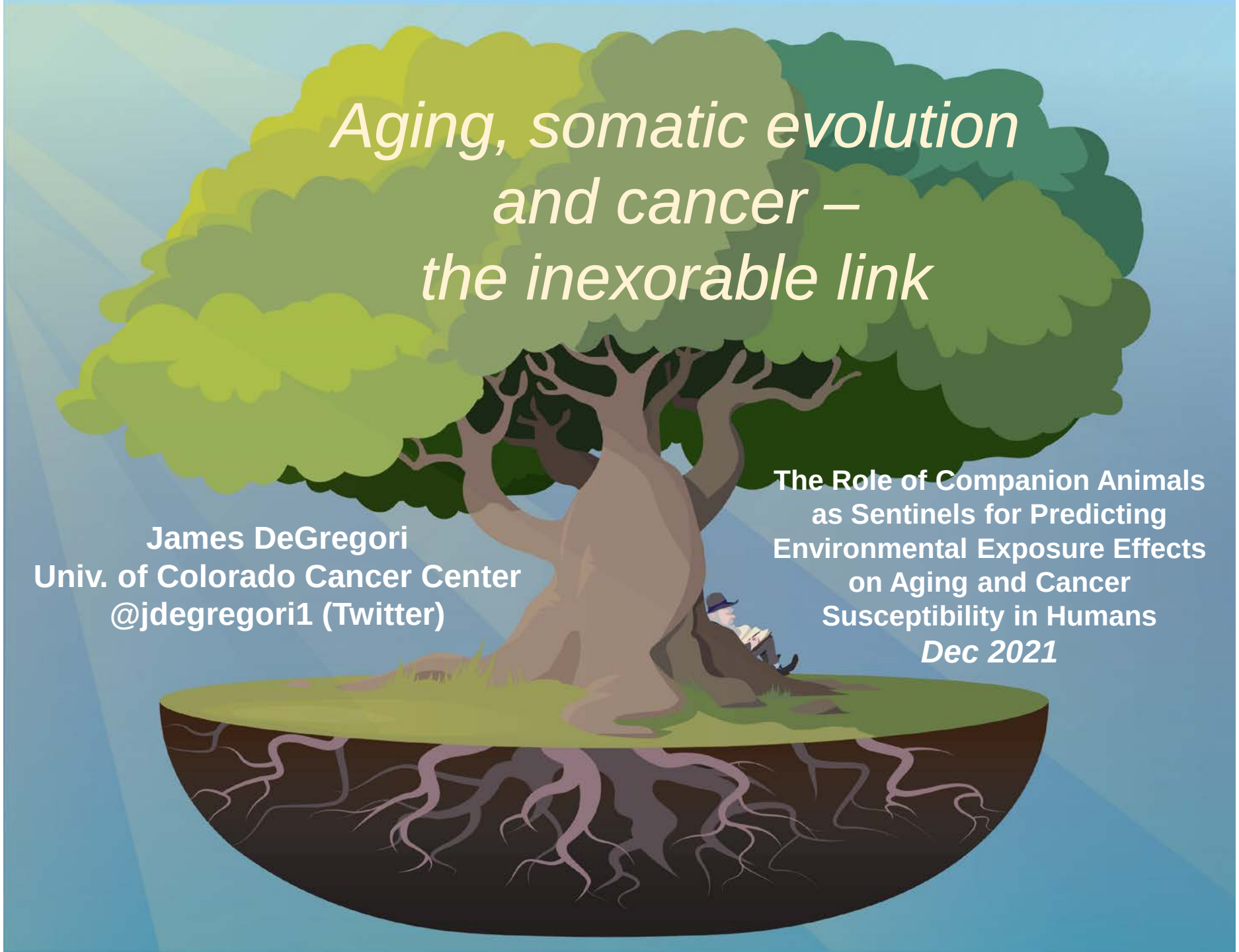
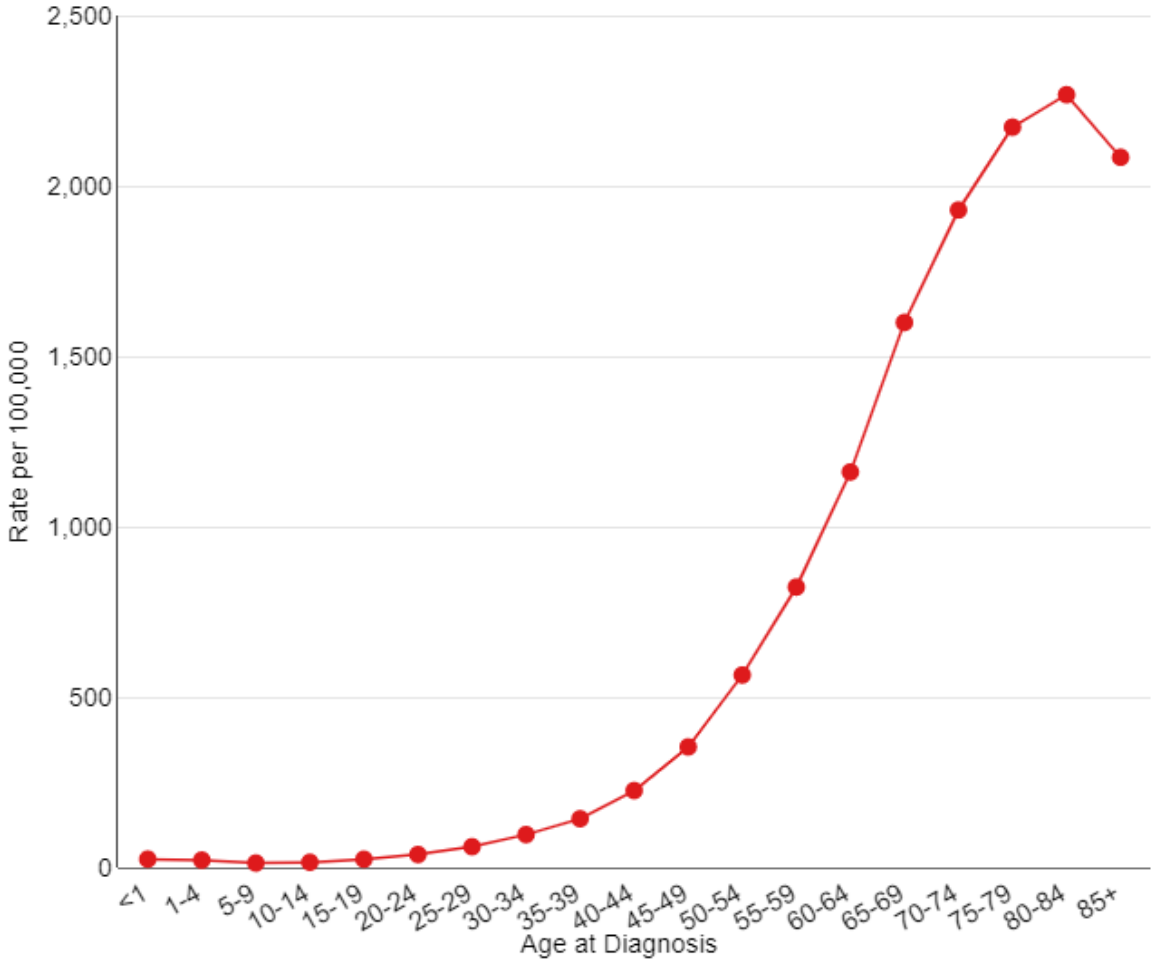
Aging, somatic evolution and cancer – the inexorable link



James DeGregori
Univ. of Colorado Cancer Center
@jdegregori1 (Twitter)

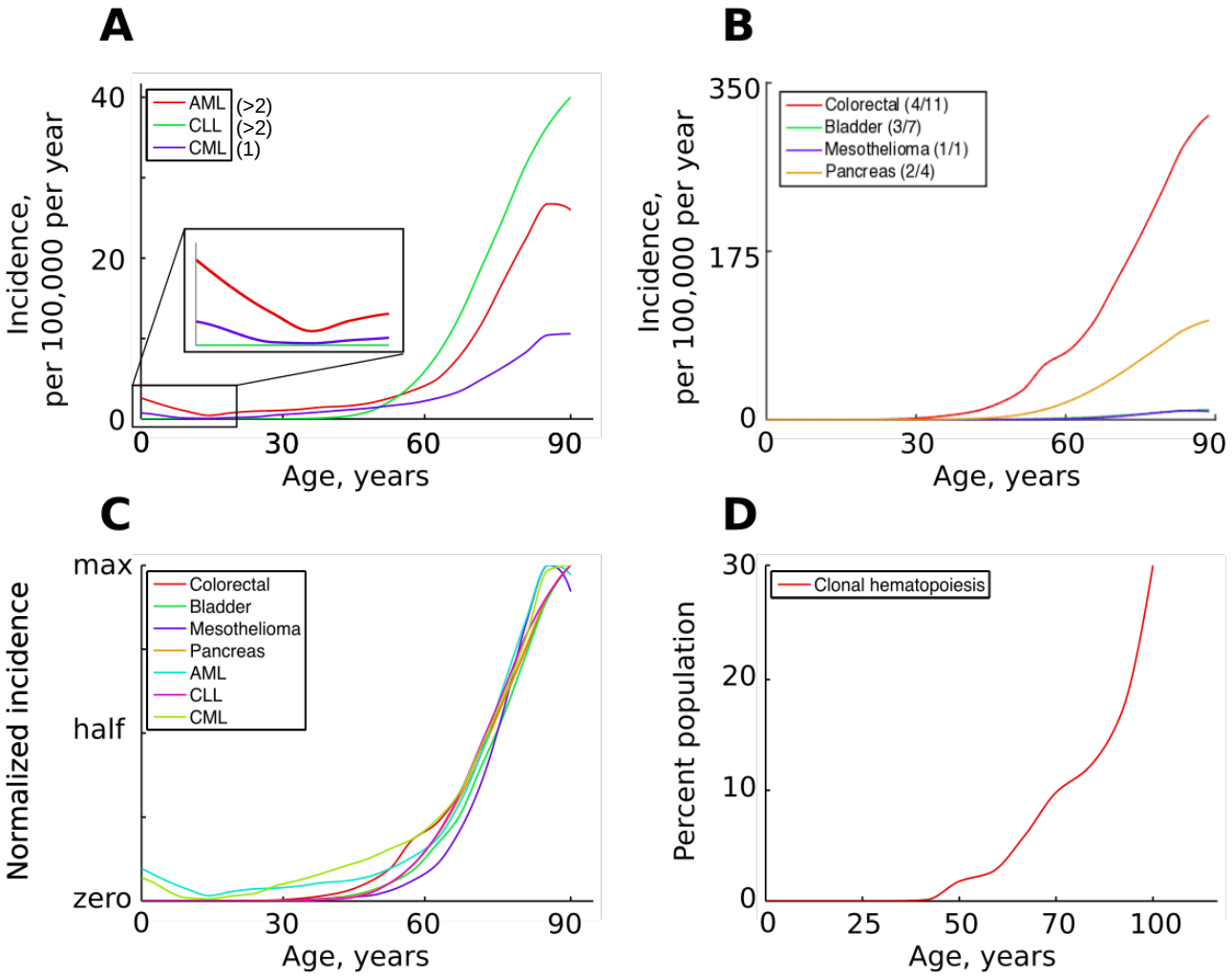
The Role of Companion Animals as Sentinels for Predicting Environmental Exposure Effects on Aging and Cancer Susceptibility in Humans
Dec 2021

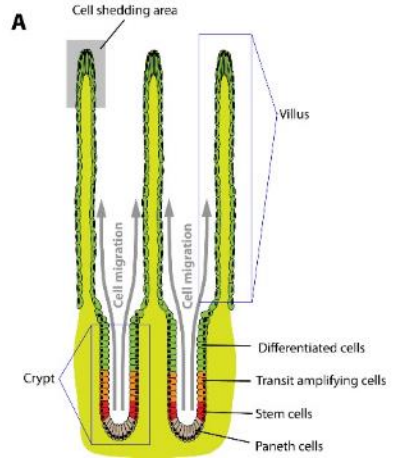
90% of cancers develop after the age of 50

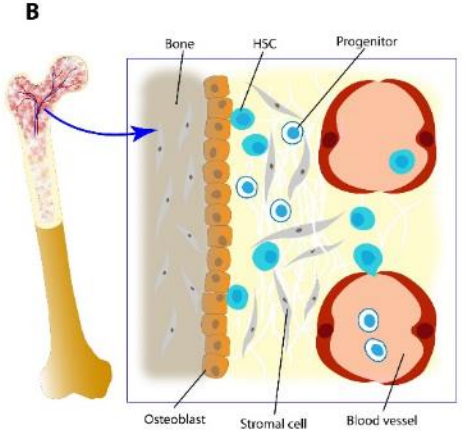


WHY?

