All along the watchtower

Immune surveillance and immunotherapy in early- and late-stage tumors

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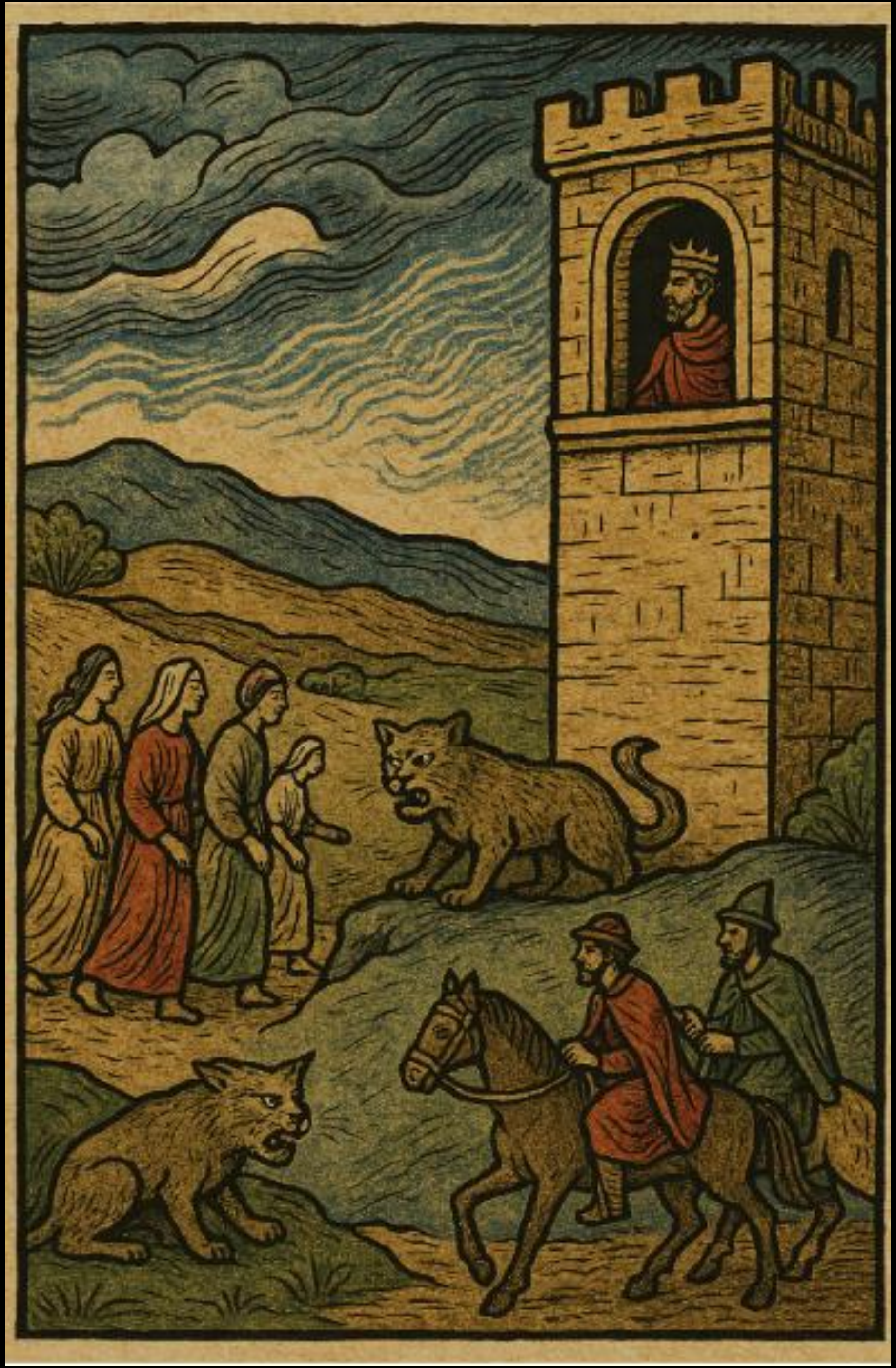
Professor, Dept of Surgery (Head & Neck Service)
Professor, Cancer Biology, GSK Graduate School of Biomedical Sciences
PI, Laboratory of Experimental Cancer Immunogenomics
PD, Clinical Fellowship in Head & Neck Oncologic Surgery

Memorial Sloan Kettering Cancer Center

Gerstner Sloan Kettering
Graduate School of Biomedical Sciences

All along the watchtower / Princes kept the view
While all the women came and went / Barefoot servants, too
Outside in the cold distance / A wildcat did growl
Two riders were approaching /And the wind began to howl



Agenda for today

Immune surveillance in cancer

Schreiber's model of "immunoediting"

Human evidence for immunoediting
- late stage cancers → immune escape
- immunotherapy-treated cancers → editing / elimination
- early stage cancers → immune equilibrium

Using this knowledge to predict immunotherapy response

First speculation of immune surveillance in cancer – 70 years ago

BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 6 1957

CANCER—A BIOLOGICAL APPROACH

I. THE PROCESSES OF CONTROL

BY

Sir MACFARLANE BURNET, M.D., F.R.S.

Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

The understanding and control of cancer is the most urgent problem of medicine to-day. The volume of research on the subject, particularly in America, is vast and heavily biased in two "practical" directions. There is a strong tendency to concentrate on investigations that may provide leads (*a*) to the elaboration of tests for the early diagnosis of cancer, and (*b*) to its cure by non-surgical means. This has led perhaps to an undue interest in the biochemical aspects and especially the enzymic activities of tumour cells. Clearly if a chemotherapeutic substance is to be found it will be something which can differentially inhibit some processes by which tumour cells differ from normal cells. Such a bias is both inevitable and desirable, but it should have no influence on any attempts to gain a clear picture of the process in terms of general biological concepts.

Scientists may be divided into three groups. There are those, like myself, who believe that at every stage in scientific development it is necessary to provide the best available generalizations as a guide to effective work, both in the application of knowledge to human needs and in the planning of future research. At the other extreme are those who feel that the only valuable scientific activity is to concentrate on some significant facet of knowledge until the facts are incontrovertible and are expressible in some general statement, preferably mathematical in form, that is acceptable to all competent workers. Then we have available a defined unit of knowledge which can be used *reliably* when the time comes to apply the knowledge in any field where it is required. The great majority of scientists take an intermediate position, usually finding their immediate interest in the detailed study of a chosen field, but interested in learning of the emergence of general pictures in the various wider fields.

The present approach to a discussion of the general

growth is *growth* of cells free from the normal *control* exercised by the organism as a whole. Experience of tissue culture suggests that most or all mammalian cells have a capacity for growth when provided with appropriate nutrients. The real problem of cancer is then to understand the processes of control by which normal cells from the fertilized ovum to the end of life are maintained in morphological and functional condition appropriate to the needs of the organism at the time. Perhaps it should be stressed how much more complex and difficult to understand are the processes by which a finger retains its character than what is happening in a carcinoma of the lung. Cancer is a negative condition—a manifestation of the breakdown in one or more aspects of the positive control that welds the cells of the body into a single functioning unit—the organism as a whole.

The failure in cancer is due not to any weakness of the organism but to a change in the character of the cells rendering them in one way or another insusceptible to the normal control.

This statement is self-evident when we consider the phenomena of metastasis and experimental transplantation. When cells from a gastric carcinoma produce metastases in the liver there is nothing to suggest any weakness in the control of liver cells. The secondary nodules are clearly due to cells from the primary tumour. This is even more clearly seen in the case of experimental transplants to animals homozygous with the original host of the tumour. The same two sets of phenomena indicate also that the change in the cells is something handed on from one generation of cells to the next. In the broad sense of the term the change is a genetic one. It is immaterial at the moment whether investigation will in any given case eventually give a more precise label to the genetic change, whether it

…the failure of such a mechanism might be one of the factors permitting the emergence of clinical cancer. A decline in immunological reactivity with age could therefore contribute to the increased incidence of malignant disease in later life.

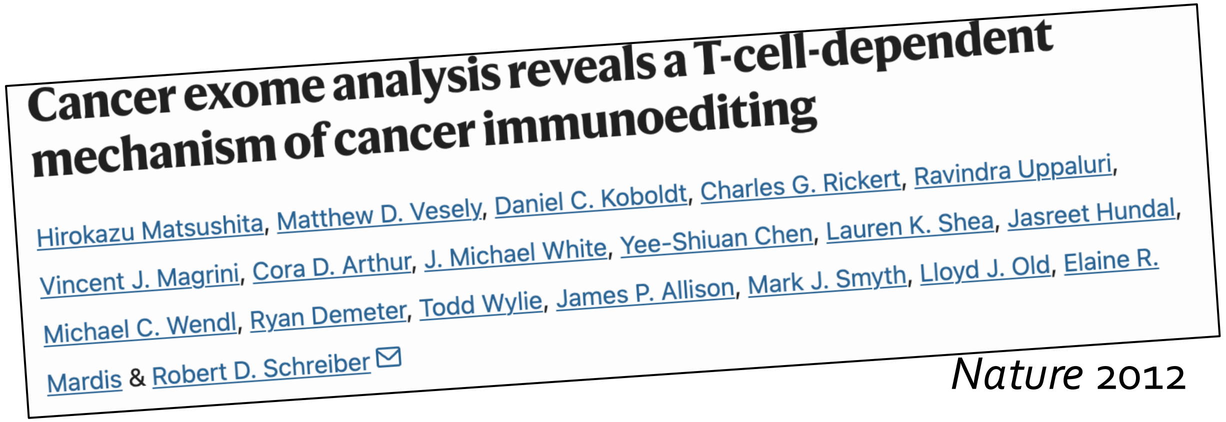
…small accumulations of tumour cells may develop and, because of their possession of new antigenic characters, be destroyed by immunological mechanisms before they become clinically evident.

If this were so, the elimination of nascent tumour cells would be a function of the immune response comparable to the rejection of homografts. Such a mechanism might well account for the failure of many potential neoplasms to progress beyond the microscopic stage.

Adaptive immunity maintains occult cancer in an equilibrium state

Catherine M. Koebel[1], William Vermi[1,2], Jeremy B. Swann[3,4], Nadeen Zerafa[3], Scott J. Rodig[5], Lloyd J. Old[6], Mark J. Smyth[3,4]* & Robert D. Schreiber[1]*

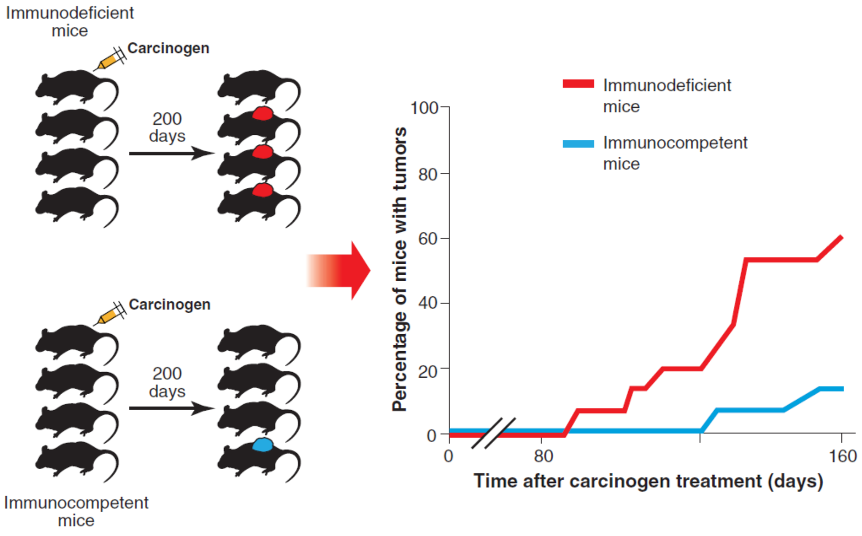
Nature 2007

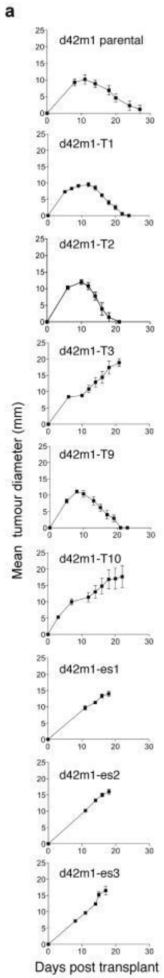


Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting

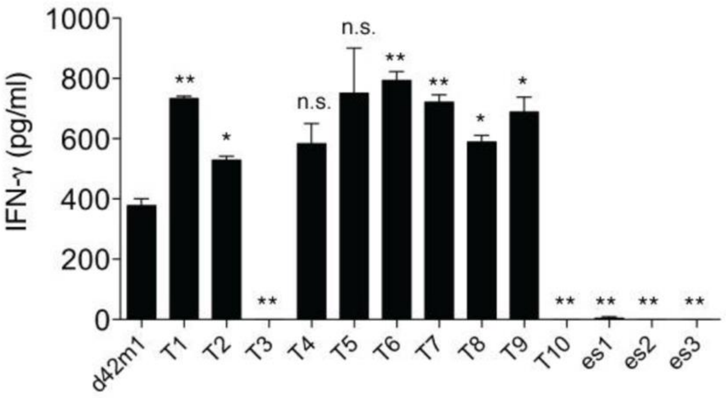
Hirokazu Matsushita, Matthew D. Vesely, Daniel C. Koboldt, Charles G. Rickert, Ravindra Uppaluri, Vincent J. Magrini, Cora D. Arthur, J. Michael White, Yee-Shiuan Chen, Lauren K. Shea, Jasreet Hundal, Michael C. Wendl, Ryan Demeter, Todd Wylie, James P. Allison, Mark J. Smyth, Lloyd J. Old, Elaine R. Mardis & Robert D. Schreiber ✉

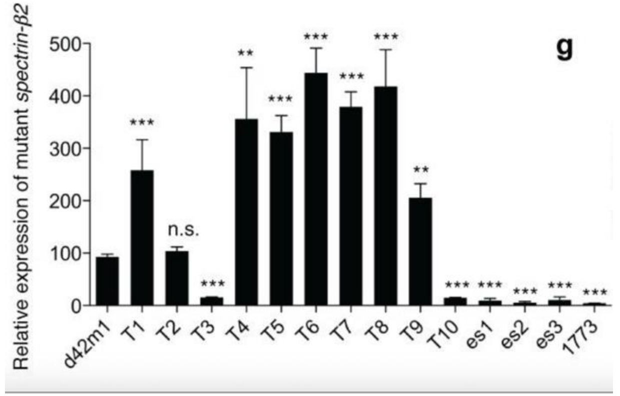
Nature 2012





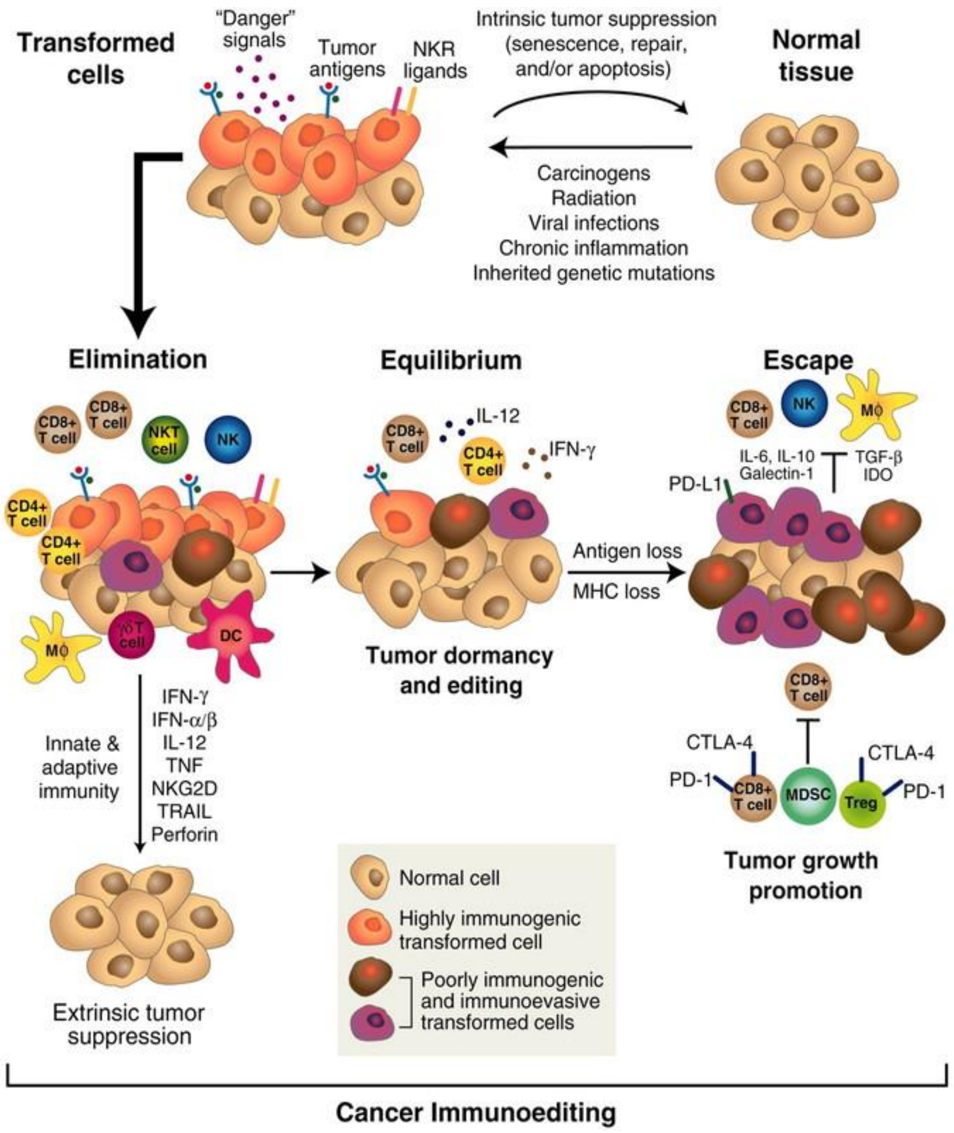
Cultured against a specific CTL clone





Immunodeficient: *Rag2*$^{-/-}$ (no T/B lymphocytes)

Paper #1 Discussion – The 3 E's of Immunoediting

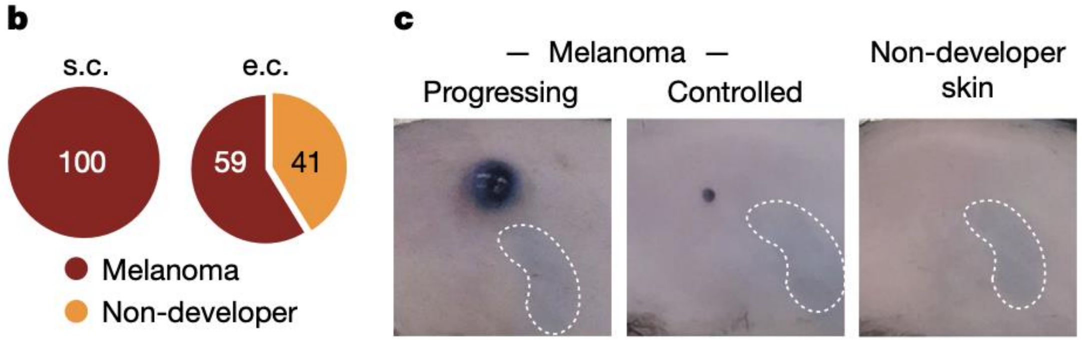


Robert Schreiber and Lloyd Old *Science* 2011

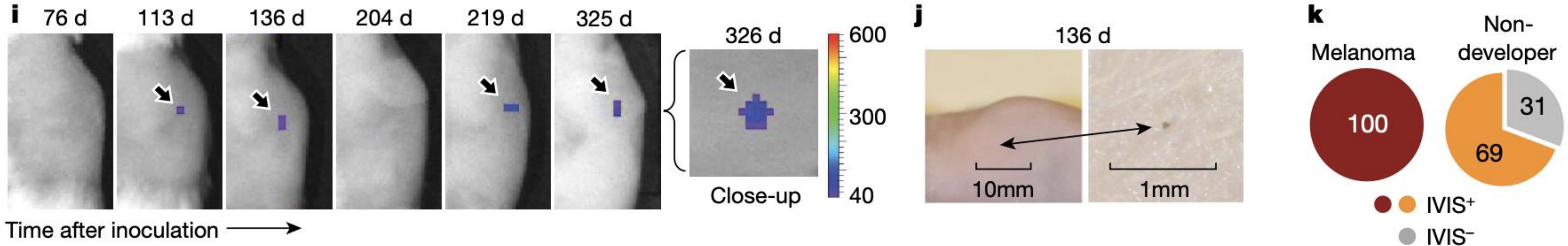
Tissue-resident memory CD8$^+$ T cells promote melanoma–immune equilibrium in skin

Nature 2019

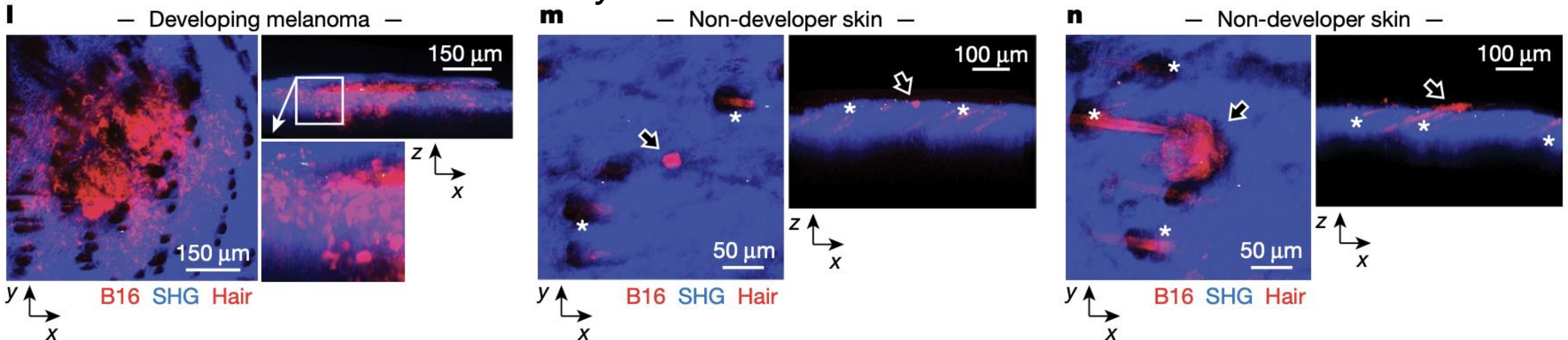
Simone L. Park[1], Anthony Buzzai[2], Jai Rautela[3,4], Jyh Liang Hor[1], Katharina Hochheiser[1,5], Maike Effern[1,6], Nathan McBain[1], Teagan Wagner[2], Jarem Edwards[7,8,9], Robyn McConville[1], James S. Wilmott[8,9], Richard A. Scolyer[8,9,10], Thomas Tüting[11], Umaimainthan Palendira[7,9], David Gyorki[5,12], Scott N. Mueller[1,13], Nicholas D. Huntington[3,4], Sammy Bedoui[1], Michael Hölzel[6], Laura K. Mackay[1,13,14]*, Jason Waithman[2,14]* & Thomas Gebhardt[1,14]*

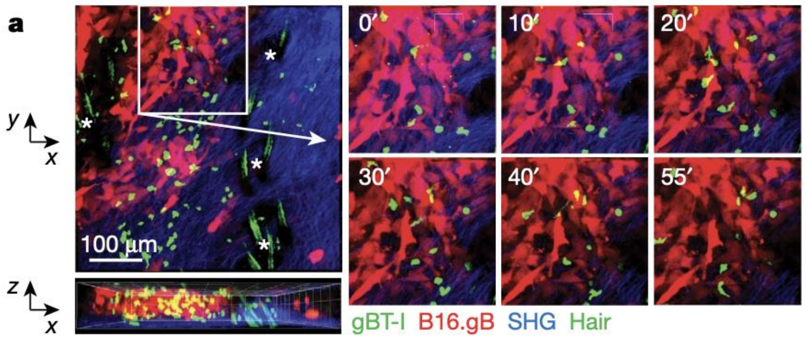


luciferase



mCherry

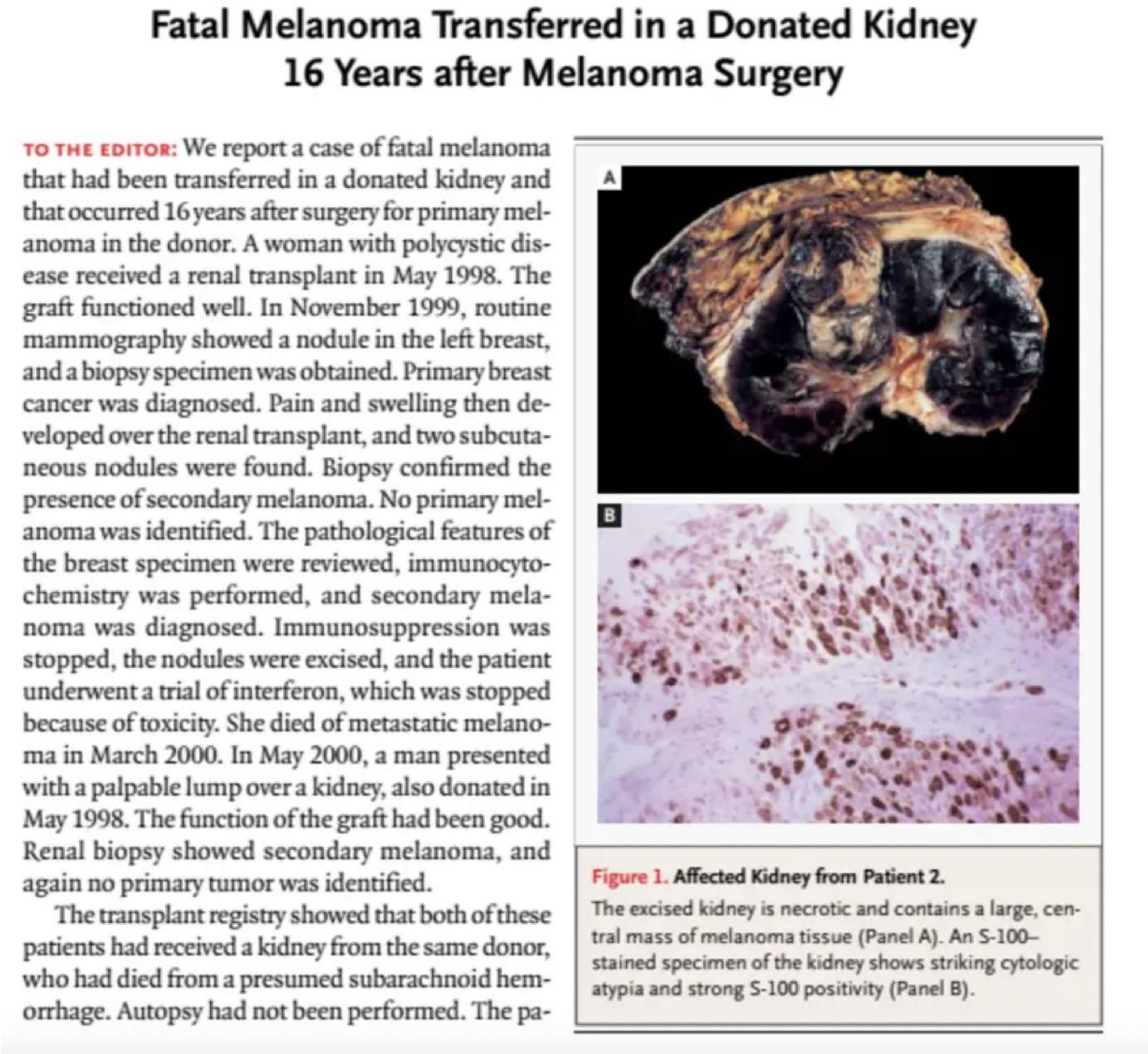




T$_{RM}$ cells survey melanoma in mouse skin

Is there evidence of immunoediting in humans?

Equilibrium?
Elimination?
Escape?



Fatal Melanoma Transferred in a Donated Kidney 16 Years after Melanoma Surgery

TO THE EDITOR: We report a case of fatal melanoma that had been transferred in a donated kidney and that occurred 16 years after surgery for primary melanoma in the donor. A woman with polycystic disease received a renal transplant in May 1998. The graft functioned well. In November 1999, routine mammography showed a nodule in the left breast, and a biopsy specimen was obtained. Primary breast cancer was diagnosed. Pain and swelling then developed over the renal transplant, and two subcutaneous nodules were found. Biopsy confirmed the presence of secondary melanoma. No primary melanoma was identified. The pathological features of the breast specimen were reviewed, immunocytochemistry was performed, and secondary melanoma was diagnosed. Immunosuppression was stopped, the nodules were excised, and the patient underwent a trial of interferon, which was stopped because of toxicity. She died of metastatic melanoma in March 2000. In May 2000, a man presented with a palpable lump over a kidney, also donated in May 1998. The function of the graft had been good. Renal biopsy showed secondary melanoma, and again no primary tumor was identified.

