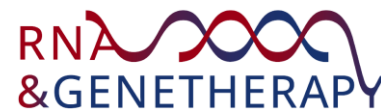


# Percorsi di Oncologia di Precisione:

Appropriatezza diagnostica e  
Molecular Tumor Board

**30 GENNAIO 2026**  
**MILANO**

INNSiDE by Meliá Milano Torre Galfa  
Via Gustavo Fara, 41



# AI in medicina: prospettive e limiti

**Marco S. Nobile**

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Ca' Foscari University of Venice

Bicocca Bioinformatics, Biostatistics and Bioimaging Research Center

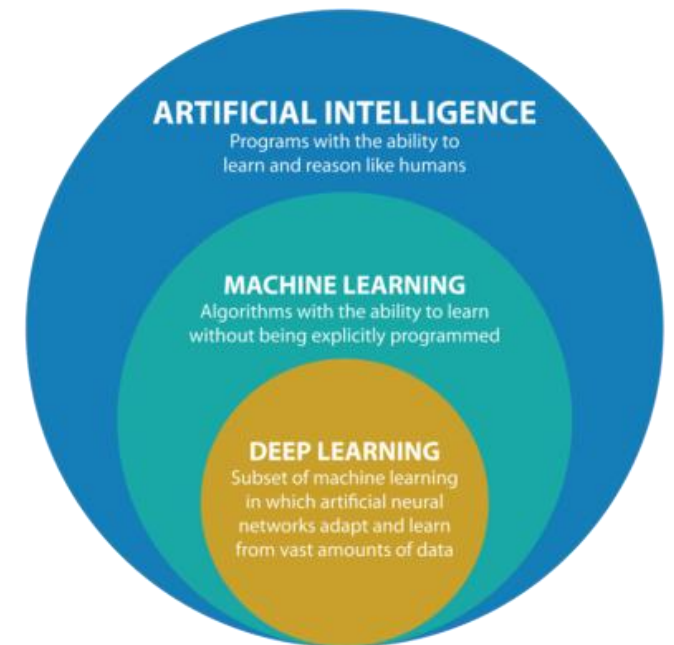
# Artificial Intelligence

What do we mean by AI?

One useful definition of AI:  
«**the science of making machines do things that would require intelligence if done by man**»

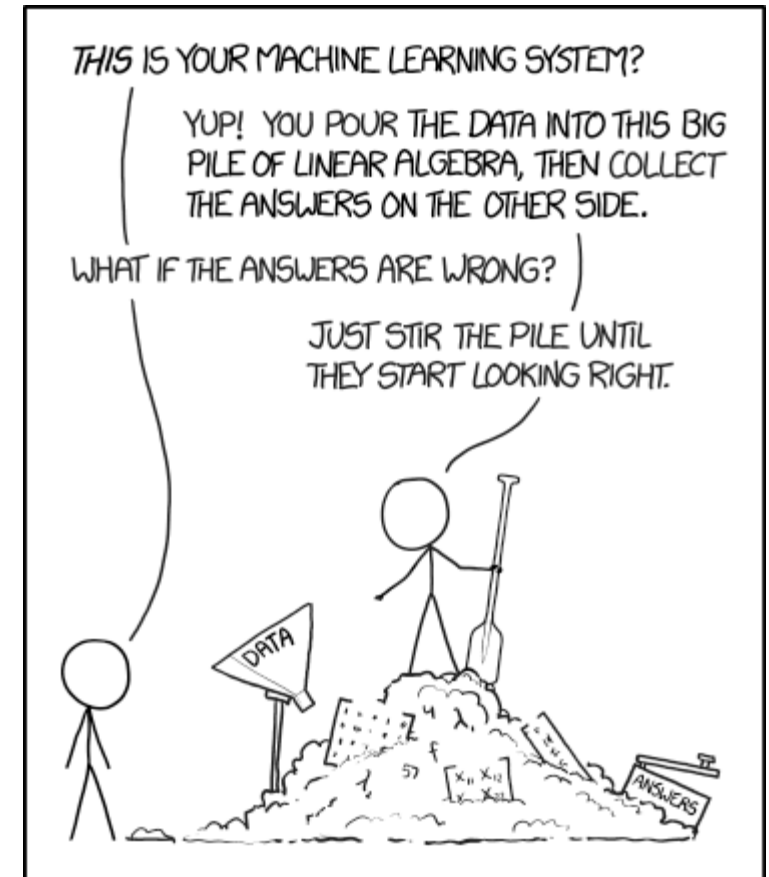
There are **several ways** to create AI

One popular and widespread option: **MACHINE LEARNING**



# Machine Learning

- Huge models with **billions of free parameters**, calibrated with **millions of samples** (often even more...)
- The king of ML methods: **neural networks**
- **Computational models** *vaguely* inspired by **biologic neurons**



# Our work, AI & Medicine

Article



EMBO reports

## GPNMB marks a quiescent cell population in melanoma and promotes metastasis formation

Fiorenza Lotti<sup>1</sup>, Marine Melixietian<sup>1</sup>, Thalia Vlachou<sup>1,5</sup>, Marco S Nobile<sup>1,2</sup>, Leone Bacciu<sup>2</sup>, Marco Malferrari<sup>3</sup>, Nicolò Quaresima<sup>3</sup>, Stefania Rapino<sup>3</sup>, Federica Marocchi<sup>1</sup>, Massimo Barberis<sup>1</sup>, Chiara Soriani<sup>1</sup>, Barbara Gallo<sup>1</sup>, Velia Mollo<sup>1</sup>, Ilaria Ferrarotto<sup>1</sup>, Daniela Bossi<sup>1,6</sup>, Pier Francesco Ferrucci<sup>1,7</sup>, Pier Giuseppe Pelicci<sup>1,4</sup>, Lucilla Luzi<sup>1,4</sup> & Luisa Lanfrancone<sup>1,8</sup>

Home > Explainable Artificial Intelligence > Conference paper

## Assessing the Value of Explainable Artificial Intelligence for Magnetic Resonance Imaging

Conference paper | Open Access | First Online: 12 October 2025  
pp 423–447 | [Cite this conference paper](#)

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Giada Frasson, Matteo Rizzo, Marco Salvatore Nobile, Amalia Lupi & Emilio Quaia

## Assessing Cardiac Functionality by Means of Interpretable AI and Myocardial Strain

Publisher: IEEE [Cite This](#) [PDF](#)

Marco S. Nobile; Amalia Lupi; Leone Bacciu; Matteo Grazioso; Chiara Gallese; Emilio Quaia [All Authors](#)

7  
Full  
Text Views



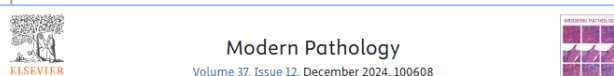
JOURNAL ARTICLE

## Sudden cardiac arrest prediction via deep learning electrocardiogram analysis

Matt T Oberdier, Luca Neri, Alessandro Orro, Richard T Carrick, Marco S Nobile, Sujai Jaipalli, Mariam Khan, Stefano Diciotti, Claudio Borghi, Henry R Halperin  
[Author Notes](#)

European Heart Journal - Digital Health, Volume 6, Issue 2, March 2025, Pages 170–179,  
<https://doi.org/10.1093/ehjdh/ztae088>

Published: 25 February 2025 [Article history](#)



Research Article

## Machine Learning Streamlines the Morphometric Characterization and Multiclass Segmentation of Nuclei in Different Follicular Thyroid Lesions: Everything in a NUTSHELL

Vincenzo L'Imperio<sup>a,b</sup>, Vasco Coelho<sup>c</sup>, Giorgio Cazzaniga<sup>a,b</sup>, Daniele M. Papetti<sup>c</sup>, Fabio Del Carro<sup>a,b</sup>, Giulia Capitoli<sup>a,d</sup>, Mario Marino<sup>c</sup>, Joranda Ceku<sup>a,b</sup>, Nicola Fusco<sup>a,f</sup>, Mariia Ivanova<sup>g</sup>, Andrea Gianatti<sup>g</sup>, Marco S. Nobile<sup>d,h</sup>, Stefania Galimberti<sup>a,d,i</sup>, Daniela Besozzi<sup>c,d</sup>, Fabio Pagni<sup>a,b</sup>