Cancers requiring different numbers of driver mutations and originating from vastly differently organized stem cell pools demonstrate very similar age-dependent incidence

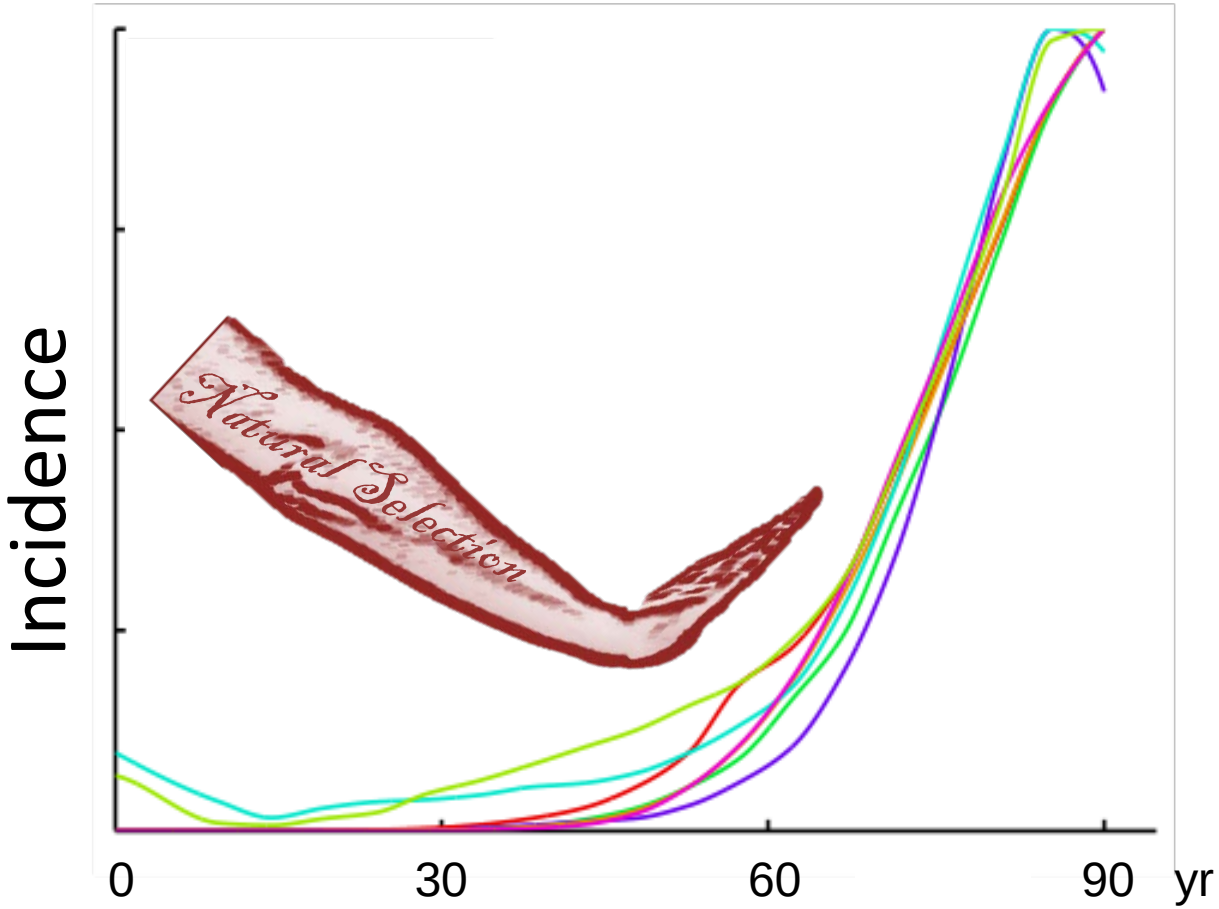




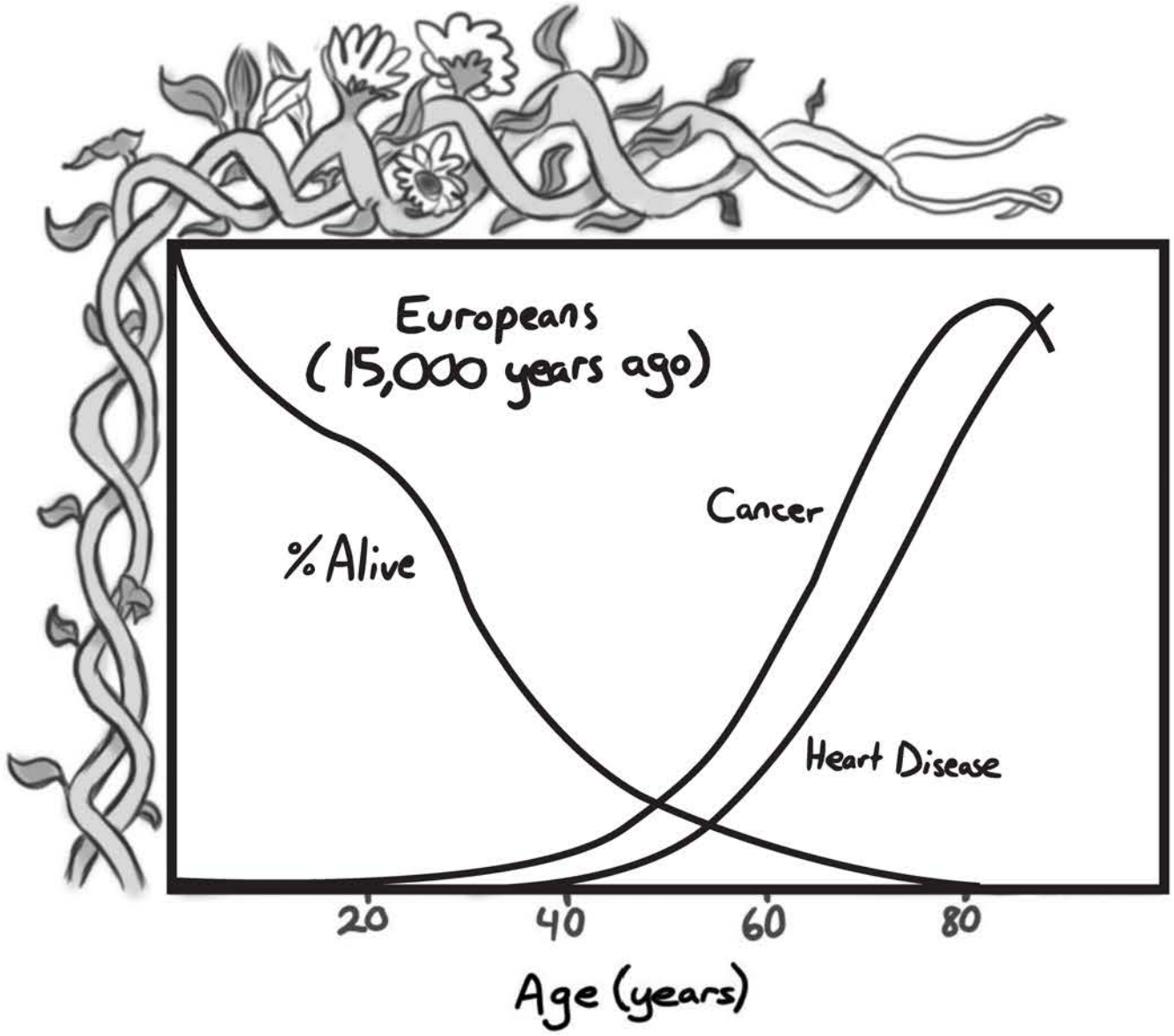


Rozhok and DeGregori, eLife, 2019

Andrii Rozhok

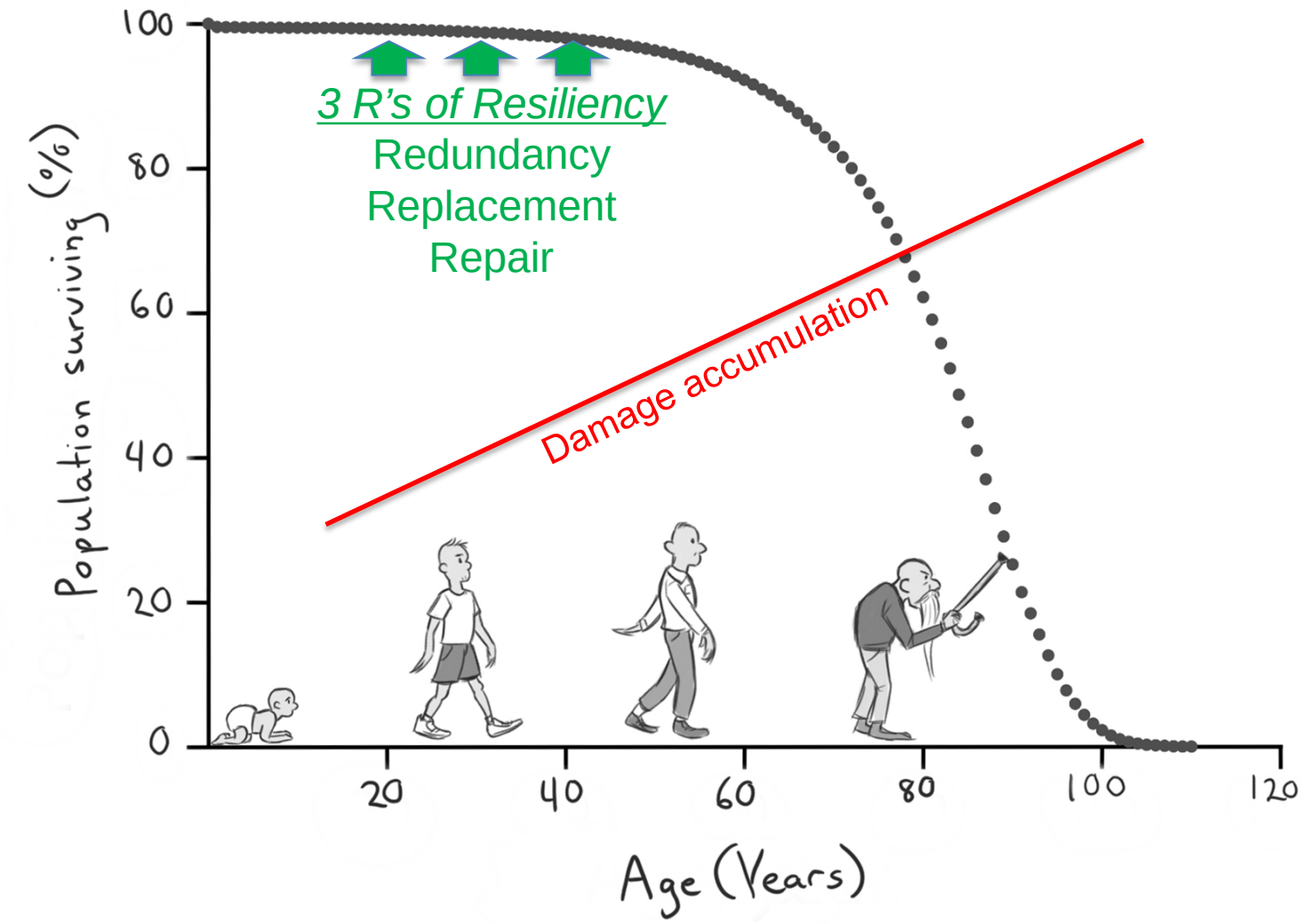

Incidence
Natural Selection
0
30
60
90
yr

There is minimal selection against cancer (and other diseases of aging) beyond the age where most individuals would already be dead by other causes



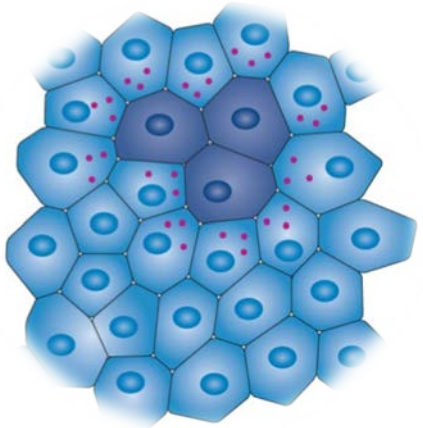
Aging theory:
R. Fisher
J. Haldane
P. Medawar
G. Williams
W. Hamilton
T. Kirkwood

Life is not linear



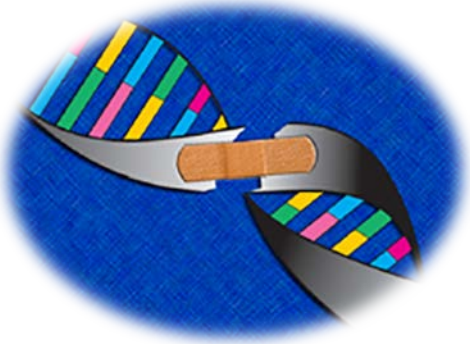
So how are tissues maintained?

Cell competition



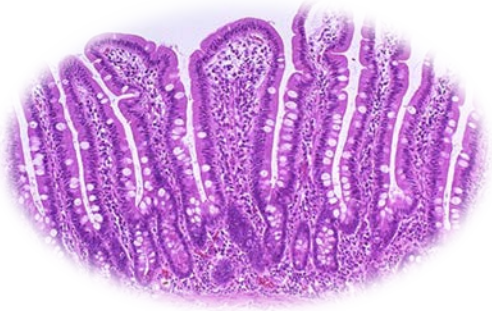
Redundancy (genetic, cellular & structural)

Cell intrinsic maintenance (DNA repair, telomeres, proteostasis)

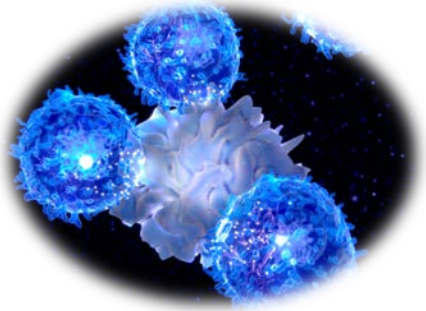


Youthful Soma

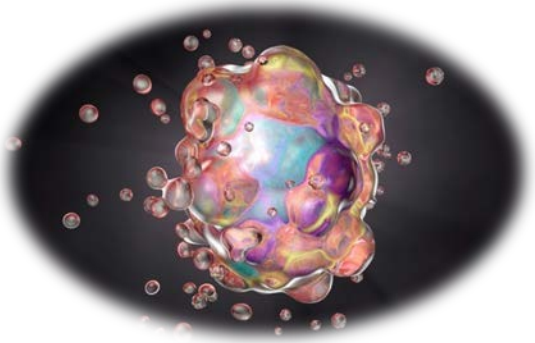
Peer pressure (normal structure favors normal phenotypes)



Immune surveillance



Cell intrinsic quality control (apoptosis, senescence)

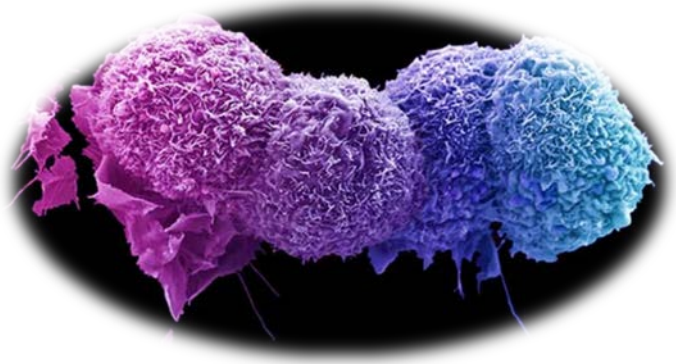


Why does it matter?

