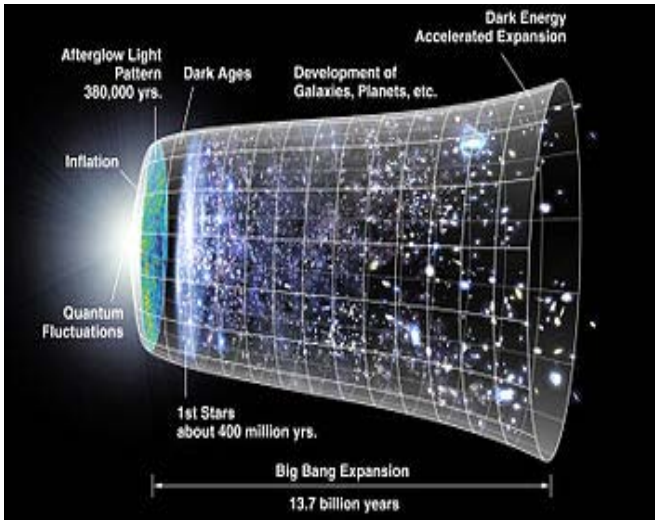
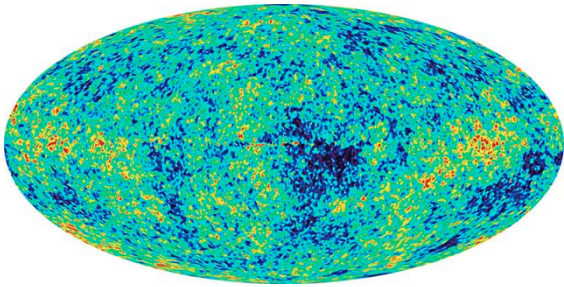
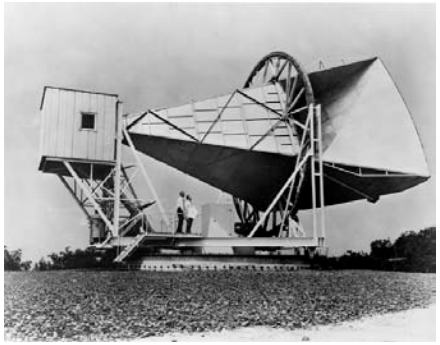
The First Three Minutes by Steven Weinberg





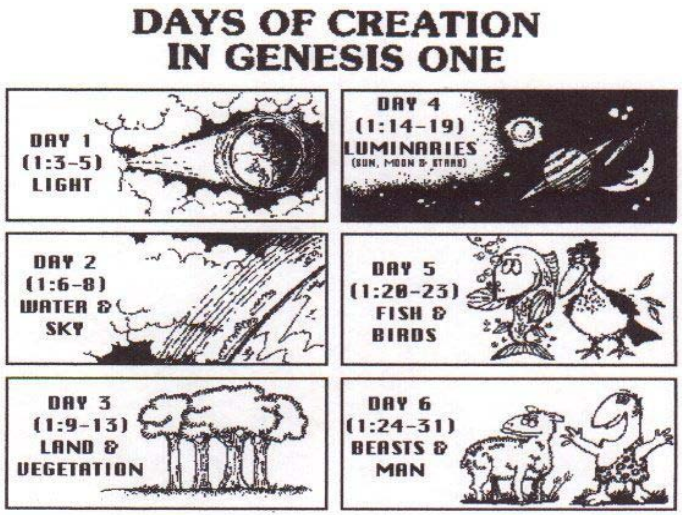




Big Bang

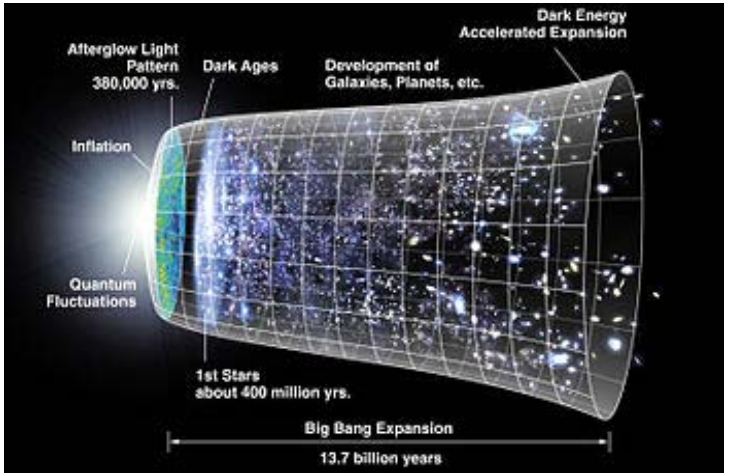
1. Universe Was Created (Time and Space)
2. Start About 13 Billions Years Ago
3. “Big Bang”
4. “Inflation”
5. Idea That The “Nature” (or rules) of the Universe Depends on What Happened Early in Creation

Question: Alternate Models of Creation?



Stepwise
(very logical)

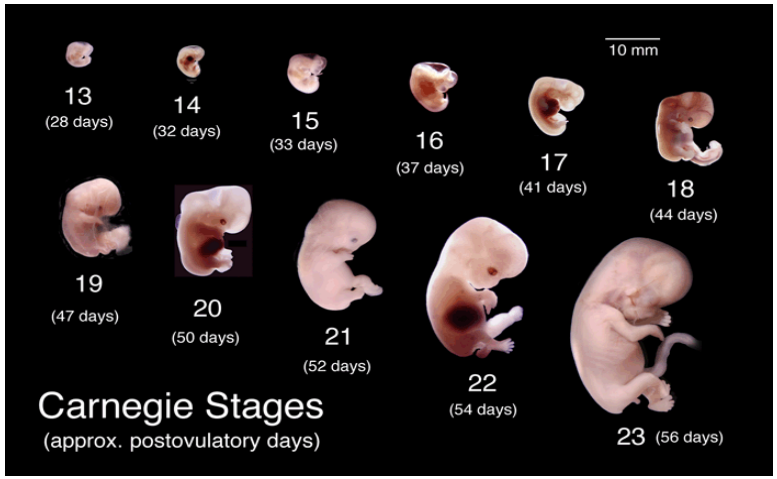
?????



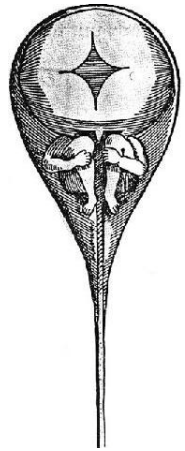
Big Bang
(true but requires stranger reasoning like string theory)

Biological Models of Creation

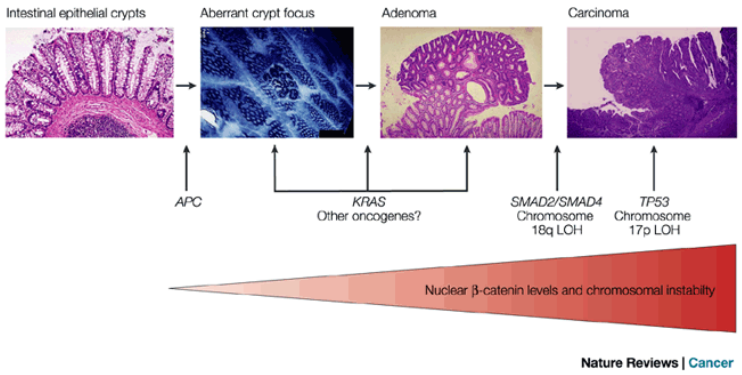
Development: Stepwise?

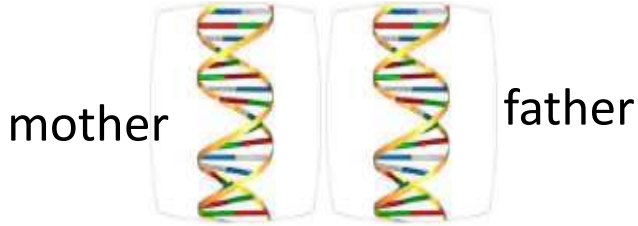


Development: Big Bang?



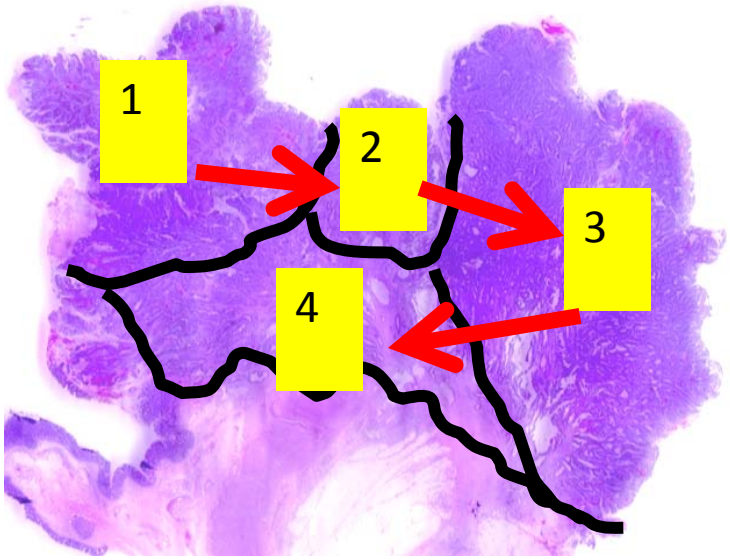
Cancer: Stepwise?



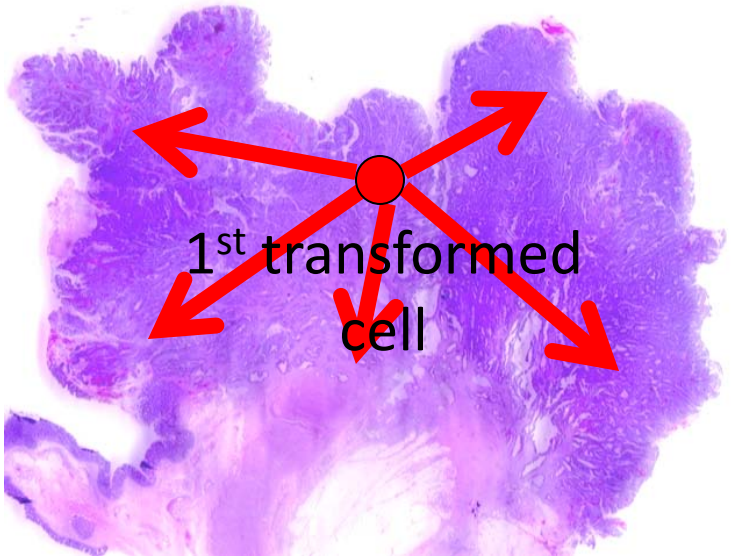


Singularity

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



Sequential or
Clonal Evolution

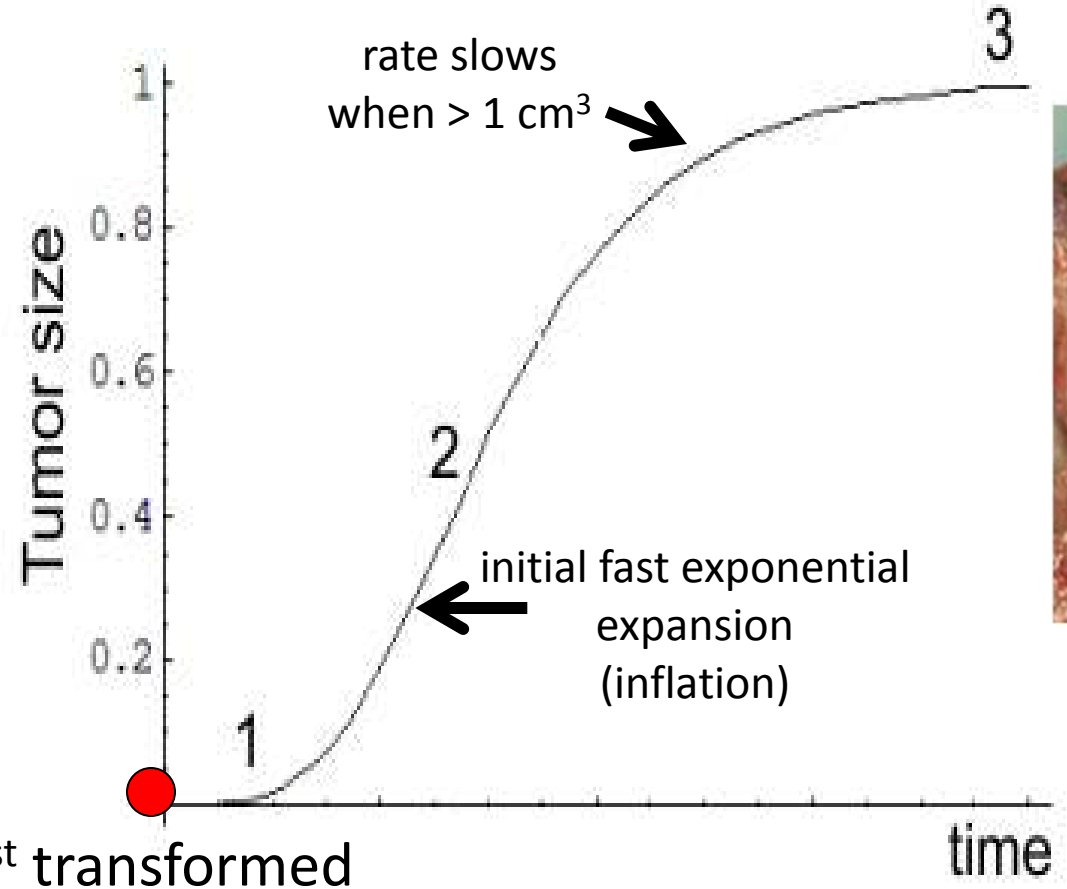


"Big Bang" (full malignant potential at transformation or phenotypic plasticity)

Age Non-uniform

Uniform Age

Observations of Tumor Growth



3 cm

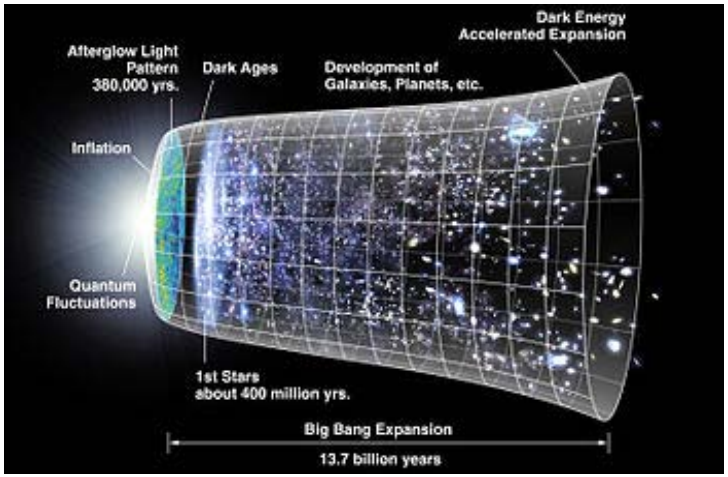
Tumors Typically Exhibit Gompertzian Growth

Are There Analogous Approaches To Describe "Creation" That:

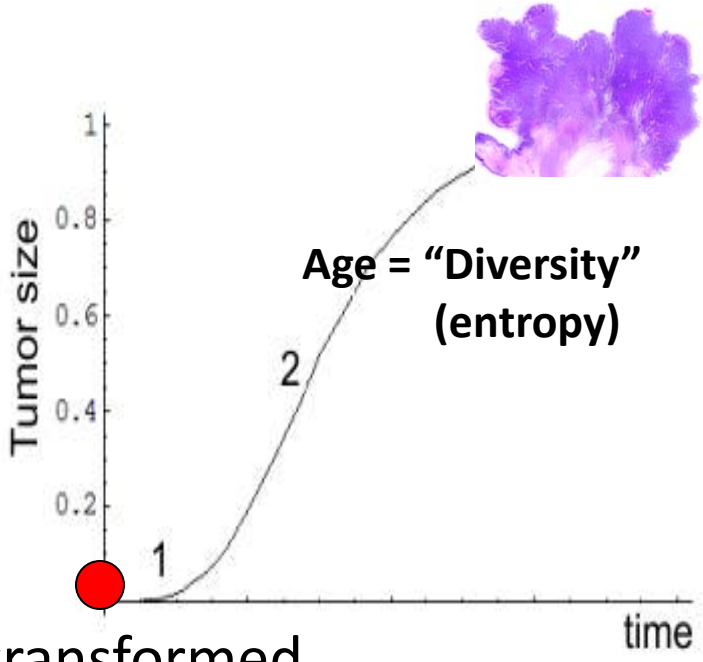
1) Starts From a Single "Point"
2) Initial "Exponential" Expansion
3) Subsequent Slowing of the Expansion

<u>Goal: Describe The First Few Cancer Cell Divisions After Transformation</u>

Age = Temperature (entropy)



Big Bang



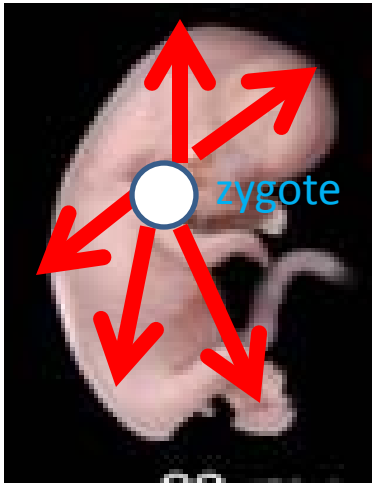
1st transformed cell

Creating Biological "Time And Space"