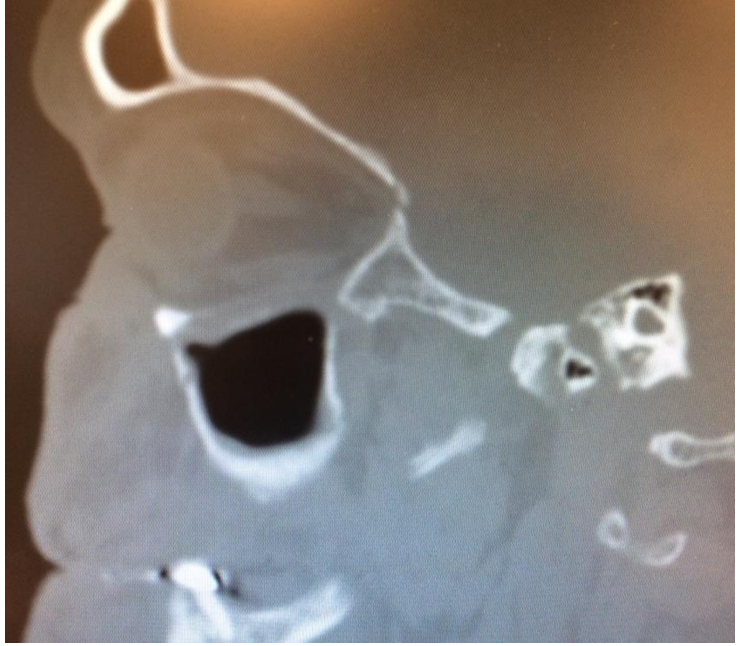
The transplant registry showed that both of these patients had received a kidney from the same donor, who had died from a presumed subarachnoid hemorrhage. Autopsy had not been performed. The pa-

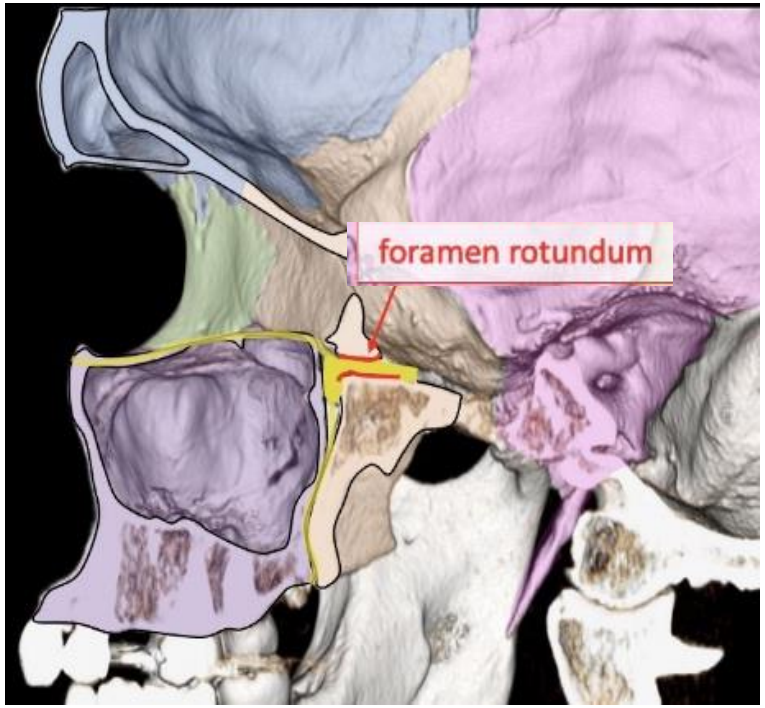
Figure 1. Affected Kidney from Patient 2.

The excised kidney is necrotic and contains a large, central mass of melanoma tissue (Panel A). An S-100–stained specimen of the kidney shows striking cytologic atypia and strong S-100 positivity (Panel B).

NEJM, 2003

Photograph used with consent





Normal, sun-exposed skin: lots of mutations in cancer driver genes

High burden and pervasive positive selection of somatic mutations in normal human skin

Iñigo Martincorena,[1] Amit Roshan,[2] Moritz Gerstung,[1] Peter Ellis,[1] Peter Van Loo,[1,3,4] Stuart McLaren,[1] David C. Wedge,[1] Anthony Fullam,[1] Ludmil B. Alexandrov,[1] Jose M. Tubio,[1] Lucy Stebbings,[1] Andrew Menzies,[1] Sara Widaa,[1] Michael R. Stratton,[1] Philip H. Jones,[2]* Peter J. Campbell[1,5]*

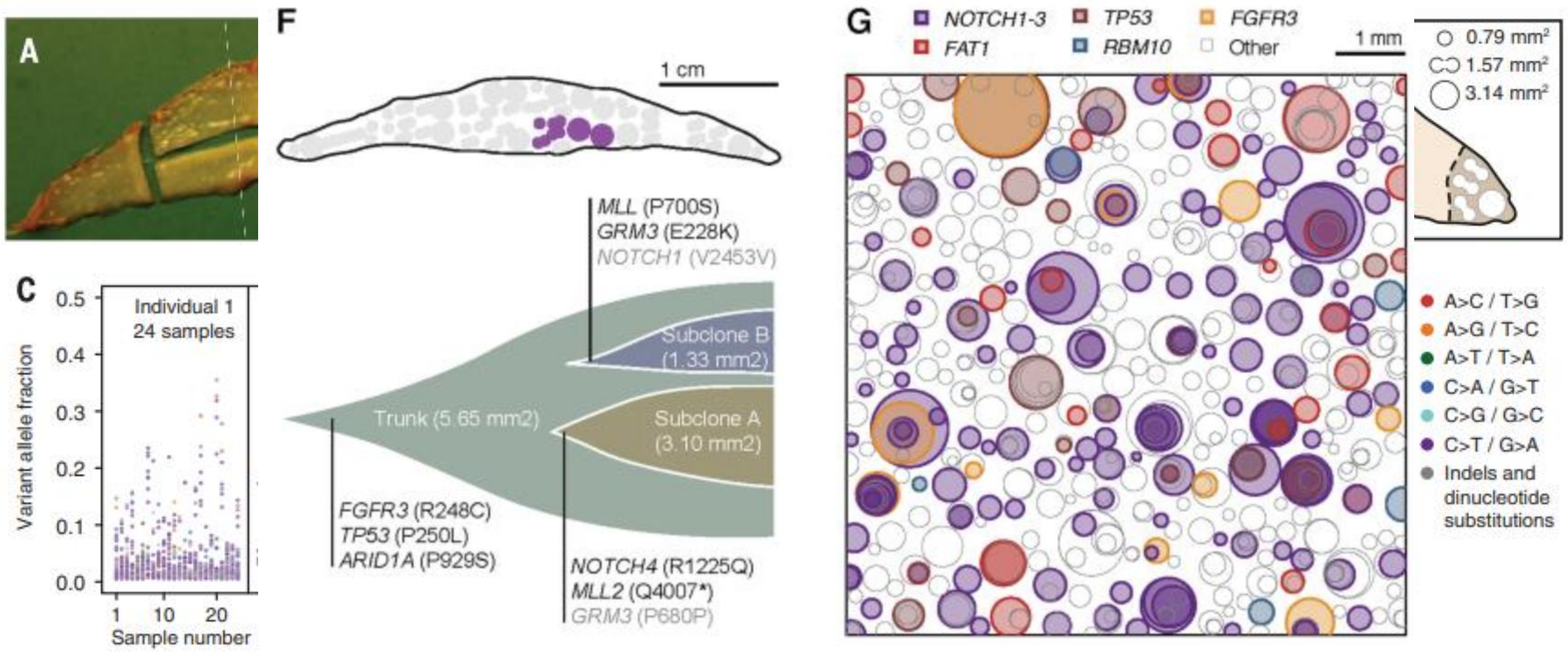
Science 2015

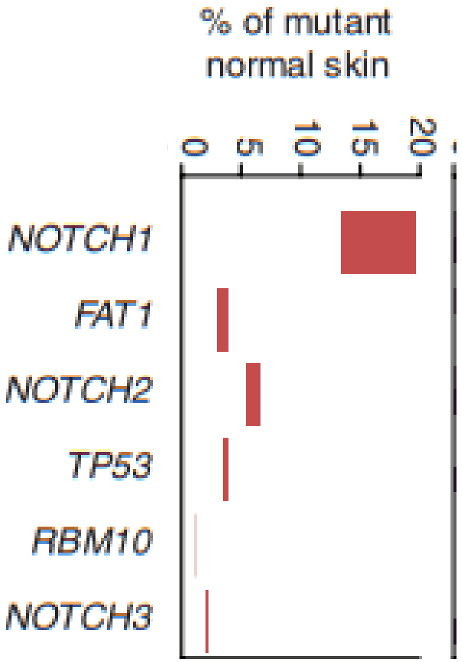
Hundreds of UV-related mutations per cell

… some mutated cells (eg, *TP53*) grow exponentially in UV-exposed skin

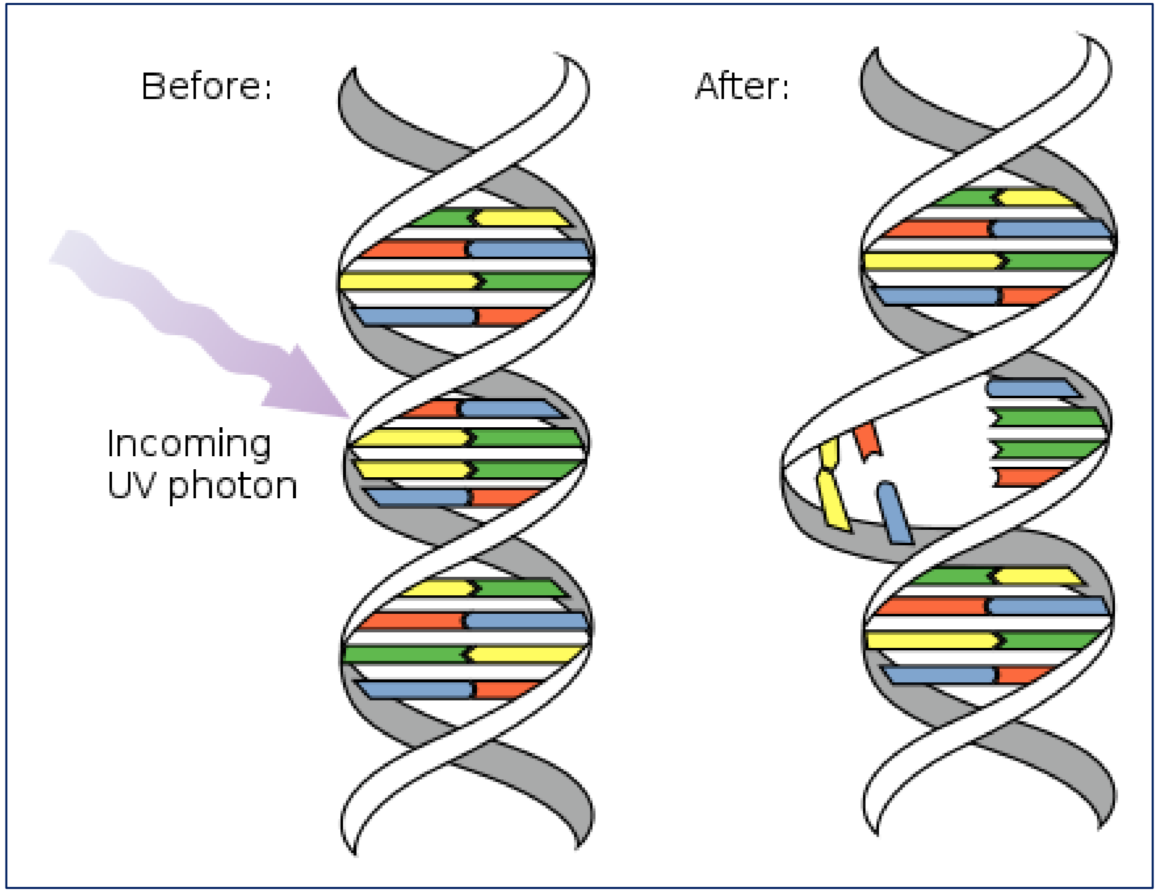
Why do we not all develop skin SCC?

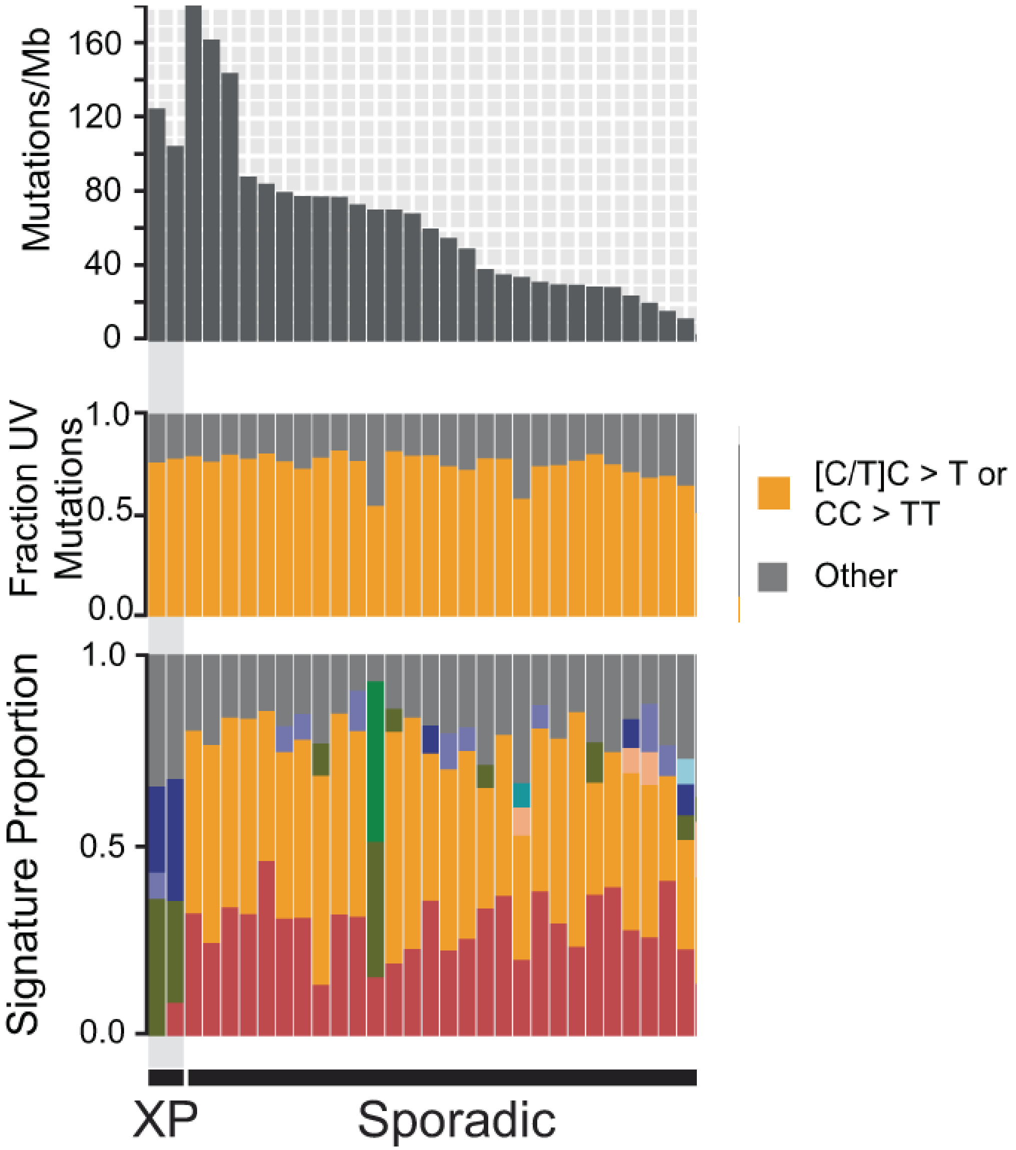
Clue: these clones stay very small





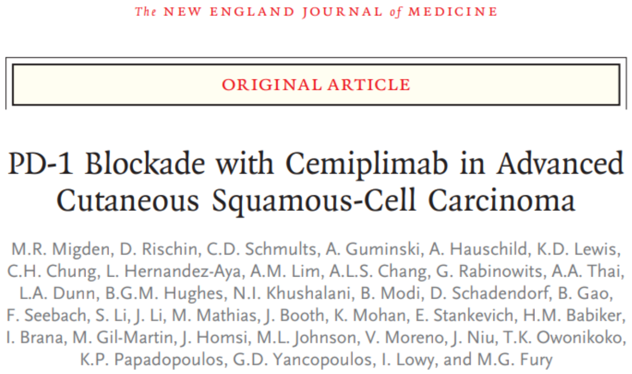
Skin SCCs: many mutations (UV signature)





Chang & Shain, NPJ Genomic Medicine 2021

Cutaneous SCC: high mutation load; highly immune-infiltrated

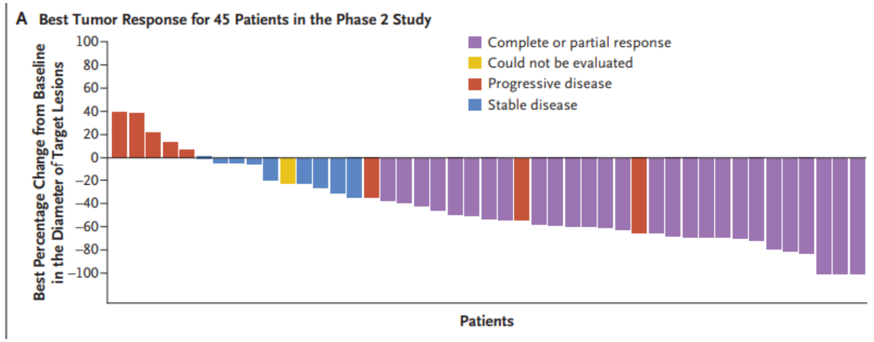


The NEW ENGLAND JOURNAL *of* MEDICINE

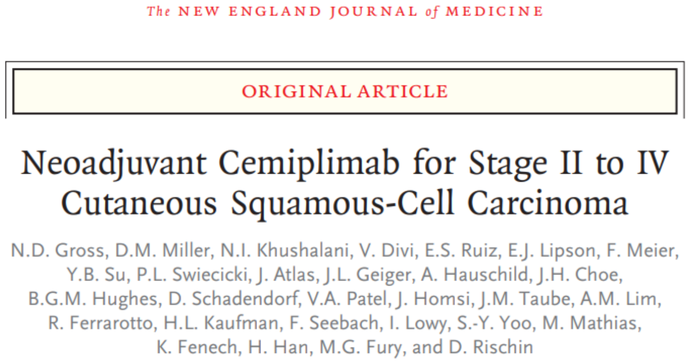
ORIGINAL ARTICLE

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury



47% ORR

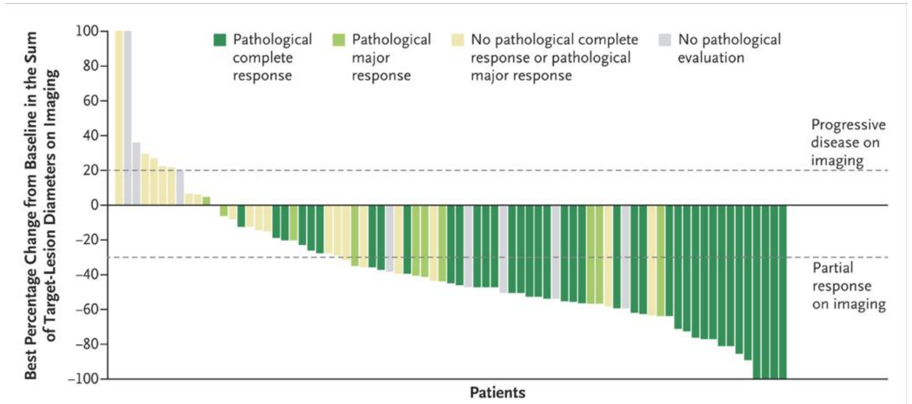


The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

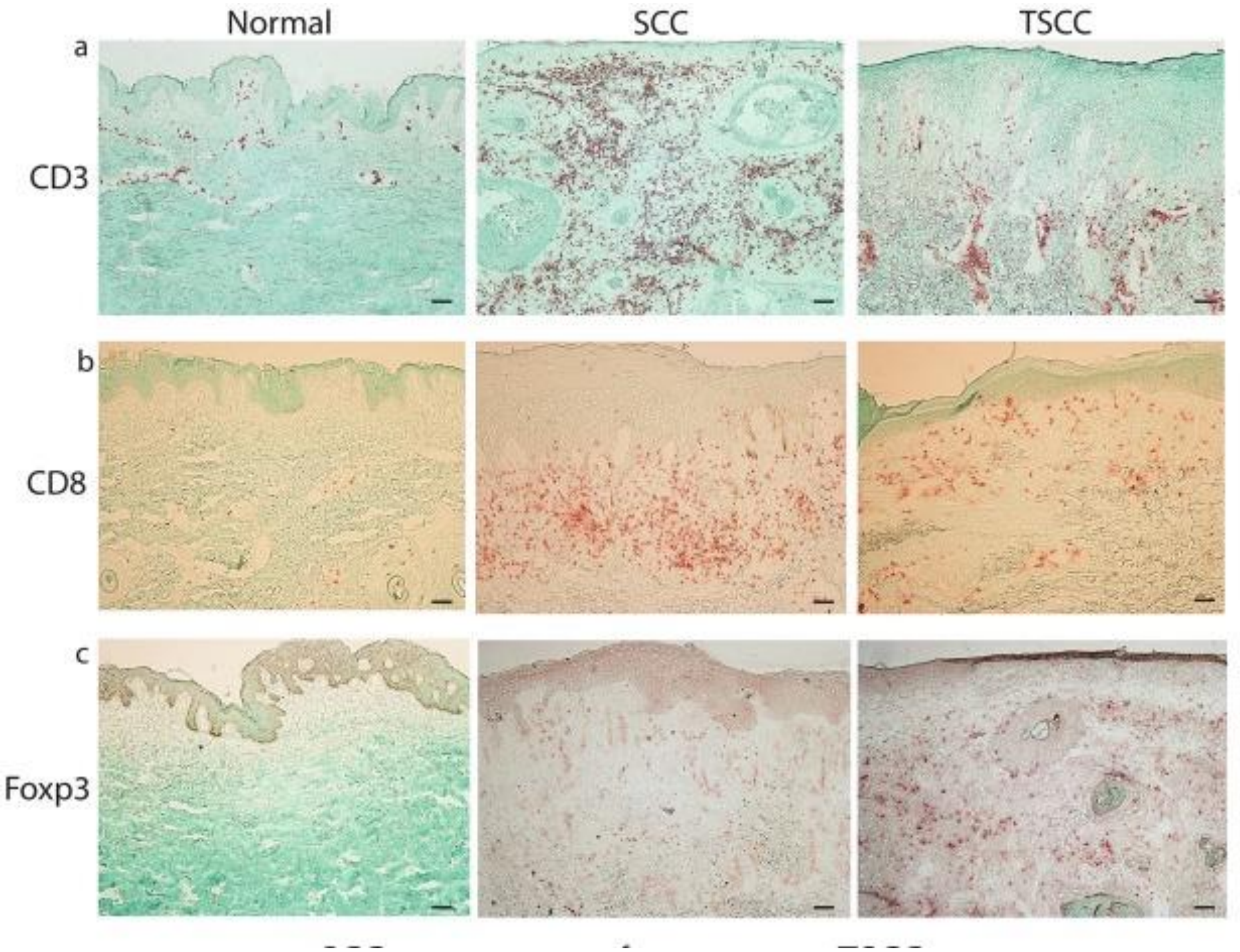
N.D. Gross, D.M. Miller, N.I. Khushalani, V. Divi, E.S. Ruiz, E.J. Lipson, F. Meier, Y.B. Su, P.L. Swiecicki, J. Atlas, J.L. Geiger, A. Hauschild, J.H. Choe, B.G.M. Hughes, D. Schadendorf, V.A. Patel, J. Homsi, J.M. Taube, A.M. Lim, R. Ferrarotto, H.L. Kaufman, F. Seebach, I. Lowy, S.-Y. Yoo, M. Mathias, K. Fenech, H. Han, M.G. Fury, and D. Rischin

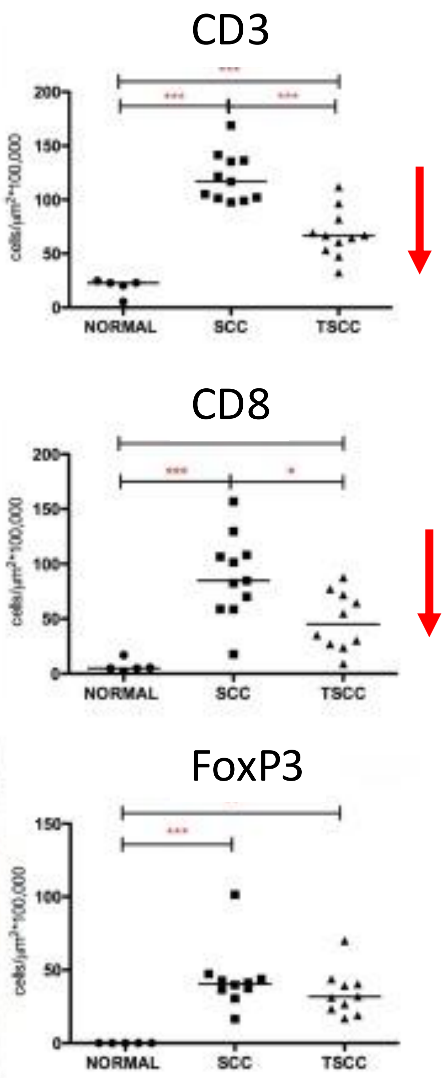


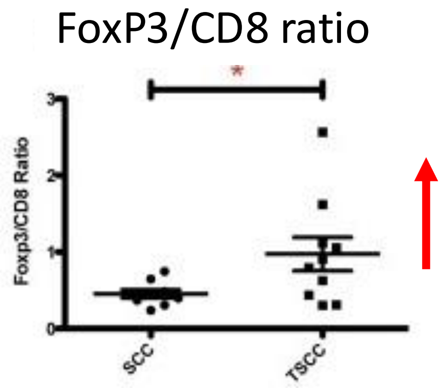
51% pCR

13% major pPR (>90%)

Organ transplant recipients: diminished adaptive immune response

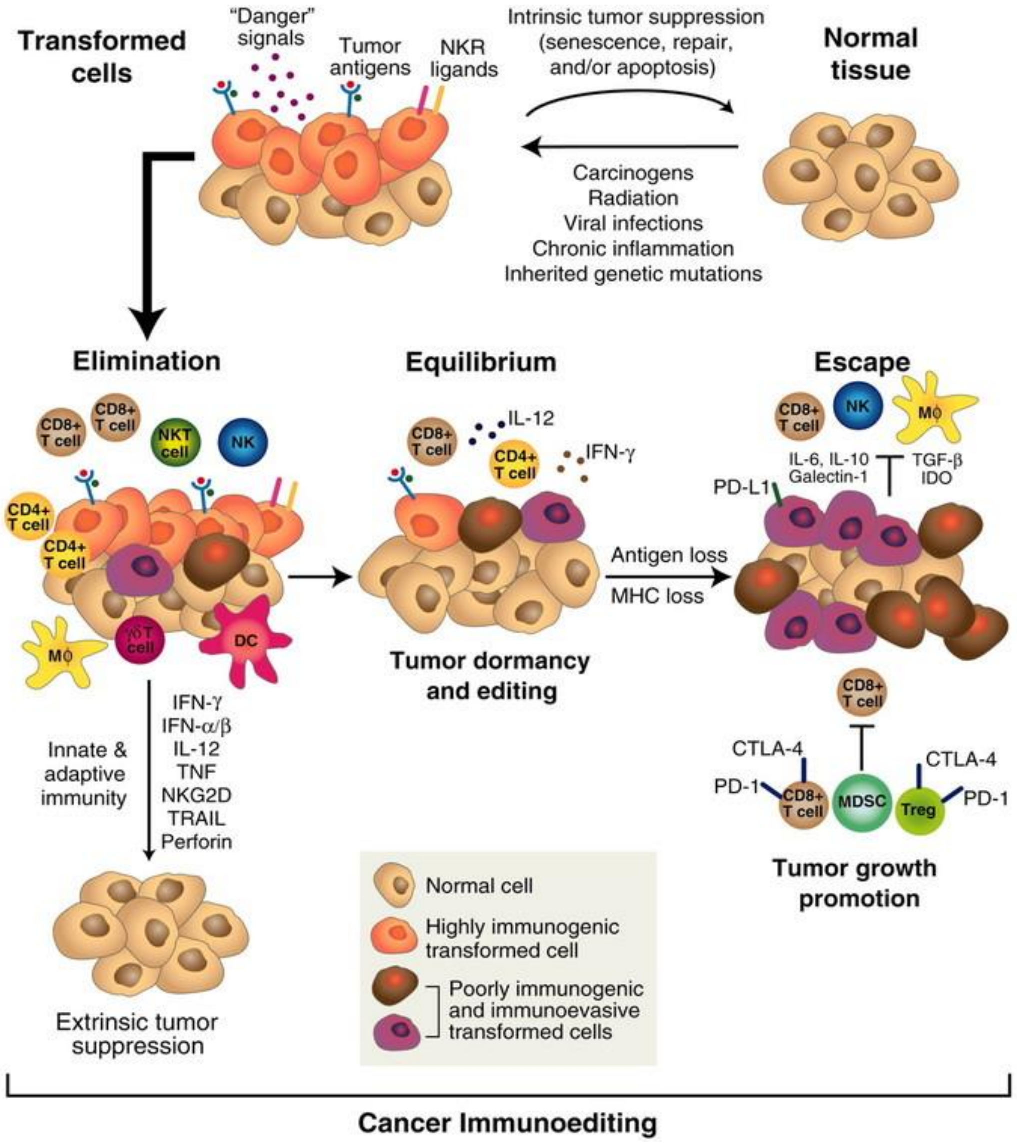






Zhang et al, PLoS One 2013
Rajesh et al, Exp Derm 2022

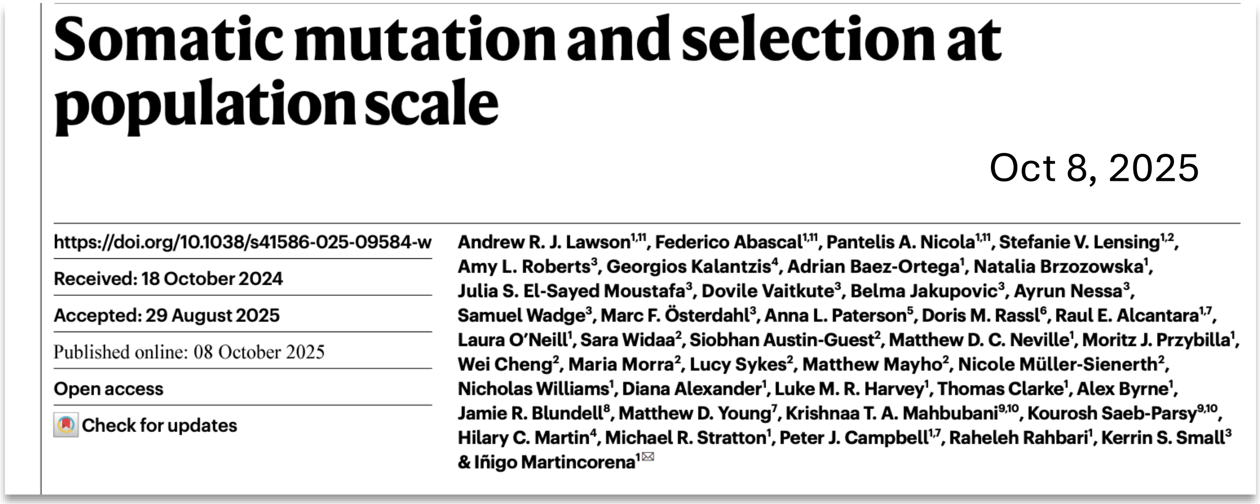
A rare opportunity to observe immune equilibrium