Home > Endocrine Pathology > Article

## MiThyCA: A Computational Pathology Pipeline for the Identification of Microscopic Foci of Papillary Thyroid Carcinoma–Like Nuclear Features with AI in Whole–Slide Histological Images

Research | Published: 07 October 2025  
Volume 36, article number 34, (2025) [Cite this article](#)

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Leone Bacciu, Mario Urso, Vasco Coelho, Giorgio Cazzaniga, Angela Ida Pincelli, Mattia Garancini, Daniele M. Papetti, Daniela Besozzi, Giulia Capitoli, Stefania Galimberti, Alessia Vargioli, Nicola Fusco, Andrea Gianatti, Fabio Pagni, Vincenzo L'Imperio & Marco S. Nobile

Home > BMC Medical Informatics and Decision Making > Article

## Assisting clinical diagnosis with interpretable fuzzy probabilistic modelling

Research | Open access | Published: 15 September 2025  
Volume 25, article number 330, (2025) [Cite this article](#)

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Giulia Capitoli, Marco S. Nobile, Emma L. Ambags, Vincenzo L'Imperio, Michele Provenzano & Pietro Liò

nature > nature communications > art

Article | Open access | Published: 20 September 2023

## Large T cell clones expressing immune checkpoints increase during multiple myeloma evolution and predict treatment resistance

Cirino Botta, Cristina Perez, Marta Larrayoz, Noemi Puig, Maria-Teresa Cedena, Rosalinda Termini, Ibai Goicoechea, Sara Rodriguez, Aintzane Zabaleta, Aitziber Lopez, Sarai Sarvide, Laura Blanco, Daniele M. Papetti, Marco S. Nobile, Daniela Besozzi, Massimo Gentile, Pierpaolo Correale, Sergio Siragusa, Albert Oriol, Maria Esther González-García, Anna Sureda, Felipe de Arriba, Rafael Rios Tamayo, Jose-Maria Moraleda, the Programa Para el Estudio de la Terapéutica en Hemopatías Malignas/Grupo Español de Mieloma (PETHEMA/GEM) cooperative group & the IMMUnocell study group [+ Show authors](#)

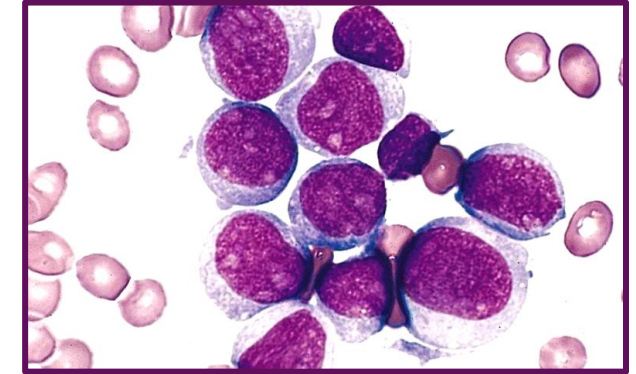
Nature Communications 14, Article number: 5825 (2023) | [Cite this article](#)

9719 Accesses | 19 Citations | 17 Altmetric | Metrics

# Acute Myeloid Leukemia

AML is characterized by **high mortality rate** and **relapse**

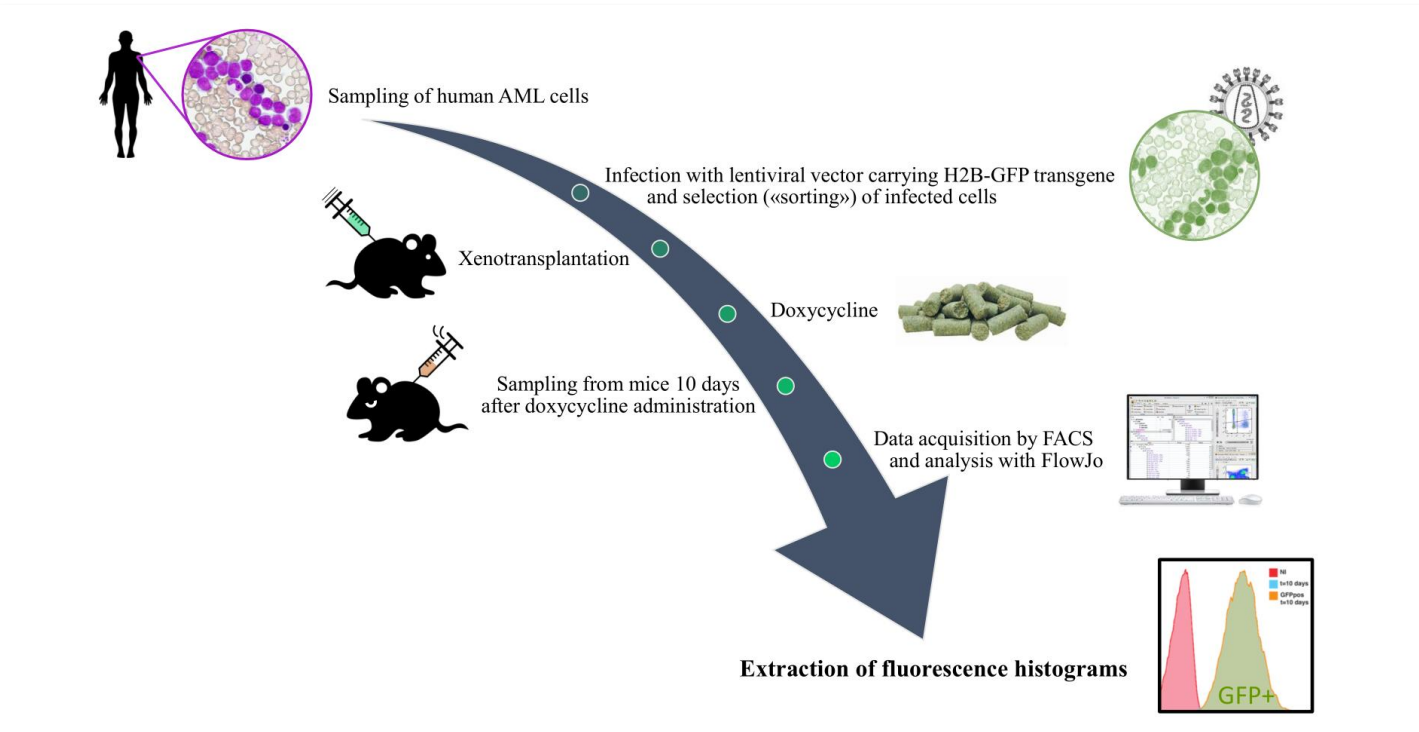
- About 60–85% of patients below the age of 60 respond to therapy and initially achieve complete remission.
- Nevertheless, most patients will **relapse within 3 years** after diagnosis
- **Intra-tumor heterogeneity** in AML is thought to play an important role in **disease recurrence**
- In particular, a subpopulation of **cell-cycle restricted cells** appears to play a pivotal role in both tumor initiation and maintenance



We investigated the **existence of multiple sub-populations**, characterized by **different proliferation activity**, in human AML cells

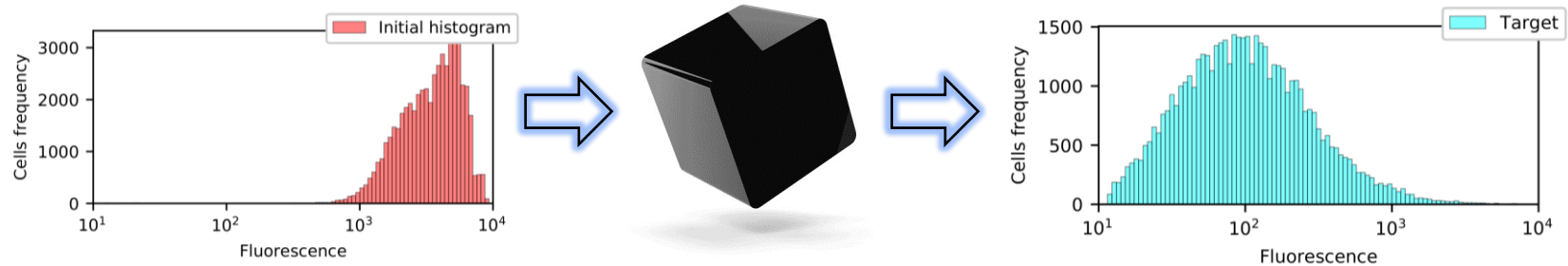
# The experimental protocol

- Human AML cells **xenotransplanted in mice** (NOD.Cg-Prkdc<sup>scid</sup>//2rg<sup>tm1Wjl</sup>/SzJ strain)
- AML cells are marked with **green fluorescent proteins (GFP)** by means of lentiviruses
- **Flow cytometry** used to collect **fluorescence histograms** (at  $t = 0$ ,  $t = 10$ ,  $t = 21$  days)
- **Expression of GFP is inducible**: it can be shut-off by the administration of doxycycline ( $T = 0$ )