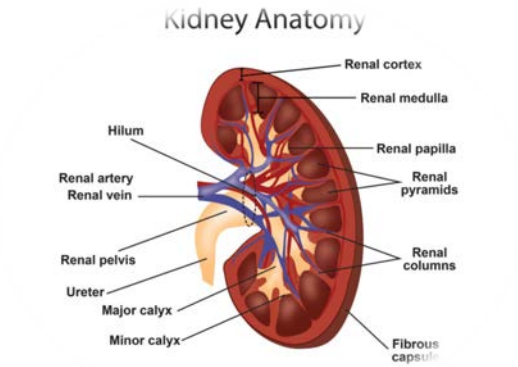
Youthful Soma

Robustness

Anti-cancer defense

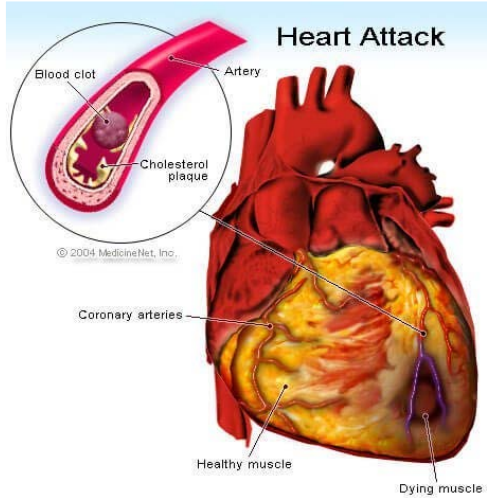


Tissue function



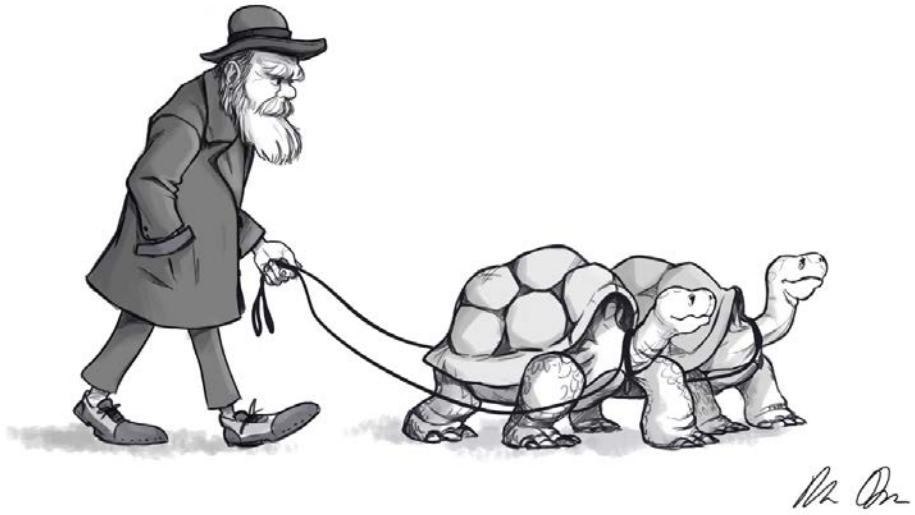
Immune defense

Disease avoidance

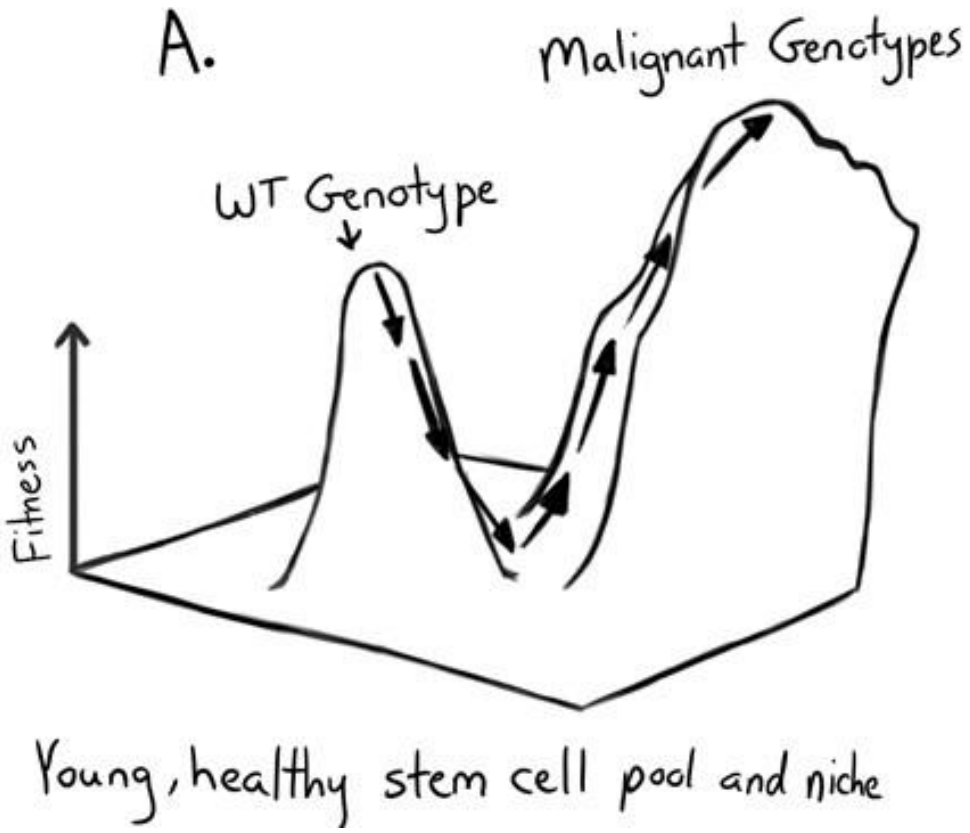


So what does the investment in tissue maintenance during youth, and the waning of this investment in old age, have to do with cancer?

Adaptive Oncogenesis



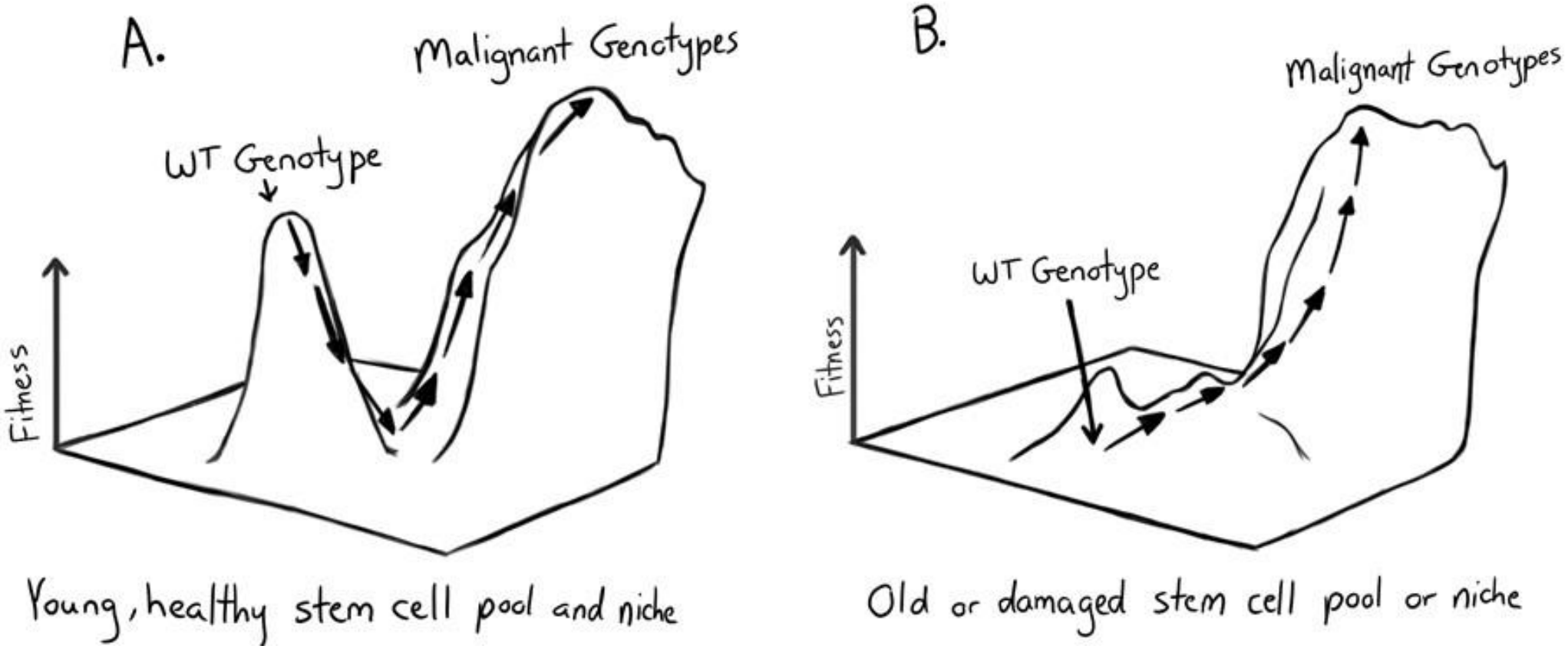
High stem cell fitness opposes somatic evolution, and thus promotes the status quo.



X-Y plane: potential phenotypes (dependent on genotypes and epigenotypes)

Inspiration from Simpson, Eldredge and Gould

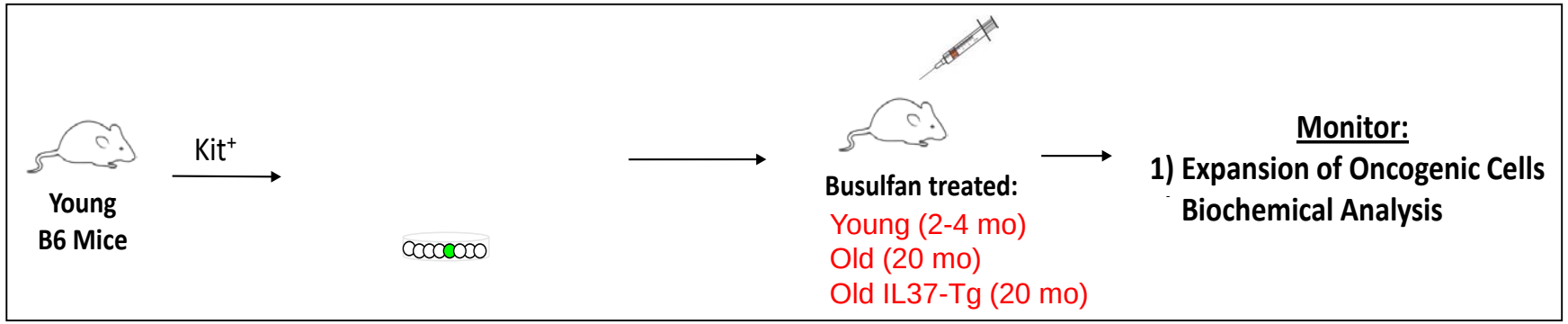
Aging/damage alters the adaptive landscape



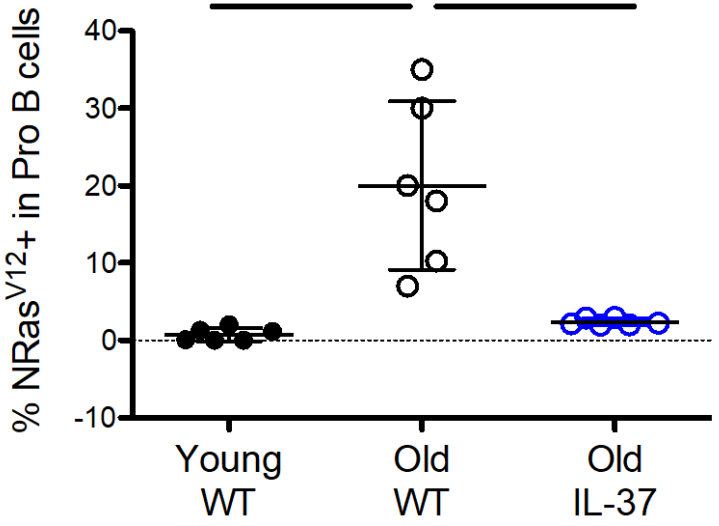
Inspiration from Simpson, Eldredge and Gould

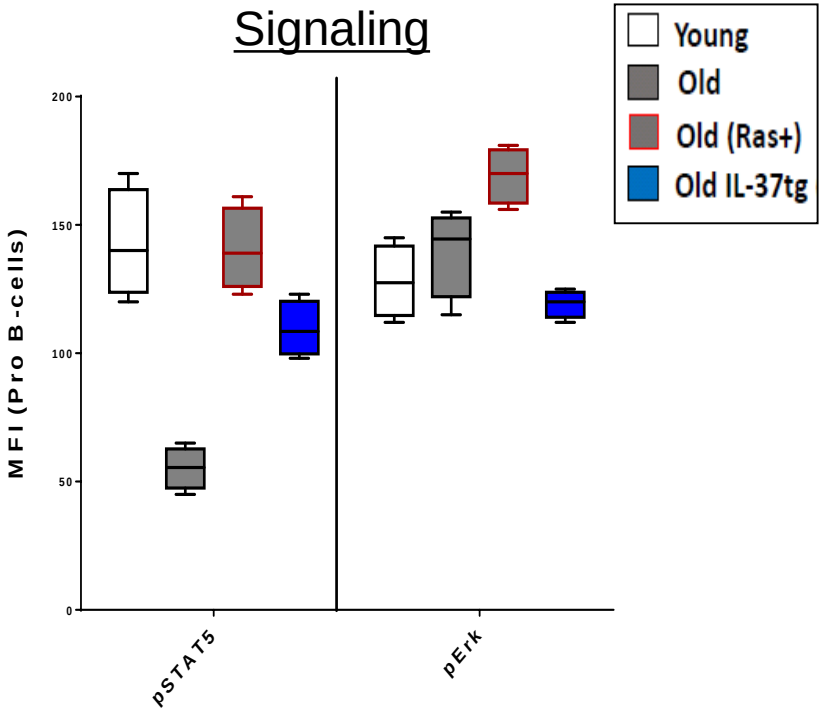
But what is the evidence for differential selection for somatic mutations depending on context?