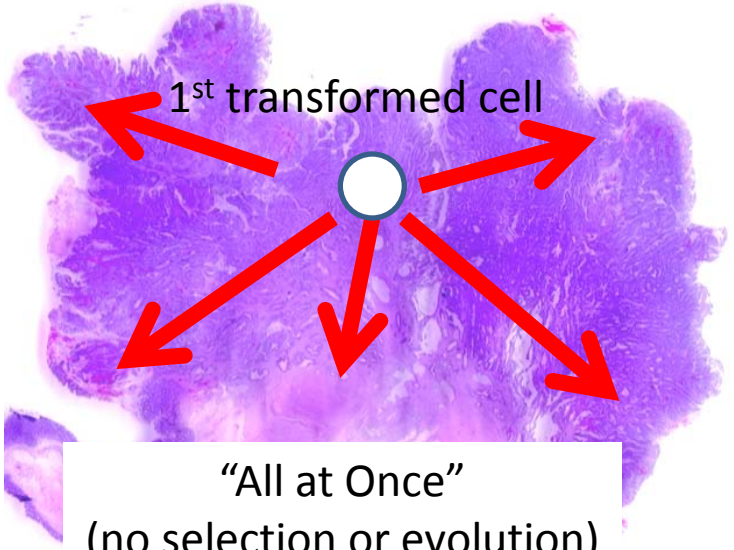
1. "Mechanism" Is Cell Division
2. "Time" = Mitotic Age (Divisions Since a Common Ancestor)
3. "Space" = Cells

   Asymmetric Divisions: Maintain Space

   Symmetric Divisions: Create or Destroy Space



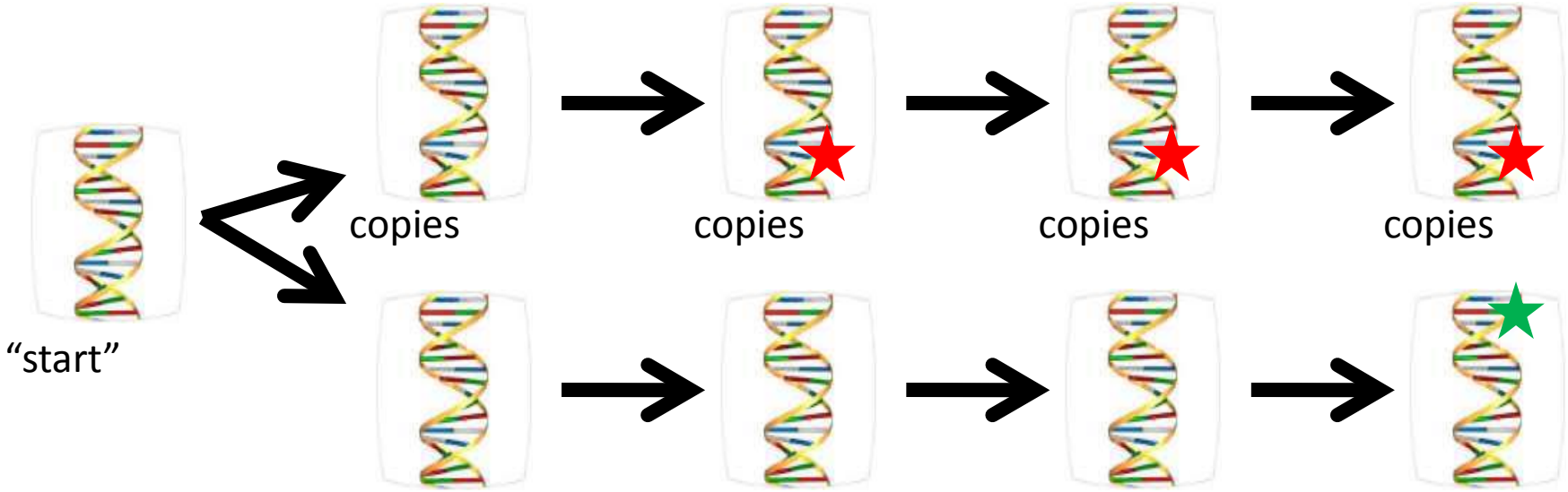
"All at Once"
(no selection or evolution)



"All at Once"
(no selection or evolution)
or Stepwise
(mutation and selection)

The Approach: “Molecular Clocks” (Coalescence Theory)

Genomes Are Almost Perfect Copies of Copies



The Greater The Time or Copies Since A Common Ancestor,
The Greater Their Differences (pairwise distance or PWD)

Low PWD → (more replication errors) → High PWD

Problem With Trees: Number of Possible Bifurcating Trees Is Large

$$= \frac{(2n-3)!}{2^{n-2}(n-2)!}$$

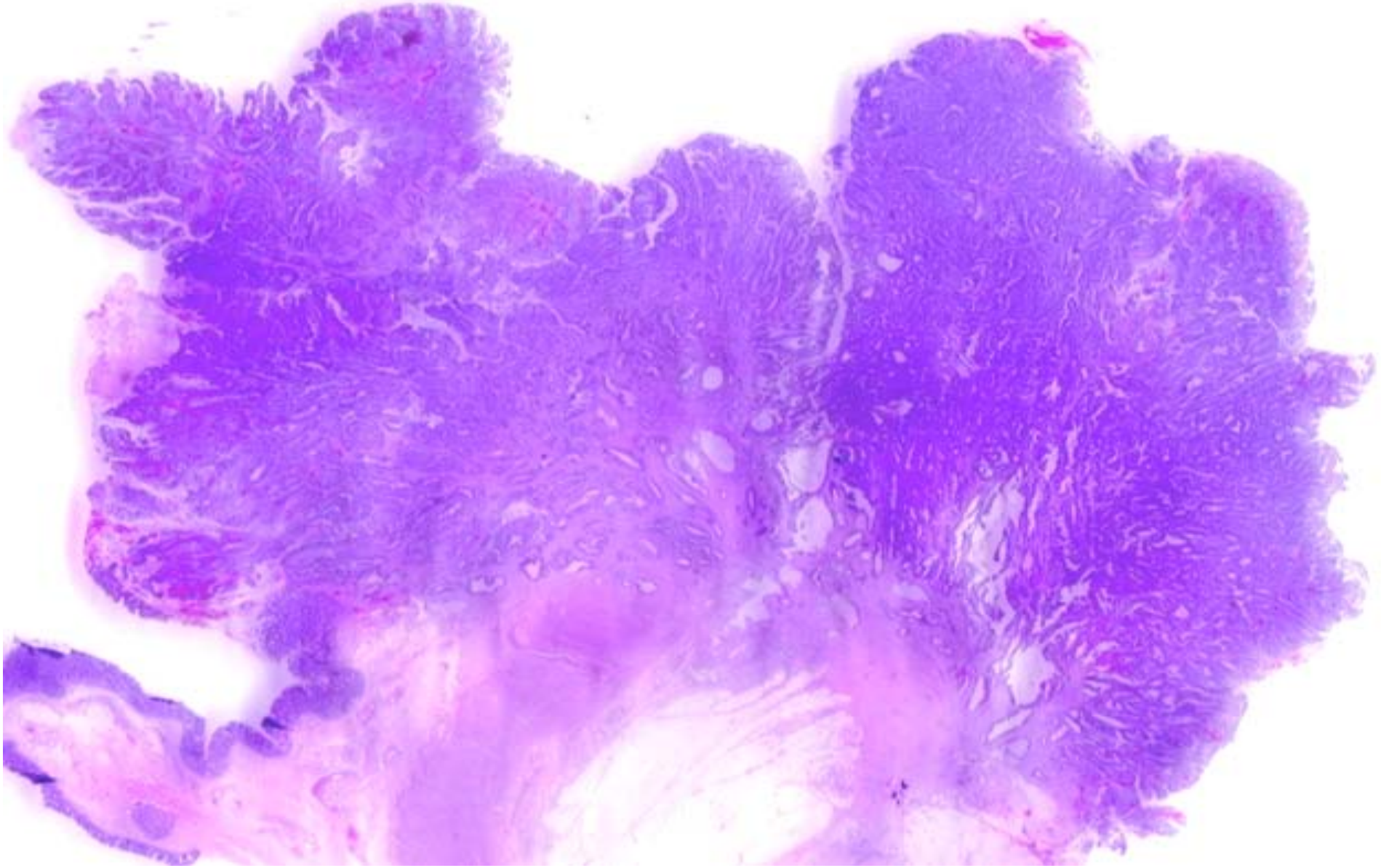
n = number of tips or cells

20 cells: 8 X 10^{21} possible bifurcating trees

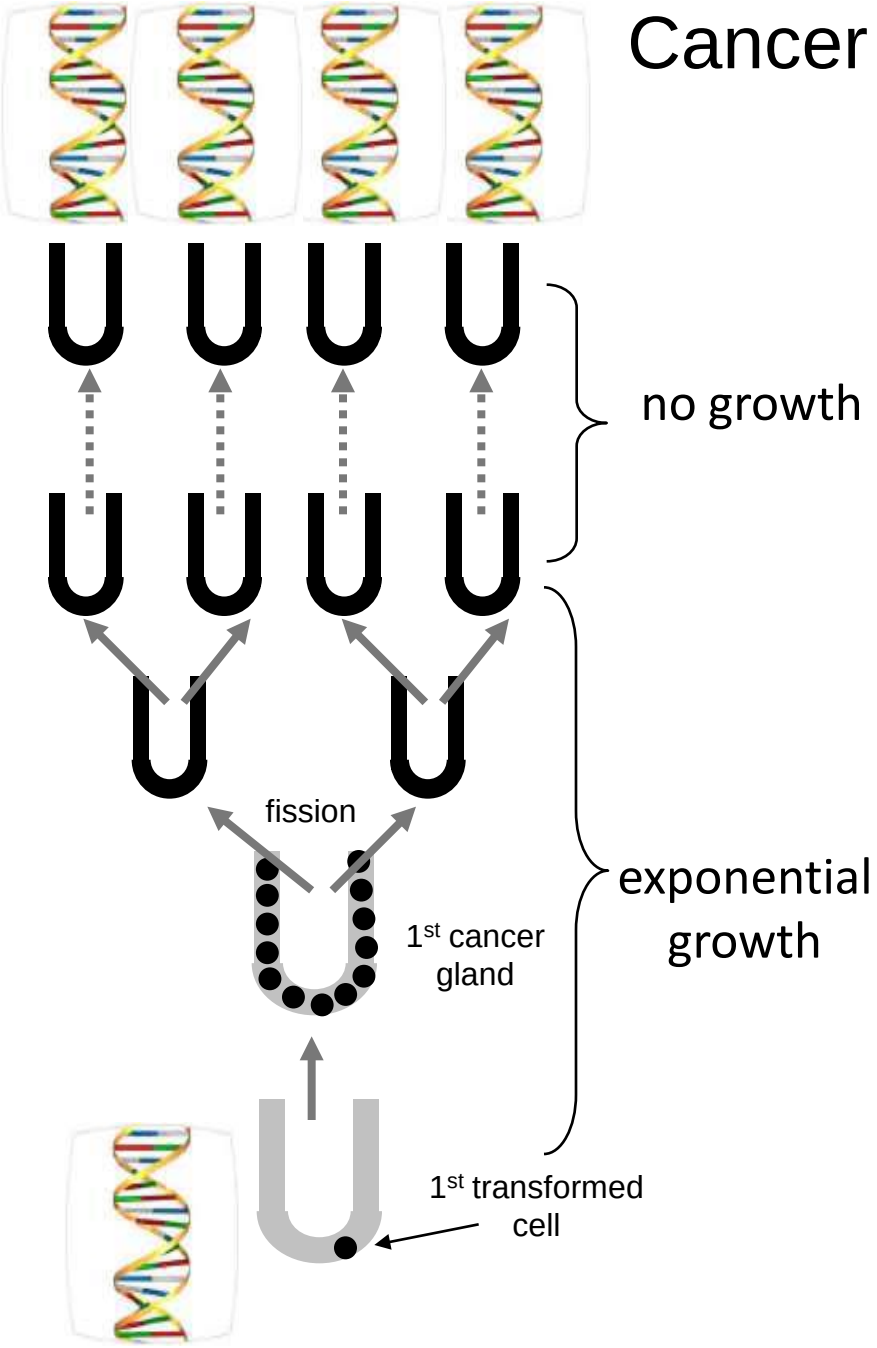
Implications: Every Cancer Has A Single Tree, But---

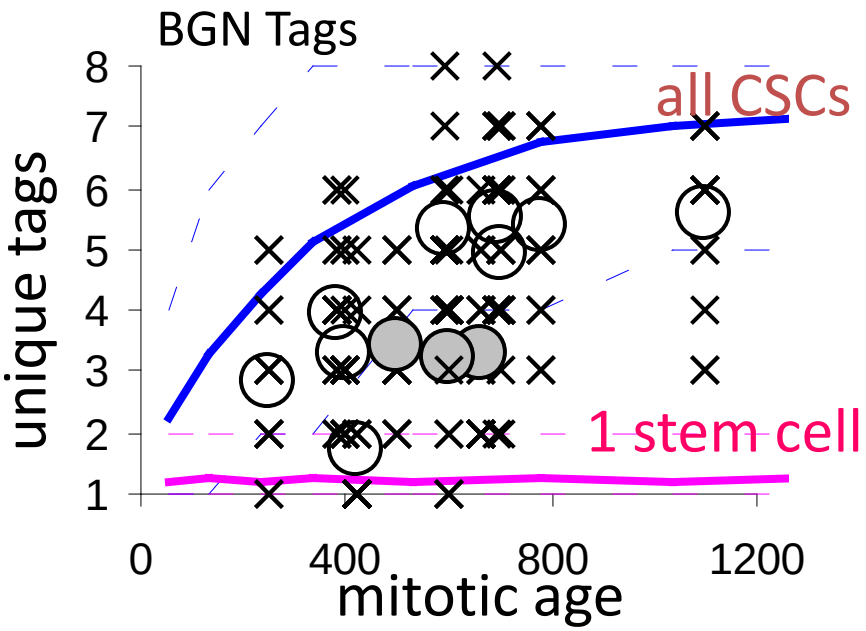
1) **Exact Modeling or Cancer Reconstruction Is "Impossible"**
2) **Almost "Anything" Is Possible (Many Possible "Coherent" or Logical Alternative Models or Experimental Scenarios are Feasible)**

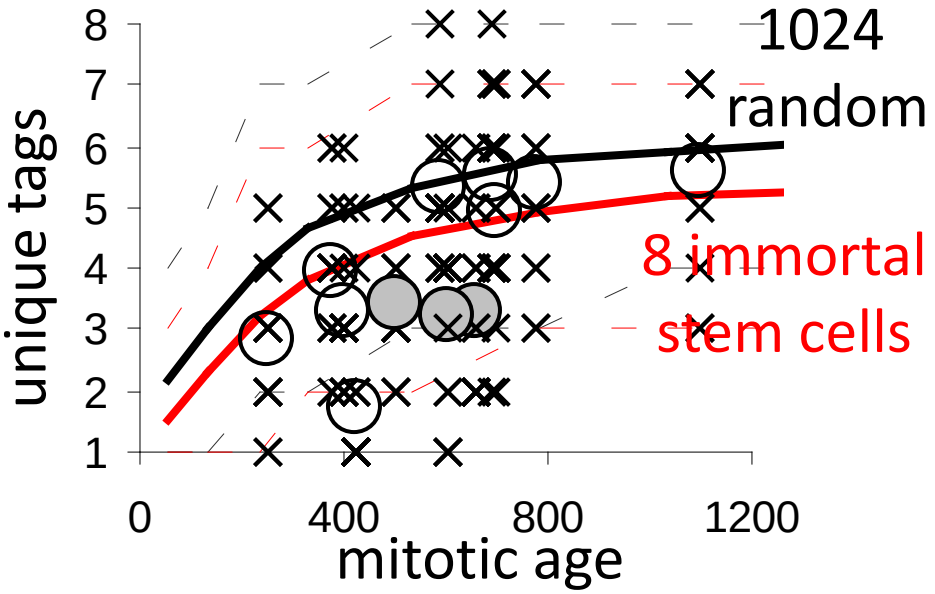
Colorectal Adenocarcinomas
Real “Death Stars” (Multiple Small Glands)