Robert Schreiber and Lloyd Old *Science* 2011

Genomic profiling of 1042 buccal swabs from healthy donors

nature



Somatic mutation and selection at population scale

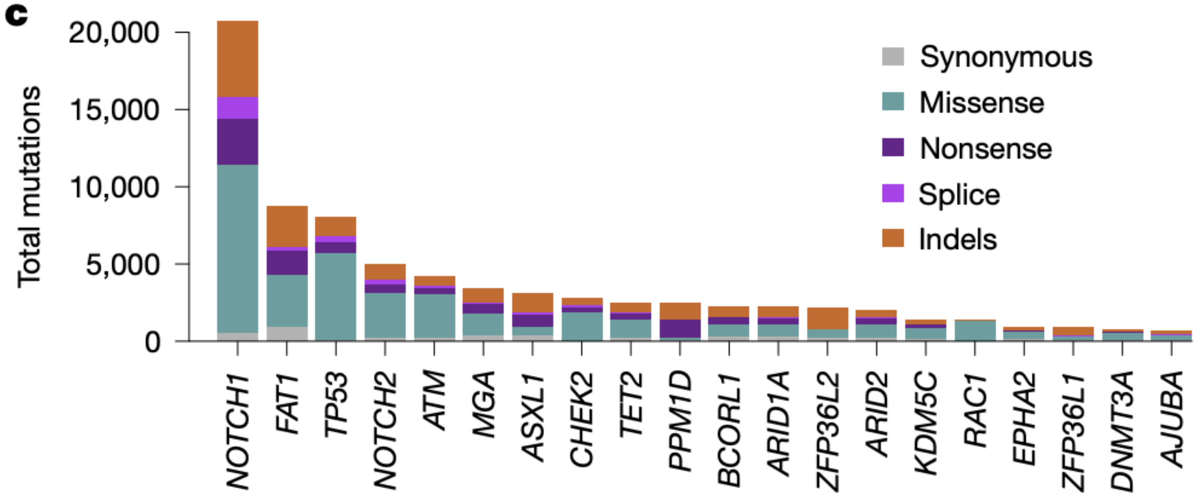
Oct 8, 2025

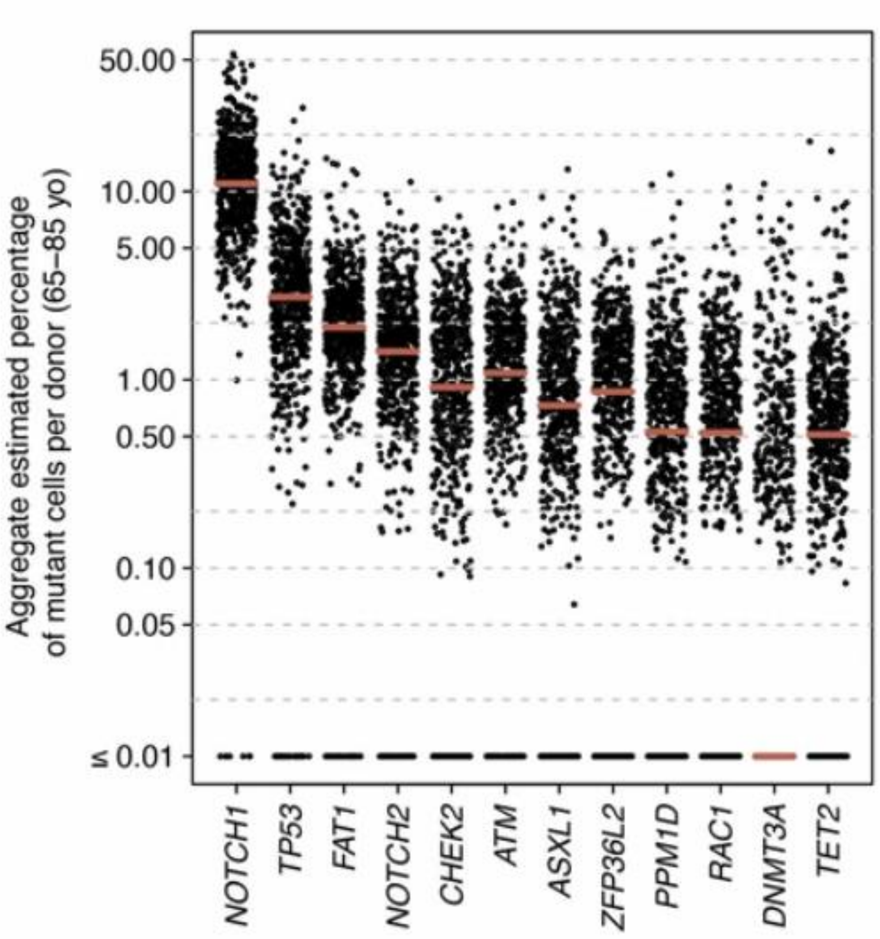
https://doi.org/10.1038/s41586-025-09584-w

Received: 18 October 2024

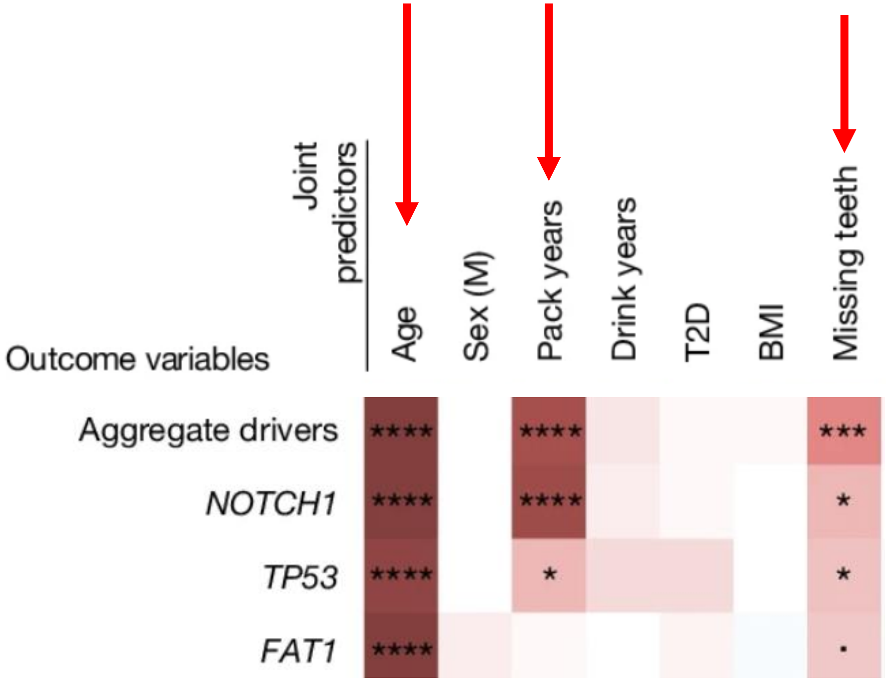
Accepted: 29 August 2025

Andrew R. J. Lawson[1,11], Federico Abascal[1,11], Pantelis A. Nicola[1,11], Stefanie V. Lensing[1,2], Amy L. Roberts[3], Georgios Kalantzis[4], Adrian Baez-Ortega[1], Natalia Brzozowska[1], Julia S. El-Sayed Moustafa[3], Dovile Vaitkute[3], Belma Jakupovic[3], Ayrun Nessa[3], Samuel Wadge[3], Marc F. Österdahl[3], Anna L. Paterson[5], Doris M. Rassl[6], Raul E. Alcantara[1,7], Laura O'Neill[1], Sara Widaa[2], Siobhan Austin-Guest[2], Matthew D. C. Neville[1], Moritz J. Przybilla[1], Wei Cheng[2], Maria Morra[2], Lucy Sykes[2], Matthew Mayho[2], Nicole Müller-Sienerth[2], Nicholas Williams[1], Diana Alexander[1], Luke M. R. Harvey[1], Thomas Clarke[1], Alex Byrne[1], Jamie R. Blundell[8], Matthew D. Young[7], Krishnaa T. A. Mahbubani[9,10], Kourosh Saeb-Parsy[9,10], Hilary C. Martin[4], Michael R. Stratton[1], Peter J. Campbell[1,7], Raheleh Rahbari[1], Kerrin S. Small[3] & Iñigo Martincorena[1]✉

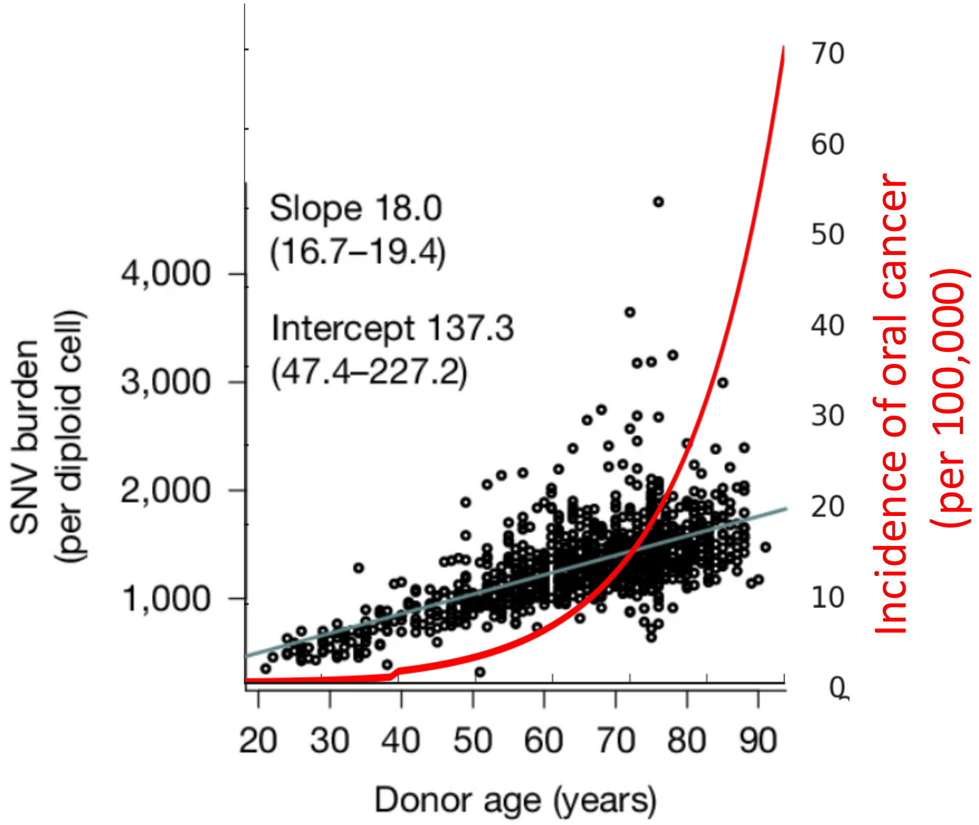




Increasing mutations in oral epithelial cells with age …



Outcome variables \ Joint predictors	Age	Sex (M)	Pack years	Drink years	T2D	BMI	Missing teeth
Aggregate drivers	****		****				***
NOTCH1	****		****				*
TP53	****		*				*
FAT1	****						·



Mutagenesis does not fully explain cancer development

10-20% of buccal epithelial cells carry cancer driver mutations by age 65

1) Why don't 10-20% of people get oral cavity squamous cell cancer?

2) If mutations provide a fitness advantage, why don't tumors just keep mutating?

10-20% of buccal epithelial cells carry cancer driver mutations by age 65

1) Why don’t 10-20% of people get oral cavity squamous cell cancer?

2) If mutations provide a fitness advantage, why don’t tumors just keep mutating?

Constraints?

are more mutations immunogenic?
does immune surveillance keep these cells in check?
[other fitness tradeoffs from deleterious mutations?]

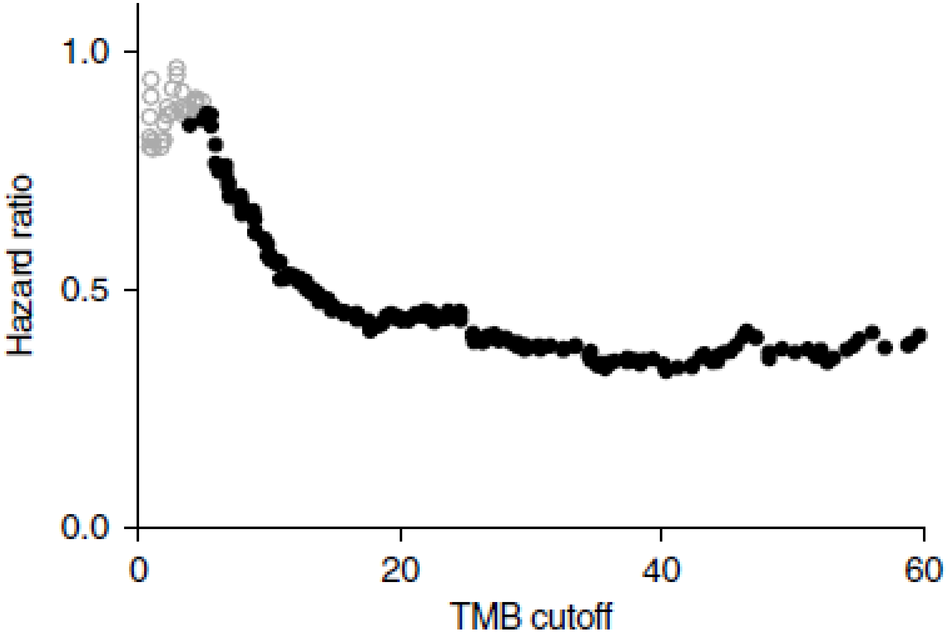
Hypothesis:

If some mutations generate immunogenic neoantigens …

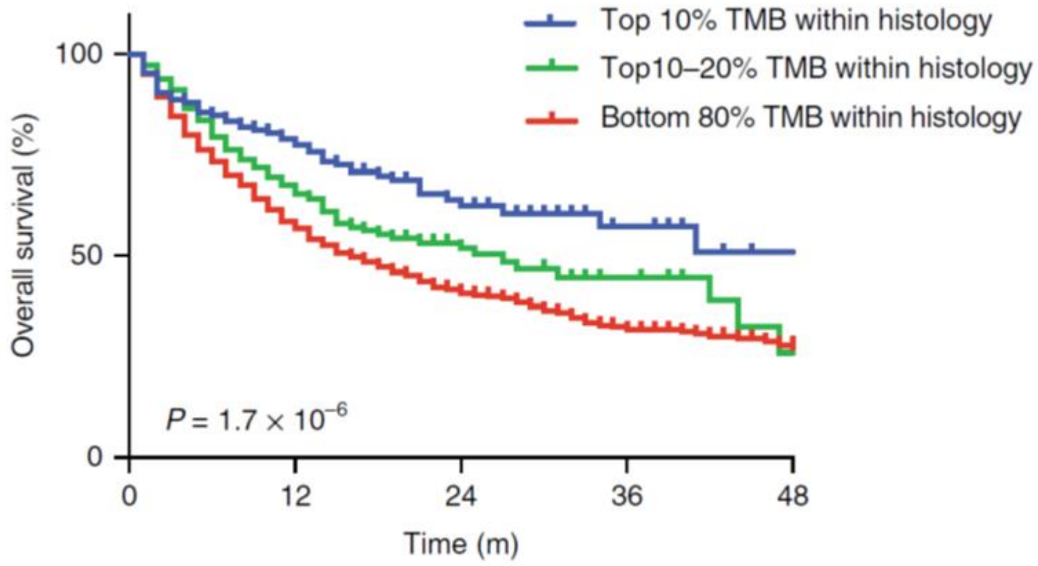
More highly-mutated tumors will be more poised to respond to immunotherapy

More mutations → more benefit from checkpoint inhibitors
1662 ICI-treated patients at MSK

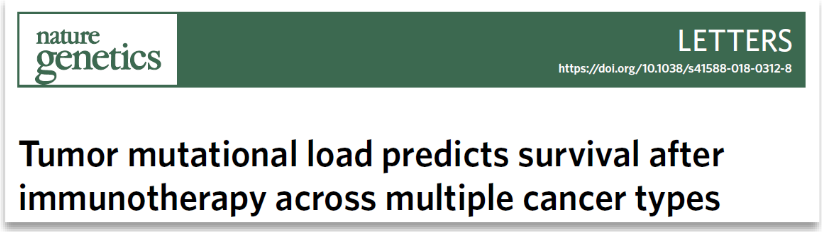
HR for survival with ICI therapy



Overall survival after ICI initiation



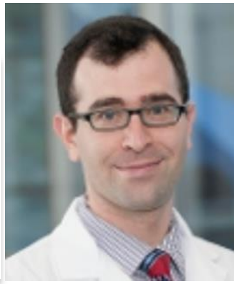
Robbie Samstein (*Nature Genetics* 2019)


nature genetics

LETTERS

https://doi.org/10.1038/s41588-018-0312-8

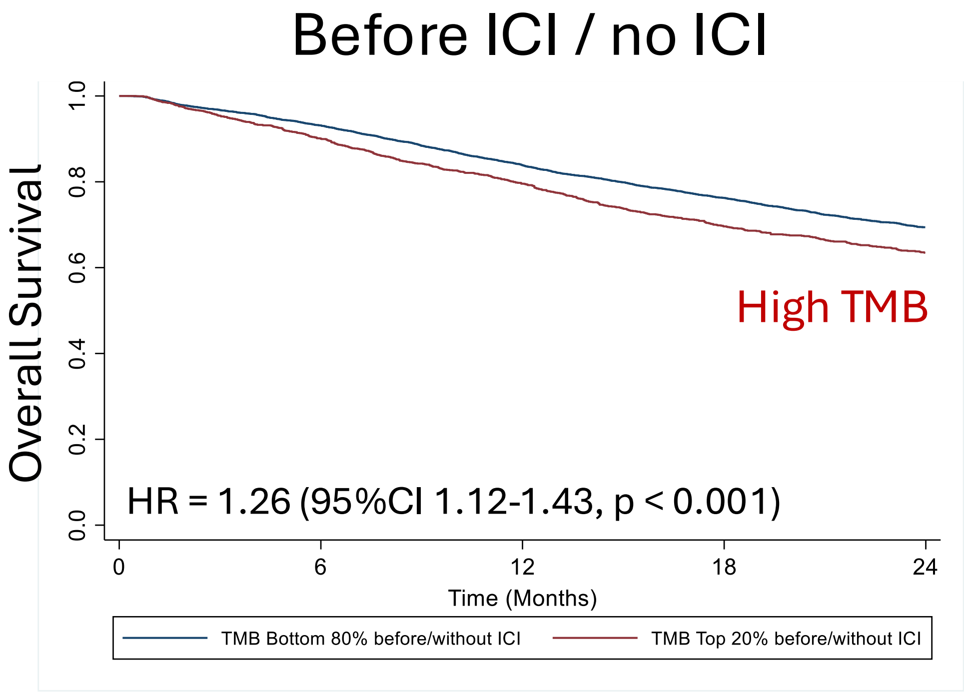
Tumor mutational load predicts survival after immunotherapy across multiple cancer types

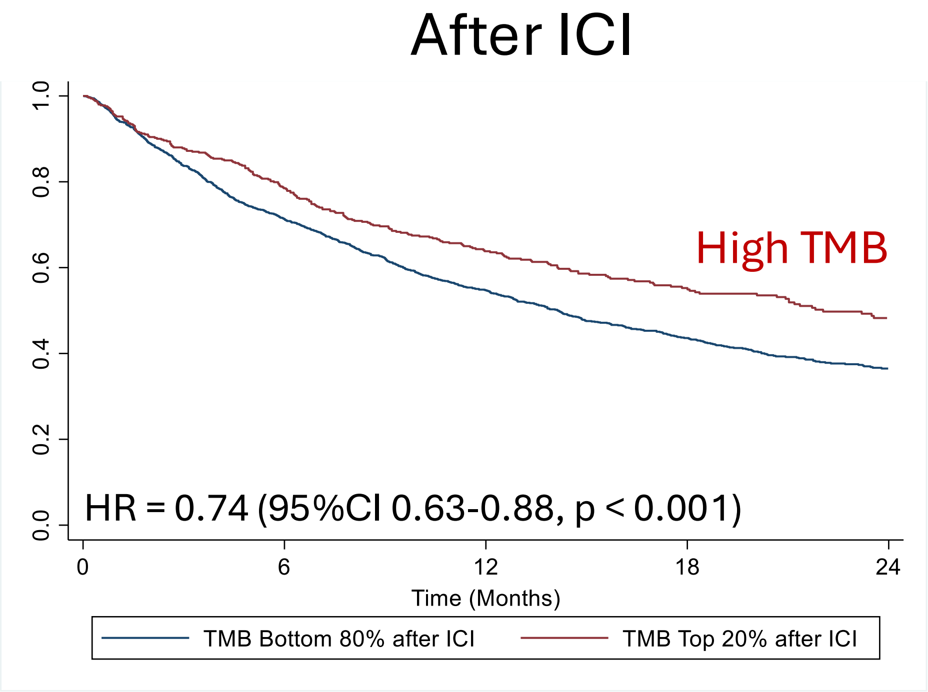


ICI, immune checkpoint inhibitors

More mutations → only beneficial in immunotherapy context

Overall Survival in 10,233 patients (2,022 ICI-treated)





ICI: immune (T cell) checkpoint inhibitor

Note: *ICI(t)* was modeled with a time-dependent covariate

nature genetics

LETTERS

The association between tumor mutational burden and prognosis is dependent on treatment context

Cristina Valero (*Nature Genetics* 2021)

Is there direct evidence of immune editing in human tumors?

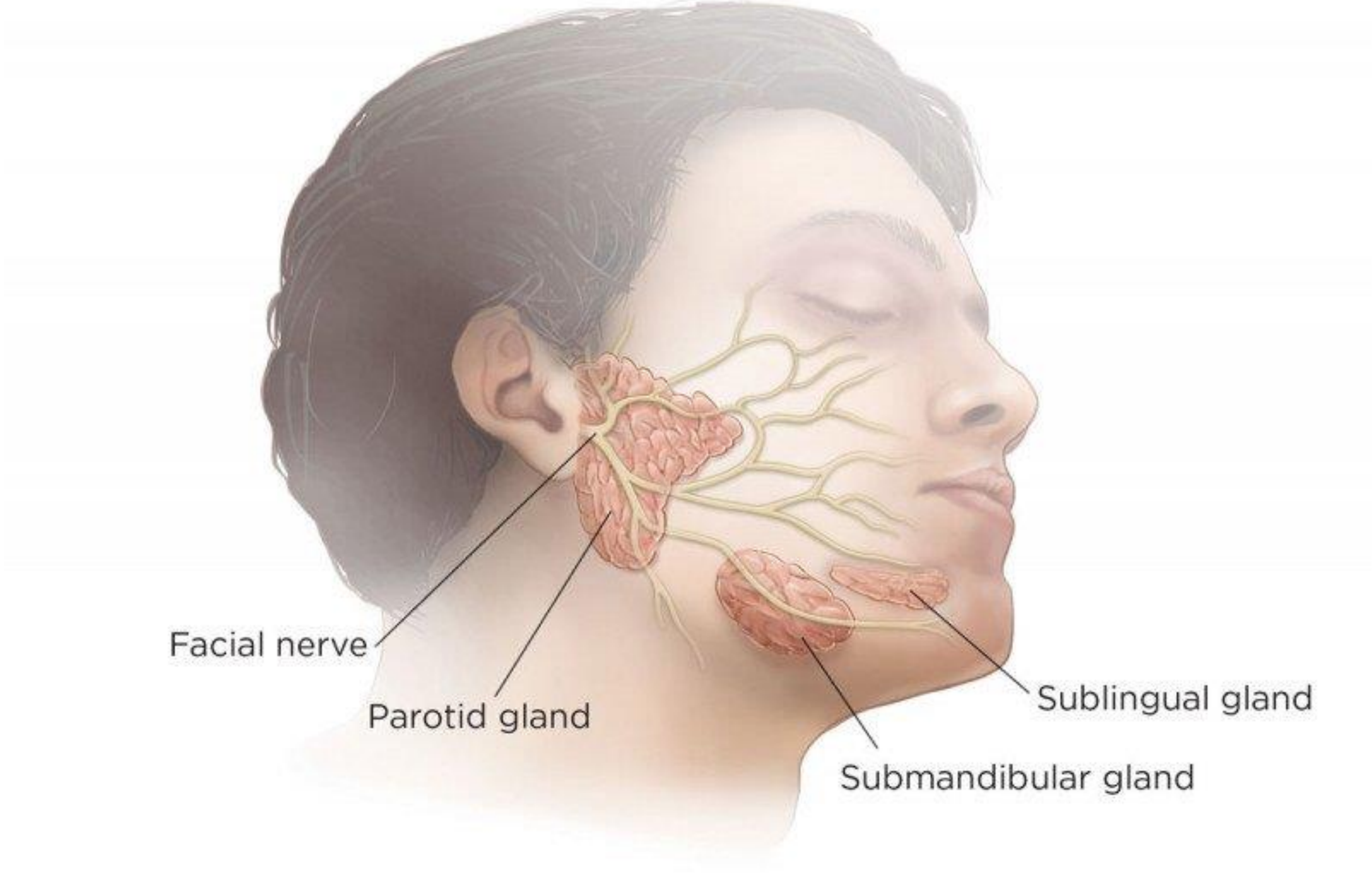
1. During immunotherapy (rejection vs escape)

2. During metastasis (escape)

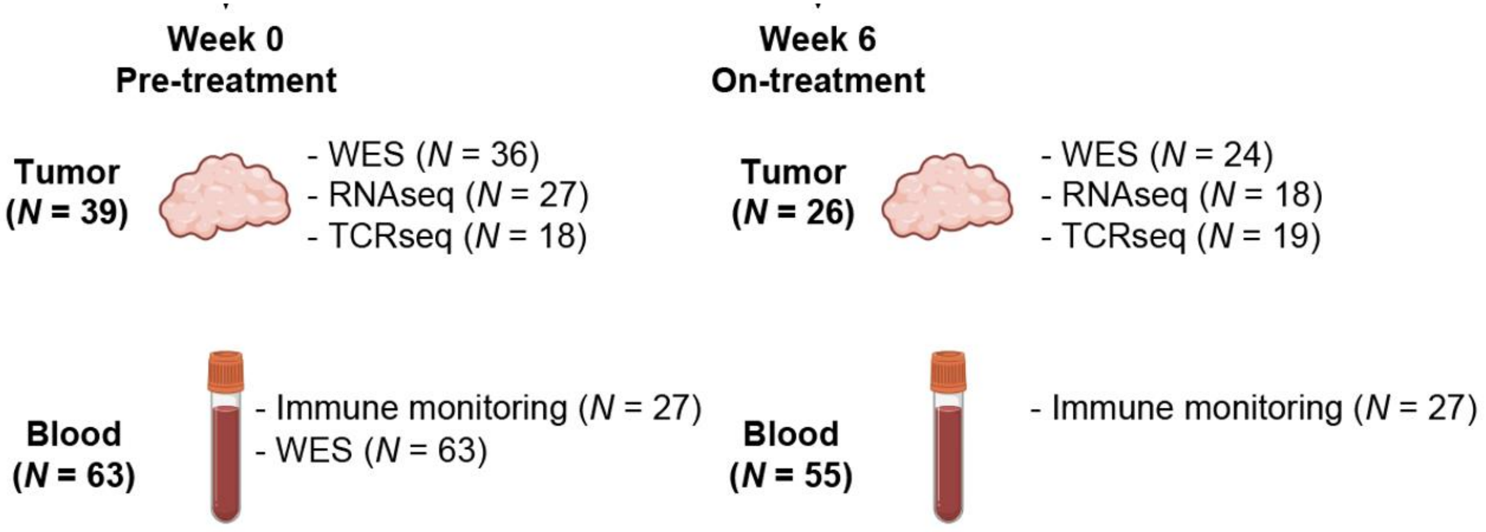
Salivary gland cancers

~20 histologic subtypes

No consensus or FDA-approved treatment for recurrent/metastatic salivary cancer



Mutational contraction in responding tumors

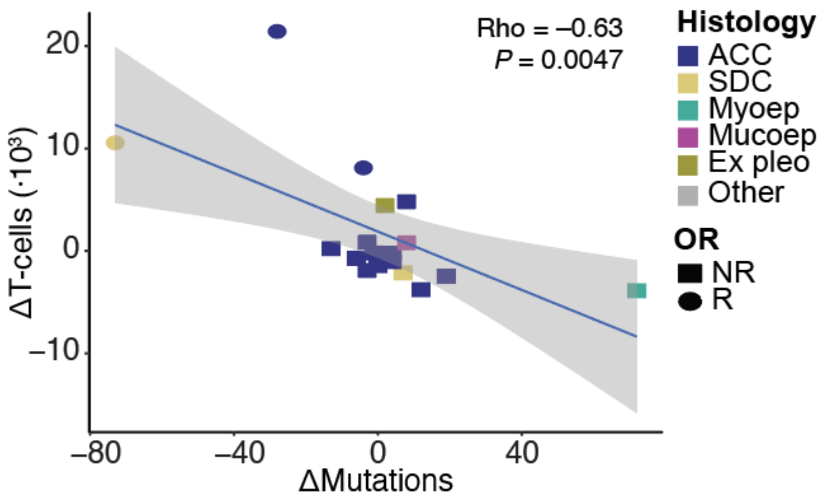


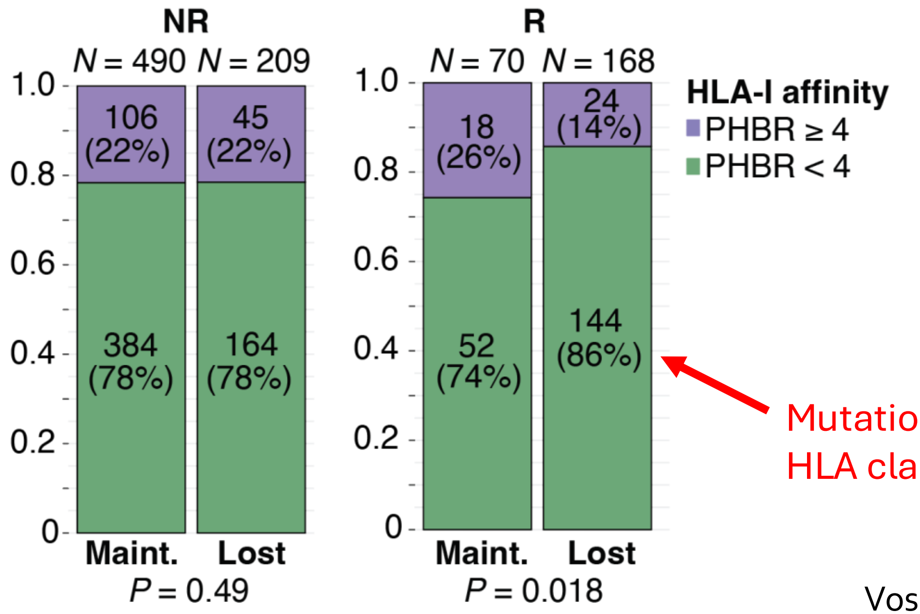
ı tumors:

