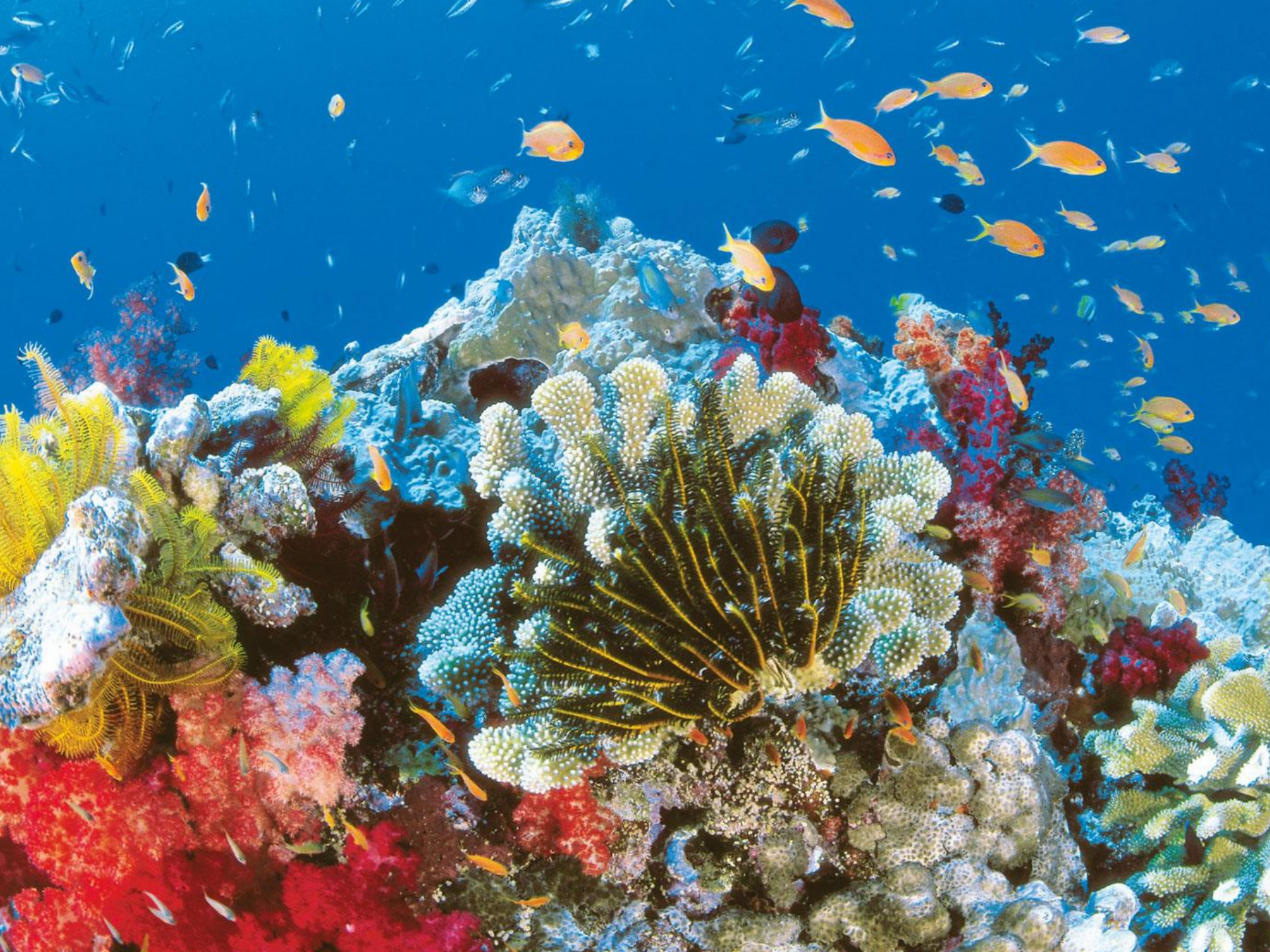
Long-term management of tumor growth and resistance

Michael Hochberg

KITP – September 10, 2014

Wissenschaftskolleg zu Berlin

INSTITUTE FOR ADVANCED STUDY



The Great Barrier Reef Food Chain


White-tipped Reef Shark


Dugong


Humpback Whale


Tiger Shark


Sea Snake


Whale Shark


Sea Turtle


Sea Eagle


Box Jellyfish

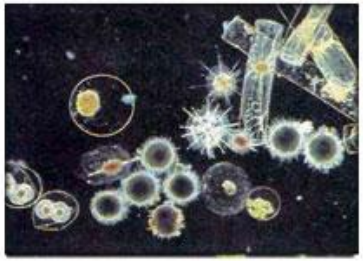

Red Bass


Clown Fish


Giant Clam

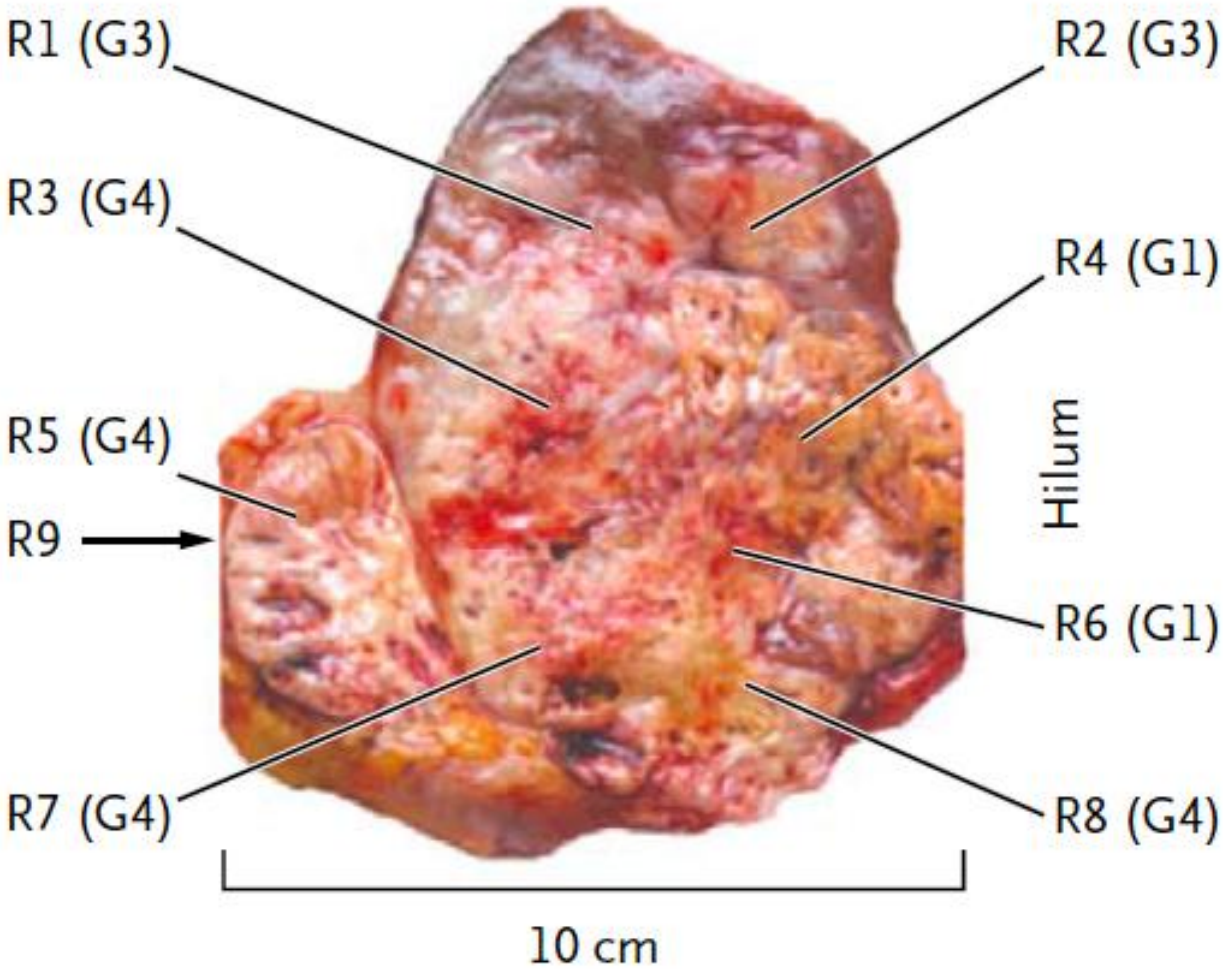

Mollusc


Sea Horse

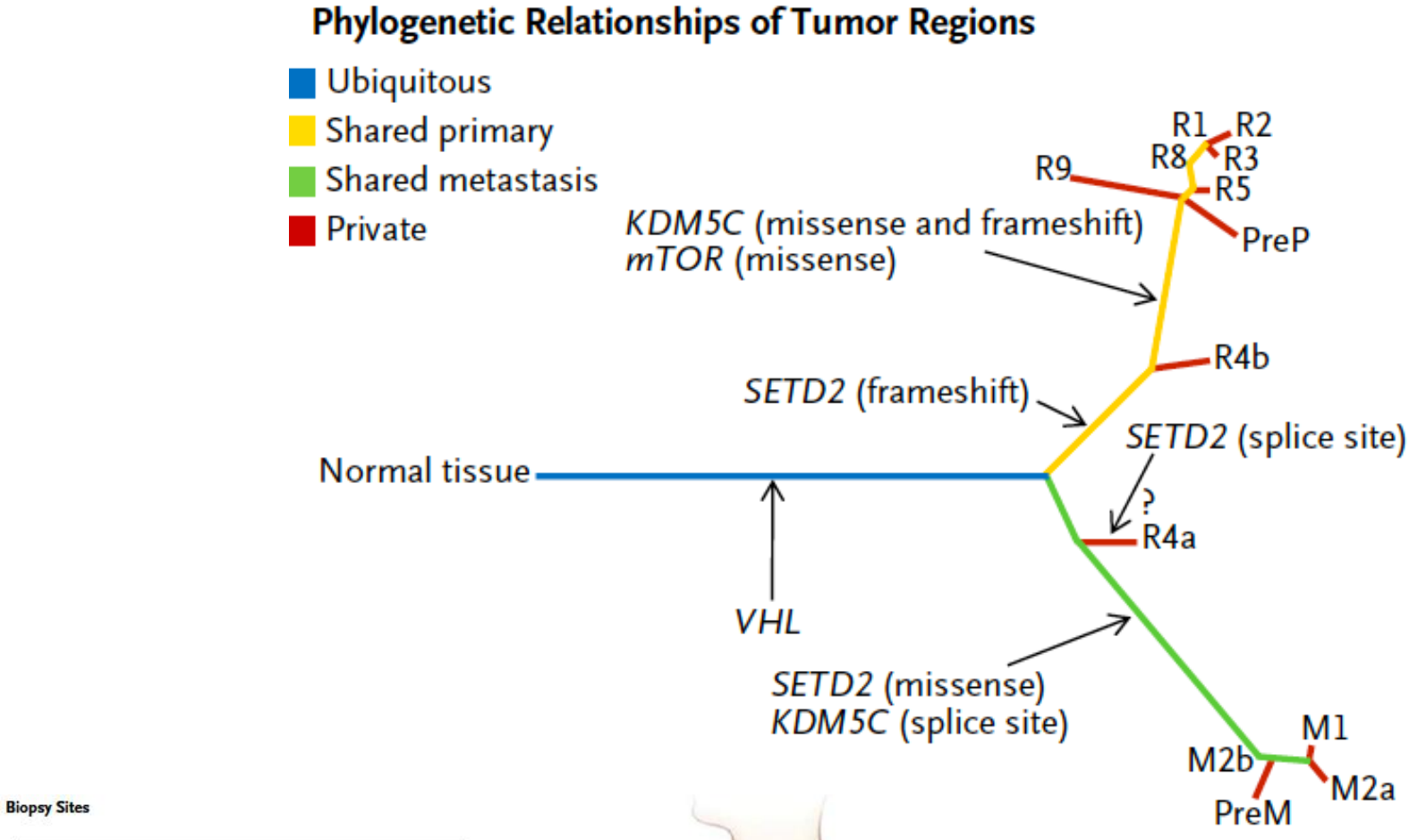

Plankton

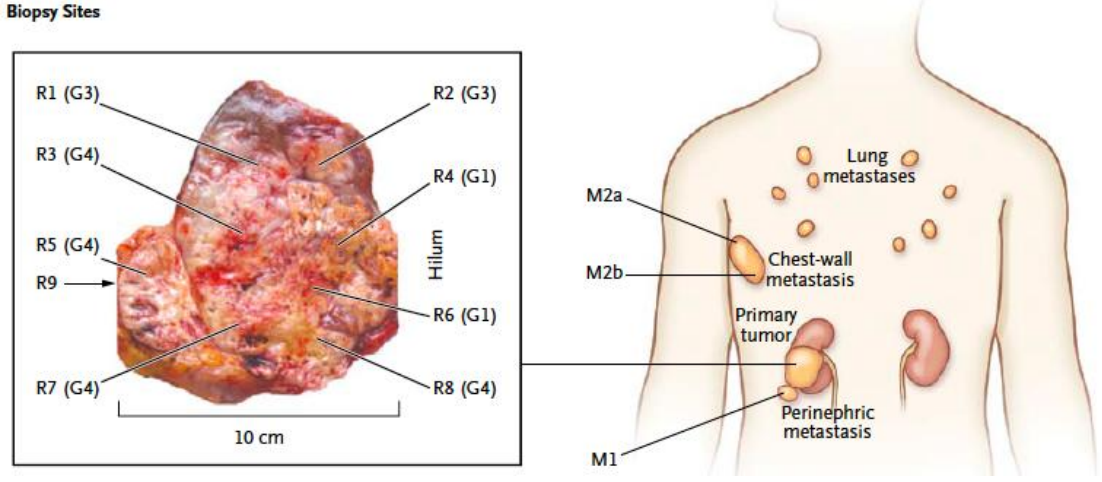

Krill


Marine Algae



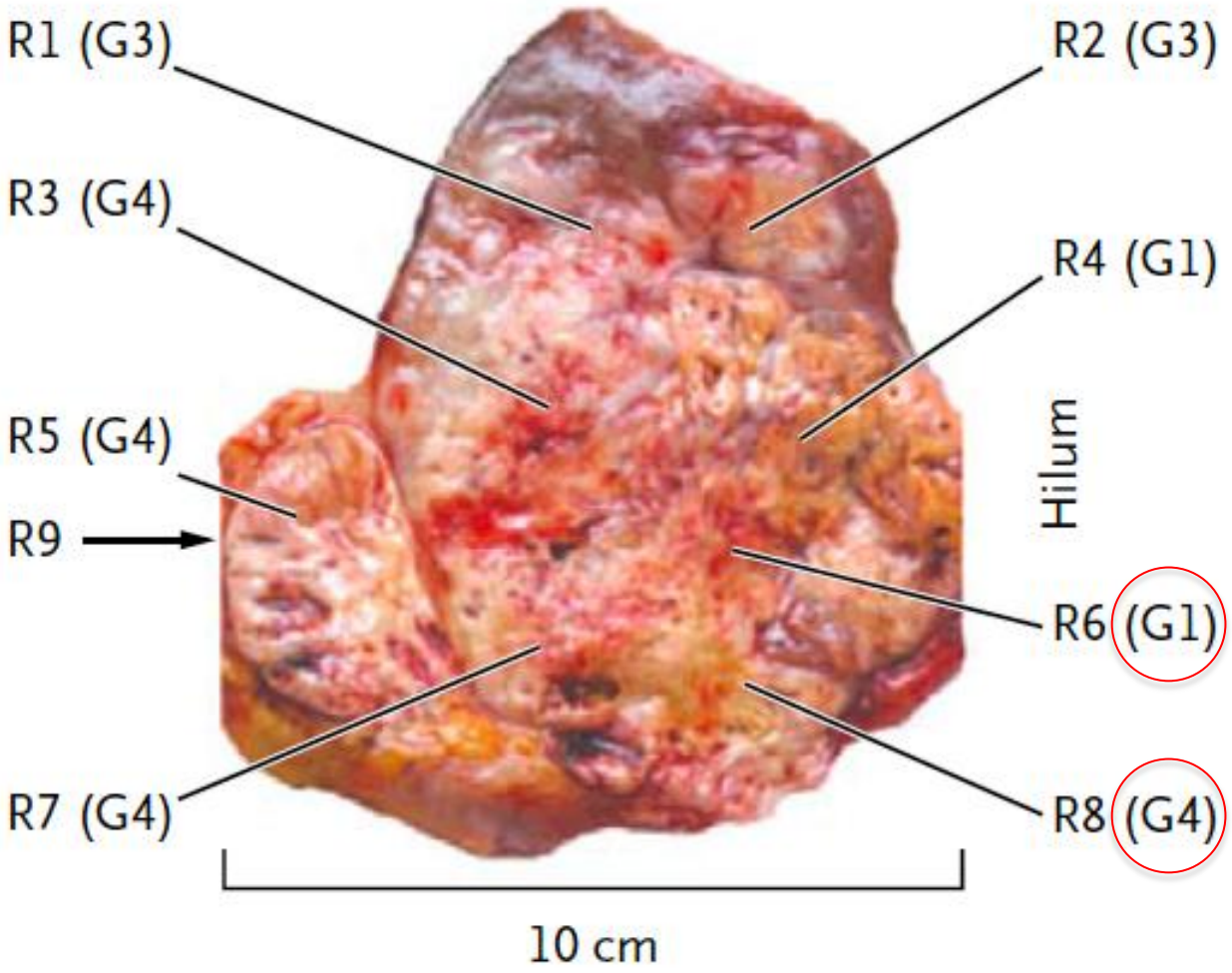
Gerlinger et al. 2012. NEJM 366(10)



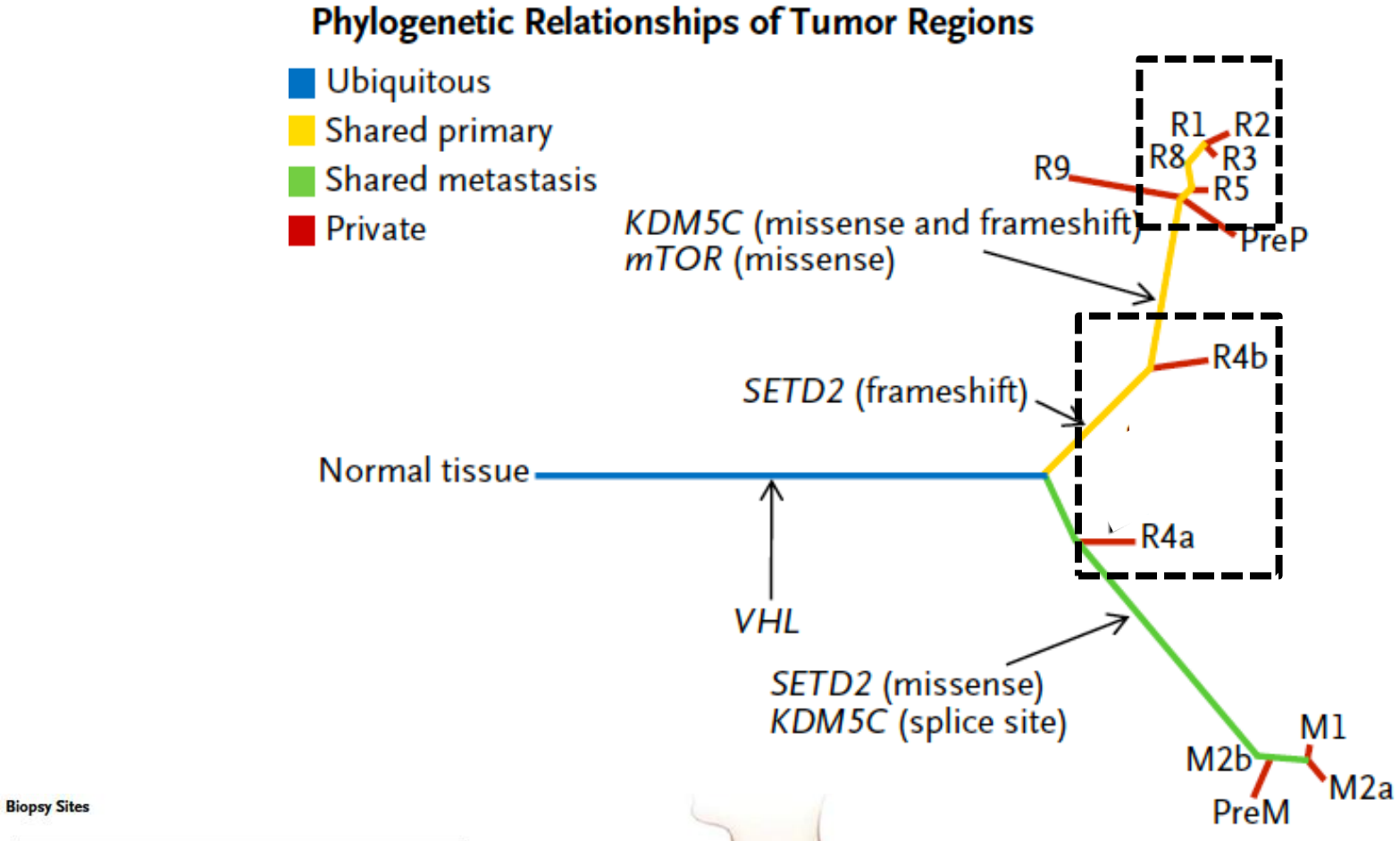


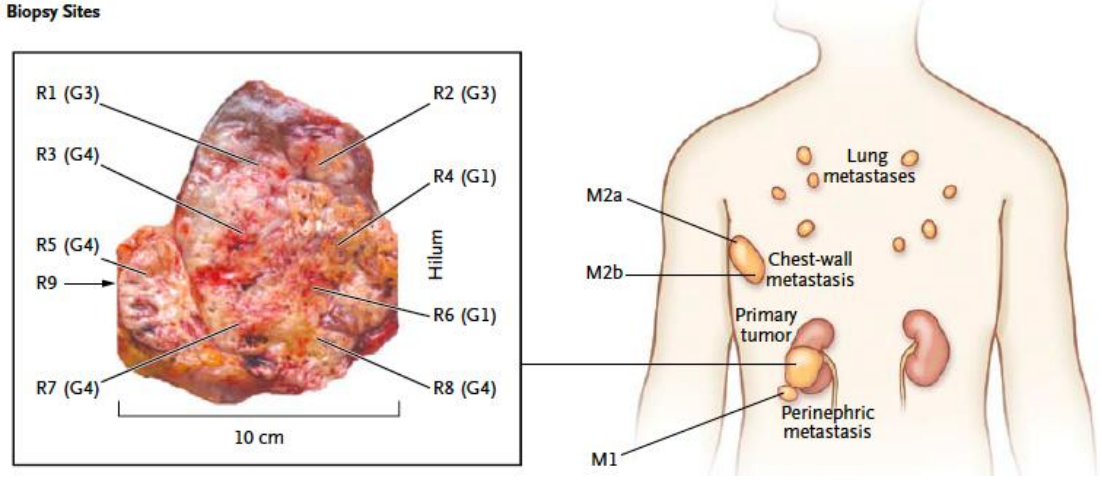
Gerlinger et al. 2012. NEJM 366(10)