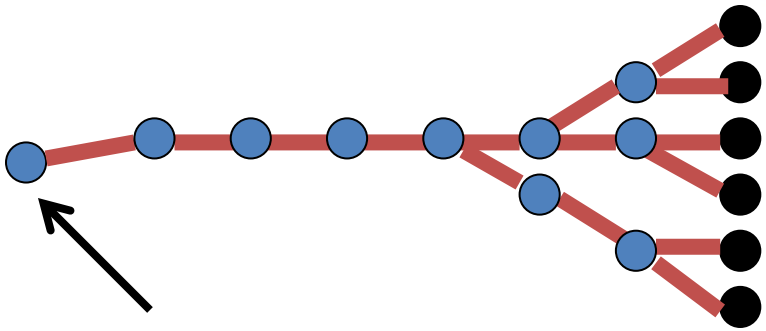
Cancer Simulations







Basic Tree Shapes

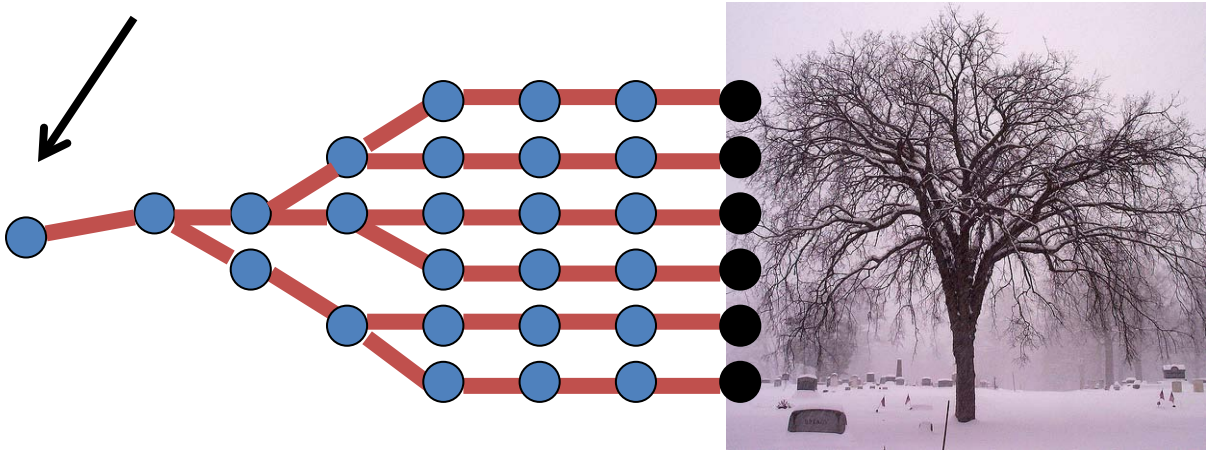


1st Transformed Cell

Palm Tree

---Few Long-lived Stem Cell Lineages

---Low Diversity

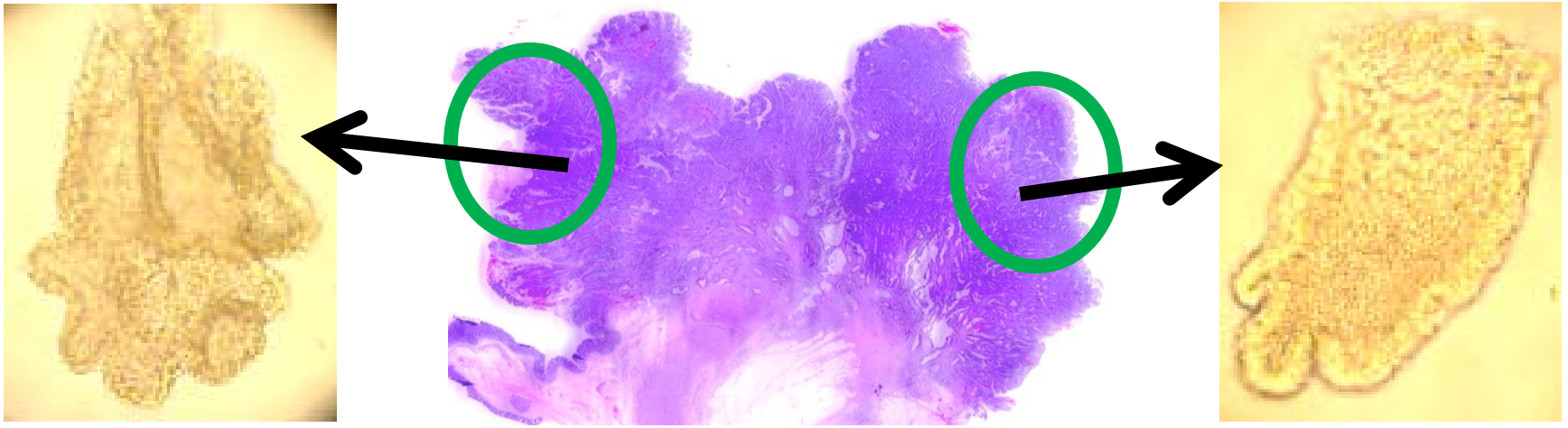


Star Shaped

--- Many Long-lived Stem Cell Lineages

--- Diverse Population (worst possible scenario for generating pre-existing resistant variants)

Human Colorectal Cancer: Intratumoral Heterogeneity



six cancer glands

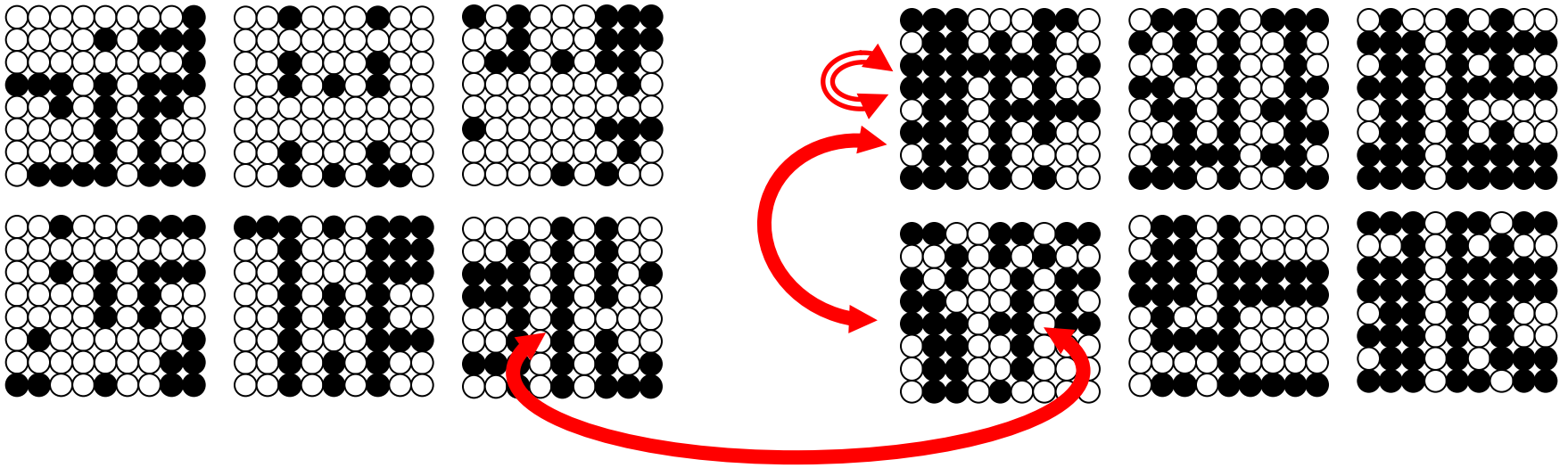
left side

5′ 3′ 5′ 3′ 5′ 3′

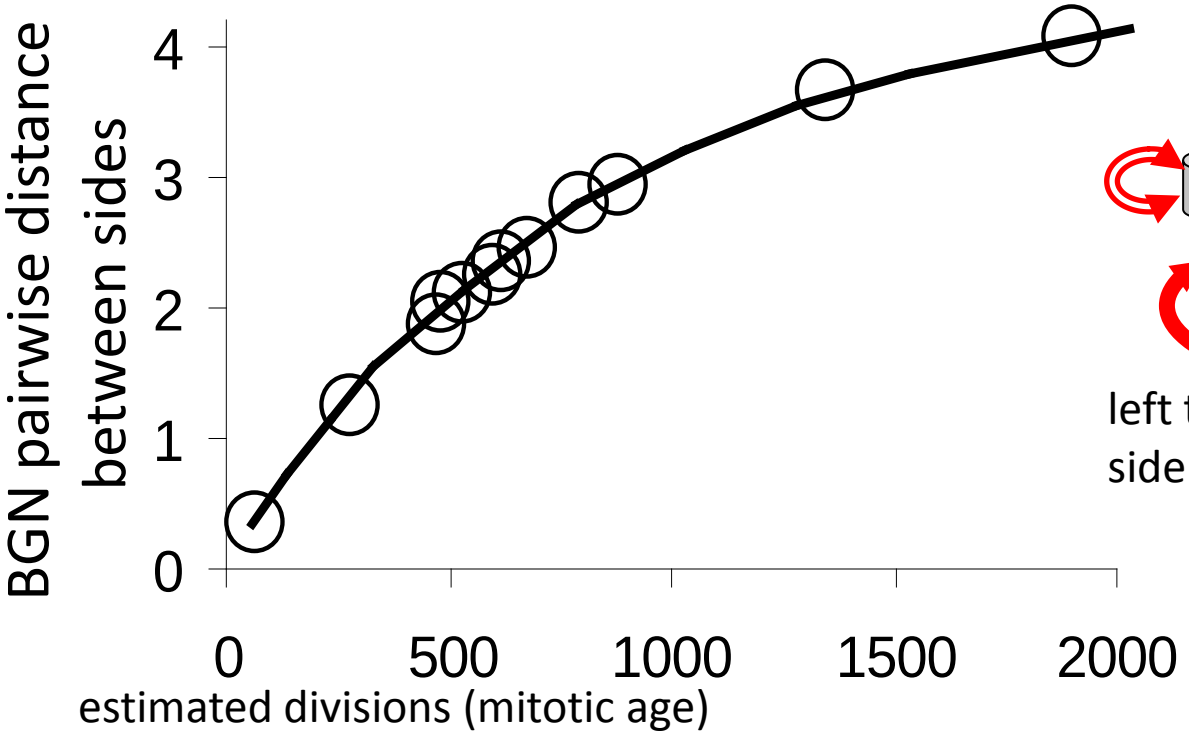
six cancer glands

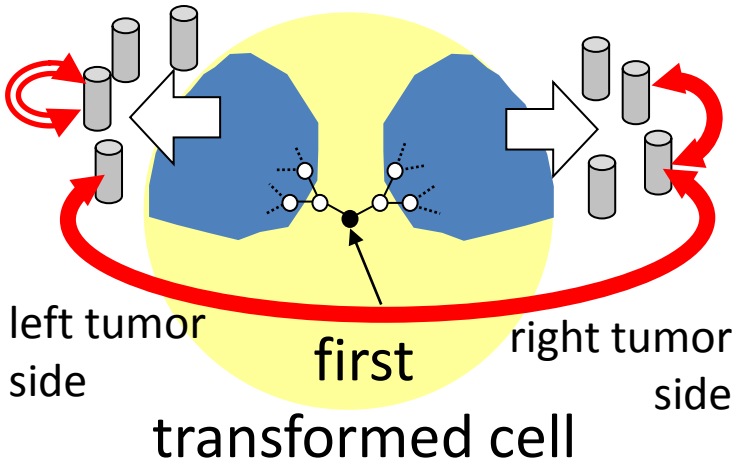
right side

5′ 3′ 5′ 3′ 5′ 3′



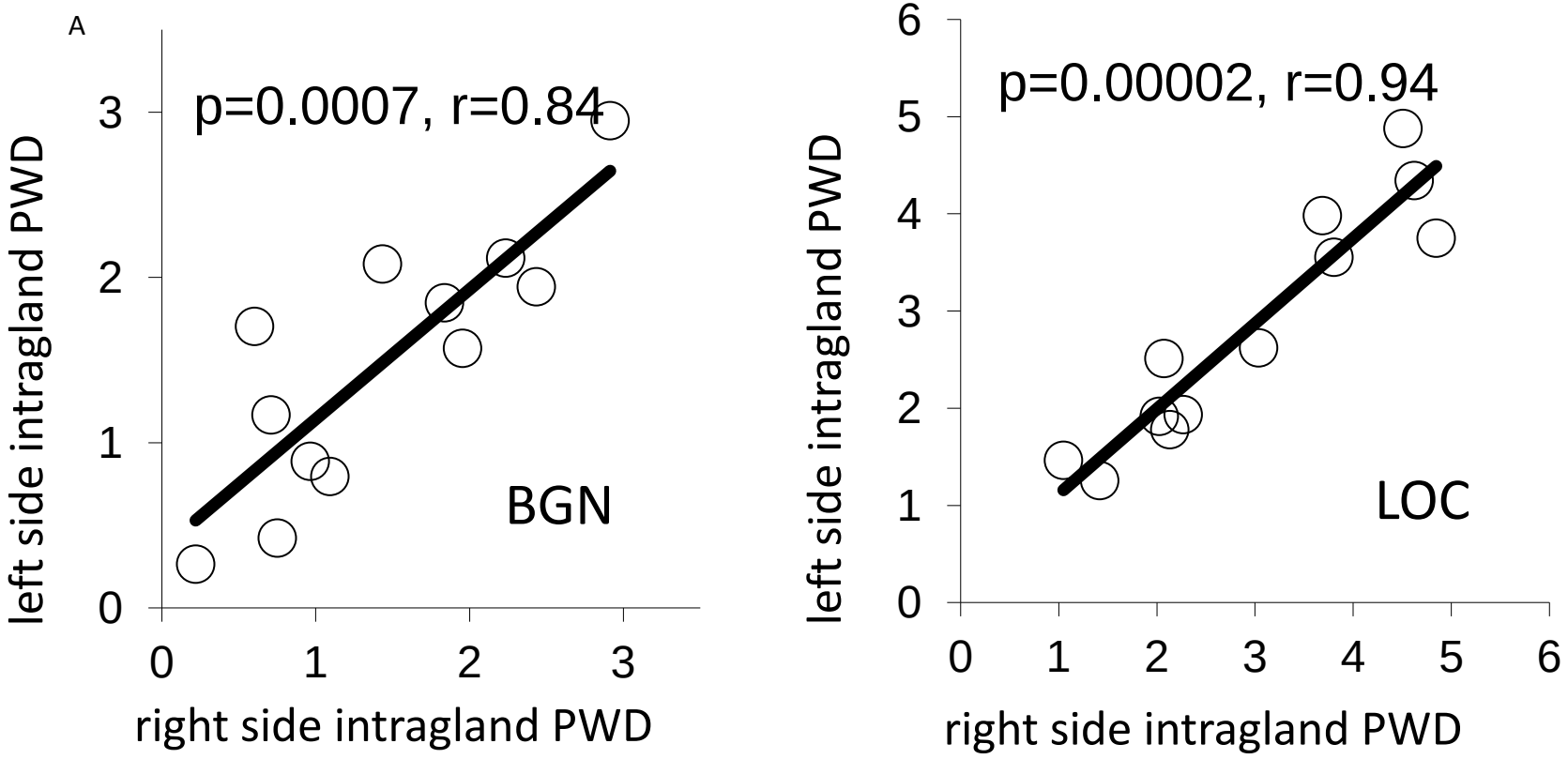
PWDs Between Cancer Sides Differ Between Cancers (N=12)



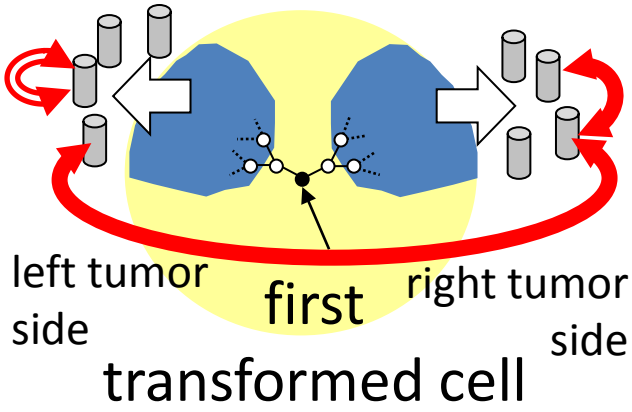


Different human cancers have different ages

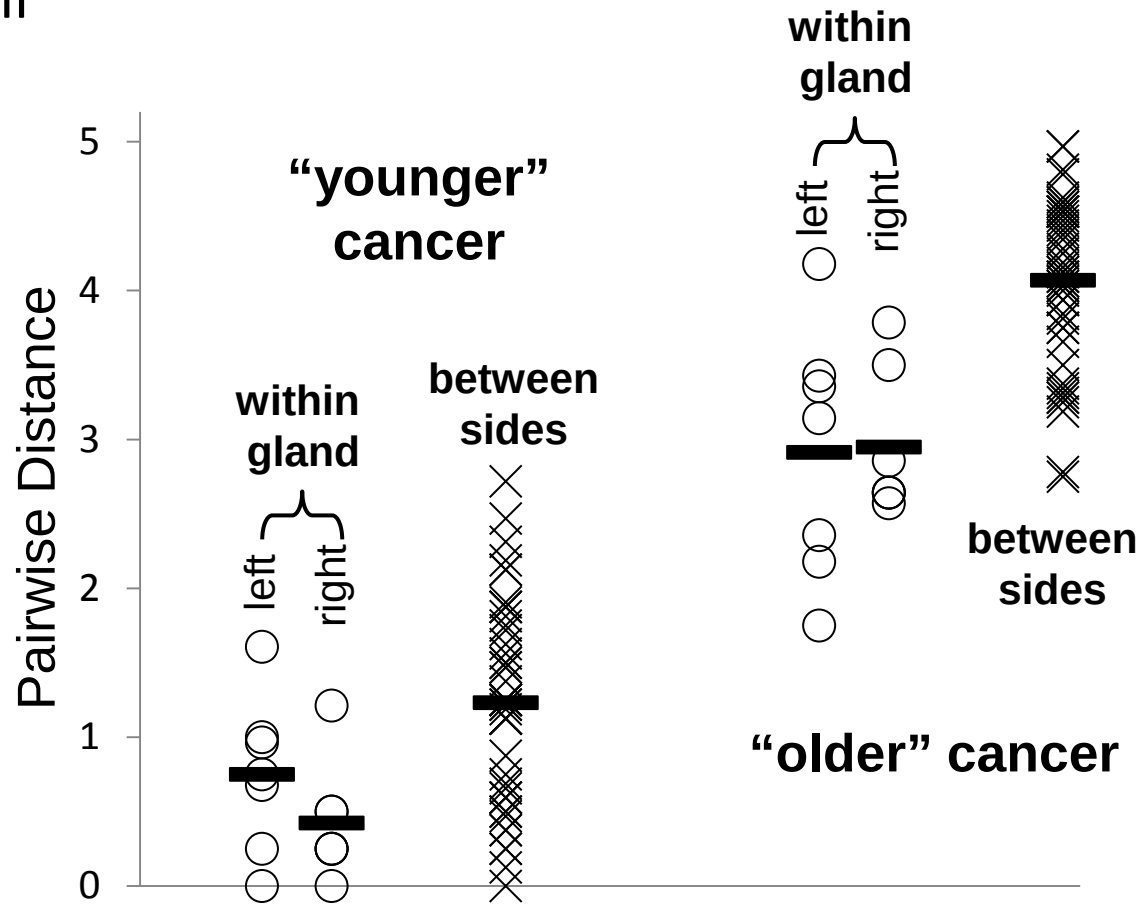
Cancer Glands From Left and Right Sides Are Similar For The 12 Human CRCs