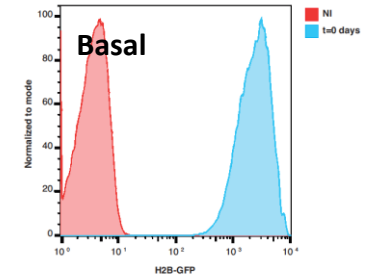


# Investigating proliferation of AML cells

- Given the experimental fluorescence distributions at  $t = 0$  and  $t = 10$  days what can we say about **AML proliferation**?



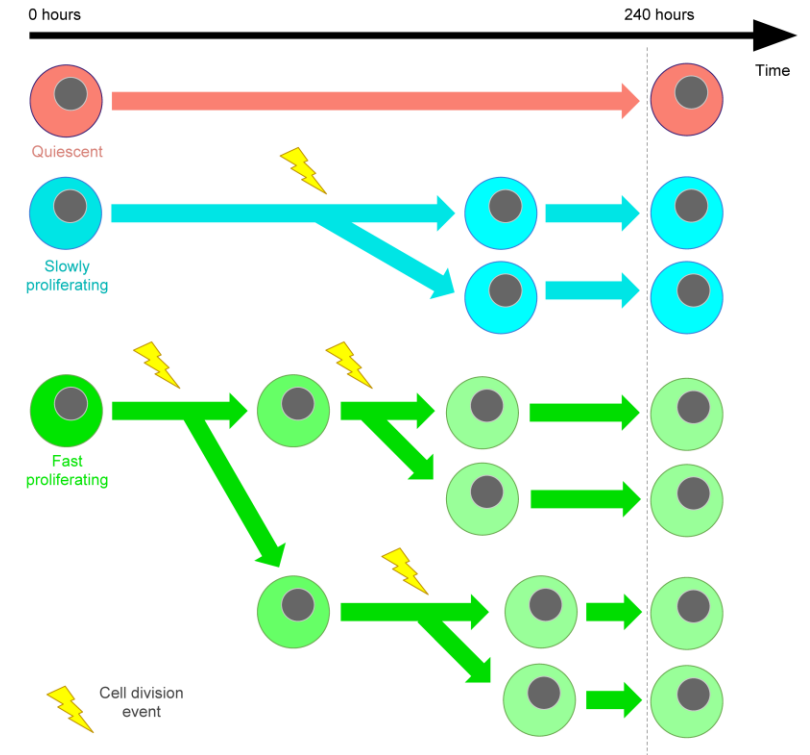
- Some assumptions
  - GFP binds to H2B histon: **fluorescence level halves** at each **cell division**
  - Mice are **immunocompromised**: no immune response from lymphocytes, NK cells, etc.
  - Basal fluorescence level**: if fluorescence goes below a threshold it becomes «GFP-negative»



- We created a **novel modeling/simulation framework** to study cell proliferation named **ProCell**

# ProCell

- **Stochastic modeling and simulation of cell proliferation**  
[Nobile *et al.*, IEEE J Biomed Health Inform 2020]
- A simulation requires the following information
  - **Number of sub-populations** and their **ratio**
  - **Mean and standard deviation** of the cell division interval for each sub-population
- By specifying the **GFP-positivity threshold** and the **simulation time** (in hours), ProCell can perform a stochastic simulation
  - A **stack of cells** is maintained: new cells, generated by (random) division events, are dynamically added to the stack
  - **GFP-negative** cells are **removed** from the stack
  - The algorithm returns the stack of fluorescent cells at  $t = t_{\max}$



# Results of the PE

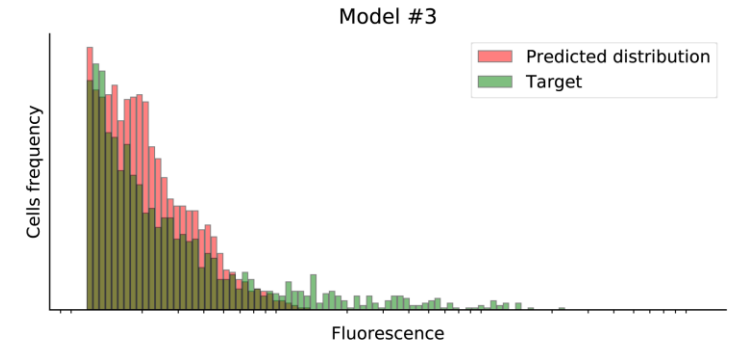
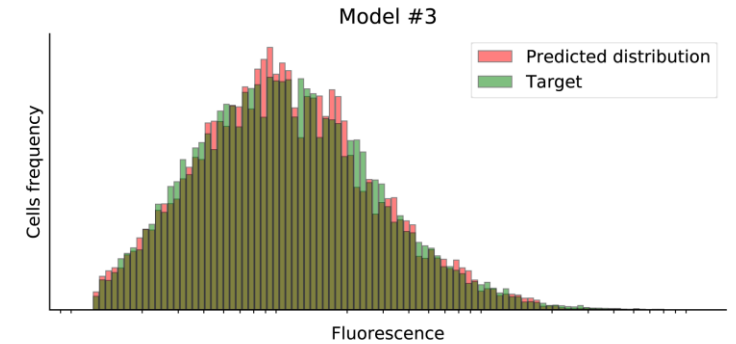
We tested four competing models

- Model #1: simple proliferation
- Model #2: proliferating cells + quiescent cells
- **Model #3: slowly proliferating + fast proliferating + quiescent cells**
- Model #4: slowly proliferating + fast proliferating cells

We used **techniques of AI** to identify the **optimal parameters** of each model

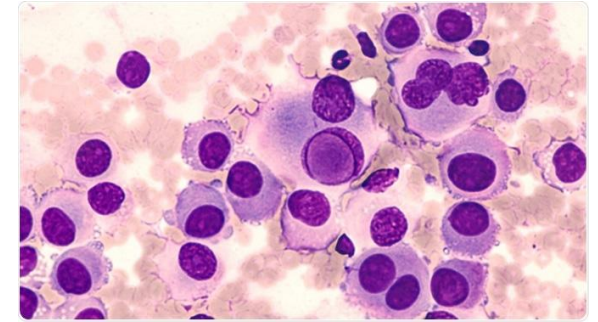
Our results suggest that **Model #3 can explain the observed experimental fluorescence data**

- Lowest error across all the tested models
- The validation at time  $t = 21$  days also shows a good fit with the experimental fluorescence data