Intra-tumor heterogeneity



Gerlinger et al. 2012. NEJM 366(10)

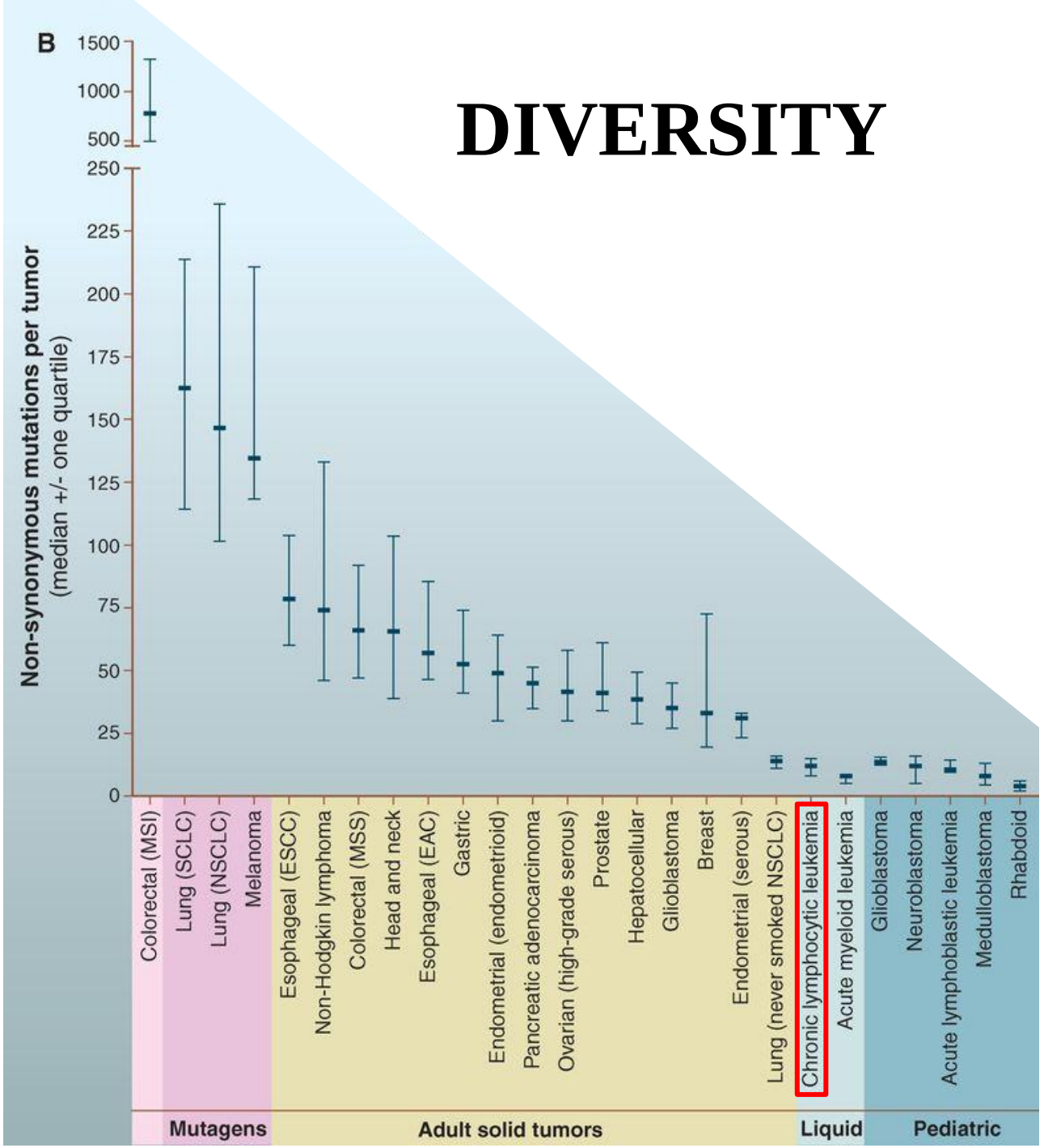




Gerlinger et al. 2012. NEJM 366(10)

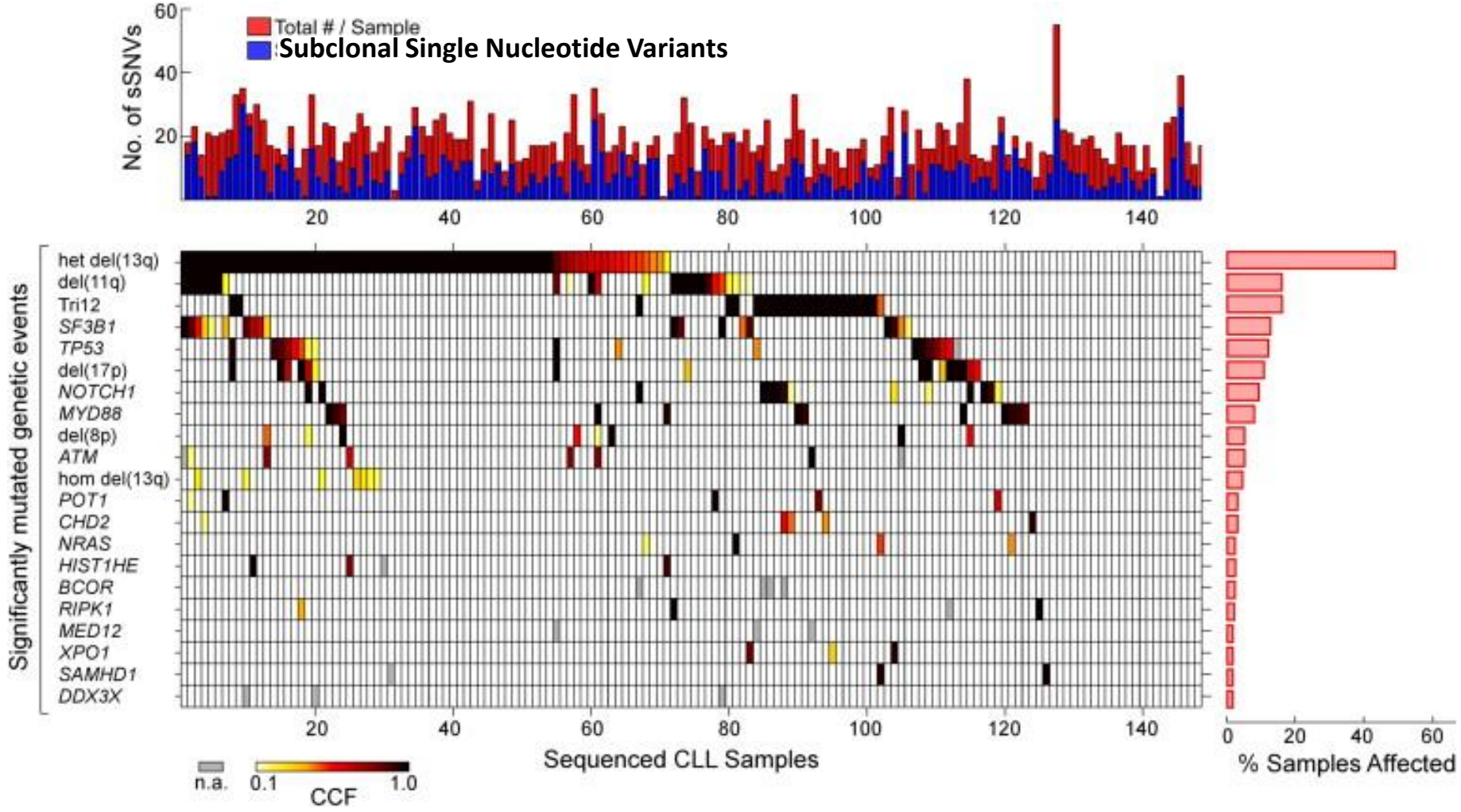
Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

DIVERSITY



Science 2013. 339:1546-1558

Chronic Lymphocytic Leukemia



Landau et al. 2013. *Cell*

Leading Edge
Essay

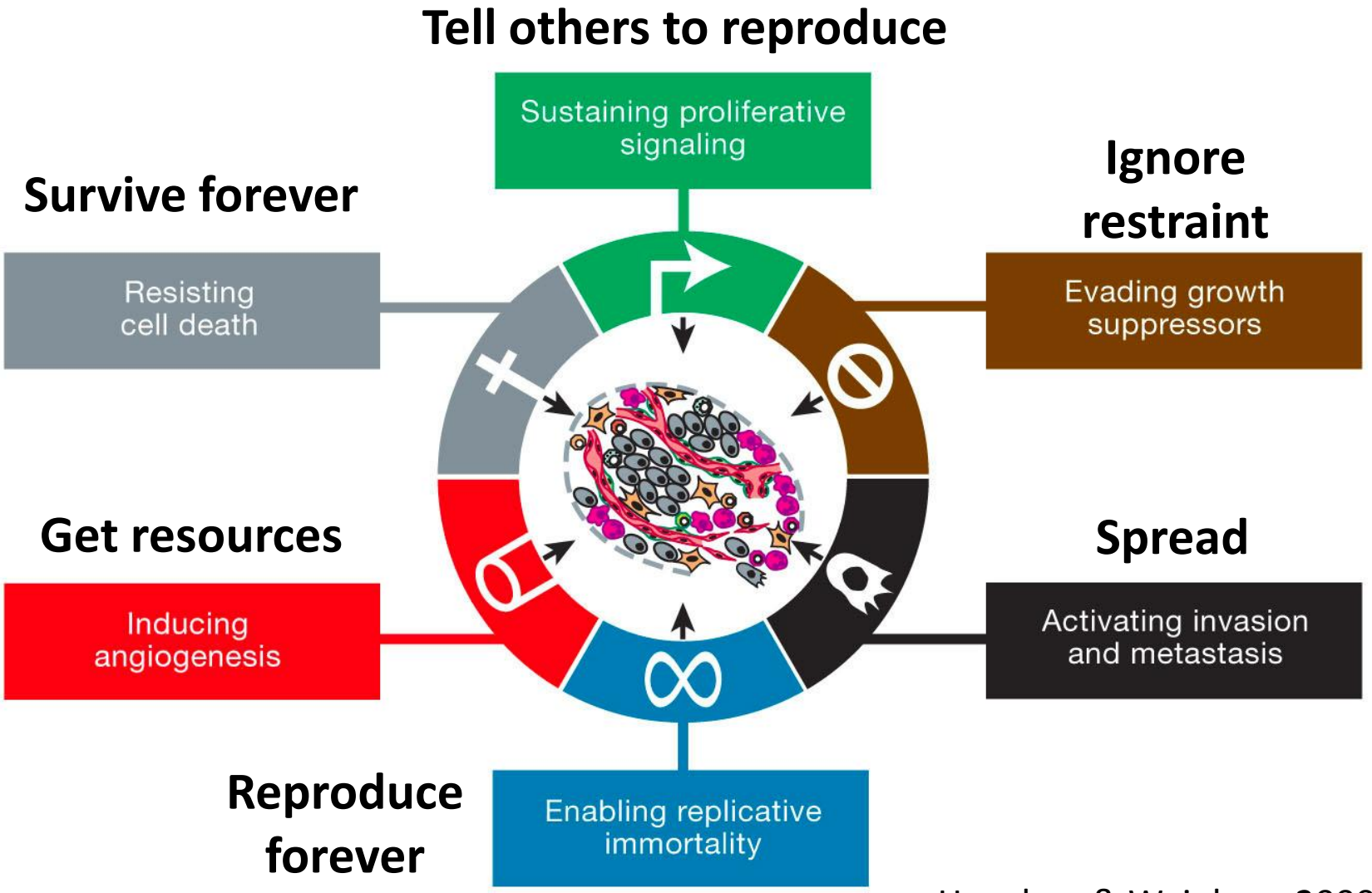
Cell

Coming Full Circle—From Endless Complexity to Simplicity and Back Again

Robert A. Weinberg[1,2,3,*]
[1]Whitehead Institute for Biomedical Research
[2]Ludwig/MIT Center for Molecular Oncology
[3]MIT Department of Biology
Cambridge, MA 02142, USA
*Correspondence: weinberg@wi.mit.edu
http://dx.doi.org/10.1016/j.cell.2014.03.004

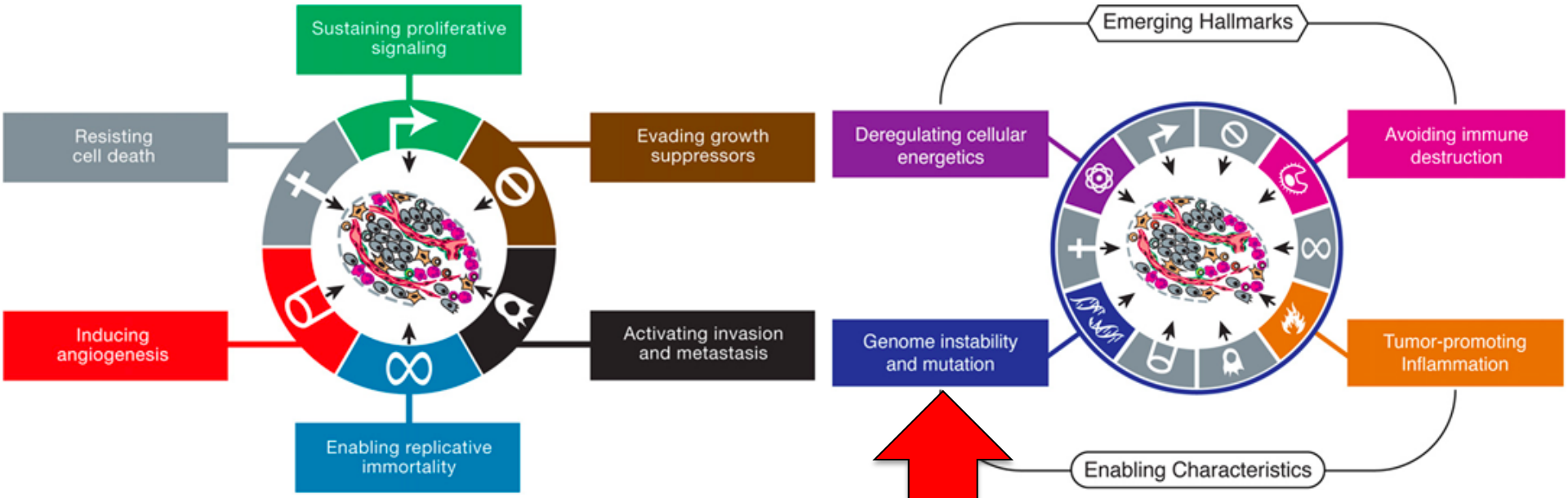
Cell has celebrated the powers of reductionist molecular biology and its major successes for four decades. Those who have participated in cancer research during this period have witnessed wild fluctuations from times where endless inexplicable phenomenology reigned supreme to periods of reductionist triumphalism and, in recent years, to a move back to confronting the endless complexity of this disease.

Hallmarks of Cancer



Hanahan & Weinberg 2000. *Cell*

2011 Redux

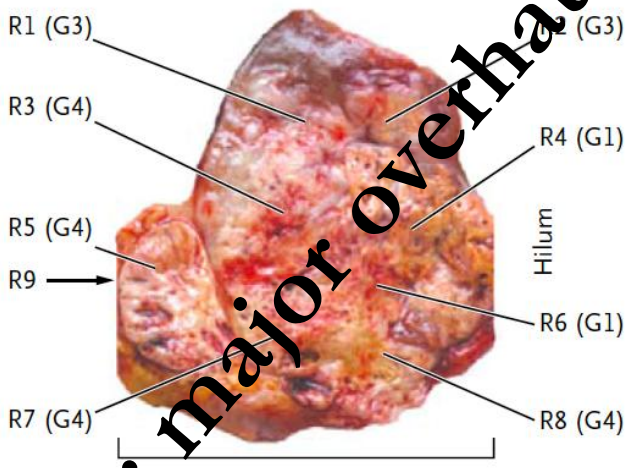


Chromosome breaks, fusions, deletions, rearrangements, aneuploidy…

Hanahan & Weinberg. 2011. *Cell*

Sudden release from constraints or sudden environmental degradation

?

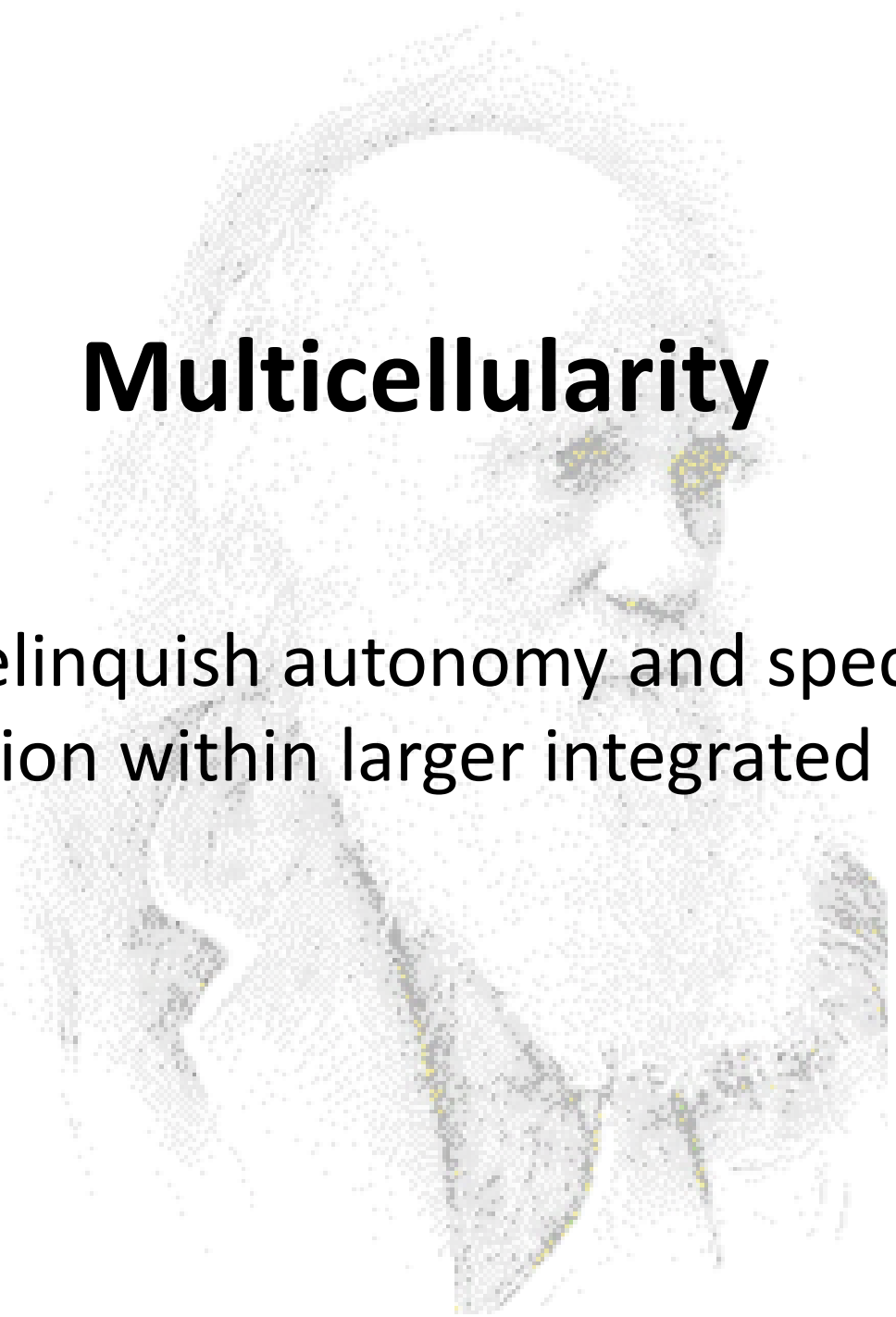


T0: major overhaul

Through millions of generations in the development of multicellularity, evolution has basically succeeded in preventing cancer

Multicellularity

Cells relinquish autonomy and specialize in function within larger integrated unit(s)



Multicellularity

Cells relinquish autonomy and specialize in function within larger integrated unit(s)

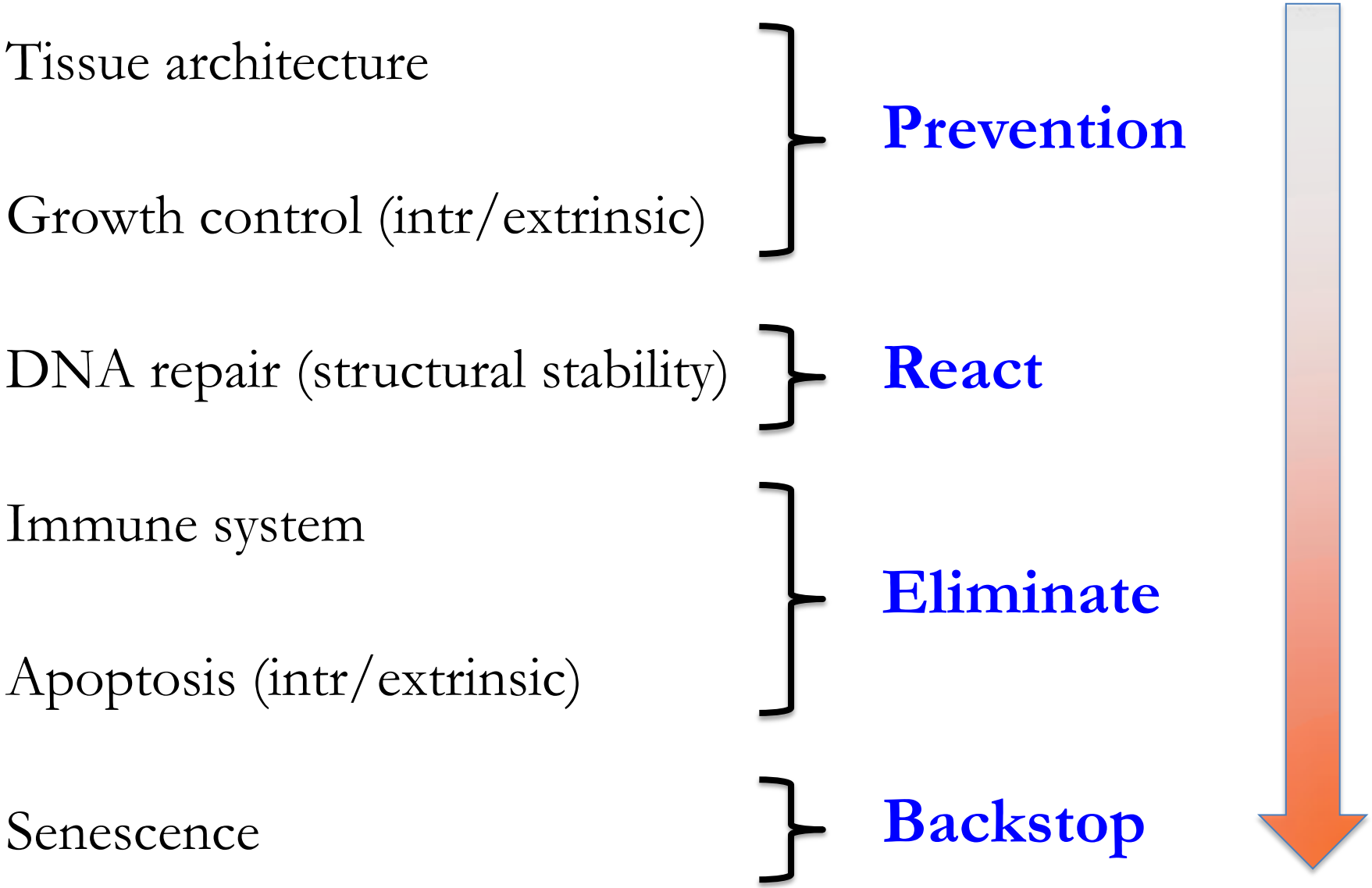
Cancer is a disease in the gain of autonomy and breakdown of function

Maintaining function: We are constantly mutating...