tions lost during regression

with Δ immune infiltration

ons ~1.8× highly presented





Mutations with higher HLA class I binding

Article

https://doi.org/10.1038/s41591-023-02518-x

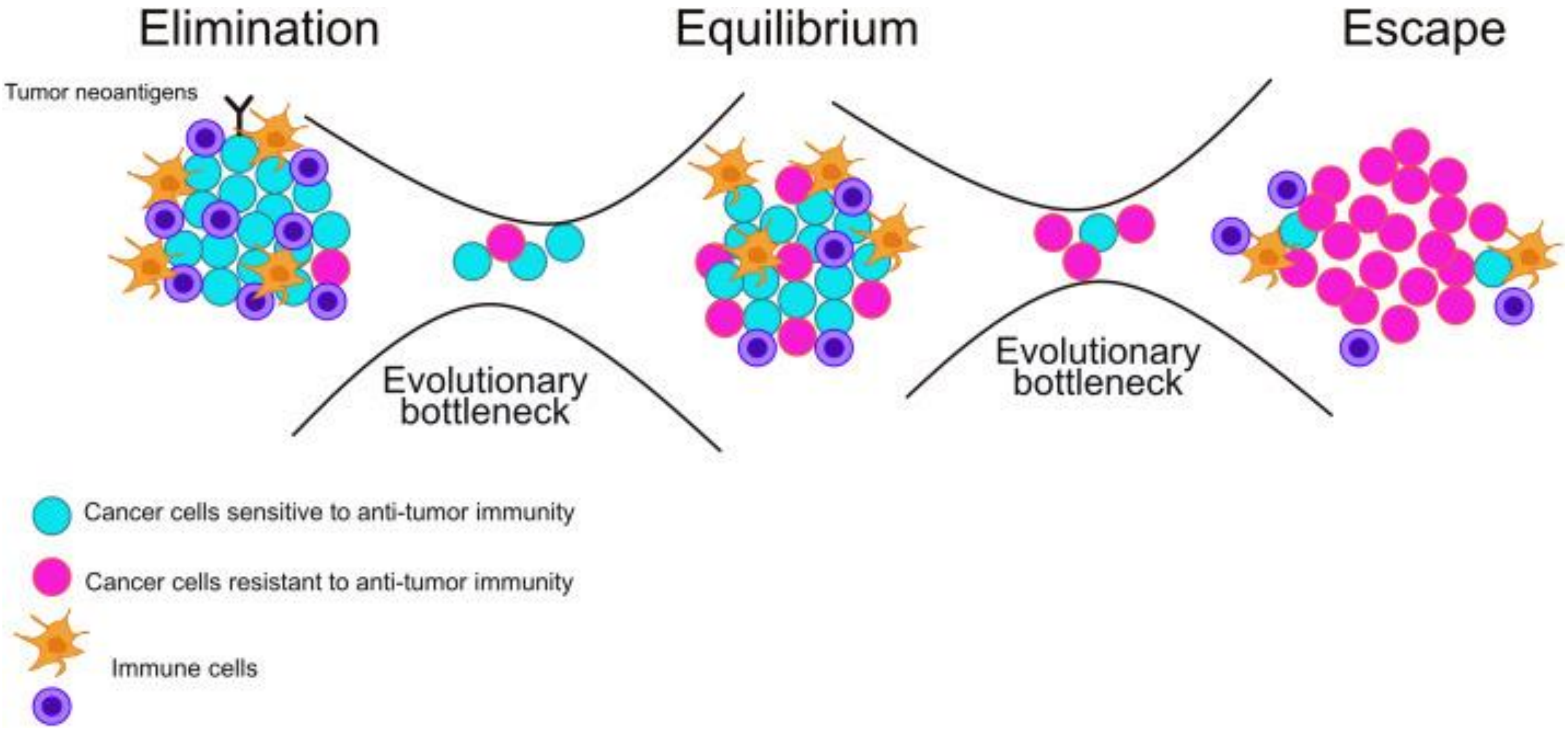
Nivolumab plus ipilimumab in advanced salivary gland cancer: a phase 2 trial

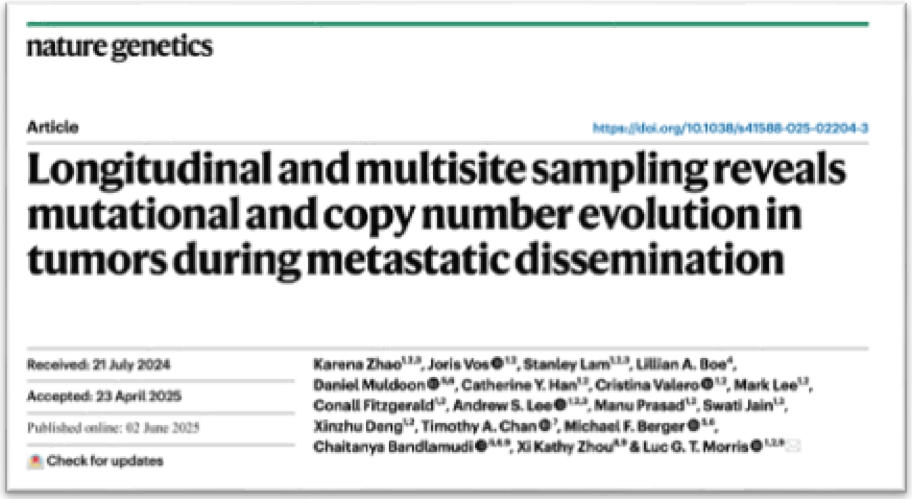
Joris Vos + Alan Ho (*Nature Medicine*, 2023)

Vos et al, Nature Med 2023

Metastasis is a bottle neck that requires tumor escape

Primary tumor → Metastasis





nature genetics

Article https://doi.org/10.1038/s41588-025-02204-3

Longitudinal and multisite sampling reveals mutational and copy number evolution in tumors during metastatic dissemination

Received: 21 July 2024

Accepted: 23 April 2025

Published online: 02 June 2025

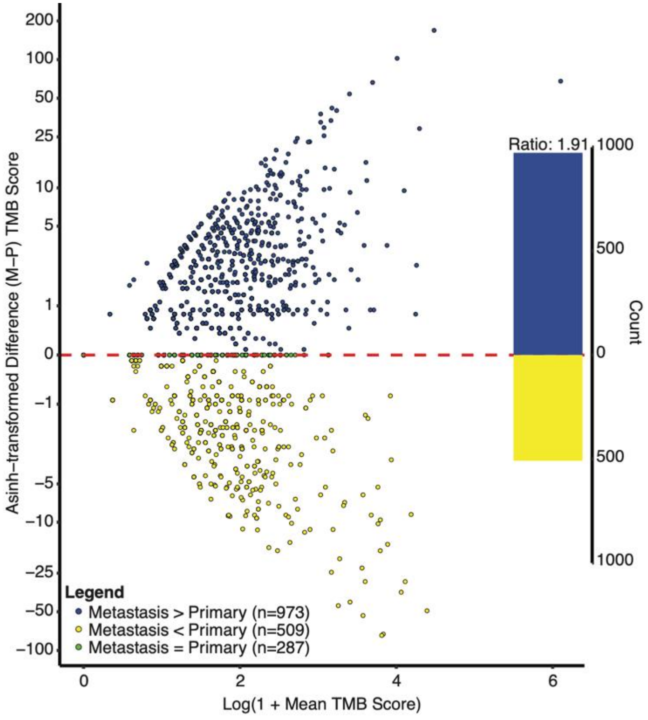
Check for updates

Karena Zhao[1,2,3], Joris Vos[1,2], Stanley Lam[1,2,3], Lillian A. Boe[4], Daniel Muldoon[5,6], Catherine Y. Han[1,2], Cristina Valero[1,2], Mark Lee[1,2], Conall Fitzgerald[1,2], Andrew S. Lee[1,2,3], Manu Prasad[1,2], Swati Jain[1,2], Xinzhu Deng[1,2], Timothy A. Chan[7], Michael F. Berger[5,6], Chaitanya Bandlamudi[5,6,8], Xi Kathy Zhou[4,8] & Luc G. T. Morris[1,2,8]

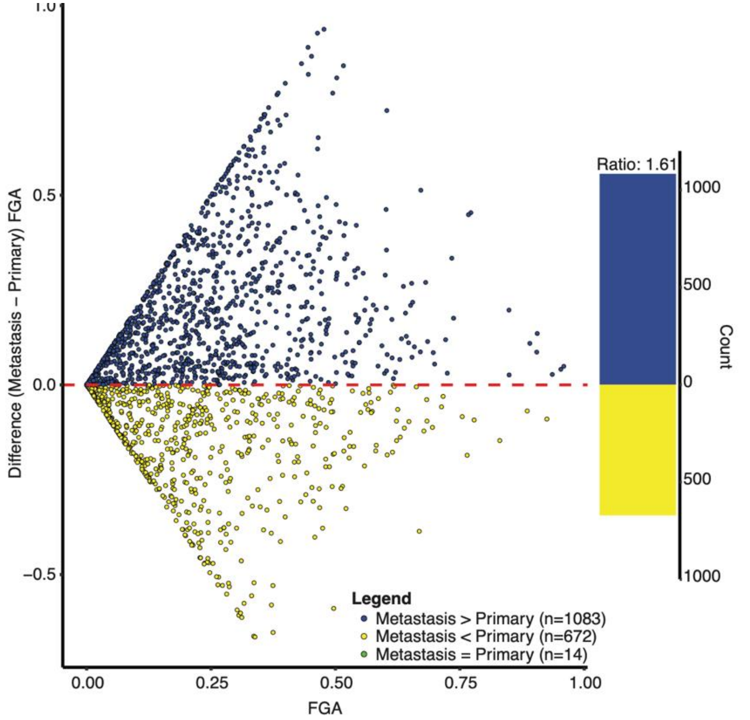
8171 samples from **3732 patients** (targeted NGS)

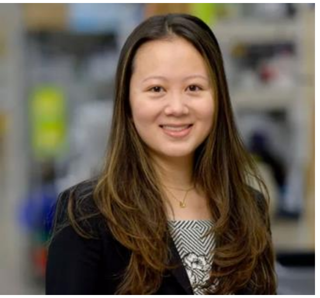
1509 – Primary-Metastasis pairs
1013 – Longitudinal samples of primary tumor
1210 – Longitudinal samples of metastases

Mutation count (TMB)

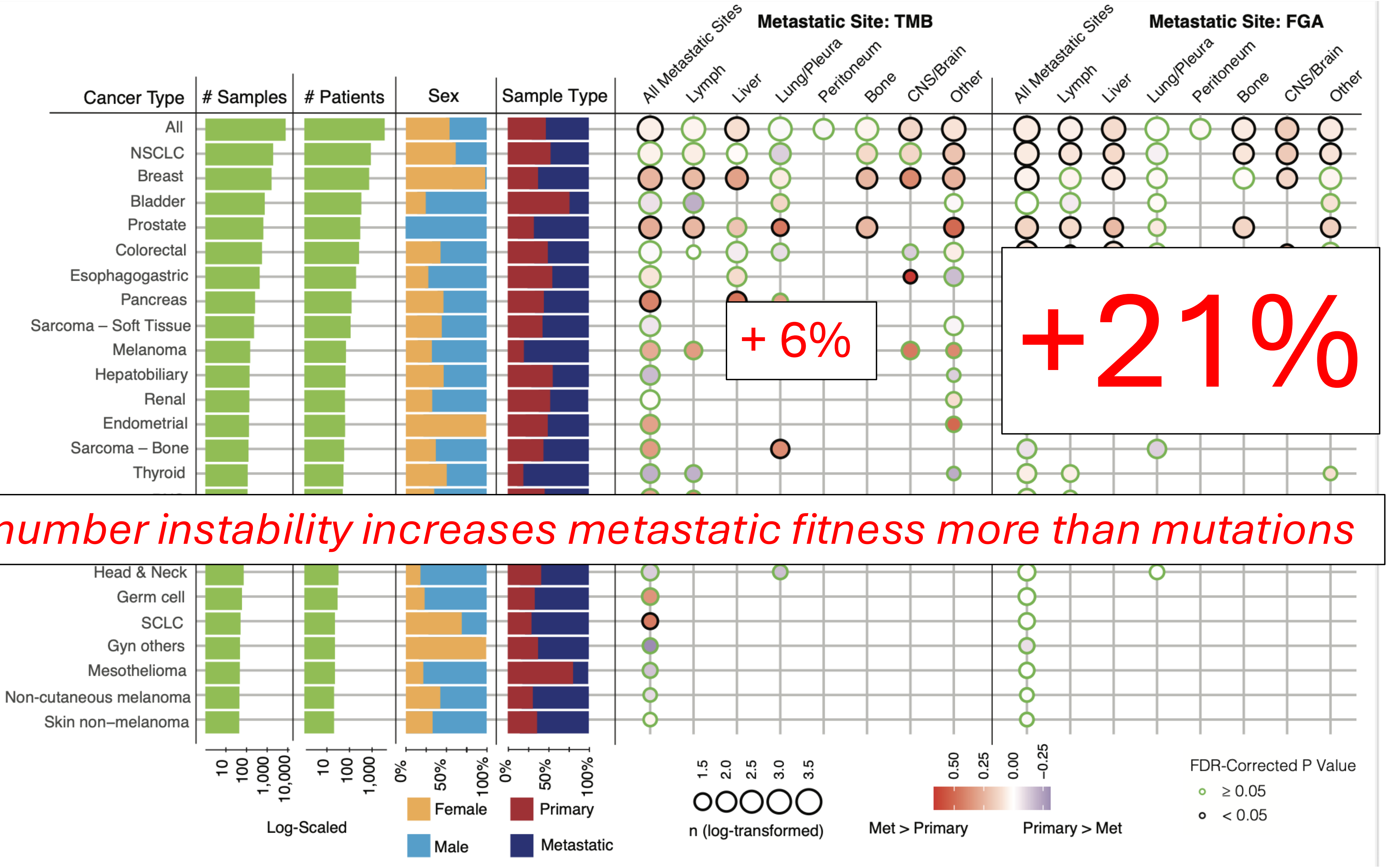


Copy number alteration (FGA)





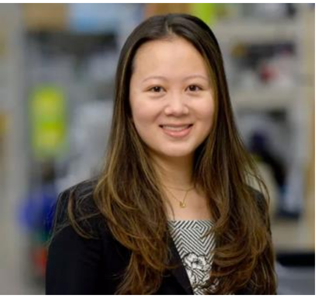
Karena Zhao



+ 6%

+21%

Copy number instability increases metastatic fitness more than mutations



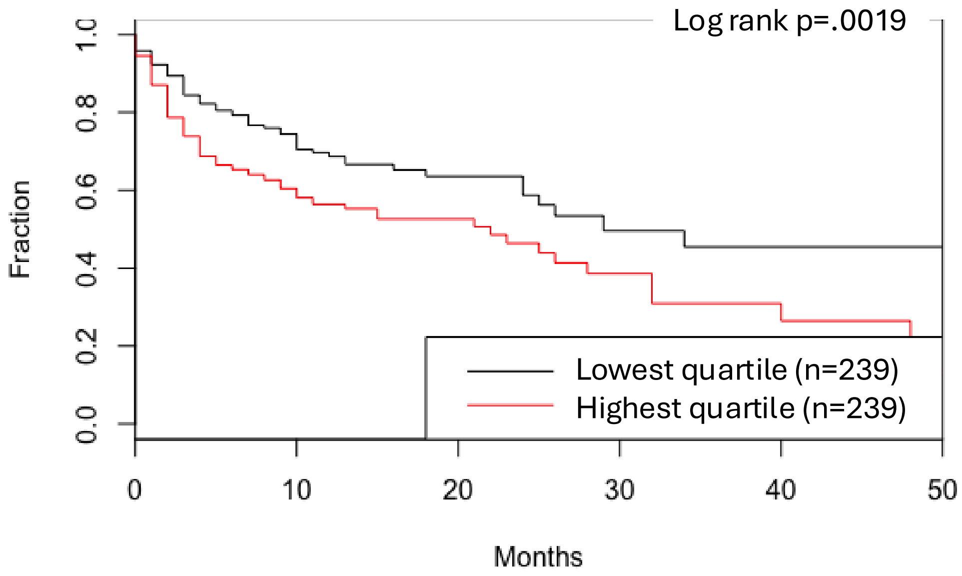
Karena Zhao

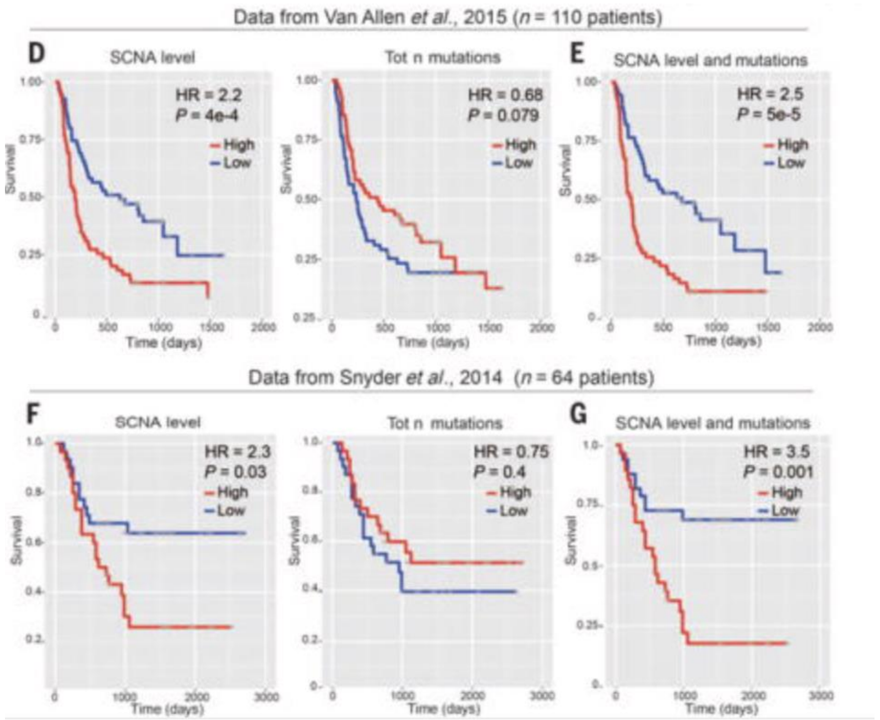
* Metastasis vs primary in multivariable mixed effects model

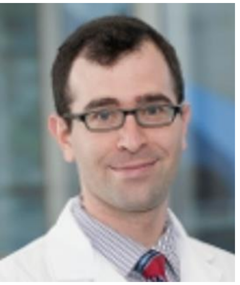
Copy number alteration (pan-cancer)

956 ICI-treated patients at MSK

OS after ICI therapy by copy number alteration







Robbie Samstein

Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy

TERESA DAVOLI, HAJIME UNO, ERIC C. WOOTEN, AND STEPHEN J. ELLEDGE Authors Info & Affiliations

SCIENCE • 20 Jan 2017 • Vol 355, Issue 6322 • DOI: 10.1126/science.aaf8399

Summary so far:

Normal tissues in the H&N develop mutations over time

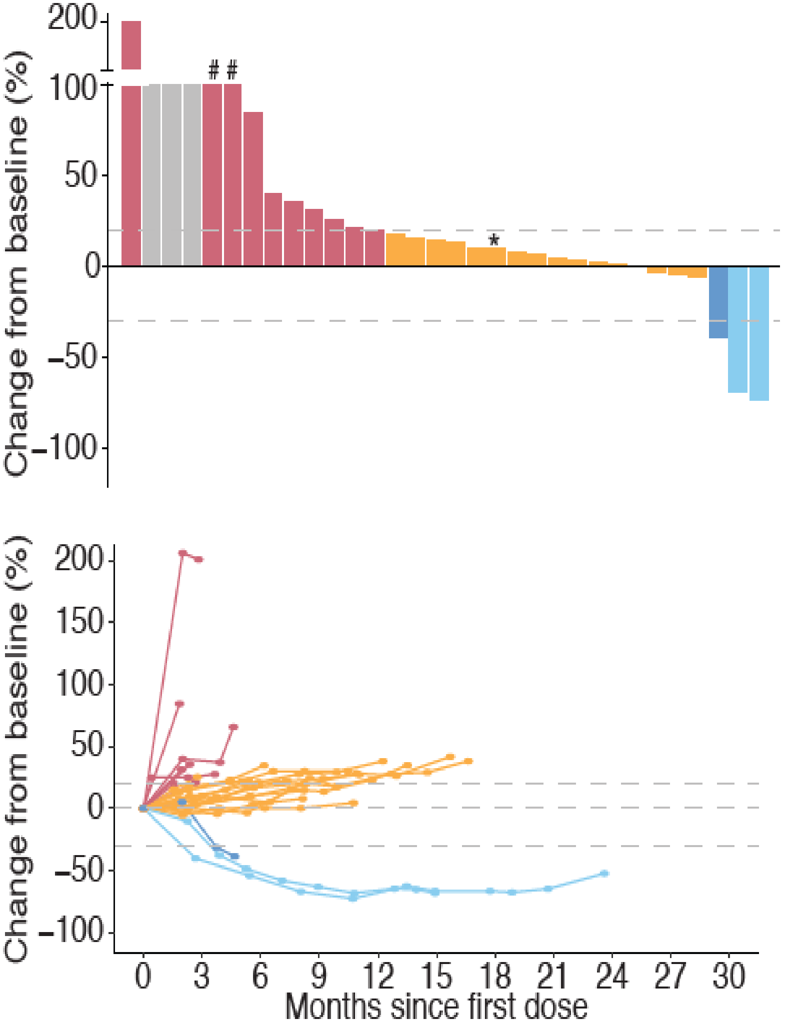
However, mutations can be immunogenic

This tradeoff constrains mutagenesis

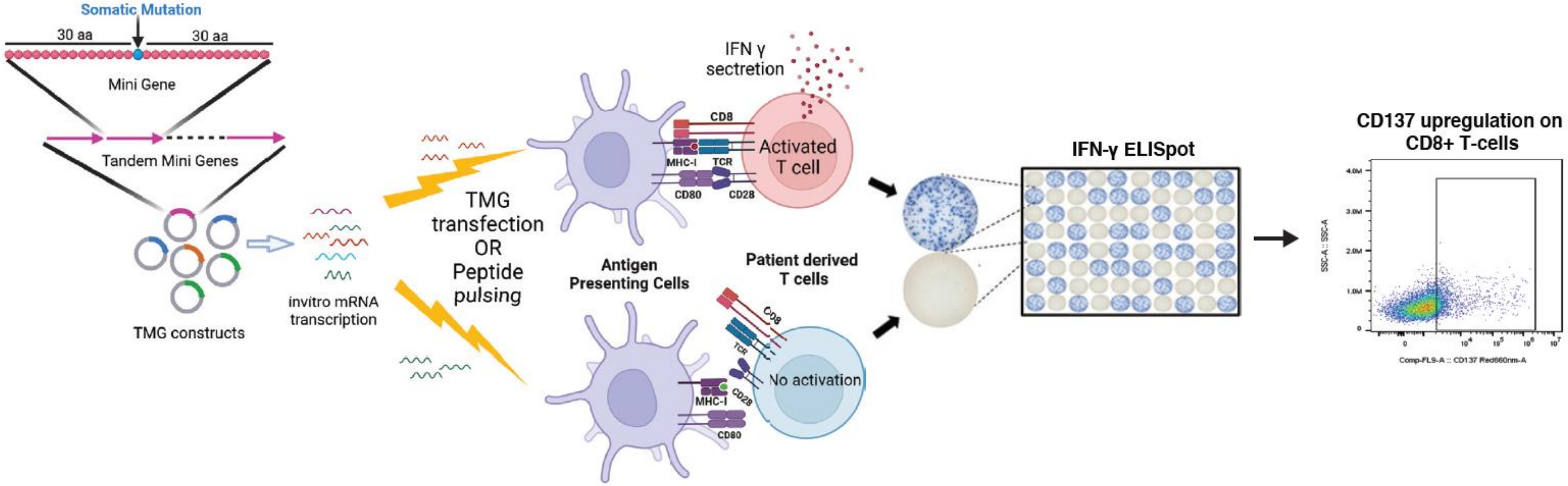
Immunogenic mutations are a vulnerability that we can target

Learning from exceptional ACC responders

Cohort 1 (ACC)



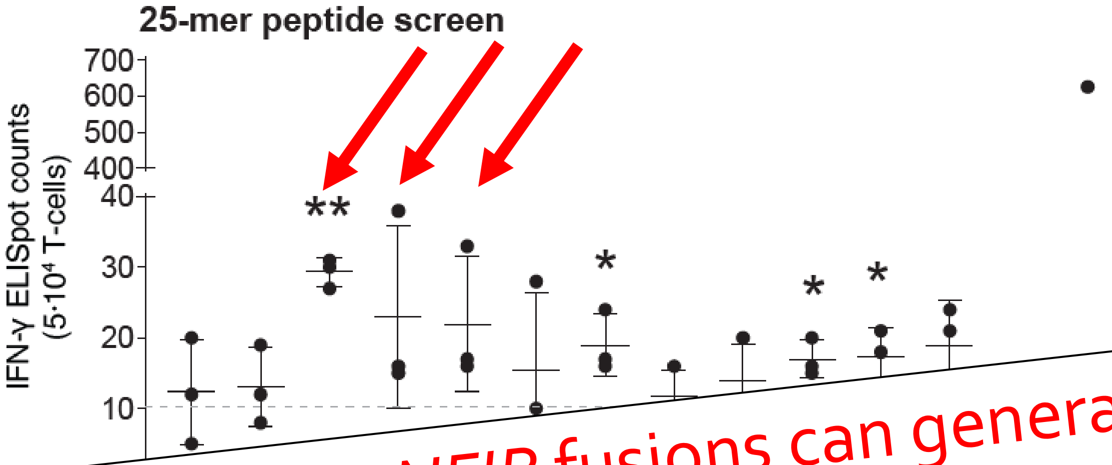
Tandem minigenes to screen neoepitopes for immunogenicity

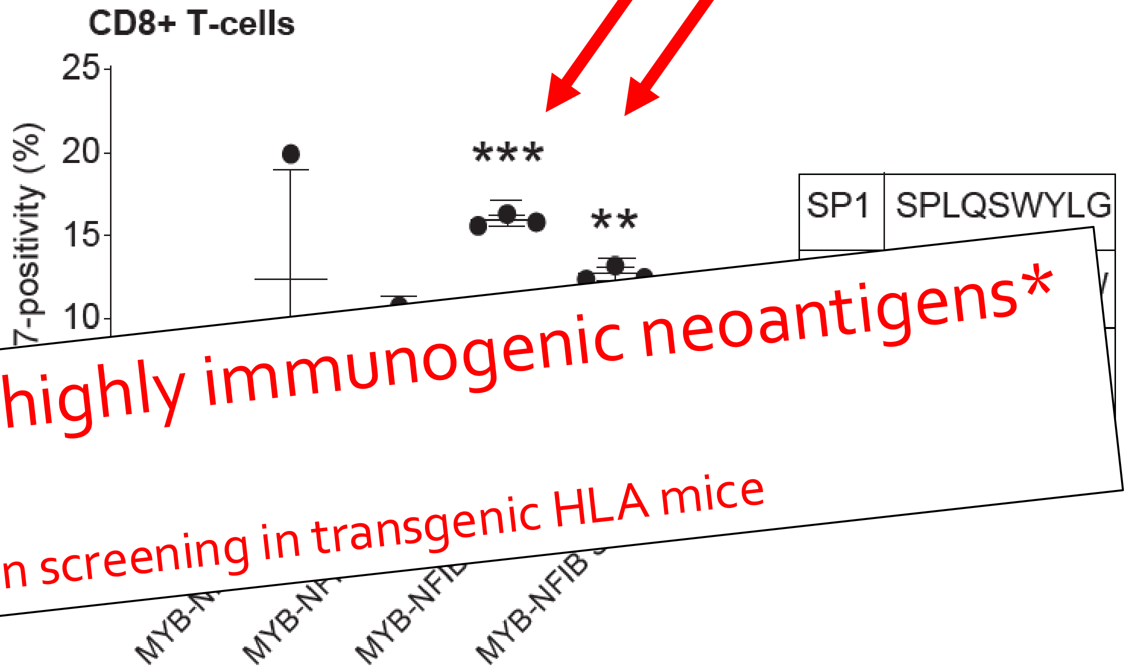


TMG described by
Eric Tran et al, *Science* 2014

Learning from exceptional ACC responders

Deconvolution of TMG hits with individual peptides

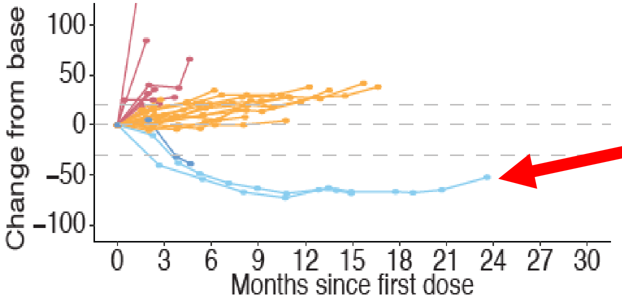




Some *MYB-NFIB* fusions can generate highly immunogenic neoantigens*

*parallel work in immunopeptidomics and neoantigen screening in transgenic HLA mice