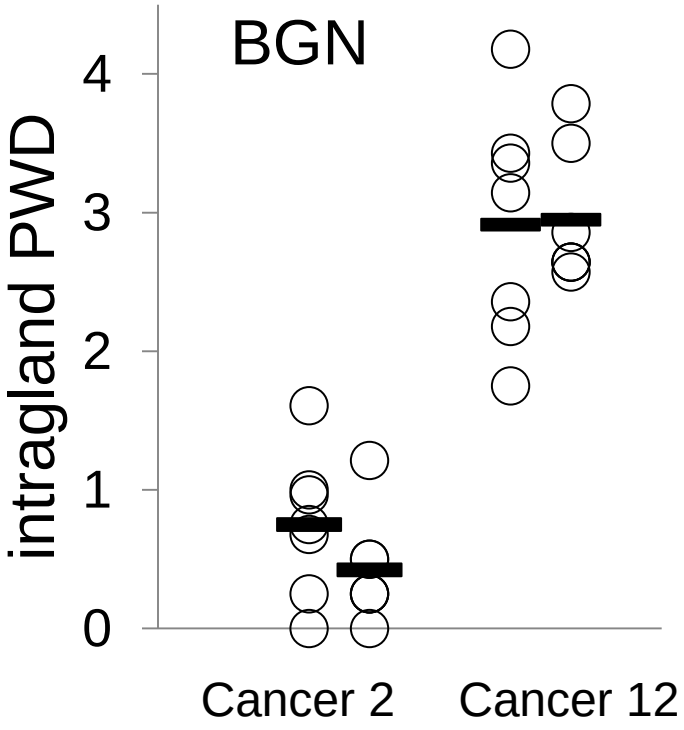
Glands Within A Cancer Have Similar Ages

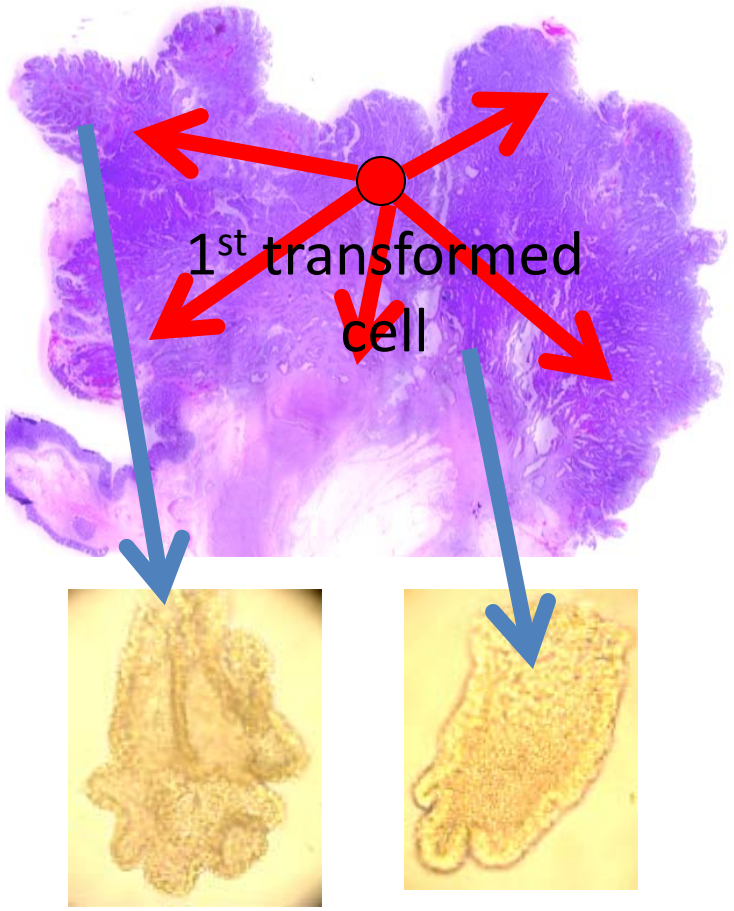


Older Cancers Have “older” Glands



Simple Models of Tumor Growth

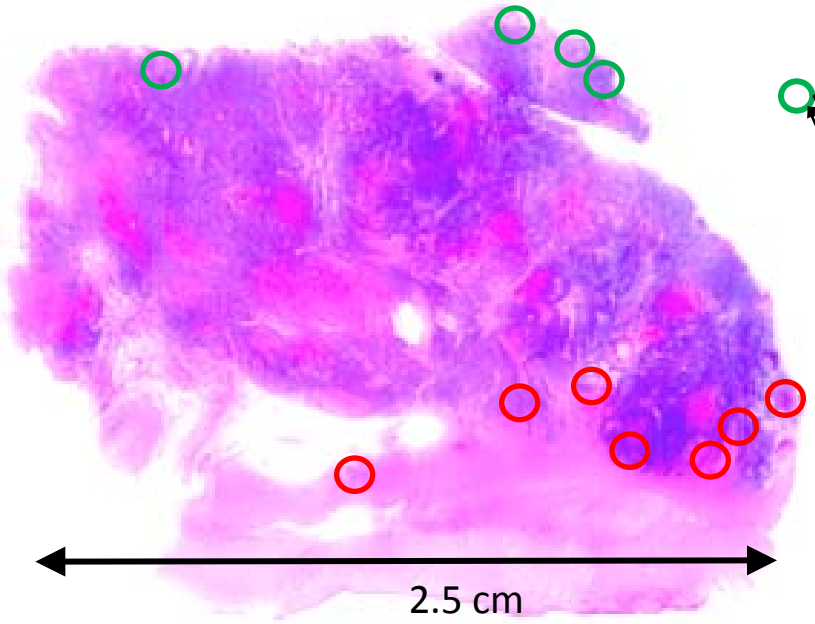


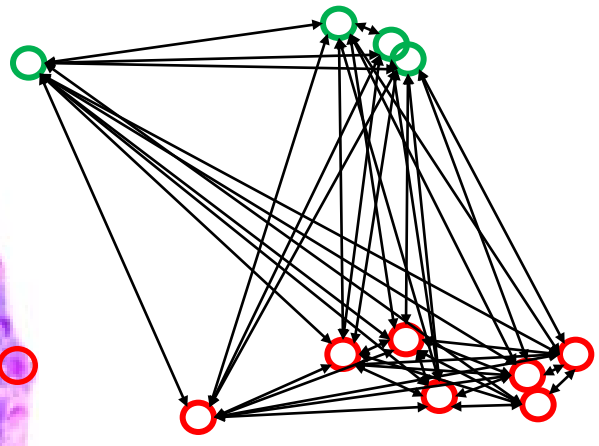


glands have similar ages or PWDs

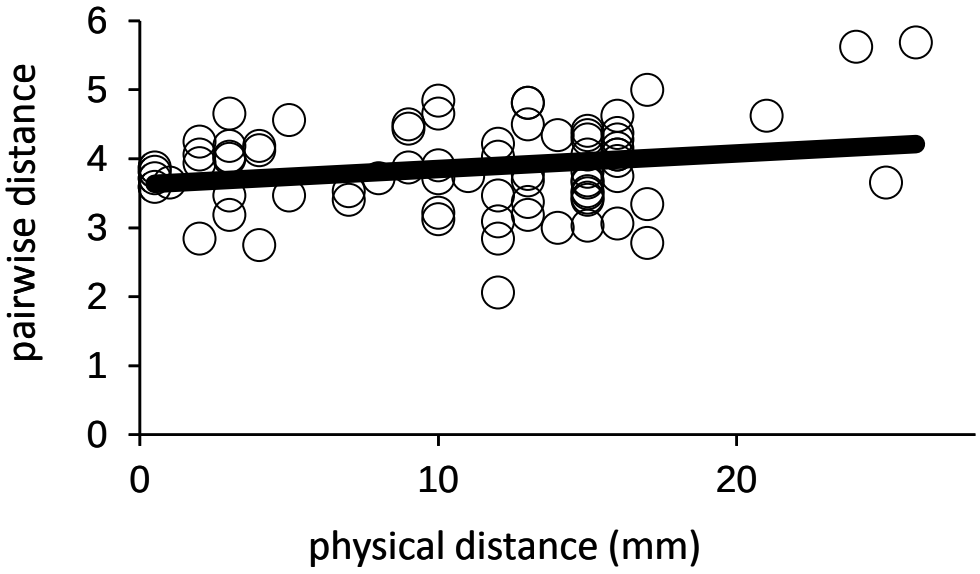
Human CRCs as Single Clonal Expansions

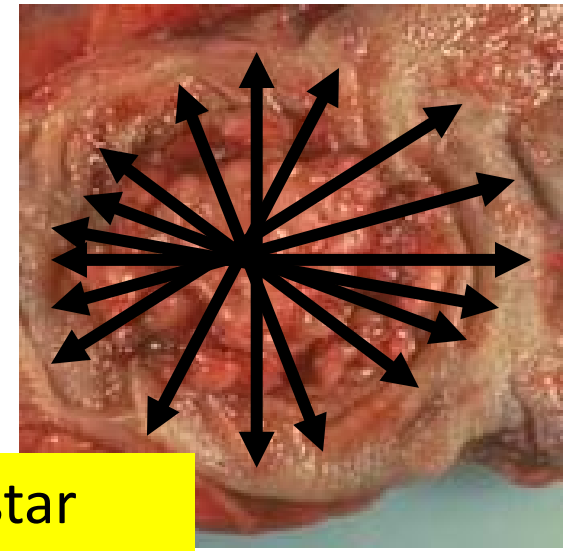
LCM





measure physical distances between glands





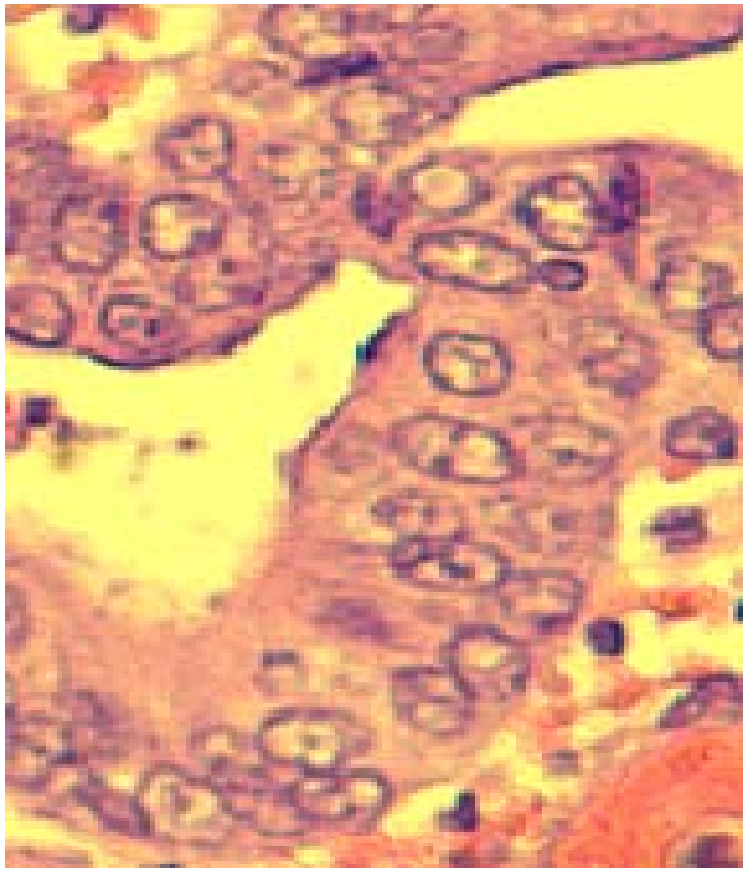
star phylogeny

A Selection Paradox

Selection in Biology Is Like Gravity (Increase Fitness)

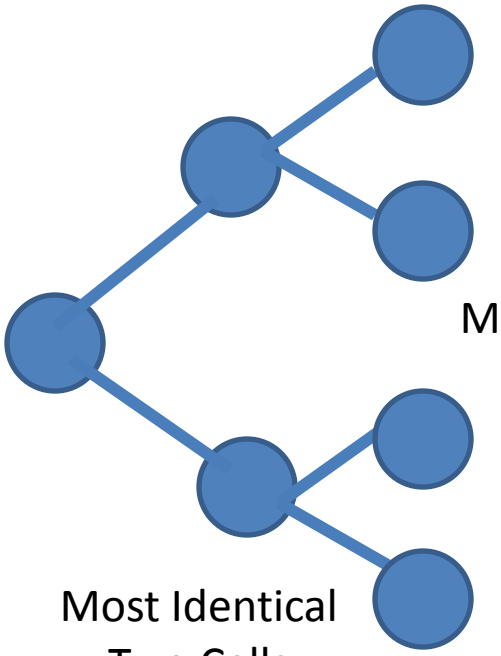
Selection Is Local: Immediate Competition
Is Between Adjacent Cells

BUT: In A Solid Tumor (Gland),
The Most Similar Cells Are
Next To Each Other
(ie daughter cells)



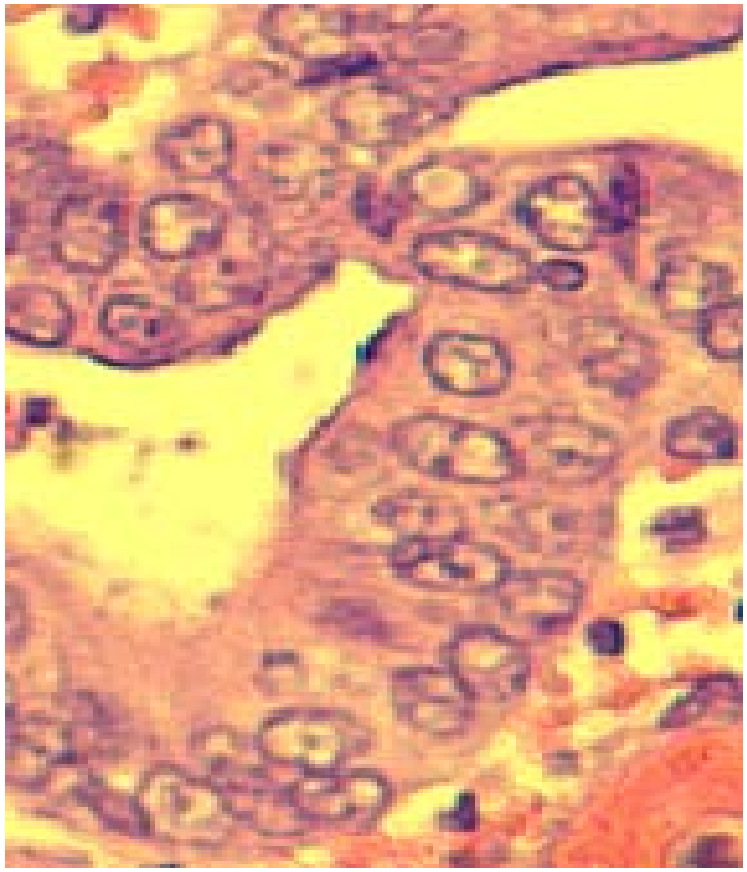
A Selection Paradox

How Different Must Two Cells Be For Efficient Selection?

