ICO Institut Català d'Oncologia

IDIBELL Oncobell program

Tertulies Tecnològiques de la Facultat de Farmacia

10 Juliol, 2025

Retos de la Medicina de Precisión en Oncología: cuando las Leyes del Cáncer chocan con las Leyes de la Medicina

Ramon Salazar

Catalan Institue of Oncology. IDIBELL. University of Barcelona

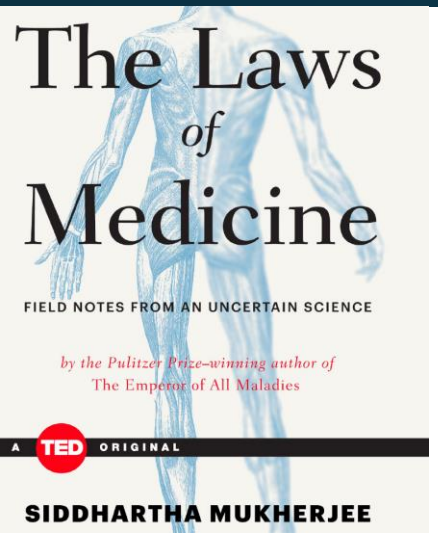
/Salut

Universitat de Barcelona

The 3 Laws of Medicine

LAW ONE

A strong intuition is much more powerful than a weak test.



Teorema de Bayes

$$P[A_n/B] = \frac{P[B/A_n] \cdot P[A_n]}{\sum P[B/A_i] \cdot P[A_i]}$$

$$\text{PPV} = \frac{\overset{\text{(true +)}}{\text{Sensitivity} \times \text{Prevalence}}}{\underset{\text{(true +)}}{\text{Sensitivity} \times \text{Prevalence}} + \underset{\text{(false +)}}{(1-\text{Specificity}) \times (1-\text{Prevalence})}}$$

PPV, NPV are more relevant than Sensitivity/Specificity

clinical context/prevalence matters

LAW TWO

"Normals" teach us rules; "outliers" teach us laws.

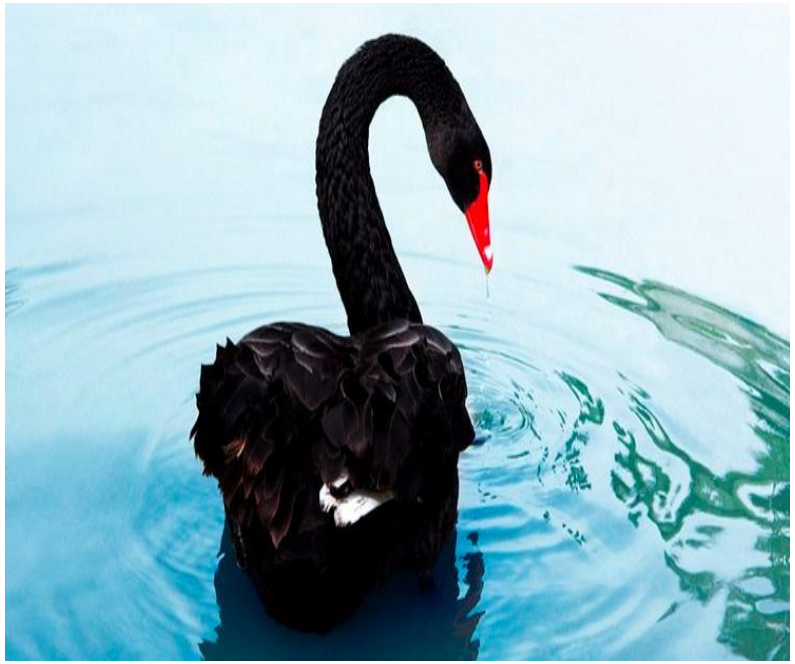
Clinical, Molecular and immunological (among others) determinants of Extreme responders

*Standard protocols for clinical criterio, sample storage, processing and molecular analyses

Few determinants-----Small Case–control:

Multiple determinants: all-comers **MVA**

BMK: **how large it would need to be to achieve adequate power for a given sample size**.



*high concordance rate for characterization of **DNA, RNA, protein and immunohistochemical** analyses across contributing laboratories

Treasure your exceptions!
Bateson, W. *The Methods and Scope of Genetics* (Cambridge Univ. Press, 1908).

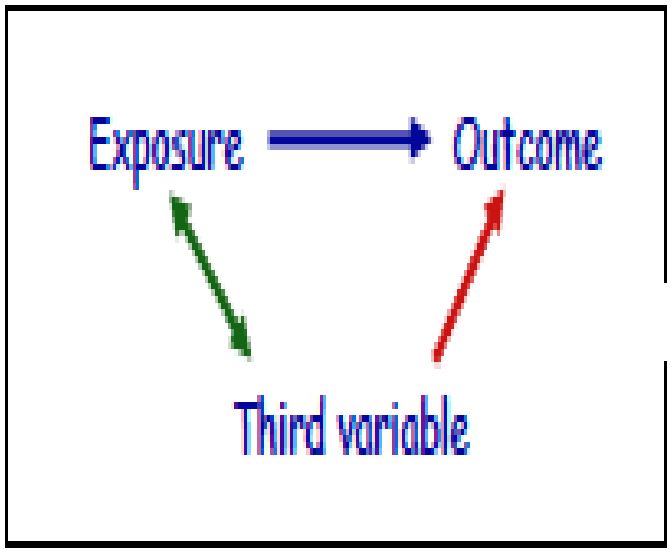
Saner et al. Nat Rev Cancer 2019

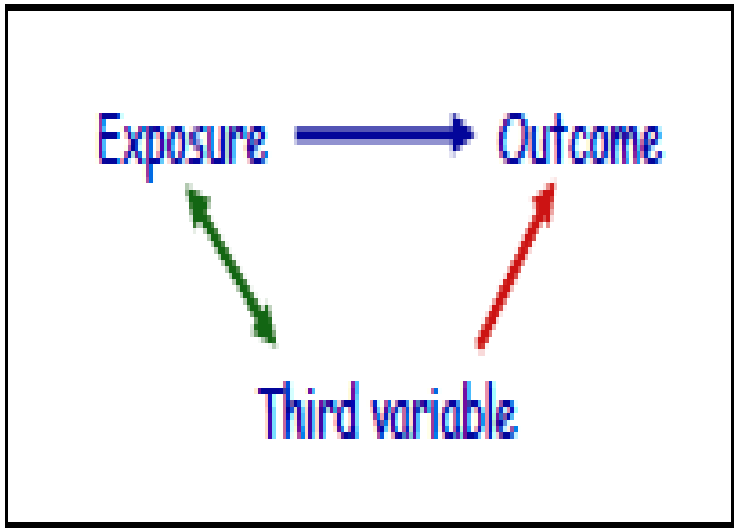
LAW THREE

medical experimen
human bias.