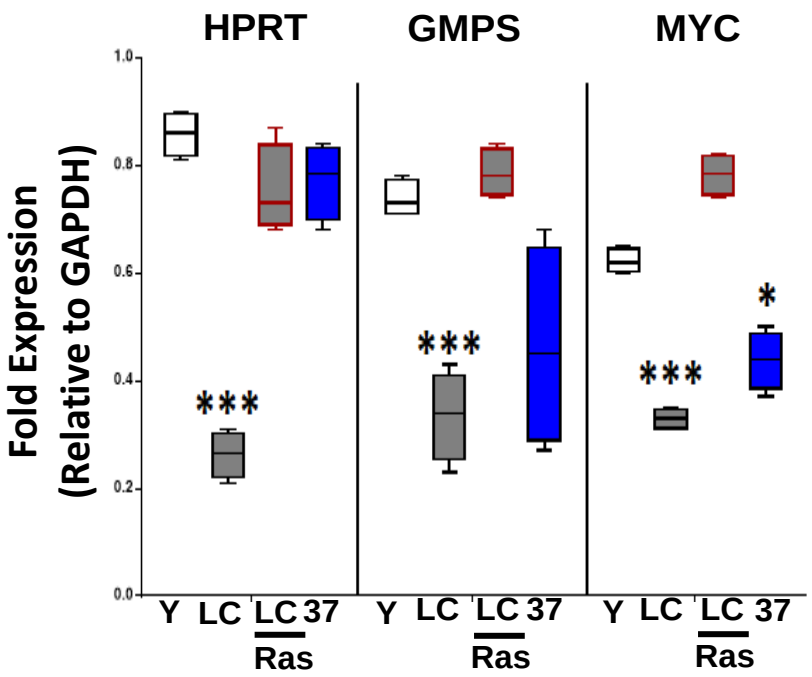
Specific oncogenic events are selected for within *aged* hematopoietic contexts *dependent on inflammation*



Curtis Henry

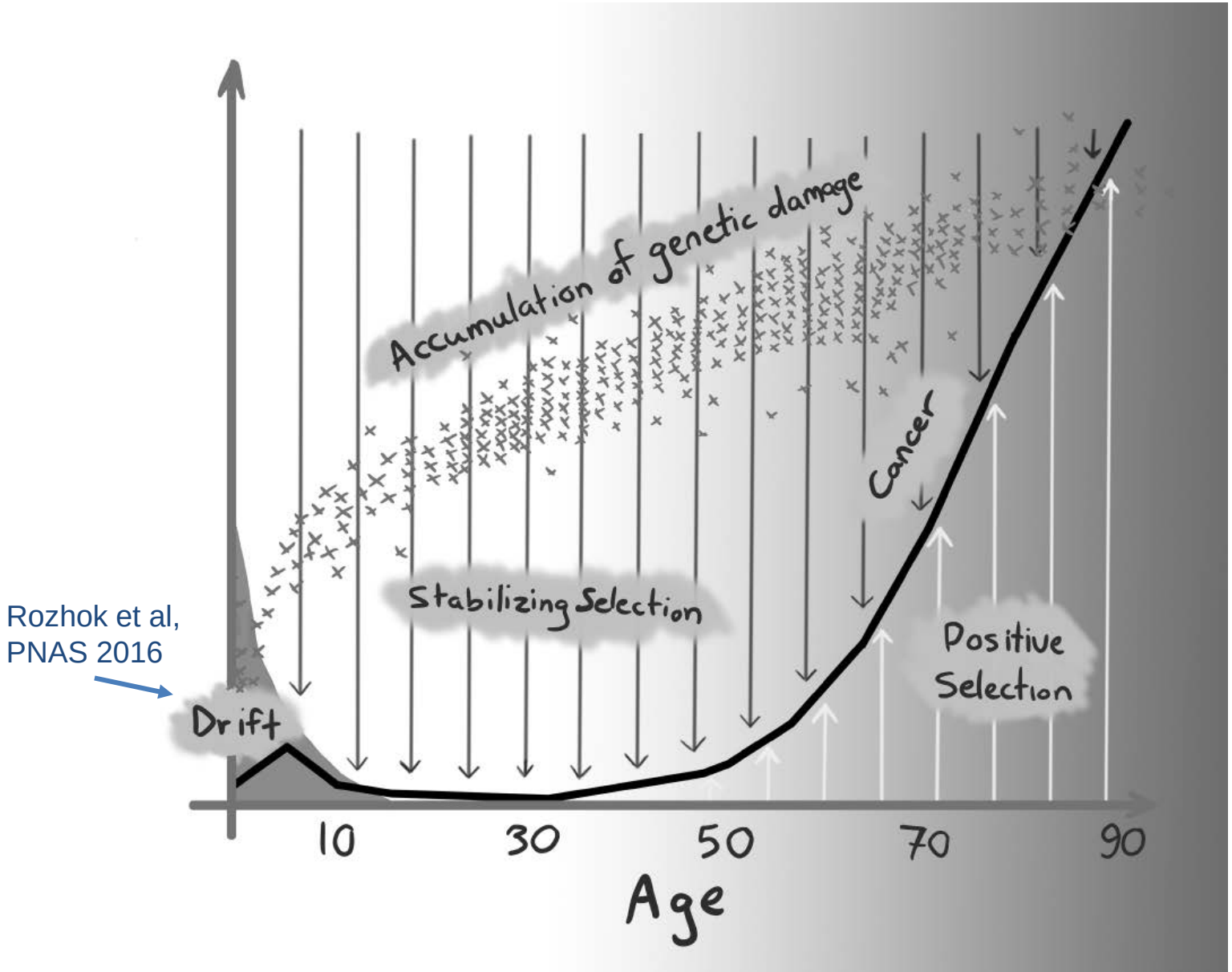






Henry et al, JCI 2015

Model: Cancer incidence is shaped by the changing age-dependent balance of drift, stabilizing selection and positive selection



Rozhok et al, PNAS 2016

Cells with Cancer-associated Mutations Overtake Our Tissues as We Age

RESEARCH

REVIEW SUMMARY

MEDICINE

Clonal hematopoiesis in human aging and disease

Siddhartha Jaiswal* and Benjamin L. Ebert*

https://doi.org/10.1038/s41586-018-0621-x

Not a complete list!!

ARTICLE

Age-related remodelling of oesophageal epithelia by mutated cancer drivers

Akira Yokoyama[1,2,14], Nobuyuki Kakiuchi[1,3,14], Yusuke Shiozawa[1], Yusuke Sato[1], Kosuke Aoki[1], Soo Ki Kim[1], Yoichi Fujii[1], Kenichi Yoshida[1], Yasuhide Takeuchi[1,4], Masahiro M. Nakagawa[1], Yoshikage Inoue[1,5], Tomonori Hirano[1,3], Yuichi Shiraishi[6], Kenichi Chiba[6], Keisuke Kataoka[7], Masashi Sanada[8], Yoshitaka Nishikawa[2], Yusuke Amanuma[2], Shinya Ohashi[2], Ikuo Aoyama[2], Hiroko Tanaka[7], Masashi Sanada[8], Shin'ichi Miyamoto[3], Shigeru Tsunoda[5], Yoshiharu Sakai[5], Maiko Narahara[9], J. B. Brown[10], Takahiro Horimatsu[2], Genta Sawada[12], Koshi Mimori[12], Sachiko Minamiguchi[4], Hironori Haga[4], Hiroshi Seno[3], Satoru Miyano[6,7], Yoshitaka Sato[11], Manabu Muto[2,15] & Seishi Ogawa[1,13,15]*, Hideki Makishima[1], Manabu Muto[2,15] & Seishi Ogawa[1,13,15]*

Article

Frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis

https://doi.org/10.1038/s41586-019-1856-1
Received: 26 February 2019
Accepted: 8 November 2019
Published online: 18 December 2019

Nobuyuki Kakiuchi[1,2,3], Kenichi Yoshida[1], Motoi Uchino[4], Takako Kihara[5], Kotaro Akaki[6], Yoshikage Inoue[3,7], Kenji Kawada[7], Satoshi Nagayama[4], Akira Yokoyama[1,2], Shuji Yamamoto[3], Minoru Matsuura[3,10], Takahiro Horimatsu[8], Tomonori Hirano[1,2,3], Norihiro Goto[5], Yasuhide Takeuchi[1,2,11], Yotaro Ochi[1,2], Yusuke Shiozawa[1], Keisuke Kataoka[1,12], Yosaku Watstani[1,2], Yoichi Fujii[1,2], Soo Ki Kim[1,3], Ayana Kon[1,3], Akinori Yoda[1,2], Yasuhito Nanya[1], Tetsuichi Yoshizato[1], Masahiro M. Nakagawa[1,3], Kenichi Chiba[1,6], Hiroko Tanaka[1,6], Masashi Sanada[1,6], Hideki Makishima[1,2], Yuichi Shiraishi[6], Kenichi Chiba[1,6], Hiroyuki Miyoshi[1,6], Hideki Ogawa[1,6], Eiji Sugihara[1,7], Taka-aki Sato[1,7], Takashi Maruyama[1,8], Hiroyuki Miyoshi[1,6], Hideki Ogawa[1,6], Jun Oishi[1,9], Ryosaku Inagaki[1,10], Yutaka Ueda[1,10], Shinya Okamoto[1,9], Hiroki Ikeuchi[1,9], Yoshiharu Sakai[1], Takaki Sakurai[11], Hironori Haga[1,5], Tsutomu Chiba[1,2,4], Osamu Takeuchi[1,2,4], Hiroshi Nakase[1,2,3], Hiroyuki Marusawa[3], Tsutomu Chiba[1,2,4], Osamu Takeuchi[1,2,4], Satoru Miyano[1,4,15], Hiroshi Seno[3] & Seishi Ogawa[1,2,13,15]*

Science

Somatic mutant clones colonize the human esophagus with age

Iñigo Martincorena[1,8,†], Joanna C. Fowler[1,8], Agnieszka Wabik[1], Andrew R. J. Lawson[1], Federico Abascal[1], Michael W. J. Hall[1,2], Alex Cagan[1], Kasumi Murai[1], Krishnaa Mahbubani[1,3], Michael R. Stratton[1], Rebecca C. Fitzgerald[2], Penny A. Handford[4], Peter J. Campbell[1,5], Kourosh Saeb-Parsy[3], Philip H. Jones[1,†]

RESEARCH ARTICLES
Cite as: I. Martincorena et al., Science 10.1126/science.aau3879 (2018).

Article

Somatic inflammatory gene mutations in human ulcerative colitis epithelium

https://doi.org/10.1038/s41586-019-1844-5
Received: 27 February 2019
Accepted: 31 October 2019
Published online: 18 December 2019

Kosaku Nanki[1,2,7], Masayuki Fujii[1,3,7], Mariko Shimokawa[1], Mami Matano[1], Shingo Nishikori[1,4], Sholchi Date[1,4], Ai Takano[1], Kohta Toshimitsu[1,2], Yuki Ohta[1], Sirirat Takahashi[1], Shinya Sugimoto[1,2], Kazuhiro Ishimaru[1,3], Kenta Kawasaki[1,2], Yoko Nagai[4], Ryota Ishii[5], Kosuke Yoshida[1,2], Nobuo Sasaki[1,2], Toshifumi Hibi[2,6], Soichiro Ishihara[3], Takanori Kanai[2] & Toshiro Sato[1,2]*