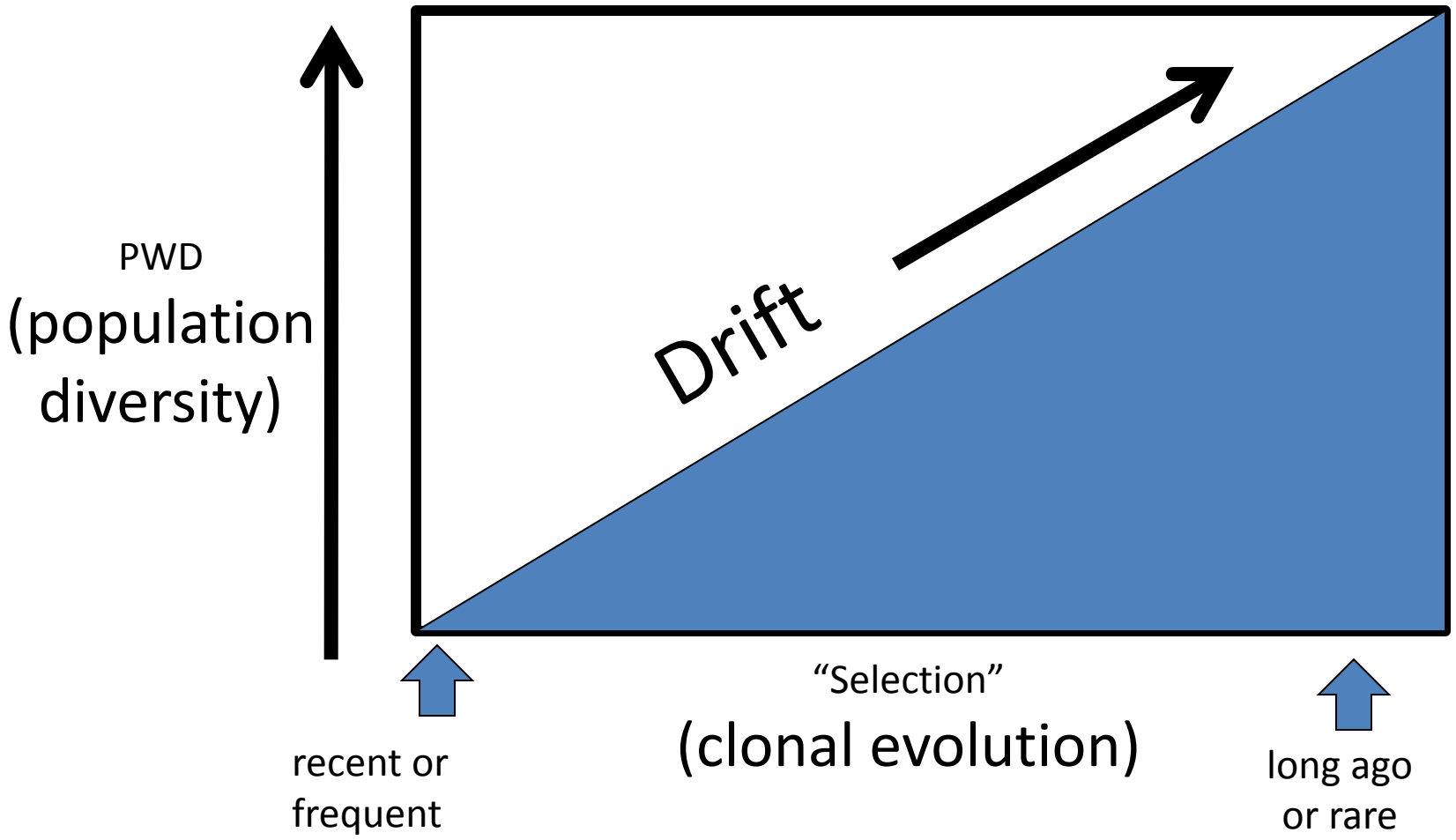


Most Identical Four Cells

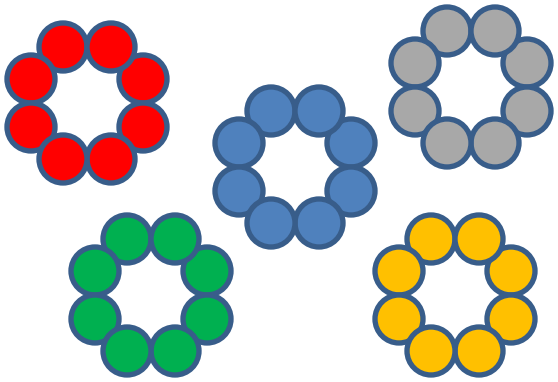
Most Identical Two Cells



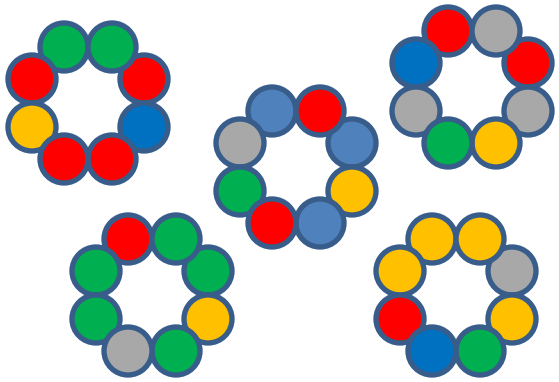
Evolution Parameter Measurements



Genomic Heterogeneity Between Adjacent Cells Means Weak or No Selection



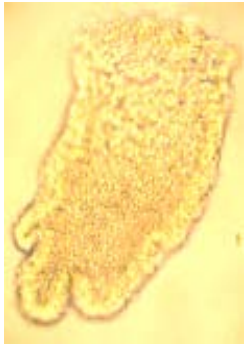
OR

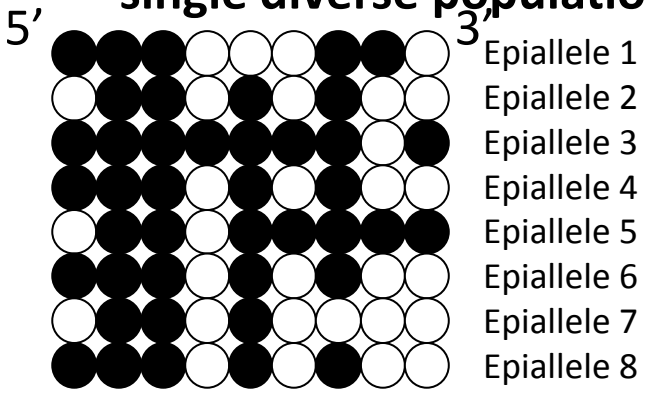


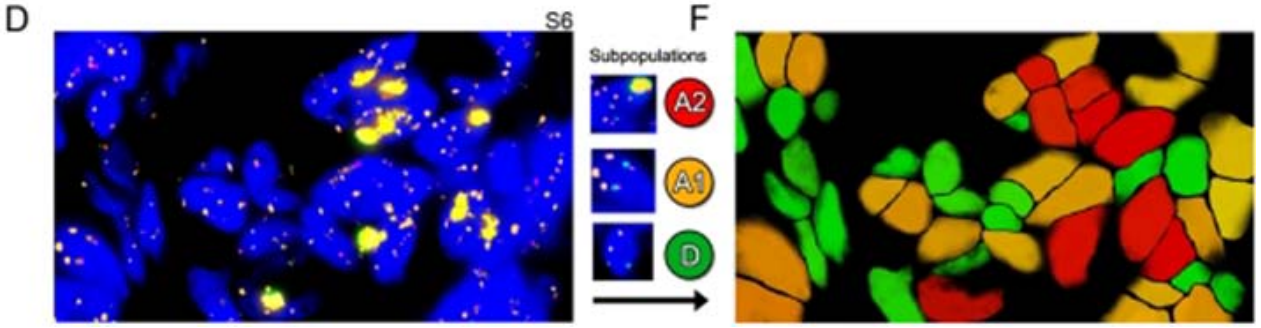
multiple small subclones

single diverse population

Cancer Gland
(~8,000 cells)



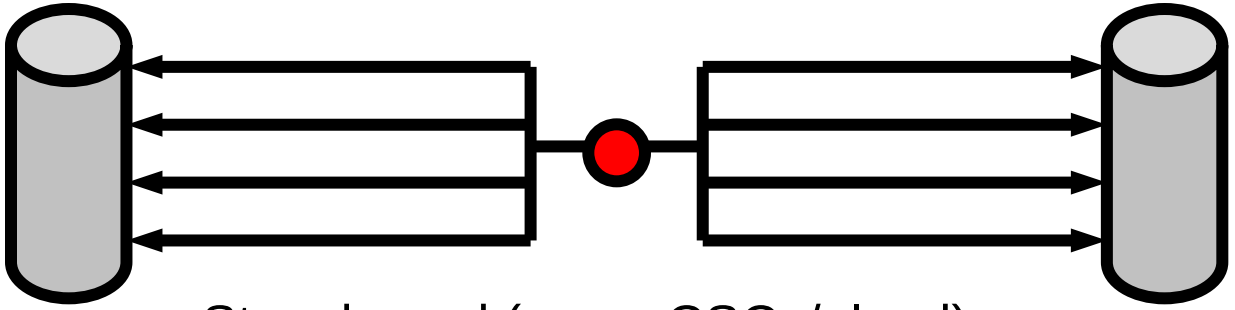




FISH Studies

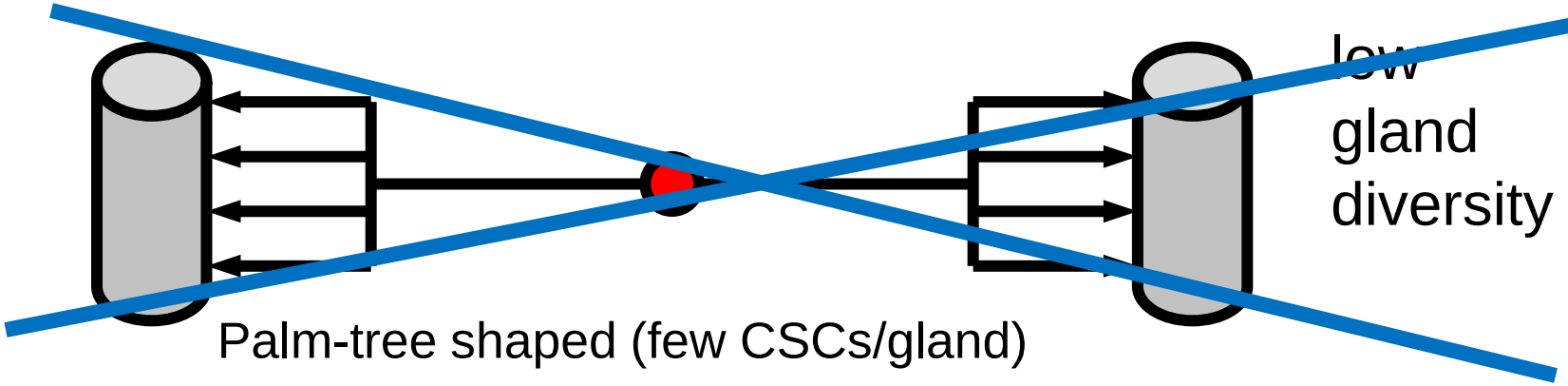
N. Navin *et al*., *Genome Res*. **20**, 68 (2010)

Human Colorectal Cancer Trees



high gland diversity

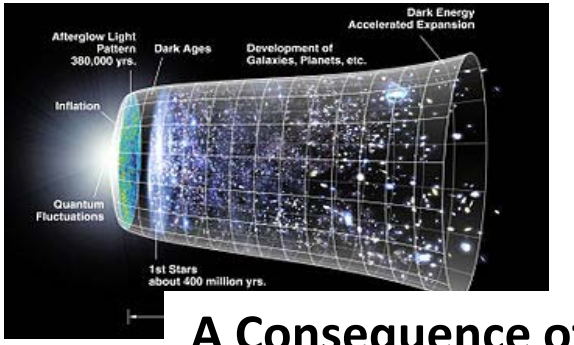
Star shaped (many CSCs/gland)

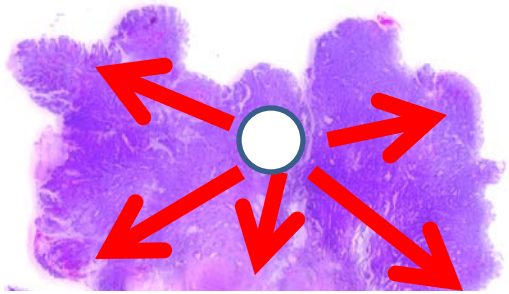


low gland diversity

Palm-tree shaped (few CSCs/gland)

Interestingly, all parts of the same tumor tend to have similar diversity or "age"



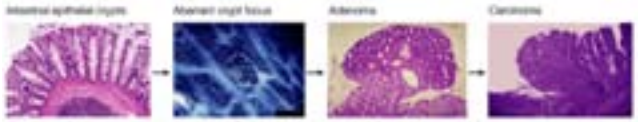


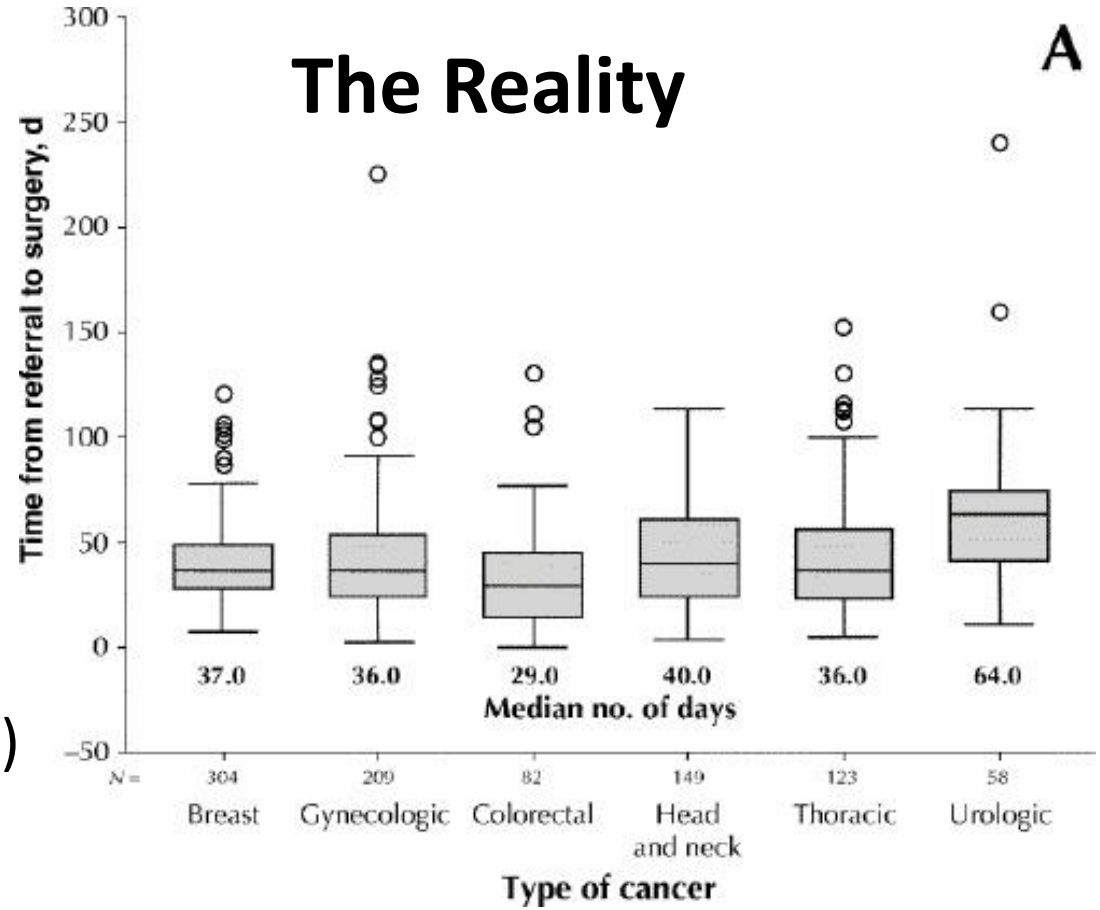
A Consequence of a Defined "Start" or Origin AND Rapid Expansion AND Lack of Selection?

Preventing Cancer Death (Metastasis)

If We Believe Bob A, One Way To Prevent Metastasis
May Be With A Fast Helicopter (out race the death star)

"Time Matters!"
(fast evolving populations)

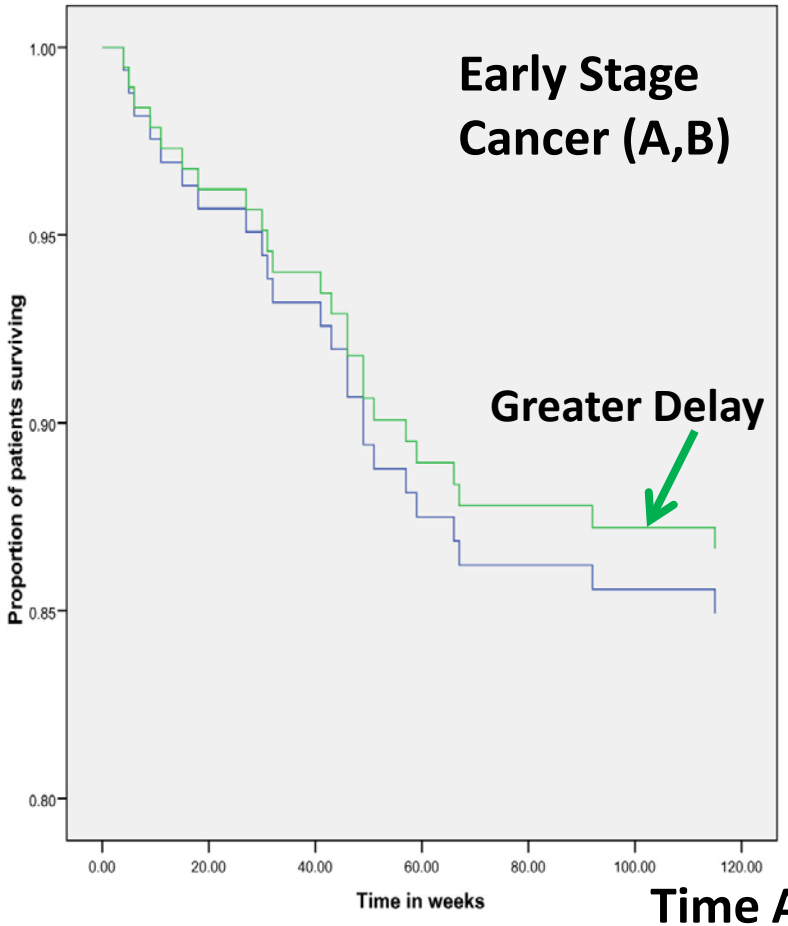


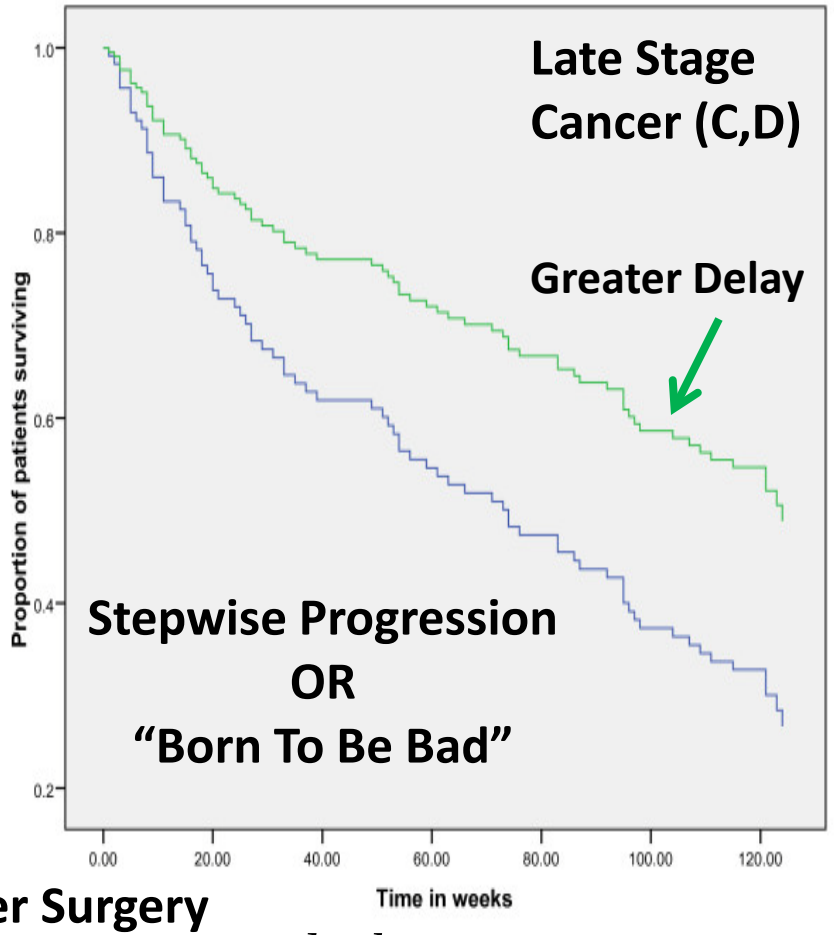


Does delay in diagnosing colorectal cancer in symptomatic patients affect tumor stage and survival? A population-based observational study
BMC Cancer 2010, **10**:332

