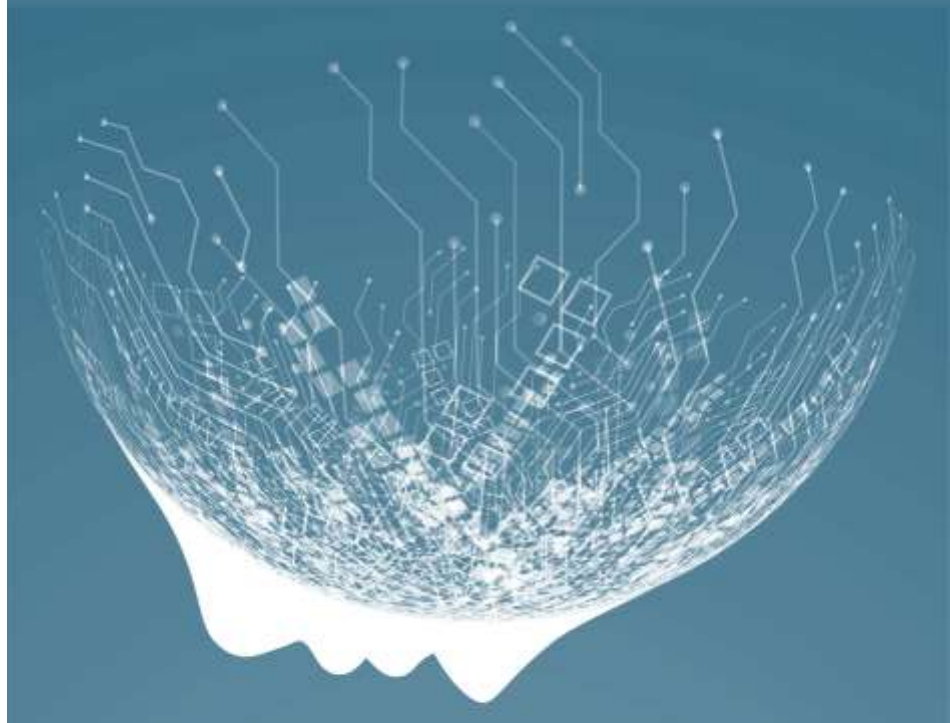
HEAL Italia e il contributo dell'Intelligenza Artificiale alla Diagnostica 4.0

Prof. Andrea Isidori

Sapienza Università di Roma

Spoke 4



SPOKE 4
Precision Diagnostics

- PRESENTAZIONE DELLO SPOKE

54 ricercatori (64)

13 enti affiliati

In collaborazione con Spoke 2, Spoke 6 e Spoke 8

REVIEW

Precision Medicine, AI, and the Future of Personalized Health Care

Kevin B. Johnson[1,2,*], Wei-Qi Wei[1], Dilhan Weeraratne[3], Mark E. Frisse[1], Karl Misulis[1,4], Kyu Rhee[3], Juan Zhao[1] and Jane L. Snowdon[3]

The convergence of artificial intelligence (AI) and precision medicine promises to revolutionize health care. Precision medicine methods identify phenotypes of patients with less-common responses to treatment or unique healthcare needs. AI leverages sophisticated computation and inference to generate insights, enables the system to reason and learn, and empowers clinician decision making through augmented intelligence. Recent literature suggests that translational research exploring this convergence will help solve the most difficult challenges facing precision medicine, especially those in which nongenomic and genomic determinants, combined with information from patient symptoms, clinical history, and lifestyles, will facilitate personalized diagnosis and prognostication.

CHAT GPT

L'**IA** è in continua evoluzione, trovando ogni giorno nuove applicazioni

perplexity

Copilot

Editorial

THE LANCET

AI in medicine: creating a safe and equitable future

Forbes

FORBES > INNOVATION > HEALTHCARE

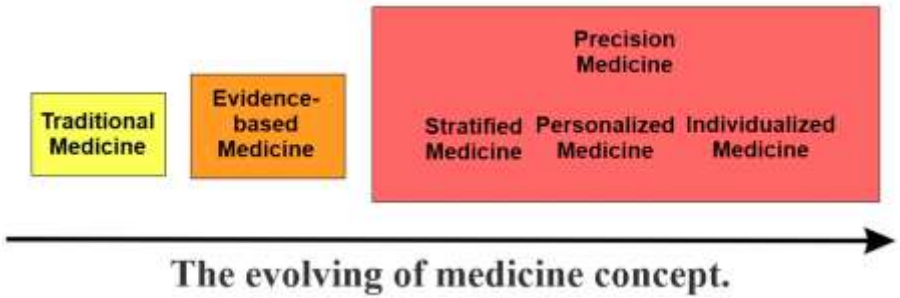
Precision Diagnostics Can Save Money In Healthcare: What's Holding Them Back?

THE LANCET

Editorial

Precision medicine: improving accuracy, reducing error

La **medicina di precisione** costituisce ad oggi l'evoluzione naturale dell'evidence based medicine



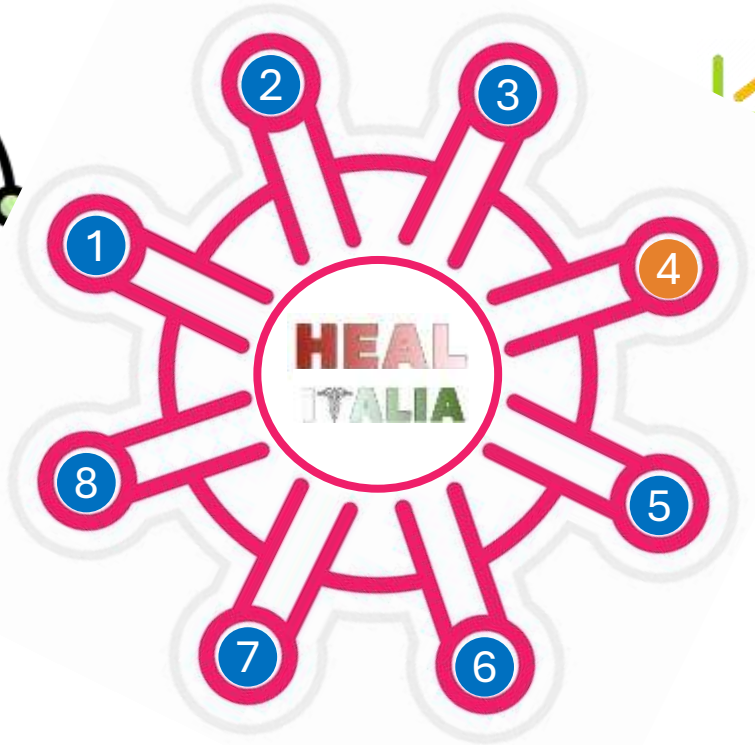
The evolving of medicine concept.

Precision Diagnostics Market to Reach USD 143.96 billion by 2028 Thanks to Growing Emphasis on Early Cancer Diagnostics and Increased Penetration of Advanced Diagnostics Technology

Global precision diagnostics market was valued at $51.09 billion in 2021, and it is expected to reach a value of USD 143.96 billion by 2027, at a CAGR of 13.03% over the forecast period (2022–2028).

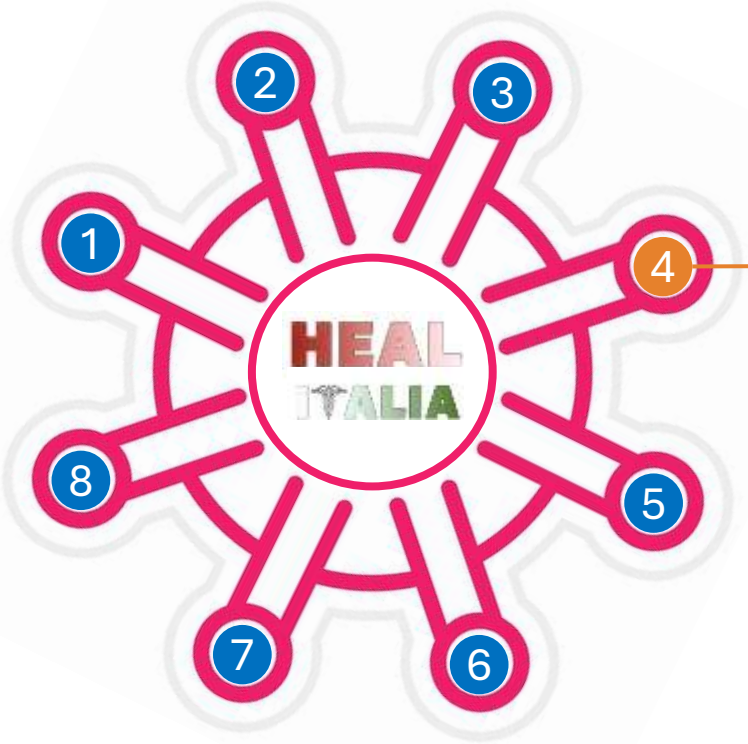
Sustainability

Therapeutic Failures (> 40%)



Intelligenza

na di Precisione



SPOKE 4

Obiettivo dello Spoke: Creare nuove pathway diagnostiche al fine di ottenere una diagnosi:

Rapida | Accessibile | Precoce | Costo-efficace | Precisa

In quali patologie?