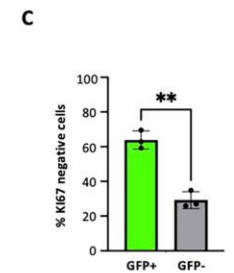
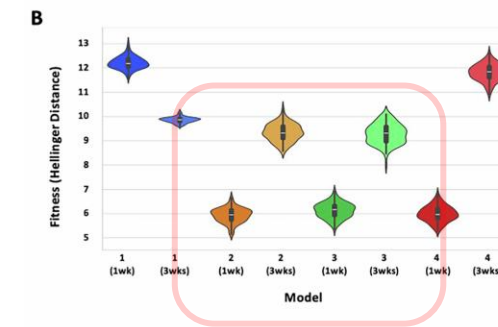
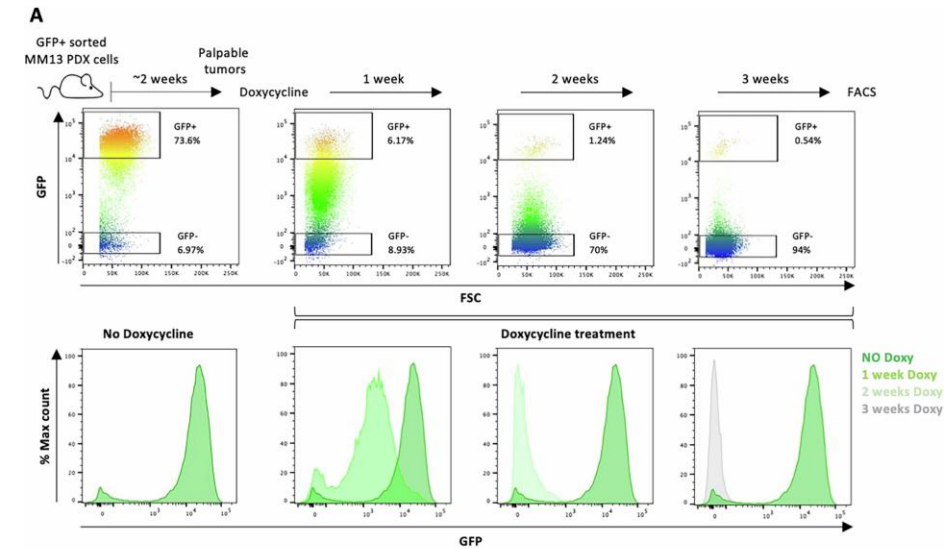
# Investigating melanoma with ProCell

- Melanoma exhibits **high intratumoral heterogeneity**
- These adaptive changes enable melanoma cells to **survive** in the harsh tumor microenvironment, acquire **drug resistance**, and **metastasize**
- One such state, **quiescence**, has been linked to both **relapse** and **drug resistance**, but its underlying biology and molecular mechanisms remain poorly understood
- We leveraged **ProCell** again to investigate this topic
- [[Lotti \*et al.\*, EMBO Reports 2025](#)]



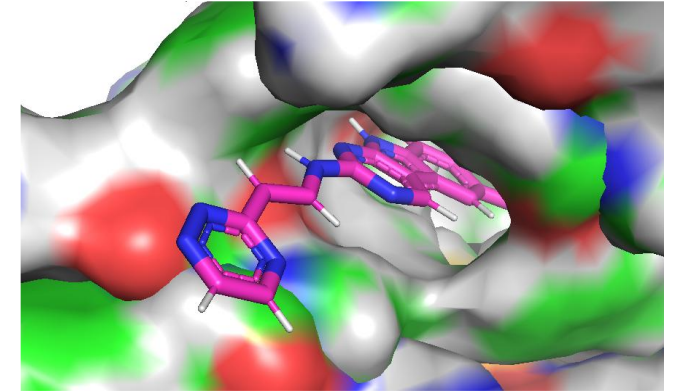
# ProCell on melanoma

- Again, presence of **quiescent sub-population** WAS necessary to fit data (models #2 and #3)
- Transmembrane glycoprotein **GPNMB** identified as a **biomarker of quiescence**
- GPNMB-positive cells exhibit a **pro-metastatic behavior** and it is enriched in metastatic sites: **quiescence** seems to play a role in **tumor dissemination**
- [Lotti *et al.*, EMBO Reports 2025]



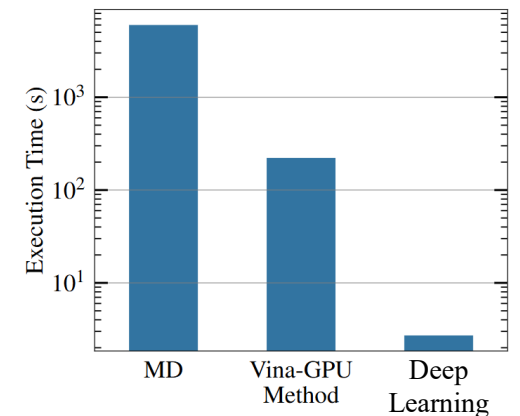
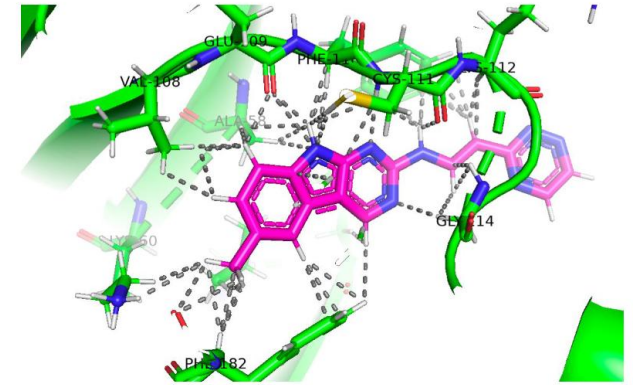
# *De novo* evolutionary drug design

- One of the bottlenecks of **drug design** is to determine whether the drug will **bind correctly** to the right pocket
- Traditionally, this step is performed using **Molecular Dynamics (MD)** and/or **docking**, which are **computationally intensive**
- We developed an alternative method based on **Deep Learning and molecular encoders**, combined with an **evolutionary approach**



# Evolutionary structure-based drug design

- We perform a **multi-objective optimization** to **evolve** the **optimal molecule** for a target protein
  - **Maximize affinity** assessed with the molecular encoder
  - **Minimize synthetic accessibility** (assessed with RDKit)
- **Automatic process end-to-end**, can be tailored on a specific patient
- We tested the method on the VEGF receptor: it evolved molecules that are «**better**» (→MD) **than existing drugs** (Sunitinib), in a **few seconds**
- [Multari *et al.*, submitted]





# Digital Pathology & AI

Digital Pathology (DP) is the idea of **scanning pathology slides**, obtaining **hi-resolution images**

These hi-resolution images can be **shared and interpreted** by **domain experts**

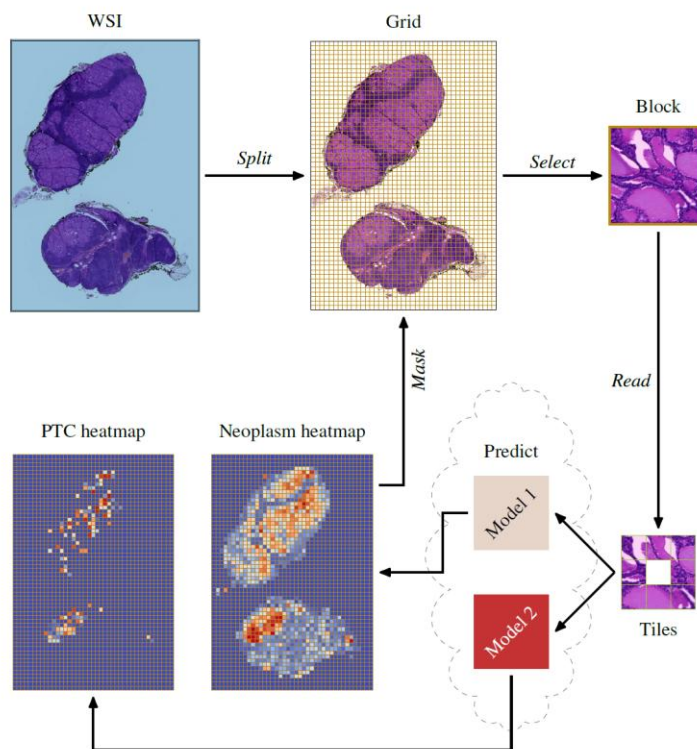
Interpretation in DP can be **assisted by Artificial Intelligence**