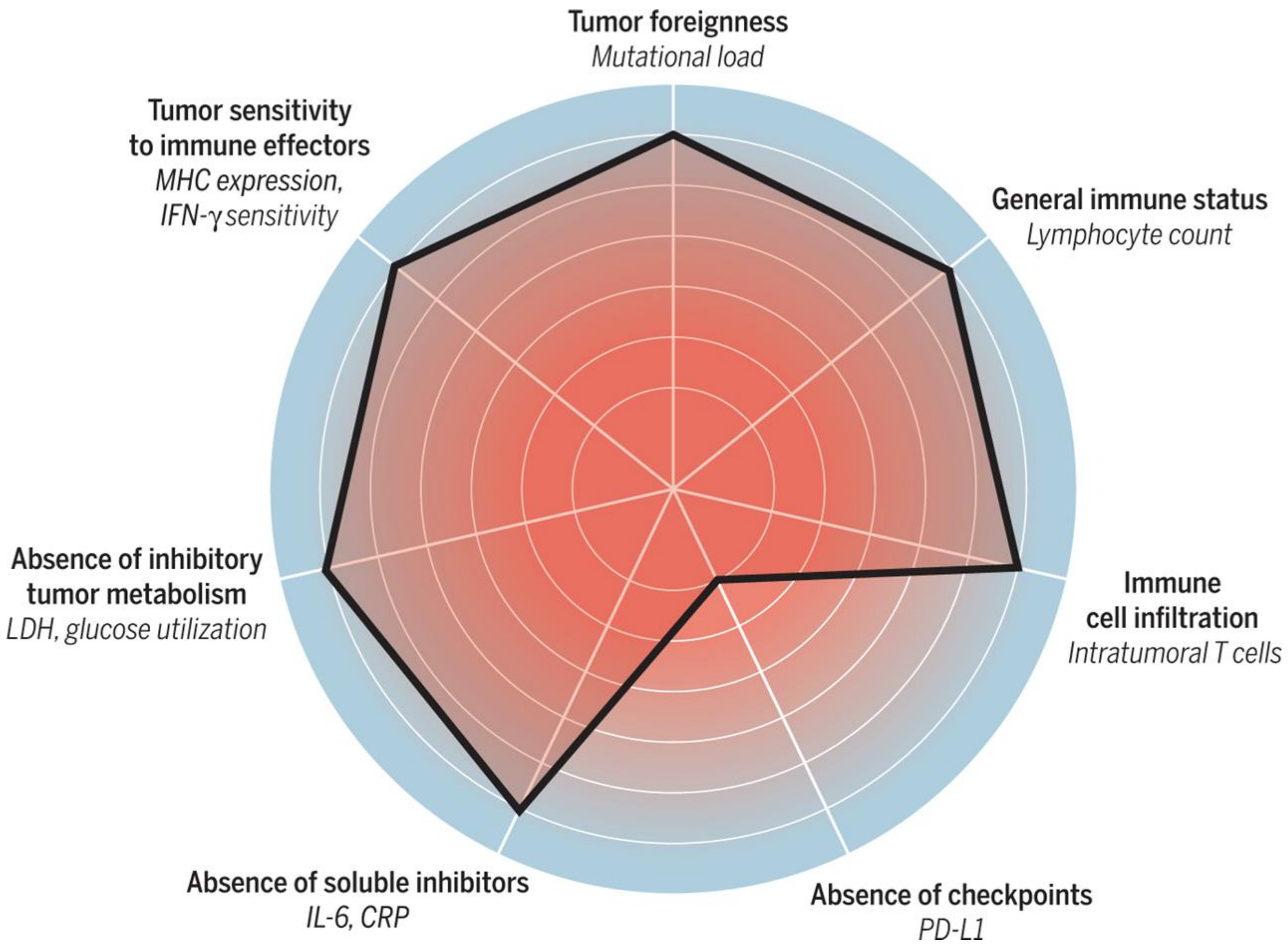
Swati Jain



At progression:
B2M truncating mutation

Vos et al. *Nature Medicine* 2023

Understanding immune escape with the “cancer immunogram”



Blank, Ribas and Schumacher, *Science* 2016

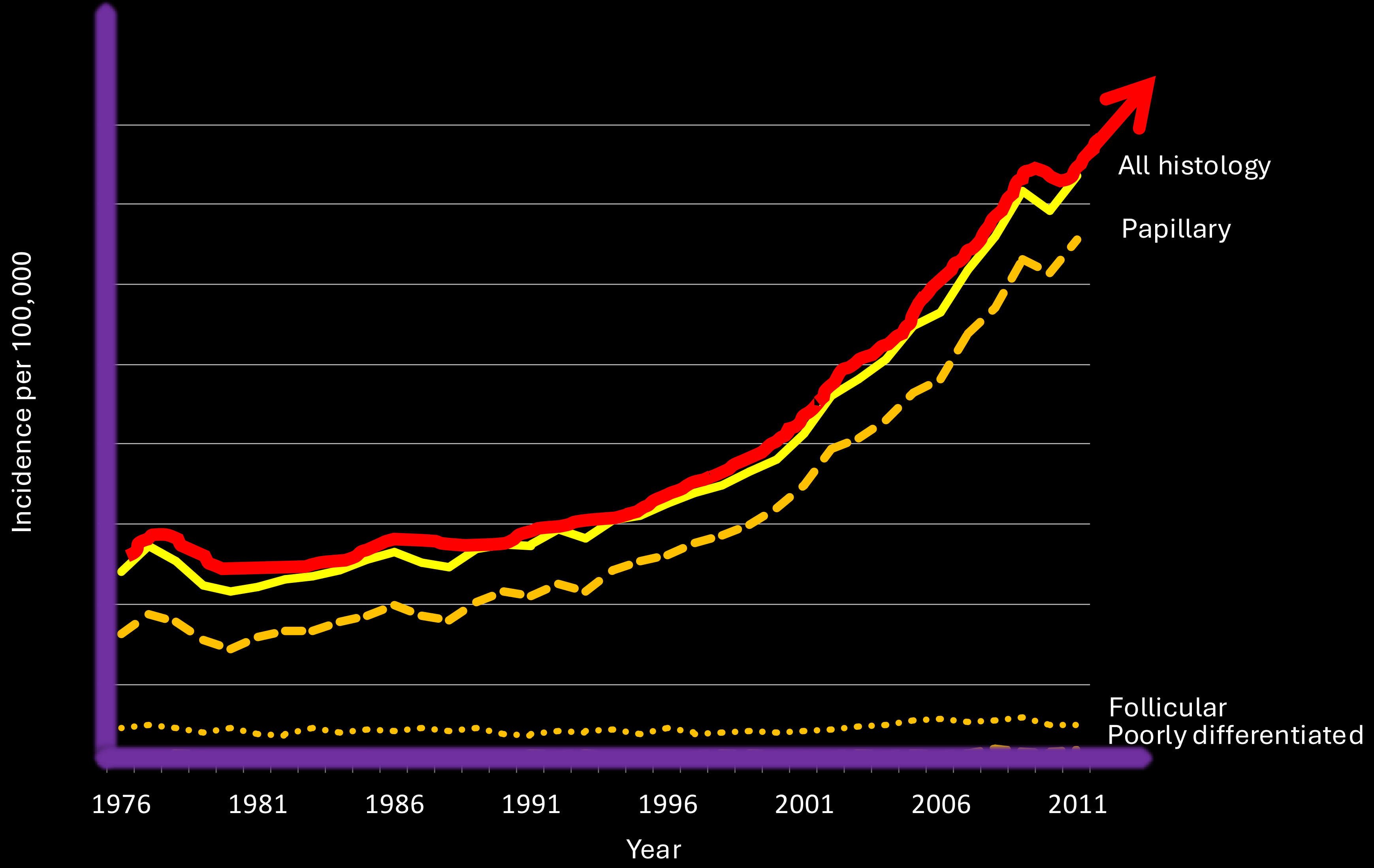

UNITED STATES OF
HALF DOL
LIBERTY
IN GOD
WE TRUST
1973

The fate of a nascent tumor under immune surveillance

Immune *escape*

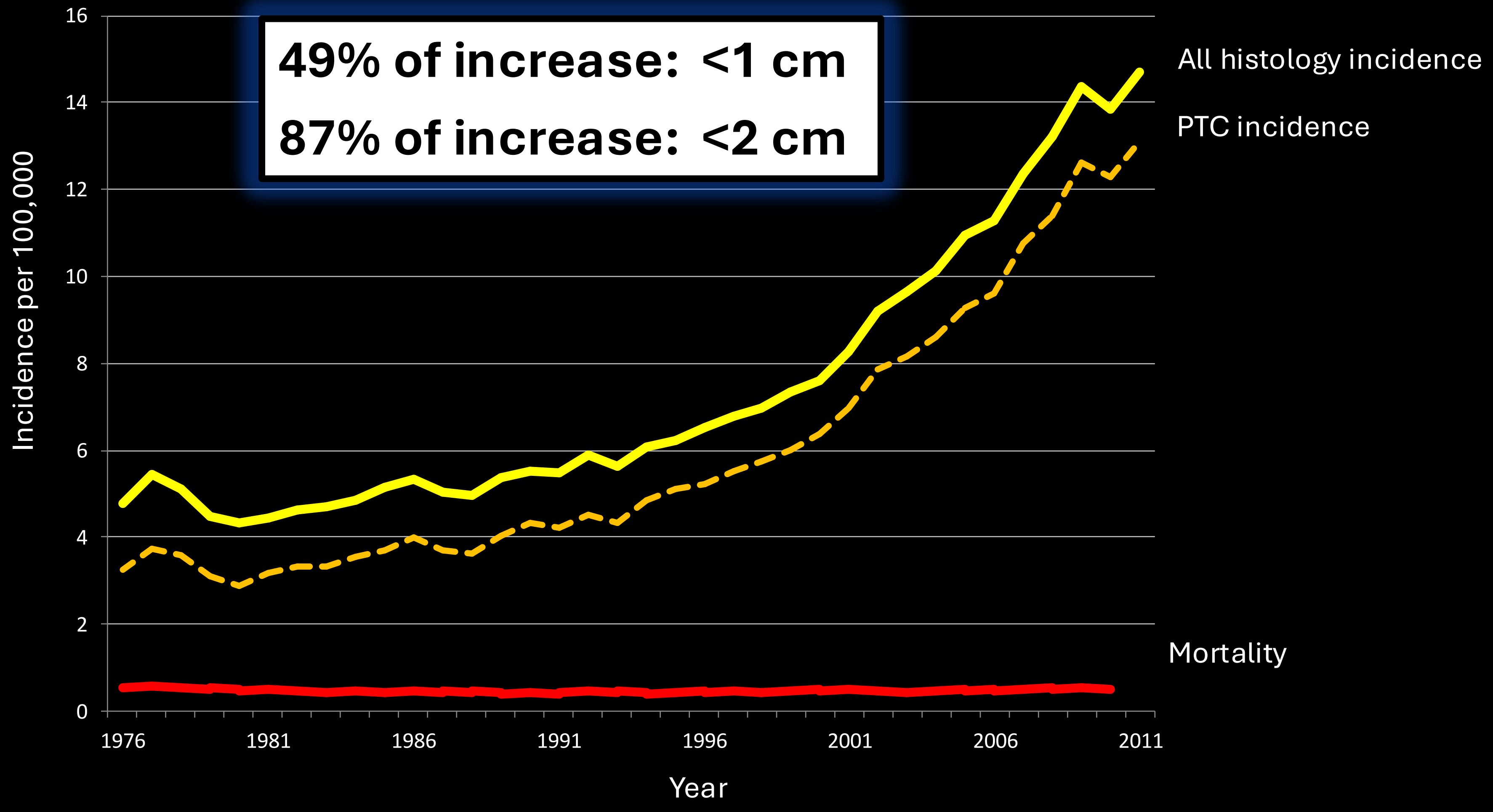
Immune *equilibrium*

Trends in thyroid cancer incidence in the US



Data from NCI SEER registry, 2014

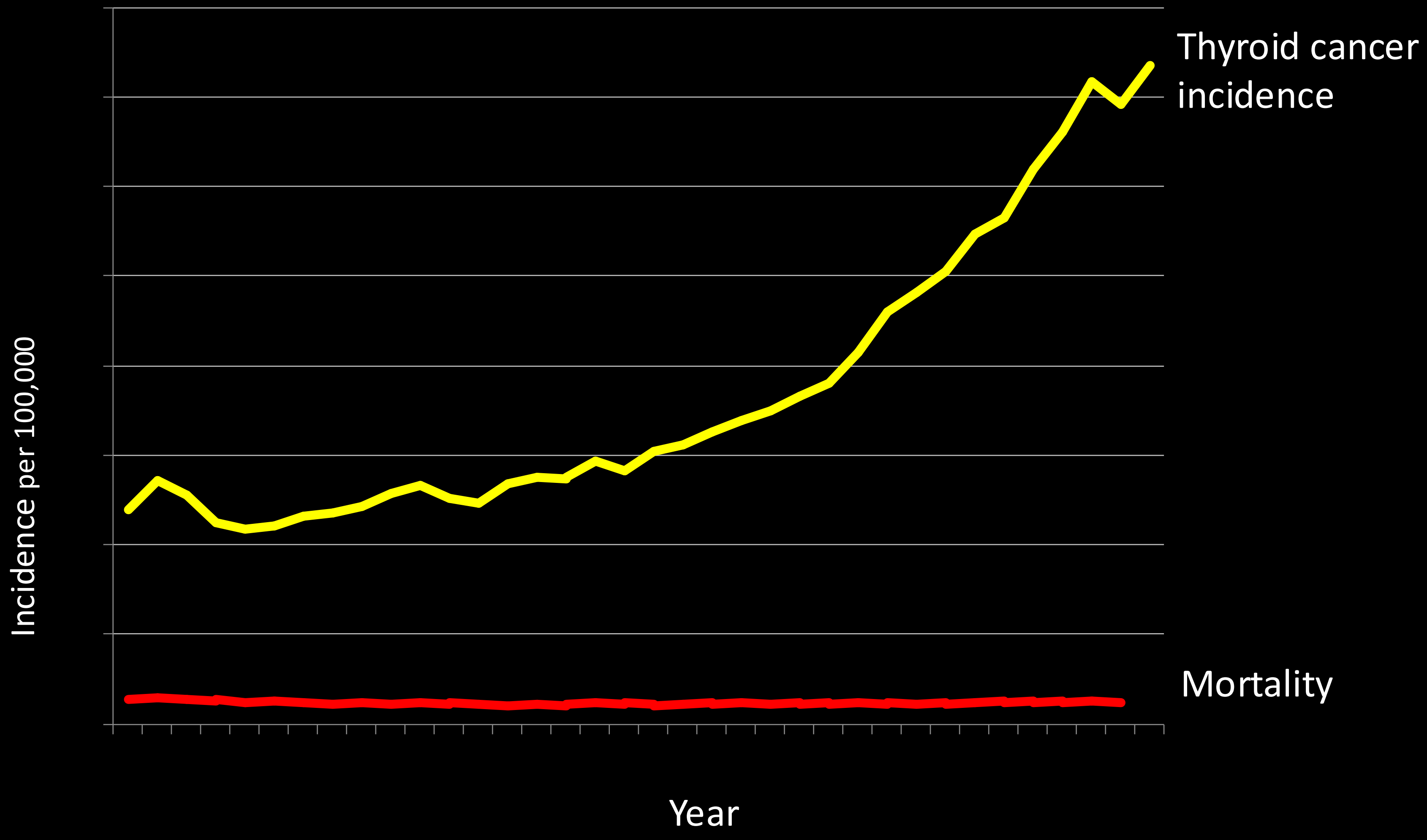
Trends in thyroid cancer incidence in the US

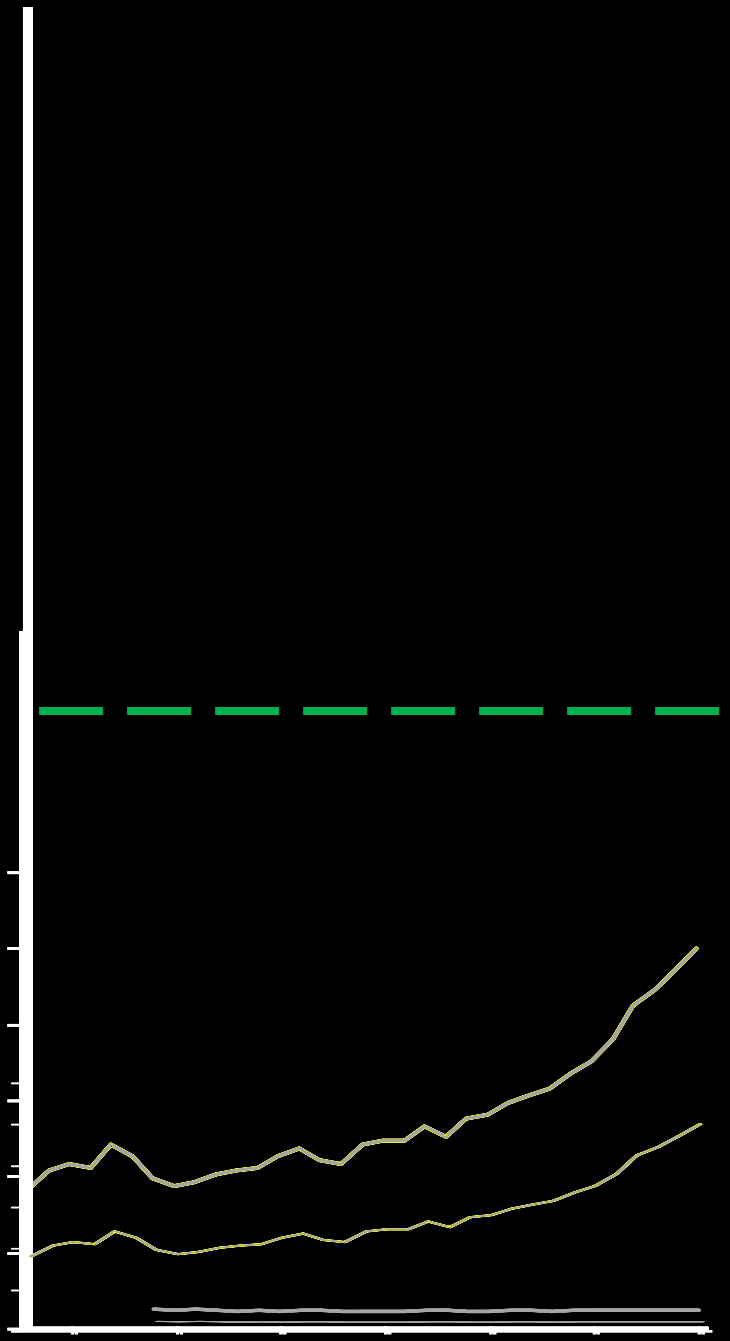


49% of increase: <1 cm

87% of increase: <2 cm

Why is only one line going up?



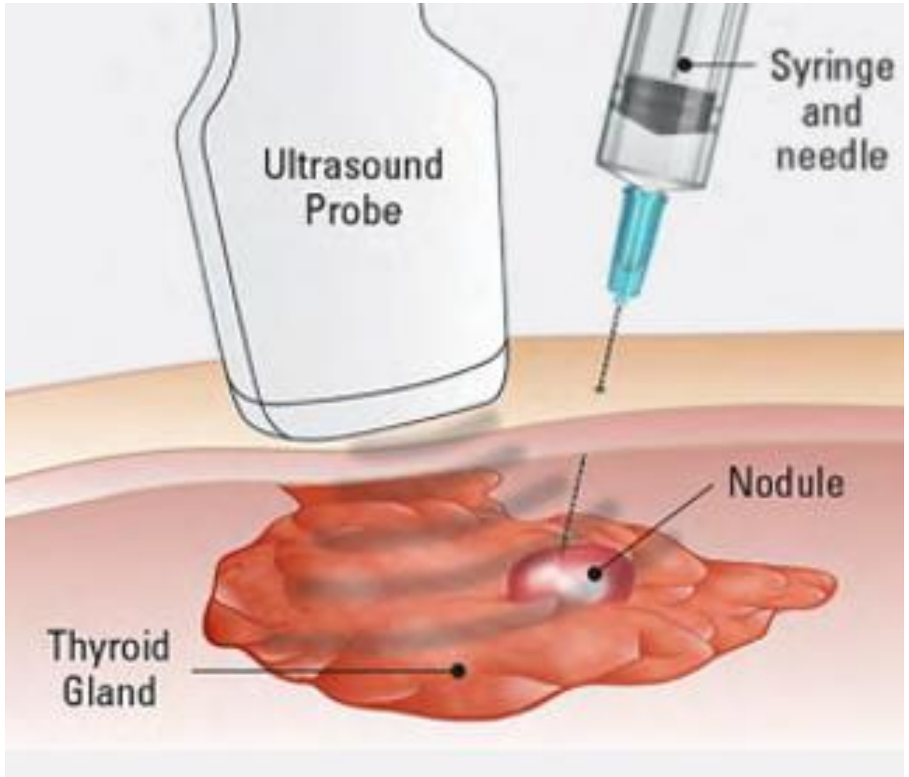


# of cancers

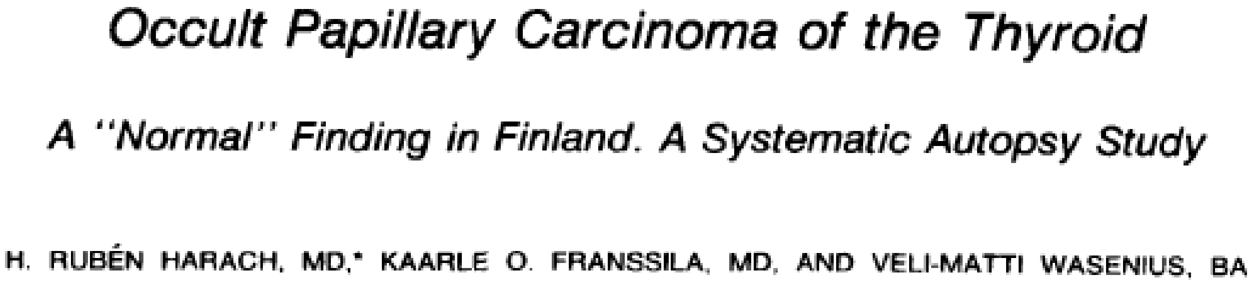
# of diagnoses

# of deaths

Not an epidemic of *disease*, but of *diagnosis*



The subclinical reservoir



Occult Papillary Carcinoma of the Thyroid

A "Normal" Finding in Finland. A Systematic Autopsy Study

H. RUBÉN HARACH, MD,* KAARLE O. FRANSSILA, MD, AND VELI-MATTI WASENIUS, BA

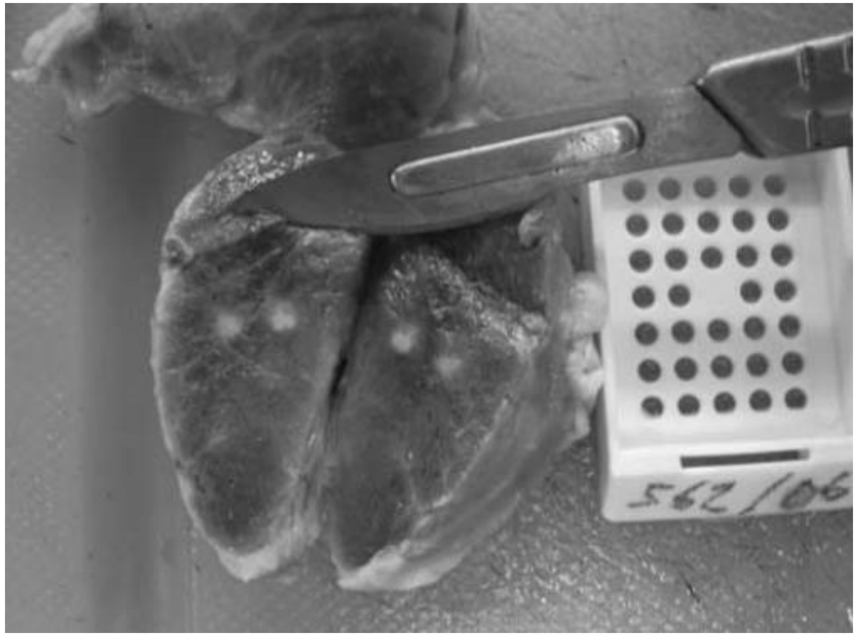
101 thyroid glands
2-3mm sections → 36% prevalence

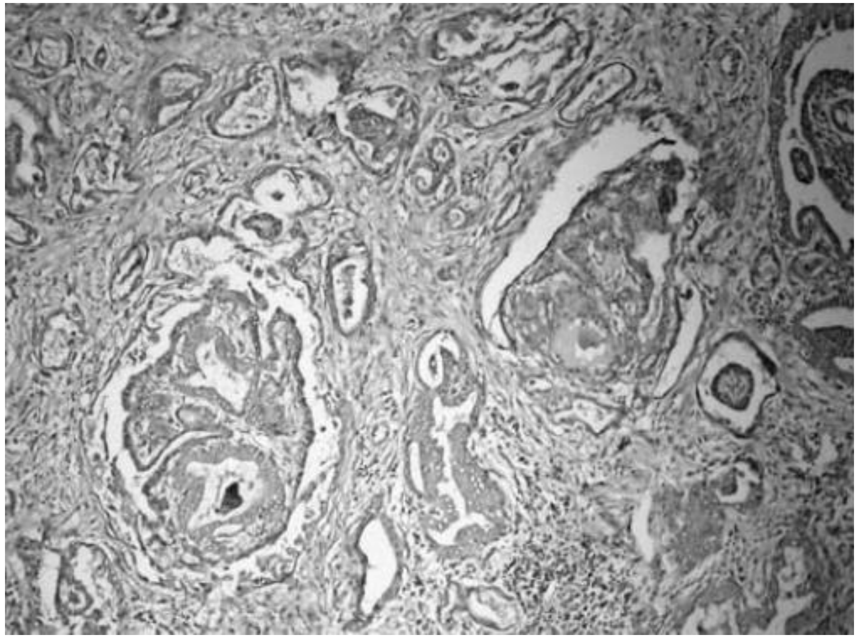
(prostate cancer = 40-60%)

Cancer 1985

The prevalence is similar in men and women …

But women are diagnosed with 3x as many thyroid cancers

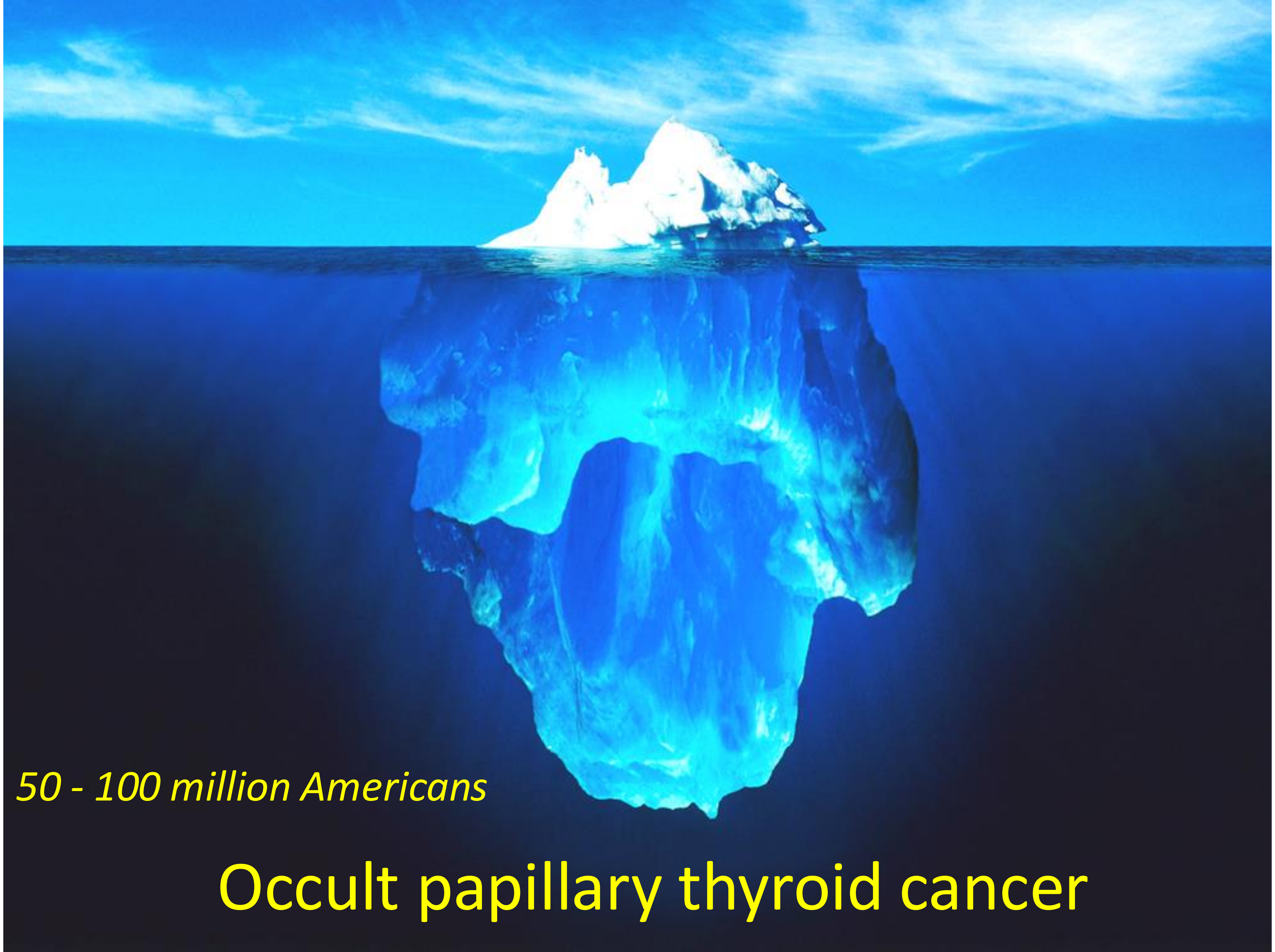




The subclinical reservoir

1000 to 1

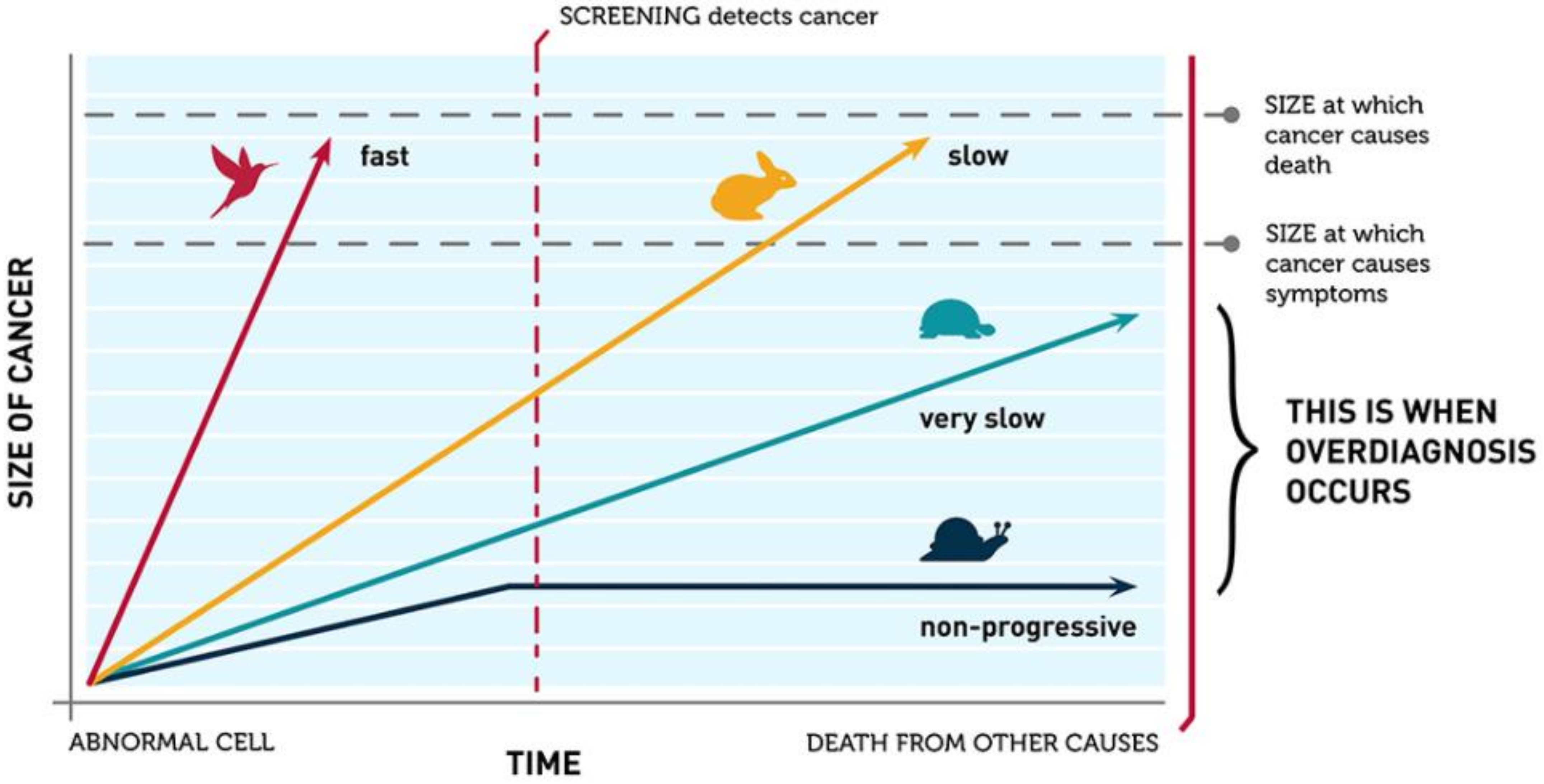
Ratio of sub-clinical cancers to detected cancers