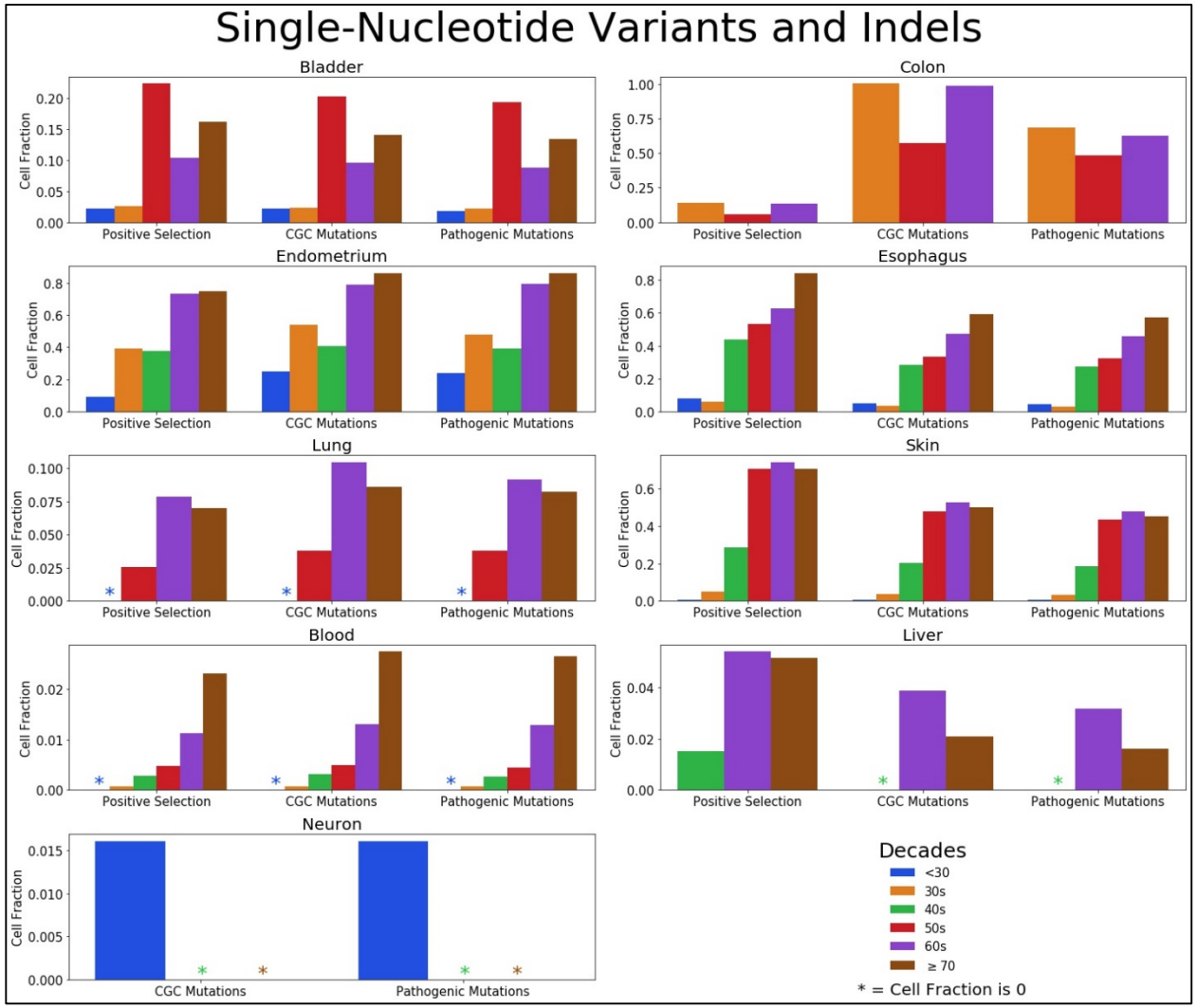
Article

The mutational landscape of normal human endometrial epithelium

https://doi.org/10.1038/s41586-020-2214-z
Received: 19 December 2018
Accepted: 20 March 2020
Published online: 22 April 2020

Luiza Moore[1,2], Daniel Leongamornlert[1], Tim H. H. Coorens[1], Mathijs A. Sanders[1,3], Peter Ellis[1,4], Stefan C. Dentro[1,5], Kevin J. Dawson[1], Tim Butler[1], Raheleh Rahbari[1], Thomas J. Mitchell[1], Francesco Maura[1,6], Jyoti Nangalia[1], Patrick S. Tarpey[1], Simon F. Brunner[1], Henry Lee-Six[1], Yvette Hooks[1], Sarah Moody[1], Krishnaa T. Mahbubani[7,8,9], Mercedes Jimenez-Linan[2], Jan J. Brosens[10], Christine A. Iacobuzio-Donahue[11,12], Inigo Martincorena[1], Kourosh Saeb-Parsy[1,8], Peter J. Campbell[1] & Michael R. Stratton[1]*

Cells with Cancer-associated Mutations Overtake Our Tissues as We Age



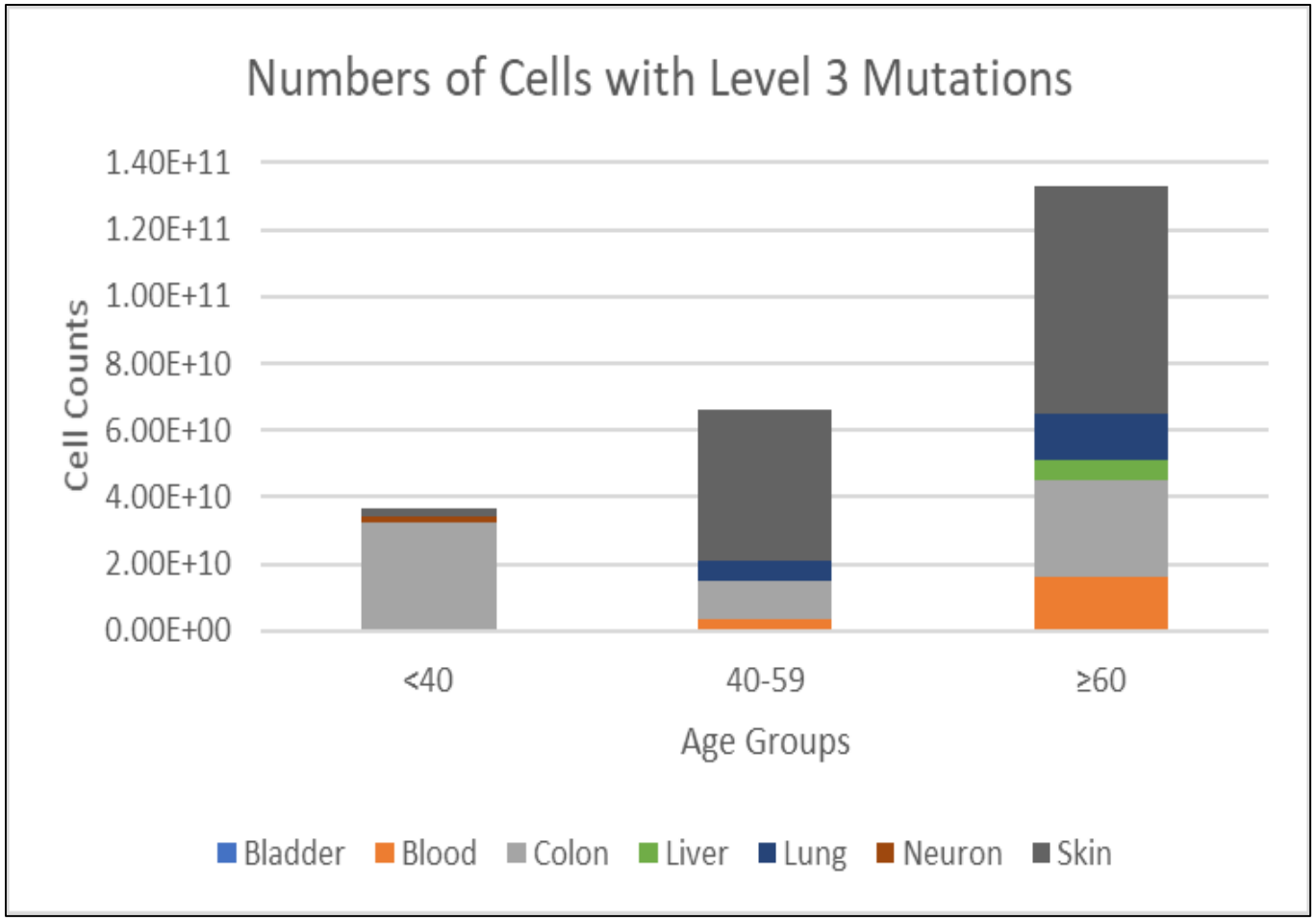
- Expansions with cancer-associated mutations become more prevalent with age.
- Kinetics differ for different tissues.

CGC = Cancer Gene Consensus
Pathogenic – FATHMM algorithm

Edward Evans

Evans and DeGregori, *Aging AND Cancer*, 2021

Cells with Cancer-associated Mutations Overtake Our Tissues as We Age



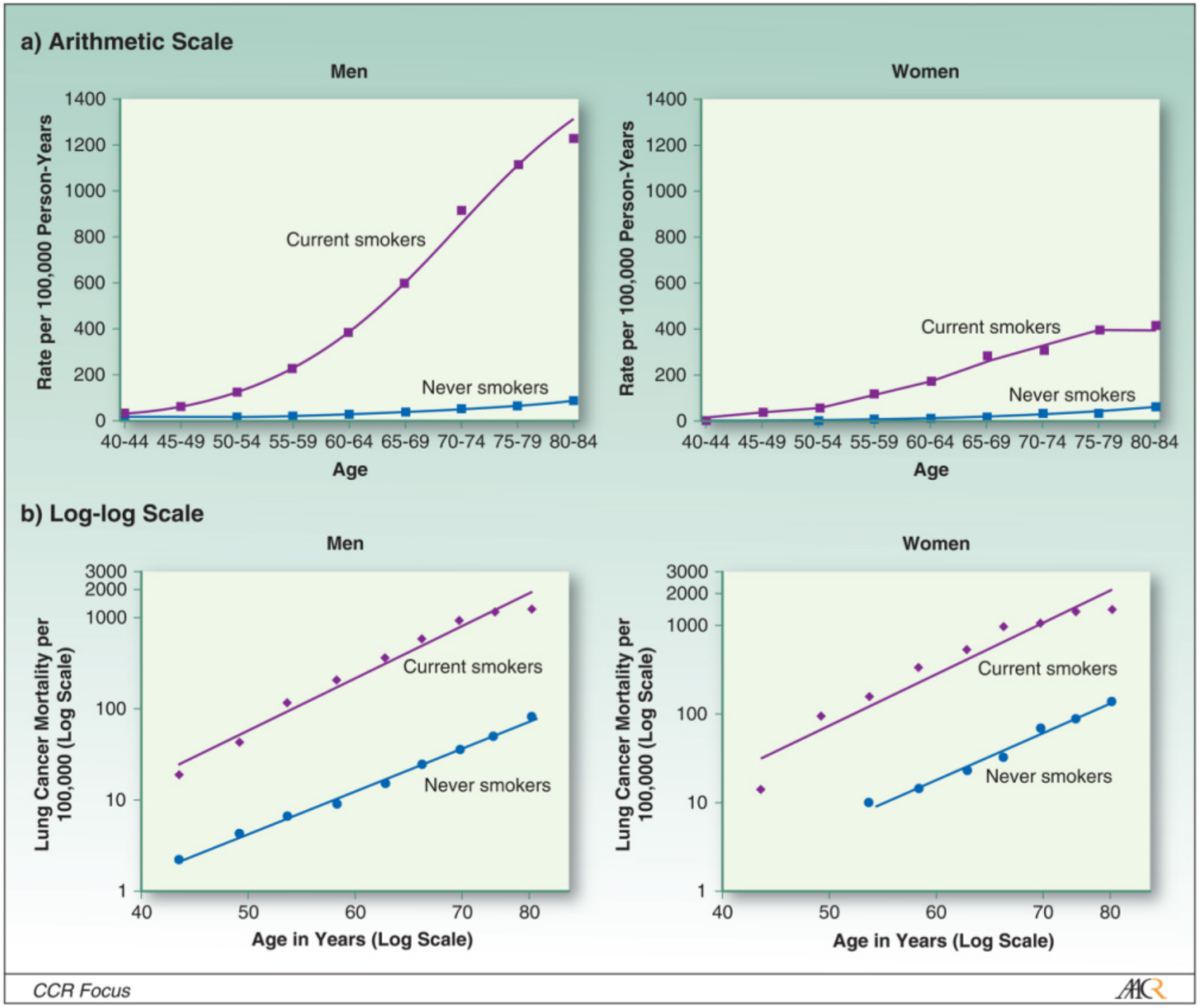
- Most older and cancer-free individuals possess at least a *100 billion cells* that harbor at least one oncogenic mutation
- And yet ~40% of us will develop cancer, which will almost always arise from a single oncogenically initiated cell
- What do the other 99,999,999,999 cells with "oncogenic" mutations do?

Evans and DeGregori, *Aging AND Cancer*, 2021

Edward Evans

Whether you get lung cancer is largely determined by smoking.

When you get it is determined by your age.



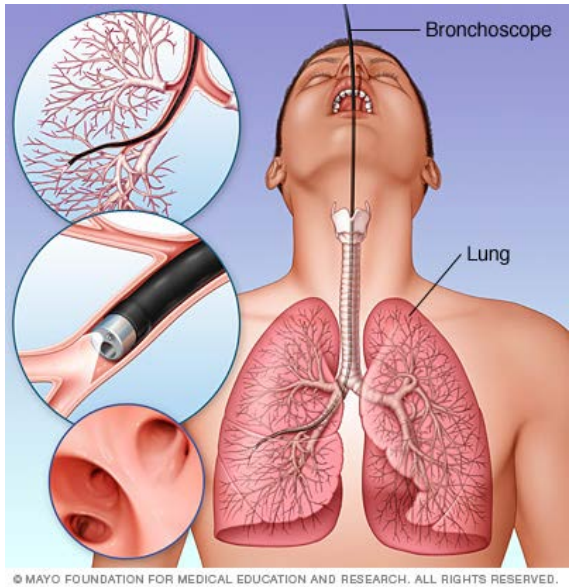
CCR FOCUS

Lung Cancer in Never Smokers: Clinical Epidemiology and Environmental Risk Factors

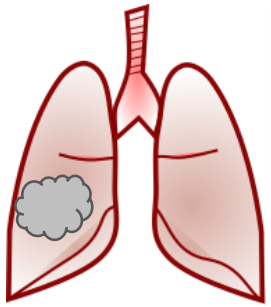
Jonathan M. Samet,[1] Erika Avila-Tang,[1] Paolo Boffetta,[2] Lindsay M. Hannan Susan Olivo-Marston,[4] Michael J. Thun,[3] and Charles M. Rudin[1]

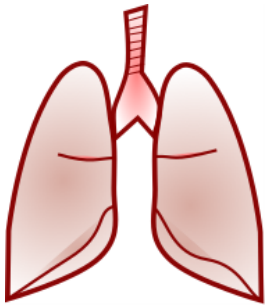
How does smoking status influence oncogene-driven clonal expansions in the lung?