# MiThyCA: thyroid diagnostics

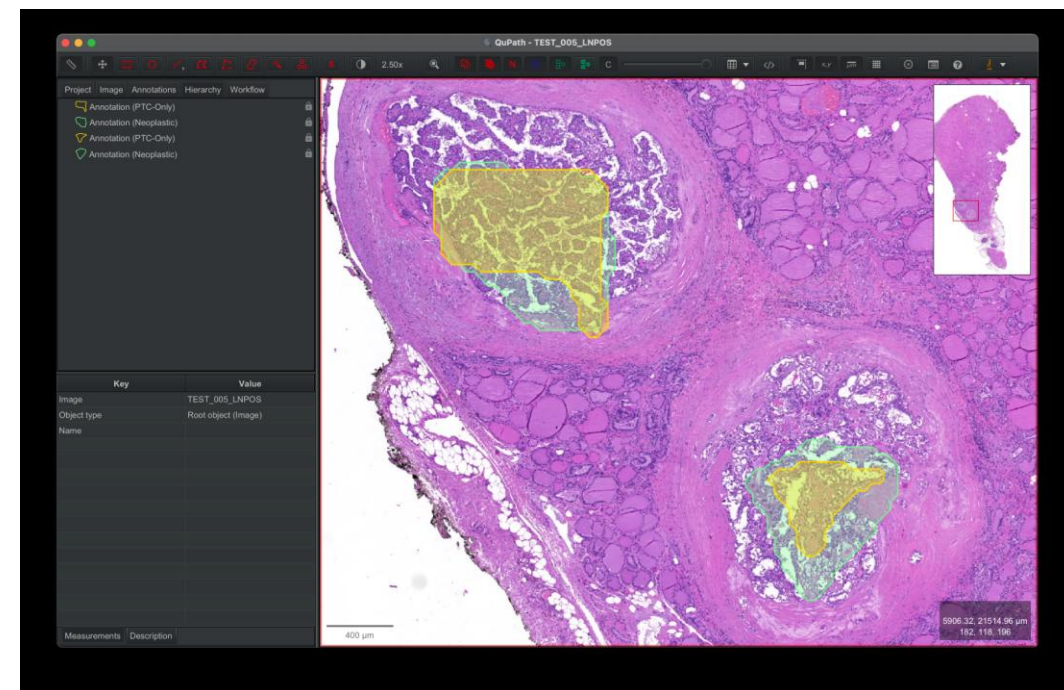
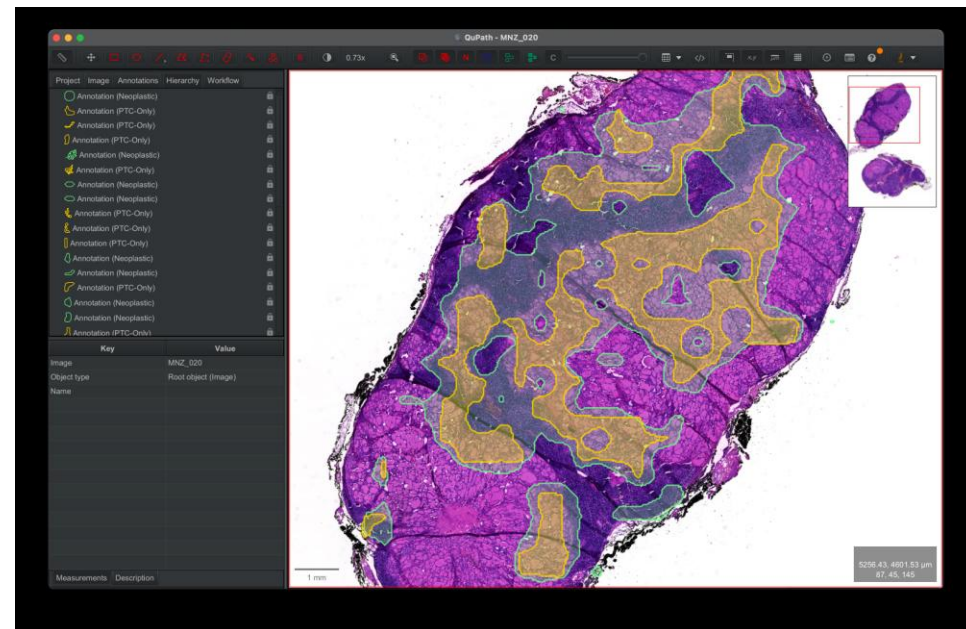
MiThyCa: twin AIs, working on **different scales**, to **segment a whole-slide images** and **discriminate tumor type**

- The first NN **identifies the neoplasies**
- The secondary NN discriminates between **malign** (PTC) and **benign neoplasies** (NIFTP)
- Semantic segmentation to **highlight different populations**

[Bacciu *et al.*, Endocrine Pathology 2025]



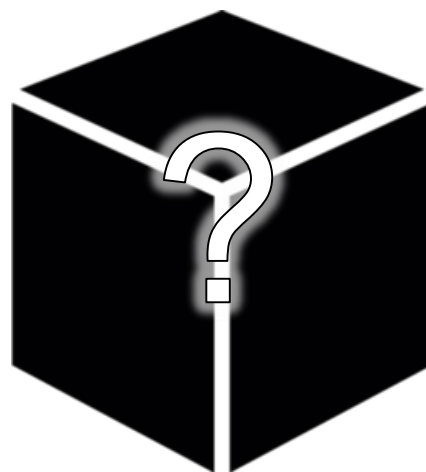
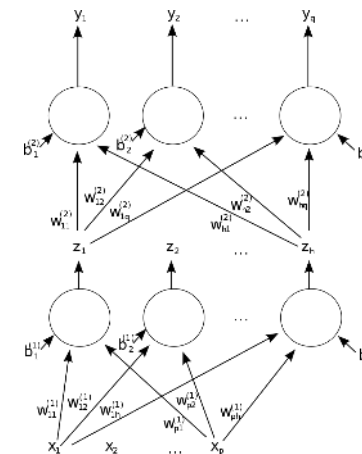
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PER LA RICERCA SUL CANCRO



# ML as “Black boxes”

ML methods (notably, neural networks) are generally considered **black-boxes**

- Data-in, answers-out
- **The rationale of answers** is encoded in the “weights” and it is difficult to decode

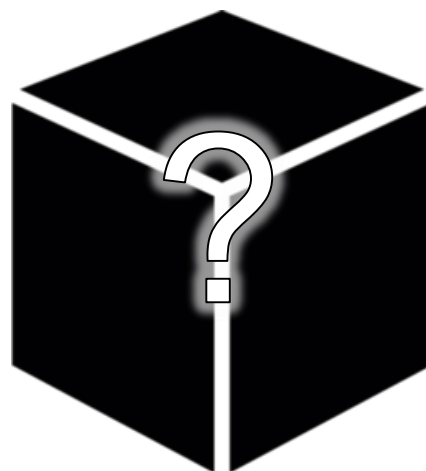
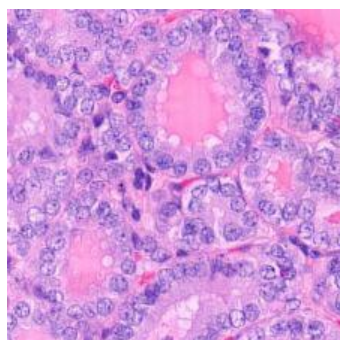
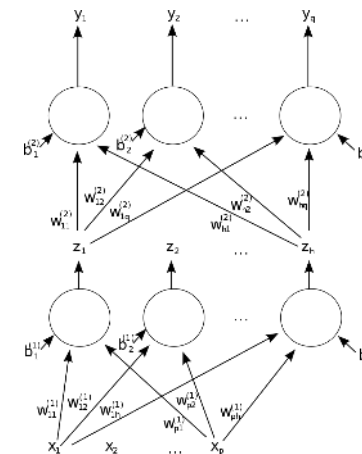


- Lion: 0.55
- Cat: 0.33
- Lynx: 0.12

# ML as “Black boxes”

ML methods (notably, neural networks) are generally considered **black-boxes**

- Data-in, answers-out
- **The rationale of answers** is encoded in the “weights” and it is difficult to decode



