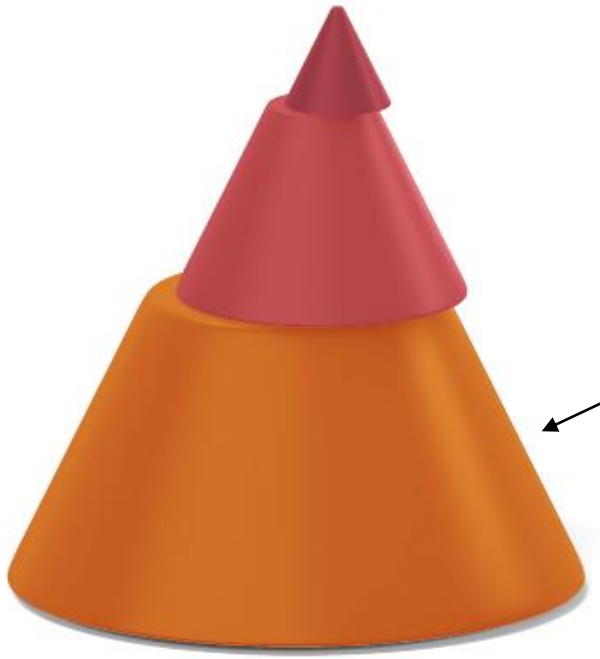
Associazione Italiana per l'Intelligenza Artificiale

AI Algorithms for Digital Therapeutics

Prof. Gianluigi Greco – Head of the Department of Mathematics and Computer Science, University of Calabria
President of the Italian Association for Artificial Intelligence

The role of artificial intelligence in the digital medicine

THE DIGITAL TRANSFORMATION



Digital Health

Technologies, platforms and systems that engage users for purposes related to lifestyle improvement, well-being and health. Other objectives may be to **acquire, store or transmit health data**, or to support clinical activities. To be deployed, applications in this area **do not require clinical trials**, nor regulatory supervision from any type of national or international body

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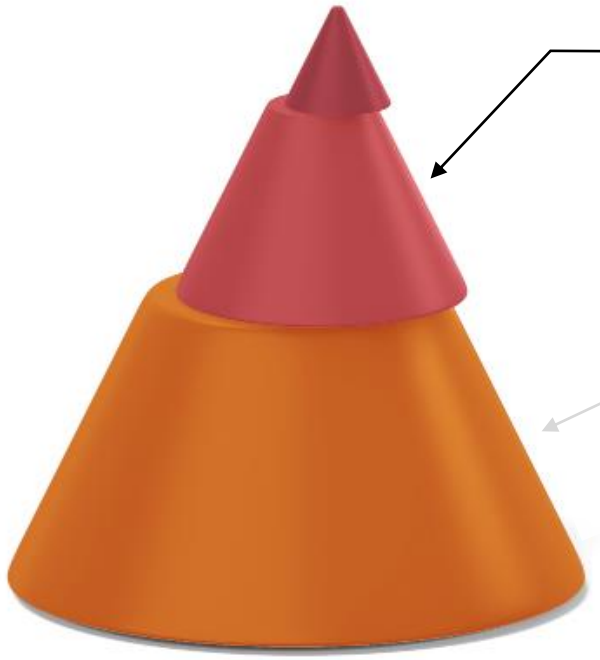


Digital Medicine

Software and hardware for clinical measurements and/or to intervene directly on health. **They require clinical efficacy trials** and are typically classified as medical devices

Digital Health

Technologies, platforms and systems that engage users for purposes related to lifestyle improvement, well-being and health. Other objectives may be to **acquire, store or transmit health data**, or to support clinical activities. To be deployed, applications in this area **do not require clinical trials**, nor regulatory supervision from any type of national or international body

THEORY AND PRACTICE

THEORY

The digital medina is based on software and hardware solutions, which **do not necessarily** have to use artificial intelligence techniques

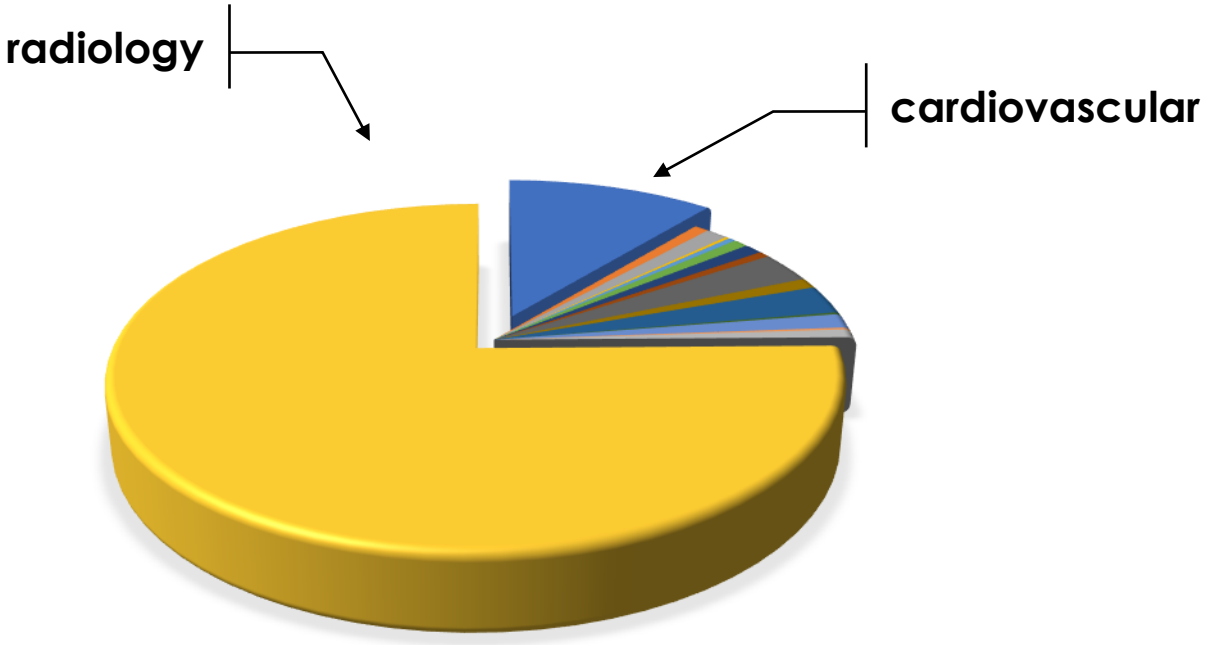
THEORY AND PRACTICE

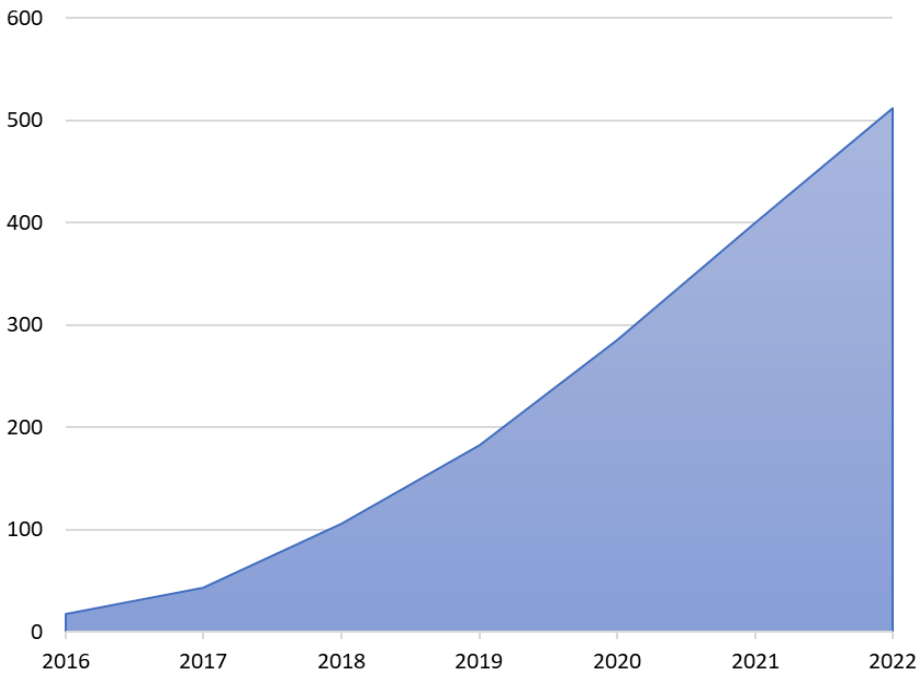
512 DEVICES APPROVED FDA APPROVED **+AI**

THEORY

PRACTICE

The digital medina is based on software and hardware solutions, which **do not necessarily** have to use artificial intelligence techniques





ALGORITHMS IN MEDICINE

More and more applications

x10 The number of algorithms using Artificial Intelligence in the medical field **has increased 10-fold** in the last year!

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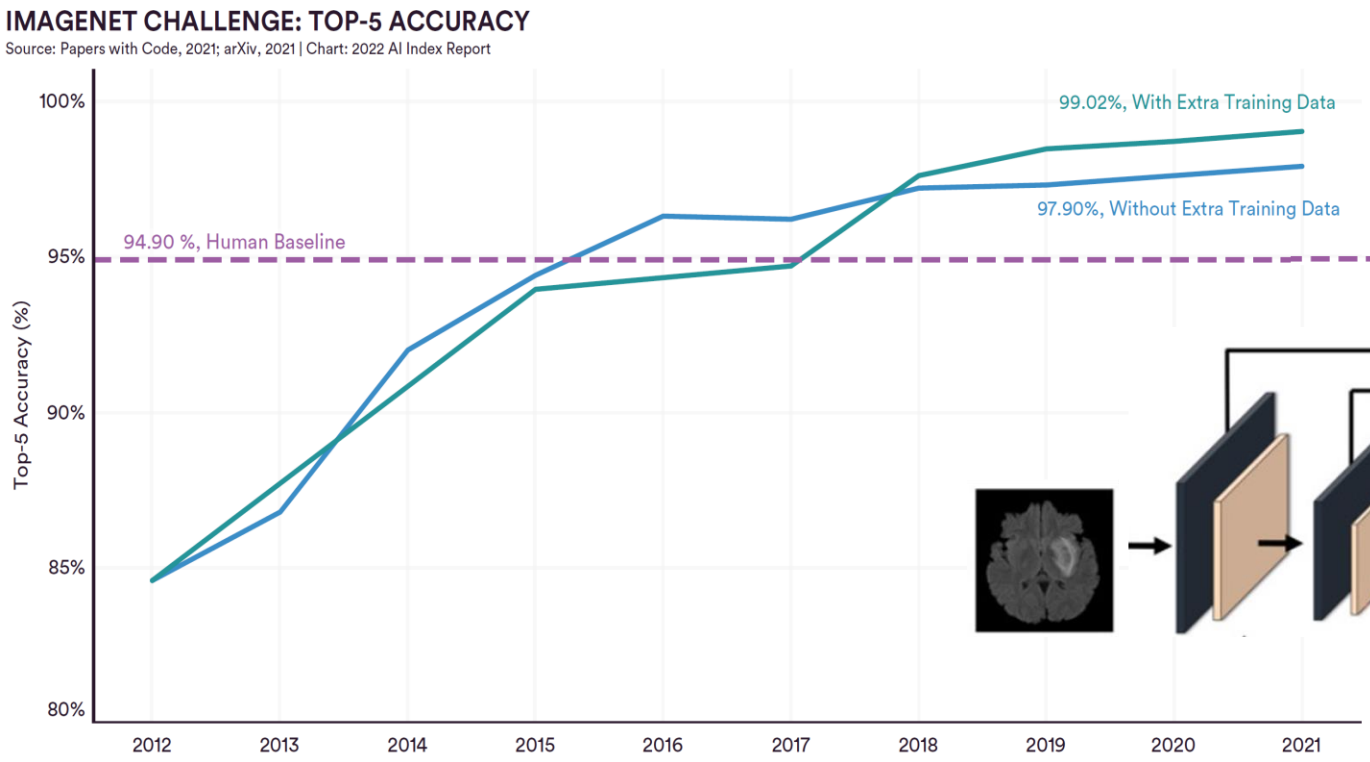
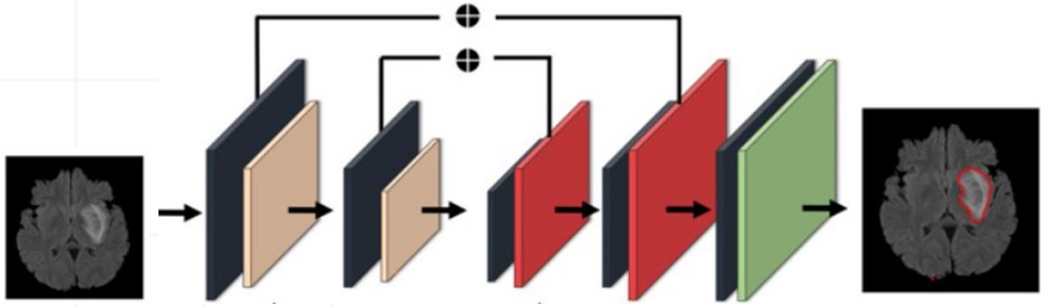
Artificial Intelligence Index Report 2022