1,000 to 1,000,000 lesions to DNA per cell, per day

Disease suppression mechanisms evolved within populations

Maintaining function



Hochberg & Kokko. *ms*

Maintaining function

Tissue architecture

Growth control (intr/extrinsic)

Prevention

DNA repair (structural stability)

React

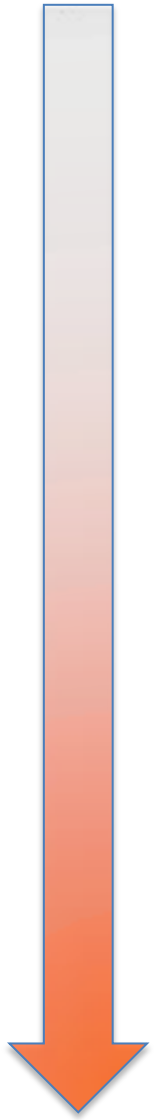
Immune system

Apoptosis (intr/extrinsic)

Eliminate

Senescence

Backstop



Maintaining function

Tissue architecture

Growth control (intr/extrinsic)

} **Prevention**

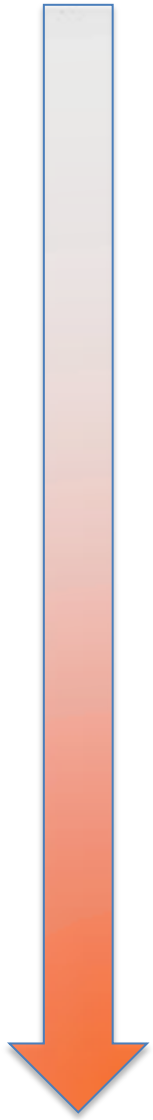
DNA repair (structural stability) } **React**

Immune system

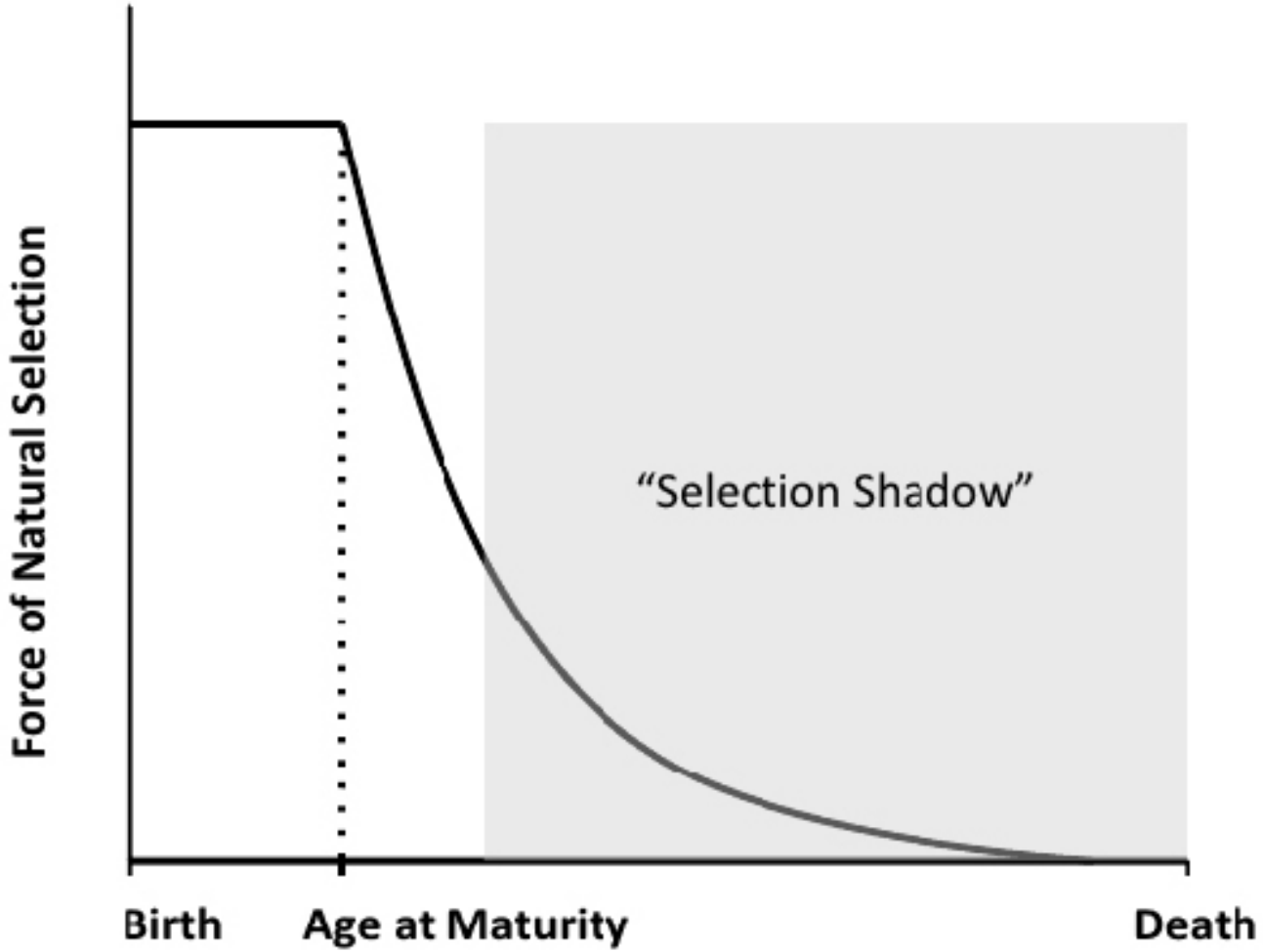
Apoptosis (intr/extrinsic)

} **Eliminate**

Senescence } **Backstop**

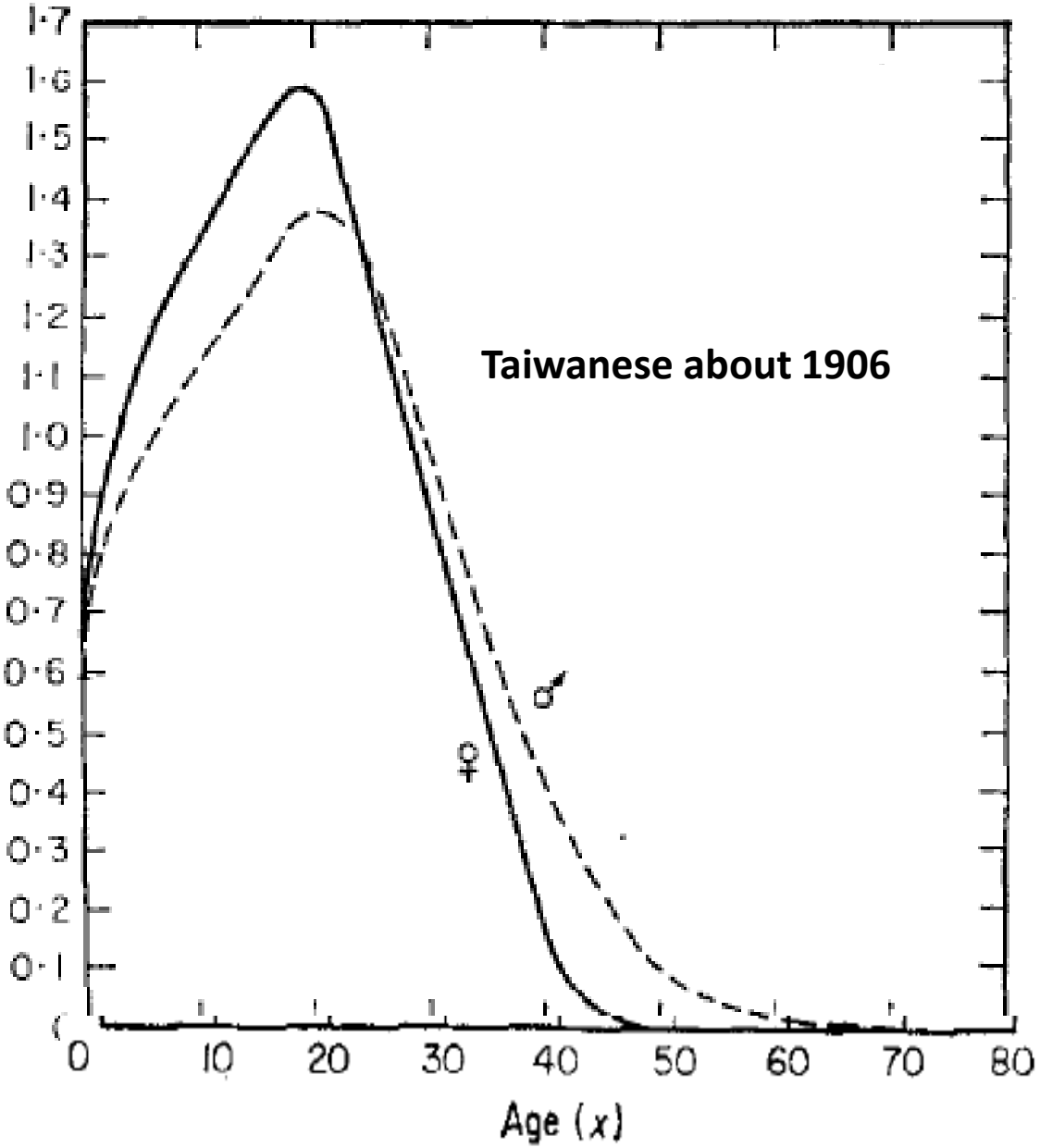


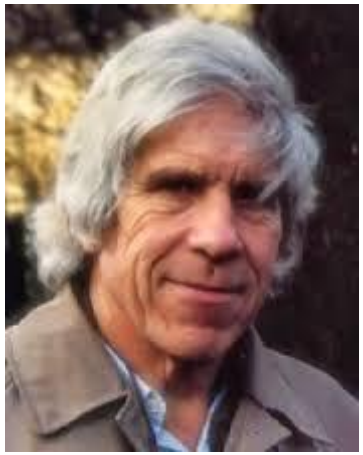
Multicellular maintenance is expected to be most efficient near reproductive maturity



Fabian & Flatt. 2011. *Nature Education Knowledge*

What makes it to the gene pool?

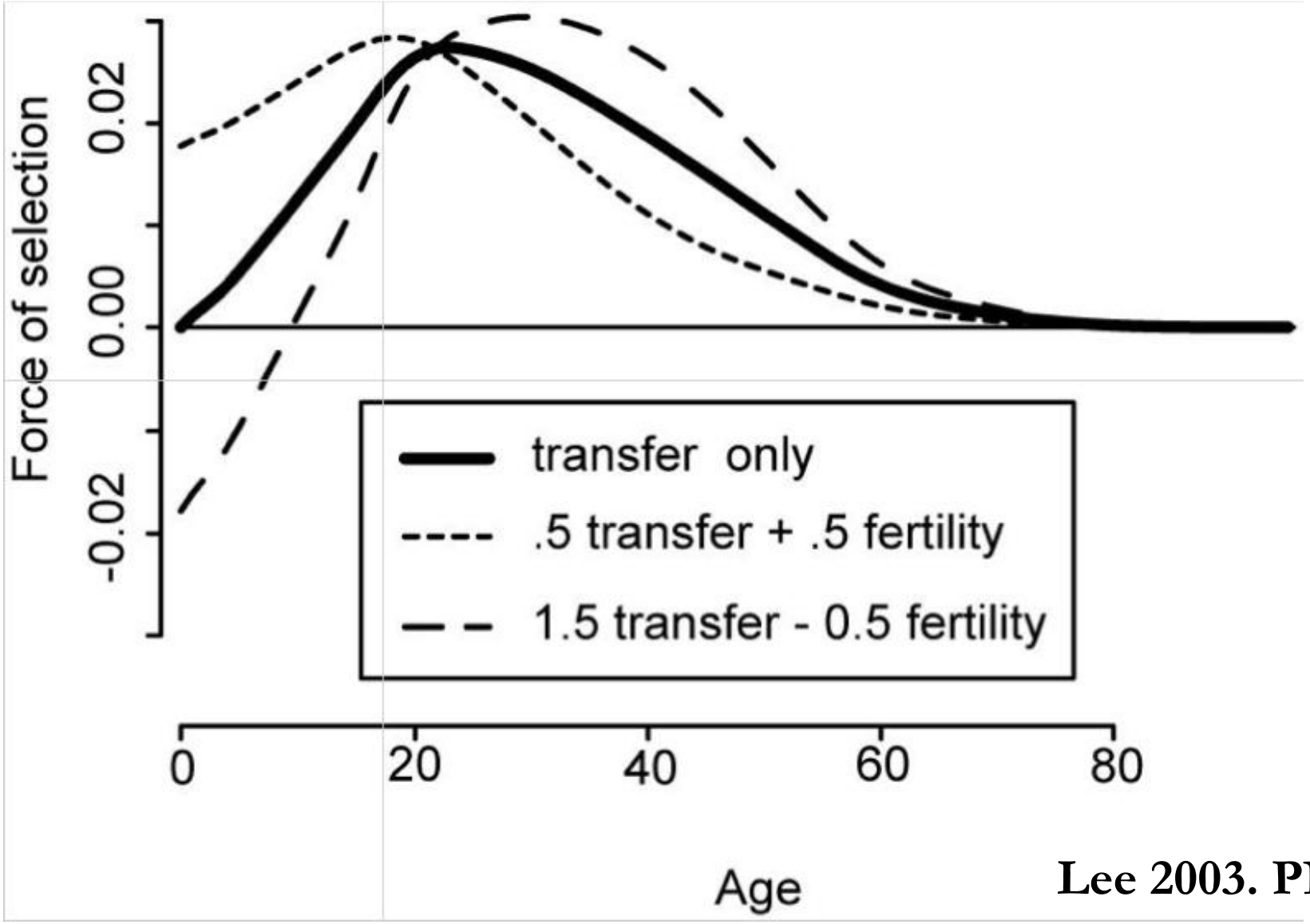




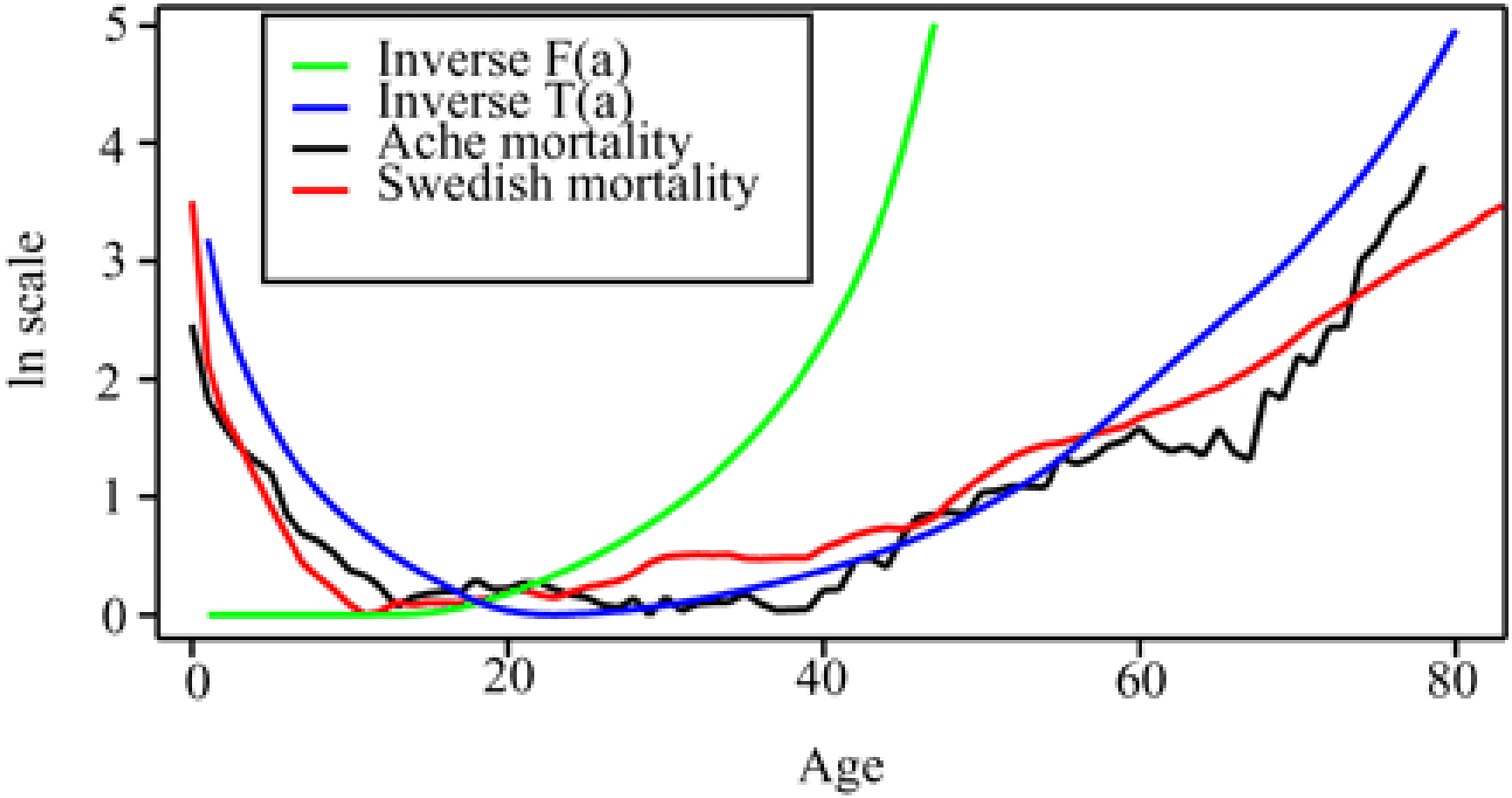
W.D. Hamilton

Hamilton 1966

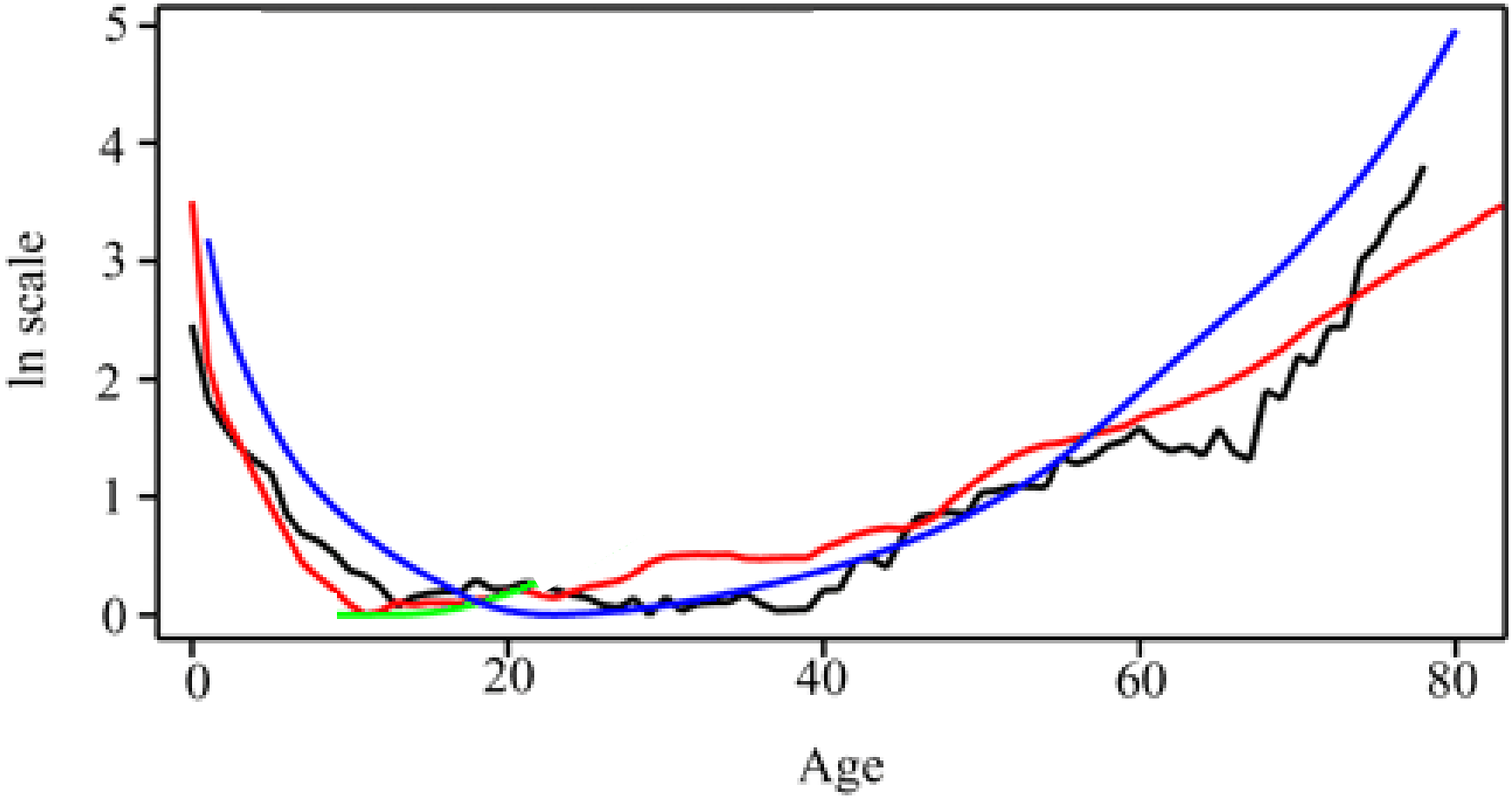
What makes it to the gene pool?