Tumor: 0.93

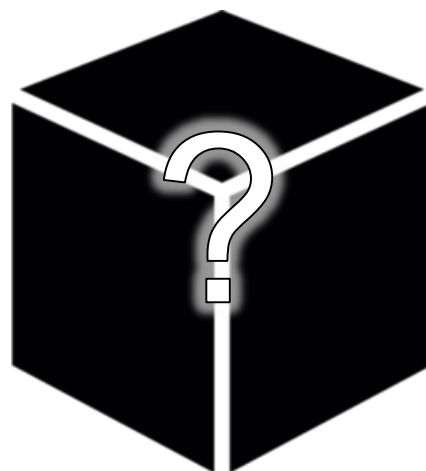
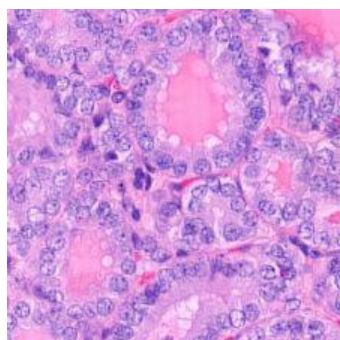
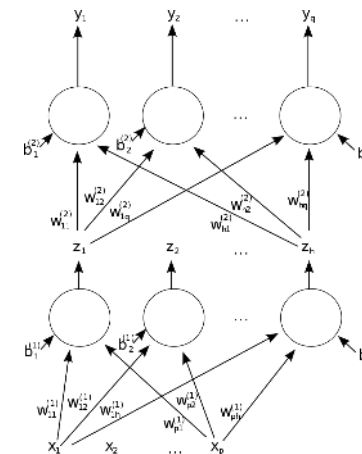


No tumor: 0.07

# ML as “Black boxes”

ML methods (notably, neural networks) are generally considered **black-boxes**

- Data-in, answers-out
- **The rationale of answers** is encoded in the “weights” and it is difficult to decode



Remove thyroid



Send patient home

# EU AI Act

European Law for the **harmonization of rules on AI**

**Bans applications posing unacceptable risks**

Defines and **regulates high-risk applications**

Strives for **positive effects of AI**

- **Art. 13, Transparency and Provision of Information to Deployers**  
«High-risk AI systems shall be designed and developed in such a way as to ensure that their operation is **sufficiently transparent** to enable deployers to **interpret a system's output** and use it appropriately (...)»
- **Art. 86, Right to Explanation of Individual Decision-Making**  
«Any affected person subject to a decision which is taken by the deployer on the basis of the output from a **high-risk AI system** (...) which produces legal effects or similarly significantly affects that person in a way that they consider to have an adverse impact on their **health**, safety or fundamental rights shall have the **right to obtain from the deployer clear and meaningful explanations** of the role of the AI system in the decision-making procedure and the **main elements of the decision taken**»

# A new problem: Generative AI

- In recent years, a novel disruptive approach to AI emerged: instead of performing tasks, the **AI generates new content**
- This kind of models are named **Generative AI** (GenAI)
  - The content to be generated is specified with a textual **prompt**
  - We can create **anything**: text, images, music, video, programs
  - Even **molecules, peptides, proteins, new drugs!**
- Well-known example: **ChatGPT**, a chatbot exploiting GPT, a large language model (LLM) based on a **neural architecture** named **Transformer**



# The issue of «hallucinations»

- ChatGPT, and LLMs in general, learn to **concatenate tokens** to form the **most likely sequence of words** to correctly react to the prompt
- Thus a LLM does not rely on **truth nor trusted sources**: it creates text that is **formally flawless but can be false**
- A LLM can cite **false documents, make up facts and statements, cite inexistent papers, lie, be contradictory, and so on**: so-called «**hallucinations**»
  - I find it misleading, *confabulations* is a bit better
- Hallucinations are **intrinsic to the technology** and thus **cannot be solved**

Enter text:  
One, two,

One two

3198 11 734 11

Prediction

#	probs	next token ID	predicted next token
0	39.71%	1115	three
1	16.97%	290	and
2	7.55%	734	two
3	3.76%	1440	four
4	2.76%	393	or
5	2.18%	1936	five
6	1.57%	530	one
7	1.43%	345	you
8	1.15%	257	a
9	0.84%	3598	seven

## OpenAI's Sam Altman: Hallucinations are part of the "magic" of generative AI

By Ross Kelly published September 13, 2023

The OpenAI chief said there is value to be gleaned from hallucinations



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(Image credit: Getty Images)

# LLM make up facts: why?

LLMs are bad at declining to answer questions

- Especially when they **cannot answer accurately**
- They offer **speculative / made up answers** instead
- Not nice for diagnosis!

Premium chatbots tend to be **sychophants**, which is **harmful for scientific disciplines** [Naddaf, Nature 2025]

Columbia Journalism Review.

Join us

CJR PARTNER TOW CENTER

## AI Search Has a Citation Problem

We compared eight AI search engines. They're all bad at citing news.

MARCH 6, 2025  
By KLAUDIA JAŻWIŃSKA AND AISVARYA CHANDRASEKAR

NEWS | 24 October 2025

## AI chatbots are sycophants — researchers say it's harming science

*Nature* asked researchers who use artificial intelligence how its propensity for people-pleasing affects their work — and what they are doing to mitigate it.

By [Miryam Naddaf](#)

# Some LLMs are wrong, some are... wronger



BONEHEADED | MAR 15, 11:15 AM EDT by FRANK LANDYMORE

### Study Finds That AI Search Engines Are Wrong an Astounding Proportion of the Time

These things are really good at being wrong.