Rare | Oncologiche | Cardiovascolari | Metaboliche

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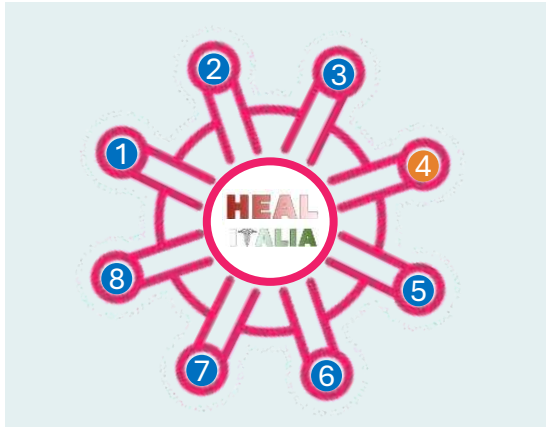
WP 1

Ricerca di nuovi markers mini-invasivi e avanzati di diagnosi precoce

WP 2

Nuovi strumenti di diagnosi biologica avanzata nell'inquadramento di patologie complesse e oncologiche



WP 3

Ricerca di nuove soluzioni basate sull'AI per l'analisi e acquisizione di immagini digitali

WP 4

Verso una nuova frontiera network-based nel management delle patologie poligeniche e tumorali

What we are doing...

WP1 **Ricerca di nuovi markers mini-invasivi e avanzati di diagnosi precoce**

- Nuovi algoritmi MRI basati su IA per guidare la **biopsia prostatica** per una rilevazione più efficace del tumore

- **IA applicata alla TC** per rilevare **metastasi polmonari** e differenziare i sottotipi istologici

- Modelli di **AI** → predire il **rischio di morte cardiaca improvvisa** nello scompenso cardiaco → Uso più efficiente dei defibrillatori cardiaci impiantabili

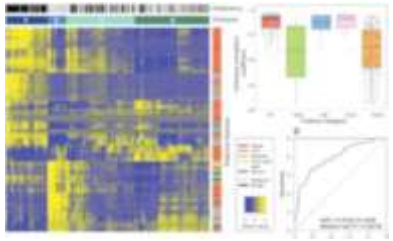
300 pazienti

What we are doing...

WP2

Nuovi strumenti di diagnosi biologica avanzata nell'inquadramento di patologie complesse/oncologiche

Intelligenza artificiale → Medicina di Precisione



- **Radiomica** per una diagnosi di precisione nel **carcinoma mammario** e **pancreatico**

- Approccio multi-omico + AI (istopatologia, radiologia, genomica) nei **tumori ematologici**
  → stratificazione e prognosi

- **Software** per analisi automatizzata delle cellule tumorali circolanti nel **carcinoma mammario e polmonare**

250 pazienti

Review > Cancers (Basel). 2023 Apr 26;15(9):2491. doi: 10.3390/cancers15092491.

Value of Artificial Intelligence in Evaluating Lymph Node Metastases

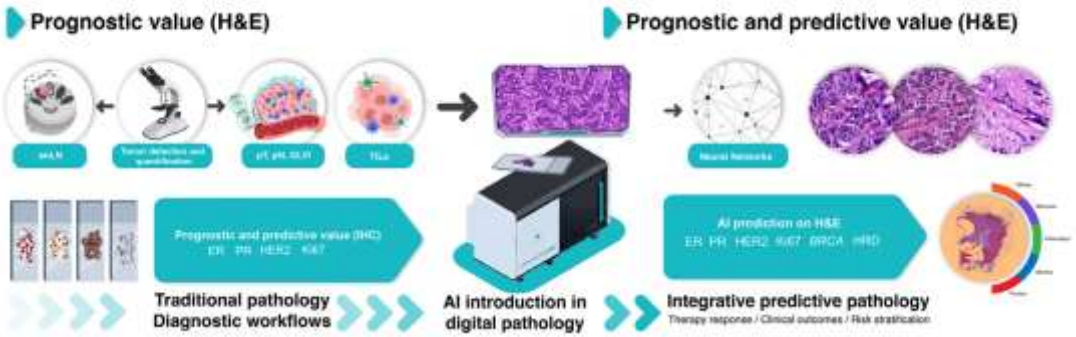
Nicolò Caldonazzi [1], Paola Chiara Rizzo [1], Albino Eccher [2], Ilaria Girolami [3], Giuseppe Nicolò Fanelli [4], Antonio Giuseppe Naccarato [4], Giuseppina Bonizzi [5], Nicola Fusco [5 6], Giulia d'Amati [7], Aldo Scarpa [1], Liron Pantanowitz [8], Stefano Marletta [1 9]

What we are doing...

WP3

Ricerca di nuove soluzioni basate sull'AI per l'analisi e acquisizione di immagini digitali

Intelligenza artificiale → Medicina di Precisione



Creazione di un'infrastruttura di ultima generazione per la raccolta e l'analisi di immagini digitali, attraverso:

Nuovo **scanner** di ultima generazione

ÆQUIP

Sistema di standardizzazione *AI-assisted*

Nuova WorkStation

Sistema di archiviazione automatizzato

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Virchows Arch. 2024 Sep;485(3):453-460. doi: 10.1007/s00428-024-03823-7. Epub 2024 May 14.

Digital pathology structure and deployment in Veneto: a proof-of-concept study

Albino Eccher [1], Stefano Marletta [2 3], Marta Sbaraglia [4], Angela Guerriero [4], Mattia Rossi [5], Giovanni Gambaro [5], Aldo Scarpa [6], Angelo Paolo Dei Tos [4]

Nuovo **scanner** di ultima generazione

ÆQUIP

Sistema di standardizzazione *AI-assisted*

Nuova WorkStation

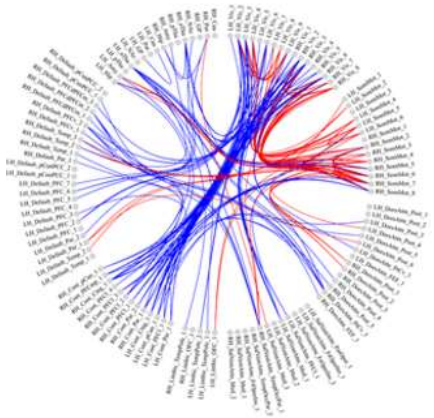
Sistema di archiviazione automatizzato

Tutto integrato in un sistema informatico di laboratorio (LIS)

What we are doing...

WP4

Verso una nuova frontiera network-based nel management delle patologie poligeniche e tumorali



Analisi computazionale *network-based* dei dati clinici → diagnosi precoce e previsione dell' aggravamento

70 pazienti

Network e *decision-curve* analysis per identificare biomarcatori RMN e miRNA nei pazienti con sospetto **carcinoma prostatico** → diagnosi precoce e individualizzata

400 pazienti

SPOKE 4
Precision Diagnostics

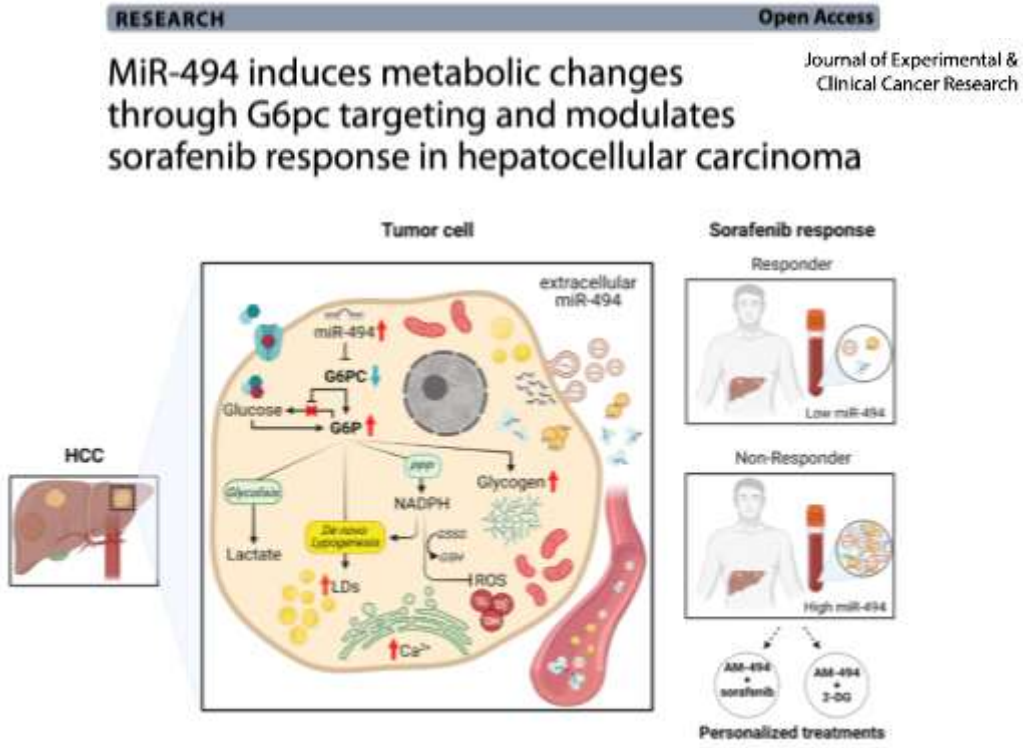
La biologia molecolare come strumento di medicina personalizzata