Smokers or former smokers with CT scan detected nodules.



Cancerous lesion vs Benign or no lesion





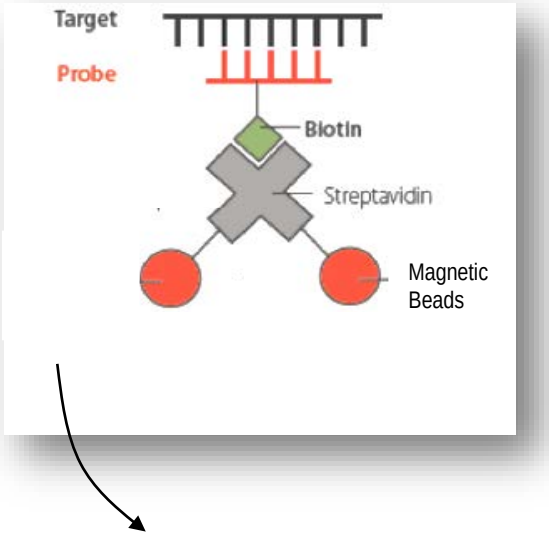
Involved site vs Contralateral

Involved site vs Contralateral

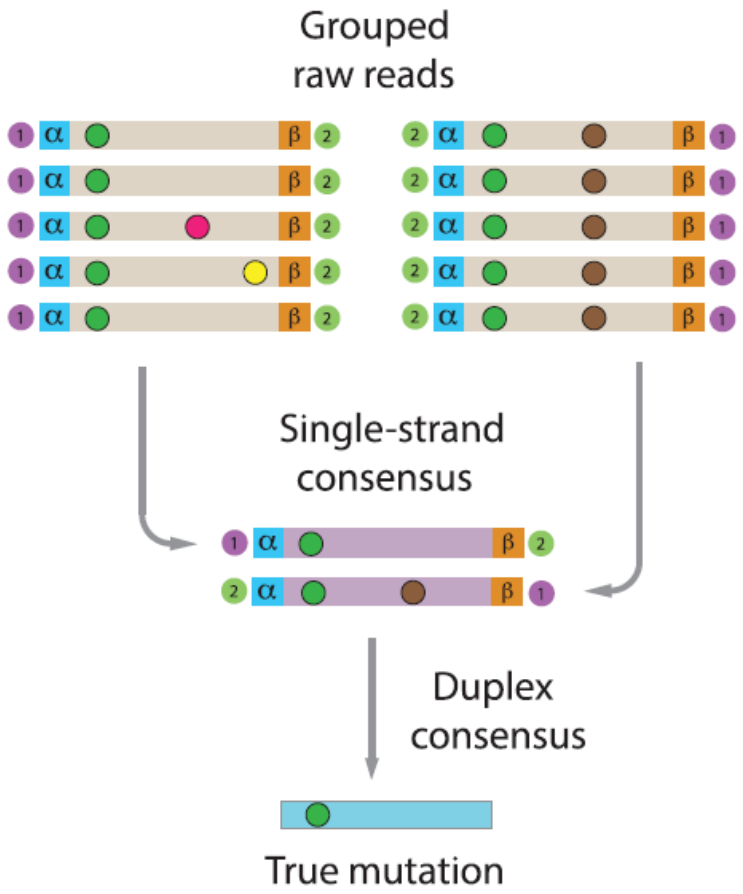
Edward Evans

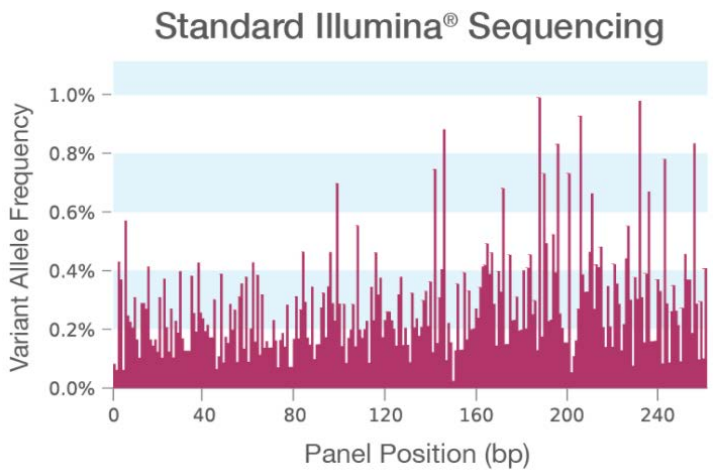
And
York Miller
Moumita Ghosh
Dan Merrick
Tullia Bruno