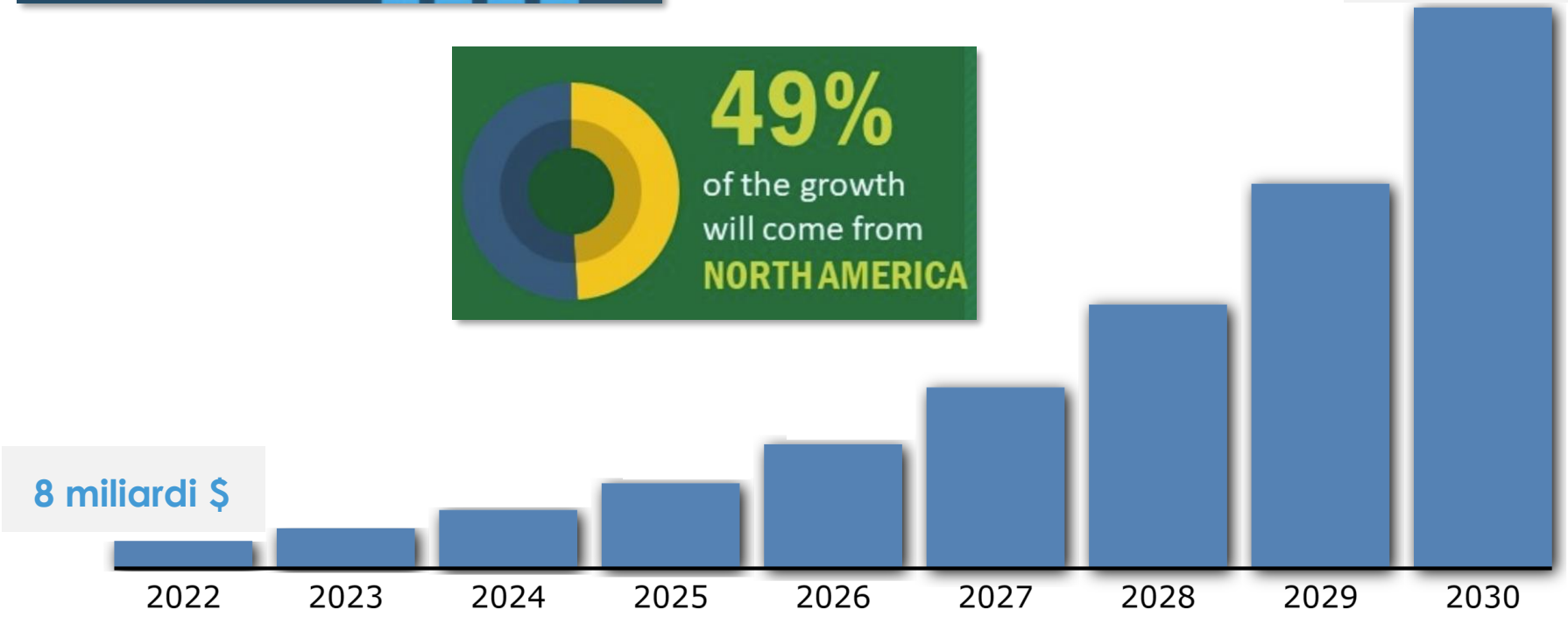
Stanford University Human-Centered Artificial Intelligence



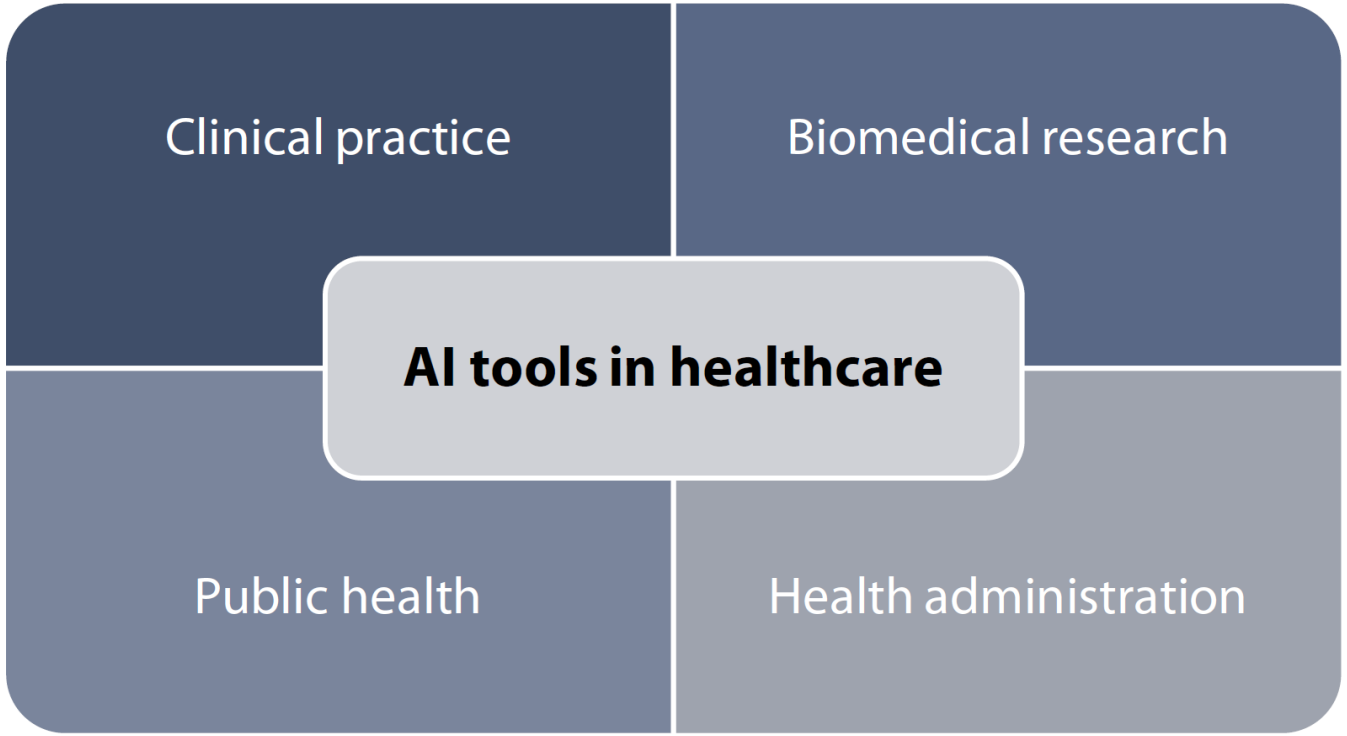
superuman performances



AI&HEALTH MARKET



AI&HEALTH DOMAINS



European Parliament

EPRS | European Parliamentary Research Service
Scientific Foresight Unit (STOA)
PE 729.512 – June 2022

DOMAINS FOR AI IN HEALTCARE

Public health

- **Surveillance**: AI can help identify specific demographics or geographical locations where the prevalence of disease or high-risk behaviours exist; it can also help to implement digital epidemiological surveillance

- **Global health**: AI may provide opportunities to address health challenges in low-and middle-income countries (LMICs); these challenges include acute health workforce shortages and weak public health surveillance systems;

- **Drug discovery**: recently developed AI approaches provide new solutions to enhance the efficacy and safety evaluation of candidate drugs based on big data modelling and analysis;

DOMAINS FOR AI IN HEALTCARE

Biomedical reserach

- **Clinical research**: mainstream medical knowledge resources are already using ML algorithms to rank search results, including algorithms that learn from users'search behaviour;

- **Personalized medicine**: strongly relies on a scientific understanding of how an individual patient's unique characteristics, such as molecular and genetic profiles, make this patient vulnerable to a disease and sensitive to a therapeutic treatment;

DOMAINS FOR AI IN HEALTCARE

Health administration

- Healthcare systems are characterized by a heavy administrative **workflow** with a wide range of actors and institutions, comprising patients (e.g. management of billing), health professionals, healthcare facilities and organisations (e.g. patient flow), imaging facilities, laboratories (e.g. supply chain of consumables), pharmacies, payers, and regulators.
- **AI can perform routine and burocratic tasks in a more efficient**, accurate and unbiased fashion
- Applications to **scheduling**, patient flow management, identification of fraudulent activities

DOMAINS FOR AI IN HEALTCARE

Clinical Practice

- **Radiology and digital pathology**: segmentation with limited human supervision to automatically localise and delineate the boundaries of anatomical structures or lesions;
- **Emergency medicine**: improve patient prioritisation during triage; organisational planning and management within the emergency department;
- **Surgery**: integration of diverse sources of information (patient risk factors, anatomic information, etc.) in the development of better surgical decisions;
- **Home care**: self-management of chronic diseases and diseases that affect the elderly;

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DeMaCS

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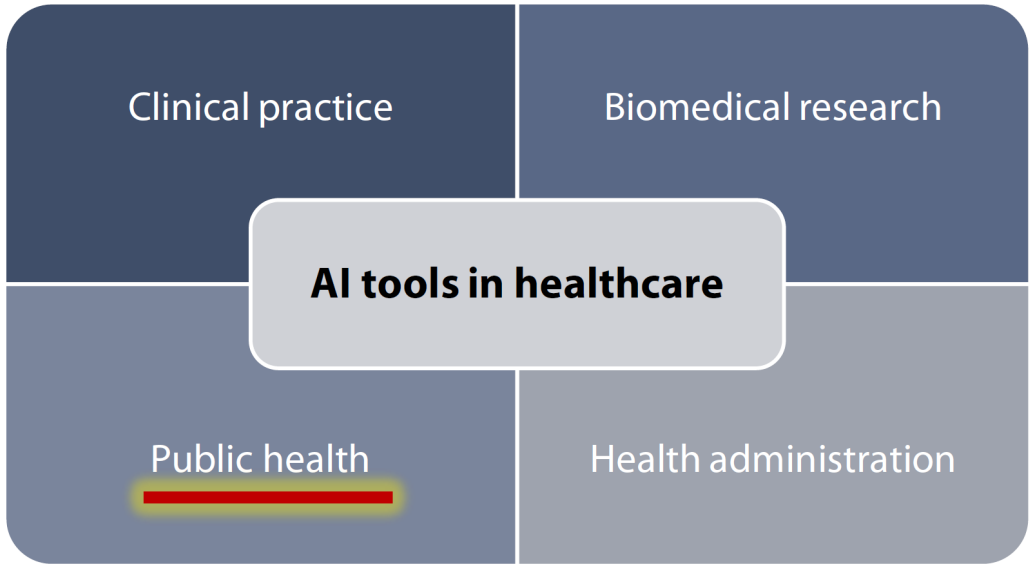
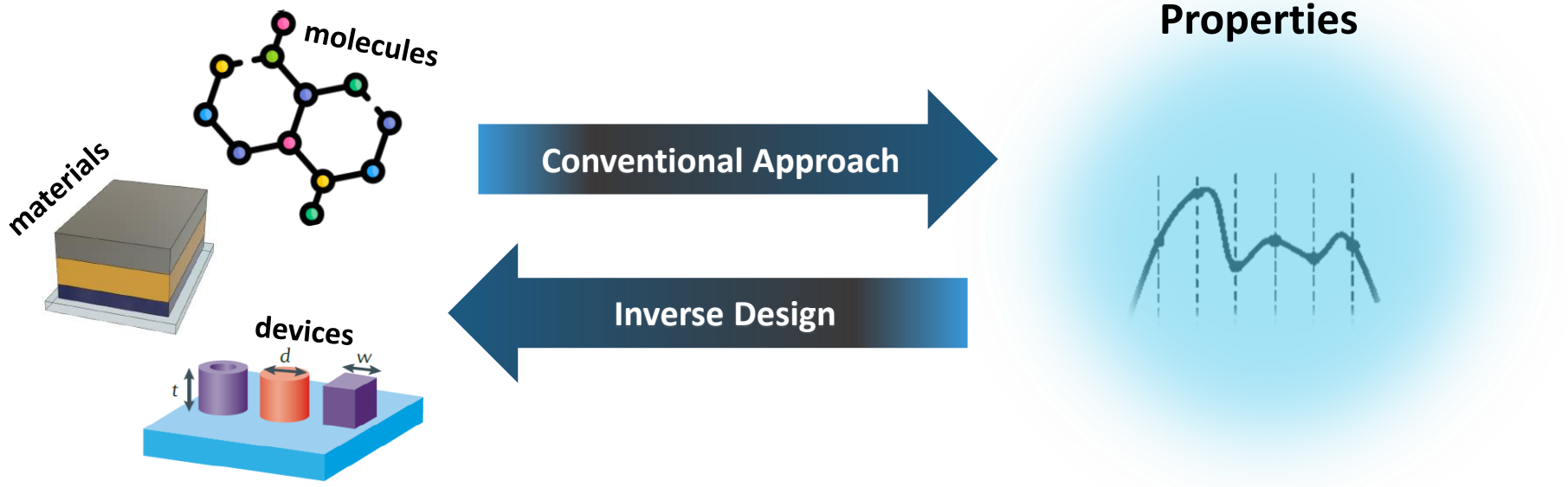


DRUG/MOLECULE DESIGN

INVERSE DESIGN

In fields such as Engineering, Chemistry and Physics, the design of device structures is progressively supported by **Deep Learning** methods

Objective: design materials, devices or tools based on the properties they should exhibit



PROPERTIES OF INTEREST

Functional Properties:

- Bind to a specific target receptor or enzyme

Physicochemical Properties:

- Molecule's chemical structure and behavior, such as solubility, stability, boiling point, melting point, and chemical reactivity

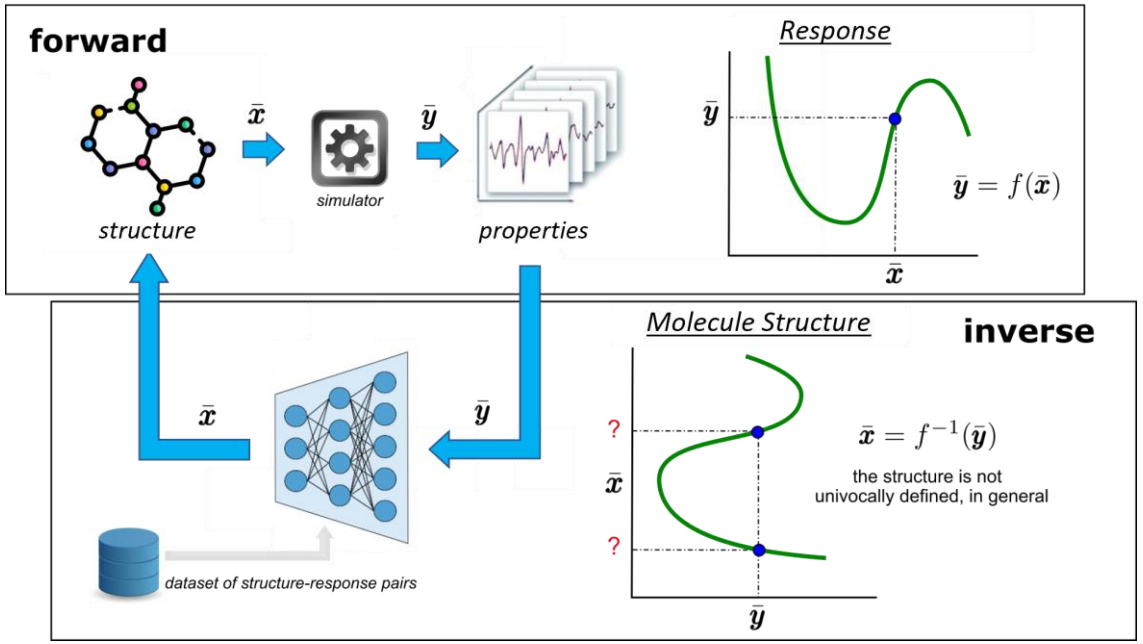
Toxicity and Safety:

- In a biological or environmental context, it's important to consider molecules toxicity and safety profile

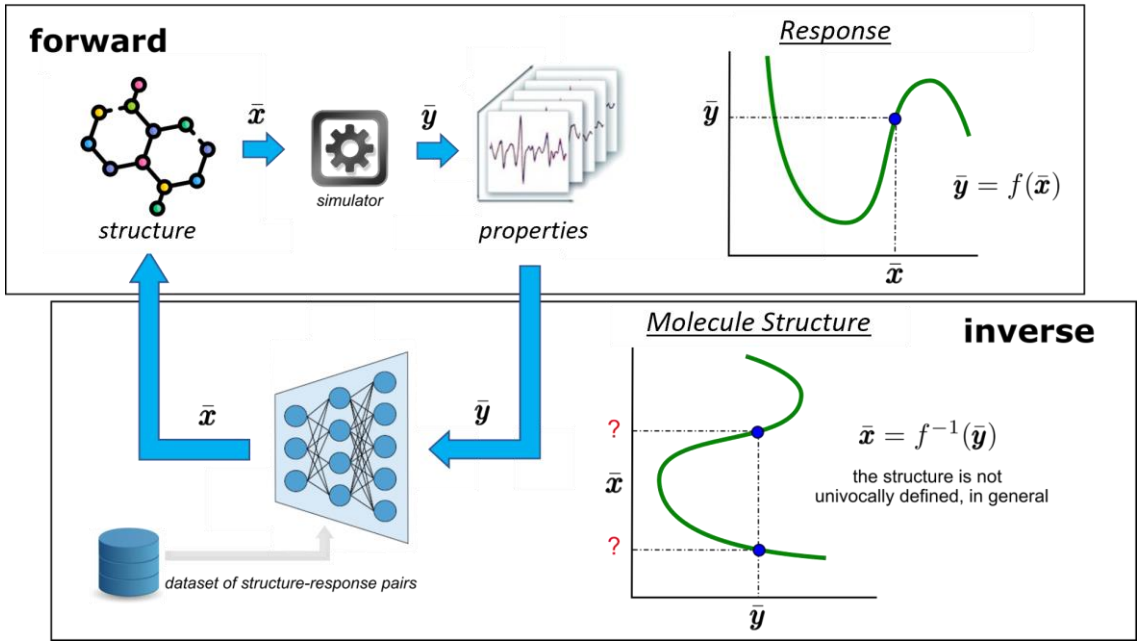
Specific Target or Application-Related Properties:

- For instance, if you're designing a molecule for use in a particular type of semiconductor, you would need to focus on properties relevant to that application, like charge carrier mobility or bandgap

ISSUES

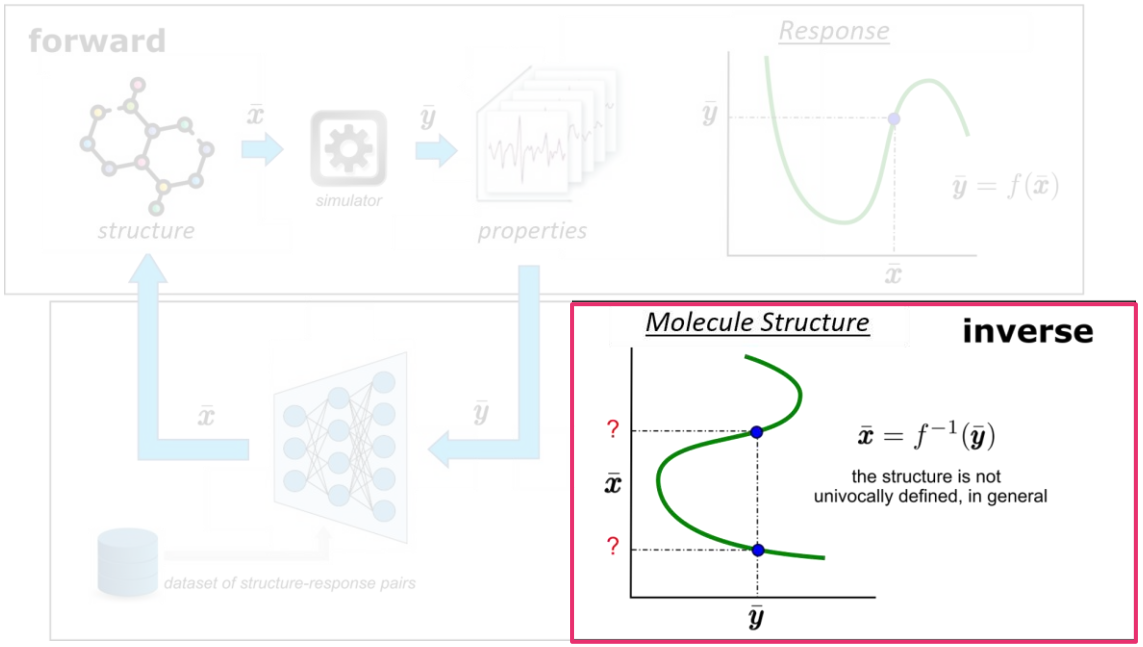

forward
structure
simulator
properties
Response
$\bar{y} = f(\bar{x})$
inverse
Molecule Structure
$\bar{x} = f^{-1}(\bar{y})$
the structure is not univocally defined, in general
dataset of structure-response pairs

ISSUES

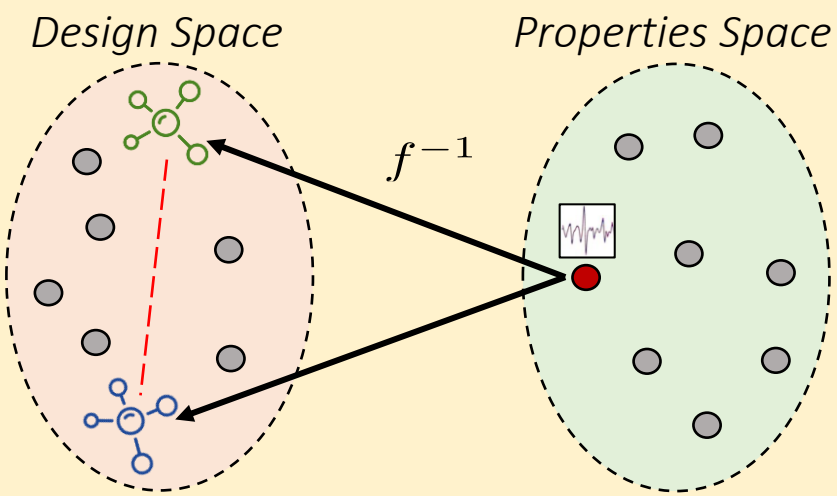


- ✕ **Non-uniqueness of the solution**

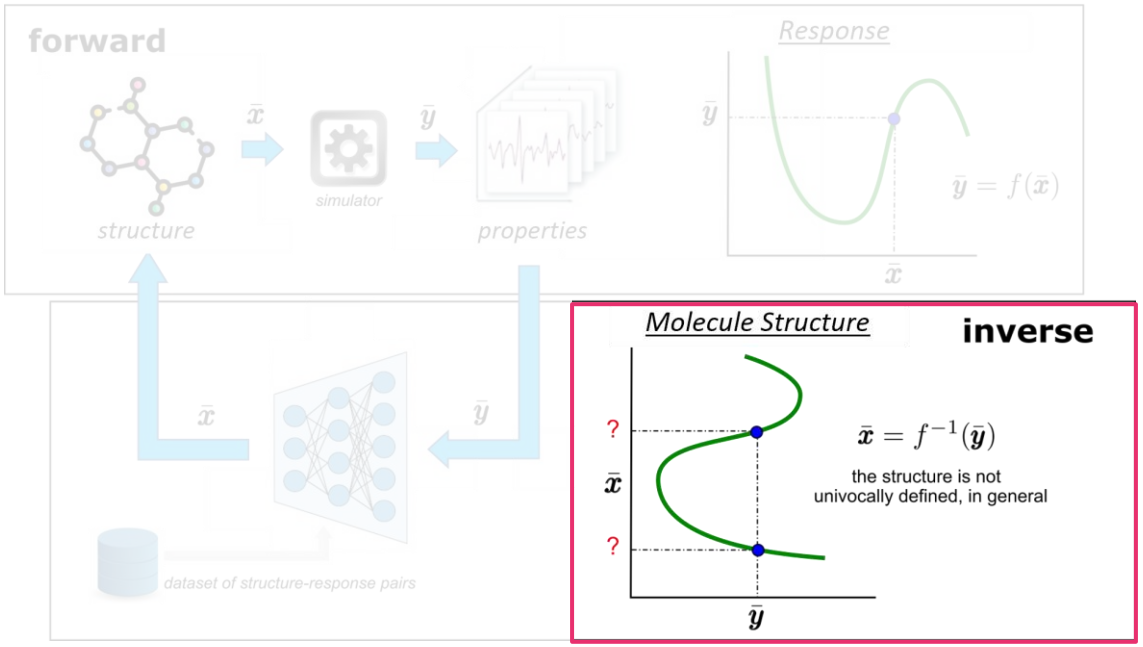
ISSUES



- ✕ **Non-uniqueness of the solution**
- ✕ **Drastically different molecules can produce very similar responses.**



ISSUES



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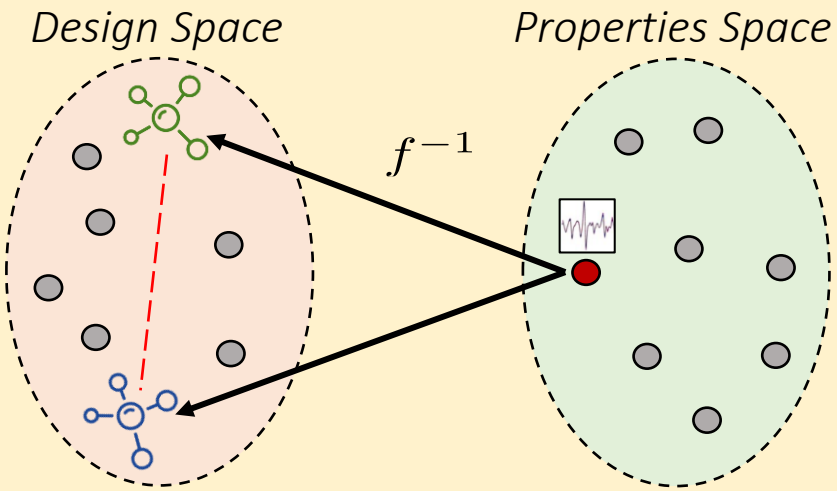
- ✕ **High dimensionality of the design space**



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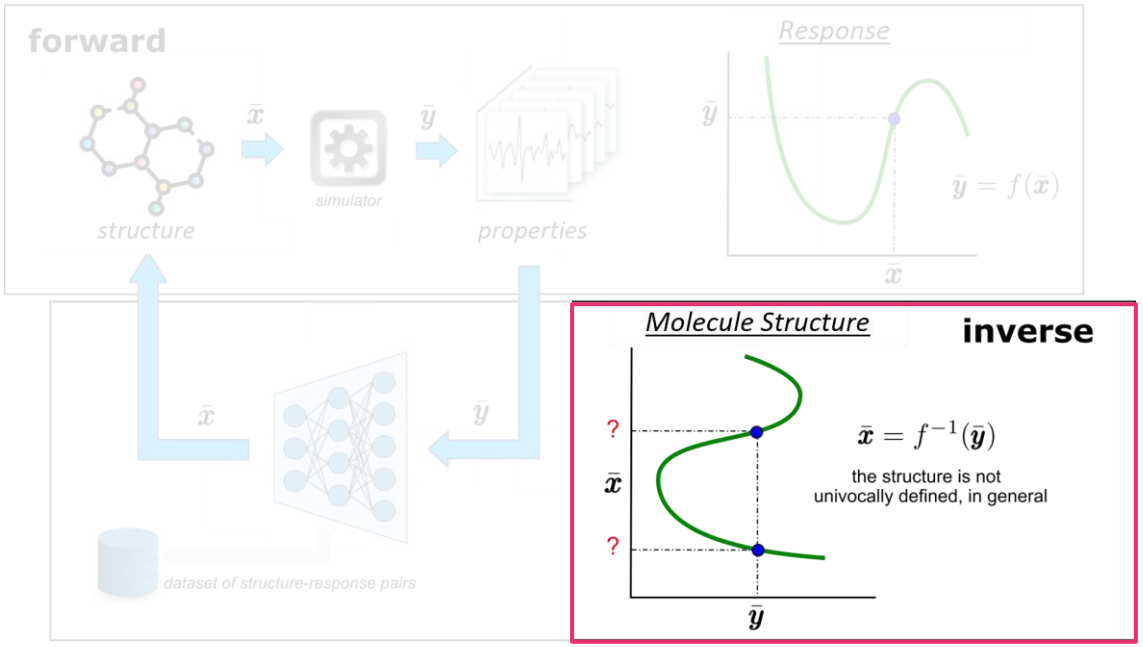
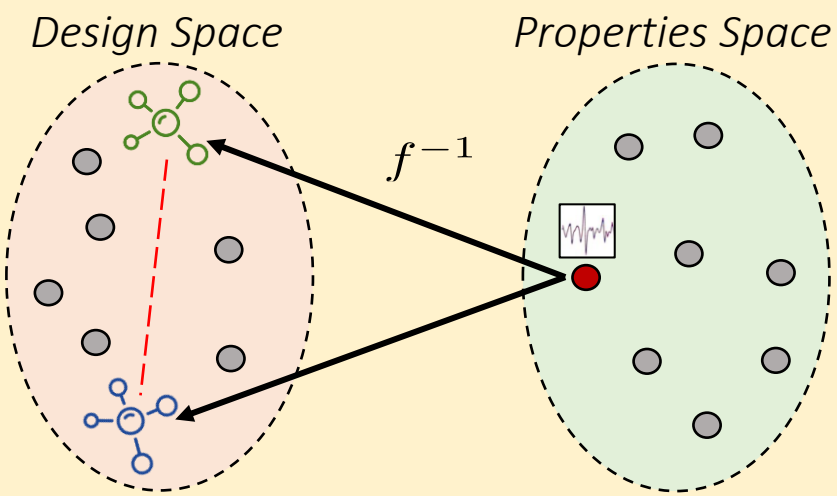


- ✕ **Non-uniqueness of the solution**
- ✕ **Drastically different molecules can produce very similar responses.**
- ✕ **High dimensionality of the design space**
- ✕ **Feasibility constraints on the design**



FEASIBILITY CONSTRAINTS

Chemical Feasibility:

Adhering to valence rules, satisfying octet rules for most atoms, and **avoiding strained or unstable configurations**.