Il micro-RNA 494 ha dimostrato un ruolo cruciale nella **riprogrammazione metabolica** in cellule di carcinoma epatocellulare

Ruoli potenziali:

- Biomarcatore di **risposta alla terapia con sorafenib**
- **Bersaglio terapeutico** per strategie combinate con sorafenib o altri farmaci oncologici

Alcuni esempi di applicazione pratica della diagnostica di precisione



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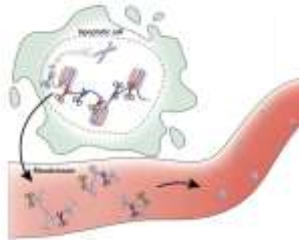
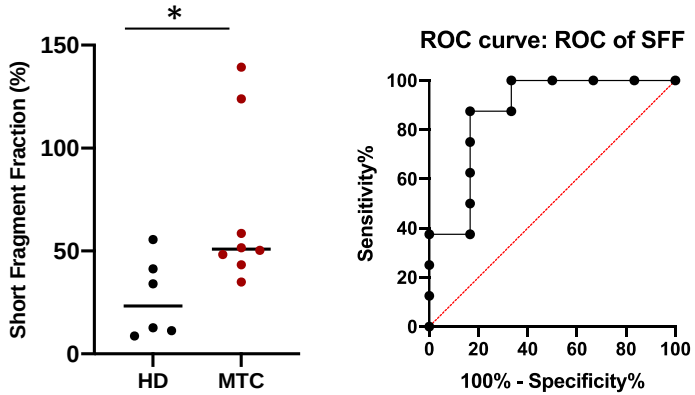
Analysis of cfDNA **Fragmentation** from MTC samples *versus* healthy allowed to identified 2 microRNA High in MTC patients

(Kavish et al. 2021)





Fragmentation

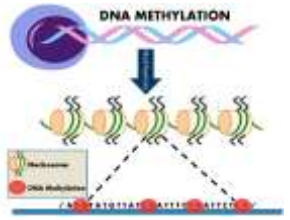
measurement can distinguish MTC patients

from healthy controls

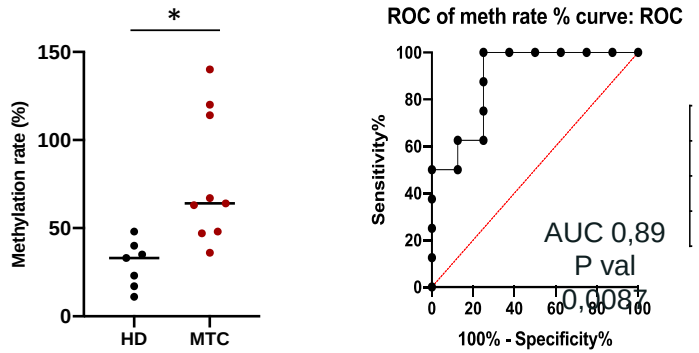
NOVEL DIAGNOSTIC BIOMARKERS

(can be added to the current use circulating biomarkers calcitonin and CEA to increase diagnostic sensitivity in a patient with thyroid nodule)

Analysis of cfDNA **methylation** of specific genome region from MTC plasma samples



(Wise et al. 2016)



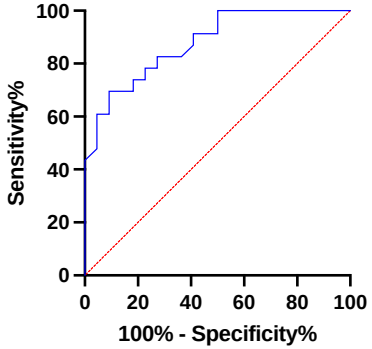
detection of CG dinucleotic

methylation levels in the MGMT gene identifies MTC patients at diagnosis and is significantly higher in patients with more aggressive tumors

NOVEL DIAGNOSTIC and PROGNOSTIC BIOMARKERS

Citarella A et al .Biomark Res. 2023 doi: 10.1186/s40364-023-00522-4.

Analysis of RNA from MTC samples *versus* healthy allowed to identified 2 microRNA High in MTC patients vs Healthy



Area under the ROC curve	
Area	0.8775
Std. Error	0.04915
95% confidence interval	0.7811 to 0.9738
P value	<0.0001

microRNA-26b-5p and microRNA-451a novel **diagnostic markers**

(can be added to the current use circulating biomarkers calcitonin and CEA to increase diagnostic sensitivity in a patient with thyroid nodule)

Besharat ZM et al 2023 doi: 10.1007/s40618-023-02115-2.

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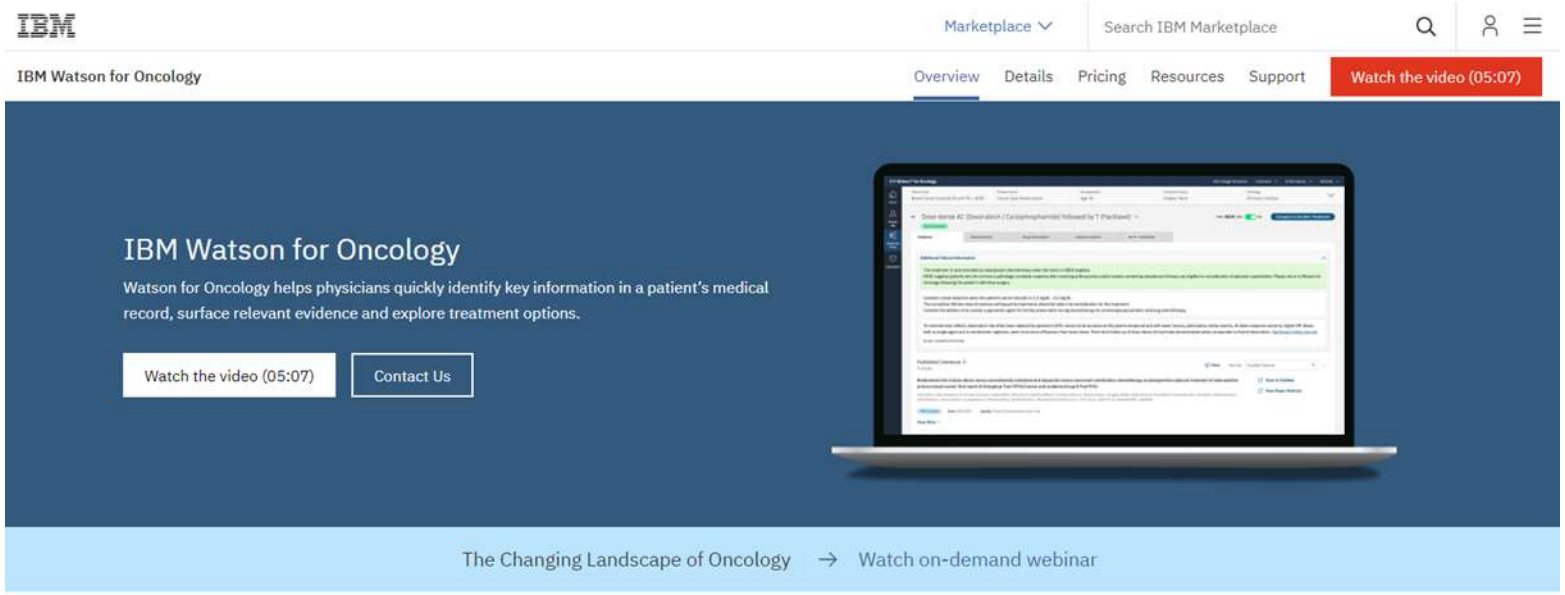