Median Delay of 23.5 weeks

Survival

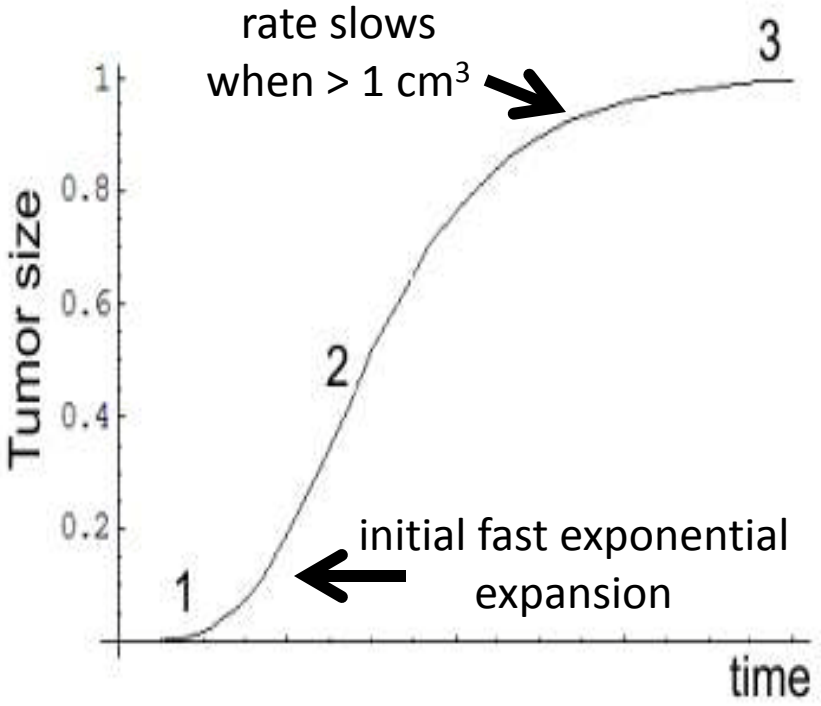




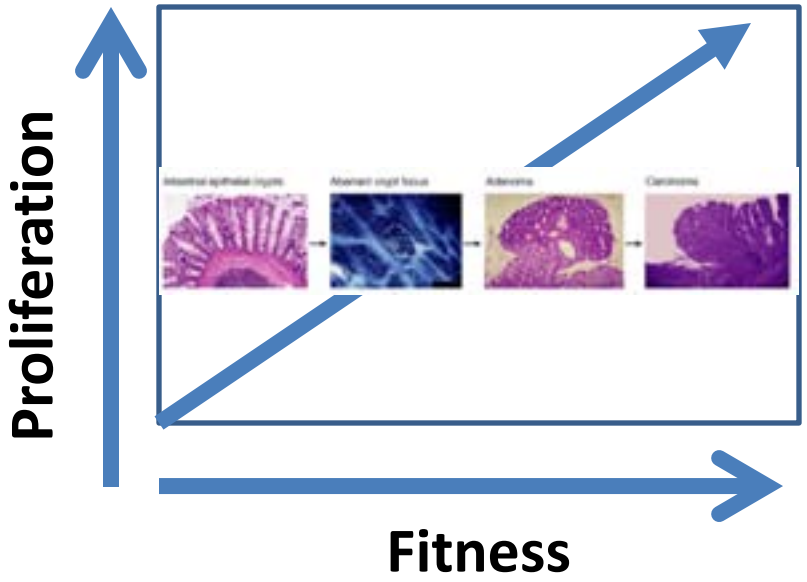
Time After Surgery

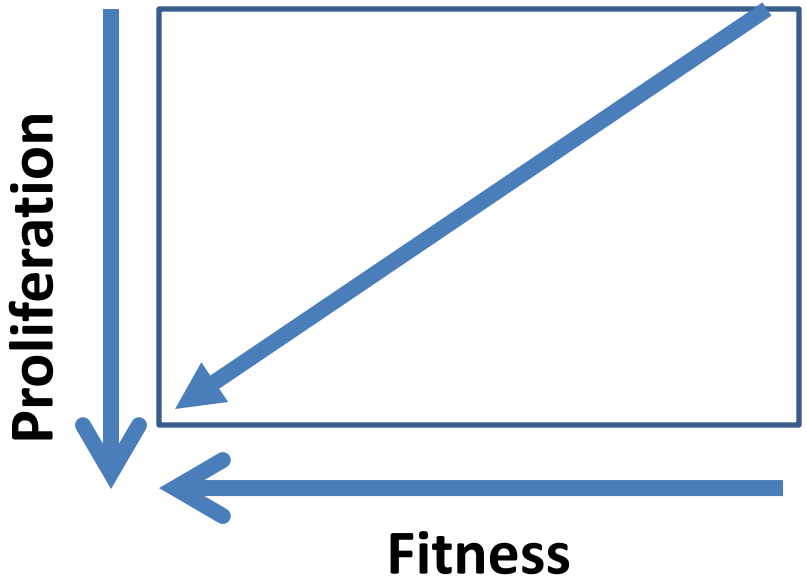
$$p = 1 - (1 - (1 - (1 - u)^{d})^{k})^{Nm}$$

Why Does Tumor Growth Slow With Time?

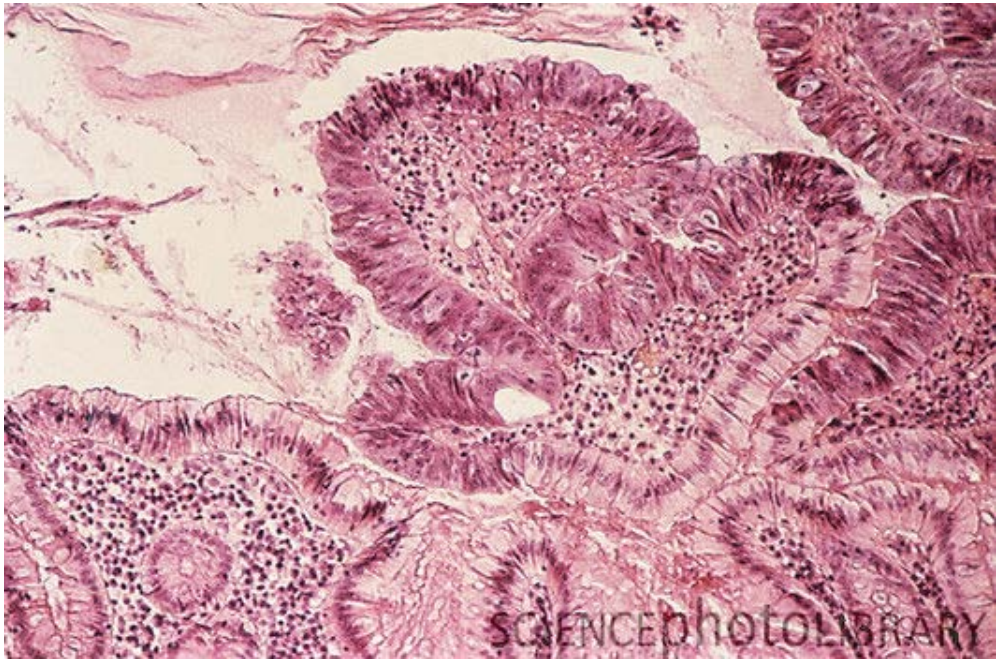


Tumors Typically Exhibit Gompertzian Growth



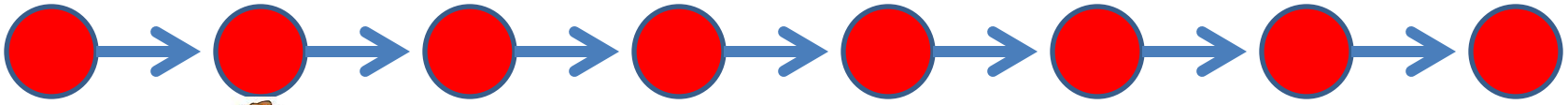


Muller's Ratchet
(most mutations are neutral or deleterious)



1mm

3 cm

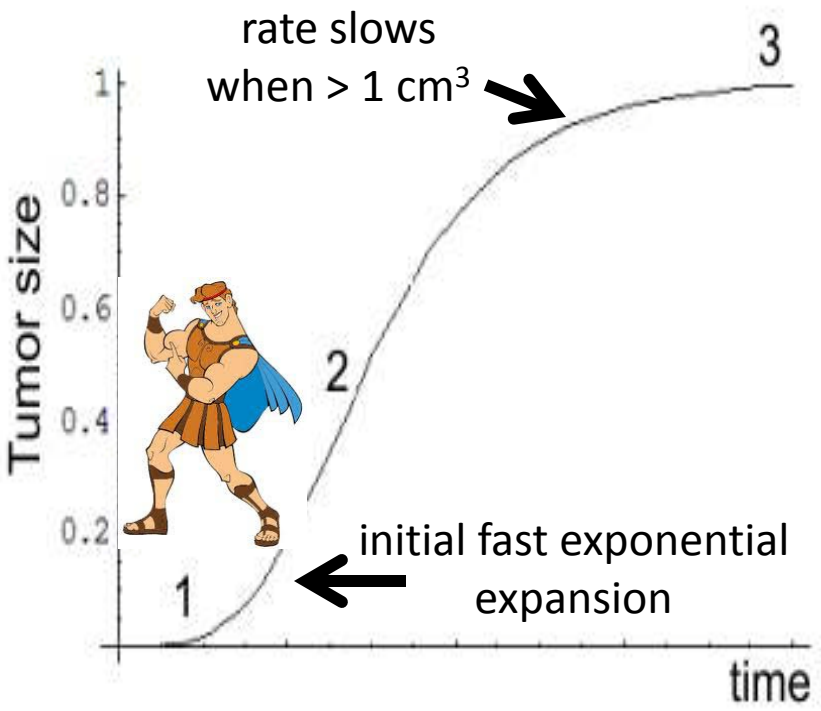


1st transformed cell

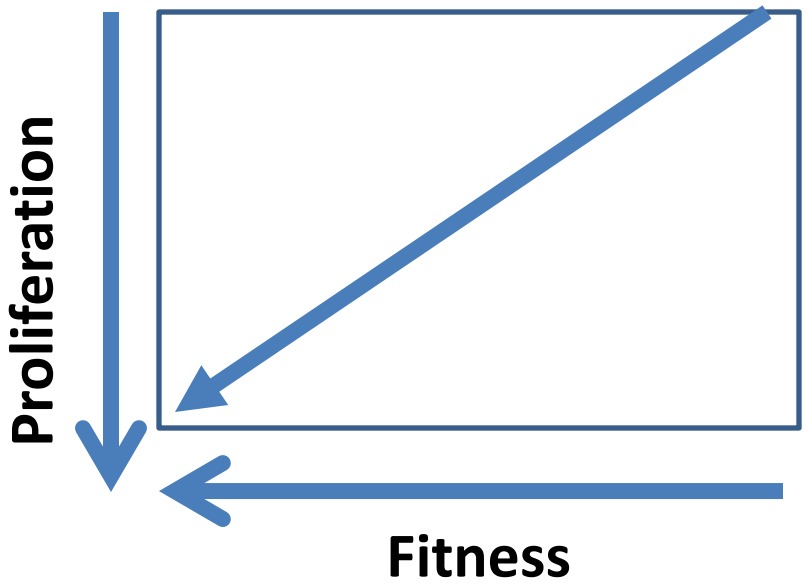
Many mutations and divisions later

Present day Cancer cell

Why Does Tumor Growth Slow With Time?

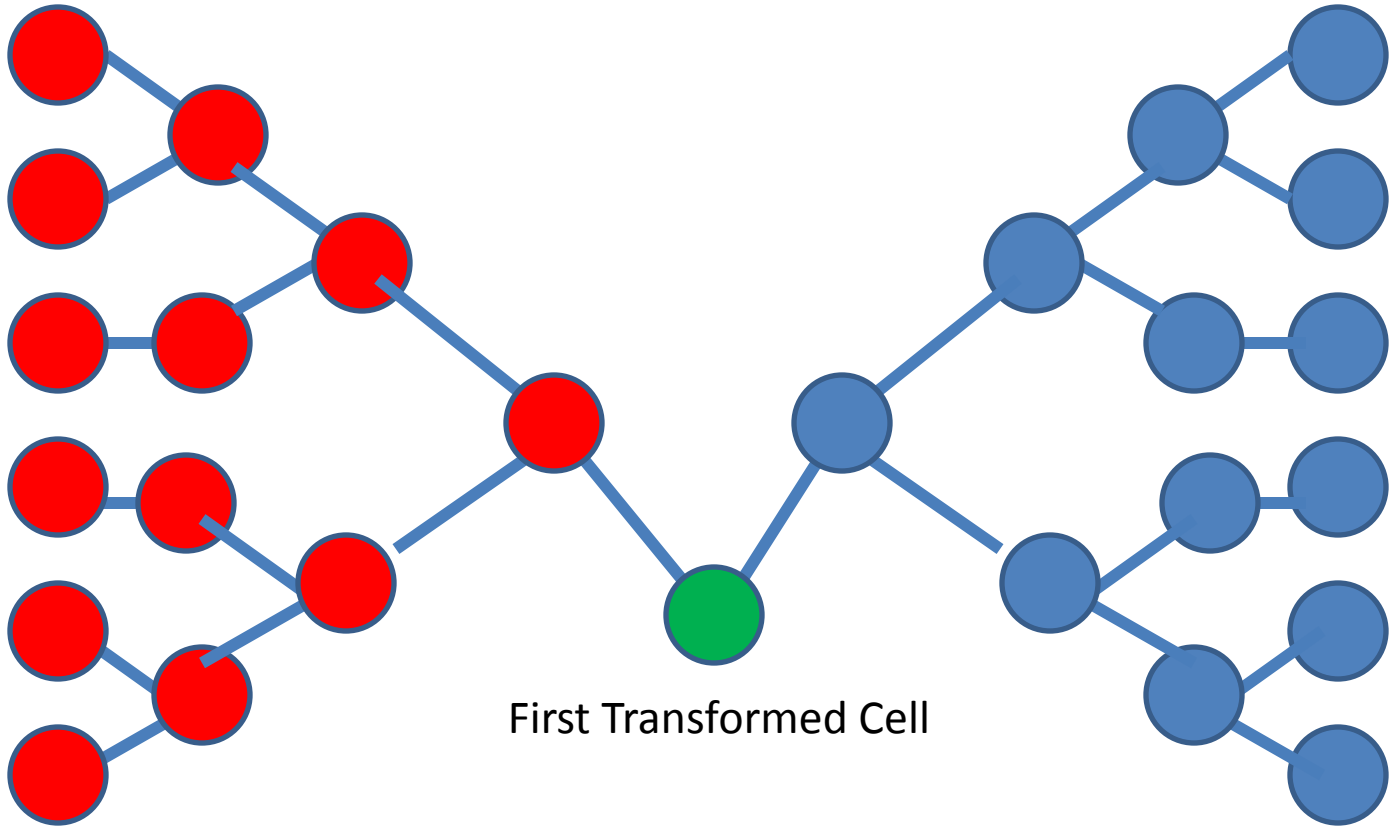


Tumors Typically Exhibit Gompertzian Growth

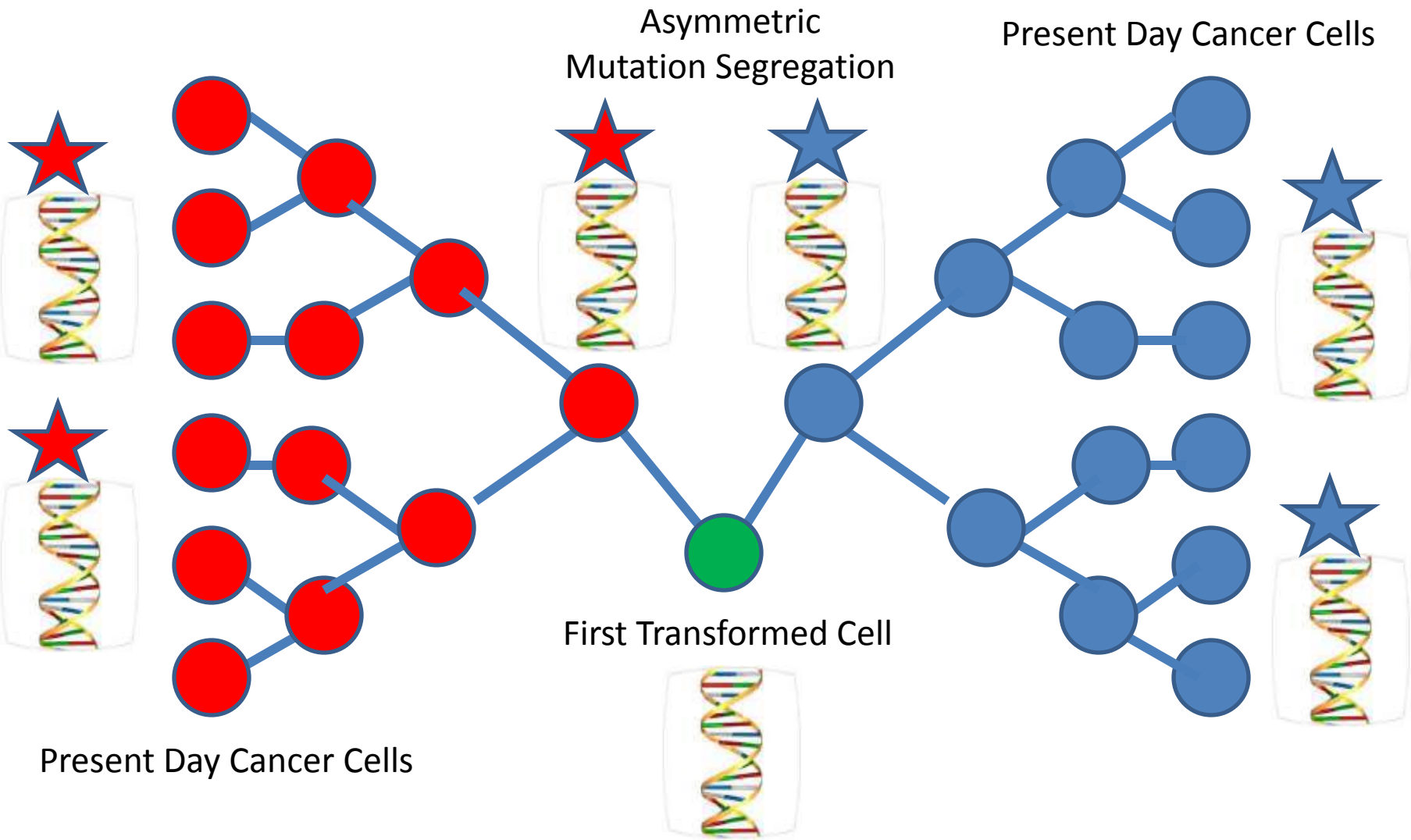


How To Measure The First Few Cancer Cell Divisions (Coalescence Theory)