Synthetic Accessibility:

The designed molecule should be synthesizable using available or reasonable synthetic methods. Complex or exotic reactions and reagents may be impractical, costly, or impossible to implement.

Reaction Conditions:

Extremely high temperatures, pressures, or toxic reagents can be prohibitive. **Hazardous or toxic materials and reactions** should be avoided or properly managed. Short shelf life or chemical instability can be problematic.

Cost:

High **production costs** can make a molecule economically unviable.

Regulatory and Compliance Constraints:

Compliance with safety, environmental, and legal regulations is essential.

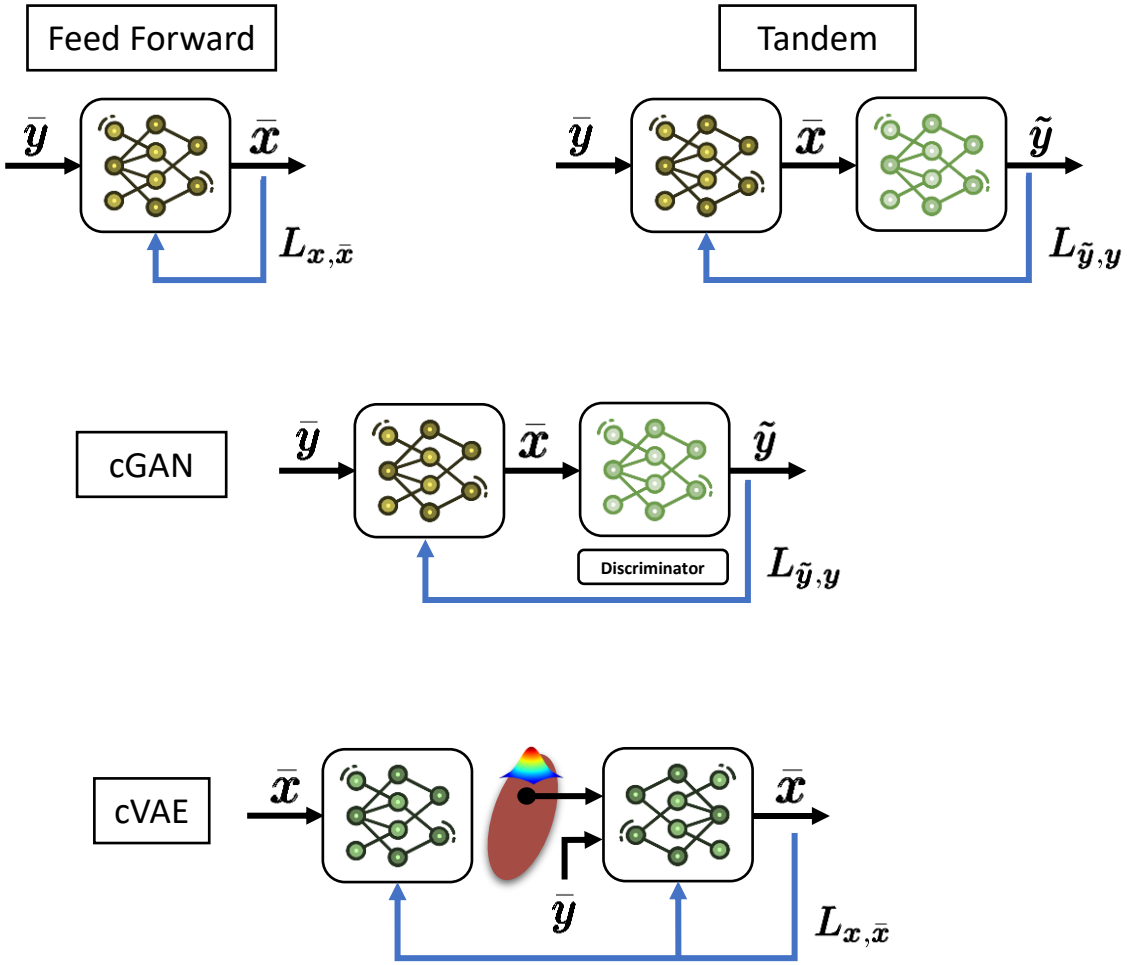
Purity and Characterization:

The designed molecule should be synthesizable with a high degree of purity, and methods for characterizing and quality control should be established.

STATE OF THE ART

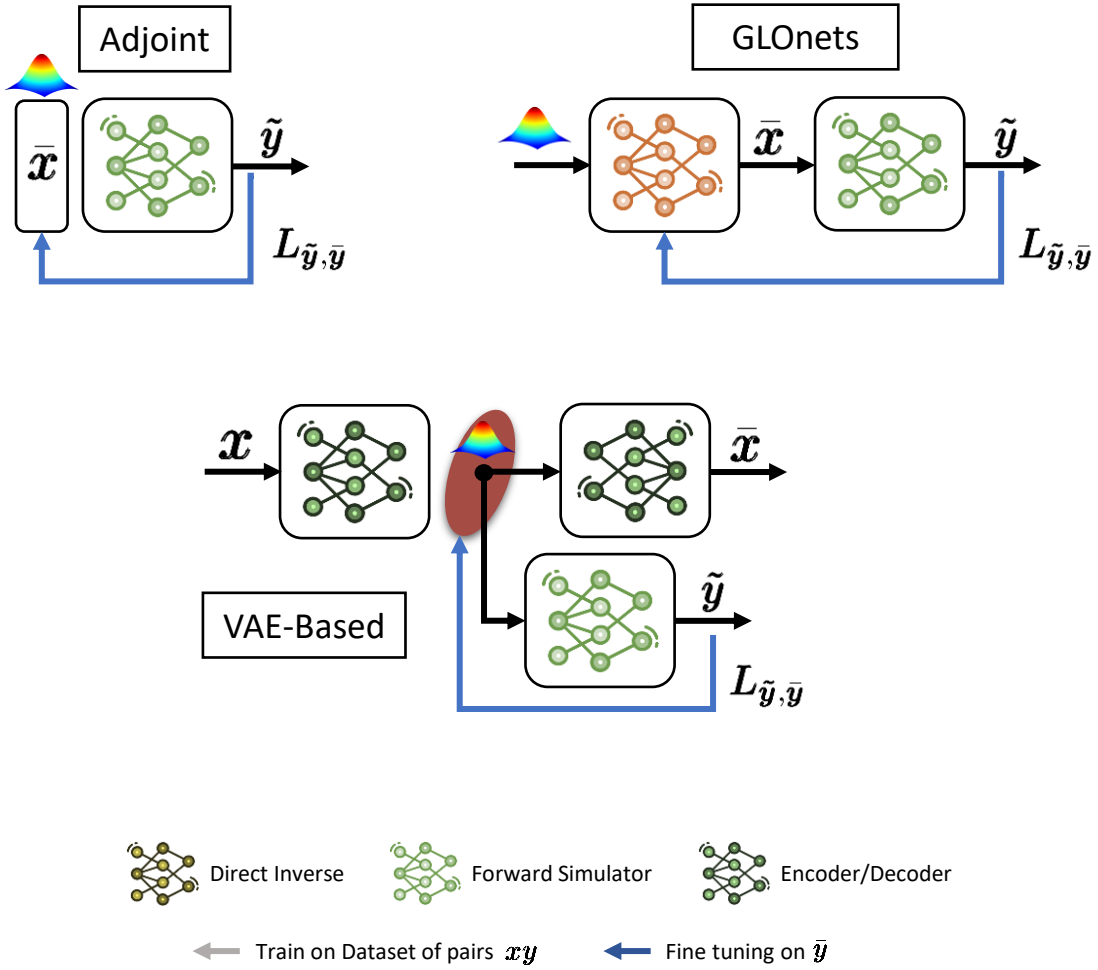
Output-INDEPENDENT

NOT requiring fine-tuning on the desired $\bar{y}$



Output-DEPENDENT

Requiring fine-tuning on the desired $\bar{y}$



STATE OF THE ART

Output-INDEPENDENT
NOT requiring fine-tuning on the desired $\bar{y}$

Output-DEPENDENT
Requiring fine-tuning on the desired $\bar{y}$

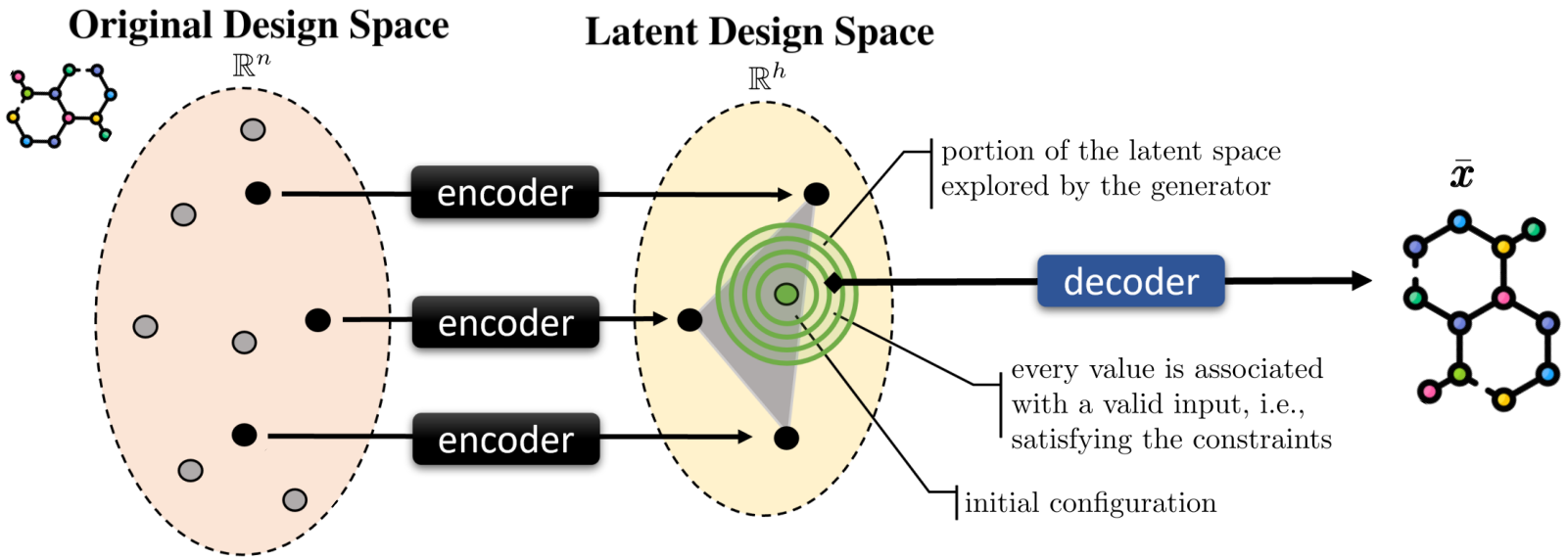
Most architectures work at the level of the **original (highly dimensional) design space**

No feasibility constraint considered in the design process

Random init to start the exploration/optimization in the design space

GIDnet – IJCAI 2023

We **embed the design space** into a suitably-defined latent space to deal with complex representations going beyond plain numerical values