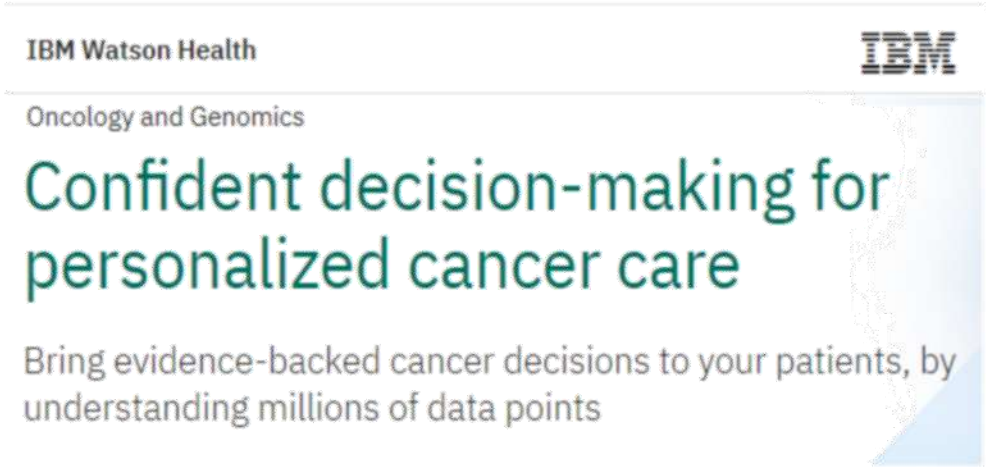

- Promised transformative cancer care
- Failed due to poor alignment with clinical workflows
- Highlight The need for clinician-AI collaboration

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A Human-Centered Evaluation of a Deep Learning System Deployed in Clinics for the Detection of Diabetic Retinopathy

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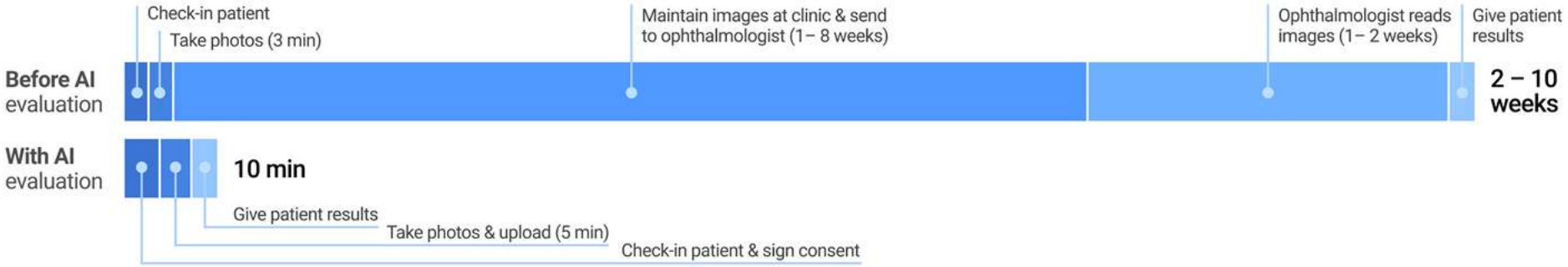
Laura M. Vardoulakis
Google Health
Palo Alto, CA
lauravar@google.com

- Strong performance in trials, struggled in real-world clinics.
- Challenge: Variability in imaging conditions.
- Lesson: The importance of rigorous real-world validation.



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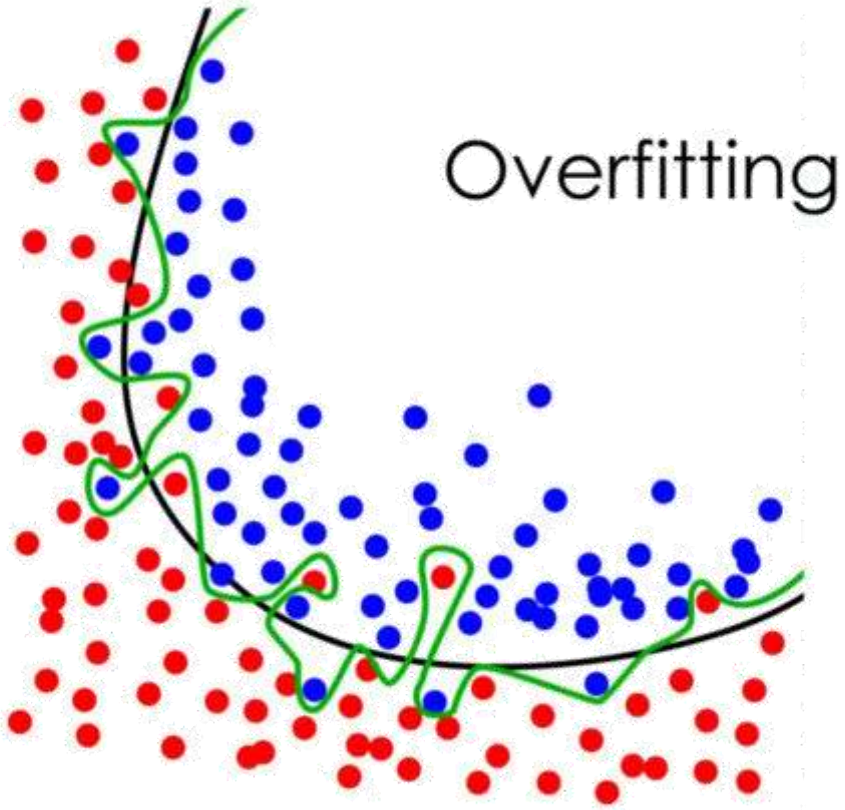
AI is currently very good at finding patterns and relationships within big datasets

Which of those are actually meaningful?



"the production of an analysis that corresponds too closely or exactly to a particular set of data, and may therefore fail to fit additional data or predict future observations reliably"

David J. Leinweber
The Journal of Investing Spring 2007

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PRECISION VS. PERSONALIZED MEDICINE

- Precision Medicine is a step towards Personalized medicine, in that it uses more variables to stratify patients, but is not completely individualized

- “Personalized” medicine would individualize treatment for each patient, changing not only types of agents but doses and regimens based on purely individual characteristics

Thanks to Manuela Petti

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Network Medicine

Hub: proteins with a relevant biological role

→ Centrality measures in a network

Local hypothesis: the proteins involved in the same disease tend to interact with each other forming a disease module

→ Network modularity

A.-L. Barabási et al, Nat. Rev. Genet., 2011

nature REVIEWS GENETICS

Network medicine: a network-based approach to human disease

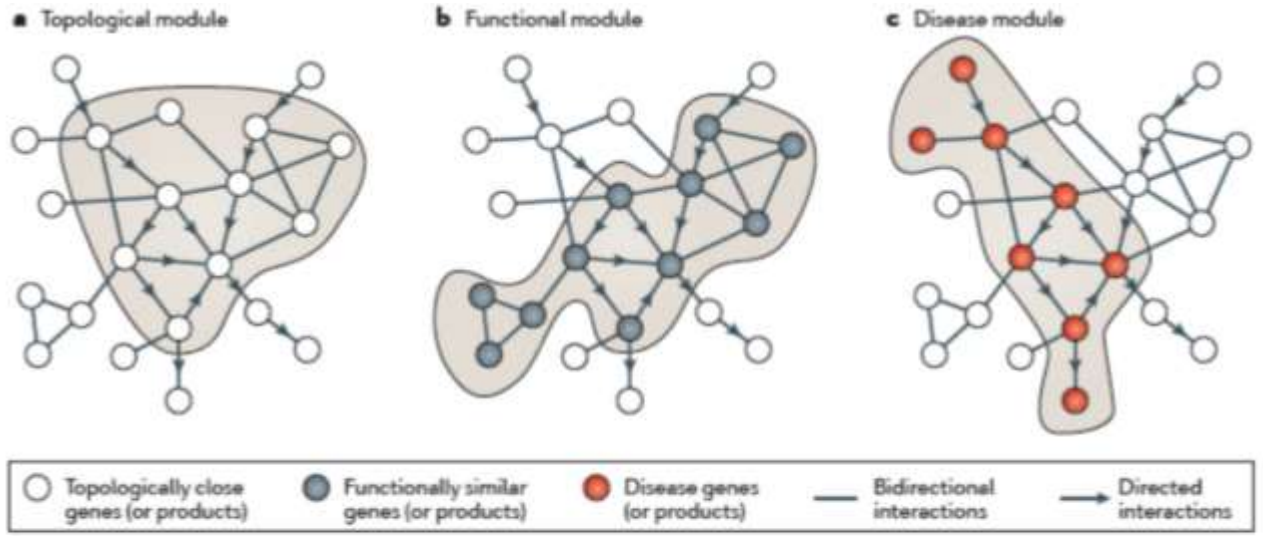

Figure 2 | **Disease modules.** Schematic diagram of the three modularity concepts that are discussed in this Review. **a** | Topological modules correspond to locally dense neighbourhoods of the interactome, such that the nodes of the module show a higher tendency to interact with each other than with nodes outside the module. As such, topological modules represent a pure network property. **b** | Functional modules correspond to network neighbourhoods in which there is a statistically significant segregation of nodes of related function. Thus, a functional module requires us