Soroll

Biaix





Casual

Sistemàtic

LAW THREE

medical experimen
human bias.

Salut/ ICO Institut Català d'Oncologia

Què és un biaix?

- Definició general de **biaix cognitiu**: tendència a cometre **errors sistemàtics** a les anal. lisis cognitives per factors subjectius o dreceres heurístiques (herència del *"fight or flight"*)
  - Sovint són subconcients, quan són conscients comporten sectarisme, frau...etc
  - Hi ha descrits **més de 180 tipus de biaixos cognitius** a la literatura de psicología i neurociència.
    - Aquest número pot variar segons les classificacions o denominacions
- Impacten la **presa de decisions**
  - professionals/científiques
  - personals
  - i en les dinàmiques d'equips

Tipus de biaix?

- **Biaix personal**: judicis i percepcions influenciats per les pròpies experiències, emocions o creences, que poden afectar les decisions i interaccions amb altres persones.
  - Exemple: Biaix d'afinitat, biaix de gènere…etc
- **Biaix d'equip**: quan es manifesten dins d'un grup i afecten negativament les dinàmiques d´equip, sovint relacionades amb la pressió social, l'autoritat o la cerca de consens sense qüestionar les decisions.
  - Exemple: Biaix de grup (groupthinking)…etc
- **Biaix científic**: afecta el procés de recerca o les decisions mèdiques, sovint influenciat per preferències, selecció inadequada de mostres o altres factors que distorsionen els resultats.
  - Exemple: Biaix de confirmació, biaix de publicació…etc

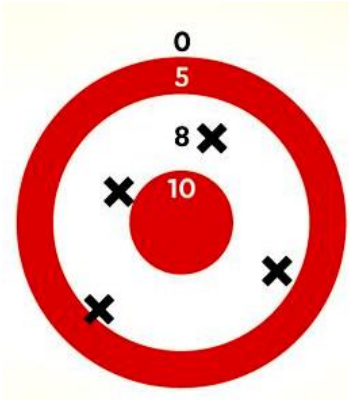
LAW THREE

medical experimen
human bias.

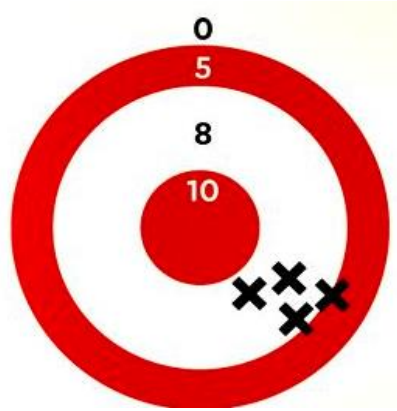
Salut/ ICO Institut Català d'Oncologia

Scientific Noise/Bias

generate bad/fake/pseudo science



More than 50 scientific biases are described in different disciplines
Some frequent exemples in Biomedicine…



Confirmation bias

publication bias.
ancorage bias

Selection bias

Evaluation bias

Survivor or Inmortal time bias

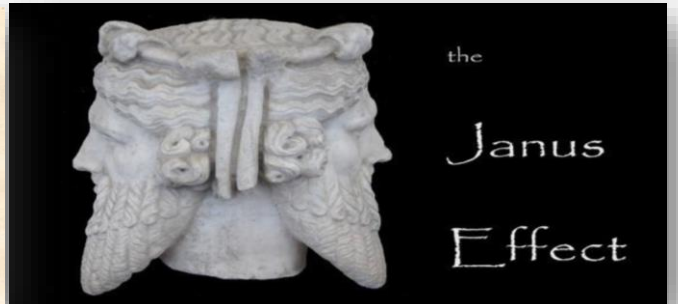
Cluster bias[1]

[1]Fooled by randomness.
by Nassim Taleb

Multiple testing

Procustes*

Janus effect**



- ***If you torture your data long enough, they will tell you whatever you want to hear***

NEJM 1993, 329:1196-1199

Patel et al.. J Clin Epid, 2015**

Cuidado con el Big Data… alto riesgo de *multiple testing*

- series de datos que presentan una perfecta asociación con un paralelismo impecable a la baja a lo largo de los años, como son el número anual de divorcios en el estado de Maine y el consumo “per cápita” anual de margarina en los Estados Unidos.
- Causalidad o casualidad?