Lee 2003. PNAS

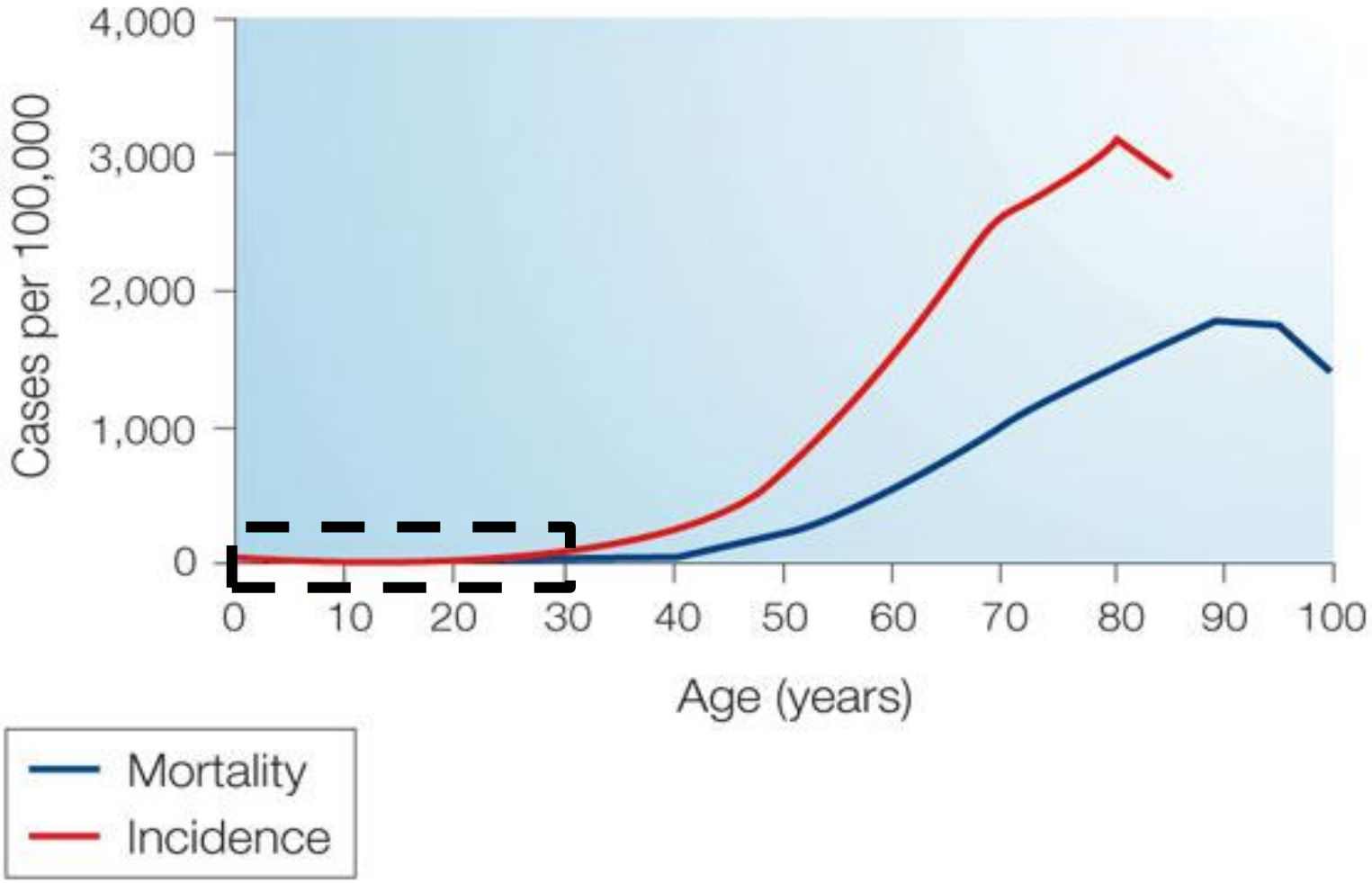


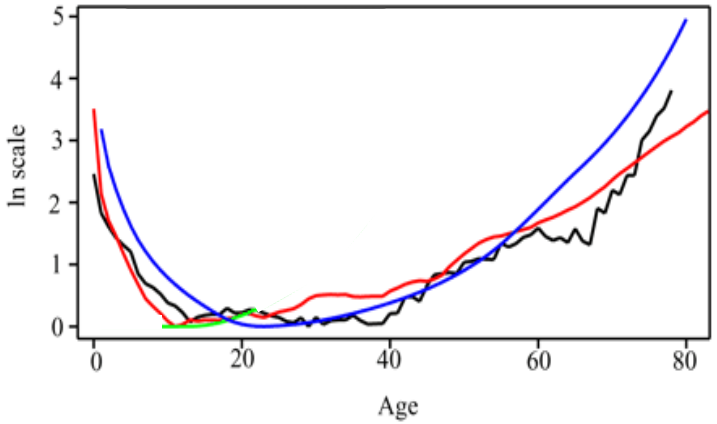
Lee 2003. PNAS

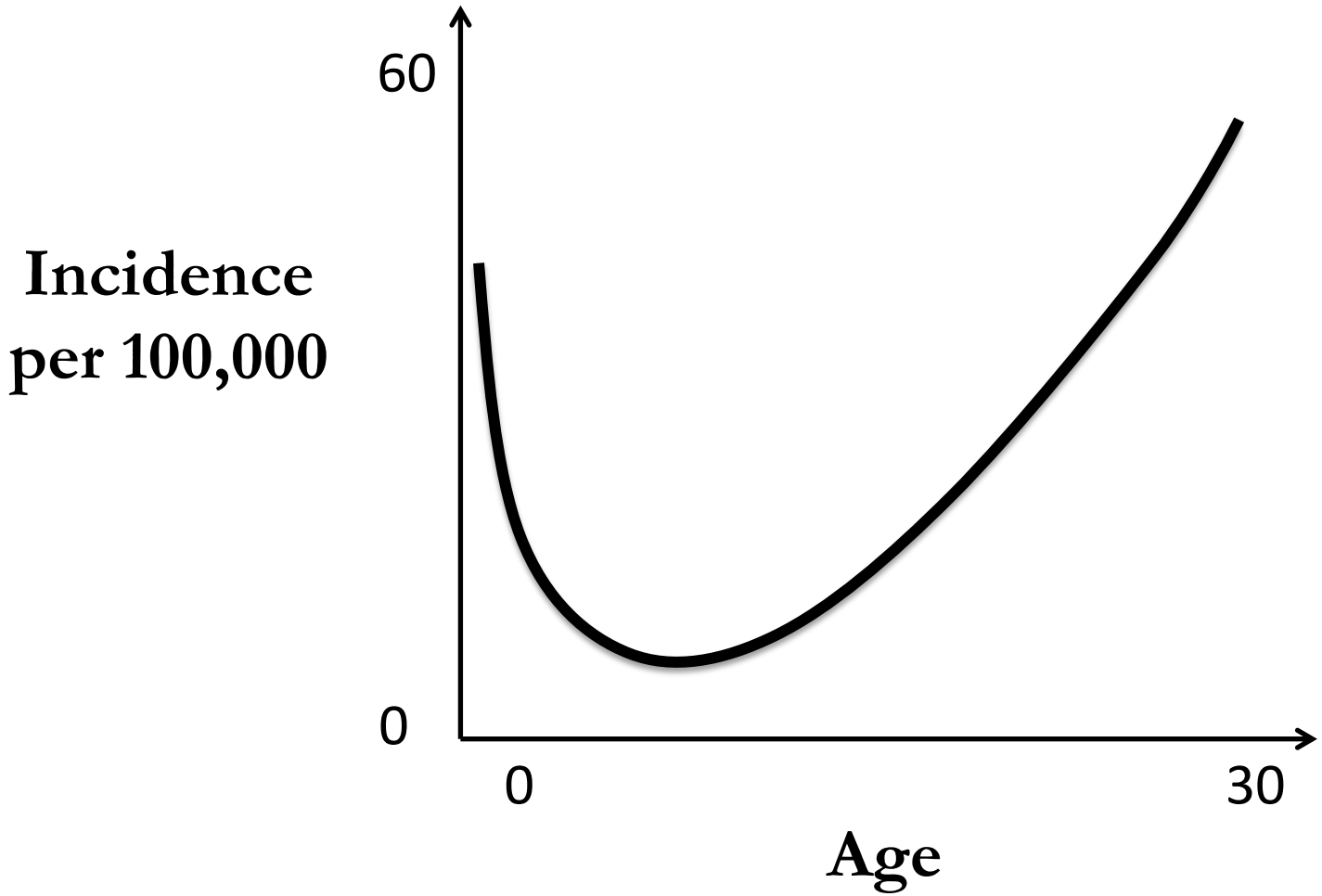


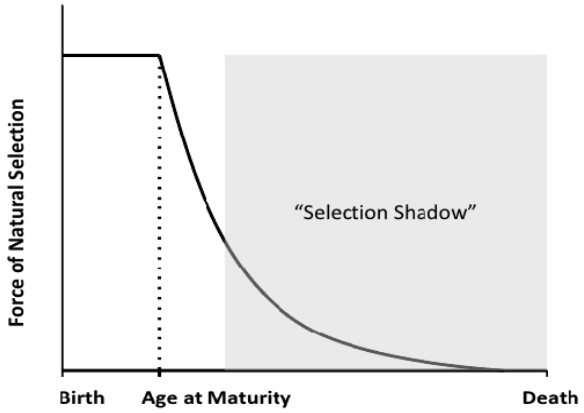
Lee 2003. PNAS

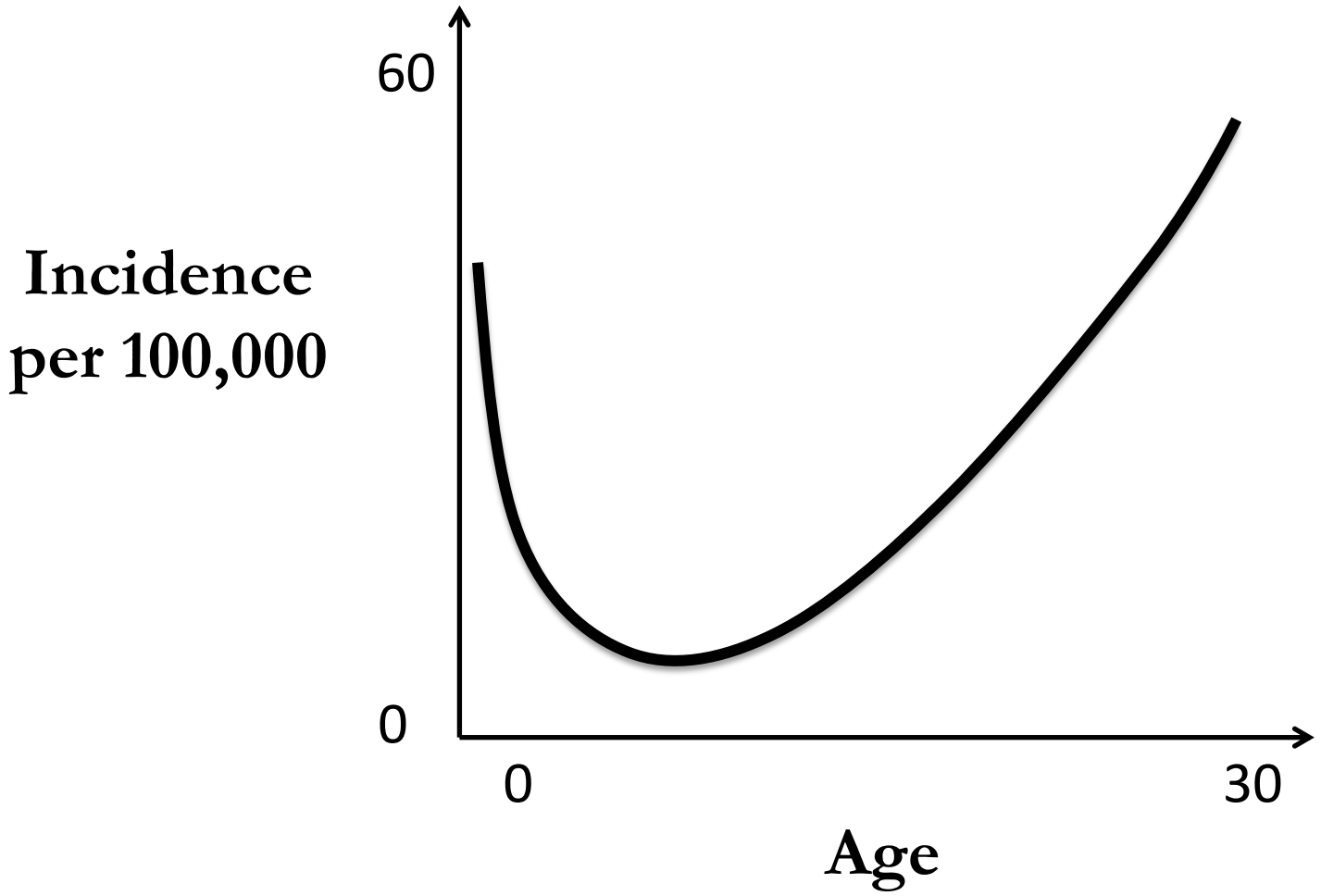
Cancer rate and mortality associate with age




ln scale
0
1
2
3
4
5
0
20
40
60
80
Age


Incidence
per 100,000
60
0
0
30
Age


Force of Natural Selection
"Selection Shadow"
Birth
Age at Maturity
Death


Incidence per 100,000
60
0
0
30
Age

COMMENT

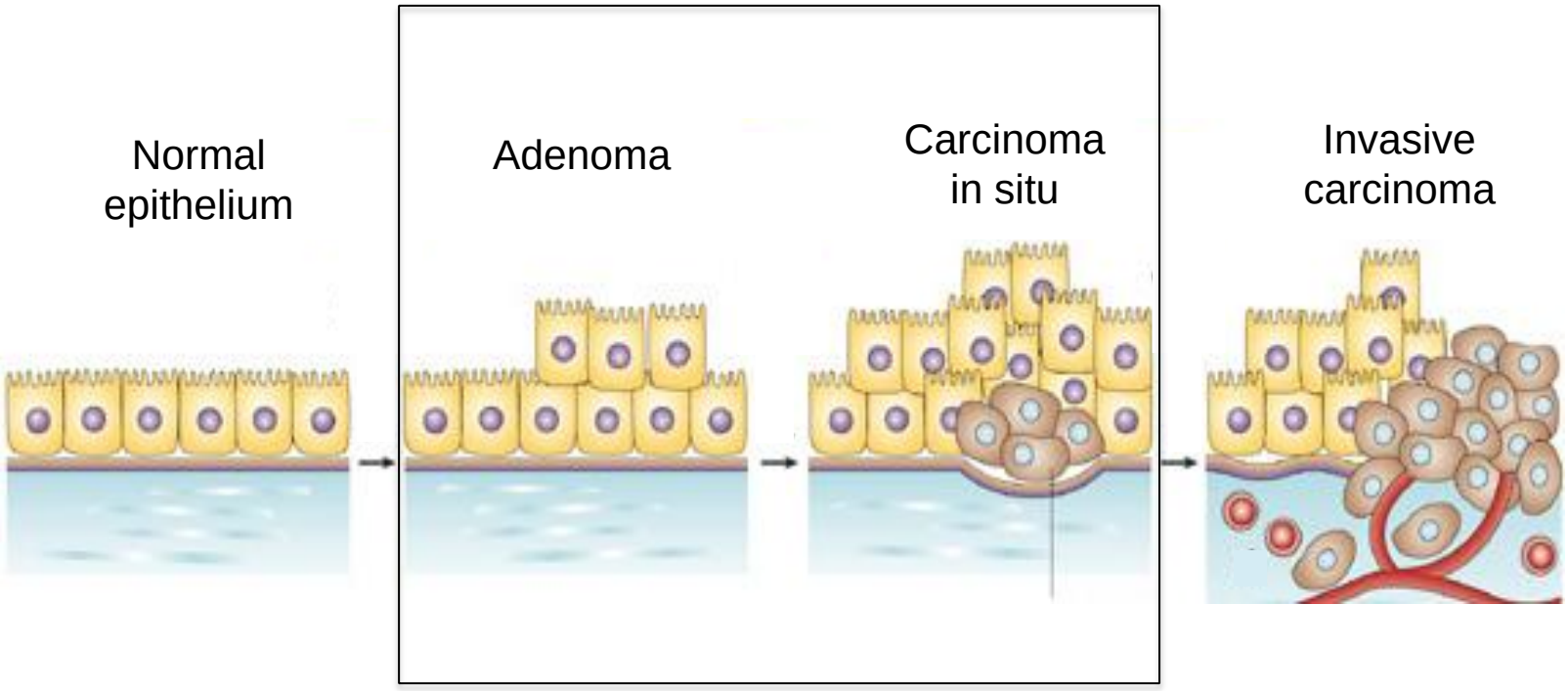
CLINICAL INSIGHTS

Does everyone develop covert cancer?

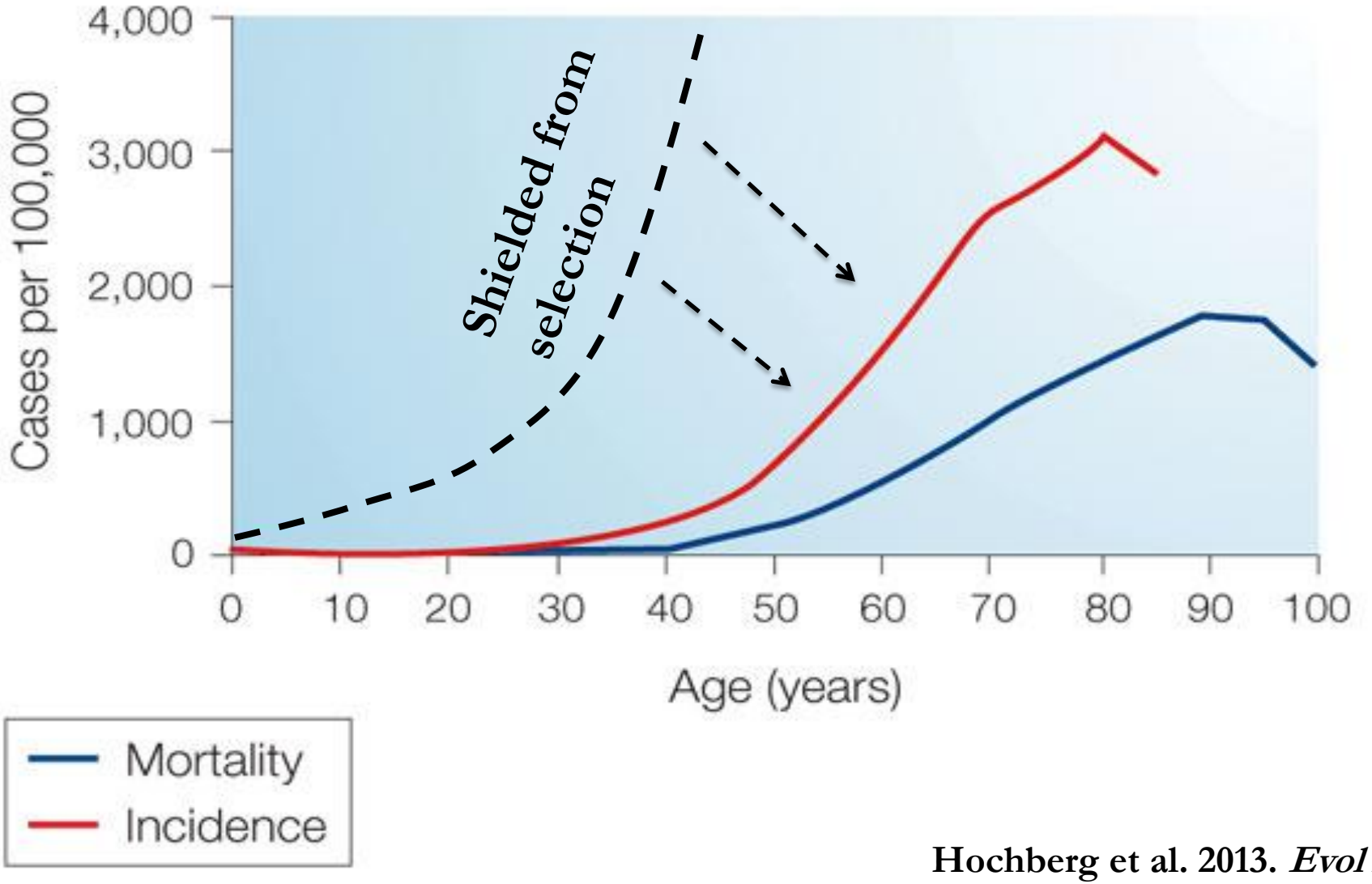
Mel Greaves

Abstract | Around one in three individuals, if they live long enough, will have a confirmed clinical diagnosis of overt cancer, and there is increasing evidence that many of us — I contend all of us — develop covert cancer.