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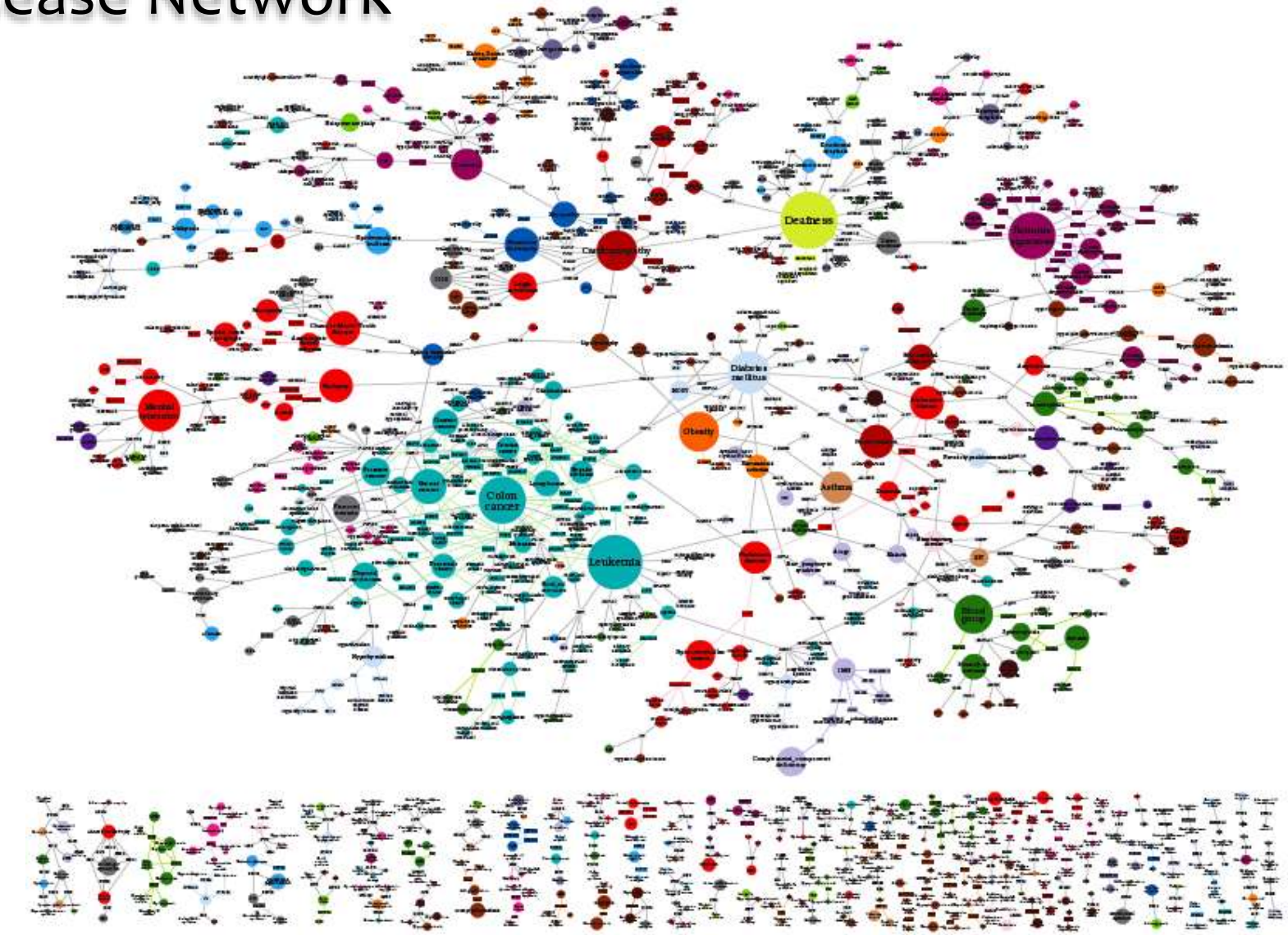
Human Disease Network

Joseph Loscalzo, Chairman of the Department of Medicine, Harvard University



Goh et al, PNAS, *2007*

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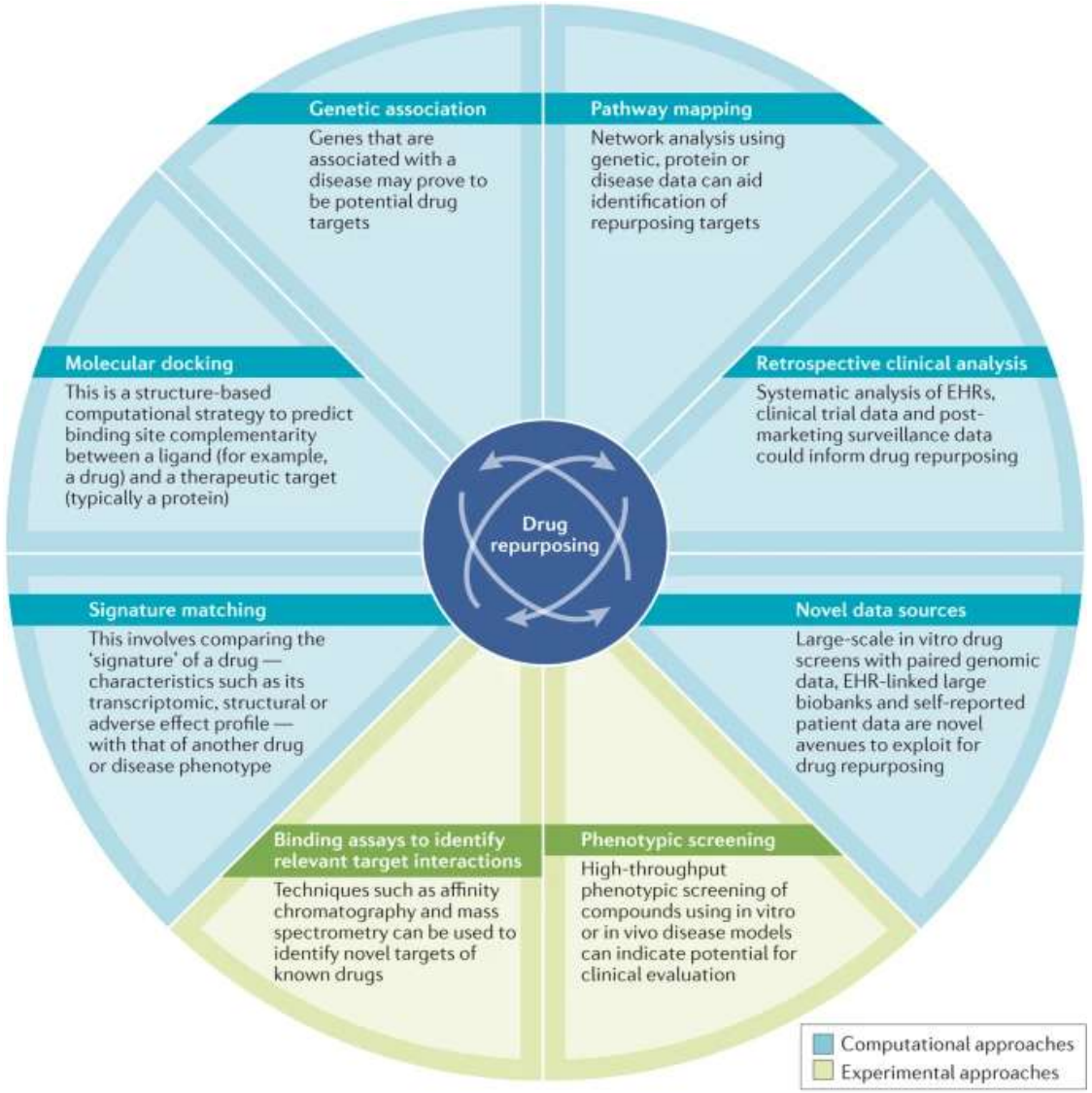
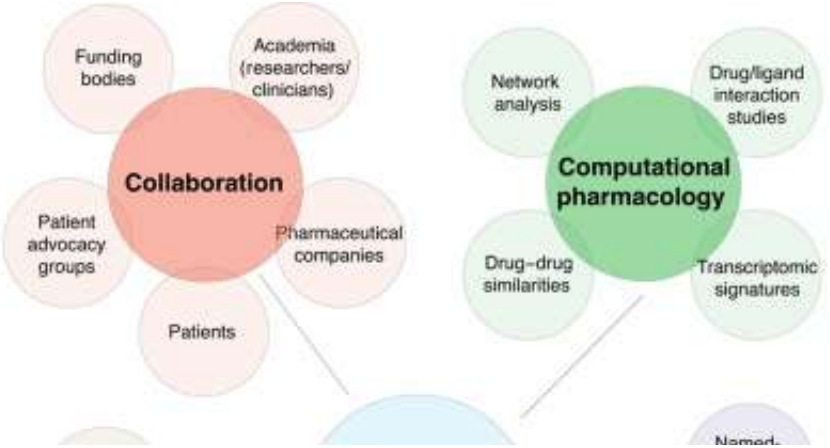
Can Drug/Biomarker Repurposing Accelerate Precision Oncology?