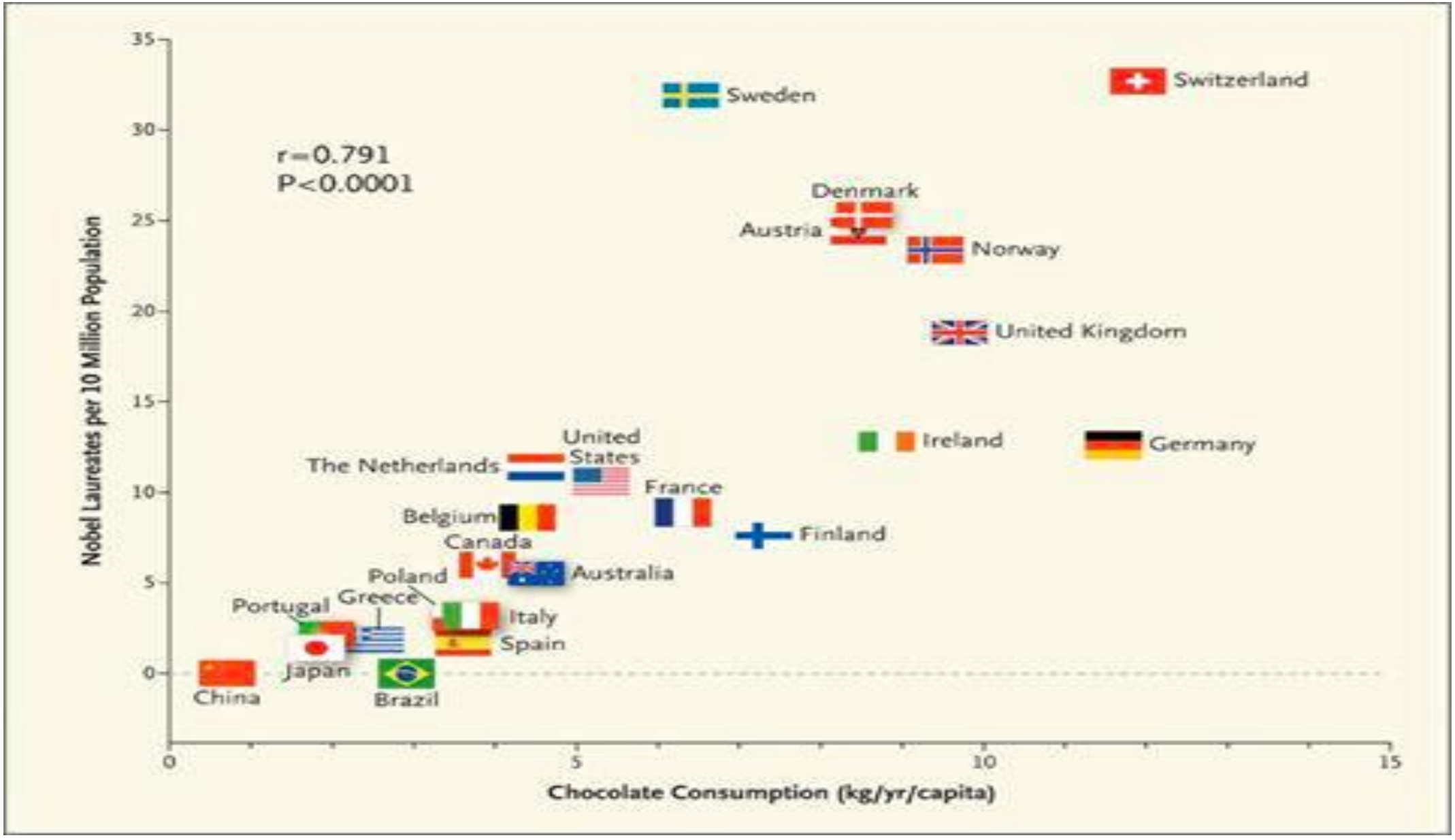
Ejemplos Big Data

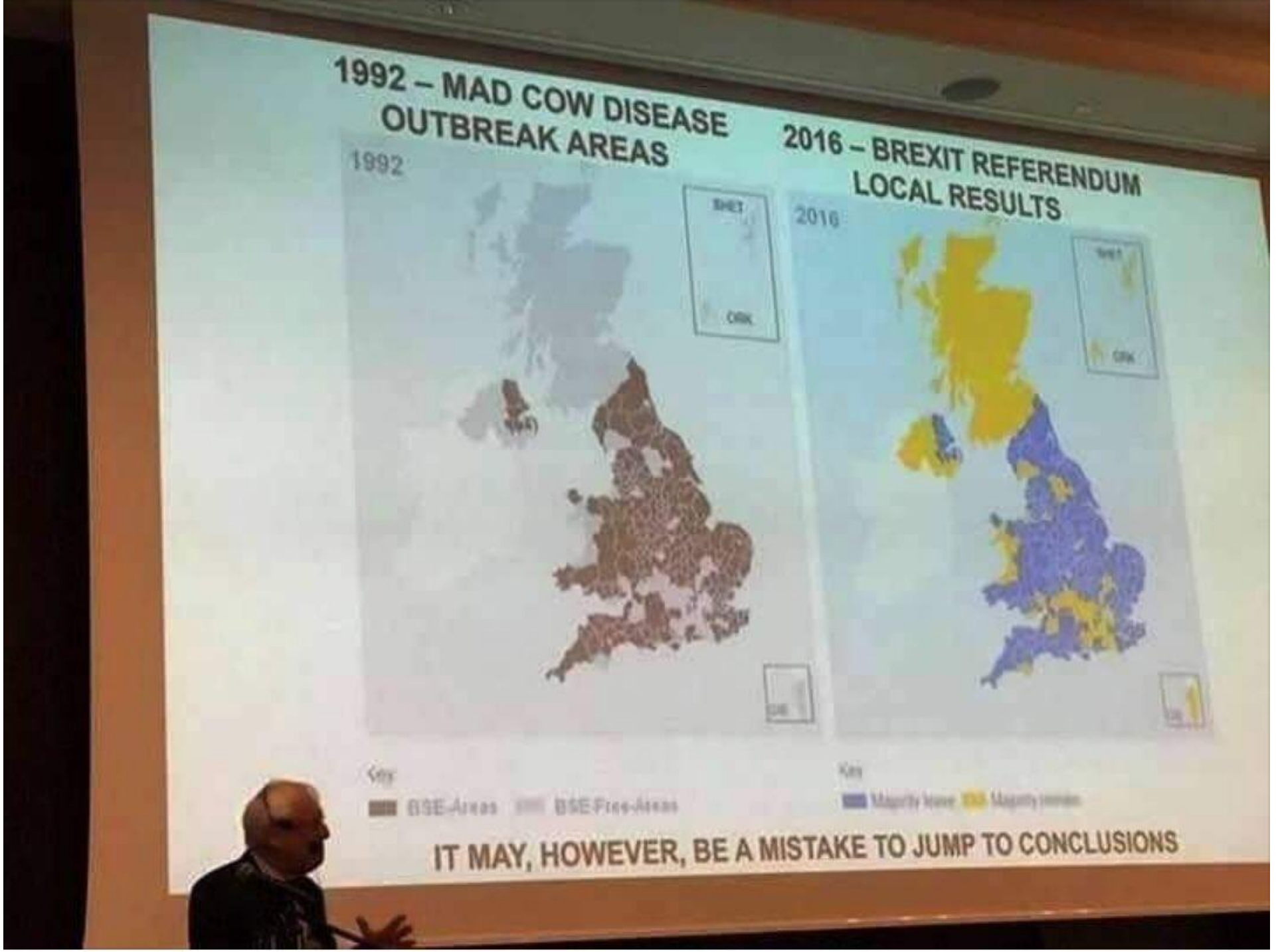
- correlación inversa perfecta que se aprecia entre la temperatura en superficie del planeta tierra (al alza) y la cifra de piratas marinos (a la baja), desde 1800.
- son causa la una de la otra?
  - La creación de un máster de piratas marinos no es una buena decisión en el ámbito de la lucha contra el cambio climático.
- Es pura casualidad?
- o hay un tercer factor causal que explique las dos tendencias?