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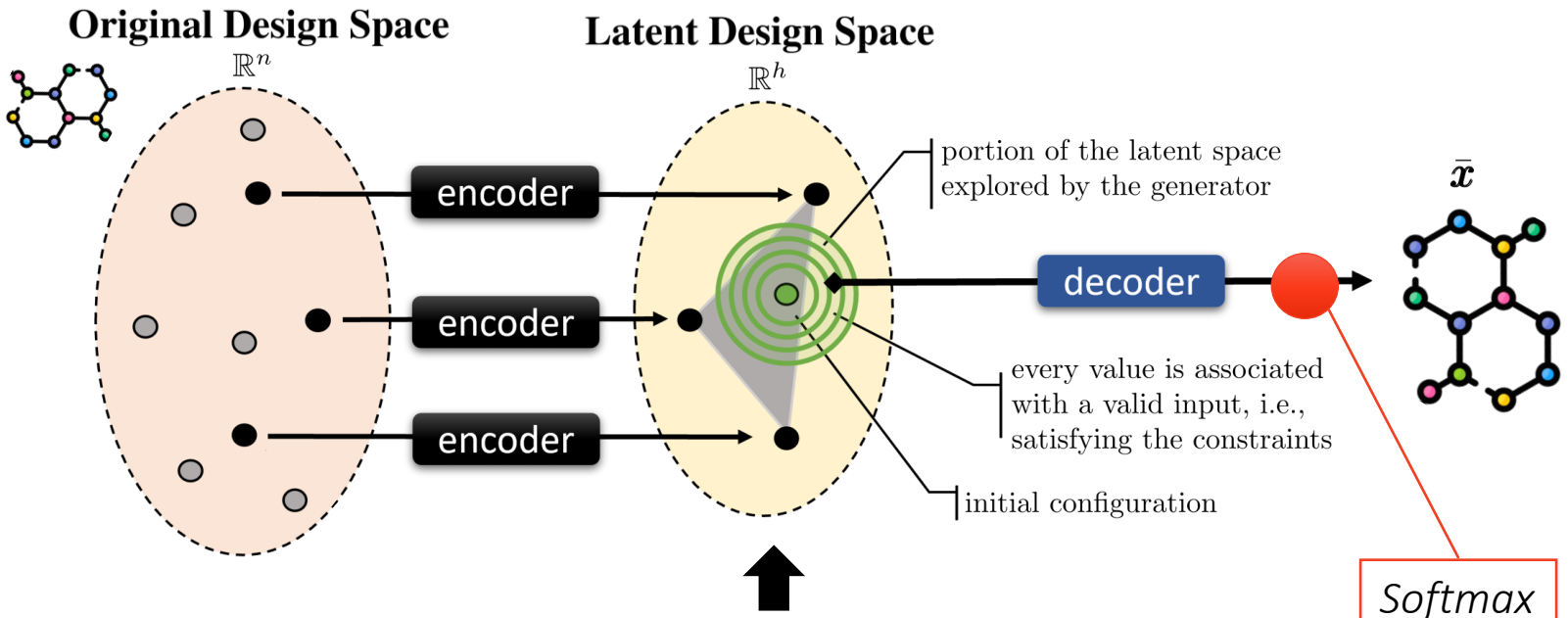

Softmax

We restrict the latent design space to **feasible regions**

Reconstruction Loss **To enforce constraints**

$$\sum_{i=1}^{q} \boxed{||\mathtt{D}(\mathtt{E}(\boldsymbol{x}_i)) - \boldsymbol{x}_i||_2} + \lambda_0 \cdot \Gamma(\boldsymbol{x}'_{i,1}, ..., \boldsymbol{x}'_{i,\ell})$$

$$\sum_{j=1}^{\ell} \boldsymbol{x}'_{i,j} = 1 \text{ and } 0 \leq \boldsymbol{x}'_{i,j} \leq 1$$

$$\Gamma(\boldsymbol{x}'_{i,1}, ..., \boldsymbol{x}'_{i,\ell}) = -((\boldsymbol{x}'_{i,1})^2 + \cdots + (\boldsymbol{x}'_{i,\ell})^2)$$

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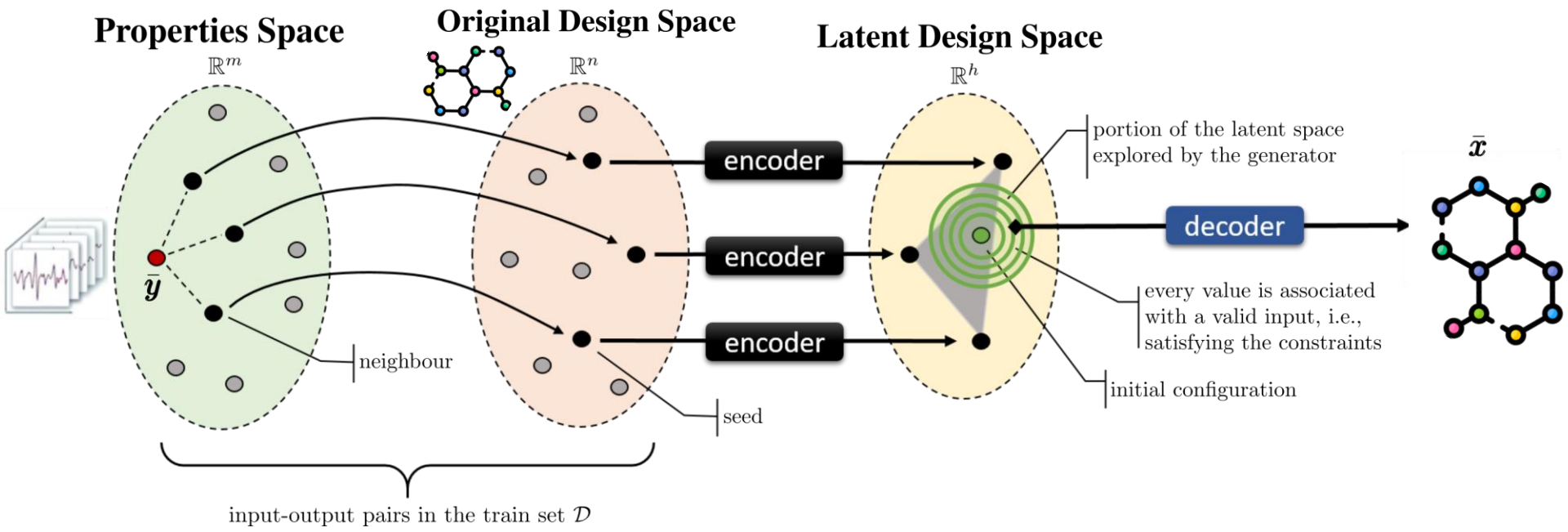
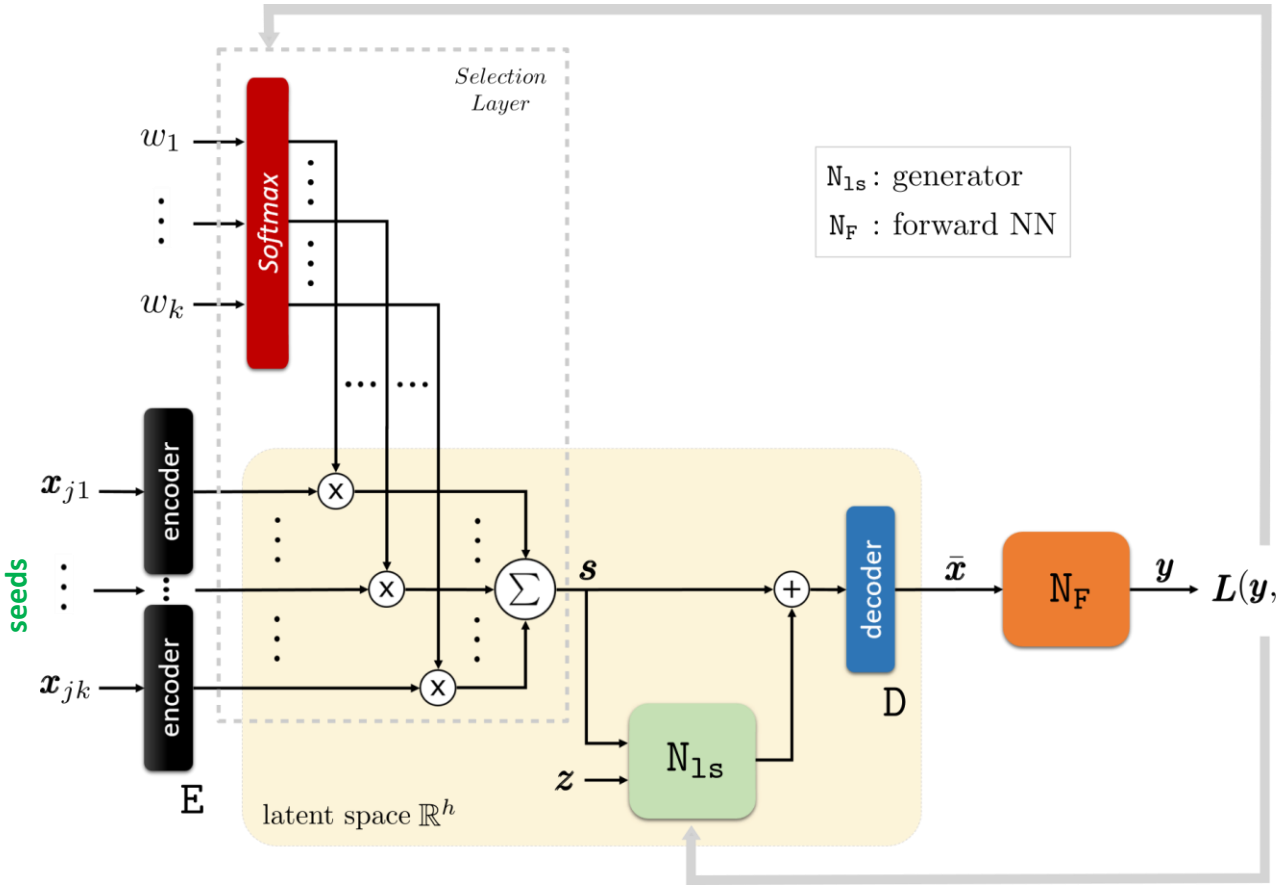
We **embed the design space** into a suitably-defined latent space to deal with complex representations going beyond plain numerical values

Rather than using a «blind» generator that tries to compute the solution by starting from some random initialization, we **start the exploration of the latent space by first looking at the dataset and identifying educated guesses called seeds**:



GIDnet – IJCAI 2023

We provide an **exploration mechanism** togheder with a mechanism (*Selection Layer*) such that the network can **automatically choose a starting point** for the exploration, as one of the given seeds, or alternatively, as a linear combination of the seeds



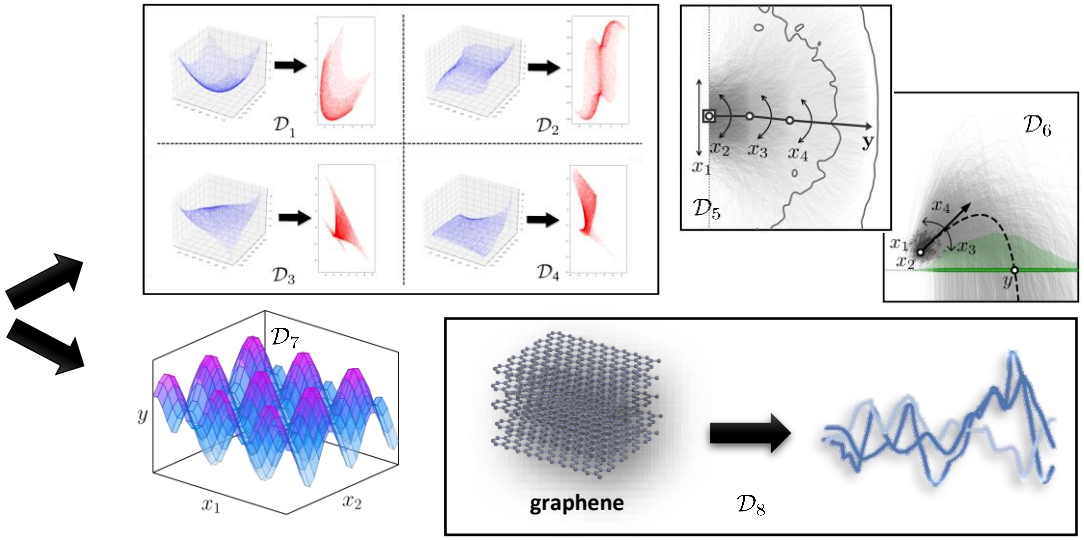
$$L(y, \bar{y}) = ||y - \bar{y}||_2 + \lambda_1 \cdot \Gamma(w_1, ..., w_k) + \lambda_2 \cdot \varepsilon(x)$$

Push the selection layer towards a single choice

Regularization term for constraints

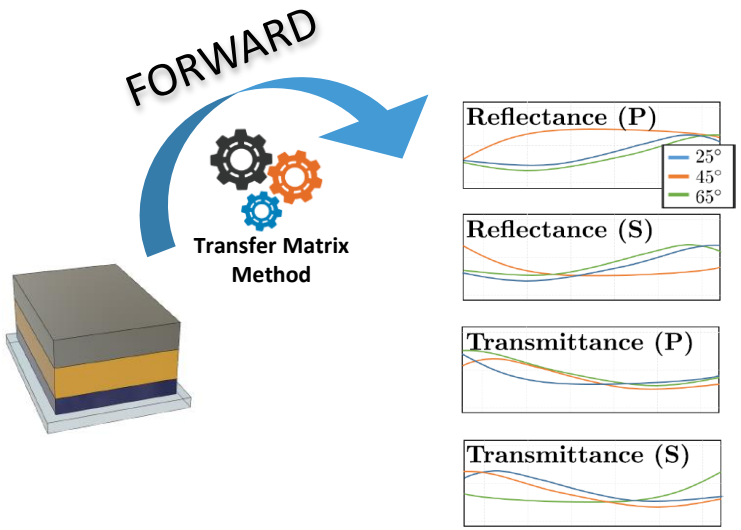
GIDnet – IJCAI 2023

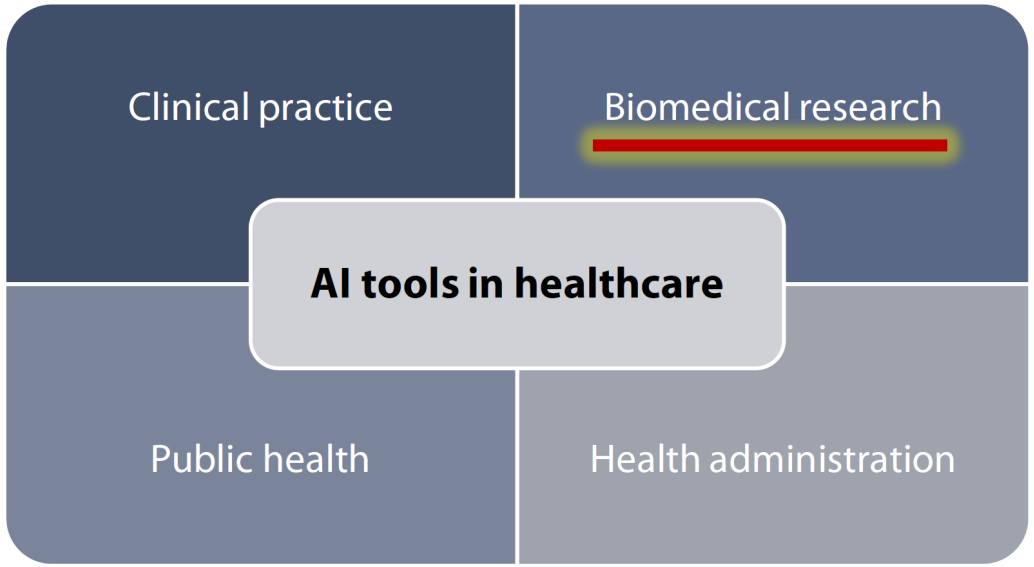
	Name	$Dim(\boldsymbol{x})$	$Dim(\boldsymbol{y})$	Source
$\mathcal{D}_i$	f_i	3	2	[*here*]
$\mathcal{D}_5$	Ballistics	4	1	[Kruse *et. al* 2021]
$\mathcal{D}_6$	Robotic arm	4	2	[Kruse *et. al* 2021]
$\mathcal{D}_7$	Sine Wave	2	1	[Ren *et. al* 2020]
$\mathcal{D}_8$	Multilayer Stacks	5	256	[Chen *et. al* 2019]