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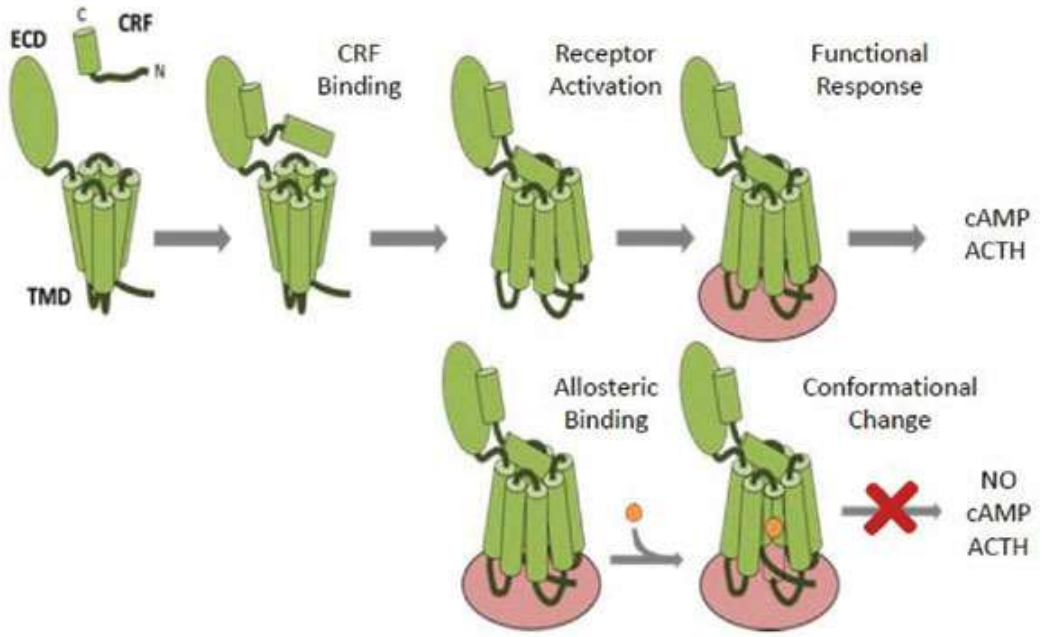
A breakthrough in CRF1 antagonist pharma history

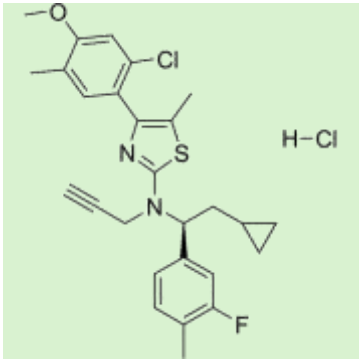


Preclinical Research

Antidepressant-Like Effects of the Corticotropin-Releasing Factor 1 Receptor Antagonist, SSR125543, and the Vasopressin 1b Receptor Antagonist, SSR149415, in a DRL-72s Schedule in the Rat

Caroline Louis, Caroline Cohen, Ronan Depoortère & Guy Griebel

Neuropsychopharmacology **31**, 2180–2187 (2006) | Cite this article



COMPLETED

A Trial Evaluating the Efficacy and Tolerability of SSR125543 in Outpatients With Major Depressive Disorder (AGATE)

ClinicalTrials.gov ID NCT01034995

Sponsor Sanofi

Information provided by Sanofi

Last Update Posted 2011-04-14

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Precision Diagnostics

La sfida

Dal laboratorio alla pratica clinica

Nelle malattie Rare

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STUDENTI LAUREATI DOCENTI PERSONALE CONTATTI cerca nel sito IT

Home Ricerca Una speranza terapeutica per i pazienti affetti da iperplasia surrenalica congenita

Una speranza terapeutica per i pazienti affetti da iperplasia surrenalica congenita

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia

Authors: Richard J. Auchus, M.D., Ph.D., Oksana Hamidi, D.O., Rosario Pivonello, M.D., Ph.D., Irina Bancos, M.D., Gianni Russo, M.D., Selma F. Witchel, M.D., **Andrea M. Isidori, M.D., Ph.D.,** et al. for the CAHtalyst Adult Trial Investigators* Author Info & Affiliations

Published June 1, 2024 | DOI: 10.1056/NEJMoa2404656

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Circadian clock disruption impairs immune oscillation in chronic endogenous hypercortisolism: a multi-level analysis from a multicentre clinical trial

Valeria Hasenmajer,[a] Emilia Sbardella,[a] Francesca Sciarra,[a] Chiara Simeoli,[b] Claudia Pivonello,[c] Filippo Ceccato,[d,e] Riccardo Pofi,[f] Marianna Minnetti,[a] Flavio Rizzo,[a] Davide Ferrari,[a] Ilaria Bonaventura,[a] Federica Barbagallo,[g] Elisa Giannetta,[a] Danilo Alunni Fegatelli,[h] Simone Conia,[i] Roberto Navigli,[i] Giorgio Arnaldi,[j] Carla Scaroni,[d,e] Rosario Pivonello,[b] Daniele Gianfrilli,[a,l] Mary Anna Venneri,[a,l] and Andrea M. Isidori[a,k,l,*]