Ejemplos Big Data

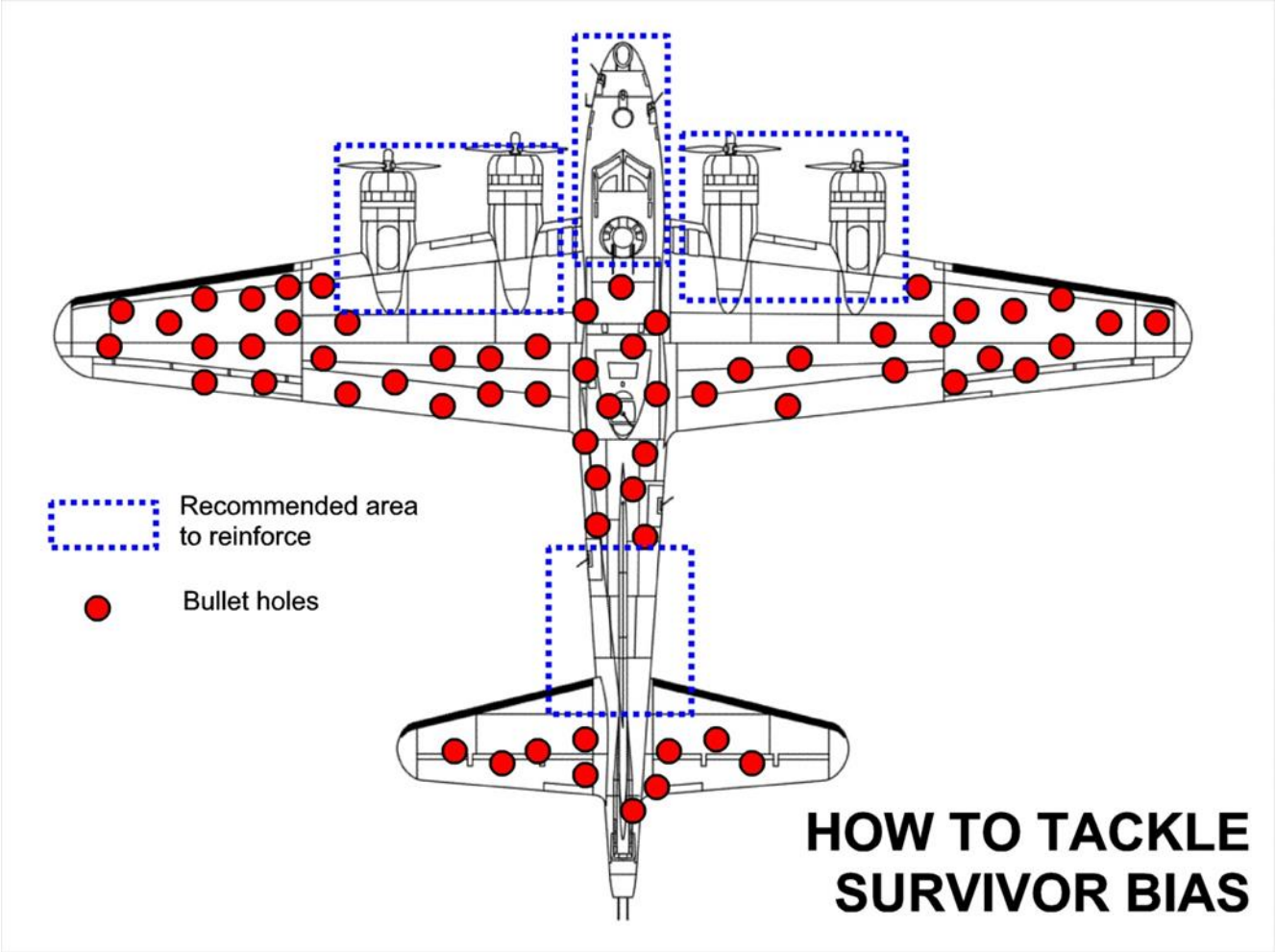
- La cifra de ventas de las compañías de helados a lo largo de los meses y el número de hectáreas de bosque quemado. Son dos series de datos asociadas porque cuando suben las ventas, aumenta la superficie quemada y cuando bajan las ventas disminuye la superficie quemada.
- ¿Quiere esto decir que si comemos helado tenemos más riesgo de que nos ataquen los tiburones ?

Consumo de chocolate x càpita & Premios Nobel




1992 – MAD COW DISEASE OUTBREAK AREAS
1992
SHET
ORK
2016 – BREXIT REFERENDUM LOCAL RESULTS
2016
SHET
ORK
Key
BSE-Areas
BSE-Free-Areas
Key
IT MAY, HOWEVER, BE A MISTAKE TO JUMP TO CONCLUSIONS

Sesgo del superviviente



Ejemplo de relacion causal¿?

- La cifra de colesterol y el riesgo cardiovascular son dos series de datos que están asociadas (si el colesterol sube, el riesgo sube)
- relación causal (el colesterol elevado es la causa del incremento del riesgo cardiovascular)???

Otros errores sistemáticos
Lectura crítica de la literatura médica
(donde está la bolita)