50 - 100 million Americans

Occult papillary thyroid cancer

Not every cancer needs to be detected



NCI Division of Cancer Prevention

Explaining survival measures to patients

Overall survival – probability of not dying (of anything)

Net cancer survival

Disease-specific survival – probability of not dying *of this cancer*

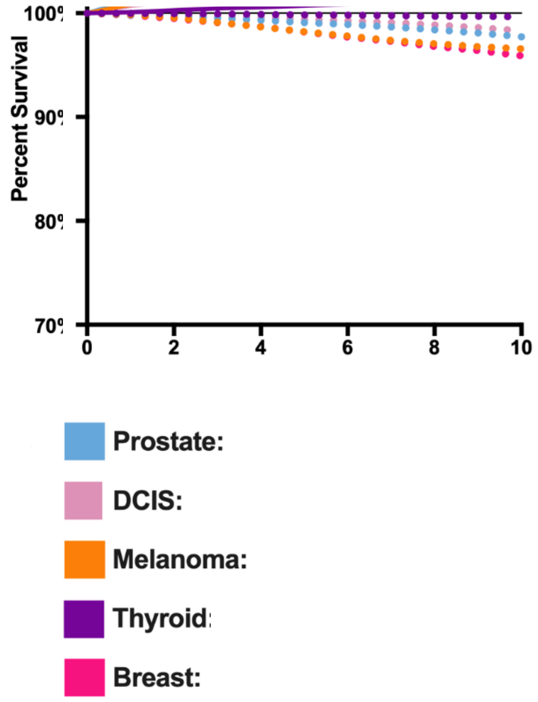
Relative survival – probability of not dying, *compared to similar people without cancer**

**matched for age, sex, and race*

Survival in patients with early stage* cancers

—— **Relative Survival (RS)**

······· **Disease-Specific Survival (DSS)**



Many overdiagnosed cases … and

“The healthy user effect”

Not every cancer diagnosis portends an earlier death.

“Your life prior to diagnosis probably means more for your survival than this cancer diagnosis itself.”

*Stage 1, Gleason 6, or DCIS

RS: survival compared to a non-cancer comparison cohort, matched for age, sex, race and time period

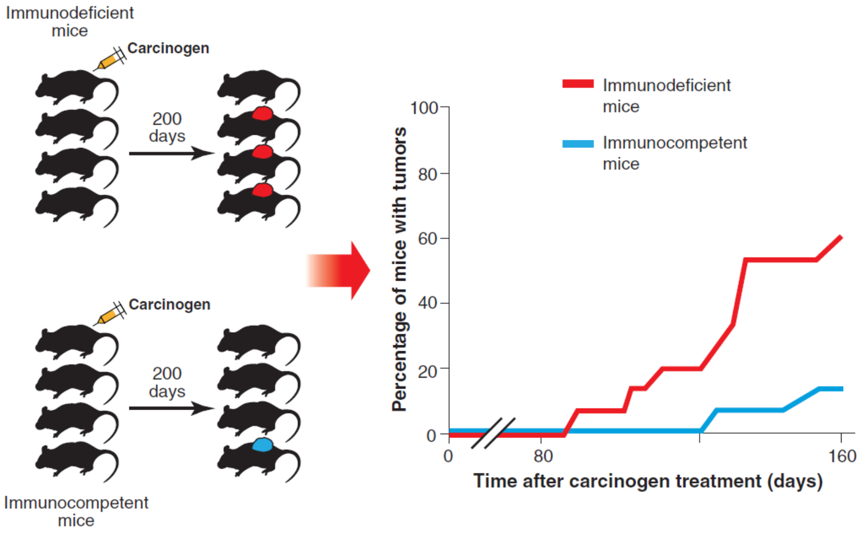
Marcadis et al, *JAMA Int Med* 2019

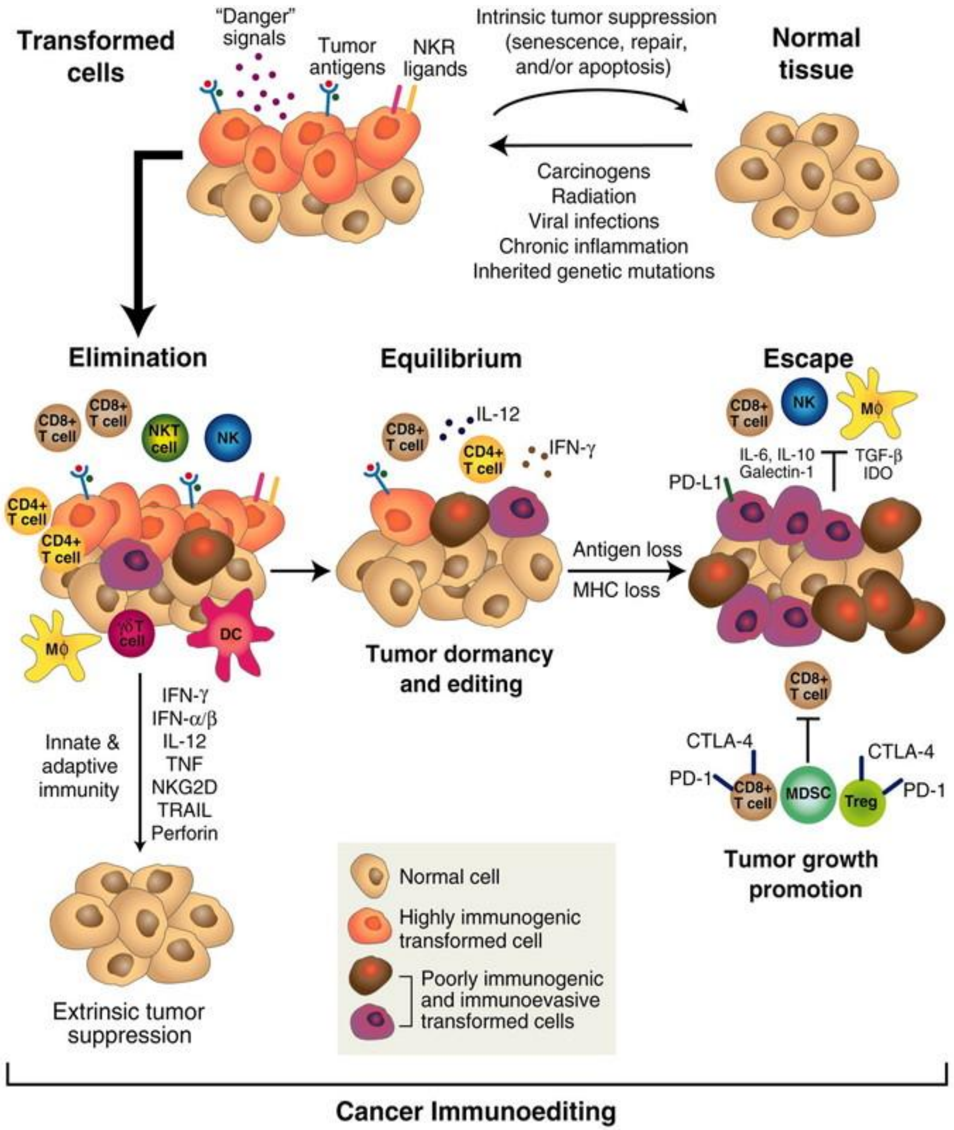
Are indolent cancers good because they are small… or small because they are good?

Adaptive immunity maintains occult cancer in an equilibrium state

Catherine M. Koebel[1], William Vermi[1,2], Jeremy B. Swann[3,4], Nadeen Zerafa[3], Scott J. Rodig[5], Lloyd J. Old[6], Mark J. Smyth[3,4]* & Robert D. Schreiber[1]*

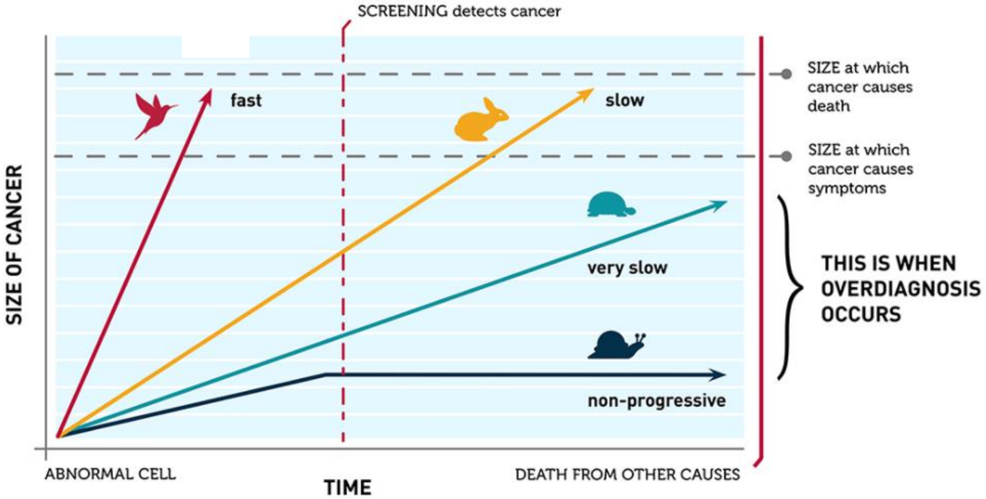
Nature 2007





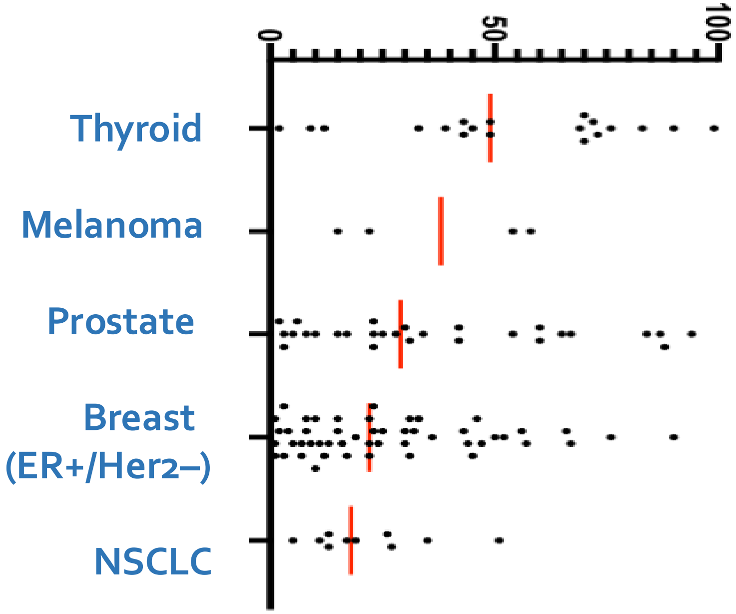
Robert Schreiber and Lloyd Old *Science* 2011

Cancers in equilibrium are “overdiagnosed”



NCI Division of Cancer Prevention

% of cases overdiagnosed



VS.

Less prone to overdiagnosis

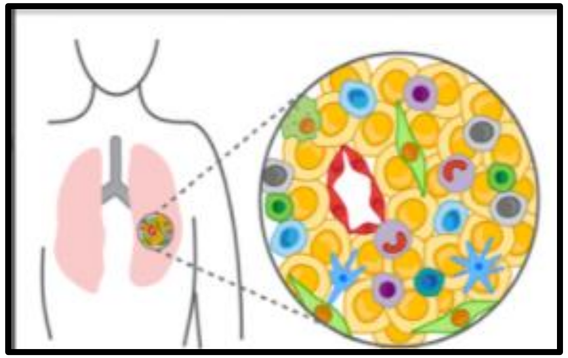
Esophageal

Head & Neck SCC

Pancreas

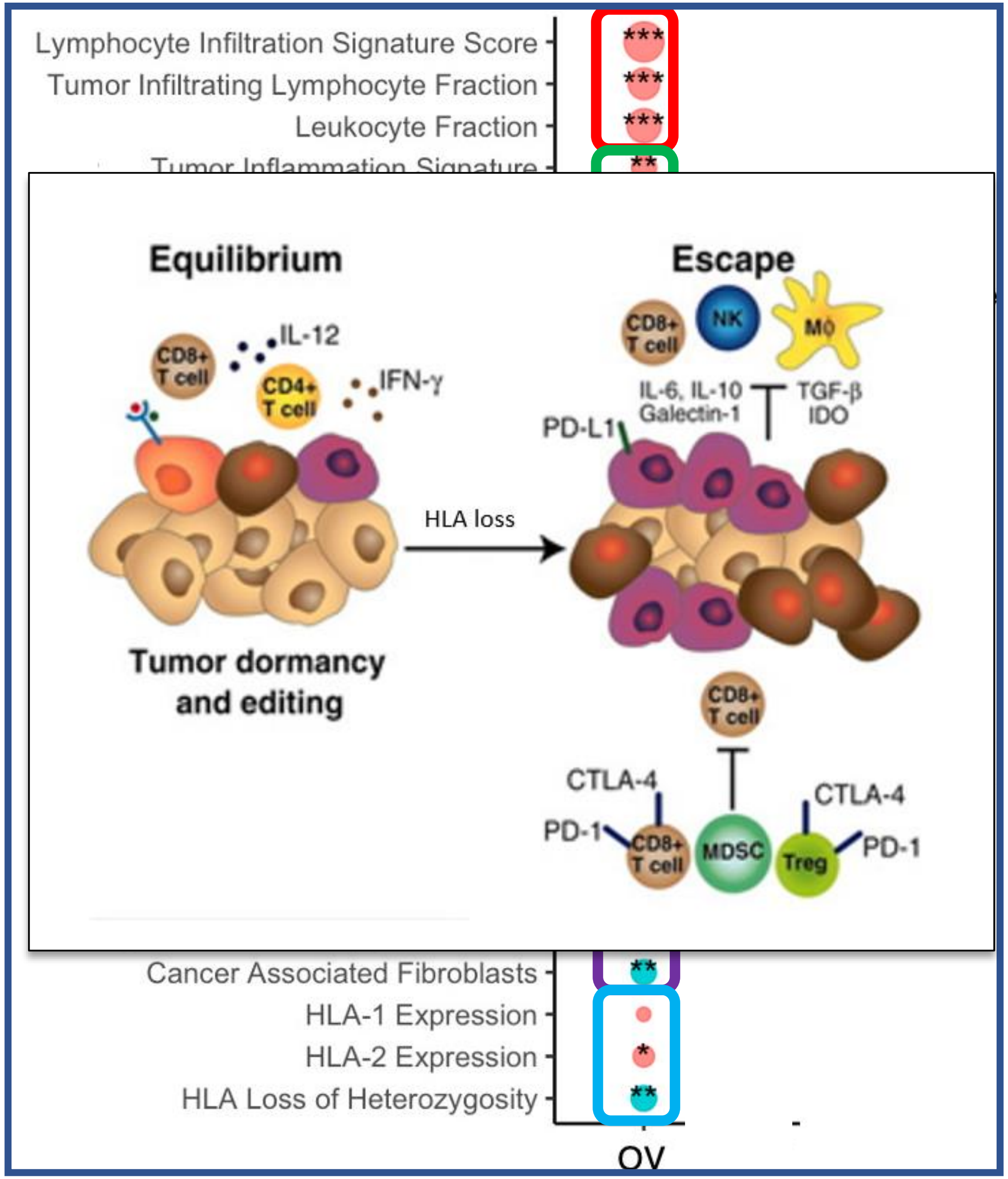
Gastric

Breast (TNBC)



Compare large vs small

Immune microenvironment
(RNA-sequencing)
Antigen presentation
(HLA LOH/expression)
T cell clonality
(TCR repertoire)



OV: thyroid, ER+/Her2- breast, lung squamous, lung adeno, melanoma, prostate
nOV: pancreatic, esophageal, gastric, head & neck SCC, triple negative breast

Overdiagnosis-prone cancers (OV)

Larger tumors have:

Much less immune infiltration
Much less anti-tumor immunity
More immunosuppressive cells
More clonal T cell repertoire
Loss of HLA

All signs of immune escape

Non-overdiagnosed cancers (nOV)

No differences
No signs of immune escape


Abhi
Pandey

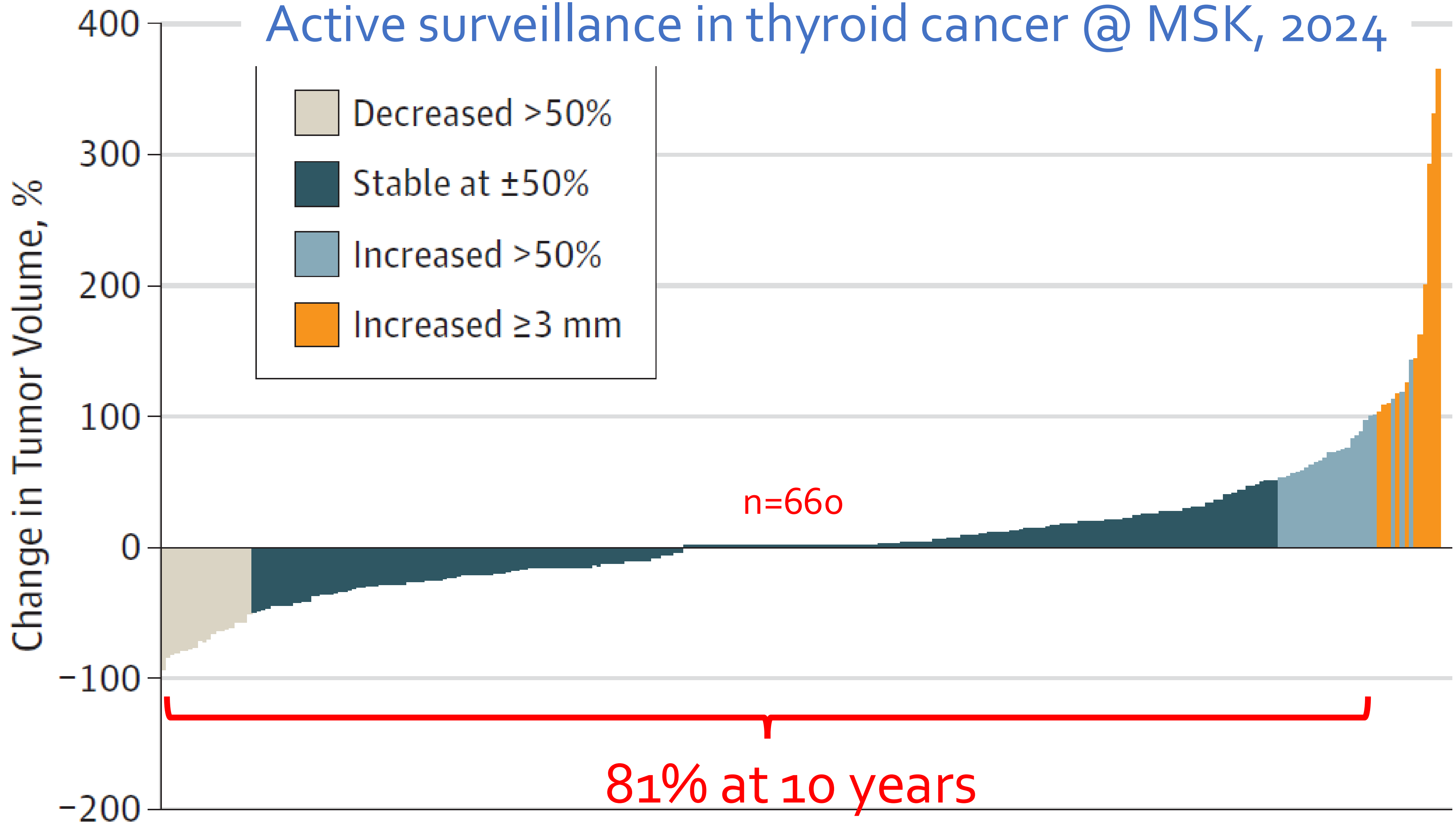

David
Kuo


Joris
Vos

Cancer Cell 2023

Primum non nocere

Active surveillance in thyroid cancer @ MSK, 2024



n=660

81% at 10 years

Tuttle … Morris, *Thyroid* 2022
Tuttle … Morris, *JAMA Oto-HNS* 2017

How do we avoid low-value & harmful interventions?

Prostate cancer
Papillary thyroid cancer
DCIS ?

Don't just do something …
Stand there!

Part II

Can this knowledge help us predict immunotherapy response?

“All models are wrong, but some are useful”

George Box, FRS

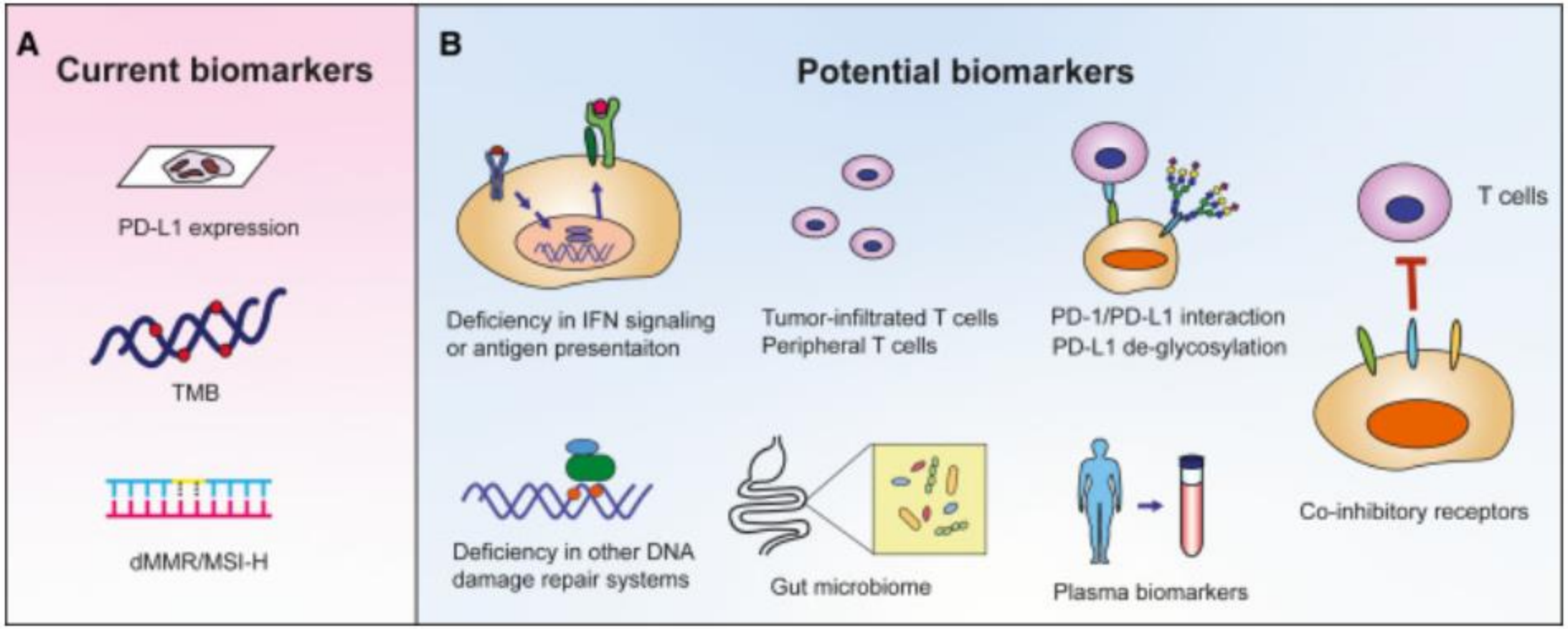
English statistician

Why do we need predictive biomarkers for IO drugs?