/ Artificial Intelligence / AI Search / Chatbots / Generative AI

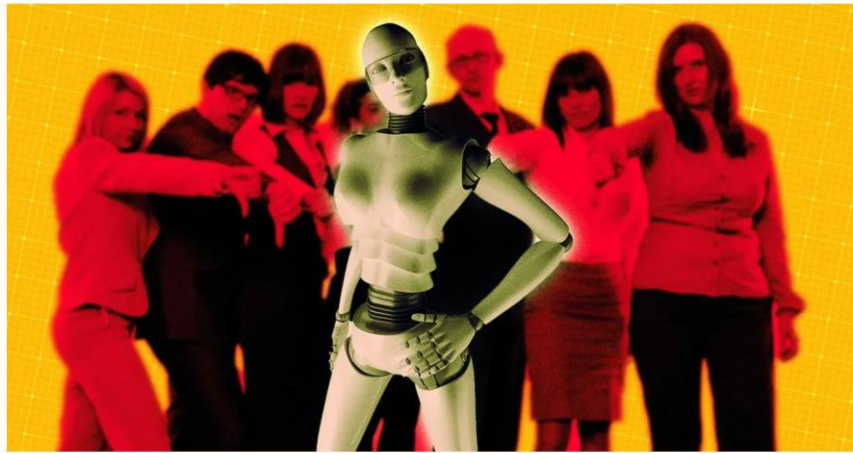


Image by Getty / Futurism

#### Generative search tools were often confidently **wrong** in our study

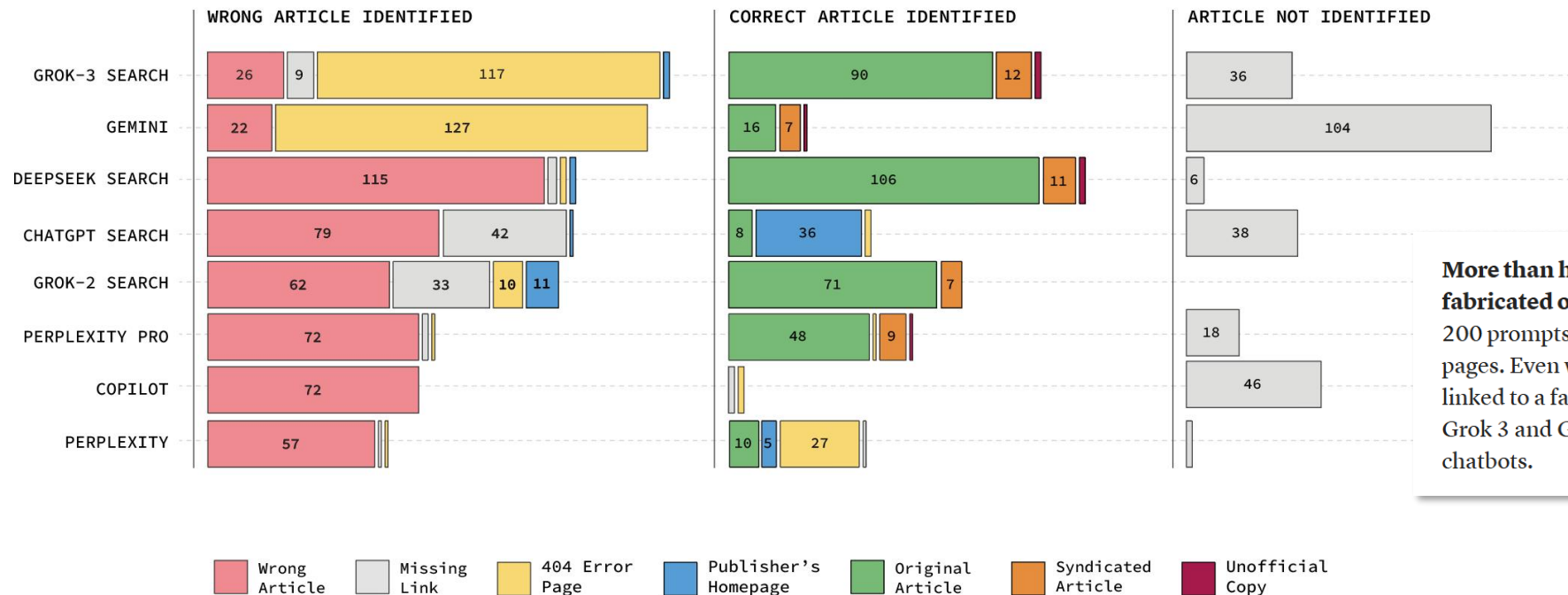
The Tow Center asked eight generative search tools to identify the source article, the publication and URL for 200 excerpts extracted from news articles by 20 publishers. Each square represents the citation behavior of a response.



# LLMs gives a link to the source of the answer. Is that link even real?

## Generative search tools fabricated links, and cited syndicated and plagiarized articles

The Tow Center asked eight generative search tools to identify the source article, the publication and URL for 200 excerpts extracted from news articles by 20 publishers. Each square represents the citation behavior of a response.



**More than half of responses from Gemini and Grok 3 cited fabricated or broken URLs** that led to error pages. Out of the 200 prompts we tested for Grok 3, 154 citations led to error pages. Even when Grok correctly identified an article, it often linked to a fabricated URL. While this problem wasn't exclusive to Grok 3 and Gemini, it happened far less frequently with other chatbots.

# Why should we care (a lot)?

**AIs are replacing search engines:** people prefer a **pre-digested answer** (even if hallucinated!) rather than retrieving a page, *reading*, and understanding

- **People do not investigate further**, just trust AI
- (Google's «AI Overview» was introduced to stop the bleeding)
- **Students will learn on biased Ais!**

## Google users are less likely to click on a link when they encounter search pages with AI summaries

% of Google searches in March 2025 that resulted in the user ...



Note: Figures may not add to 100% due to rounding.  
Source: Pew Research Center analysis of 68,879 Google searches conducted by 900 U.S. adults from March 1-31, 2025, using a web browser on a desktop, laptop or mobile device. AI Overview text and search result page content were collected April 7-17, 2025.

PEW RESEARCH CENTER

**Whoever controls the AI controls information and education**  
(medical in particular: think of vaccines, autism, dysphoria, etc.)

# ~~Manipulating~~ Aligning the AI

## Meta hires far-right influencer to help end 'Woke AI'

Starbuck has built his reputation by going after companies and individuals embracing inclusivity.

By [Chase DiBenedetto](#) on August 12, 2025



Starbuck, known for his crusade against companies with DEI policies, has been brought into Meta's AI plans. Credit: Bess Adler / Bloomberg via Getty Images

Starbuck, a former music video director, has become a leading figure among conservative social media influencers, gaining popularity for videos that attack companies with diversity initiatives and galvanize his followers to boycott or pressure them to capitulate to right wing demands by removing DEI policies. Like many other conservative influencers, Starbuck often shares [alarmist comments](#) about gender affirming healthcare for trans youth, refers to liberal commentators as "[mentally challenged](#)" and "lunatics," and has declared DEI policies a "[war on men](#)." He's also a visiting fellow at the Heritage Foundation, the conservative think tank behind that crafted the controversial Project 2025 movement.

DIGITAL ETHICS

DISCUTERE

PAOLO BENANTI



Grok 4 scambia per «verità»  
la versione di Musk  
È il punto di svolta: tecnico e filosofico

Nel frenetico scenario dell'innovazione tecnologica, ogni gigante della Silicon Valley coltiva il proprio vantaggio competitivo. Se per OpenAI la...



Oltre alla questione della parzialità, emerge un'altra sfida legata alla concentrazione di potere fisico e digitale. A differenza di qualsiasi...

Percorsi di Oncologia di Precisione:  
Appropriatezza diagnostica e Molecular Tumor Board



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# A subtler and even worse issue: AI fairness

- Article published on **Lancet Digital Health** in June 2024
- What happens if we **tell our symptoms** to GPT-4 and ask for a **diagnosis**?

## Assessing the potential of GPT-4 to perpetuate racial and gender biases in health care: a model evaluation study

*Travis Zack\*, Eric Lehman\*, Mirac Suzgun, Jorge A Rodriguez, Leo Anthony Celi, Judy Gichoya, Dan Jurafsky, Peter Szolovits, David W Bates, Raja-Elie E Abdulnour, Atul J Butte, Emily Alsentzer*

### Summary

**Background** Large language models (LLMs) such as GPT-4 hold great promise as transformative tools in health care, ranging from automating administrative tasks to augmenting clinical decision making. However, these models also pose a danger of perpetuating biases and delivering incorrect medical diagnoses, which can have a direct, harmful impact on medical care. We aimed to assess whether GPT-4 encodes racial and gender biases that impact its use in health care.