$$x=y$$

$$xx=xy$$

$$xx-y^2=xy-y^2$$

$$x^2-y^2=xy-y^2$$

$$(x+y)(x-y)=y(x-y)$$

$$(x+y)(x-y)/(x-y)=y(x-y)/(x-y)$$

$$(x+y)=y$$

$$y+y=y$$

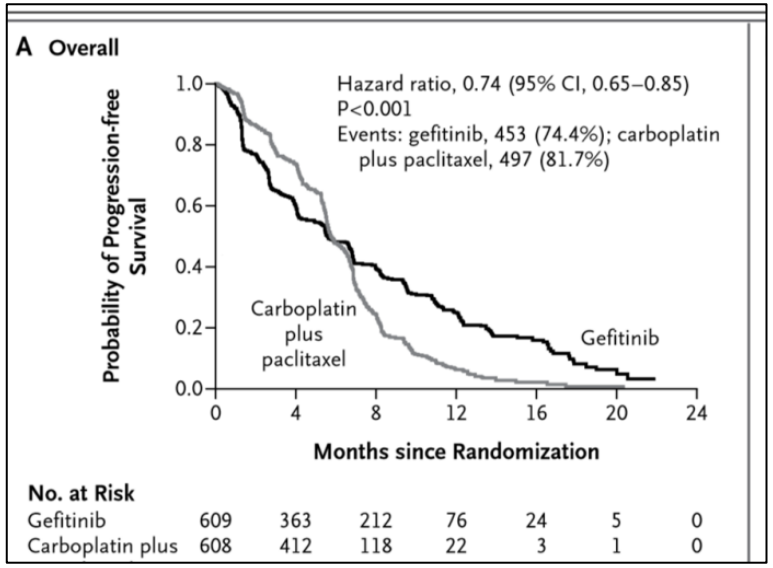
$$2y=y$$

$$2y/y=y/y$$

$$2=1$$

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Mok, NEJM 2009

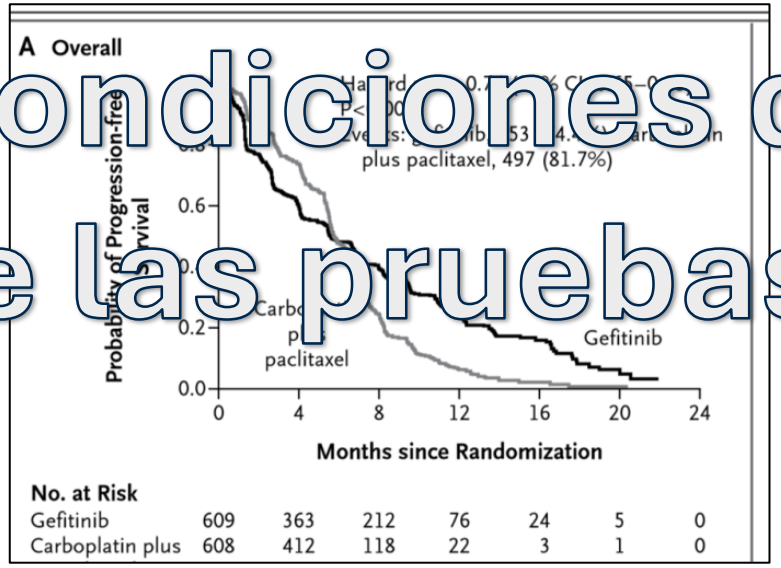


EFFICACY

The median follow-up period for the analysis of progression-free survival was 5.6 months. The median progression-free survival was 5.7 months in the gefitinib group and 5.8 months in the carboplatin–paclitaxel group, approximately coinciding with crossing of the Kaplan–Meier curves. The 12-month rates of progression-free survival were 24.9% with gefitinib and 6.7% with carboplatin–paclitaxel; a total of 950 patients had progression of disease. The study met its primary objective of demonstrating noninferiority and showed the superiority of gefitinib as compared with carboplatin–paclitaxel for progression-free survival (hazard ratio for progression or death, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). The probability that a patient would be free of disease progression was greater with carboplatin–paclitaxel in the first 6 months and greater with gefitinib in the following 16 months (Fig. 2A). Progression-free survival was longer in the gefitinib group than in the carboplatin–paclitaxel group in all clinical subgroups; the only clinical factor

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Mok, NEJM 2009

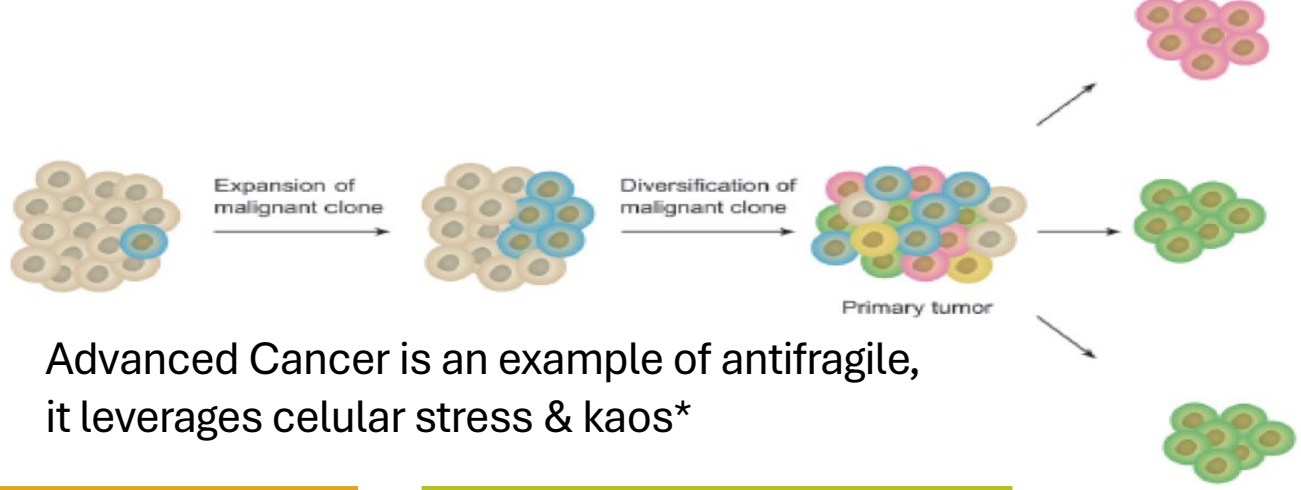


EFFICACY

The median follow-up period for the analysis of progression-free survival was 5.6 months. The median progression-free survival was 5.7 months in the gefitinib group and 5.8 months in the carboplatin–paclitaxel group, approximately coinciding with crossing of the Kaplan–Meier curves. The 12-month rates of progression-free survival were 24.9 [illegible] of disease. The study met its primary objective of demonstrating noninferiority and showed the superiority of gefitinib as compared with carboplatin–paclitaxel [illegible] dence interval [CI], 0.65 to 0.85; P<0.001). The probability that a patient would be free of disease progression was greater with carboplatin–paclitaxel in the first 6 months and greater with gefitinib in the following 16 months (Fig. 2A). Progression-free survival was longer in the gefitinib group than in the carboplatin–paclitaxel group in all clinical subgroups; the only clinical factor

condiciones de aplicación de las pruebas estadísticas

Laws of Cancer



Advanced Cancer is an example of antifragile, it leverages celular stress & kaos*

Law 1: **Complexity**

Law 2: **Heterogeneity** (& Redundancy)

Law 3: Plasticity (**Dynamic clonal evolution**)

Dimension 1: **Tumor** (histology, functional biology, molecular biology and **staging/clinical setting**)

Dimension 2: Tumor **µenvironment** (paracrine signalling, ECM, CAFs, Inmune)

Dimension 3: **Patient "host" determinants** (PK/PD, endocrine signalling, age, gender, comorbidities, other clinical and evironmental variables…)

* Antifragile. Nassim Taleb

Precision Medicine in Cancer. Challenges

https://sora.com/g/gen_01jqrxc8cmfr89e6rst7gjxbhv

When the Laws of Cancer meet the Laws of Medicine

Challenges in Biomarker Development for Cancer Precision Medicine

- Assay Variability & Lack of Standardization
- Over-Reliance on Static Cut-Offs
- Biological Complexity & Tumor Heterogeneity
- Bias and Underrepresentation in Datasets on non diverse cohorts
- Limited Multi-Omics Integration
- Low Clinical Translation Rate
- Regulatory and Infrastructure Gaps

Challenges of Cancer Precision Medicine
Heterogeneity & Redundancy examples

Benefit of BRAF inhibition in melanoma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Fig 2. A 38-year-old man with *BRAF*-mutant melanoma and miliary, subcutaneous metastatic deposits. Photographs were taken (A) before initiation of PLX4032, (B) after 15 weeks of therapy with PLX4032, and (C) after relapse, after 23 weeks of therapy.