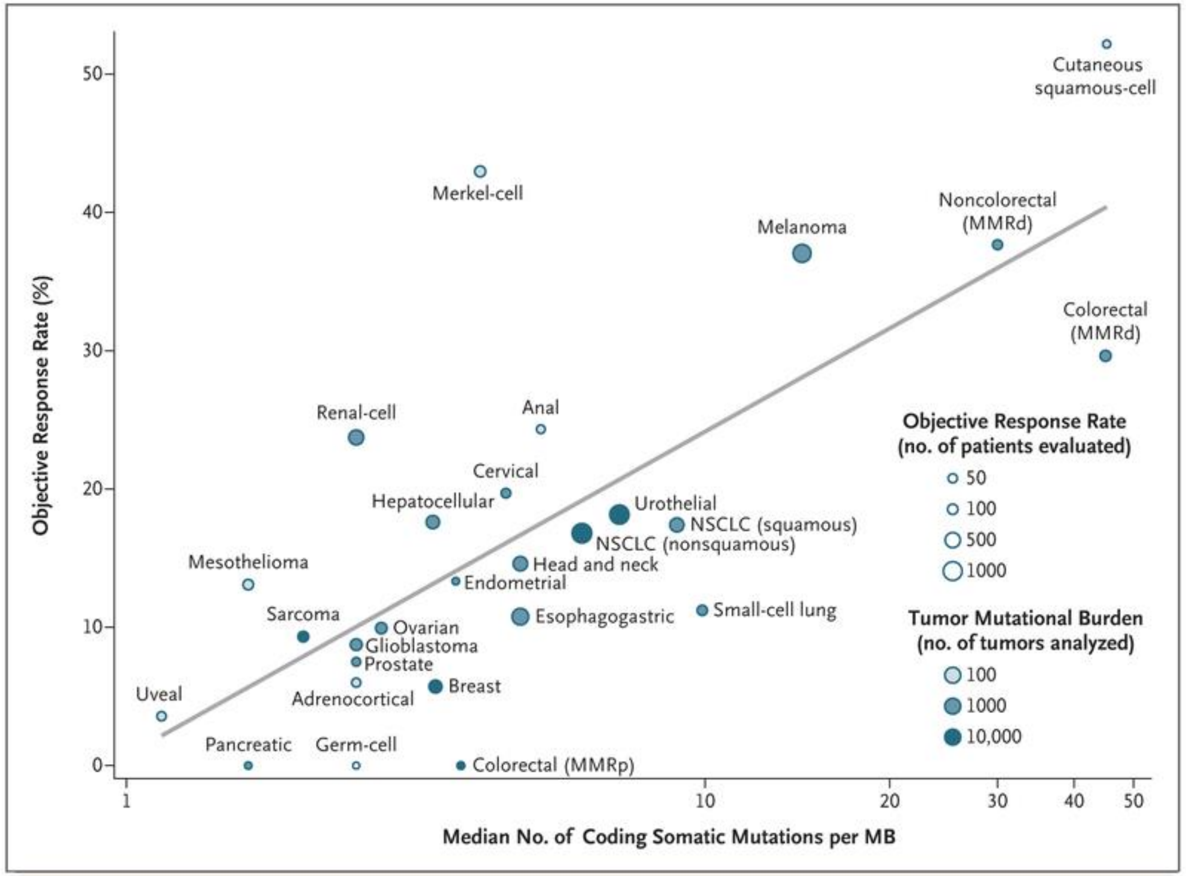
Most patients do not experience tumor response

Unselected or indiscriminate use of IO drugs is:

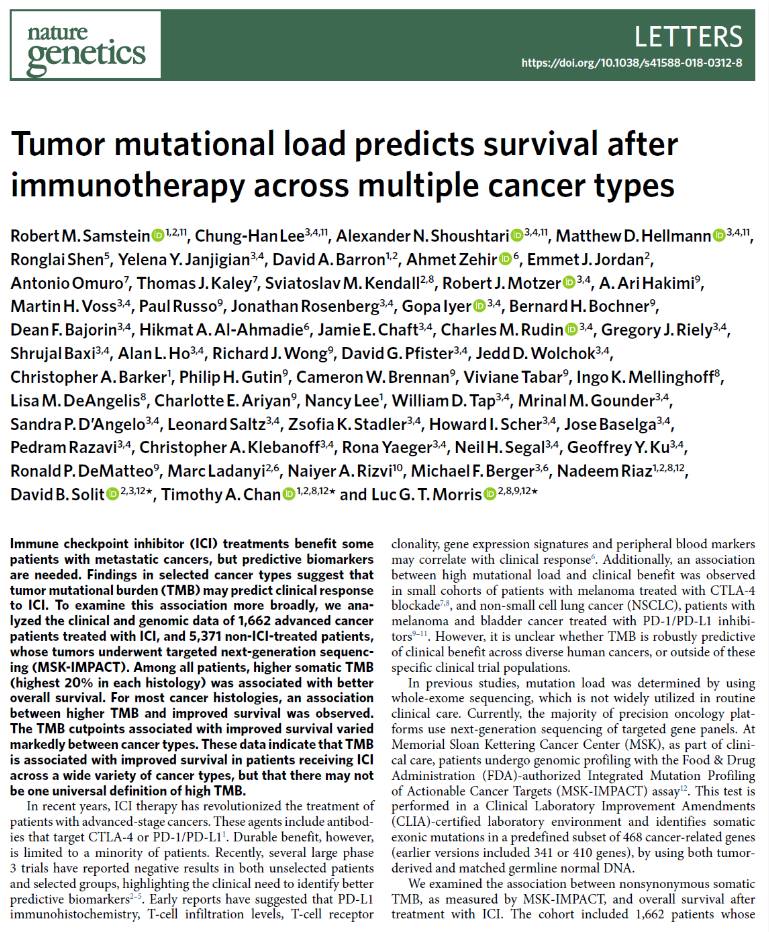
- Expensive (>$100,000 per QALY)
- Toxicity without benefit



One of our first clues: mutational load



Yarchoan, Hopkins, and Jaffee, *NEJM* 2017



nature genetics

LETTERS

https://doi.org/10.1038/s41588-018-0312-8

Tumor mutational load predicts survival after immunotherapy across multiple cancer types

Robert M. Samstein[1,2,11], Chung-Han Lee[3,4,11], Alexander N. Shoushtari[3,4,11], Matthew D. Hellmann[3,4,11], Ronglai Shen[5], Yelena Y. Janjigian[3,4], David A. Barron[1,2], Ahmet Zehir[6], Emmet J. Jordan[2], Antonio Omuro[7], Thomas J. Kaley[7], Sviatoslav M. Kendall[2,8], Robert J. Motzer[3,4], A. Ari Hakimi[9], Martin H. Voss[3,4], Paul Russo[9], Jonathan Rosenberg[3,4], Gopa Iyer[3,4], Bernard H. Bochner[9], Dean F. Bajorin[3,4], Hikmat A. Al-Ahmadie[6], Jamie E. Chaft[3,4], Charles M. Rudin[3,4], Gregory J. Riely[3,4], Shrujal Baxi[3,4], Alan L. Ho[3,4], Richard J. Wong[9], David G. Pfister[3,4], Jedd D. Wolchok[3,4], Christopher A. Barker[1], Philip H. Gutin[9], Cameron W. Brennan[9], Viviane Tabar[9], Ingo K. Mellinghoff[8], Lisa M. DeAngelis[8], Charlotte E. Ariyan[9], Nancy Lee[1], William D. Tap[3,4], Mrinal M. Gounder[3,4], Sandra P. D'Angelo[3,4], Leonard Saltz[3,4], Zsofia K. Stadler[3,4], Howard I. Scher[3,4], Jose Baselga[3,4], Pedram Razavi[3,4], Christopher A. Klebanoff[3,4], Rona Yaeger[3,4], Neil H. Segal[3,4], Geoffrey Y. Ku[3,4], Ronald P. DeMatteo[9], Marc Ladanyi[2,6], Naiyer A. Rizvi[10], Michael F. Berger[3,6], Nadeem Riaz[1,2,8,12], David B. Solit[2,3,12*], Timothy A. Chan[1,2,8,12*] and Luc G. T. Morris[2,8,9,12*]

Immune checkpoint inhibitor (ICI) treatments benefit some patients with metastatic cancers, but predictive biomarkers are needed. Findings in selected cancer types suggest that tumor mutational burden (TMB) may predict clinical response to ICI. To examine this association more broadly, we analyzed the clinical and genomic data of 1,662 advanced cancer patients treated with ICI, and 5,371 non-ICI-treated patients, whose tumors underwent targeted next-generation sequencing (MSK-IMPACT). Among all patients, higher somatic TMB (highest 20% in each histology) was associated with better overall survival. For most cancer histologies, an association between higher TMB and improved survival was observed. The TMB cutpoints associated with improved survival varied markedly between cancer types. These data indicate that TMB is associated with improved survival in patients receiving ICI across a wide variety of cancer types, but that there may not be one universal definition of high TMB.

In recent years, ICI therapy has revolutionized the treatment of patients with advanced-stage cancers. These agents include antibodies that target CTLA-4 or PD-1/PD-L1[1]. Durable benefit, however, is limited to a minority of patients. Recently, several large phase 3 trials have reported negative results in both unselected patients and selected groups, highlighting the clinical need to identify better predictive biomarkers[2–5]. Early reports have suggested that PD-L1 immunohistochemistry, T-cell infiltration levels, T-cell receptor clonality, gene expression signatures and peripheral blood markers may correlate with clinical response[6]. Additionally, an association between high mutational load and clinical benefit was observed in small cohorts of patients with melanoma treated with CTLA-4 blockade[7,8], and non-small cell lung cancer (NSCLC), patients with melanoma and bladder cancer treated with PD-1/PD-L1 inhibitors[9–11]. However, it is unclear whether TMB is robustly predictive of clinical benefit across diverse human cancers, or outside of these specific clinical trial populations.

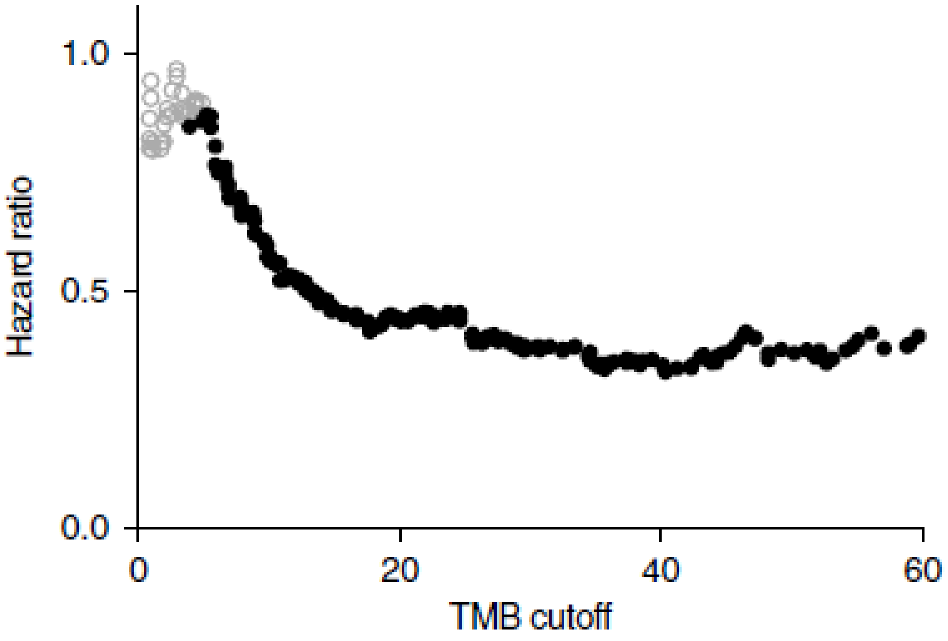
In previous studies, mutation load was determined by using whole-exome sequencing, which is not widely utilized in routine clinical care. Currently, the majority of precision oncology platforms use next-generation sequencing of targeted gene panels. At Memorial Sloan Kettering Cancer Center (MSK), as part of clinical care, patients undergo genomic profiling with the Food & Drug Administration (FDA)-authorized Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay[12]. This test is performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory environment and identifies somatic exonic mutations in a predefined subset of 468 cancer-related genes (earlier versions included 341 or 410 genes), by using both tumor-derived and matched germline normal DNA.

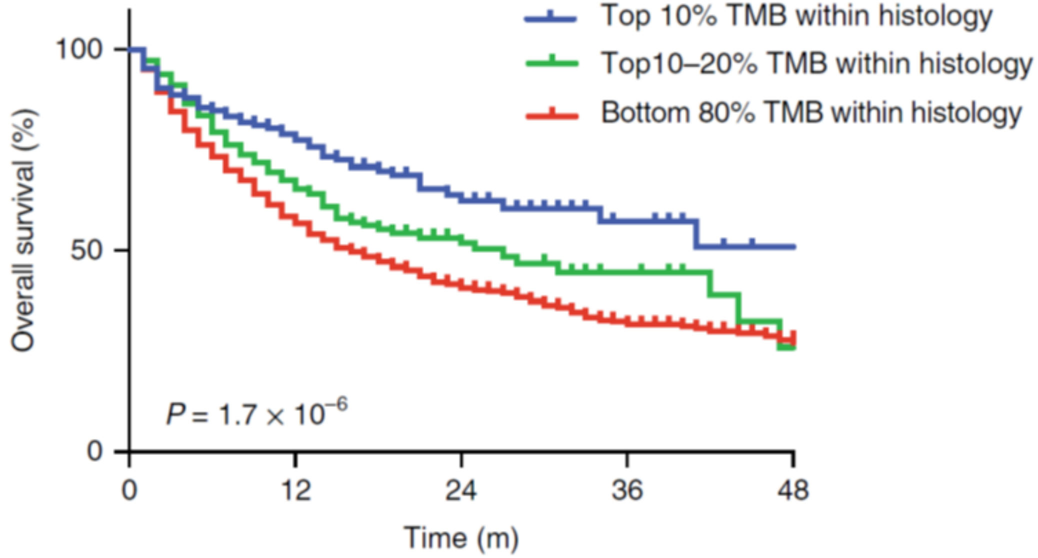
We examined the association between nonsynonymous somatic TMB, as measured by MSK-IMPACT, and overall survival after treatment with ICI. The cohort included 1,662 patients whose

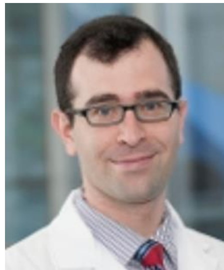
Samstein et al, *Nature Genetics* 2019

Tumor mutational load across cancer types

1662 ICI-treated patients at MSK



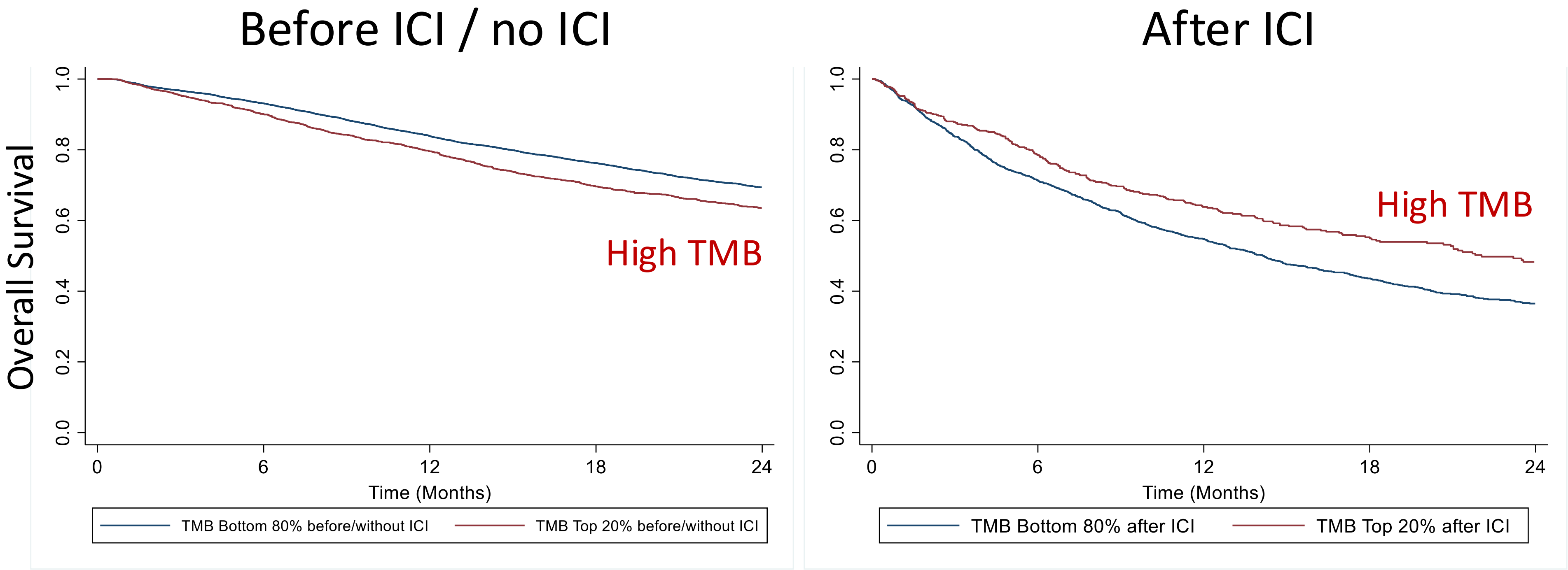

Survival from start of immunotherapy



Robbie Samstein, *Nature Genetics* 2019

Prognostic impact of TMB depends on context

Overall Survival in 10,233 patients (2,022 ICI-treated)



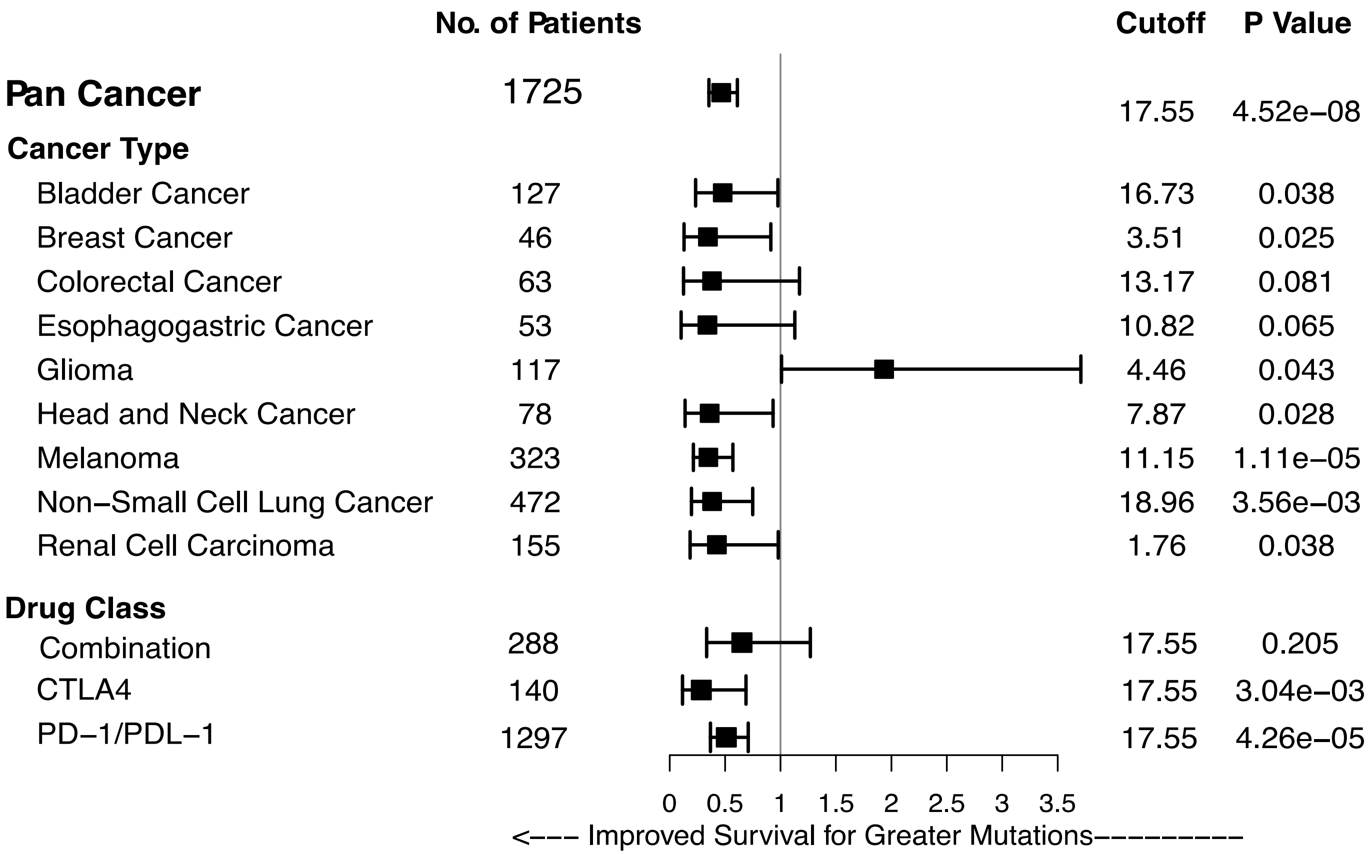
ICI: immune (T cell) checkpoint inhibitor

Note: *ICI(t)* was modeled with a time-dependent covariate

Cristina Valero (*Nature Genetics* 2021)

Tumor mutational load across cancer types

Immune checkpoint patients treated at MSK

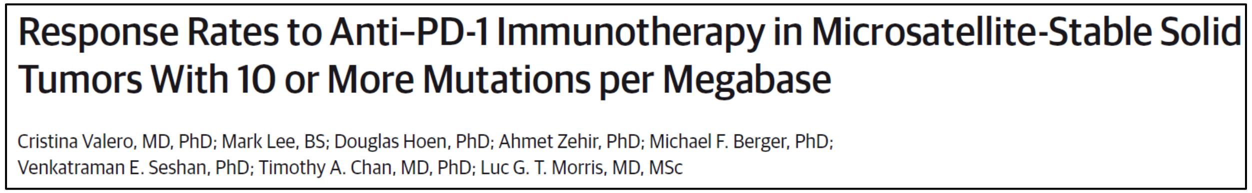


	No. of Patients	Cutoff	P Value
Pan Cancer	1725	17.55	4.52e–08
Cancer Type			
Bladder Cancer	127	16.73	0.038
Breast Cancer	46	3.51	0.025
Colorectal Cancer	63	13.17	0.081
Esophagogastric Cancer	53	10.82	0.065
Glioma	117	4.46	0.043
Head and Neck Cancer	78	7.87	0.028
Melanoma	323	11.15	1.11e–05
Non–Small Cell Lung Cancer	472	18.96	3.56e–03
Renal Cell Carcinoma	155	1.76	0.038
Drug Class			
Combination	288	17.55	0.205
CTLA4	140	17.55	3.04e–03
PD–1/PDL–1	1297	17.55	4.26e–05

Caveat: The optimal predictive cutoff varies by cancer type

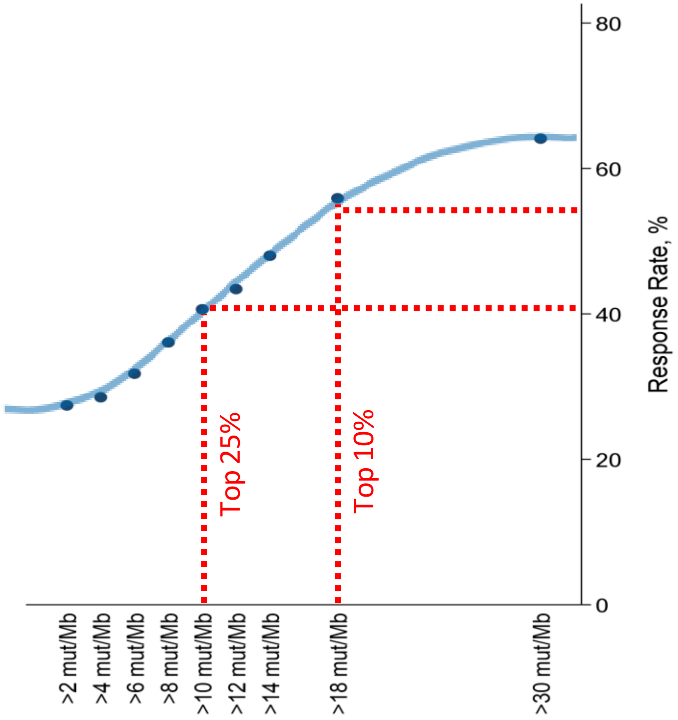
Samstein et al, *Nature Genetics* 2019

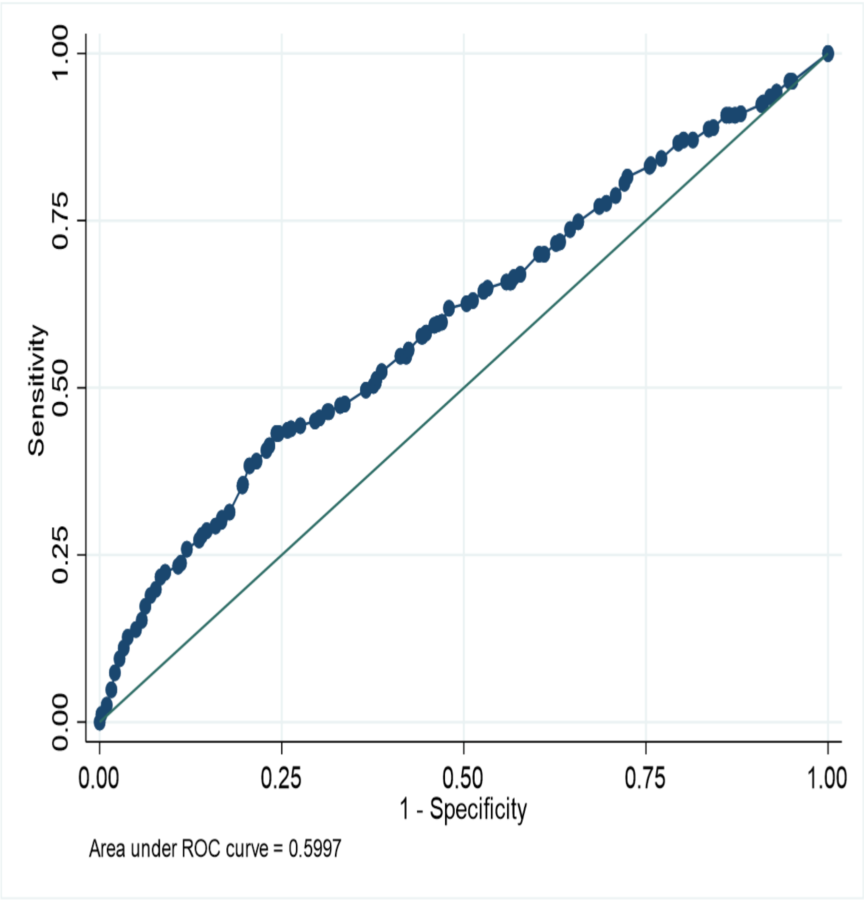
TMB has modest predictive capacity across MSS cancers



Response Rates to Anti–PD-1 Immunotherapy in Microsatellite-Stable Solid Tumors With 10 or More Mutations per Megabase

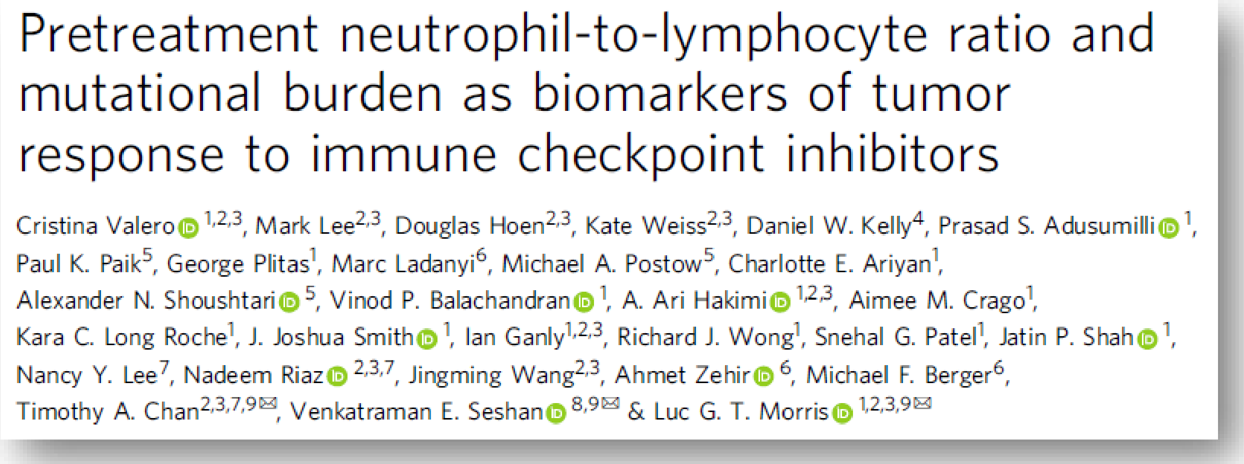
Cristina Valero, MD, PhD; Mark Lee, BS; Douglas Hoen, PhD; Ahmet Zehir, PhD; Michael F. Berger, PhD;
Venkatraman E. Seshan, PhD; Timothy A. Chan, MD, PhD; Luc G. T. Morris, MD, MSc





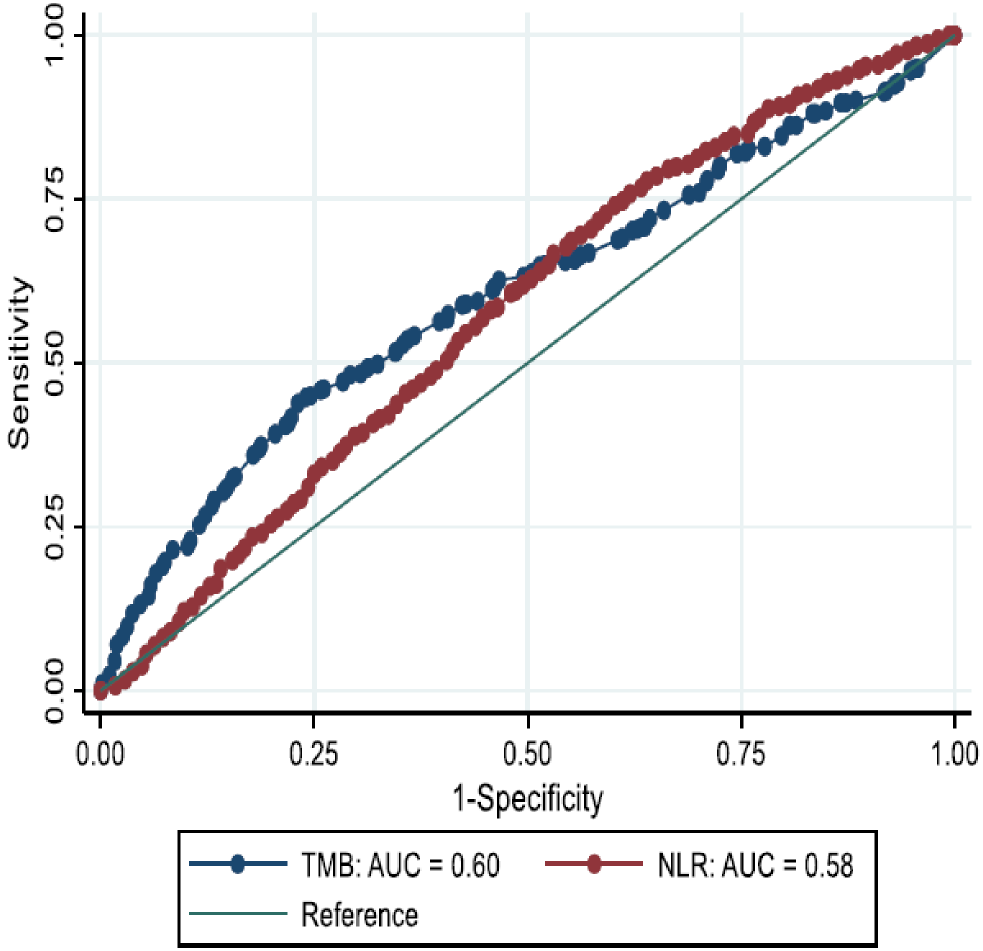
Valero et al, *JAMA Oncology* 2021

Cheap biomarkers: almost as good as TMB

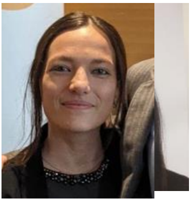


Pretreatment neutrophil-to-lymphocyte ratio and mutational burden as biomarkers of tumor response to immune checkpoint inhibitors

Cristina Valero[1,2,3], Mark Lee[2,3], Douglas Hoen[2,3], Kate Weiss[2,3], Daniel W. Kelly[4], Prasad S. Adusumilli[1], Paul K. Paik[5], George Plitas[1], Marc Ladanyi[6], Michael A. Postow[5], Charlotte E. Ariyan[1], Alexander N. Shoushtari[5], Vinod P. Balachandran[1], A. Ari Hakimi[1,2,3], Aimee M. Crago[1], Kara C. Long Roche[1], J. Joshua Smith[1], Ian Ganly[1,2,3], Richard J. Wong[1], Snehal G. Patel[1], Jatin P. Shah[1], Nancy Y. Lee[7], Nadeem Riaz[2,3,7], Jingming Wang[2,3], Ahmet Zehir[6], Michael F. Berger[6], Timothy A. Chan[2,3,7,9]✉, Venkatraman E. Seshan[8,9]✉ & Luc G. T. Morris[1,2,3,9]✉

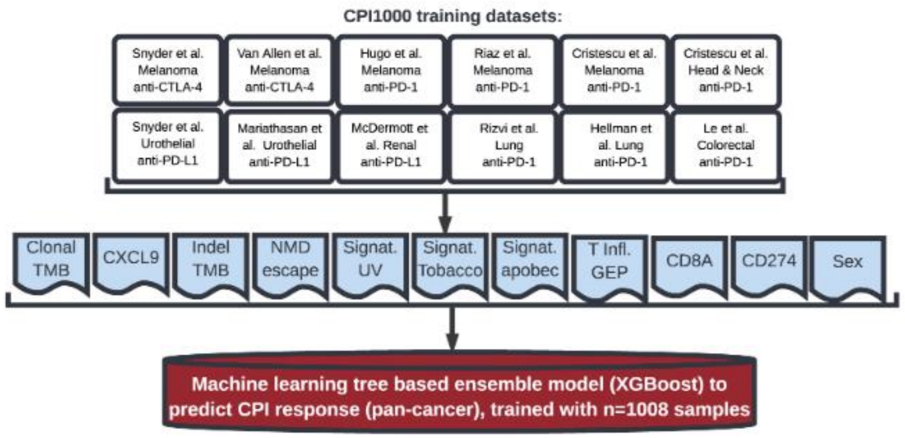


NLR and TMB expressed as percentile within cancer type.