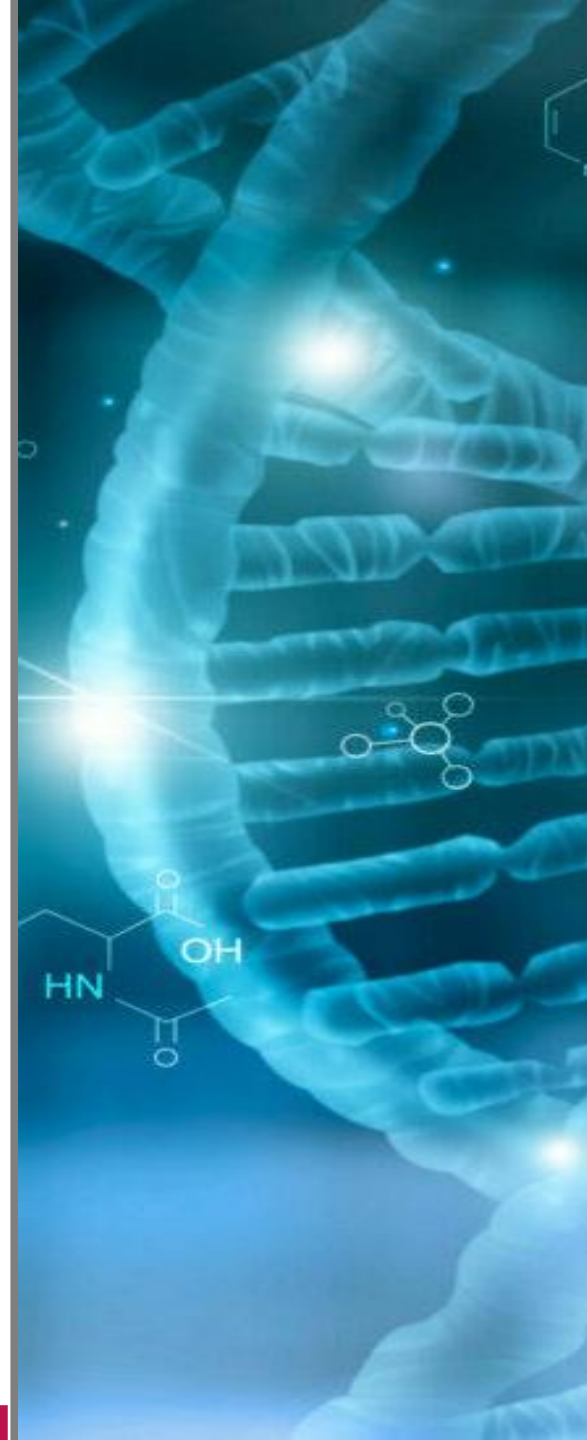
5 layers thin film metamaterials

- each layer with **thickness** within the range 1-60 nm
- material can be **Ag, Al2O3, ITO, Ni, or TiO2**
- we have to represent its thickness plus the material as a **one-hot encoding** over 5 alternatives.
- Each structure is associated with reflectance and transmittance spectra, obtained **via the transfer matrix method** simulated on an infinite glass substrate, for two polarizations, at the incident angles of 25, 45, and 65 degrees, for 200 equally spaced points over the range 450-950 nm



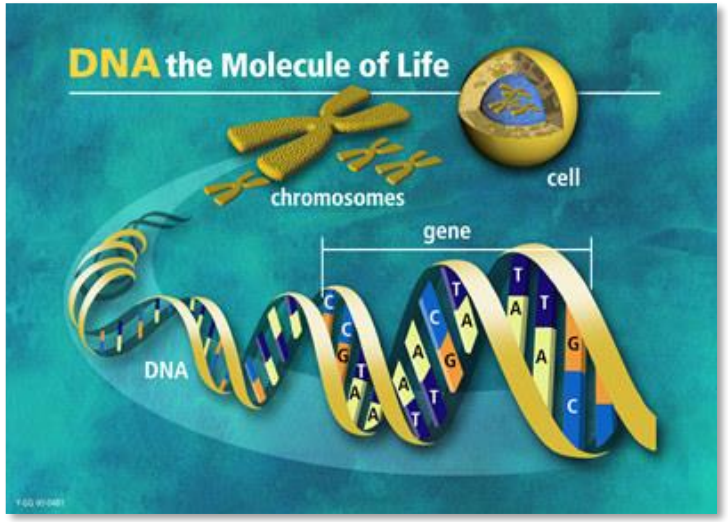


GENES SELECTION



SETTING

- In disease, cells genes are often **under-expressed** or **over-expressed**.
- **High-throughput sequencing** and **Microarrays** are efficient techniques to gather data that can be used to determine the expression pattern of thousands of genes



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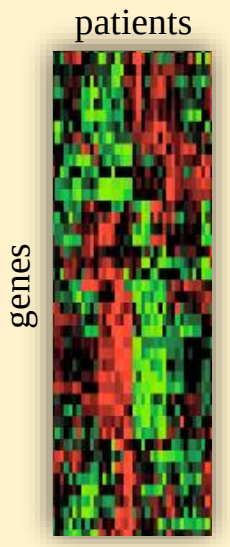
Course of Dimensionality
Thousands of genes for **few patients** (Linear dep. between genes)

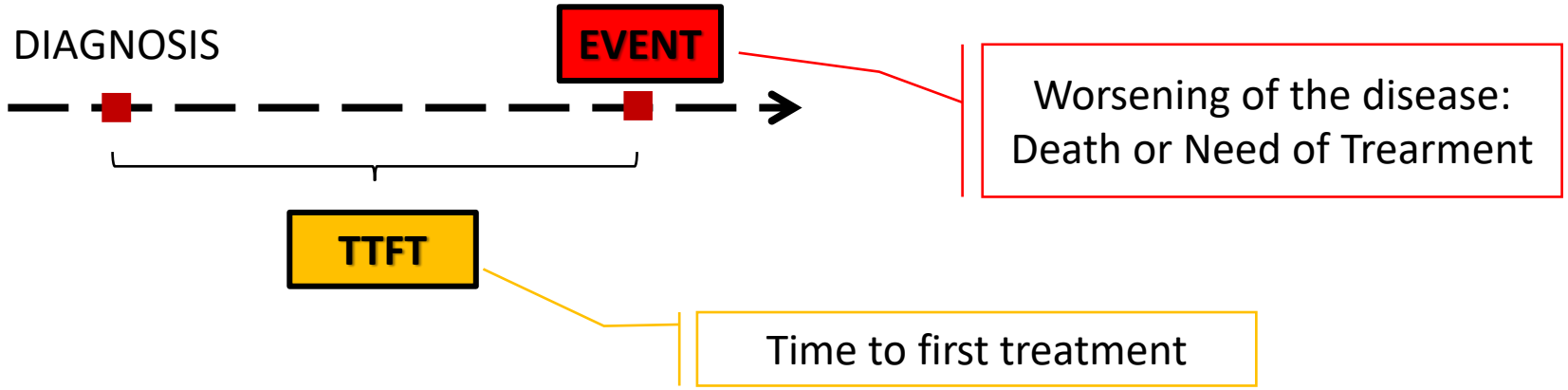
Noise and redundancy
Data collection is often **multi-centric** and carried out with **heterogeneous devices**

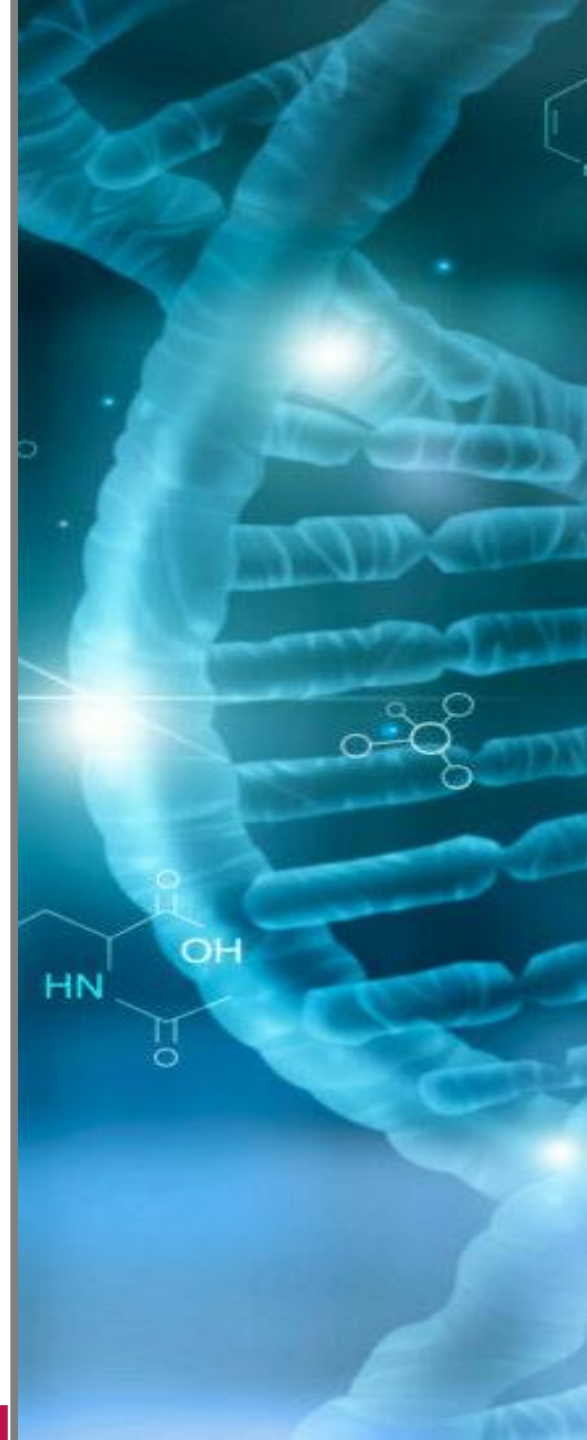
Class Imbalance
Sequencing mostly takes place on **pathological patients**



SETTING

- **Chronic Lymphocytic Leukemia (CLL)** is a hematologic neoplasm characterized by an accumulation of lymphocytes in the blood, bone marrow, and lymphatic organs (lymph nodes and spleen)
- In more than half of the patients, CLL is **diagnosed incidentally**, and some patients can remain **stable for more than 10 years**, while others may experience **rapid worsening**
- Currently, it is not possible to establish precise rules for the prevention of CLL, as **its causes are not completely clear**