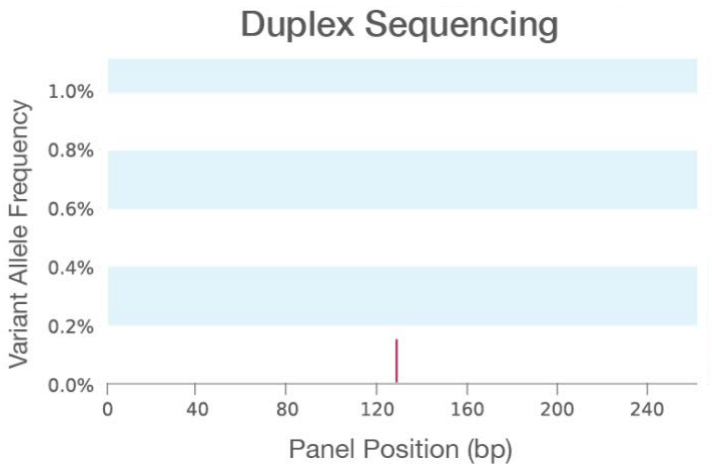
Duplex Sequencing



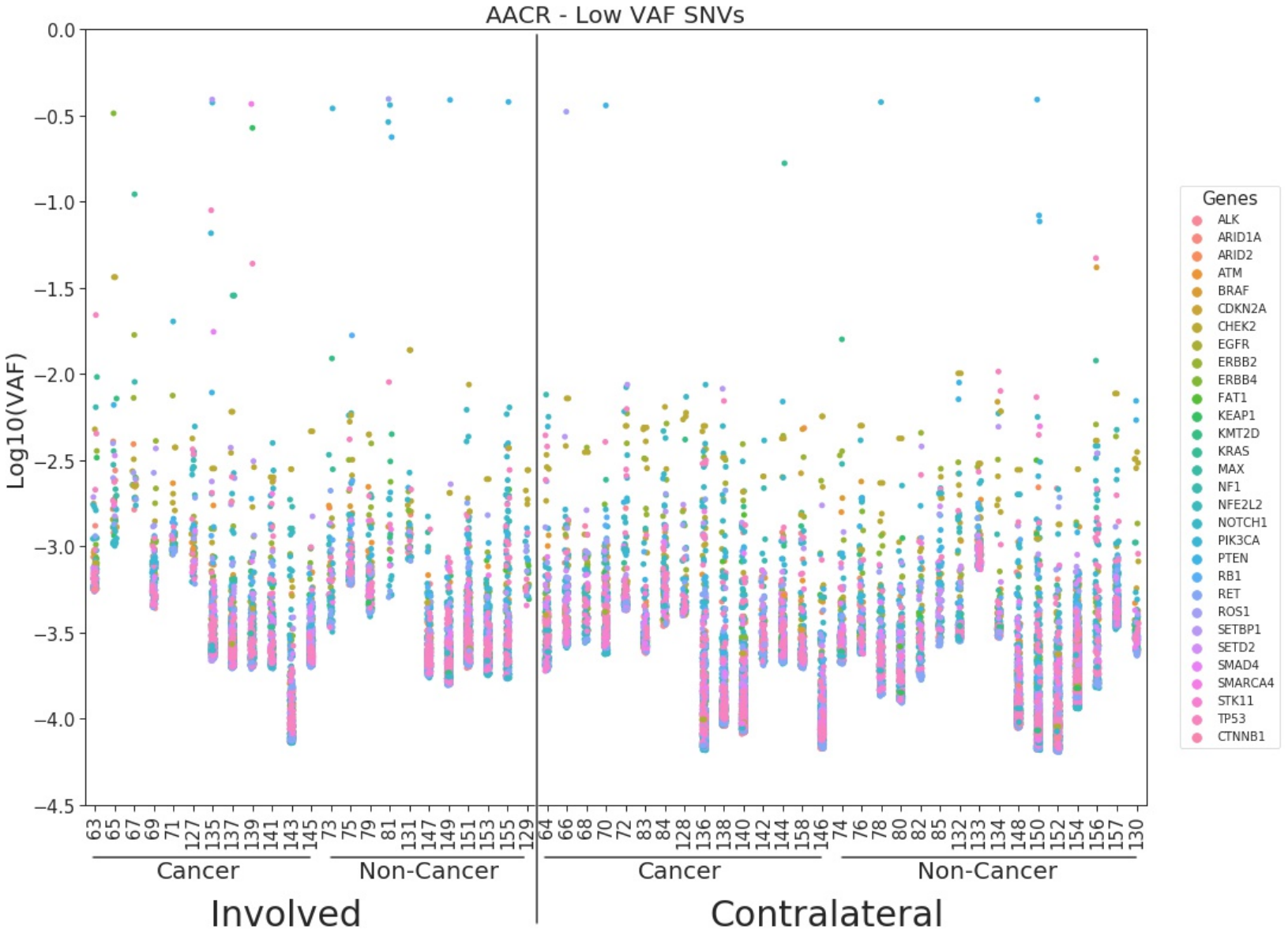
2 consecutive captures + PCR



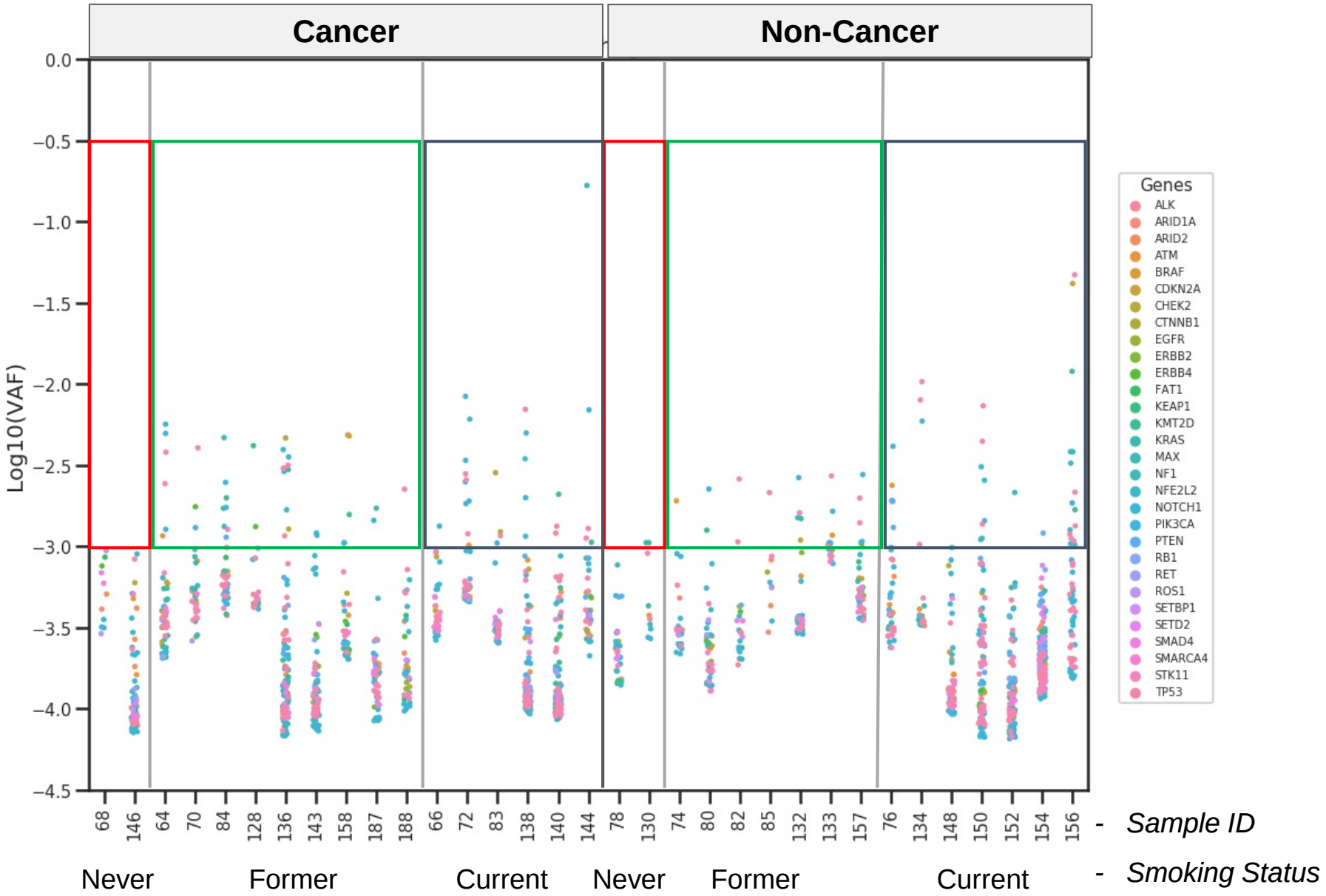




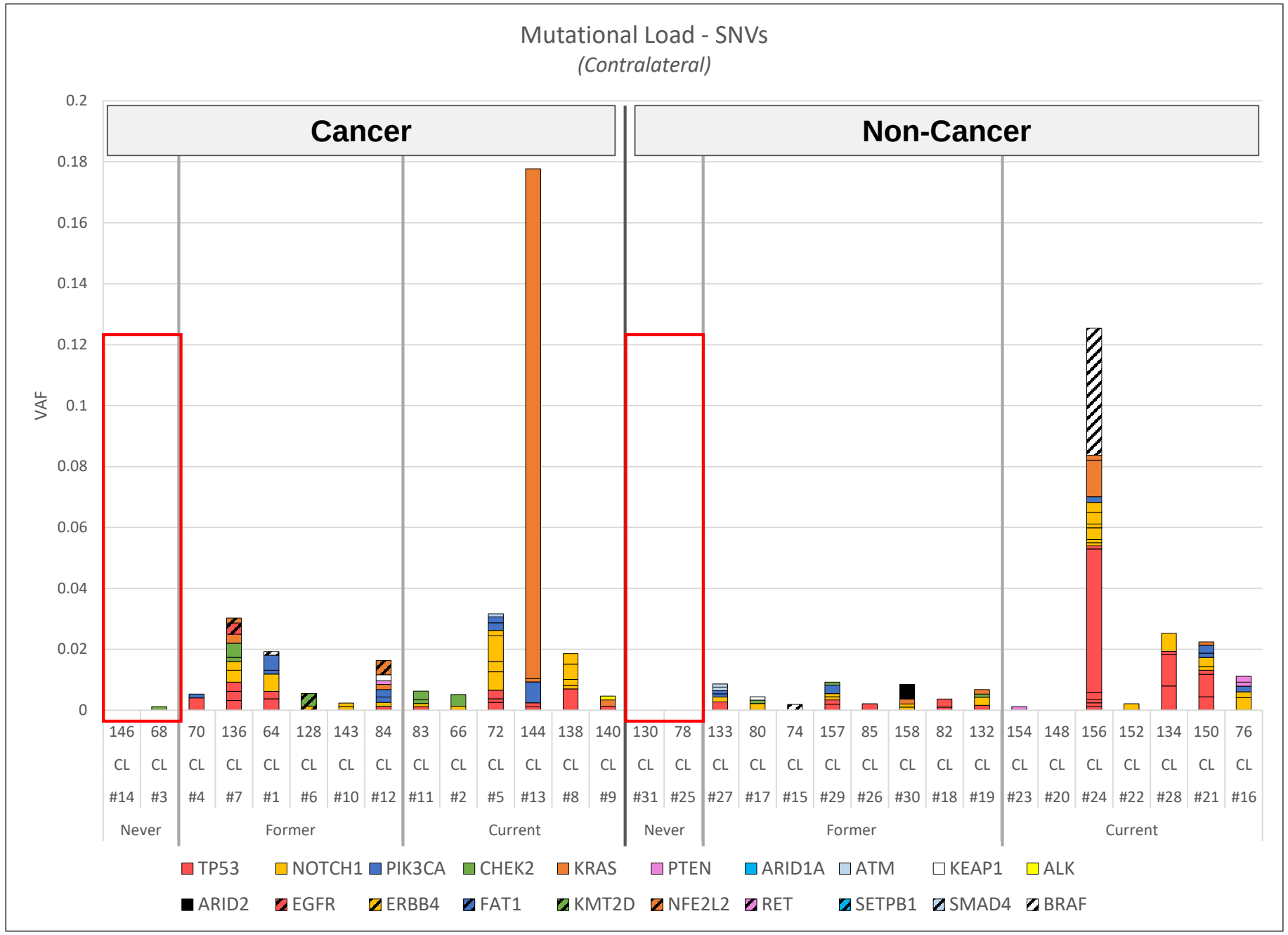
Even a small fragment of lung tissue is riddled with mutations



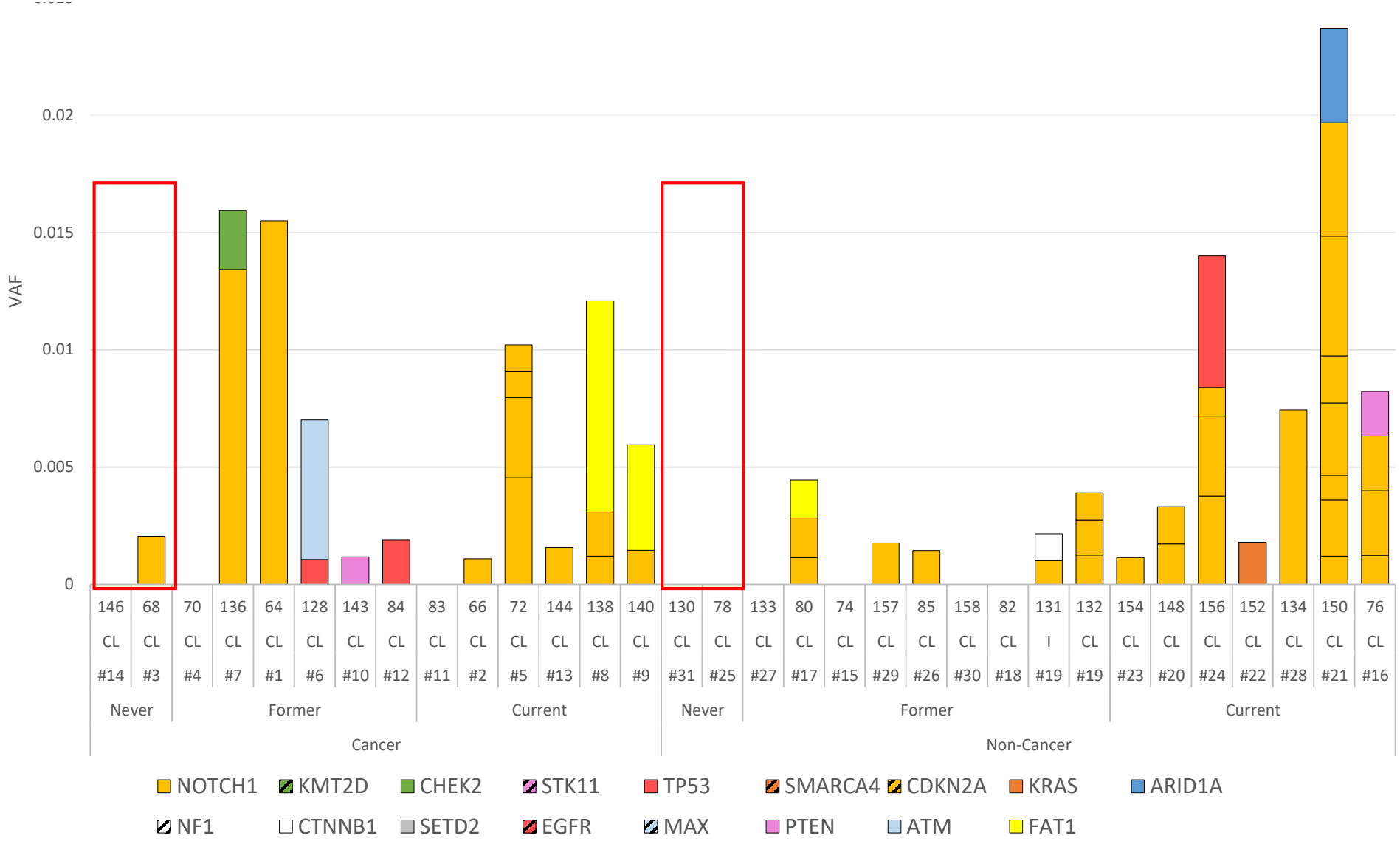
Smoking status influences selection for oncogenic variants



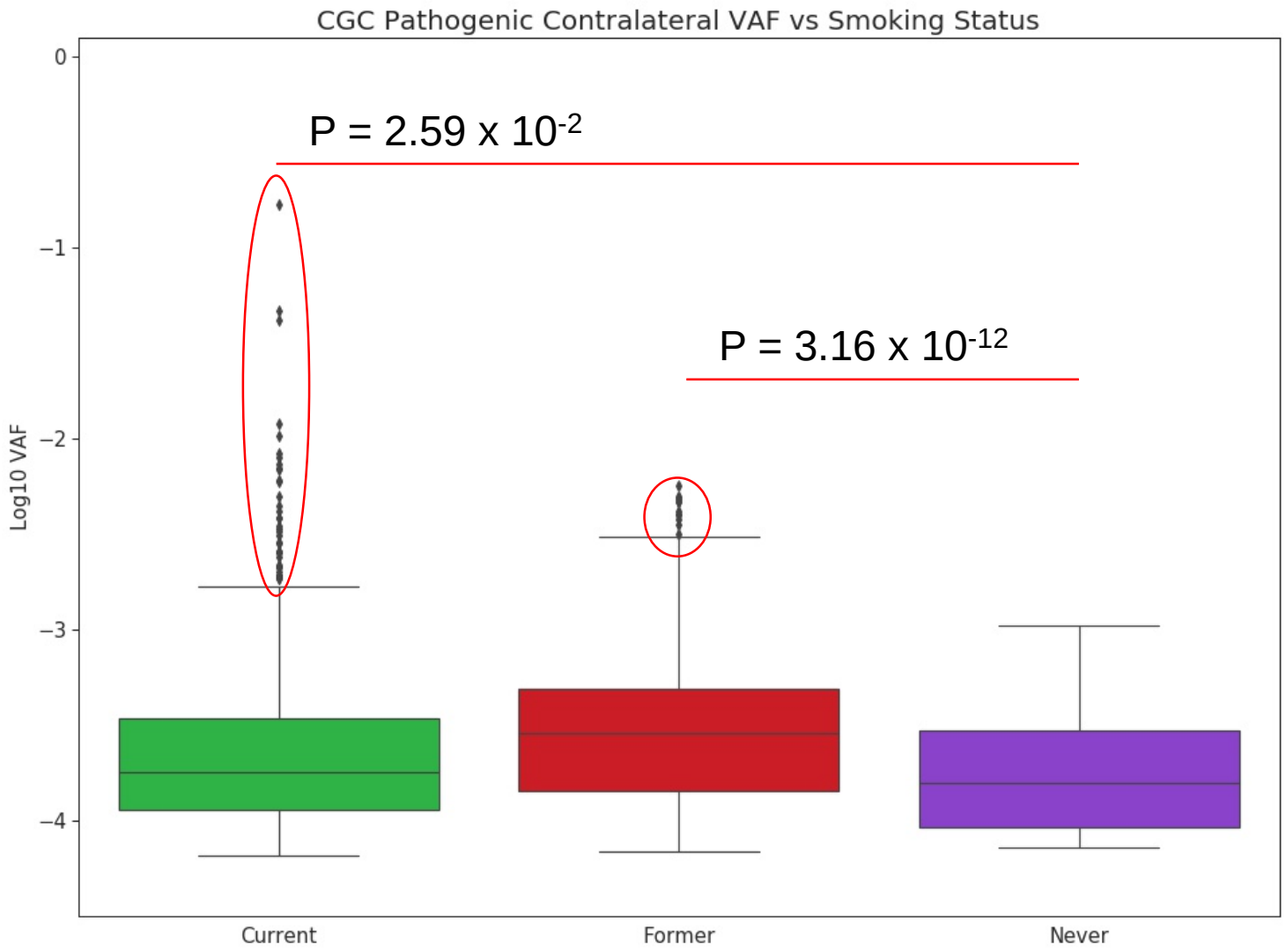
- *Sample ID*
- *Smoking Status*


Mutational Load - SNVs
(Contralateral)
Cancer
Non-Cancer
VAF
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
146 68 70 136 64 128 143 84 83 66 72 144 138 140 130 78 133 80 74 157 85 158 82 132 154 148 156 152 134 150 76
CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL CL
#14 #3 #4 #7 #1 #6 #10 #12 #11 #2 #5 #13 #8 #9 #31 #25 #27 #17 #15 #29 #26 #30 #18 #19 #23 #20 #24 #22 #28 #21 #16
Never
Former
Current
Never
Former
Current
TP53
NOTCH1
PIK3CA
CHEK2
KRAS
PTEN
ARID1A
ATM
KEAP1
ALK
ARID2
EGFR
ERBB4
FAT1
KMT2D
NFE2L2
RET
SETPB1
SMAD4
BRAF