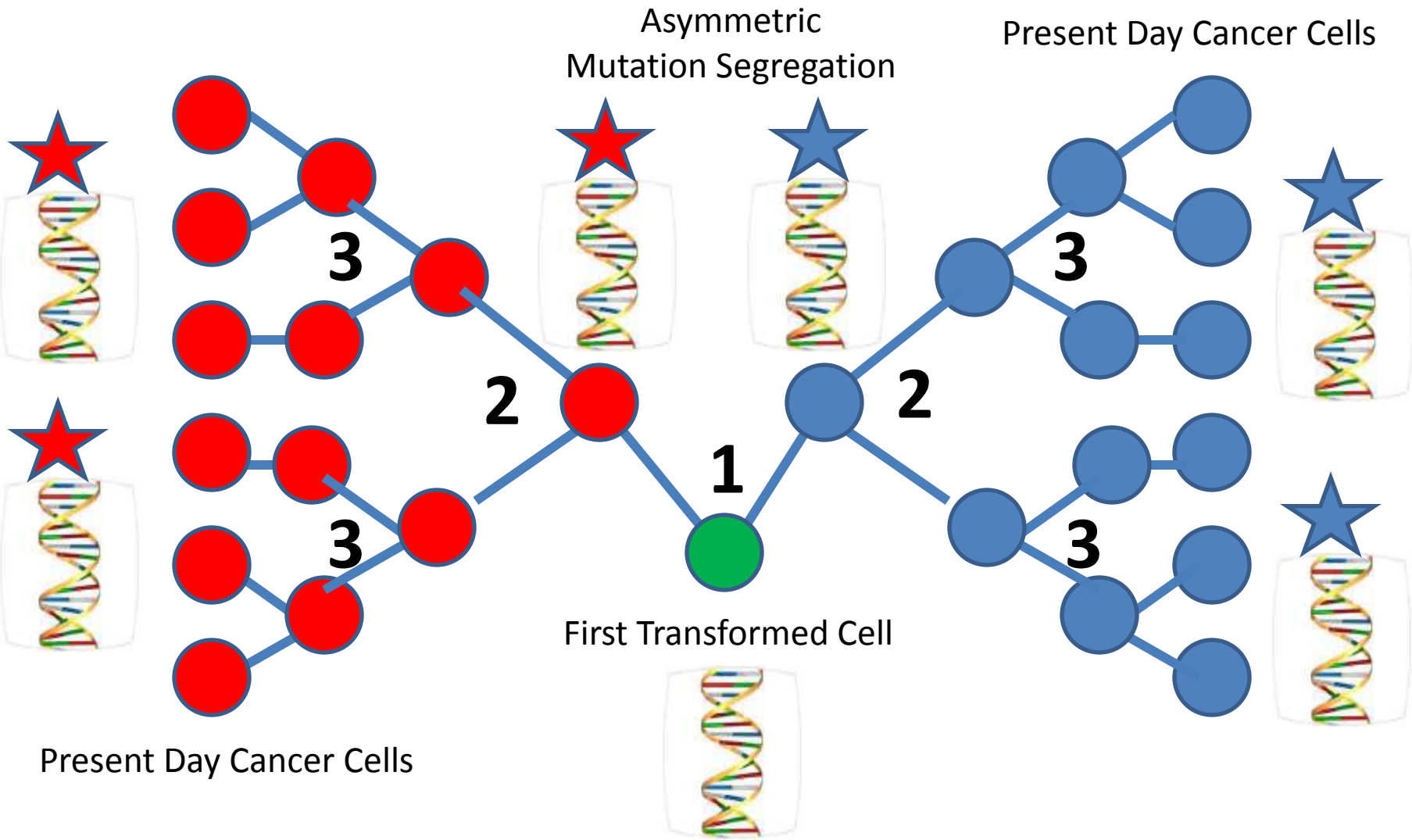
1. Every Somatic Cell Has One Parent
2. Sometimes Two Somatic Cells Share A Parent
3. Eventually All Cells Share The Same Parent

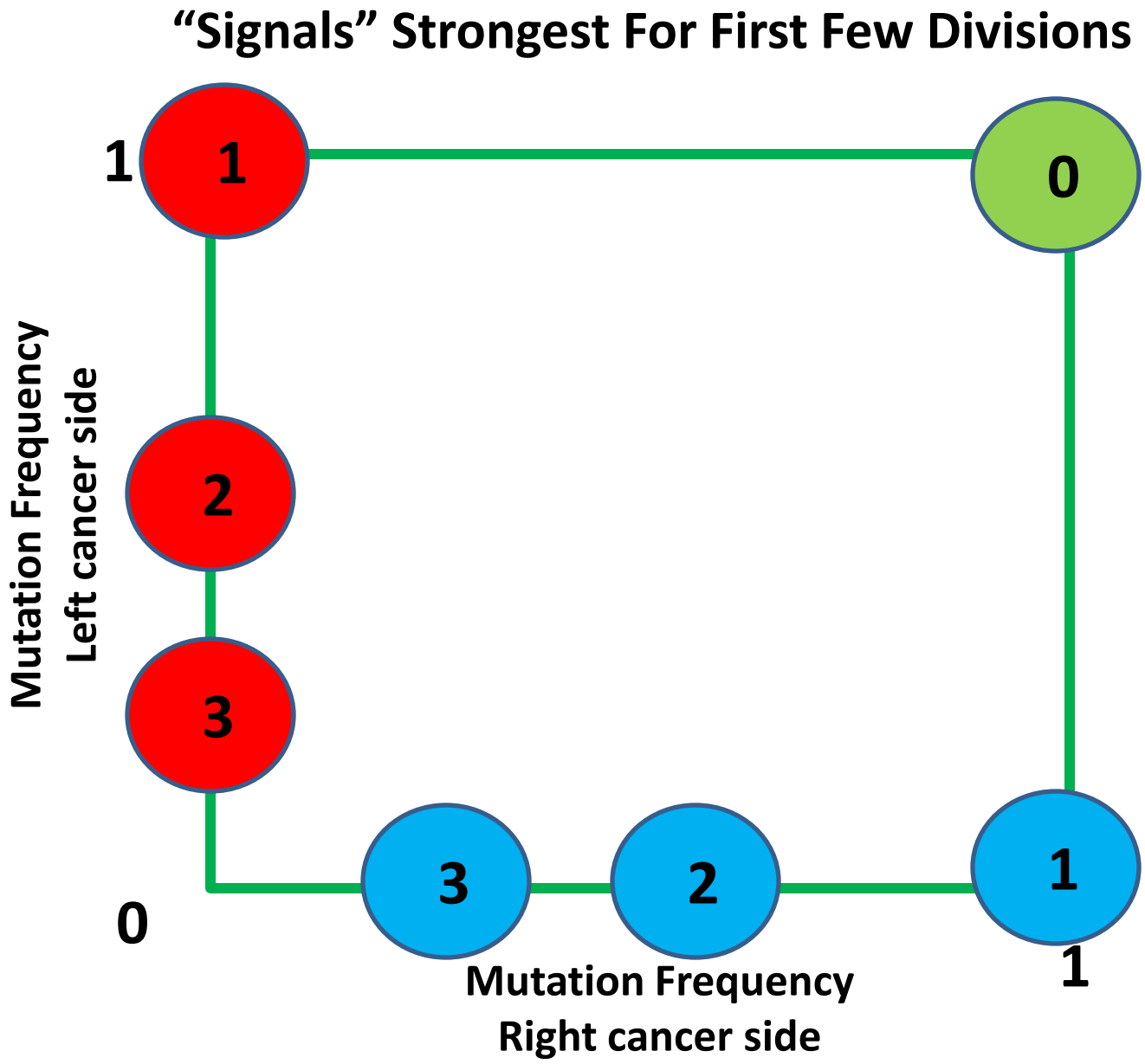


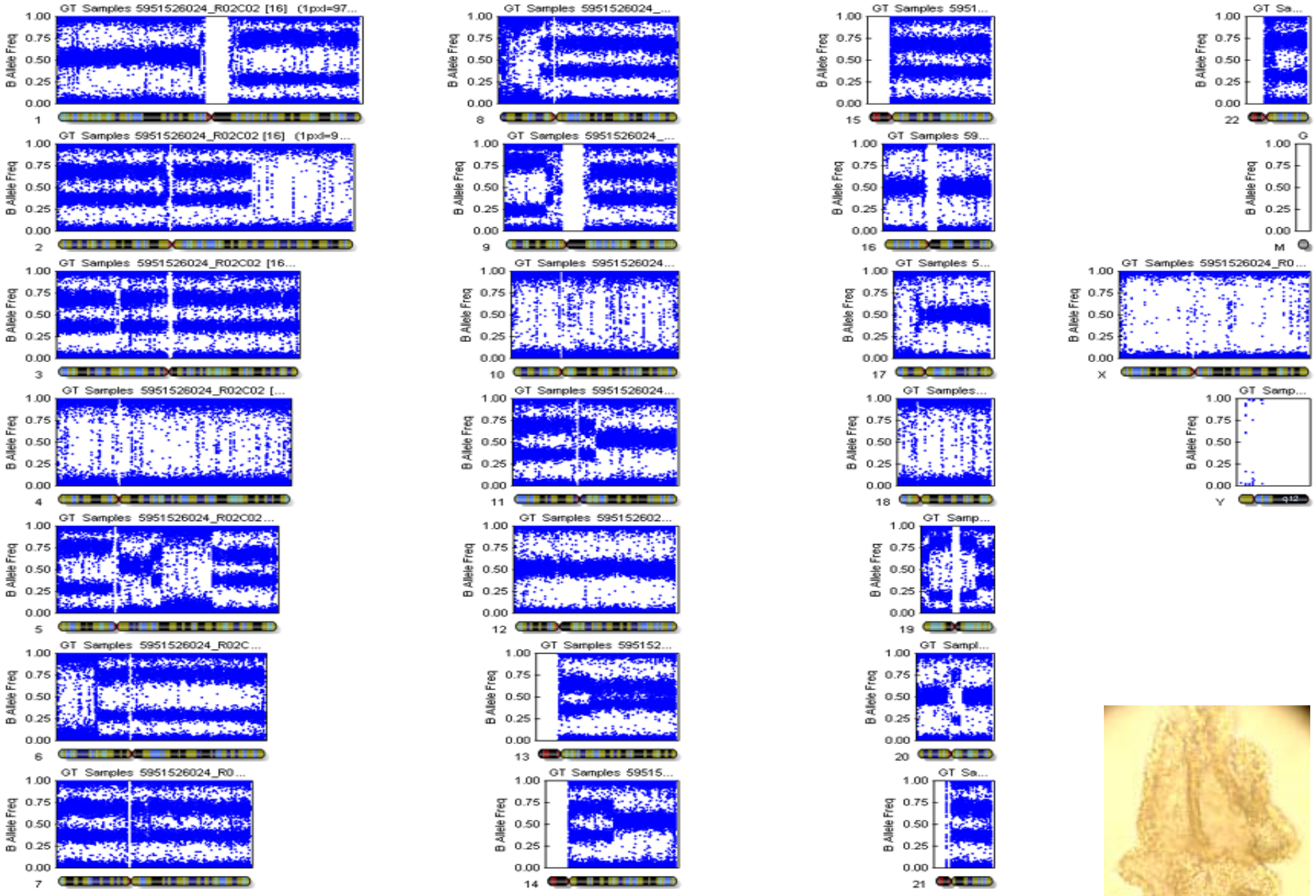
“Symmetry Breaking”



“Symmetry Breaking”

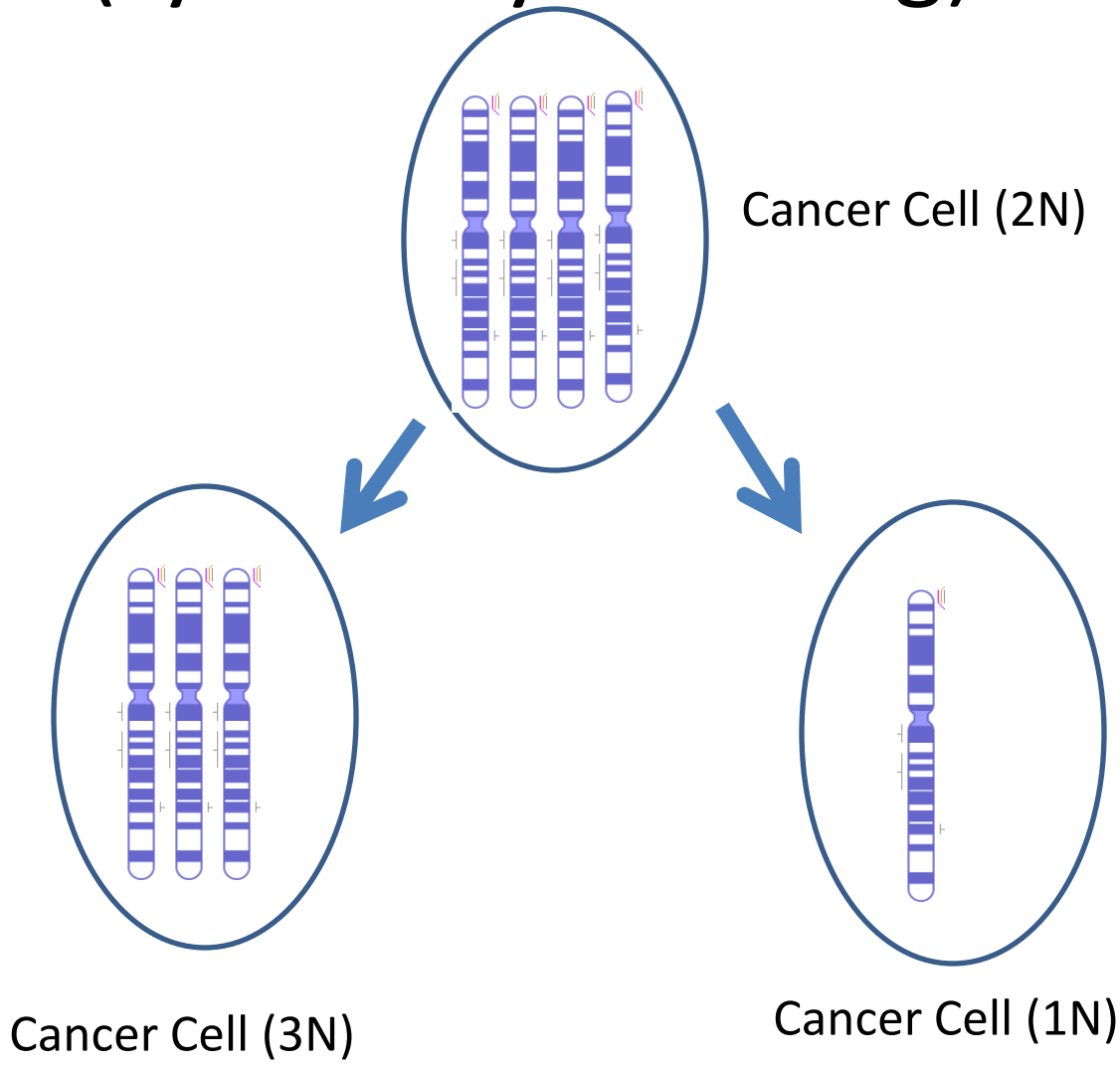



"Signals" Strongest For First Few Divisions
1
1
0
Mutation Frequency
Left cancer side
2
3
3
2
1
0
1
Mutation Frequency
Right cancer side

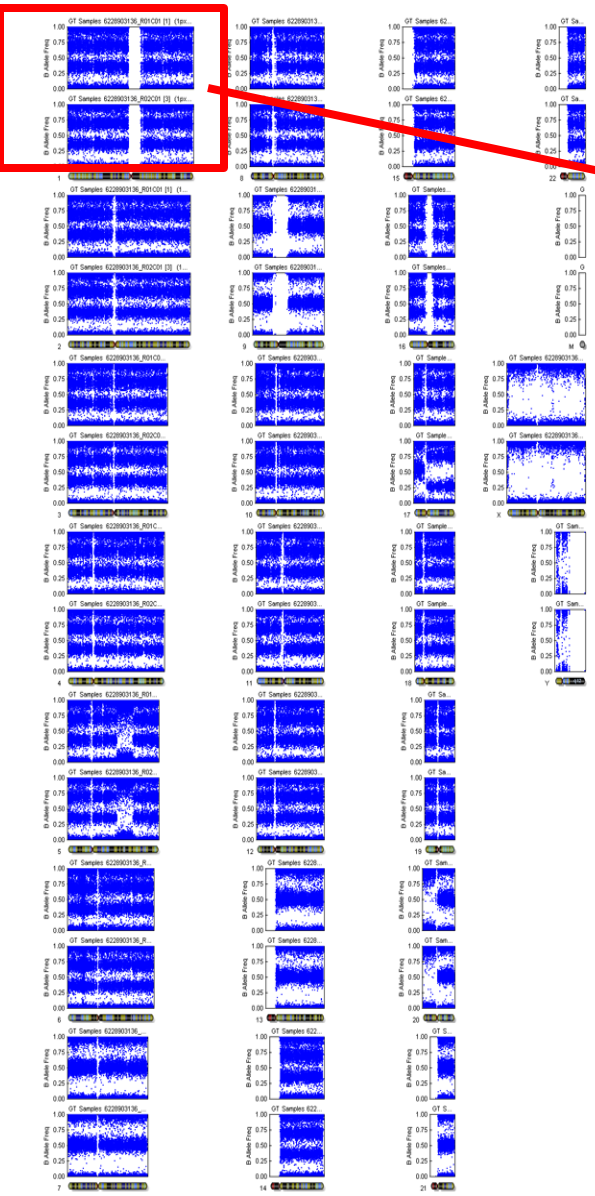


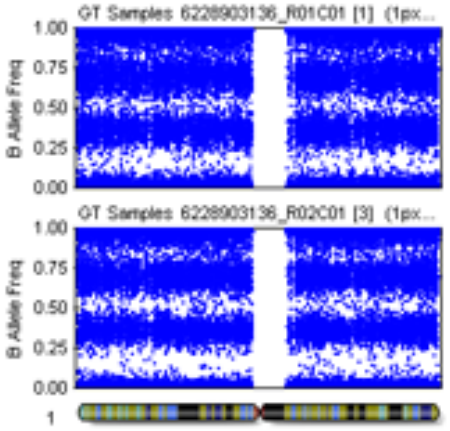
Illumina 660 SNP Microarray

Chromosomal Instability (CIN) (symmetry breaking)