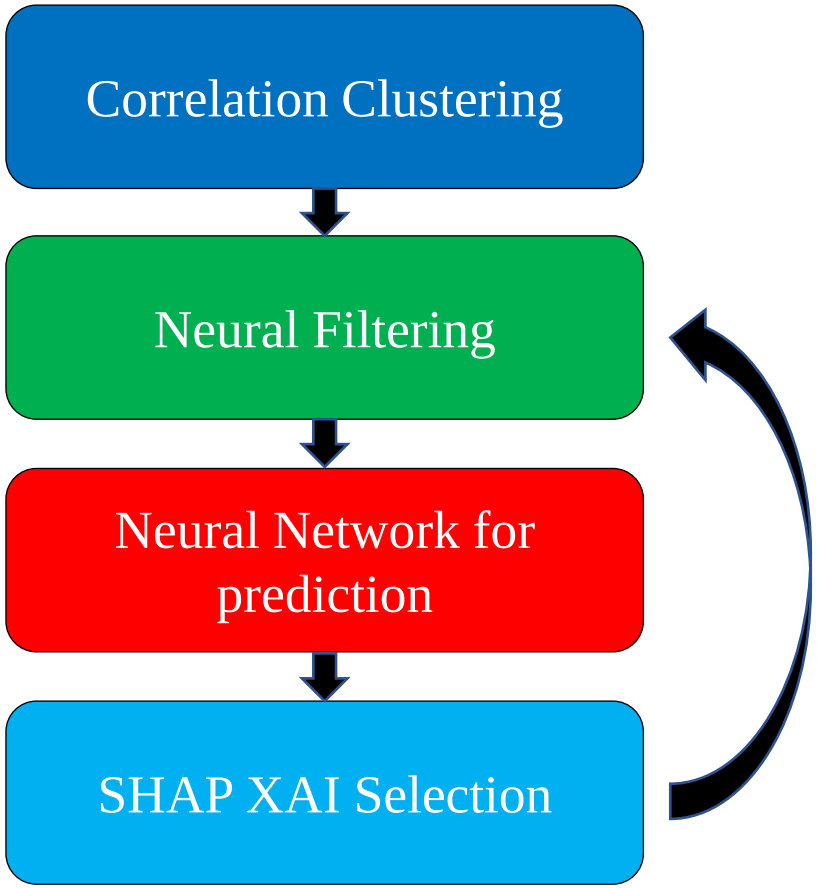


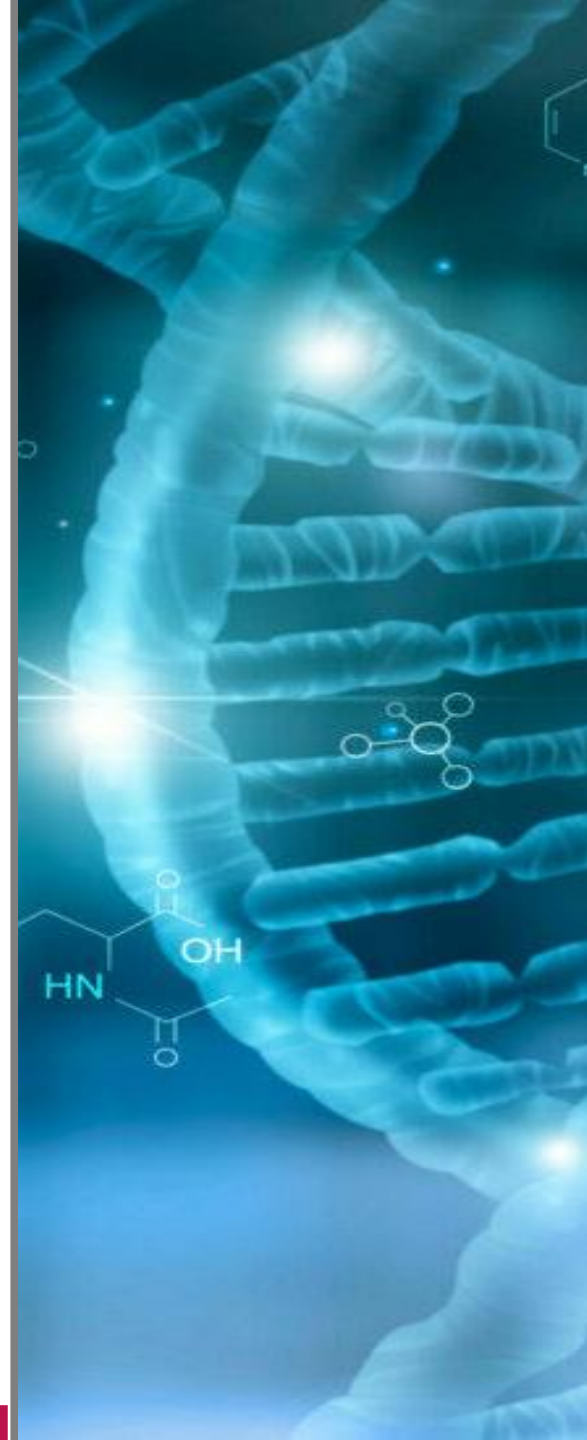
FEATURE SELECTION

The process of selecting a subset of relevant features (variables, predictors) to use in predictive models, to reduce the computational cost and to improve the performance

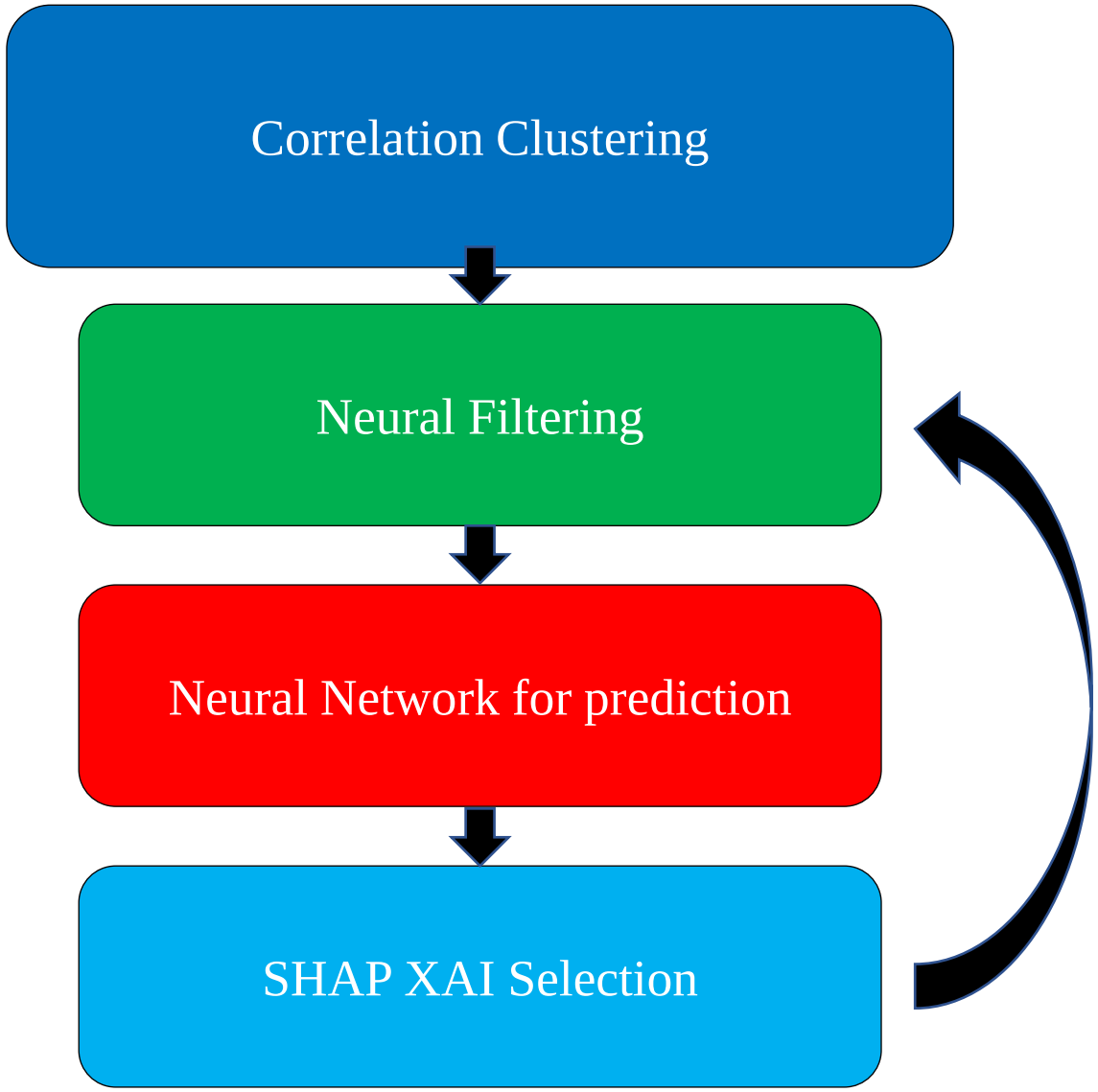
- **Main Ideas:**

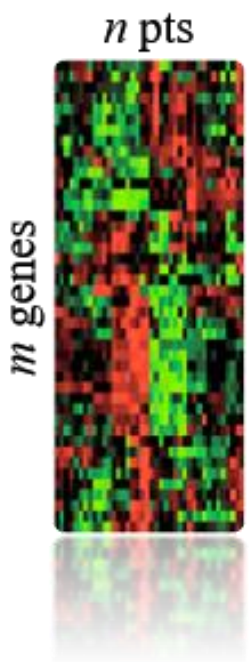
  - Iterative Procedure which selects a set of meaningful genes at each iteration
  - **Neural** approach to filter redundant genes into the genes space
  - **Ad-hoc defined EXPLAINABLE AI-based method** to select the most impactful genes