Limited Benefit of BRAF inhibition in melanoma

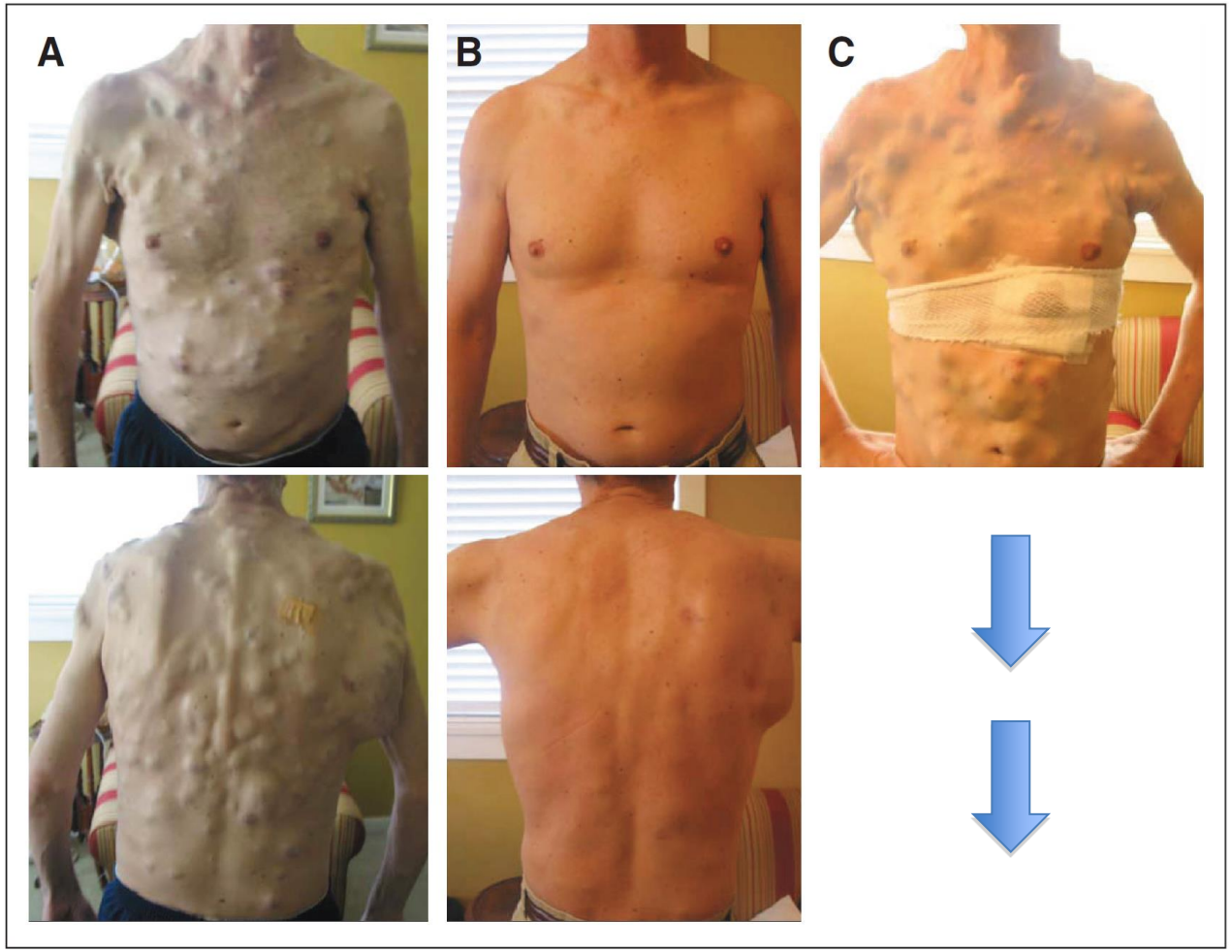
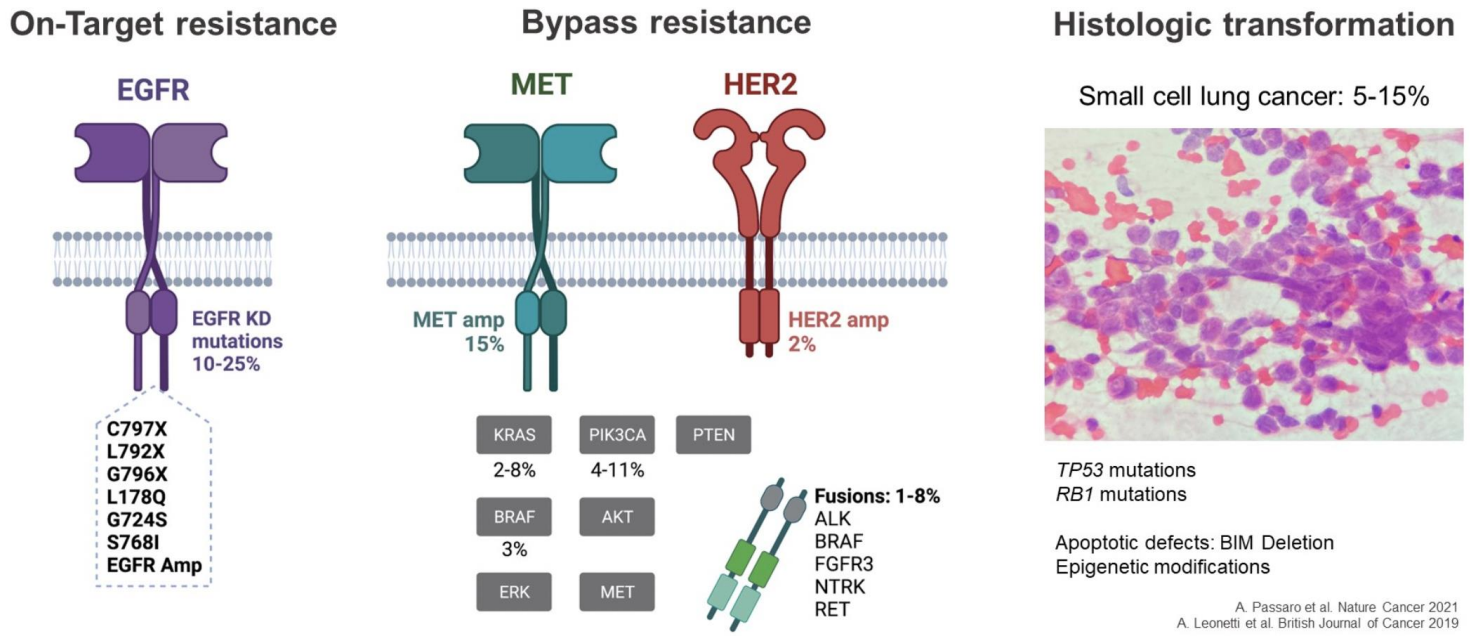


Fig 2. A 38-year-old man with *BRAF*-mutant melanoma and miliary, subcutaneous metastatic deposits. Photographs were taken (A) before initiation of PLX4032, (B) after 15 weeks of therapy with PLX4032, and (C) after relapse, after 23 weeks of therapy.