Greaves 2014 *Nat Rev Can*


Normal epithelium
Adenoma
Carcinoma in situ
Invasive carcinoma

Natural selection leading to the tolerance of early pre-cancerous and cancerous lesions



Hochberg et al. 2013. *Evol Appl*

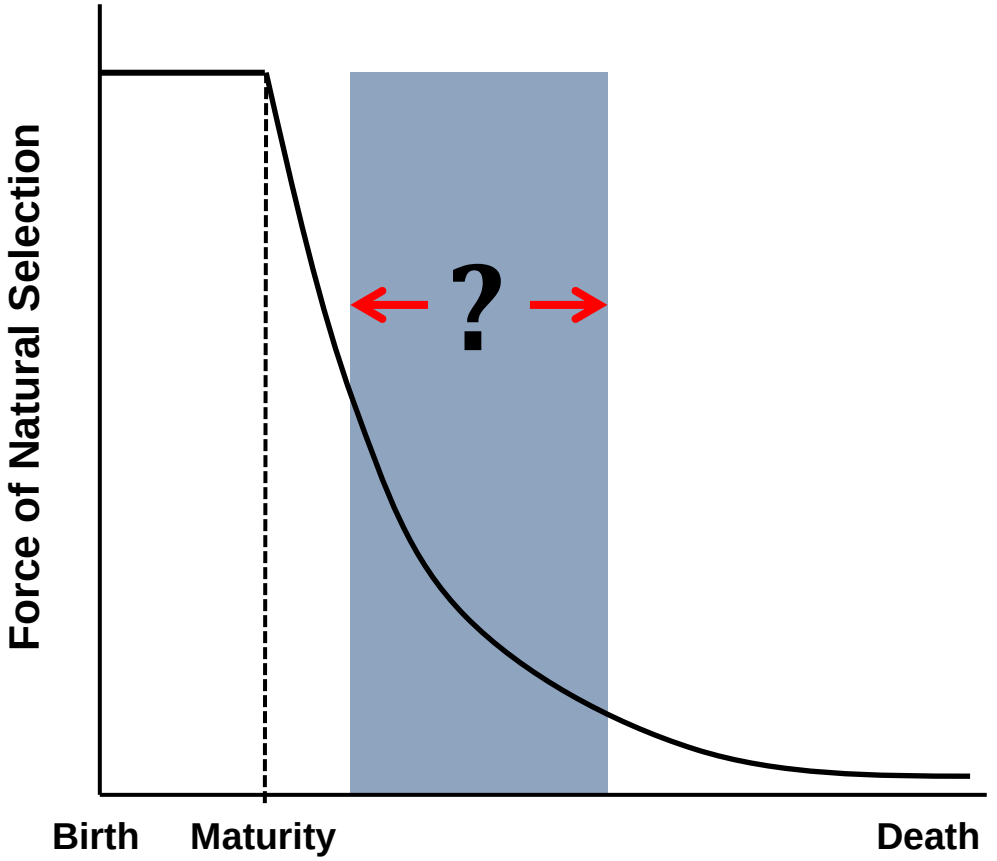
Evolved **to supress or limit cancer development at specific ages**

and/or

Cancers are multistaged, and *limited* by the occurrence of rare (epi)mutations

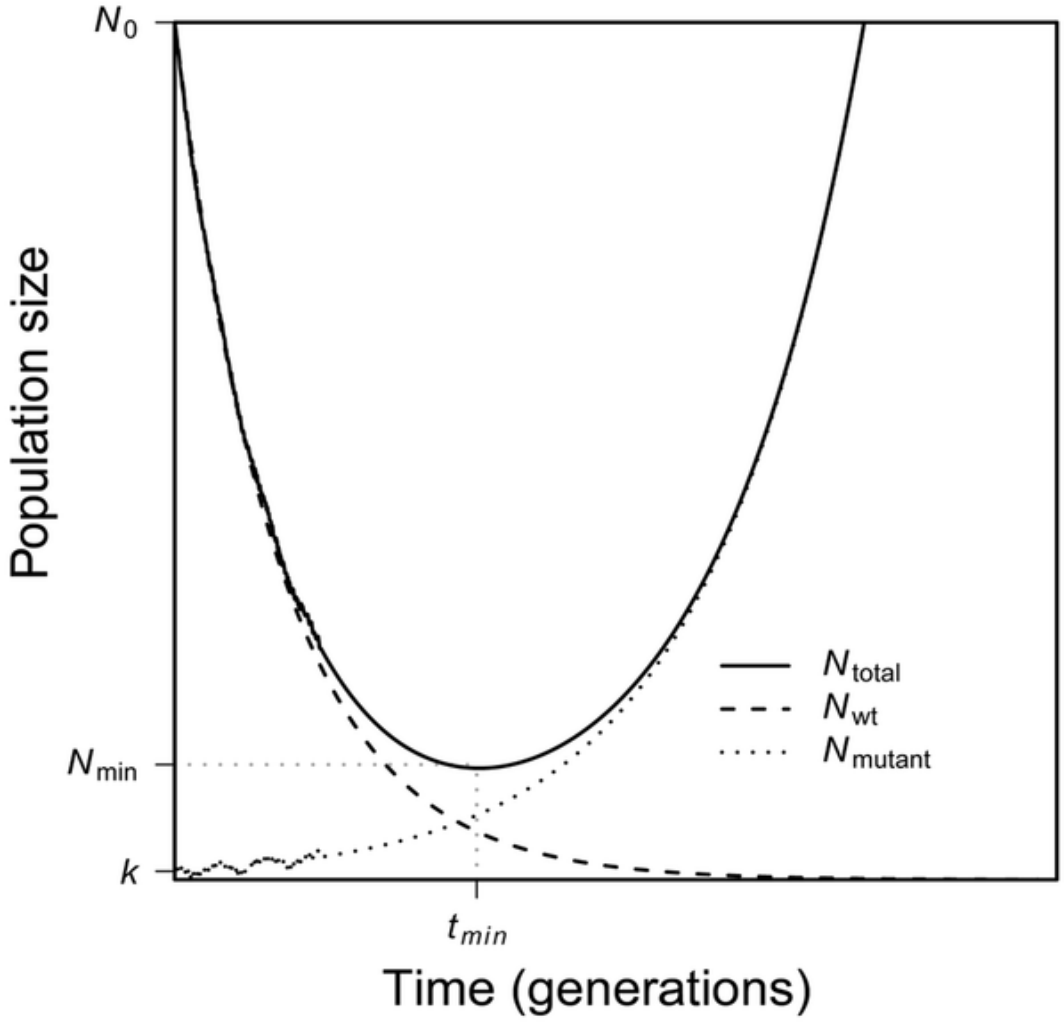
Can these insights instruct therapies?

Act once mechanisms put in place by natural selection go into decline



Hit-hard approach

“Evolutionary rescue”



Gonzalez et al. 2013. Phil T Roy Soc Lond B. 368: 20120404
Orr HA, Unckless RL 2014. PLoS Genet 10: e1004551

Relapse in multiple myeloma

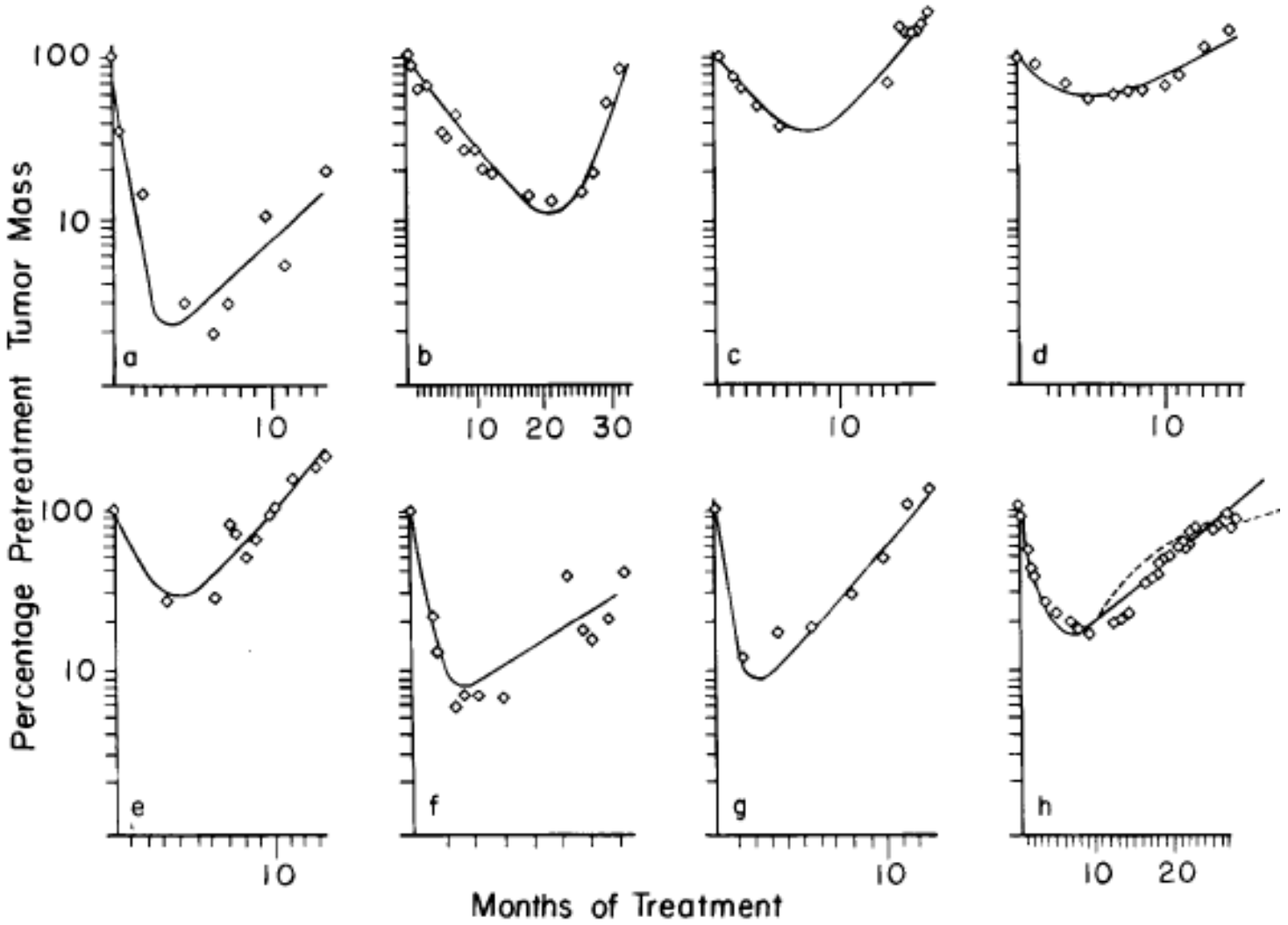


FIG. 2. Curves calculated from serial measurements of tumor mass in eight patients using the double exponential model. Fig. 2h (dotted line) illustrates the curve calculated for one patient using the exponential-Gompertzian model. Abscissa indicates months of treatment and ordinate is percentage of pretreatment tumor mass.

Hokanson et al. 1977. Cancer 39: 1077-84

Relapse in multiple myeloma

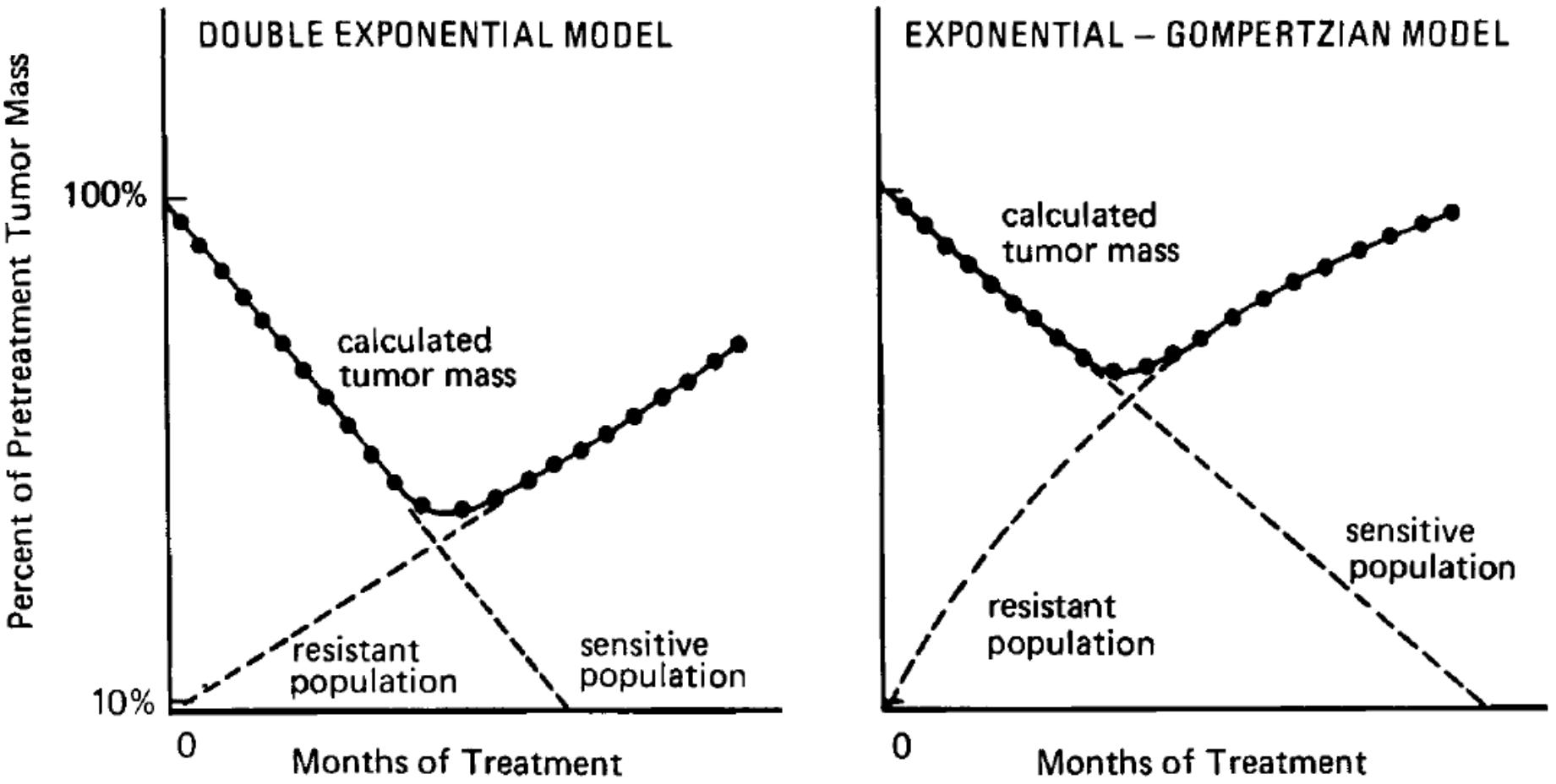
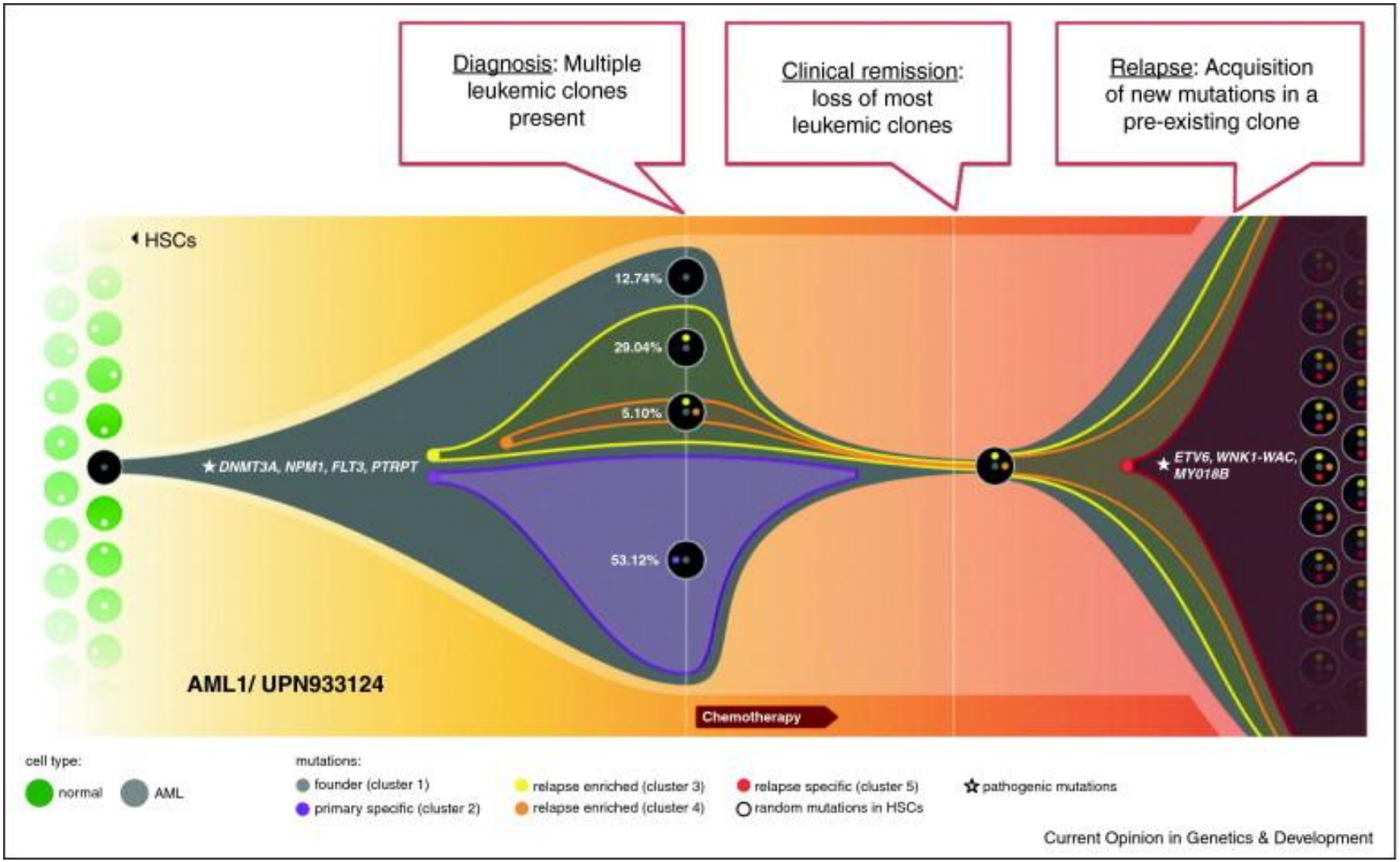


FIG. 1. Illustration of the two mathematical models used in the analysis of myeloma patient data.