Valero et al, *Nat Comms* 2021

Can we do better with more genomic/transcriptomic data? *A little*



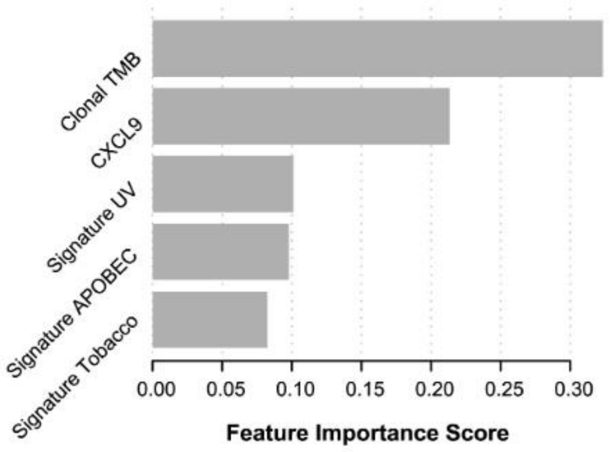
CPI1000 training datasets:

Snyder et al. Melanoma anti-CTLA-4
Van Allen et al. Melanoma anti-CTLA-4
Hugo et al. Melanoma anti-PD-1
Riaz et al. Melanoma anti-PD-1
Cristescu et al. Melanoma anti-PD-1
Cristescu et al. Head & Neck anti-PD-1
Snyder et al. Urothelial anti-PD-L1
Mariathasan et al. Urothelial anti-PD-L1
McDermott et al. Renal anti-PD-L1
Rizvi et al. Lung anti-PD-1
Hellman et al. Lung anti-PD-1
Le et al. Colorectal anti-PD-1

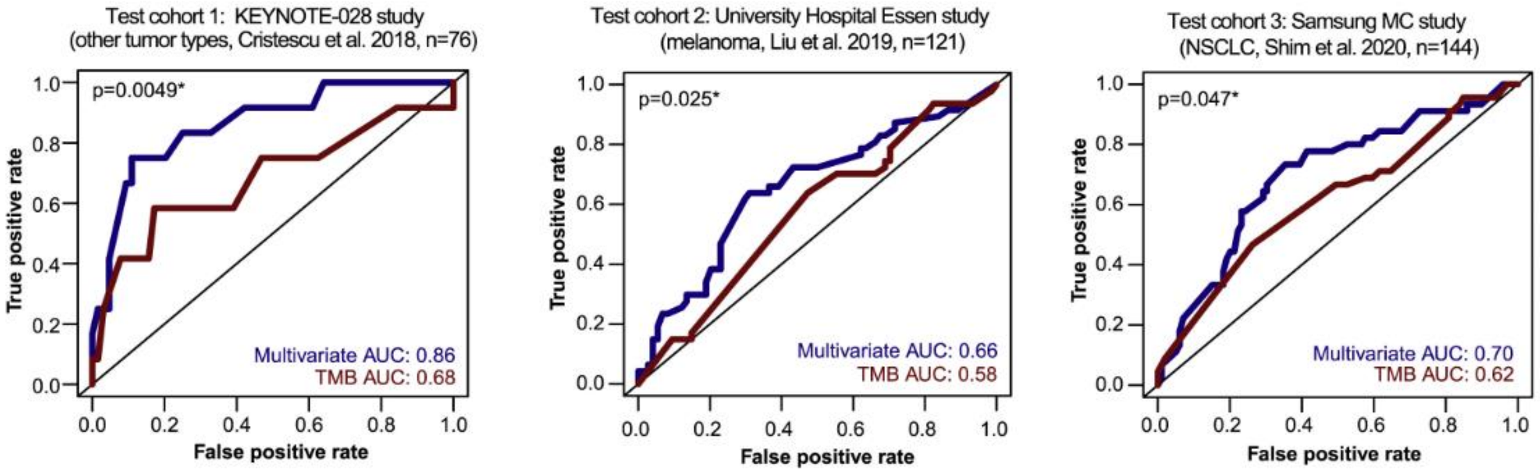
Clonal TMB | CXCL9 | Indel TMB | NMD escape | Signat. UV | Signat. Tobacco | Signat. apobec | T Infl. GEP | CD8A | CD274 | Sex

Machine learning tree based ensemble model (XGBoost) to predict CPI response (pan-cancer), trained with n=1008 samples

Final trained model (n=1008 samples), top 5 importance scores:



Testing of TMB versus multivariable CPI stratifier performance in three independent test cohorts (total n=341):



XGBoost decision tree model

11 features (from WES+RNAseq)
Average AUC of 0.72

(weighted mean, 3 test sets)

Litchfield … Swanton et al. *Cell* 2021

Summary so far:

TMB alone

Genomic models (WES and/or RNAseq)

Multi-modal models (radiology + pathology + genomics)

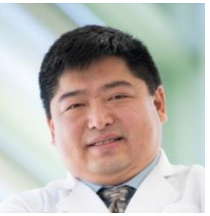
What can we get from just clinical tumor sequencing?

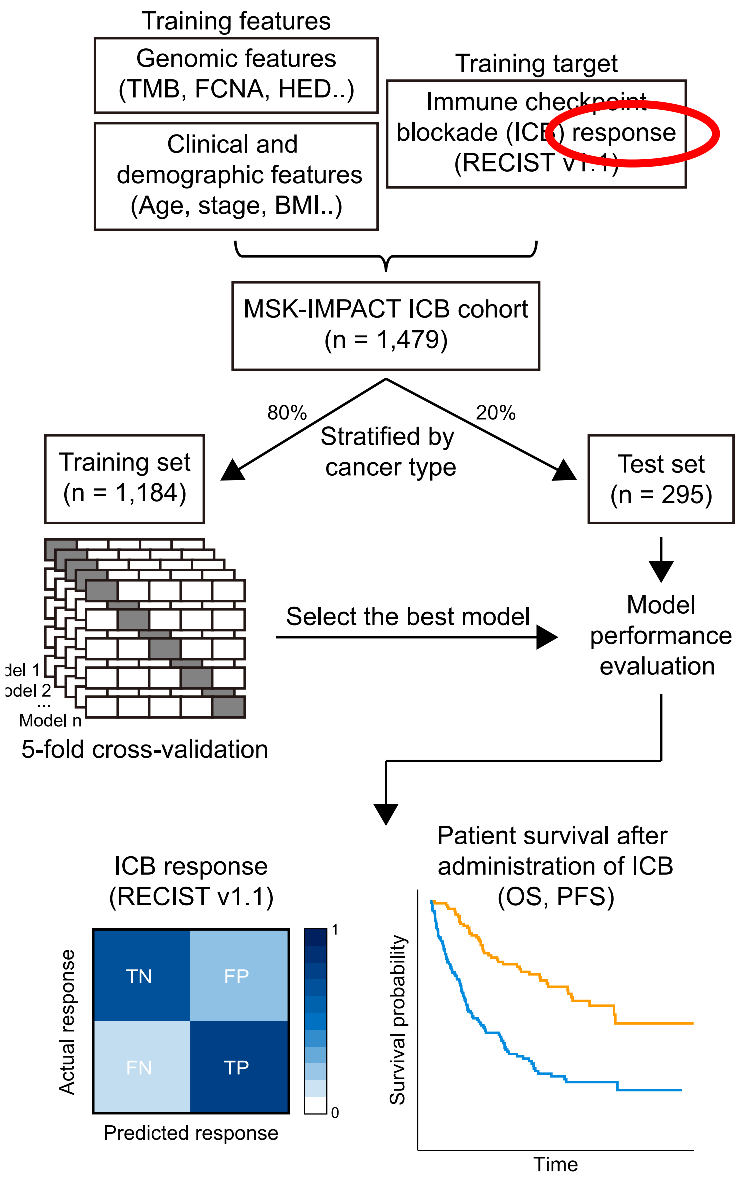
What is the best we can do with clinical-level tumor sequencing?


Chowell


Valero


Weinhold


Chan


Training features

Genomic features (TMB, FCNA, HED..)

Clinical and demographic features (Age, stage, BMI..)

Training target

Immune checkpoint blockade (ICB) response (RECIST v1.1)

MSK-IMPACT ICB cohort (n = 1,479)

80%

20%

Stratified by cancer type

Training set (n = 1,184)

Test set (n = 295)

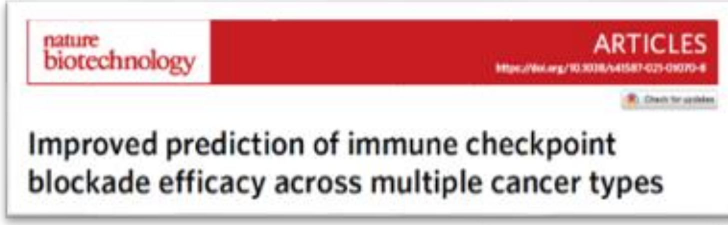
Select the best model

Model performance evaluation

5-fold cross-validation

ICB response (RECIST v1.1)

Patient survival after administration of ICB (OS, PFS)


nature biotechnology

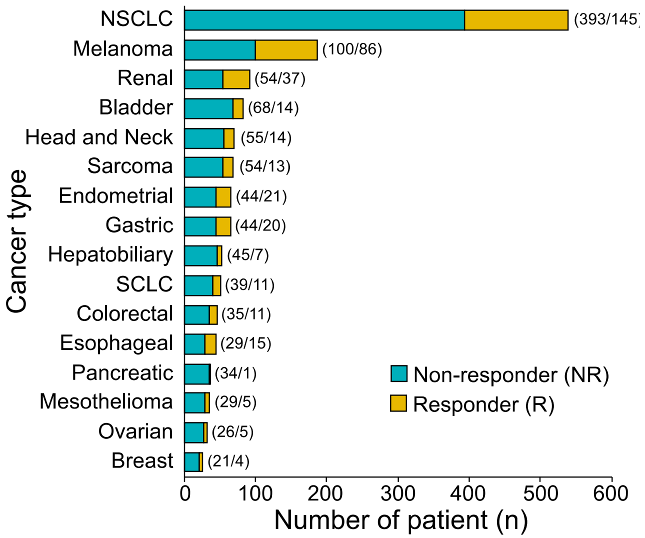
ARTICLES

Improved prediction of immune checkpoint blockade efficacy across multiple cancer types

Chowell et al, *Nature Biotechnology* 2021

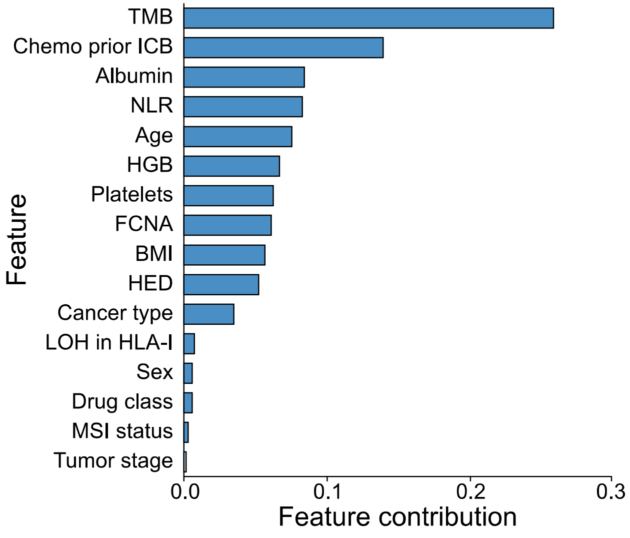
A random-forest approach to improve predictive value

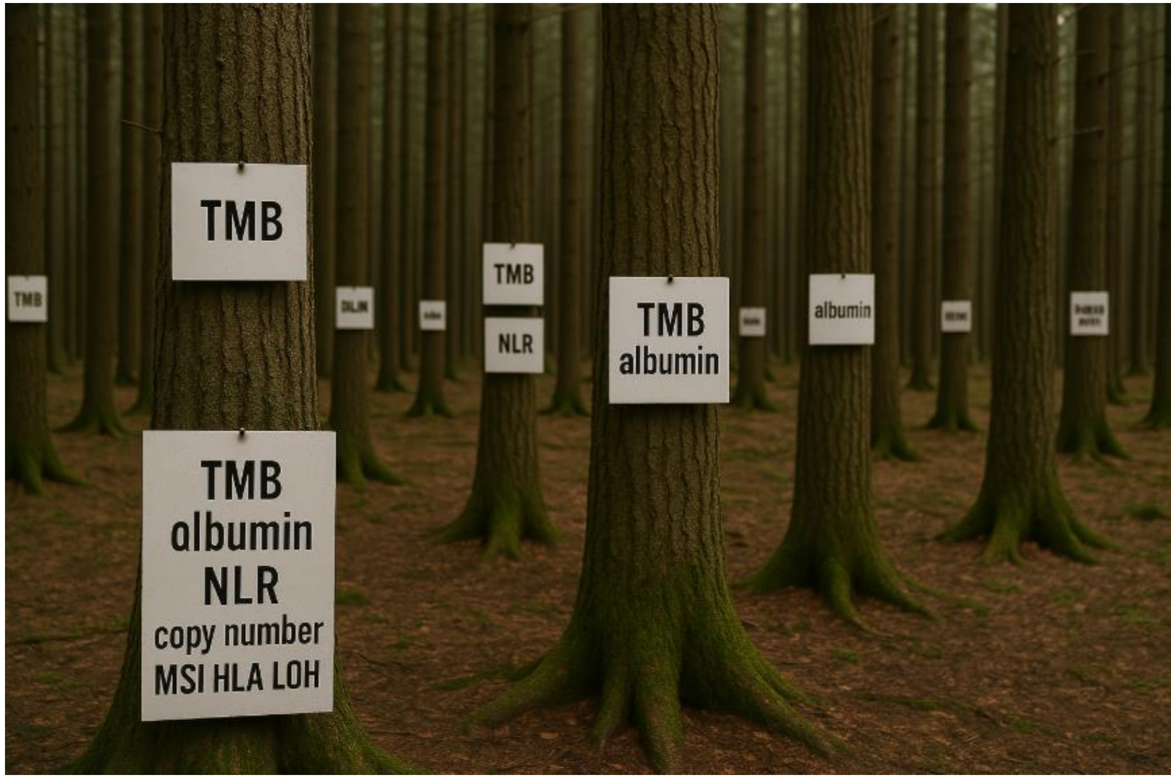
MSK NGS-IO cohort
(n=1479)



Feature contribution
(RF16)

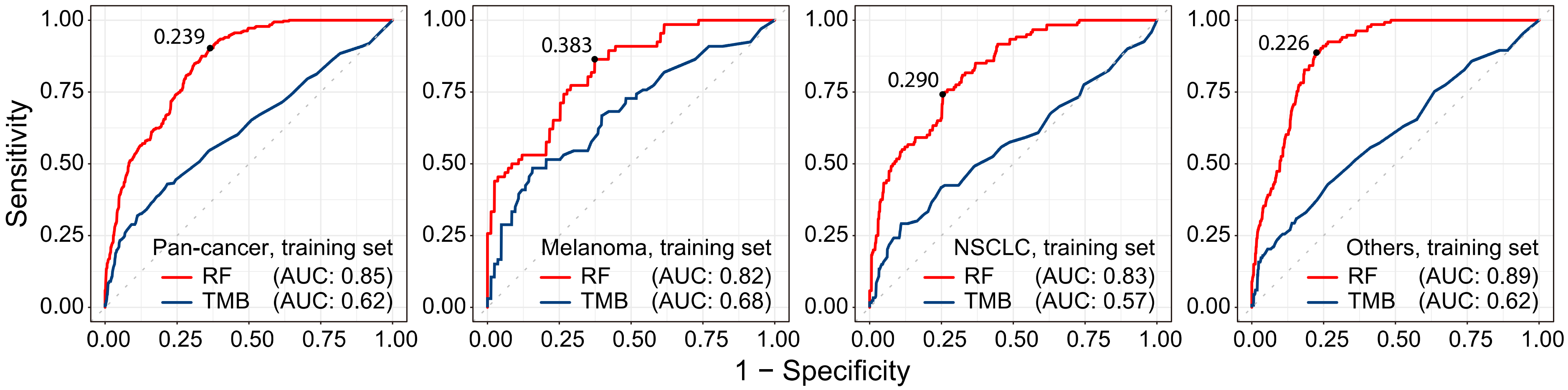
c



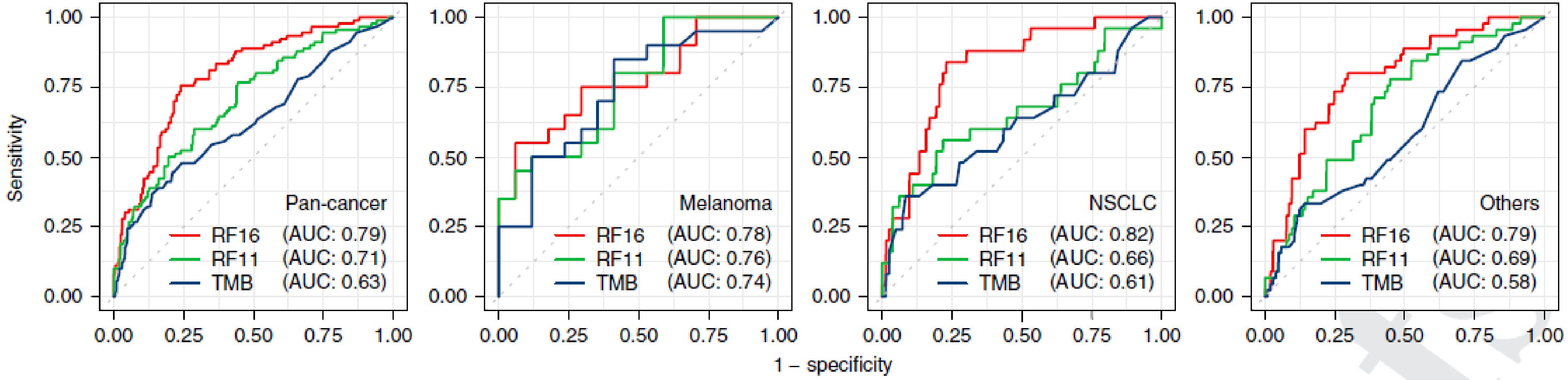


Performance of the RF model – predicting response

Training set

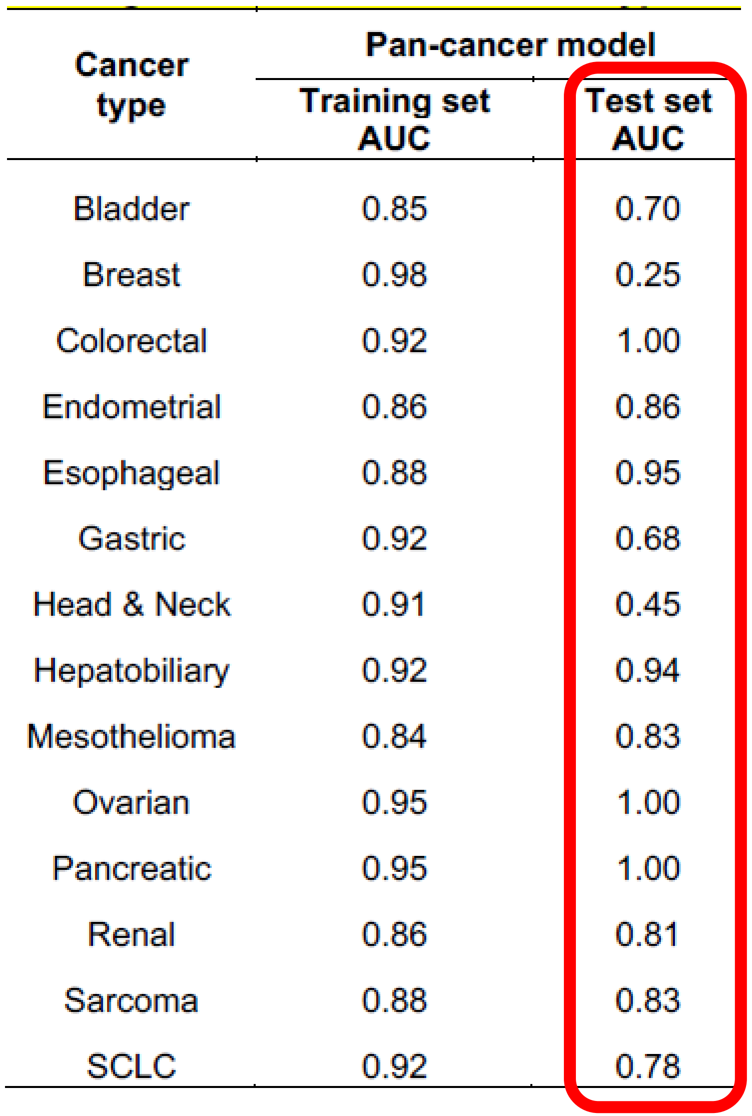


Test set



Performance of the RF model: predicting response

Non-melanoma/non-NSCLC cancer types

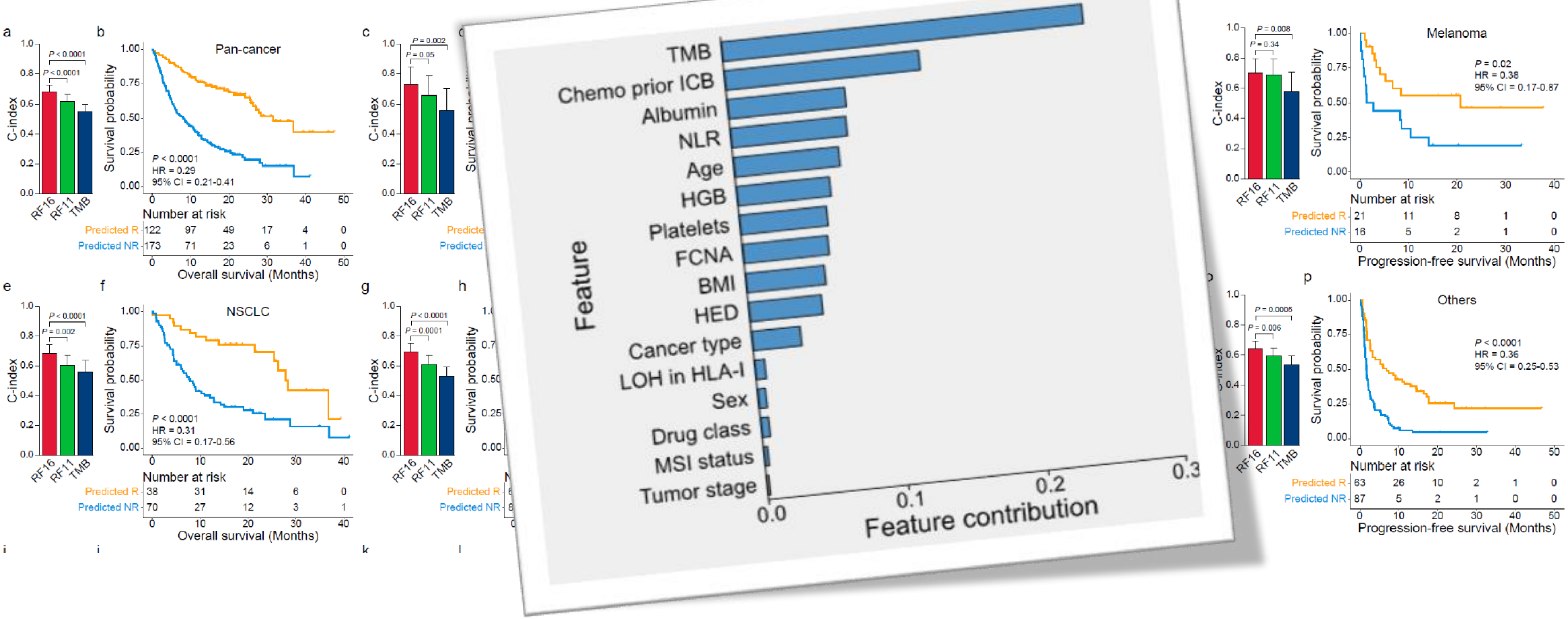


Cancer type	Pan-cancer model	
	Training set AUC	**Test set AUC**
Bladder	0.85	0.70
Breast	0.98	0.25
Colorectal	0.92	1.00
Endometrial	0.86	0.86
Esophageal	0.88	0.95
Gastric	0.92	0.68
Head & Neck	0.91	0.45
Hepatobiliary	0.92	0.94
Mesothelioma	0.84	0.83
Ovarian	0.95	1.00
Pancreatic	0.95	1.00
Renal	0.86	0.81
Sarcoma	0.88	0.83
SCLC	0.92	0.78

Performance of the RF model – predicting survival

Overall Survival

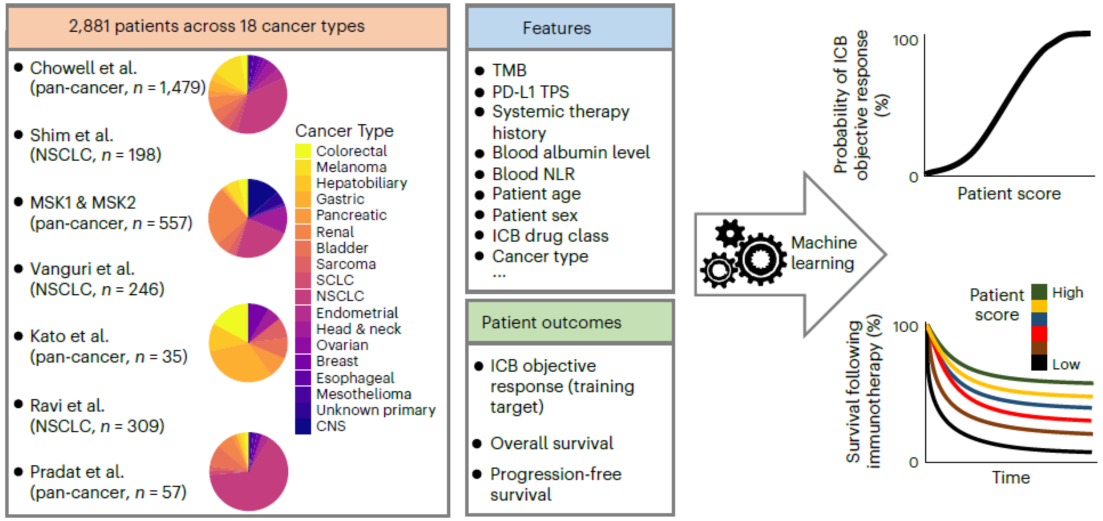
Progression-free Survival

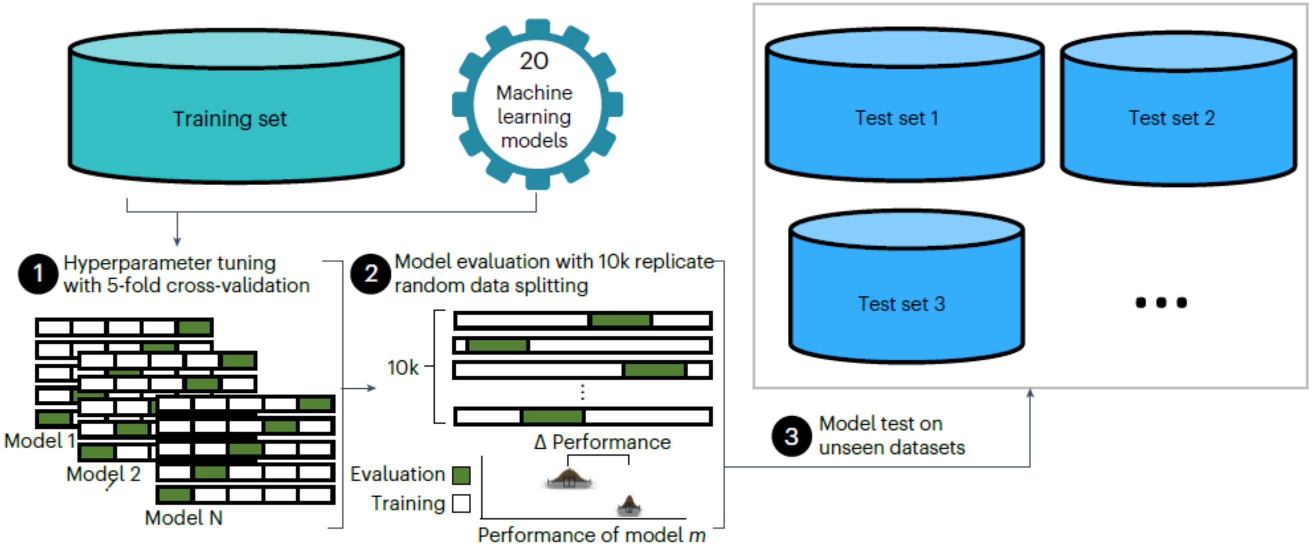


Chowell et al, *Nature Biotechnology* 2021

Do we need to take a Cybertruck to go grocery shopping?

Paper #2 – We need tools using commonplace data features





Eytan Ruppin
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Tiangen Chang

nature cancer

Article

https://doi.org/10.1038/s43018-024-00772-

LORIS robustly predicts patient outcomes with immune checkpoint blockade therapy using common clinical, pathologic and genomic features

Chang et al, *Nature Cancer* 2024

Immune surveillance: relevant in early & late-stage cancers

Normal tissues are probably replete with mutations
- *Especially as we age*
  - *Oral epithelial cells*
  - *Skin cells*

We can find evidence of immunoediting in patients
- *Immune escape in tumors that do not respond to immunotherapy*
- *Immunoediting in tumors that do respond*

Healthy persons probably have small microcancers under immune surveillance
- *Some are in equilibrium and may not ever require treatment*

Understanding these mechanisms is key to developing new strategies
- *Active surveillance has great promise for indolent tumors*
- *We can predict immunotherapy response using related clinical & genomic data*

Thanks to many friends and colleagues here today…

Morris Lab

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