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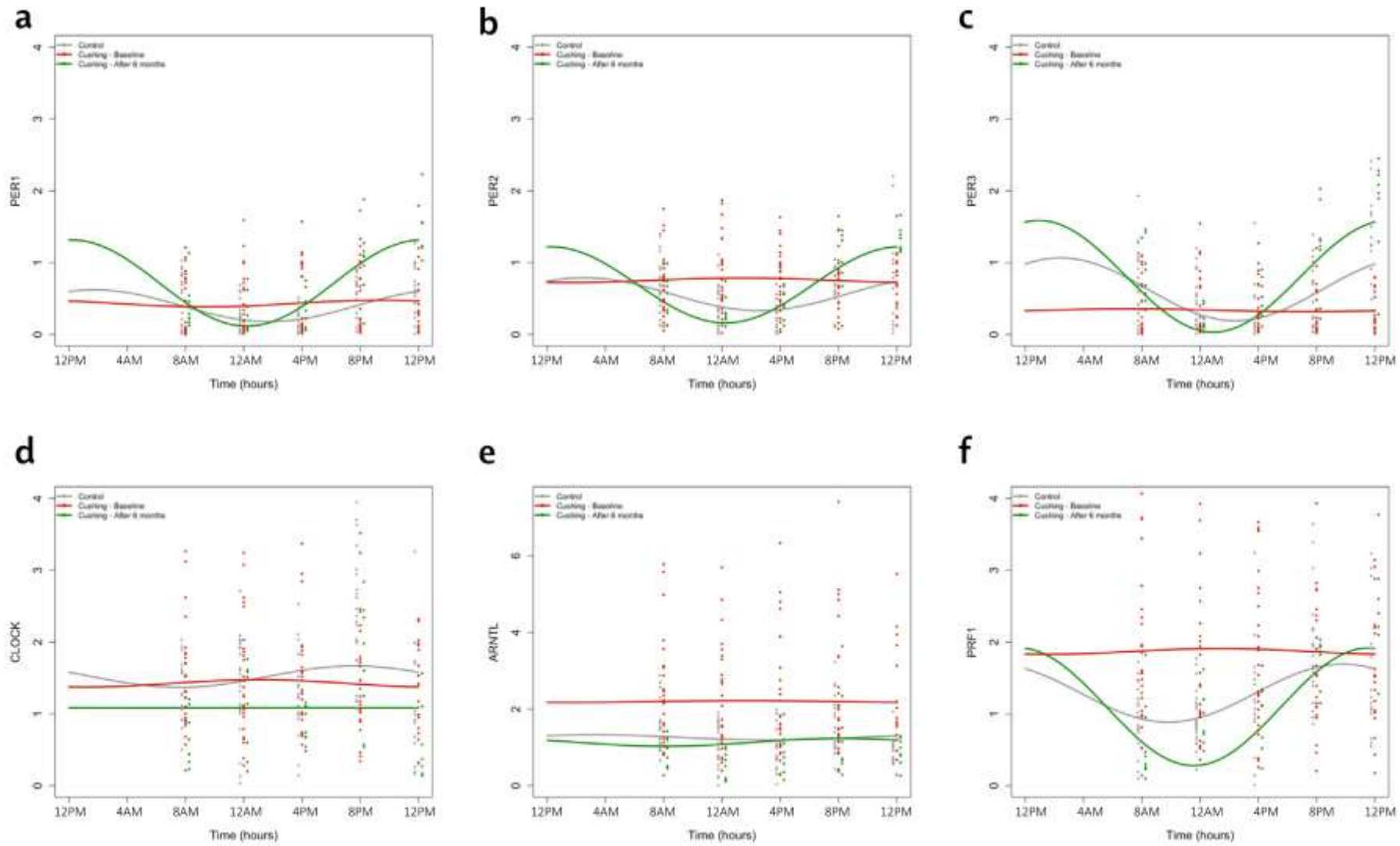
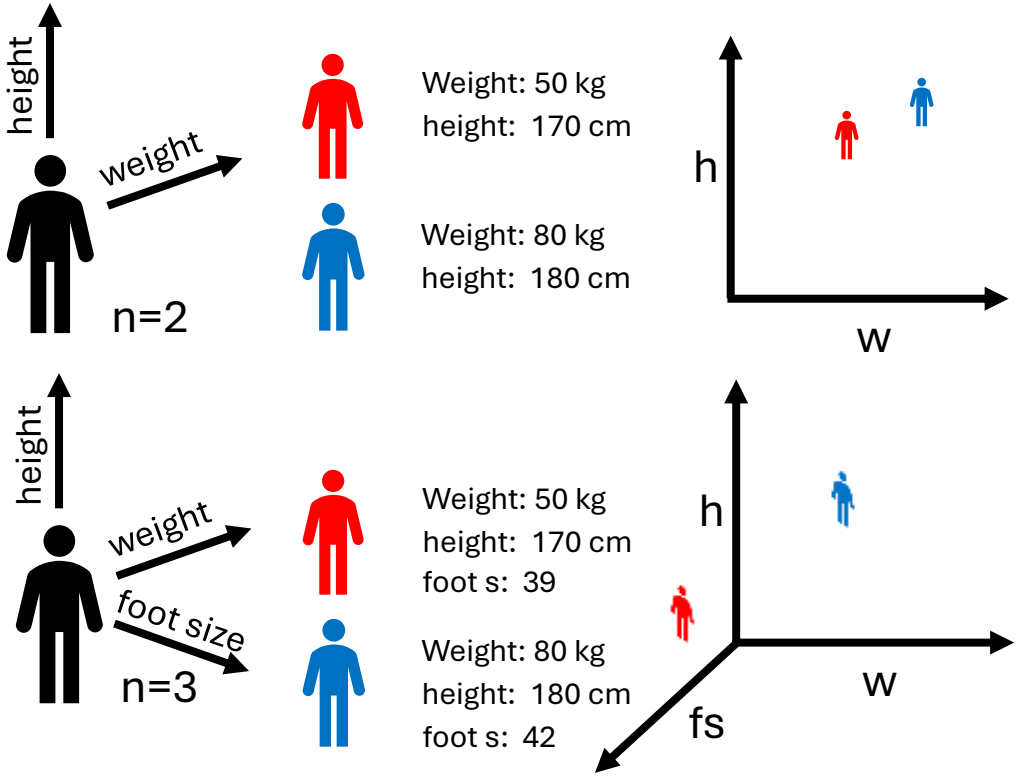
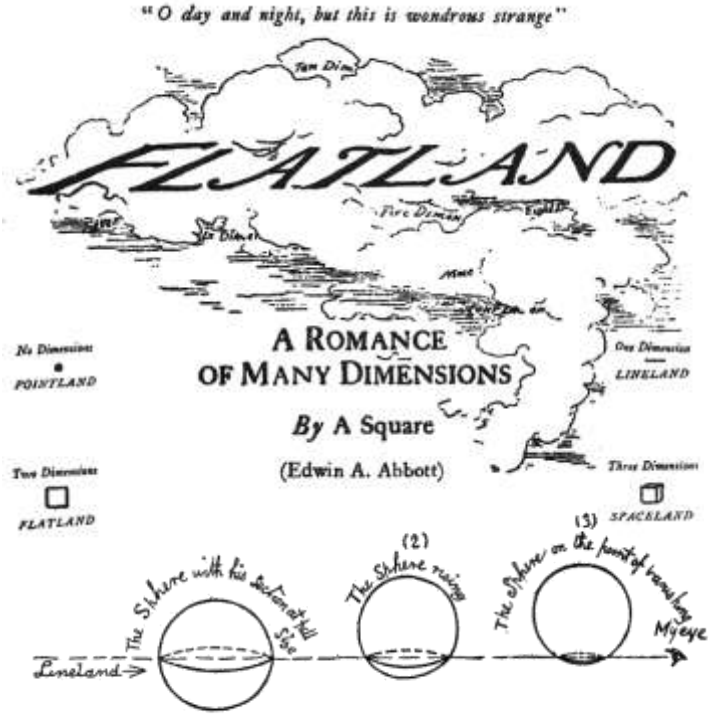
eBioMedicine
2024;110: 105462

Published Online xxx
https://doi.org/10.1016/j.ebiom.2024.105462


a
b
c
d
e
f
PER1
PER2
PER3
CLOCK
ARNTL
PRF1
Control
Cushing - Baseline
Cushing - After 6 months
12PM
4AM
8AM
12AM
4PM
8PM
12PM
Time (hours)





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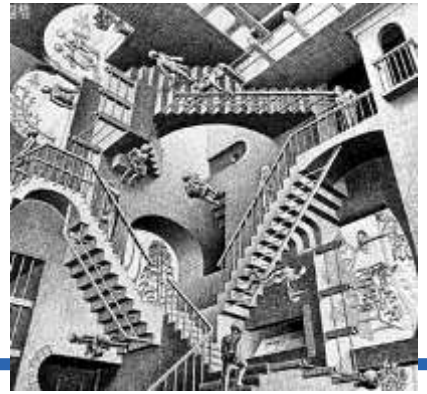

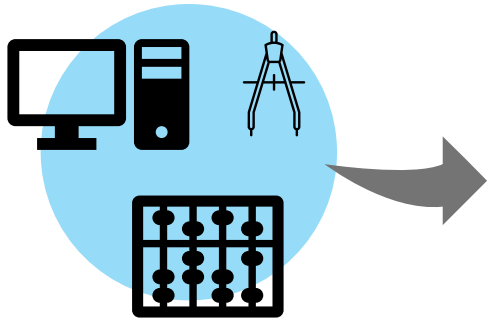

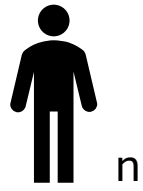

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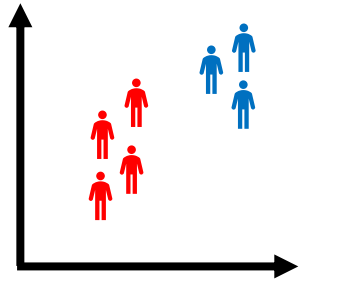
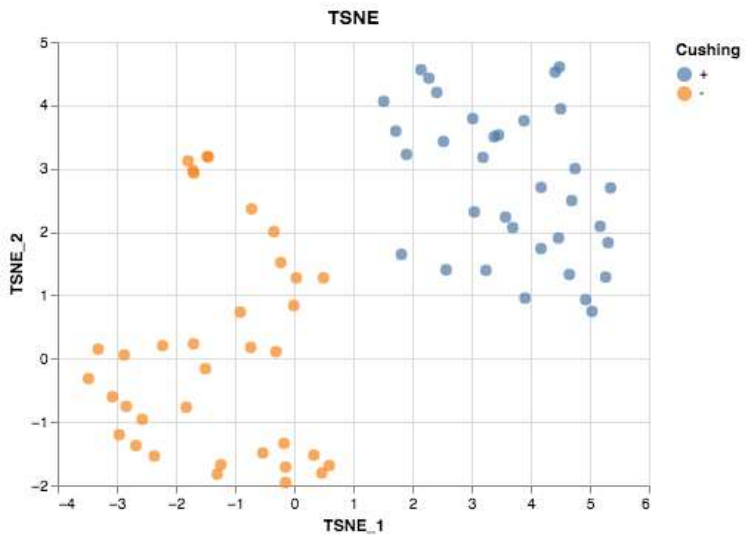
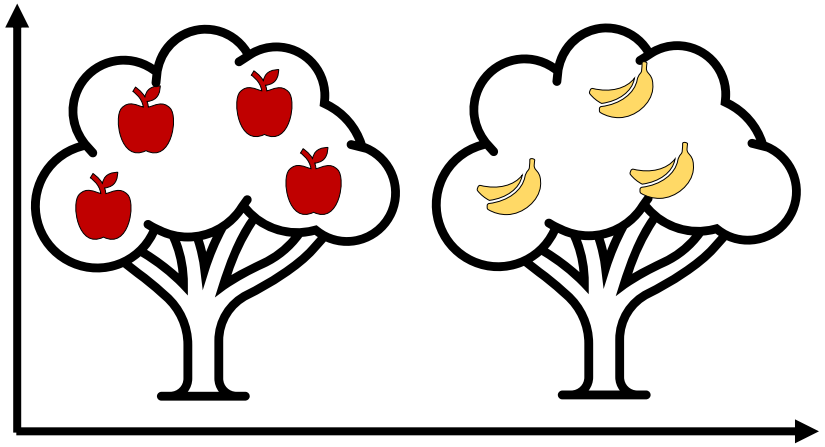