Hokanson et al. 1977. Cancer 39: 1077-84

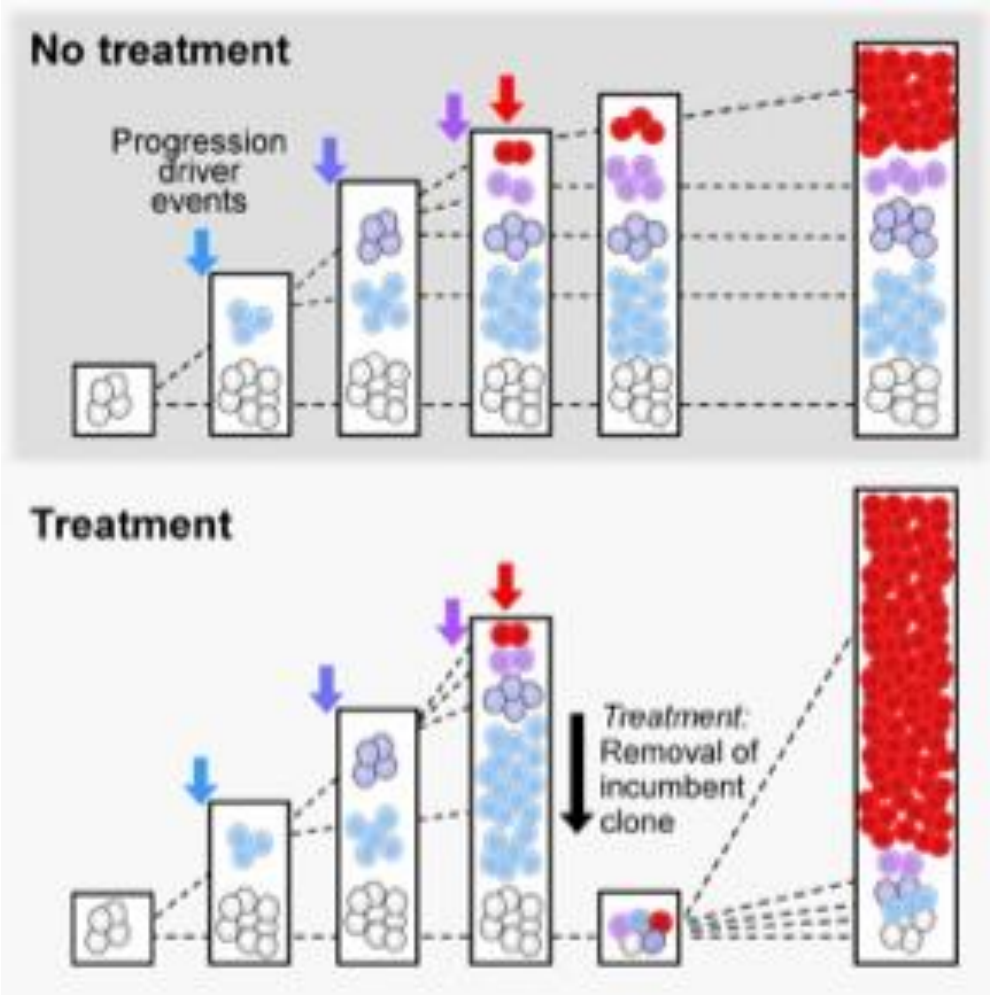
Textbook resistance



Mardis. 2012. *Current Opinion in Genetics & Development* 22, 245–250

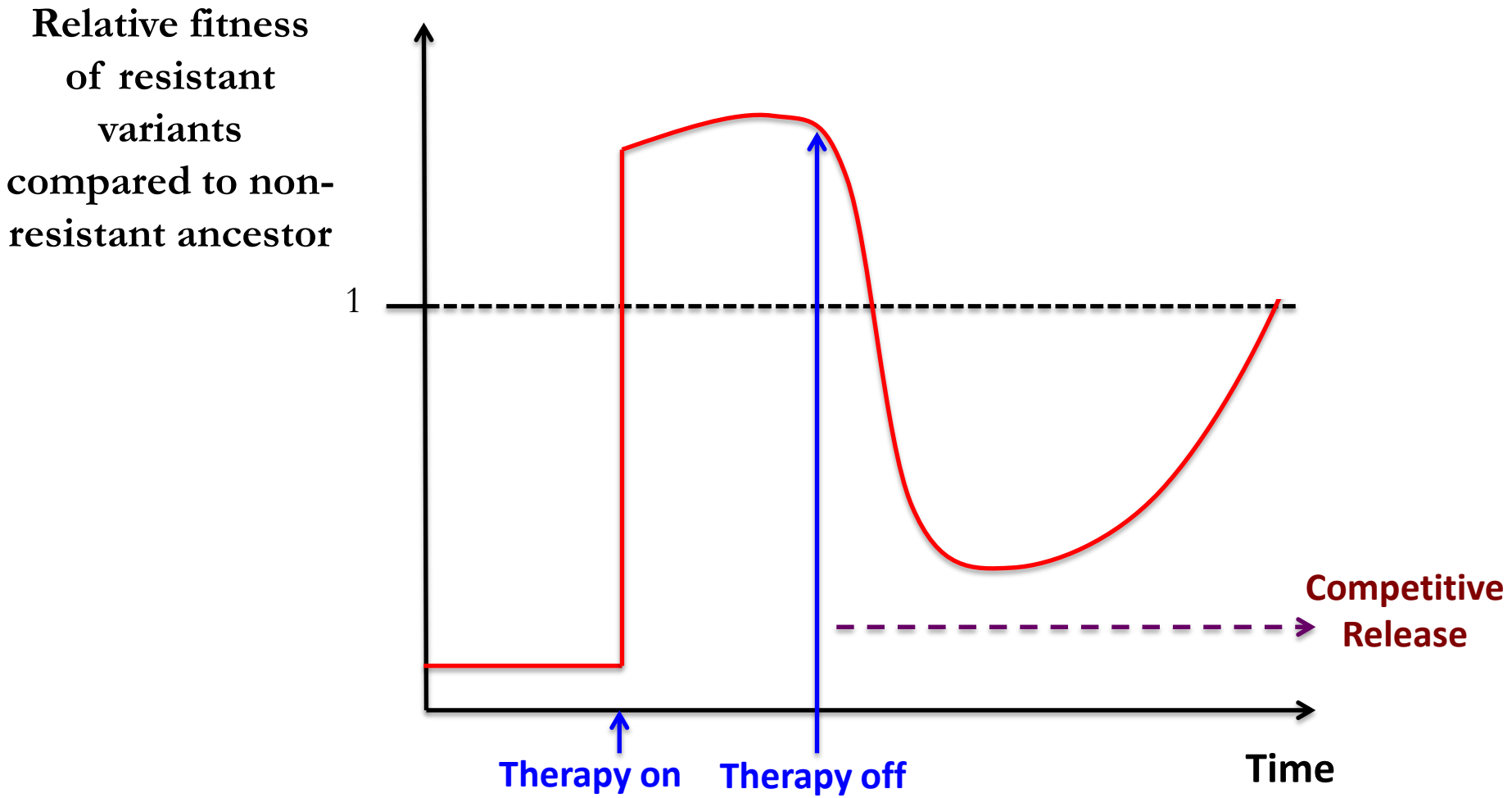
Ding *et al.* 2012. *Nature* doi:10.1038/nature10738

Competitive release

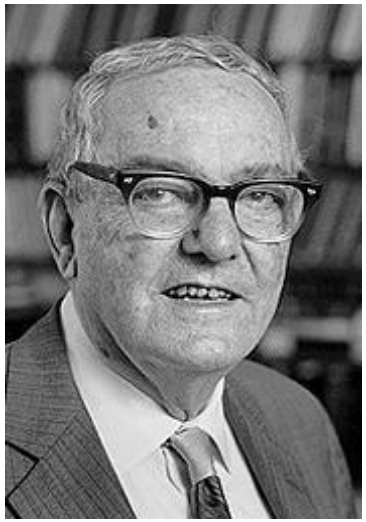


The real "enemy" is not resistance mutations per se, but rather *compensatory mutations*

Compensatory Mutations and Coadaptations



Satisfice

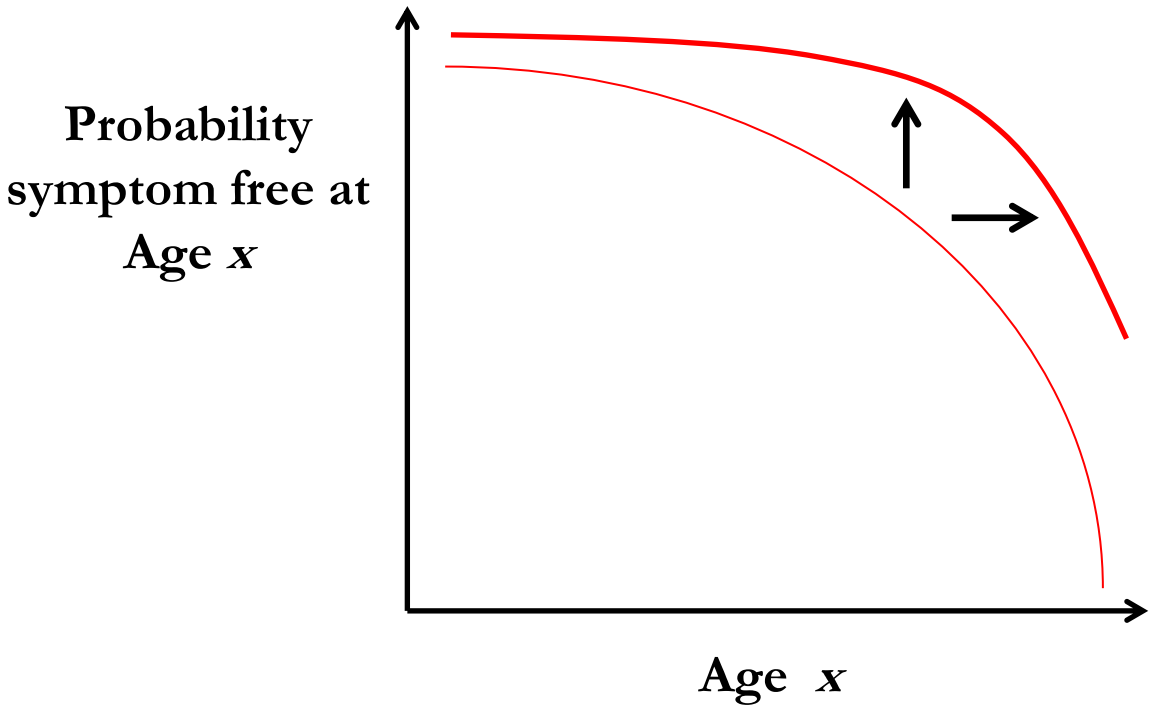


Reduce disease or disease risk to acceptable levels

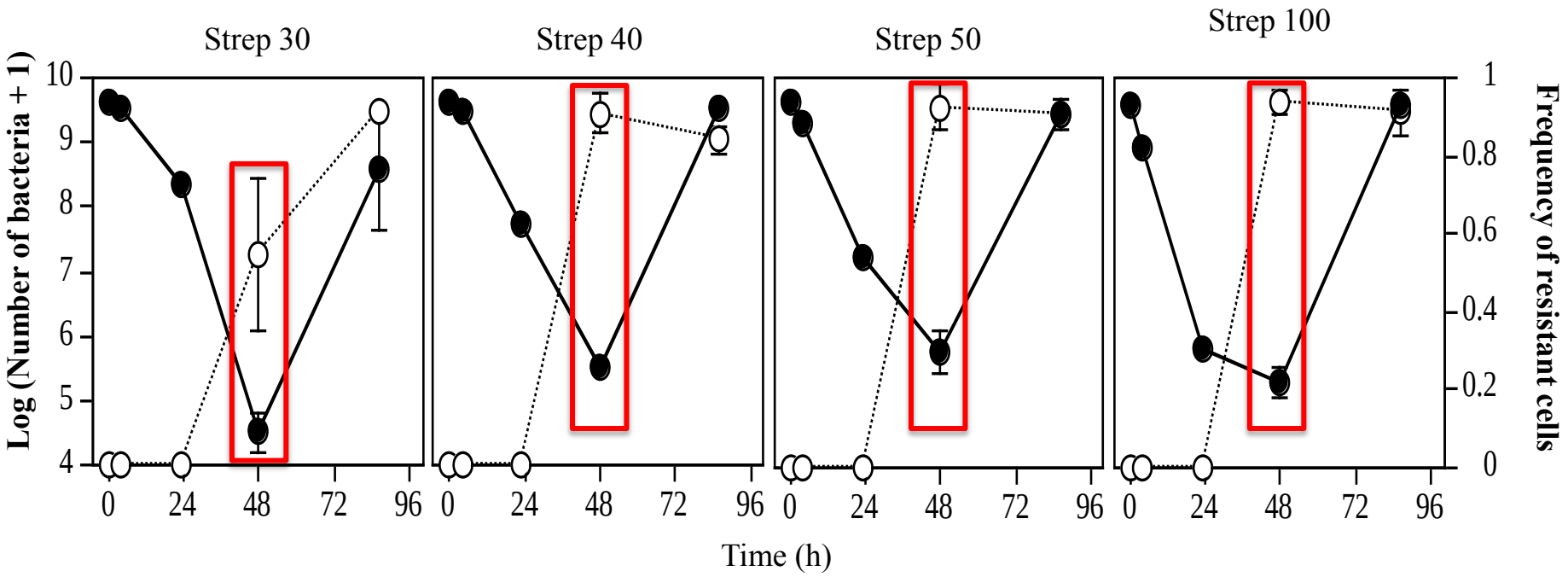
Subject to constraints (side effects) and the risk that future management will be less effective (resistance)

Simon H. 1956. *Psychological Review* 63:129-138

Goal



Slower population recovery and less resistance at low doses



Freq Resistant

Cell density

Ramsayer et al. 2013. *Evol Appl* 6:608-16

Types of prevention and management

Life style changes – *caloric, smoking, excercise, alcohol...*

Removal of pre-cancerous tissues - *polyps*

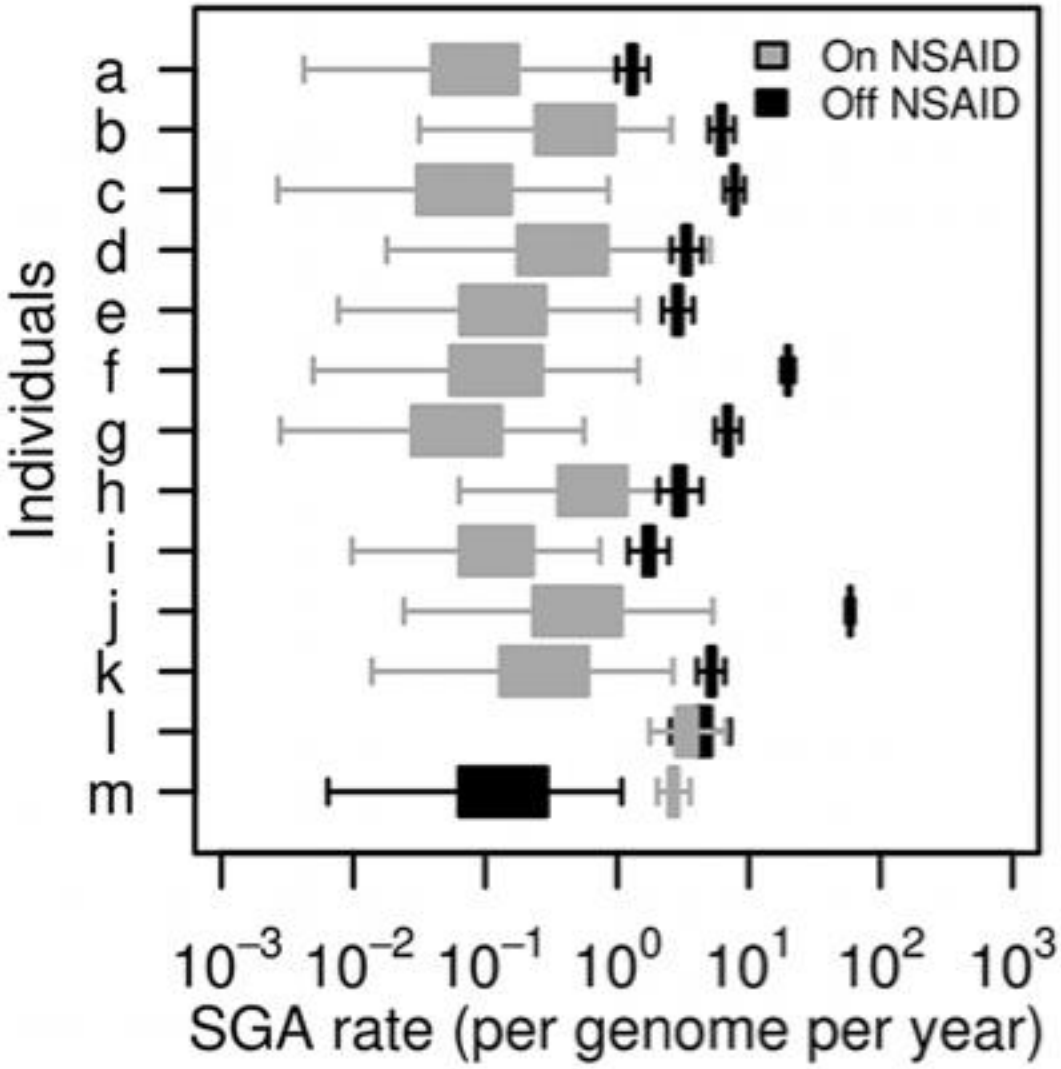
Low side-effect therapies – *tamoxifen, NonSteroidalAntiInflammatoryDrugs*

Vaccines against pathogens - *HPV*

Hochberg et al. 2013. *Evol Appl*. 6:134-43

Cancer Management – Somatic genomic abnormalities

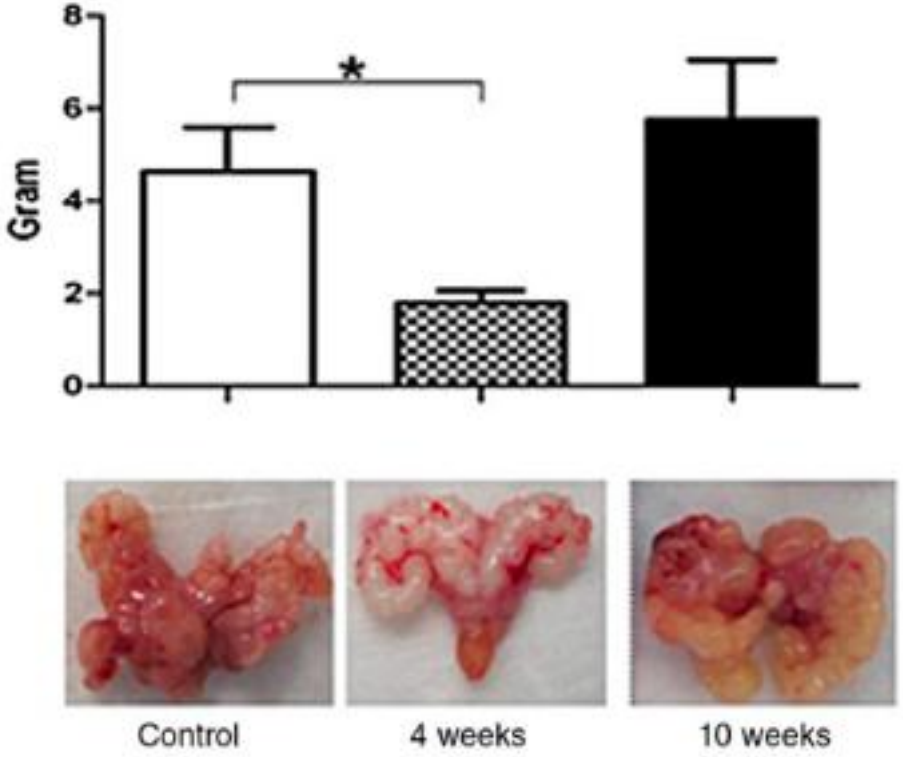
Non-Steroidal Anti-Inflammatory Drugs



Kostadinov et al. 2013. PLoS Genetics

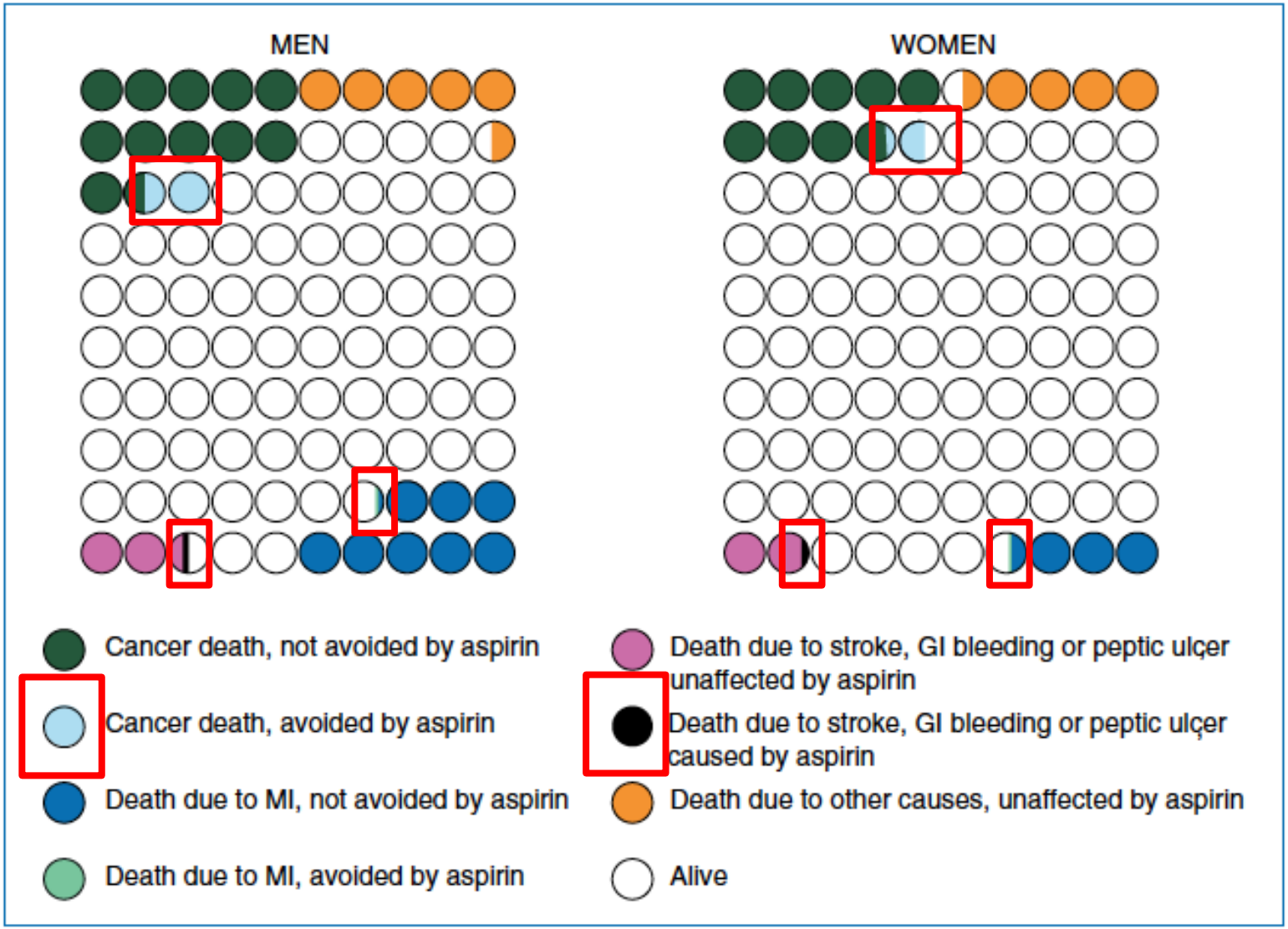
Earlier therapy with bicarbonate has inhibitory effect on metastatic, spontaneous prostate tumors in TRAMP mice

Robert Gatenby



Ibrahim-Hashim et al. 2012. *J Urol*

Aspirin effect post 55 yrs

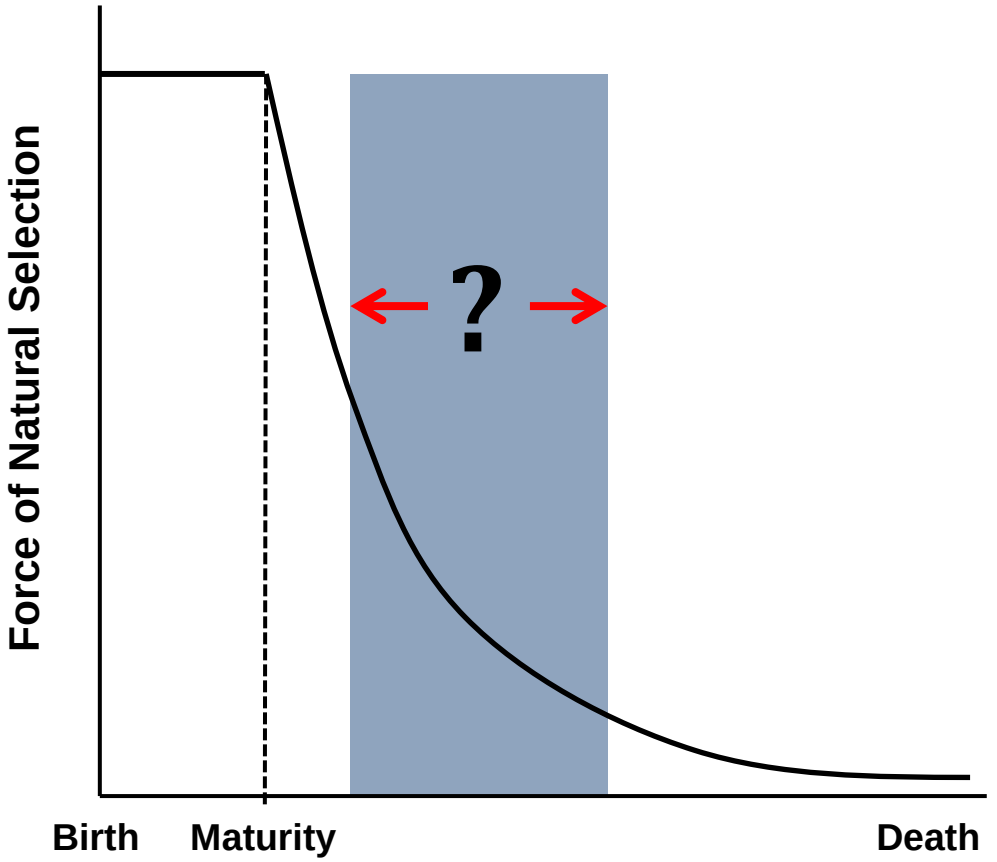


Cumulative effects of aspirin taken for 10 years starting at 55 years of age: on deaths over next 20 years in 100 average-risk men and women.