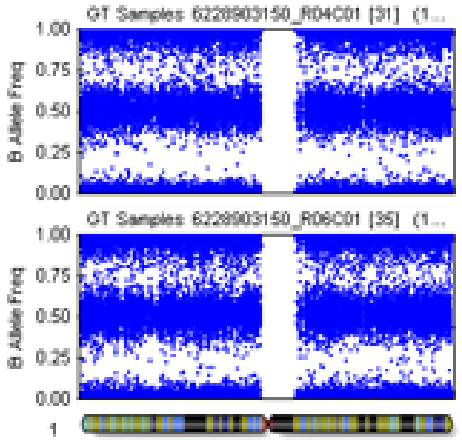


Left Side
2 cancer glands



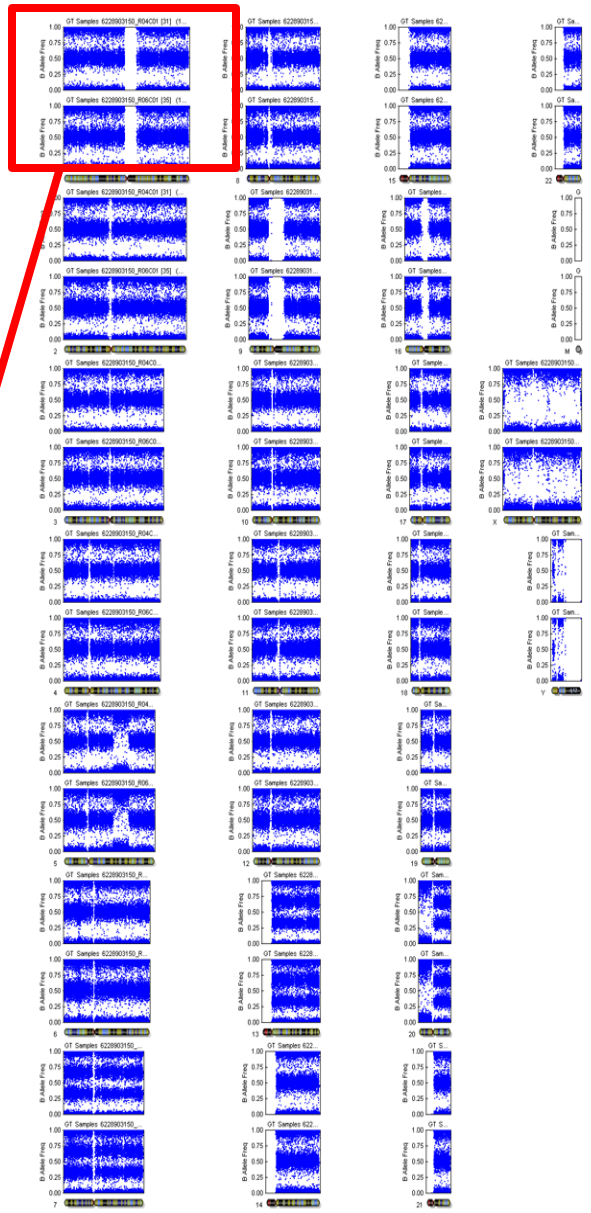


3N

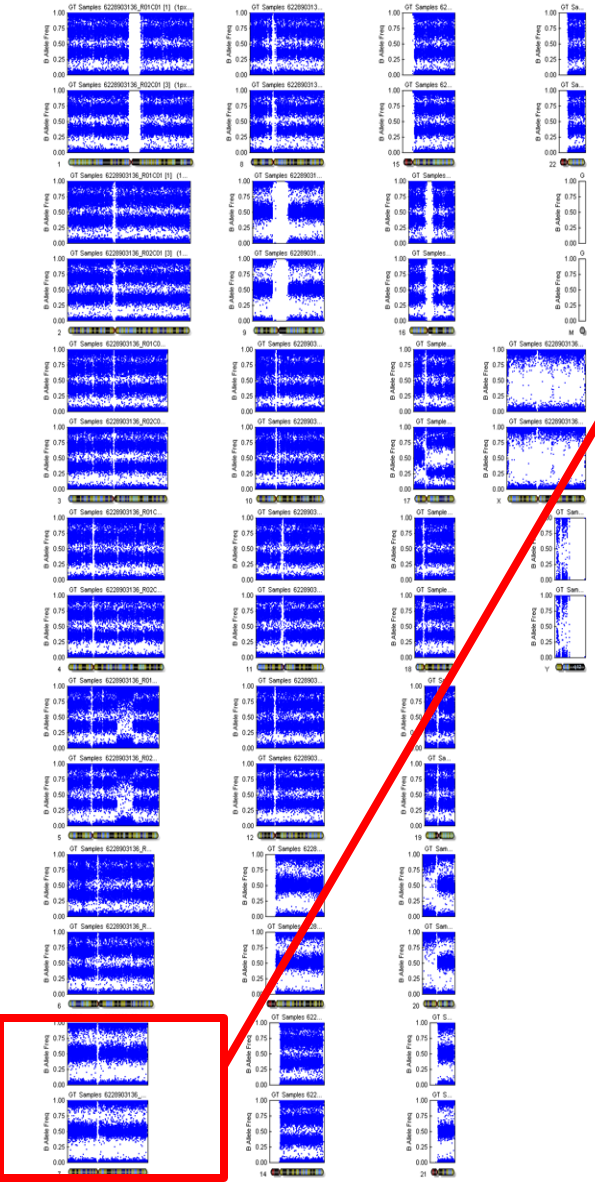


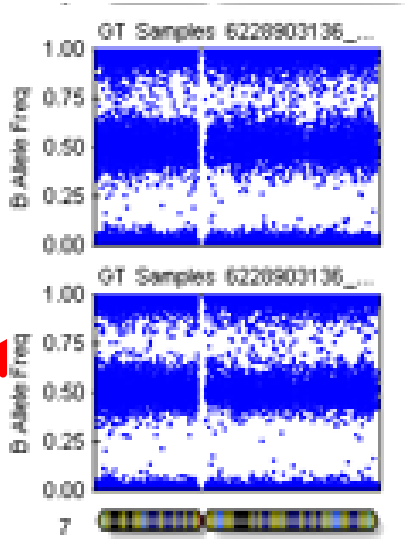
2N

Right Side
2 cancer glands

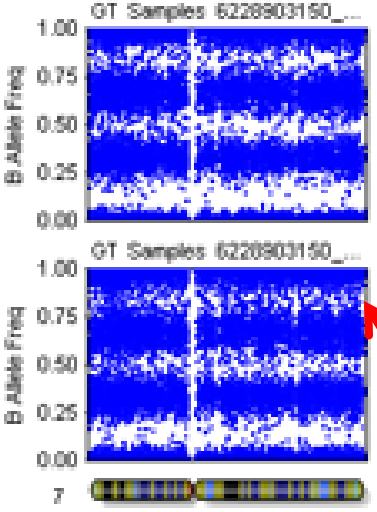


Left Side
2 cancer glands



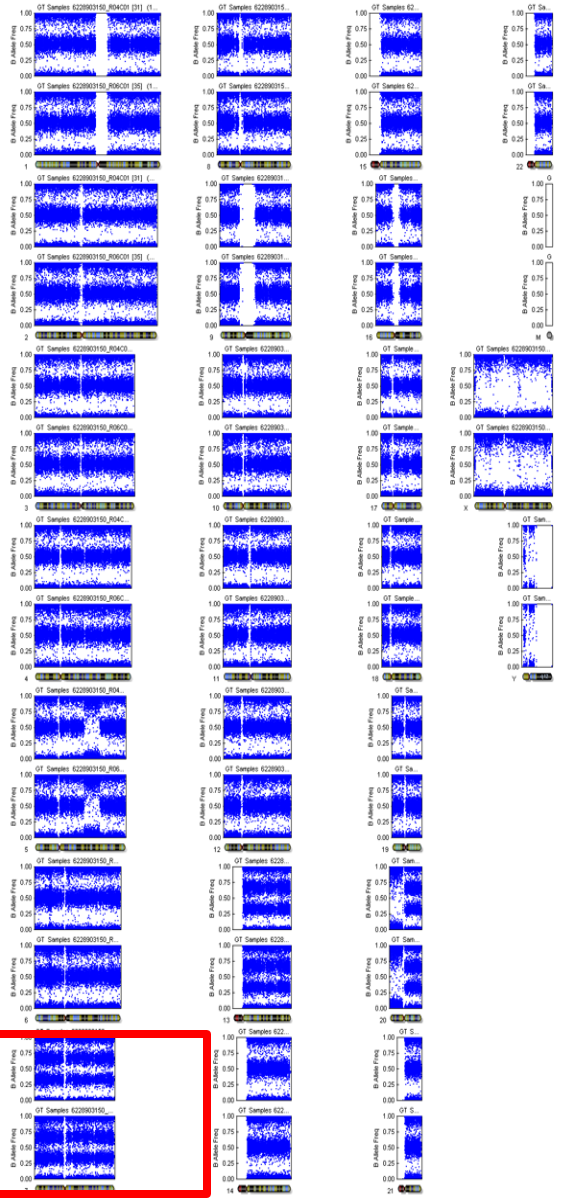


2N

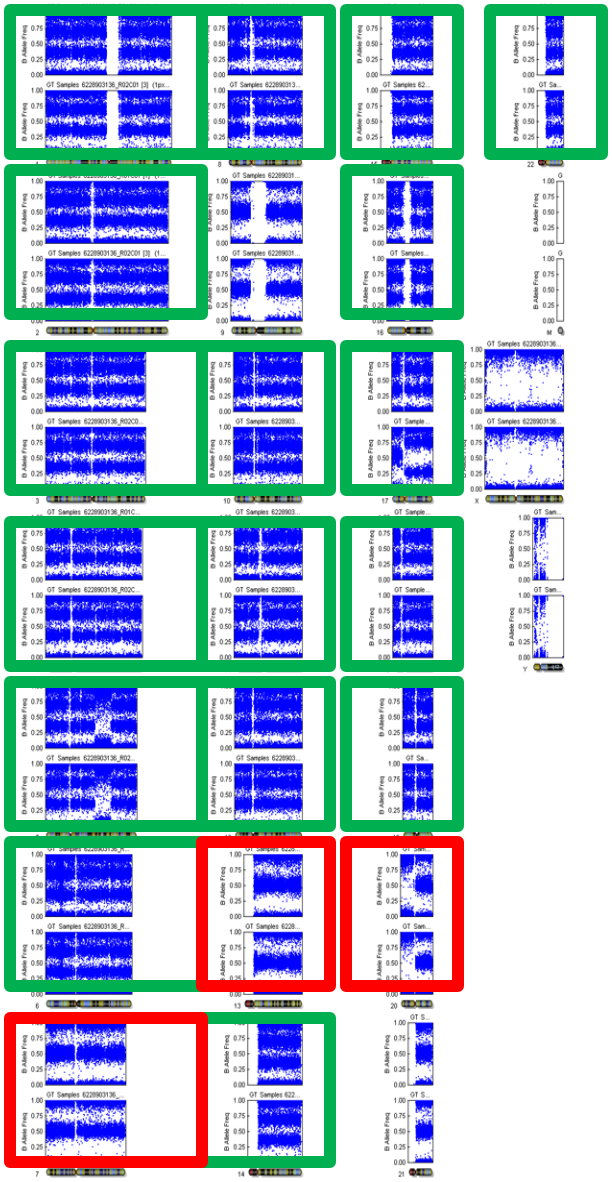


3N

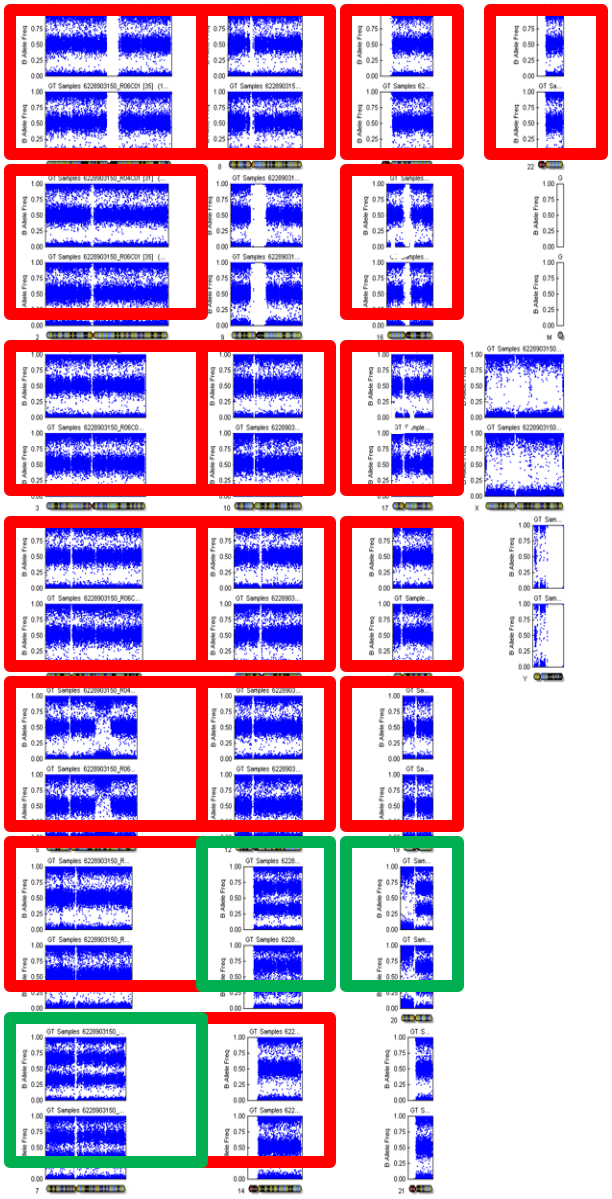
Right Side
2 cancer glands



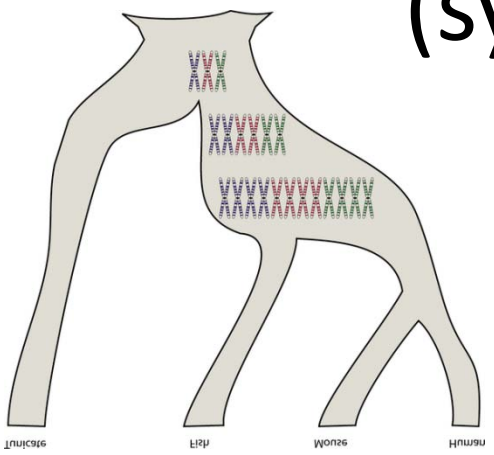
Left Side
2 cancer glands



Right Side
2 cancer glands

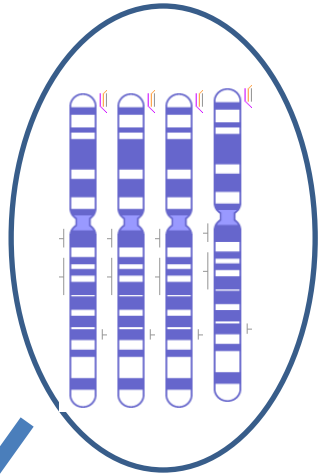


Chromosomal Instability (CIN) (symmetry breaking)

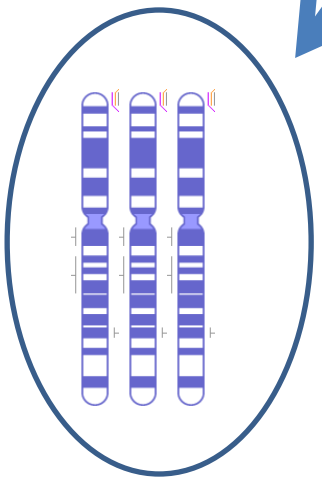


fish mouse human

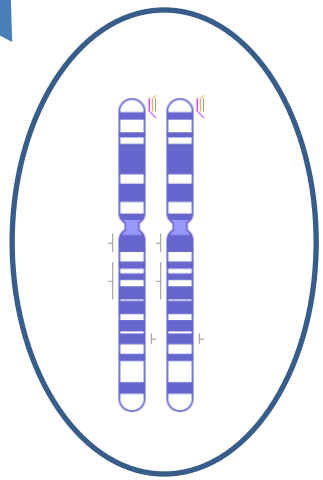
Genome duplication
Often thought to
Occur with "Speciation"



1st transformed Cell (5N?)



Cancer Cell (3N)



Cancer Cell (2N)

In the Beginning……
"Symmetry Breaking"

Present Day Cancer Cells

3

2

3

1

2

3

3

Present Day Cancer Cells

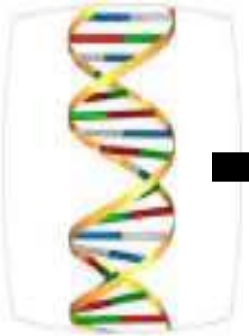
First Transformed Cell

Summary

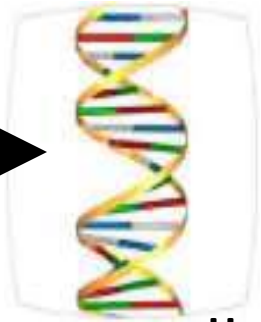
- Are There Logical Physical “Rules” To Creation?
- Possible To Apply These Rules To Human Cancer?
- Use “Logic” To Improve Measurements and Form Testable Hypothesis
- May Be Possible To “See” The Unseeable

  (Understand The “Start” of Human Cancers)

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



zygote
(start)



cancer cell
(present day)

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