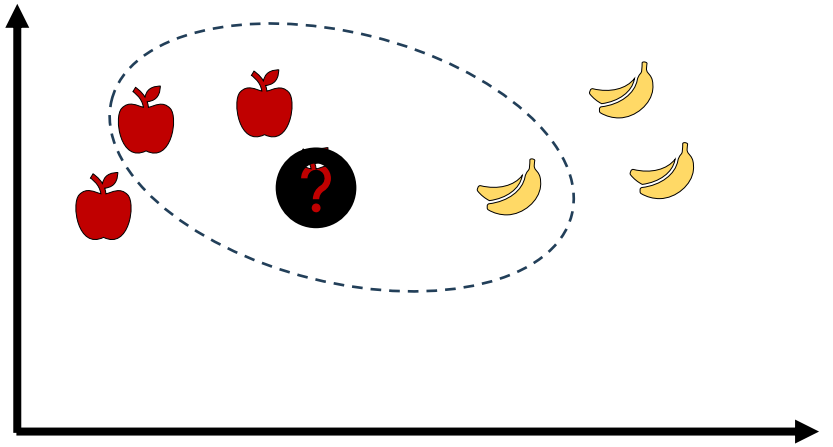
t-Stochastic Neighbour Embedding

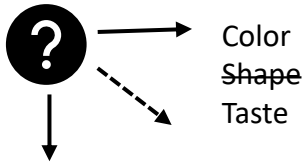
Results: machine learning analyses – classification algorithms



Effective separation between patients and controls. (using the "*se vede*" criterion)

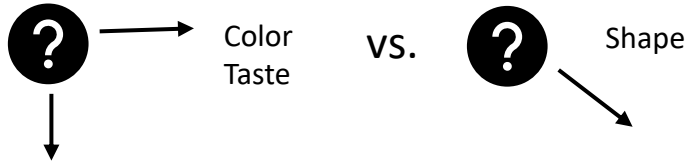






You can "blind" variables

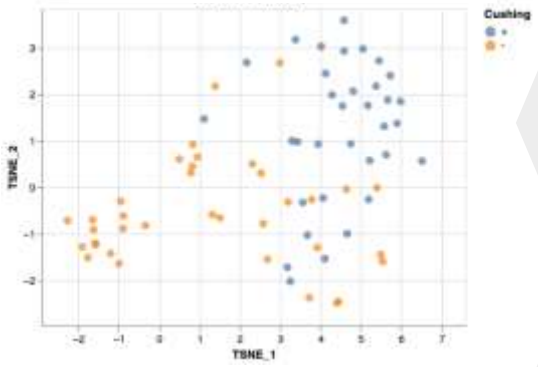
Or compare the effectiveness of different groups of variables



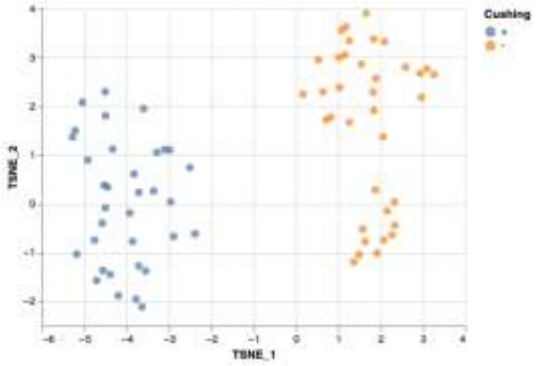
Results: machine learning analyses

1. Comparing immune profiling and circadian genes to other parameters routinely used in CS diagnosis

Group A



Group B



Group A: variables commonly associated with CS (hormones, concomitant medications, lipid and glucose profile, vital parameters…)
Group B: circadian variables (immune profiling, circadian genes expression)

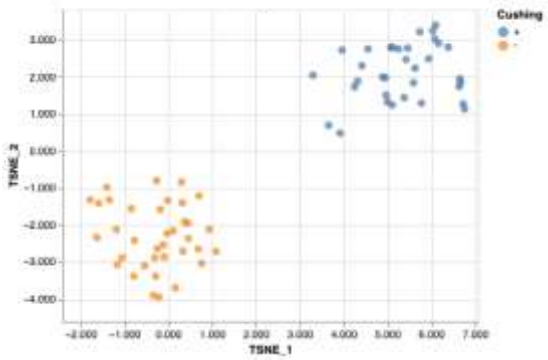
k-NN model: group B achieved a 97% accuracy, +20% compared to **group A**

ML models (**k-NN** and **SVM**) showed that Immune profiling (left) variables had a high accuracy at any time point (top panels), while circadian genes expression (right) achieved better results in identifying CS If taken all together

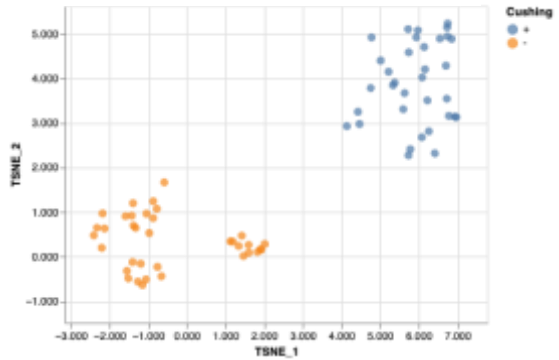
Visual representation by t-SNE

2. Comparing immune profiling to circadian genes at different time-points

8 AM

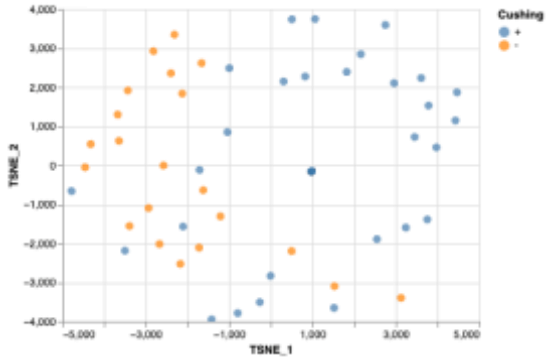


All

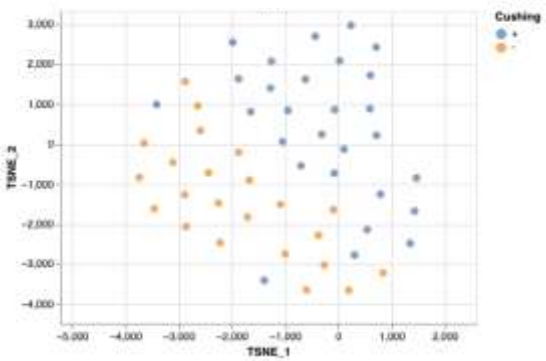


Immune profiling

8 AM



All



Circadian genes

And we don't work «alone»!

Intelligenza artificiale

Medicina di Precisione

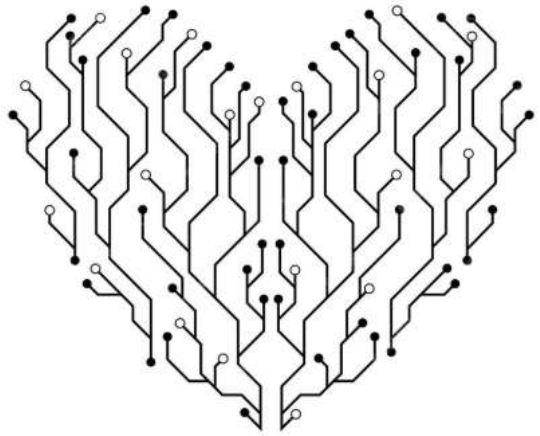
Bandi a cascata

Collaborazione con partners **esterni**

Obiettivo principale: aumentare i livelli di maturità tecnologica (TRLs)

Istituto Nazionale per le Ricerche Cardiovascolari

Assessing causal heterogenous biomarkers mapping of HFpEF patients for early diagnostic and risk stratification.



Uso di una **IA dedicata** per combinare:

- Dati clinici eterogenei
- Immagini diagnostiche
- Biomarkers (anche liquidi)

Per scoprire collegamenti causali tra le informazioni biomediche e scompenso cardiaco

SPOKE 4 - Challenges of AI in Precision Diagnostics

DATA

- Data Quality: Limited, biased datasets skew AI predictions.
- Privacy and Security: GDPR, HIPAA complicate data sharing.
- Generalizability: Overfitting limits applicability across populations.

BLACK-BOX

- Many AI models lack transparency (black box issue).
- Example: Heart disease predictions without explainability.
- Challenge: Balancing trust with usability.

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Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
HEAL ITALIA

SPOKE 4 - Challenges of AI in Precision Diagnostics

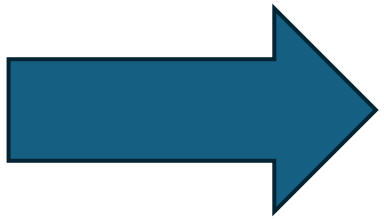
ETHICAL

- Accountability: Liability for AI-driven errors remains unclear.
- Bias: AI can reinforce healthcare inequities.
- Autonomy: Ensuring patients understand and consent to AI decisions.

REAL WORLD

- Workflow Disruption: Integrating AI into clinical practice.
- Cost: Financial burden of AI tools in resource-poor settings.
- Resistance: Overcoming skepticism among healthcare professionals.

Innovation on the Road



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