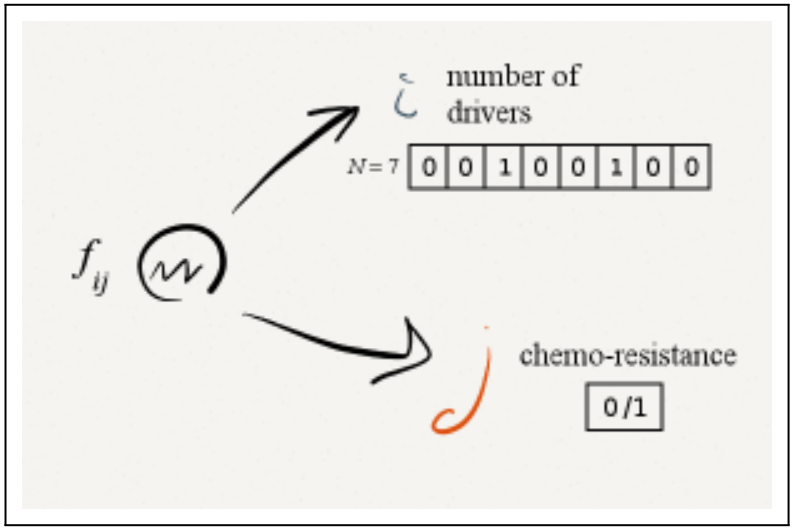
Cuzick et al. 2014. doi:10.1093/annonc/mdu225

People *at risk* achieve a lower, acceptable risk – Low burden

Act once mechanisms put in place by natural selection go into decline



Birth-death process: Conceptual framework



A. Akhmetzhanov

Cell type: (i, j) $i = \{0, 1, \ldots, N\}$, $j = \{0, 1\}$

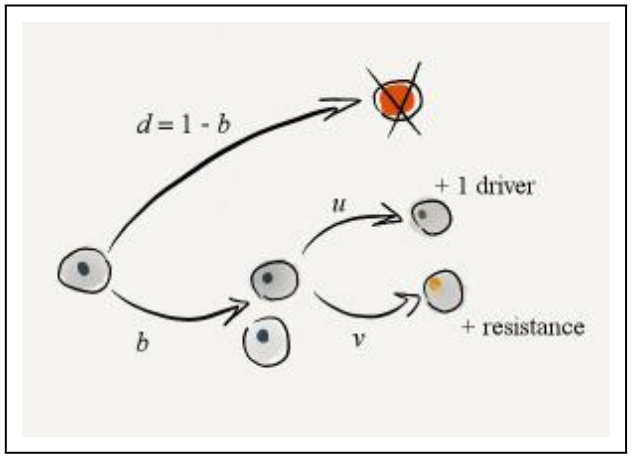
Fitness function: $f_{ij} = s(i + 1) - cj$

s – selective advantage, c – cost of resistance

+ treatment: $f_{ij} = s(i + 1) - \sigma(1 - j) - cj$

Akhmetzhanov & Hochberg. 2014. ArXiv

Discrete time Galton-Watson branching process



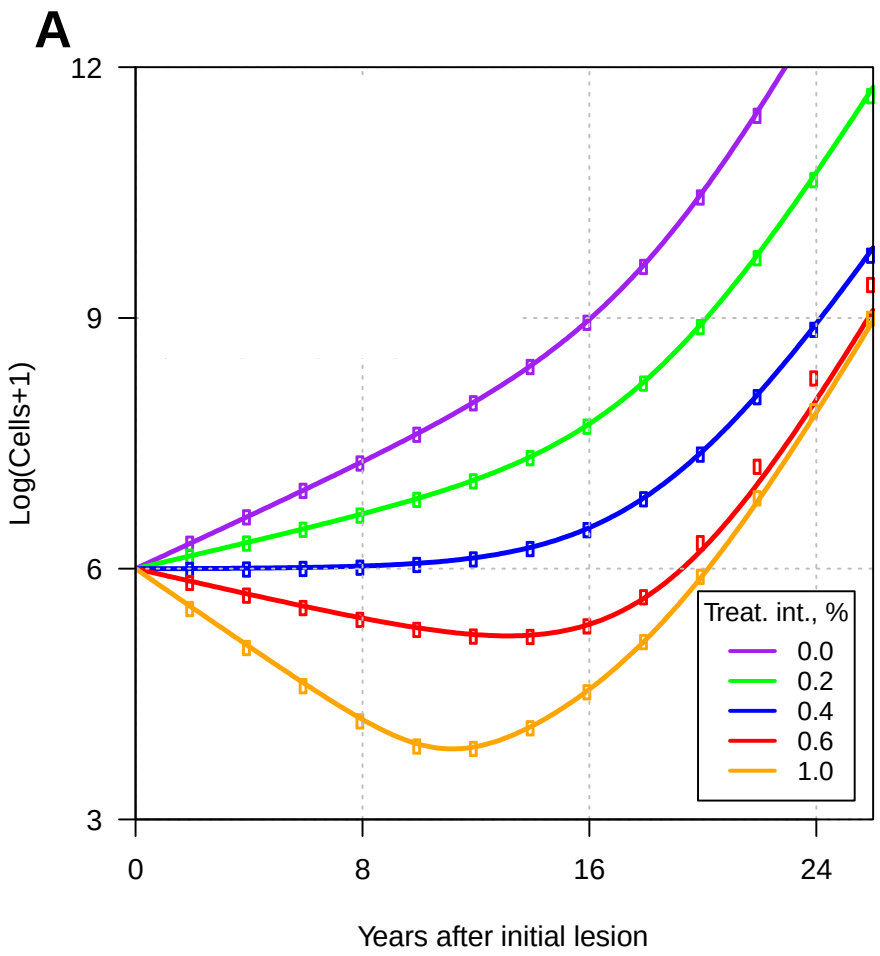
- Cell-cycle length $T = 4$ d.
- Continuous generations
- $b_{ij} = \frac{1 + f_{ij}}{2}$, $d_{ij} = 1 - b_{ij}$

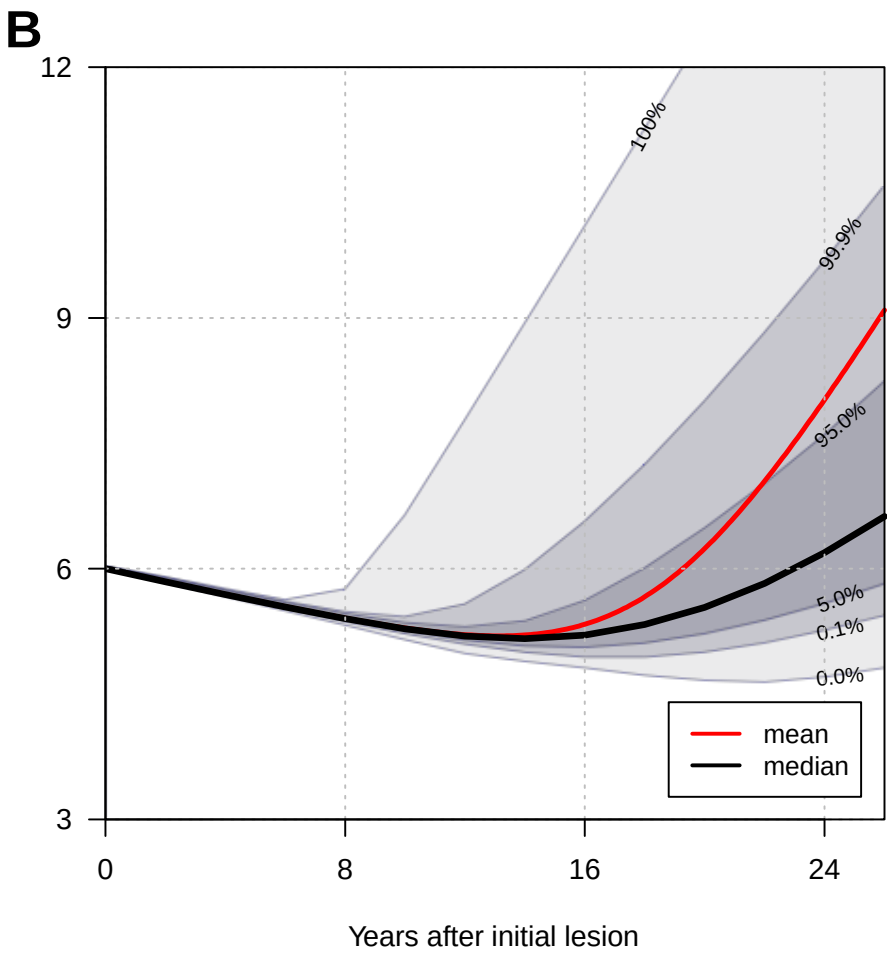
Let $n_{ij}(t)$ be the number of cells of type (i, j) at time step t. Then $n_{ij}(t + 1)$ is a sample from the multinomial distribution (# births (B_{ij}), # deaths (D_{ij}), # mutations ($M_{ij}^{(u)}$ and $M_{ij}^{(v)}$))

$$n_{ij}(t + 1) = n_{ij}(t) + B_{ij} - D_{ij} + M_{ij}^{(u)} + M_{ij}^{(v)}$$

(Durrett 2012)

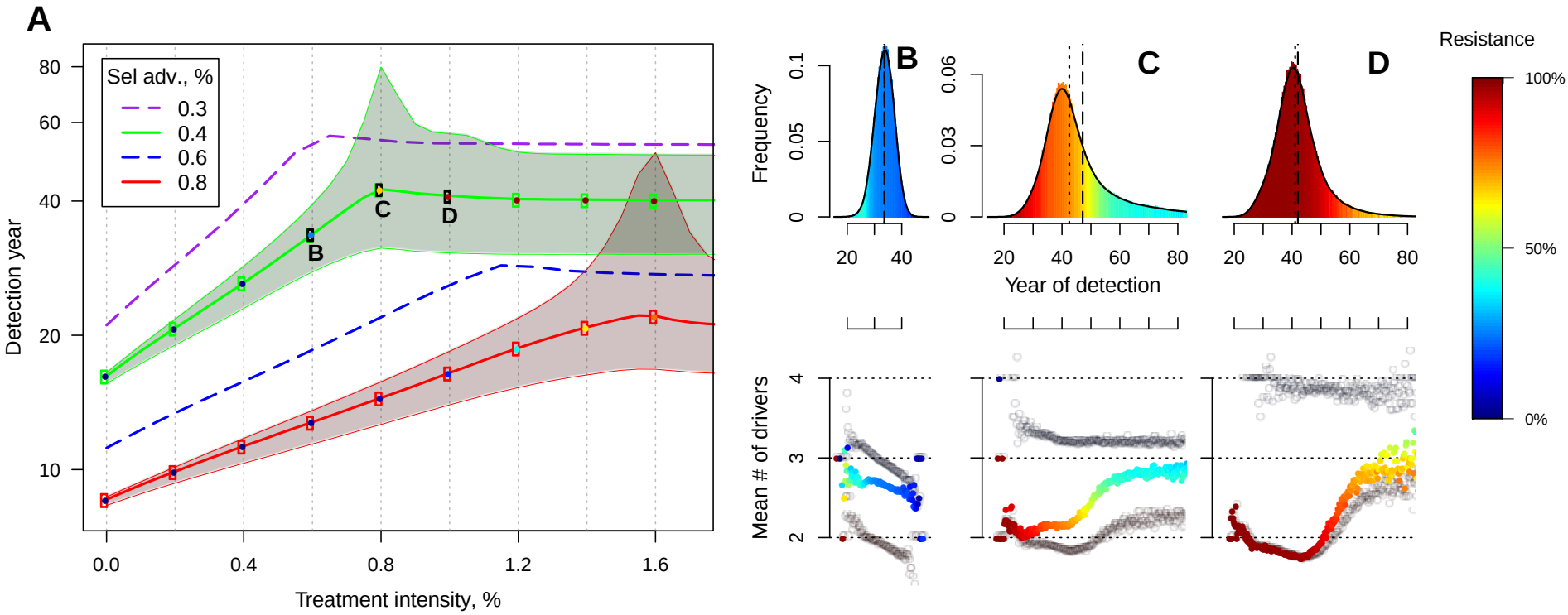
Tumor dynamics under constant low impact therapy