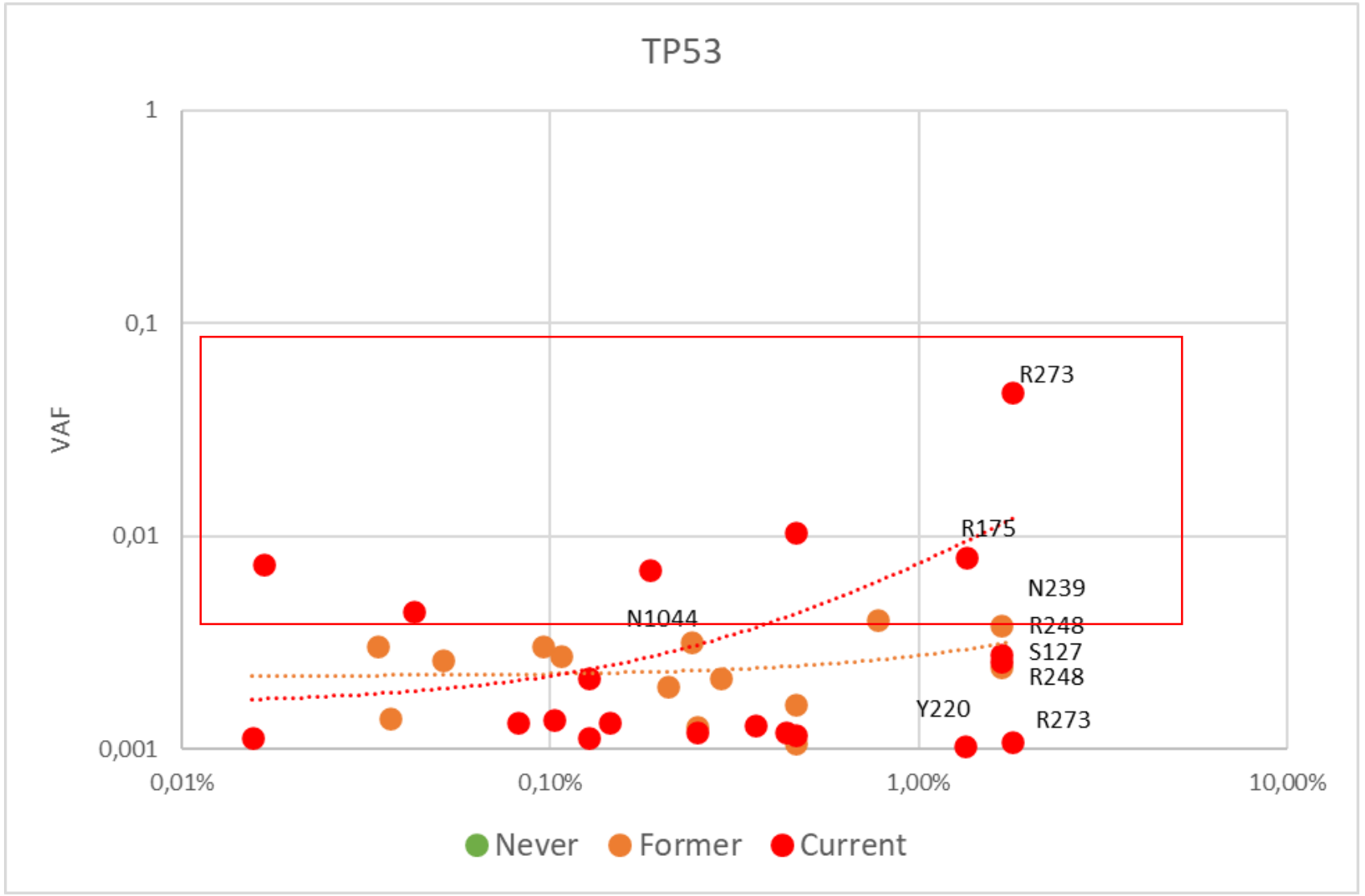
Smoking status influences selection for INDELs in tumor suppressor genes



Smoking status influences selection for oncogenic variants



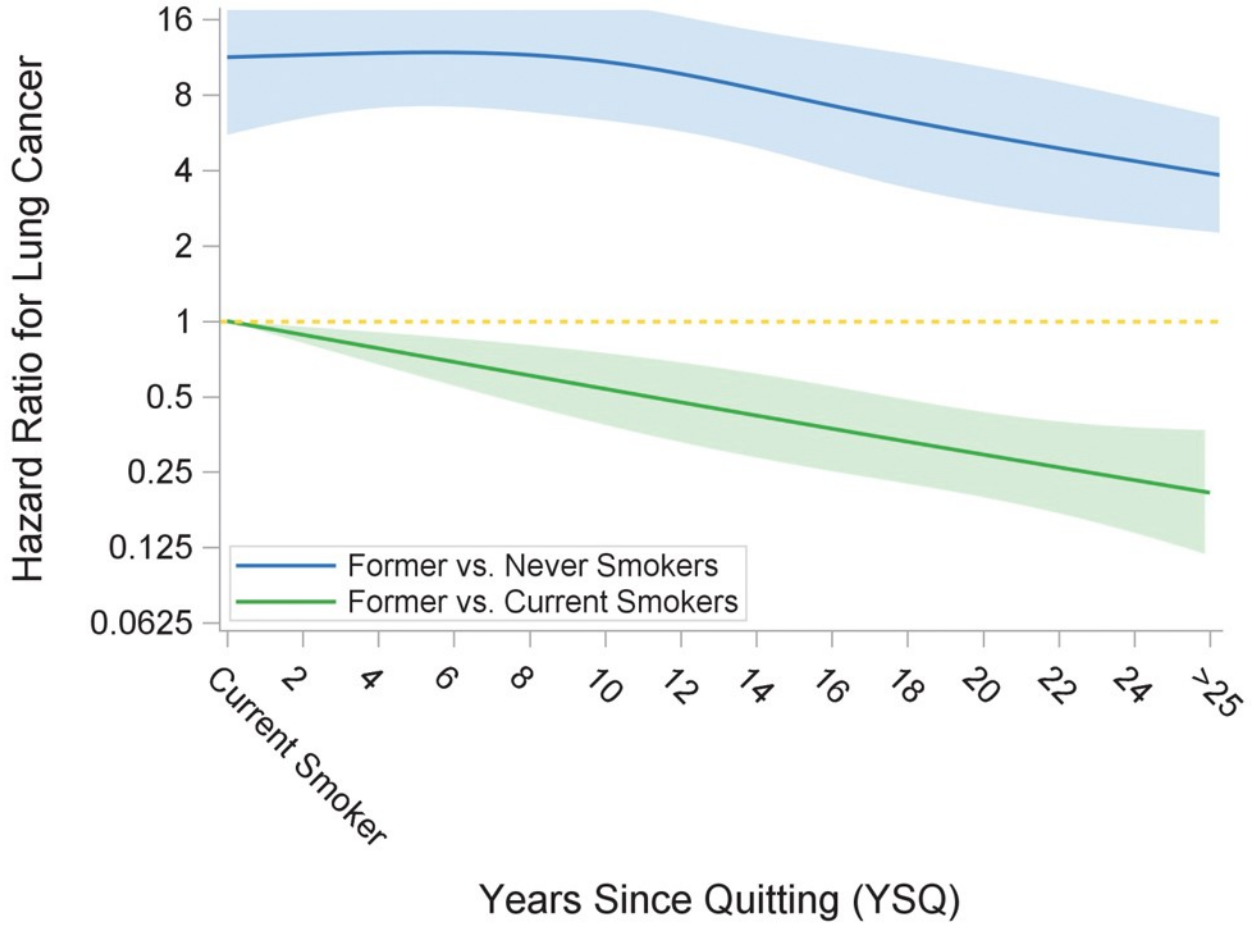
Does quitting smoking reduce selection for the most common mutations in TP53?



Fraction of variants in human cancers

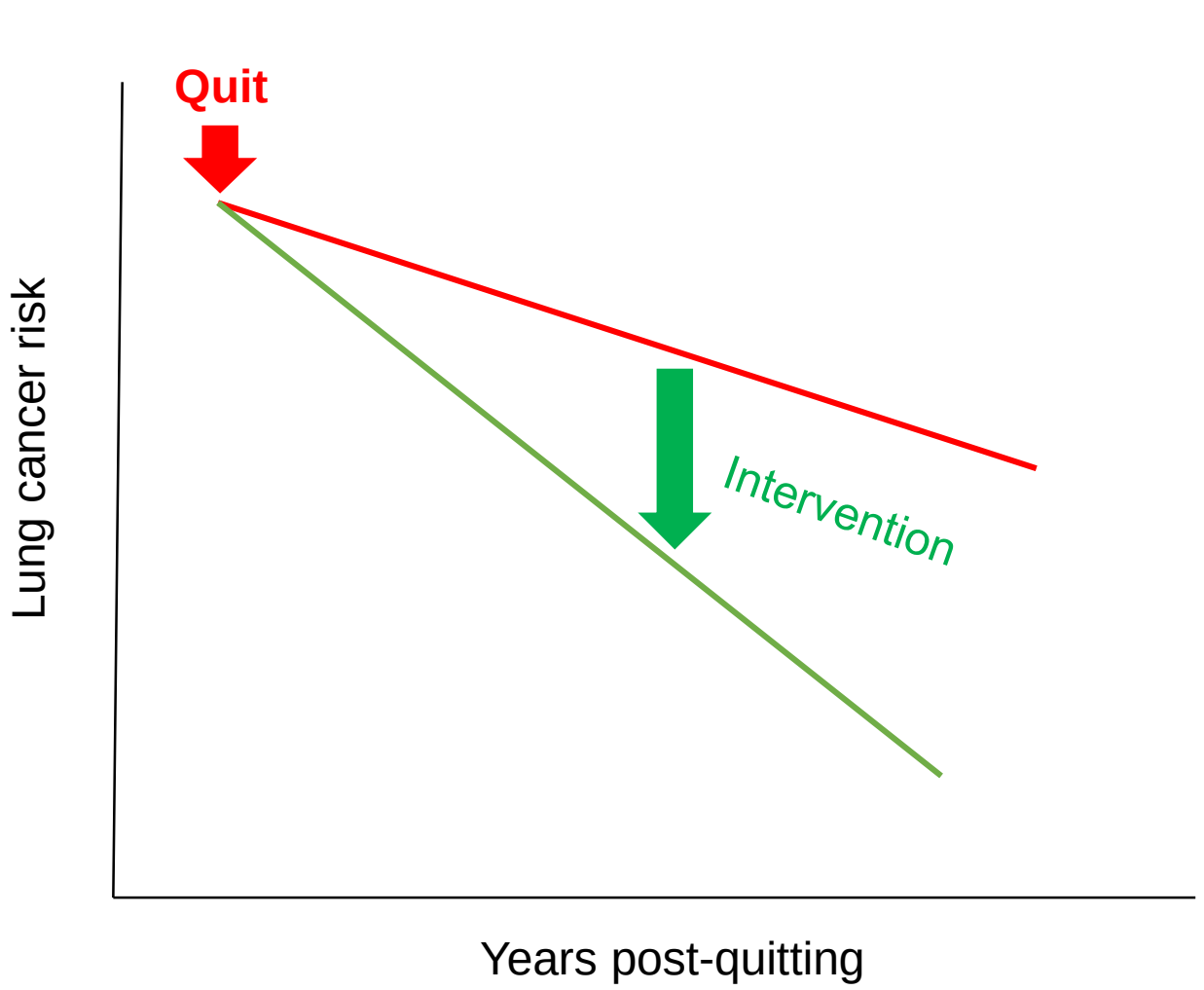
- Smoking promotes selection for oncogenic variants
- Quitting smoking may *reverse* selection for oncogenic variants
- Can we develop interventions that accelerate the restoration of more normal lung landscapes after quitting?

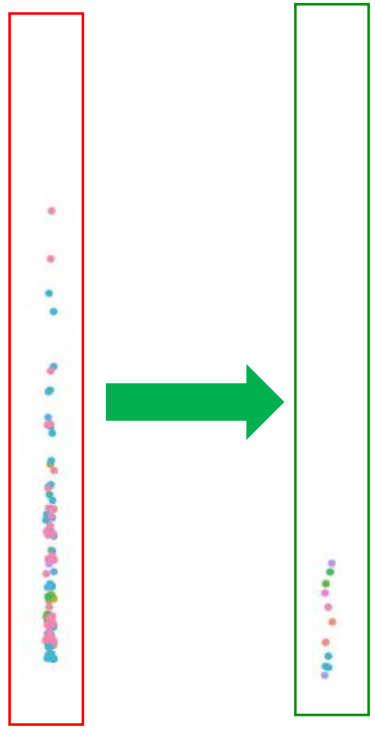
The risk of lung cancer declines with time after quitting



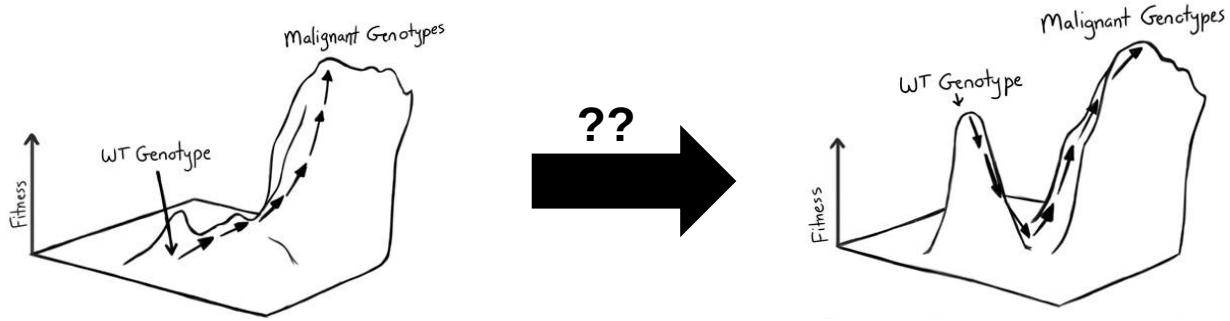
J Natl Cancer Inst, Volume 110, Issue 11, November 2018, Pages 1201–1207, https://doi.org/10.1093/jnci/djy041

Goal: develop interventions to accelerate lung cancer risk post-quitting, and surrogate measures of improvement





How about methods to restore more youthful landscapes?



- Interventions that disfavor malignant evolution?
- Will these also improve tissue function and mitigate other diseases?
- How can we track this restoration? Methods to assess adaptive landscapes?

Efforts to prevent and treat cancer should converge with similar efforts to prevent other aging-associated diseases

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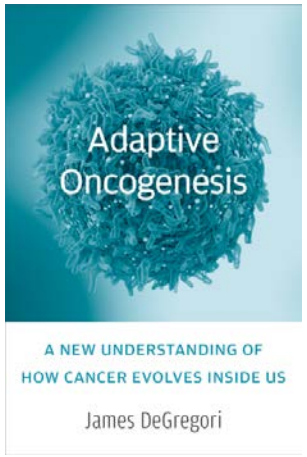

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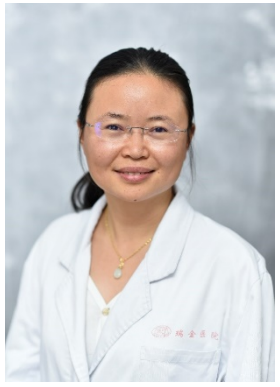

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