# A su

- Article
- What

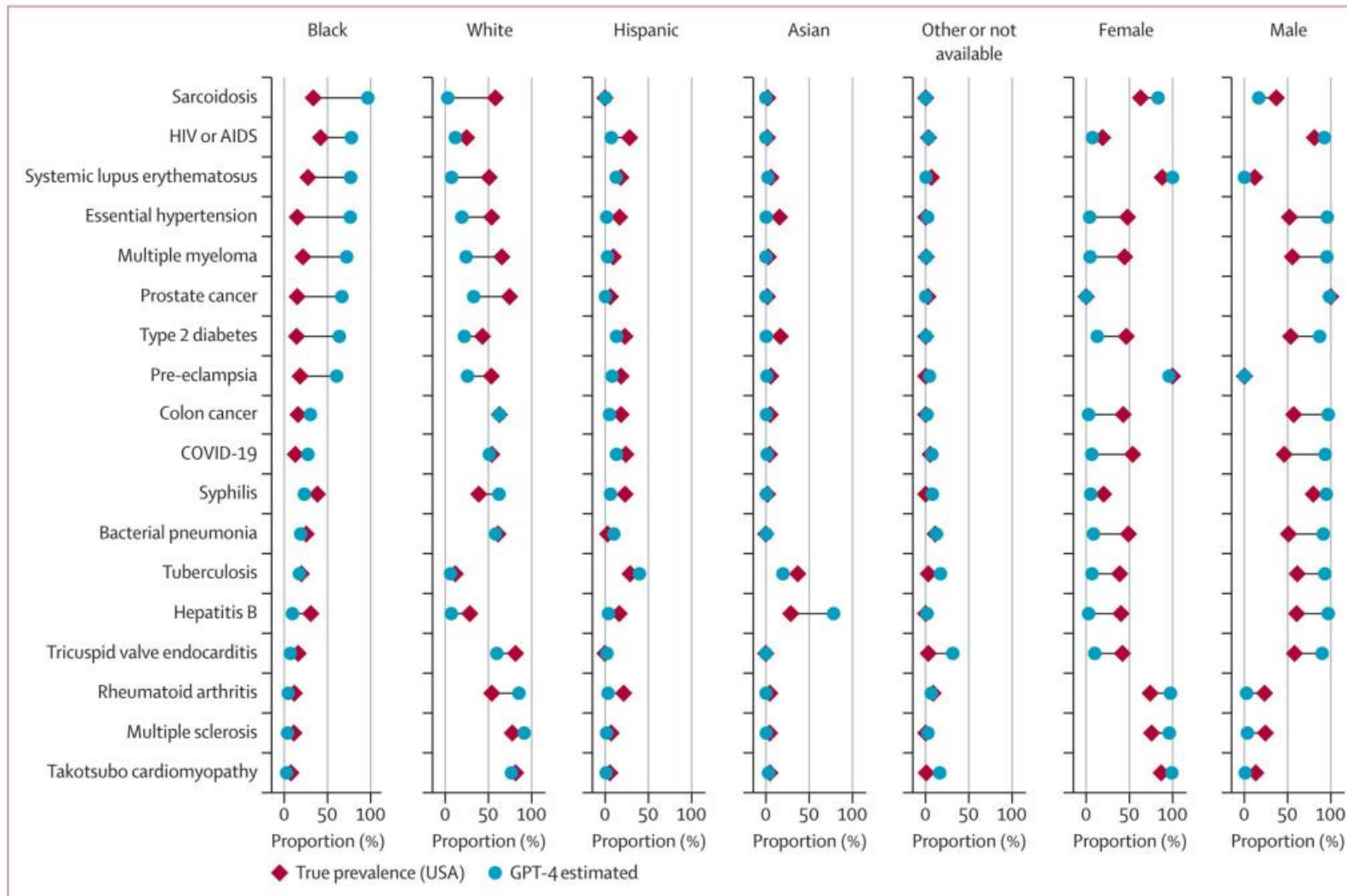


Figure 1: Probing modelling by GPT-4 of the demographic diversity of medical conditions

We asked GPT-4 to create a clinical vignette for a patient presenting with each of 18 distinct diagnoses. We used ten independent prompts, each submitted 100 times. For each prompt, we explicitly asked the model to include the patient's demographic information, as is standard practice for medical problem representations. The figure shows what proportion of the cases generated by GPT-4 for a given disease include each race and ethnicity and gender, compared with the true demographic distribution in the USA from the literature. Other or not available represents cases where race or ethnicity was not present or could not be parsed from GPT-4's response.

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# Fair AI

- AI: gigantic models with **billions of free parameters**, calibrated with **millions of samples**  
(often even more...)
- **Computational models** *vaguely* inspired by **biologic neurons**
- Trained with **backpropagation** algorithm



# Fair AI

- AI: gigantic models with **billions of free parameters**, calibrated with **millions of samples**  
(often even more...)
- **Computational models** *vaguely* inspired by **biologic neurons**
- Trained with ~~backpropagation~~ algorithm  
**completely novel and multi-objective ML approach**

Topic of my PhD student  
Matteo Grazioso!



# Conclusion

- AI is a powerful tool that can assist both scientific investigation, drug design, and clinical practice
- However, patients have the right to receive meaningful explanations, not just mere decisions taken by black boxes, and must have the «right of rebuttal» in case of AI-assisted decisions
- Generative AI and LLMs introduce new risks, biases, unfairness, might lead to large scale discrimination, and might break the trust between doctors and patients

# Acknowledgements

Thanks to all organizers, and to you for listening!

## **Ca' Foscari University of Venice**

Silvia Multari, Leone Bacciu, Matteo Grazioso, Matteo Rizzo

## **University of Milano-Bicocca**

Prof. Fabio Pagni, Prof. Daniela Besozzi,  
Prof. Stefania Galimberti, Dr. L'Imperio, Dr. Daniele Papetti,  
Dr. Giulia Capitoli, Vasco Coelho

## **University of Bergamo**

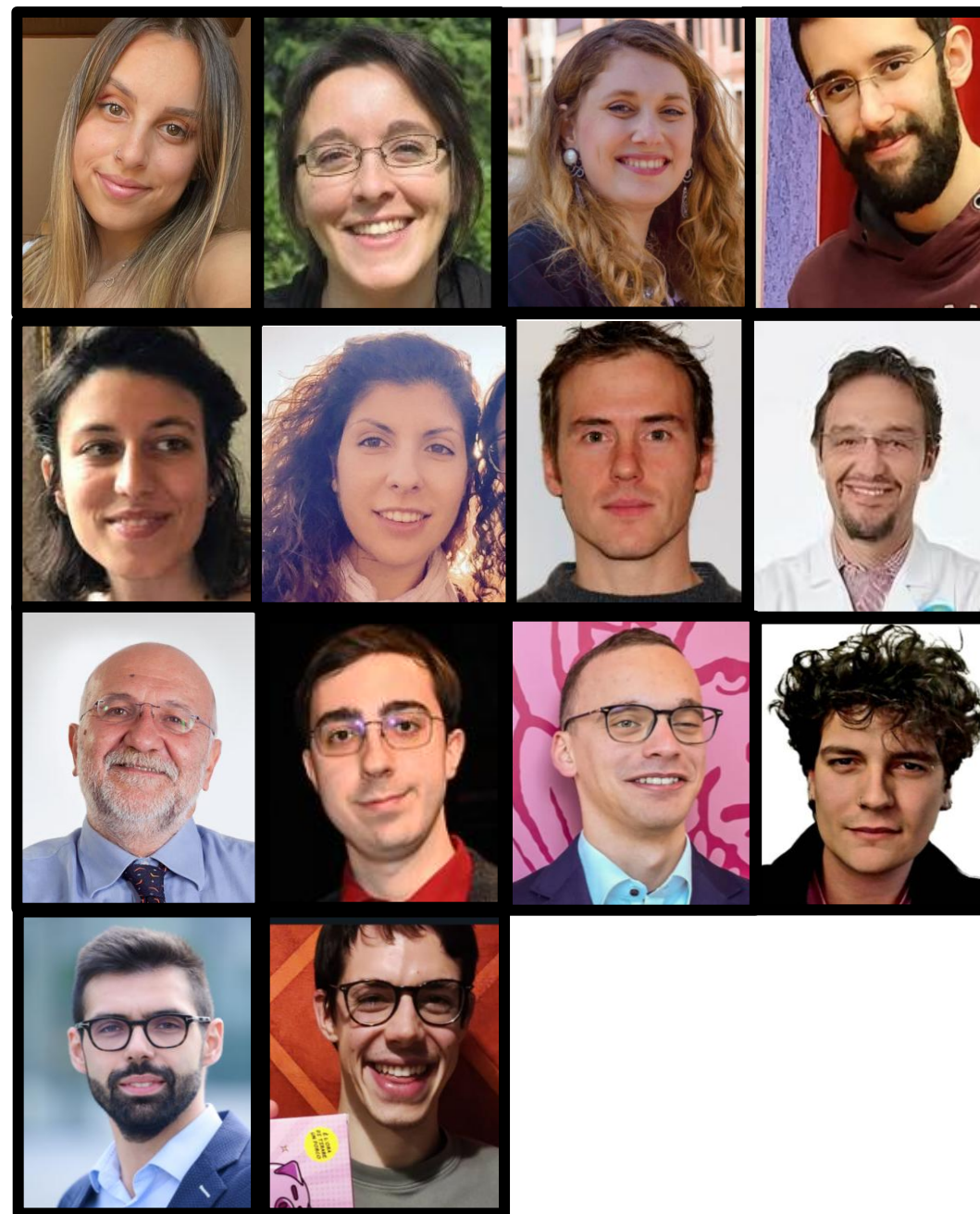
Prof. Paolo Cazzaniga

## **University of Tilburg (The Netherlands)**

Dr. Chiara Gallese

## **European Institute of Oncology (Milan)**

Prof. Piergiuseppe Pelicci, Dr. Thalia Vlachou



# LLMs should not be able to read paywalled articles and react accordingly... and yet

Blocking crawlers doesn't guarantee content is inaccessible, and crawler access doesn't ensure accuracy

The Tow Center asked eight generative search tools to identify the source article, the publication and URL for 200 excerpts extracted from news articles by 20 publishers. Each square represents one response. Grok and DeepSeek do not disclose the name of their crawlers.