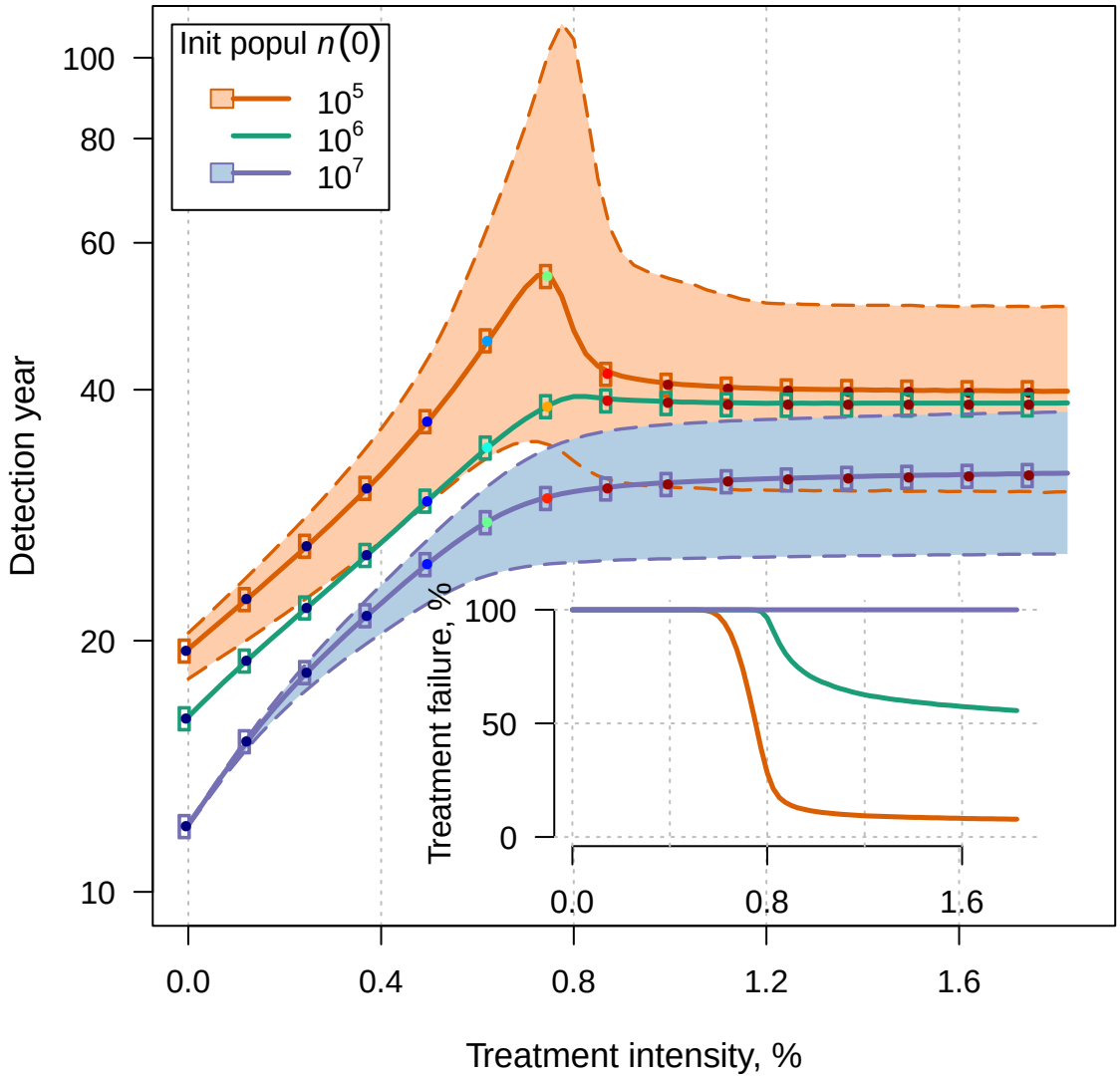
Akhmetzhanov & Hochberg. 2014. ArXiv

$$\sigma \approx 2s$$

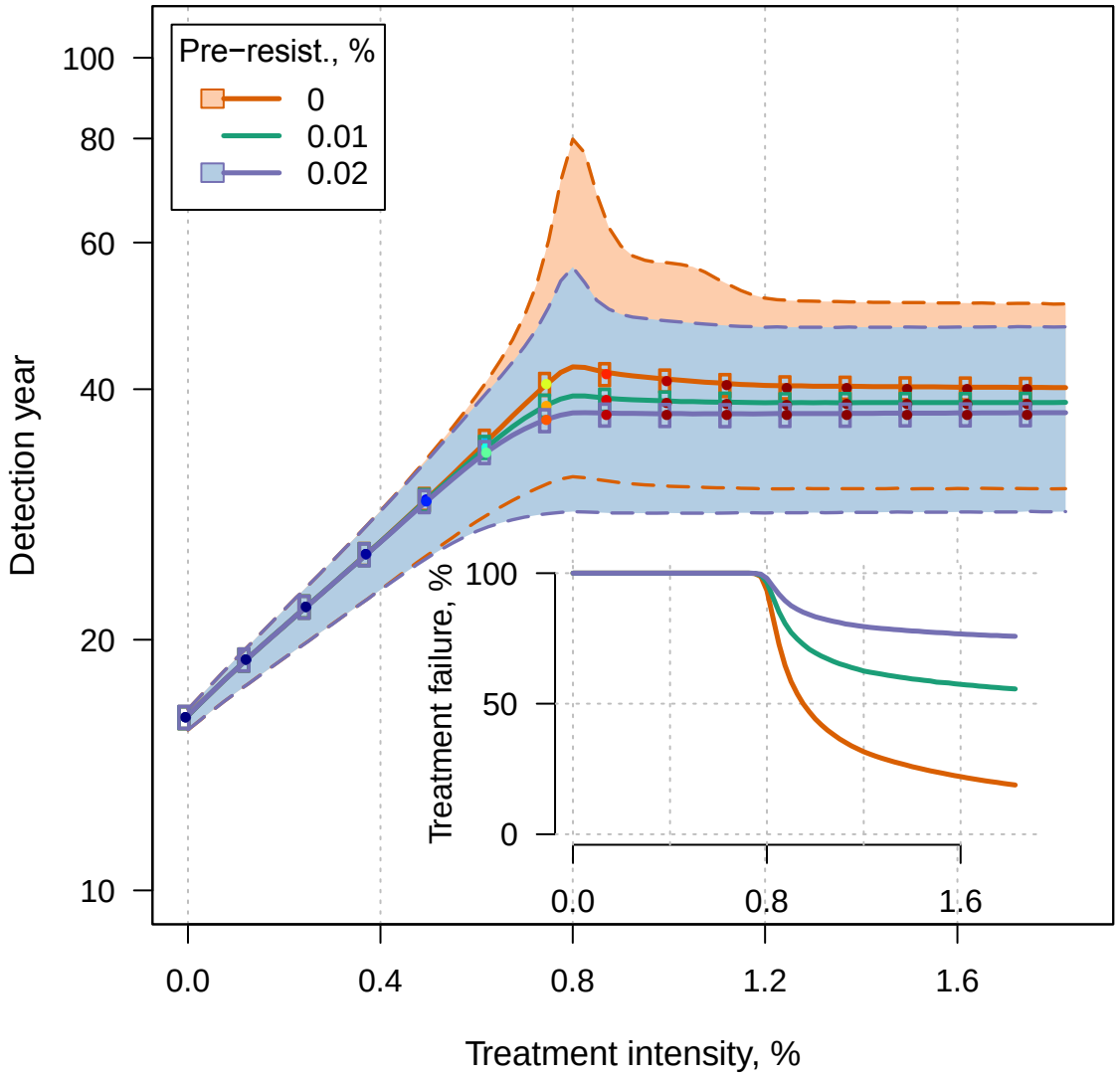


Simulation

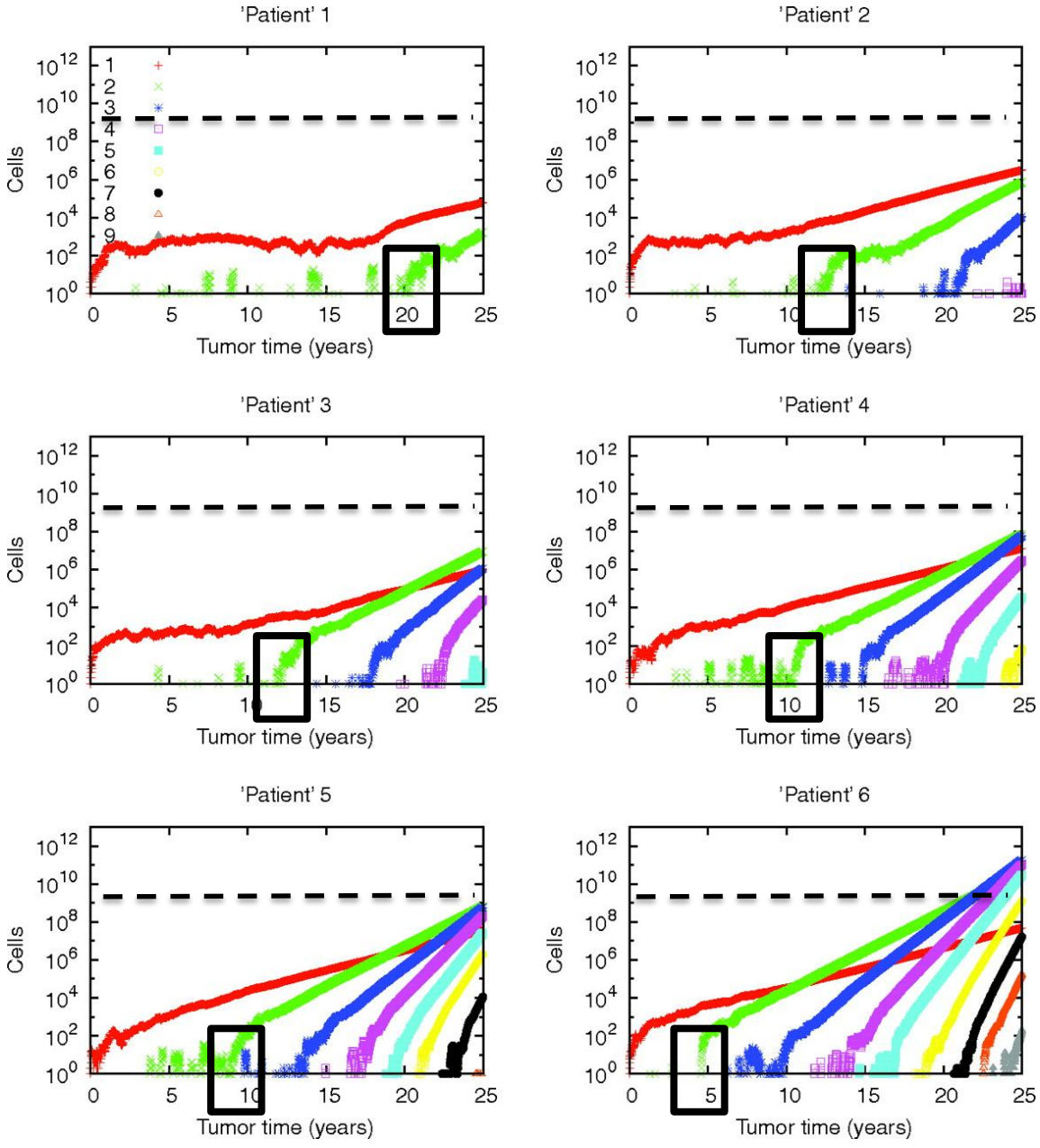
Initial tumor size



Pre-Resistance

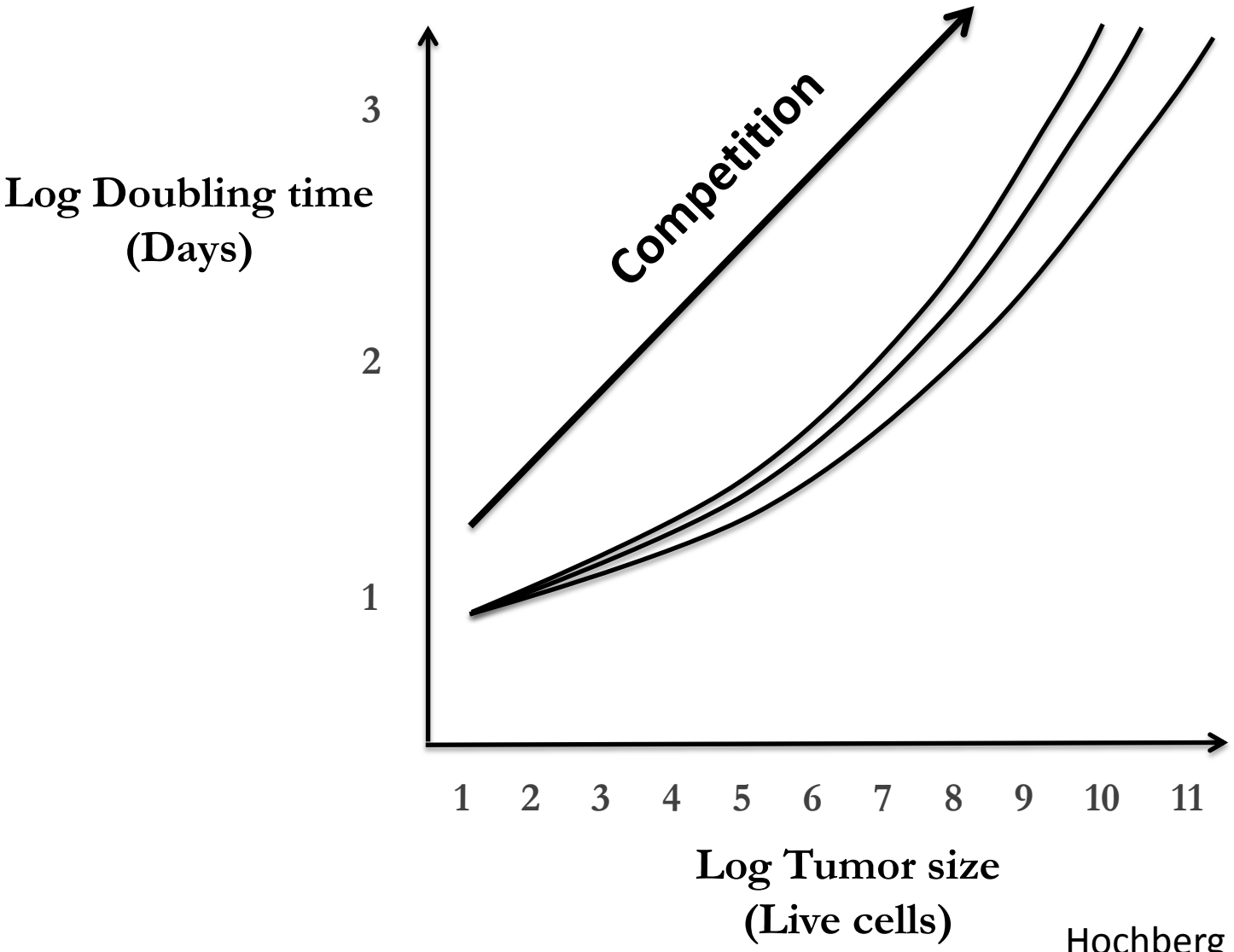


Growth depends on stochastic emergence of drivers



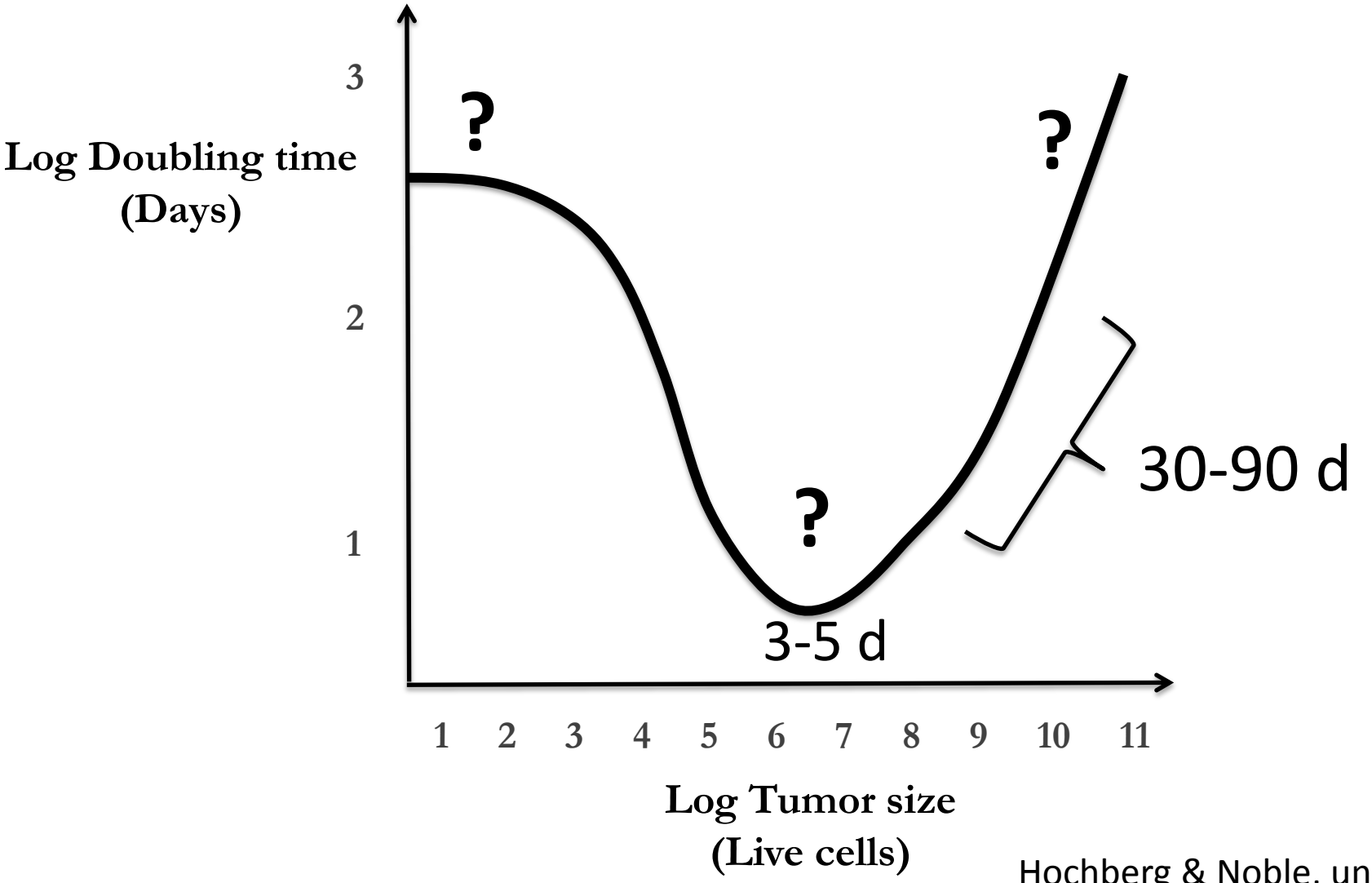
Bozic I et al. PNAS 2010;107:18545-18550

Naive expectations



Hochberg & Noble, unpub

Drivers and Competition



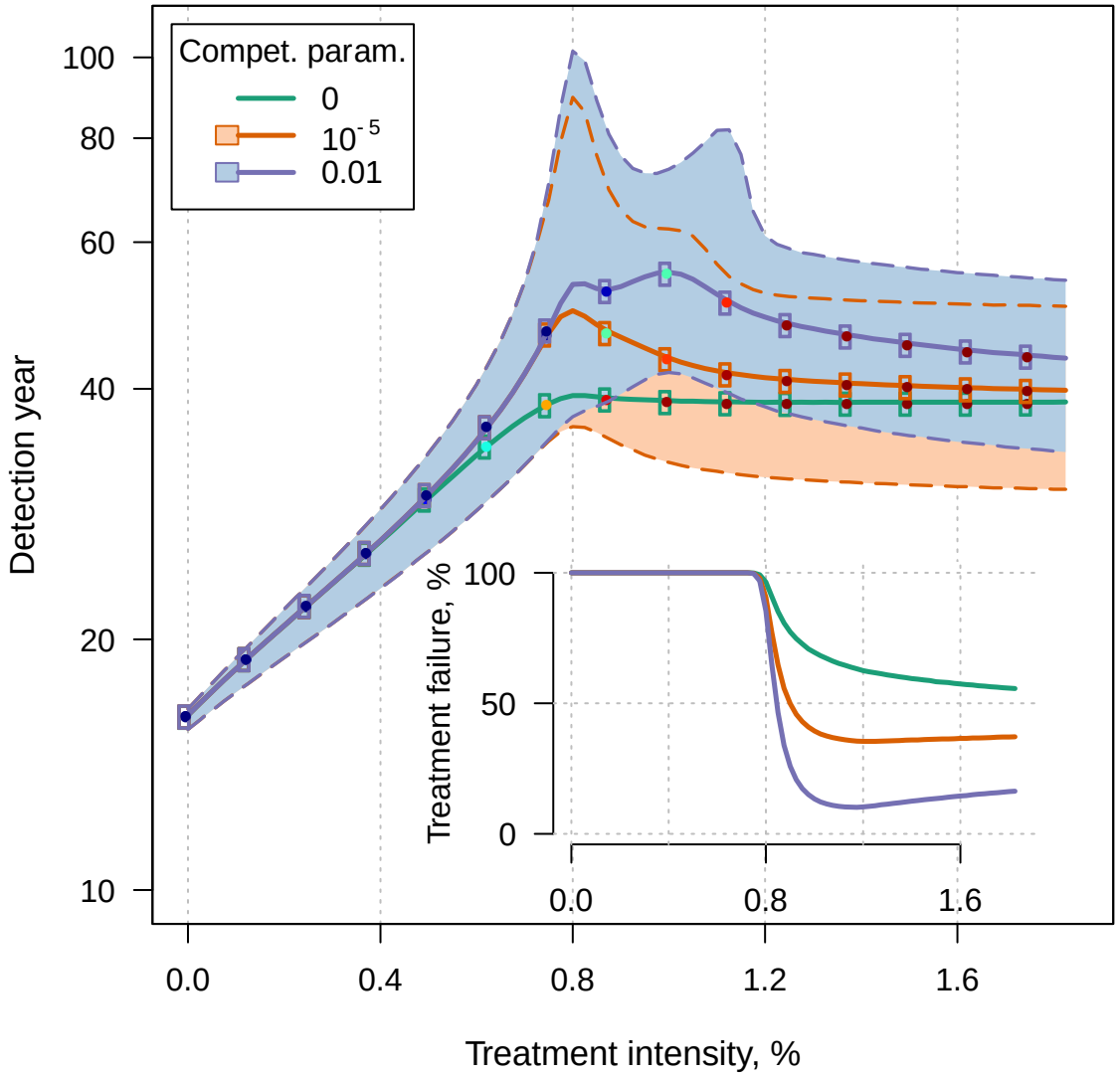
Hochberg & Noble, unpub

Fitness when cells compete

Sensitive cell-lines $f_{i0} = s(i + 1) - \sigma$

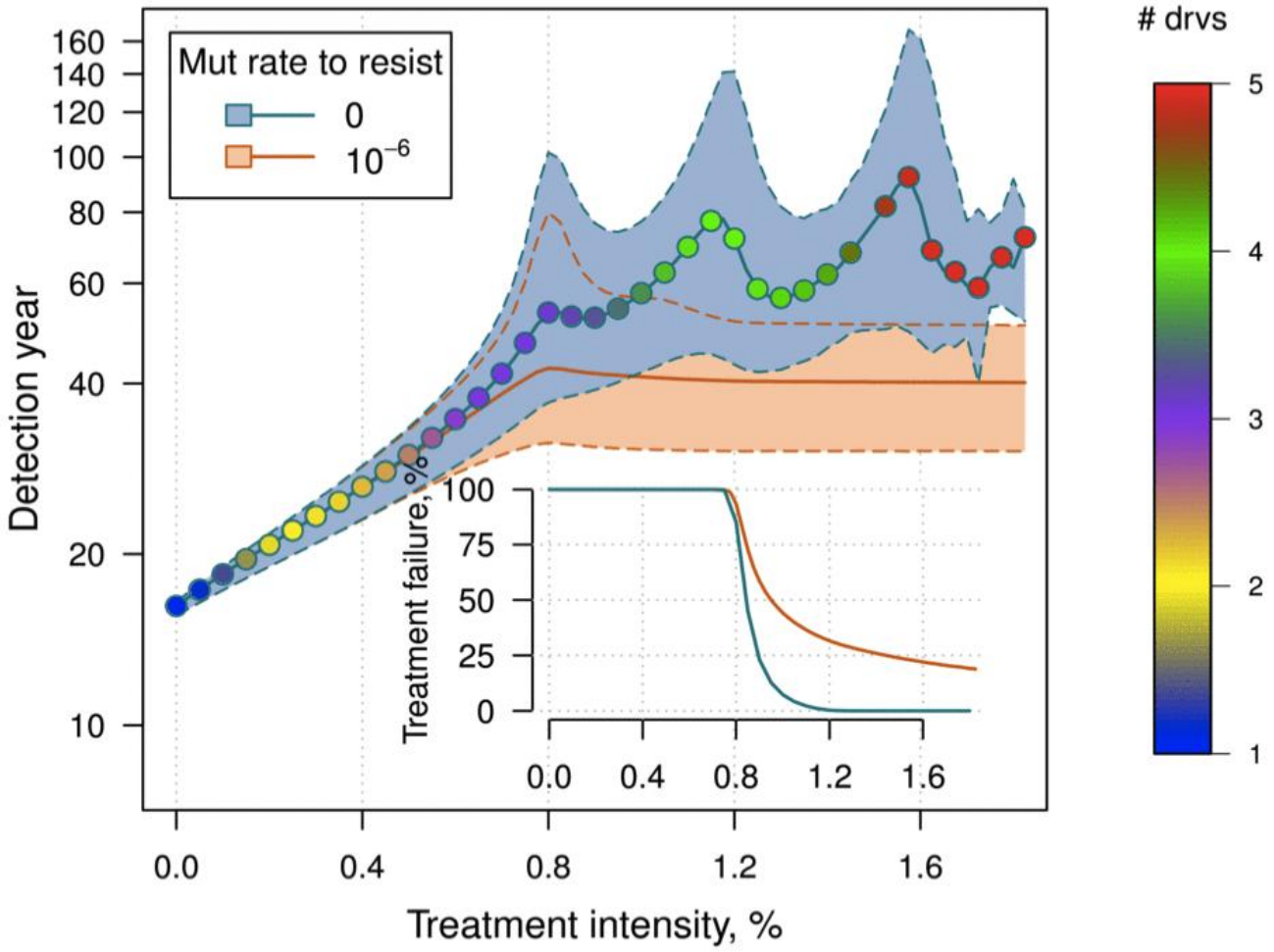
Resistant cell-lines $f_{i1} = s(i + 1)e^{-aS} - c$

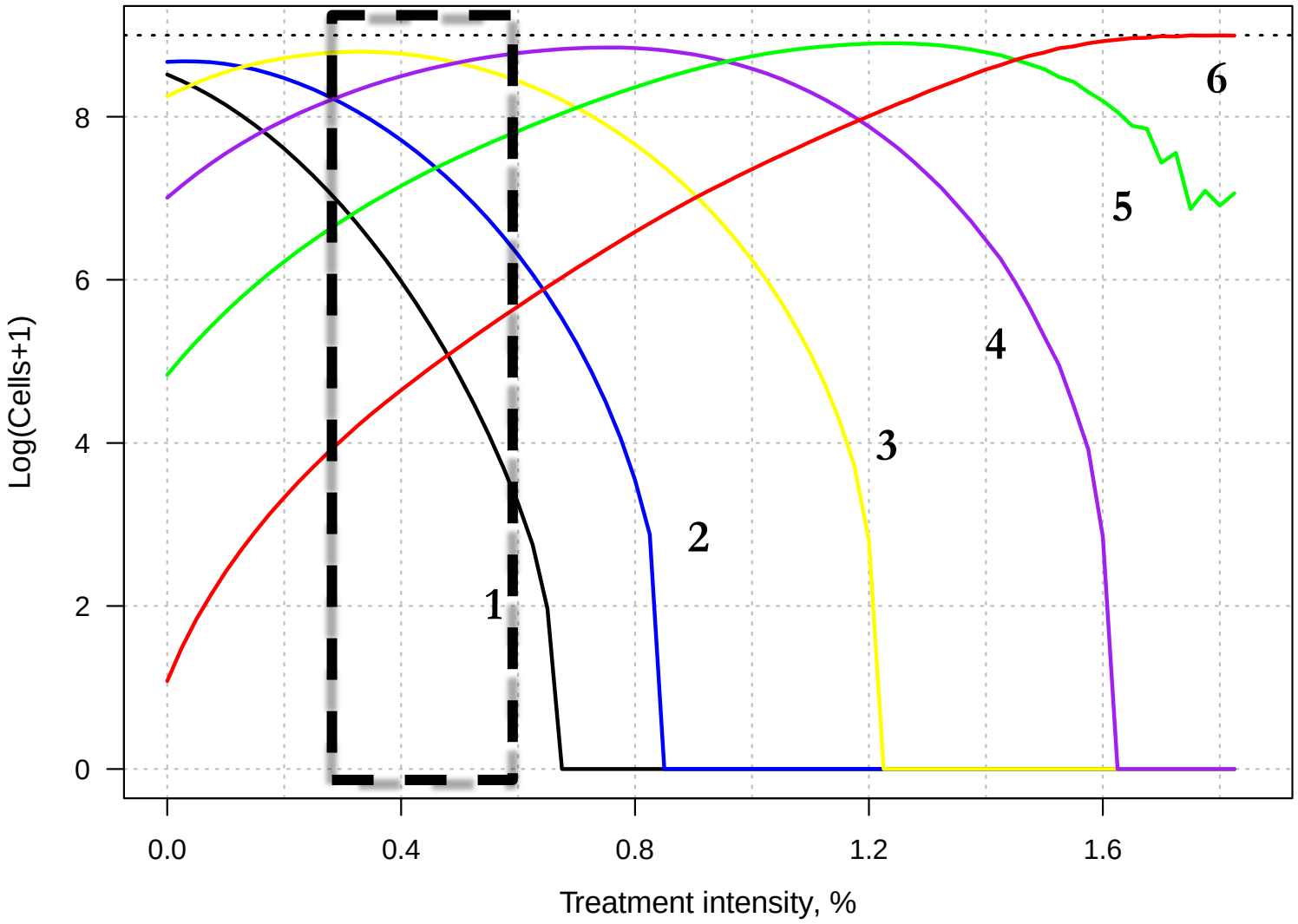
Cell – cell competition



Akhmetzhanov & Hochberg. 2014. ArXiv

More aggressive therapy selects for more aggressive subclones




Maximum tumor heterogeneity
in terms of clones with different
numbers of drivers
Log(Cells+1)
0
2
4
6
8
0.0
0.4
0.8
1.2
1.6
Treatment intensity, %
1
2
3
4
5
6

Main findings

- Approximate criterion for life-threatening tumor is emergence of the 2nd driver within 5 to 10 years
- Tumor eradication: $N_{cumul} < 1/\mu$ ($<10^5$ cells)
- Early prevention of progression in invasive carcinoma: $\sigma \approx 2s$ (0.2% cell mortality/day)
- For more advanced cancers with resistance mutations, treatment intensities slightly less than $2s$ give smaller frequencies of resistance mutations

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