Challenges of Cancer Precision Medicine
Heterogeneity Case studies

Resistance to Osimertinib



Adapted from G. Recondo. ASCO 2022

New 1st L. strategies
With superior PFS

FLAURA2: Osimertinib + Chemotherapy

MARIPOSA: Amivantamab + Lazertinib

Slide provided by E.Nadal

Solution (I): innovative/disruptive mechanisms of drug combinations (be bold!)

Multiple Low dose

- low doses of multiple MAPK pathway inhibitors (EGFR, RAF, MEK, ERK) achieves full pathway suppression and inhibits proliferation in EGFR-mutant NSCLC, without inducing toxicity.

Fernandes Neto, *et al. . Nat Commun*, 2020

Targeting persister cells

- Targeting mutagenic DNA polymerases, and other vulnerabilities (e.g., GPX4, ALOX1, ALDH, ISR, autophagy)
- Gradually increasing drug concentrations

... could reduce the emergence of persister

Russo et al. *Nature Genetics, Julyy 2022; Nat Rev Cancer Oct 2024*

Lethal Carcinogenesis

- Syntheltic lethal combination of hyperactivation of oncogenic pathways, and disruption of stress response mechanisms,

...can effectively disrupt cancer cell homeostasis and lead to cell death

Dias et al., *Cancer Discovery, July 2024*

Others...

- Other disruptive synthetic lethal combinations?
- +/- TME modulation?

Solution (II): Applications of AI & Omics Data Science

> Sci Transl Med. 2021 Jan 27;13(578):eaba4373. doi: 10.1126/scitranslmed.aba4373.

Toward robust mammography-based models for breast cancer risk

Adam Yala [1] [2], Peter G Mikhael [3] [2], Fredrik Strand [4] [5], Gigin Lin [6], Kevin Smith [7] [8], Yung-Liang Wan [6], Leslie Lamb [9], Kevin Hughes [10], Constance Lehman [9], Regina Barzilay [3] [2]

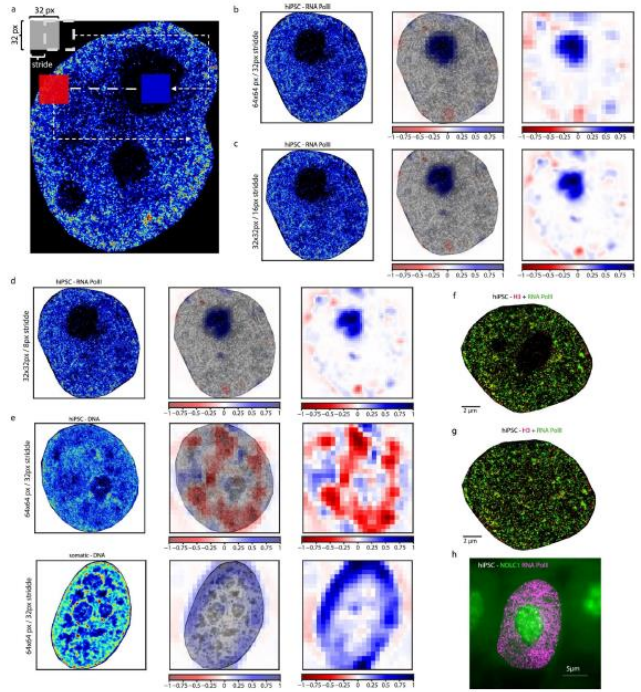
Abstract

Improved breast cancer risk models enable targeted screening strategies that achieve earlier detection and less screening harm than existing guidelines. To bring deep learning risk models to clinical practice, we need to further refine their accuracy, validate them across diverse populations, and demonstrate their potential to improve clinical workflows. We developed Mirai, a mammography-based deep learning model designed to predict risk at multiple timepoints, leverage potentially missing risk factor information, and produce predictions that are consistent across mammography machines. Mirai was trained on a large dataset from Massachusetts General Hospital (MGH) in the United States and tested on held-out test sets from MGH, Karolinska

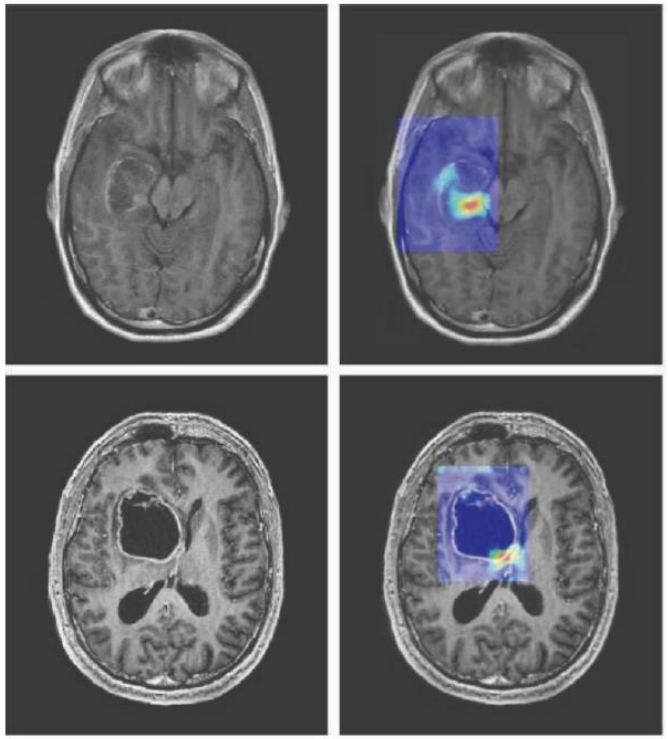
Fuente: Yala A, Mikhael PG, Strand F, Lin G, Smith K, Wan YL, Lamb L, Hughes K, Lehman C, Barzilay R. Toward robust mammography-based models for breast cancer risk. Sci Transl Med. 2021 Jan 27;13(578):eaba4373. doi: 10.1126/scitranslmed.aba4373. PMID: 33504648.

Article | Open access | Published: 27 August 2024

A deep learning method that identifies cellular heterogeneity using nanoscale nuclear features



Fuente: Carnevali, D., Zhong, L., González-Almela, E. et al. A deep learning method that identifies cellular heterogeneity using nanoscale nuclear features. Nat Mach Intell 6, 1021–1033 (2024). https://doi.org/10.1038/s42256-024-00883-x



Un algoritmo de aprendizaje profundo programado para analizar imágenes por resonancia magnética pronostica una mutación en el gen *IDH1* en los tumores de encéfalo.

Fuente: Fuente: CA Cancer J. Clin., marzo/abril de 2019. doi: 10.3322/caac.21552. CC BY 4.0.

Article | Published: 03 June 2024

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

Tian-Gen Chang, Yingying Cao, Hannah J. Sfreddo, Saugato Rahman Dhruba, Se-Hoon Lee, Cristina Valero, Seong-Keun Yoo, Diego Chowell, Luc G. T. Morris & Eytan Ruppin

Nature Cancer **5**, 1158–1175 (2024)

Fuente: Chang, TG., Cao, Y., Sfreddo, H.J. et al. LORIS robu
common clinical, pathologic and genomic features. Nat C

NIH NATIONAL CANCER INSTITUTE
LOgistic Regression-based Immunotherapy-response Score

Your information

Patient age (years): 60

Cancer type: Colorectal cancer

Previous systemic therapy: no

Blood albumin (g/dL): 4,6

Blood neutrophil-to-lymphocyte ratio: 3

Tumor mutational burden (mut/Mb): 14

Calculate

Clear

Your result

The likelihood of response to immune checkpoint blockade therapy (95% confidence interval)

51%

(40 - 60%)

This result predicts how likely you are to respond to immune checkpoint blockade therapy. The likelihood means that out of 100 patients with similar characteristics, approximately 51 may benefit from this therapy. More specifically, we're 95% confident that 40 - 60 out of 100 patients may benefit from this therapy, based on our training data. However, it's important to recognize that this is just a rough ballpark estimate. Individual patient outcomes can vary significantly, and a healthcare provider can provide a more precise assessment, taking into account a broader range of factors and personal medical history.

g-Nomic: a new pharmacogenetics interpretation software

Abstract: We present g-Nomic, a pharmacogenetics interpretation software that analyzes globally a prescribed medication taking into account the personal background genetics, drug–drug interactions, lifestyle, nutritional supplements, inhibitors, inducers, and other risks to analyze primary or secondary metabolism pathways. G-Nomic provides a set of recommendations describing the suitability of a given combination of drugs for each patient according to their genes and polymedication. G-Nomic is updated

Fuente: Sabater A, Ciudad CJ, Cendros M, Dobrokhotov D, Sabater-Tobella J. g-Nomic: a new pharmacogenetics interpretation software. Pharmgenomics Pers Med. 2019;12:75-85 https://doi.org/10.2147/PGPM.S203585

Journal of Pharmaceutical Analysis
Available online 8 January 2025, 101194
In Press, Journal Pre-proof What's this?

Original article

Identify drug-drug interactions via deep learning:a real world study

Jingyang Li [a 1], Yanpeng Zhao [c 1], Zhenting Wang [f], Chunyue Lei [d], Lianlian Wu [e], Yixin Zhang [c], Song He [c], Xiaochen Bo [c], Jian Xiao [a b]

Fuente: Jingyang Li, Yanpeng Zhao, Zhenting Wang, Chunyue Lei, Lianlian Wu, Yixin Zhang, Song He, Xiaochen Bo, Jian Xiao, Identify drug-drug interactions via deep learning:a real world study, Journal of Pharmaceutical Analysis, 2025, 101194, ISSN 2095-1779, https://doi.org/10.1016/j.jpha.2025.101194

AlphaFold

Accelerating breakthroughs in biology with AI

With the help of AlphaFold, researchers are designing more effective drugs like never before

Fuente: https://deepmind.google/discover/blog/advancing-discovery-of-better-drugs-and-medicine/
Desai D, Kantliwala SV, Vybhavi J, Ravi R, Patel H, Patel J. Review of AlphaFold 3: Transformative Advances in Drug Design and Therapeutics. Cureus. 2024 Jul 2;16(7):e63646. doi: 10.7759/cureus.63646. PMID: 39092344; PMCID: PMC11292590.

Future Prospects: AI-Driven Omics for Precision Medicine. The WIN Consortium experience

Enhanced understanding of tumor heterogeneity

Multi-Omics Integration & Systems Biology:

- Comprehensive models involving multiomics based AI predictive algorythms
- Involve sequential testing (tissue, liquid)
- International TMB

Adaptive Clinical Trials & Real-Time Decision-Making

- AI-guided continuous learning model trial adaptive designs
- N=1 clinical trials (Winther/WingPO)

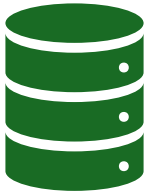
Challenge: Transparent and Validated Frameworks

- Establishing standardized protocols and reproducibility measures
- Ensuring ethical use and regulatory acceptance of AI tools

El-Deiry et al. Oncotarget, 2025, Vol. 16, pp: 140-162

Limitations of OMICs Science

Lack of standardization and validation



Variability in data quality generation, processing & analysis

Complexities, Noise & Overfiting in Interpretation of complex data.

Biological relevance not granted

Black-box models challenge clinical trust

Regulatory reluctance

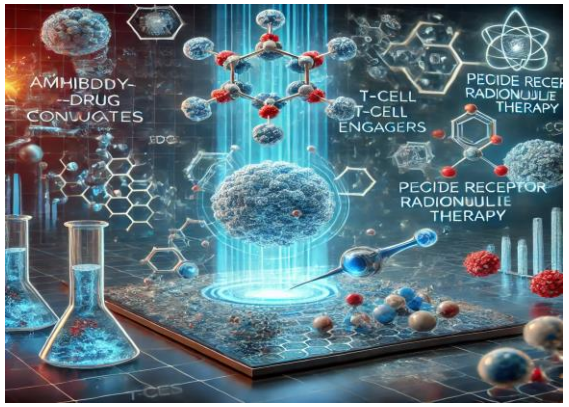
Solution (III): payload therapies

- Target binding are just transporter bystanders of chemical, radioactive or cellular payload
  - **ADCs**: Chemotherapy
  - **PRRT:** Radioactive compounds
  - **TCEs**: T-Cell negager Abs or TCRs

Summary

3

- Laws of Medicine 1 & 3…false positives/negatives
- Law of Medicine 2….treasure your exceptions
- Laws of Cancer….Complexity & Heterogeneity



3

New disruptive MoA combinations

Improve ptient-tment matching

- Omics
- AI aids
- Beware of its perils

Payload innovations

- ADCs
- PRRT
- TCEs

THANK-YOU!!!

More epistemological commentaries
on my Blog Cancer Musings
https://www.prognostictools.es/blog/cancer-musings

ramonsalazar@iconcologia.com