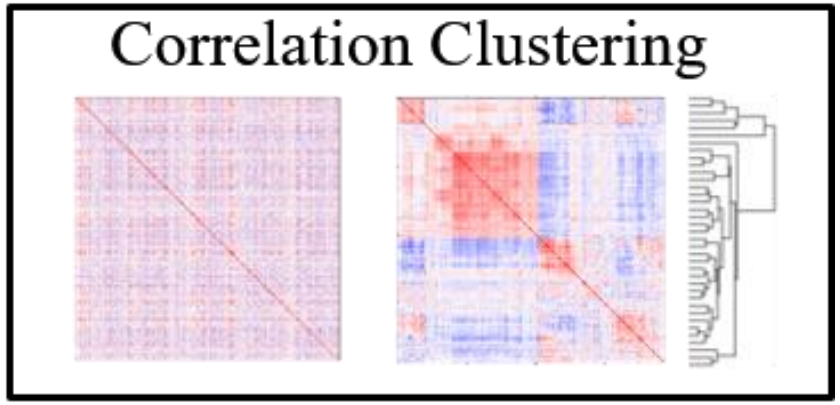




A CLOSER LOOK AT THE STEPS



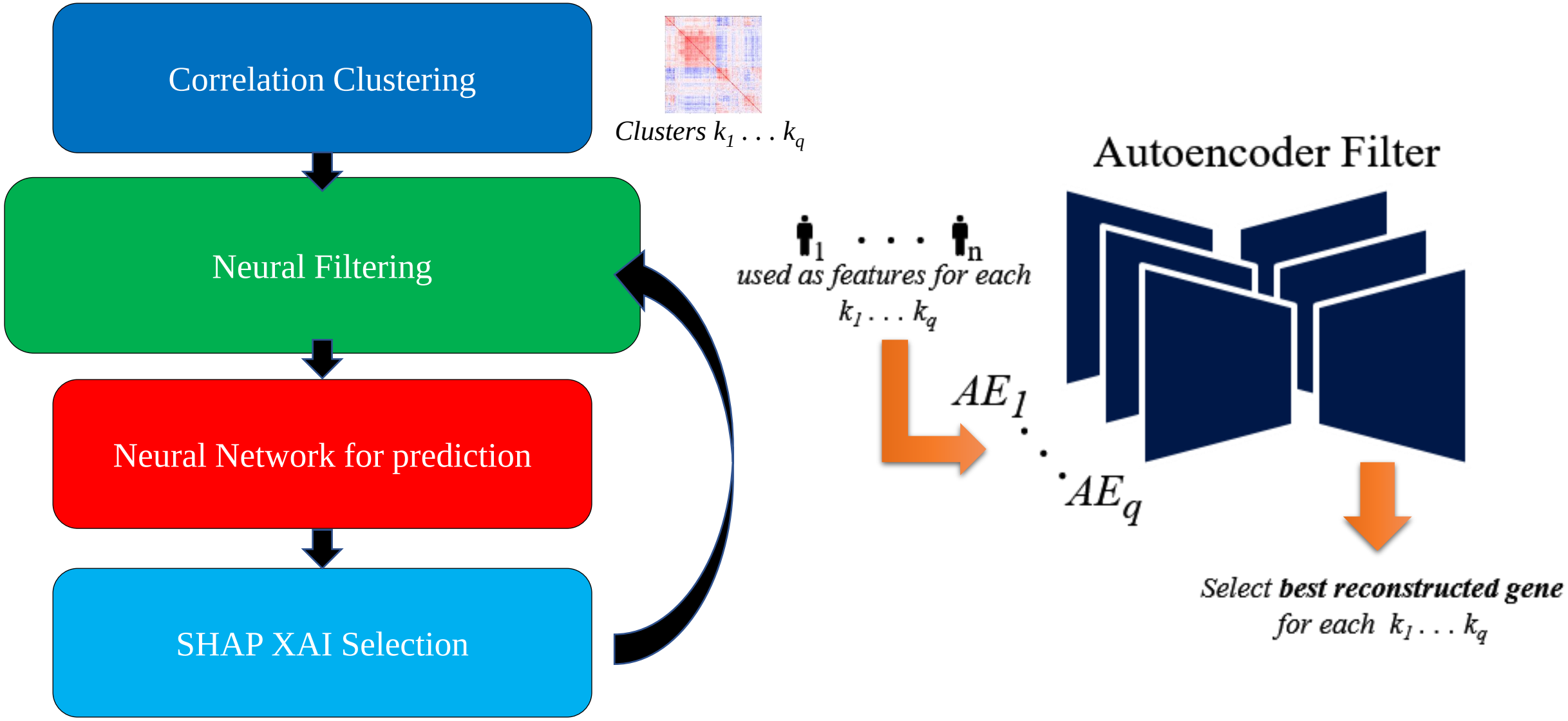




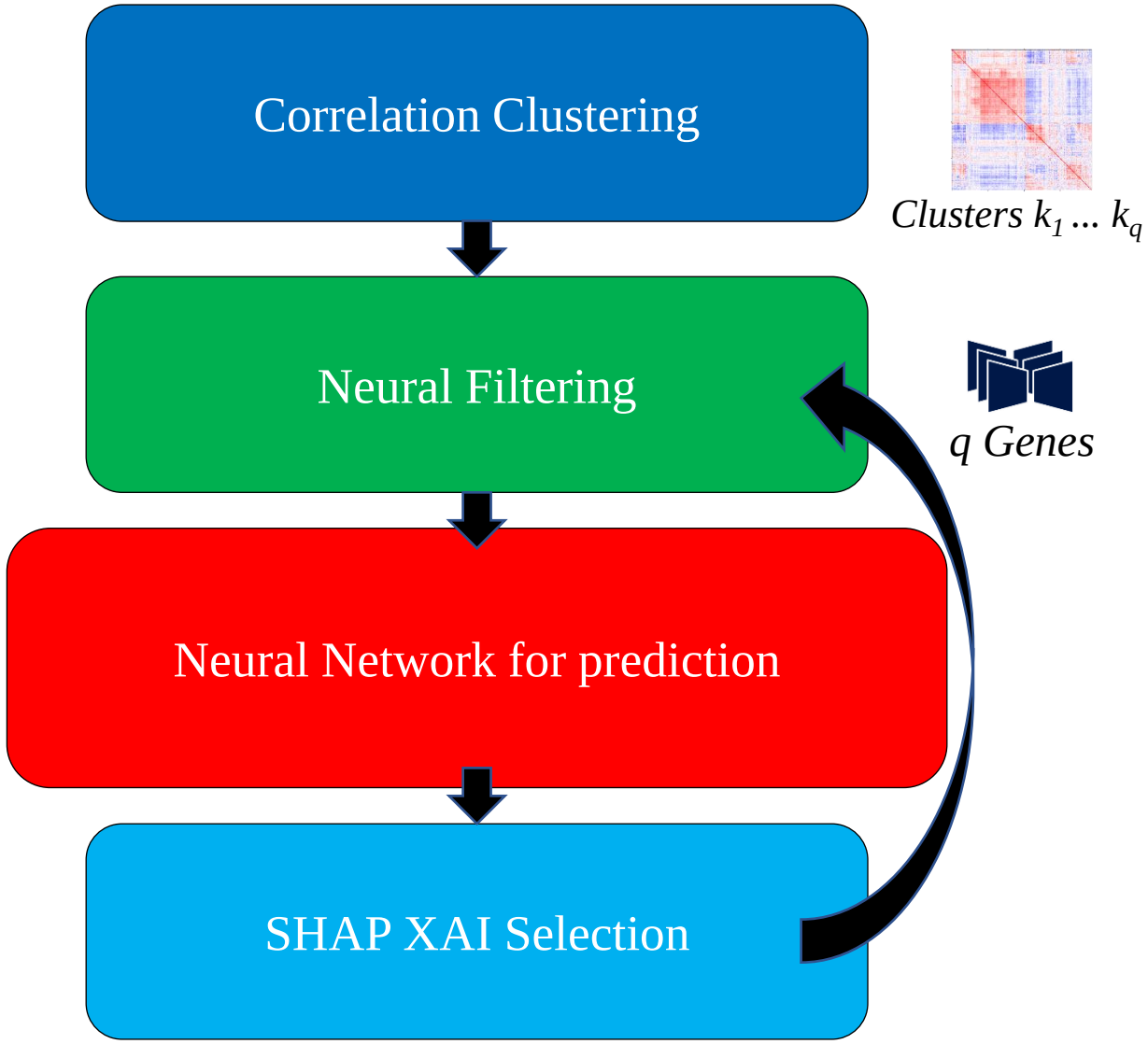
Clusters $k_1 \ldots k_q$

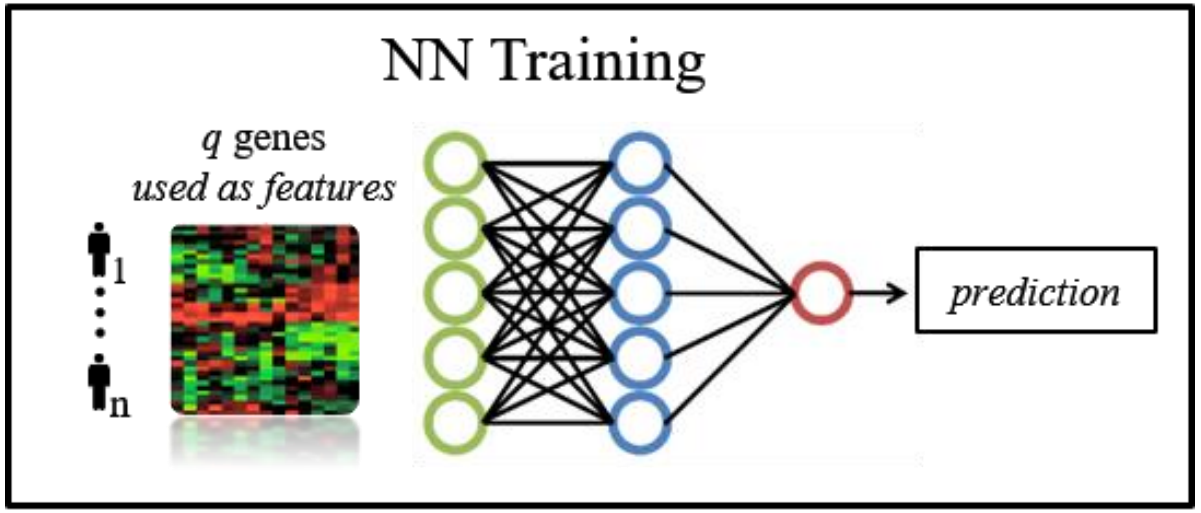
(of genes)

A CLOSER LOOK AT THE STEPS



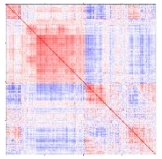
A CLOSER LOOK AT THE STEPS





A CLOSER LOOK AT THE STEPS

Correlation Clustering

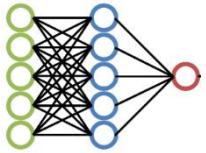


Clusters $k_1 \dots k_q$

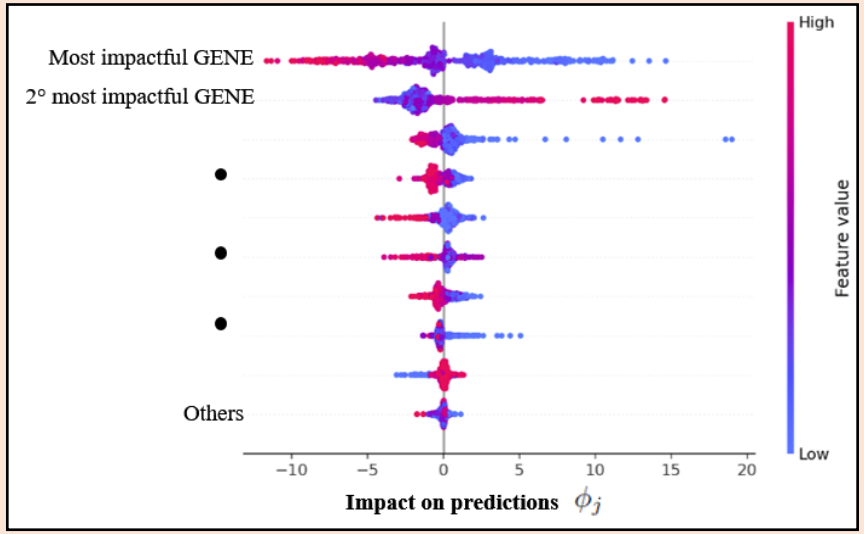
Neural Filtering

q Genes

Neural Network for prediction



SHAP XAI Selection



$$\phi_j = \sum_{S \subseteq F \setminus \{j\}} \frac{|S|!(|F| - |S| - 1)!}{|F|!} \left[f_{S \cup \{j\}}(x_{S \cup \{j\}}) - f_S(x_S) \right]$$

Filter the genes according to the correlation between SHAP values and genes values

Select and Save the most meaningful genes according an ad-hoc defined **SHAP-based score**

$$\varphi_{j,\mathtt{N}} = \frac{\sum_{i=1}^{n} |x_{i,j}| * \phi_{i,j}^2}{\sum_{h=1}^{m} \sum_{i=1}^{n} |x_{i,h}| * \phi_{i,h}^2}$$

APPLICATION TO CLL

Genes Selection using Deep Learning and Explainable Artificial Intelligence for Chronic Lymphocytic Leukemia Predicting the Need and Time to Therapy

Fortunato Morabito, Carlo Adornetto, Paola Monti, Adriana Amaro, Francesco Reggiani, Monica Colombo, Yissel Rodriguez-Aldana, Giovanni Tripepi, Graziella D'Arrigo, Claudia Vener, Federica Torricelli, Rossi Teresa, Manlio Ferrarini, Giovanna Cutrona, Antonino Neri, Massimo Gentile and Greco Gianluigi

O-CLL Dataset

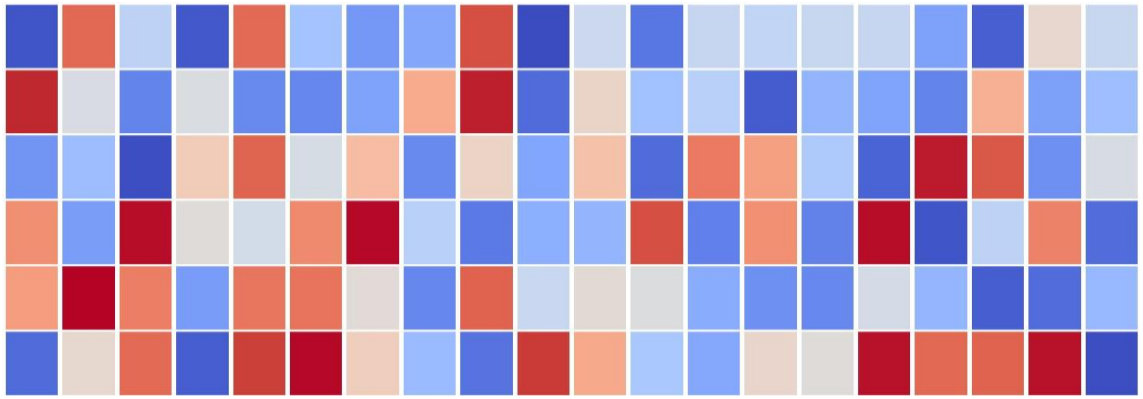
19.367 GENES

Pz1

⋮

⋮

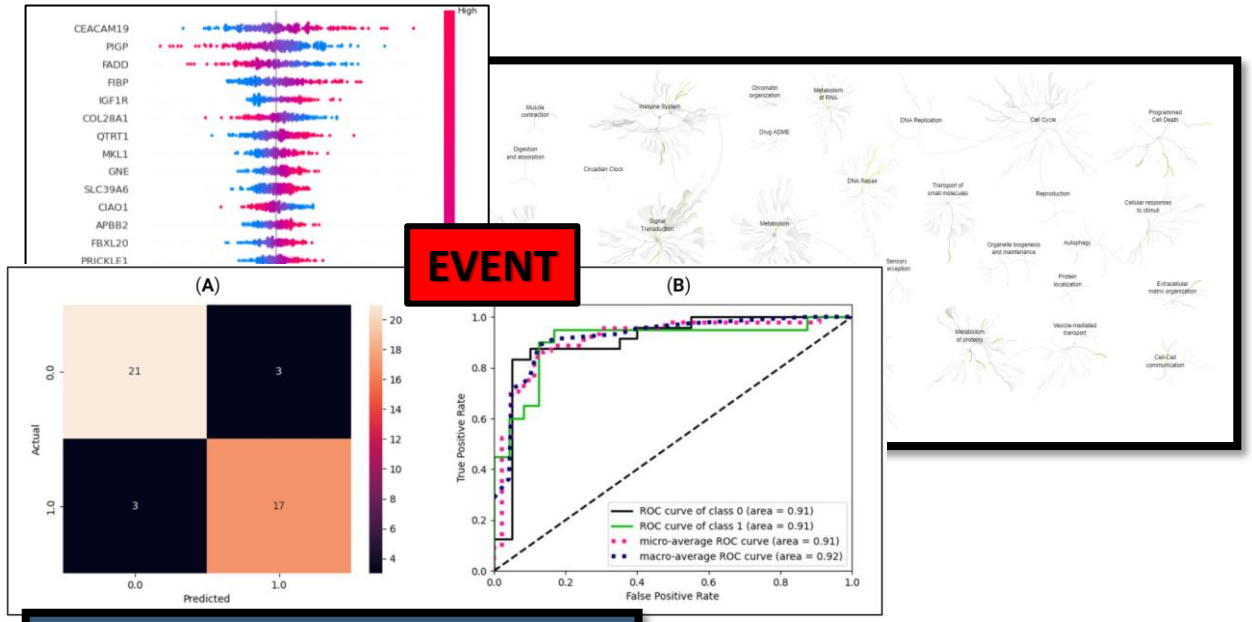
Pz 217

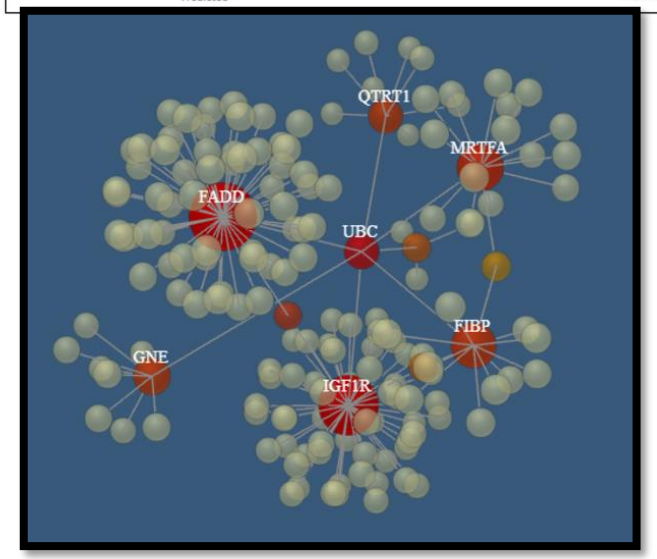


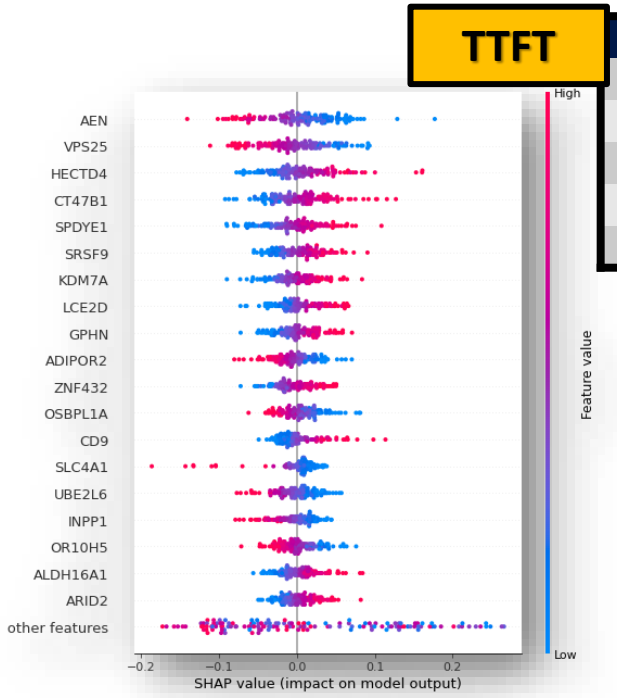
EVENT	TTFT (months)
Yes	< 24
Yes	> 24
⋮	⋮
No	
No	
⋮	

97 patients

APPLICATION TO CLL



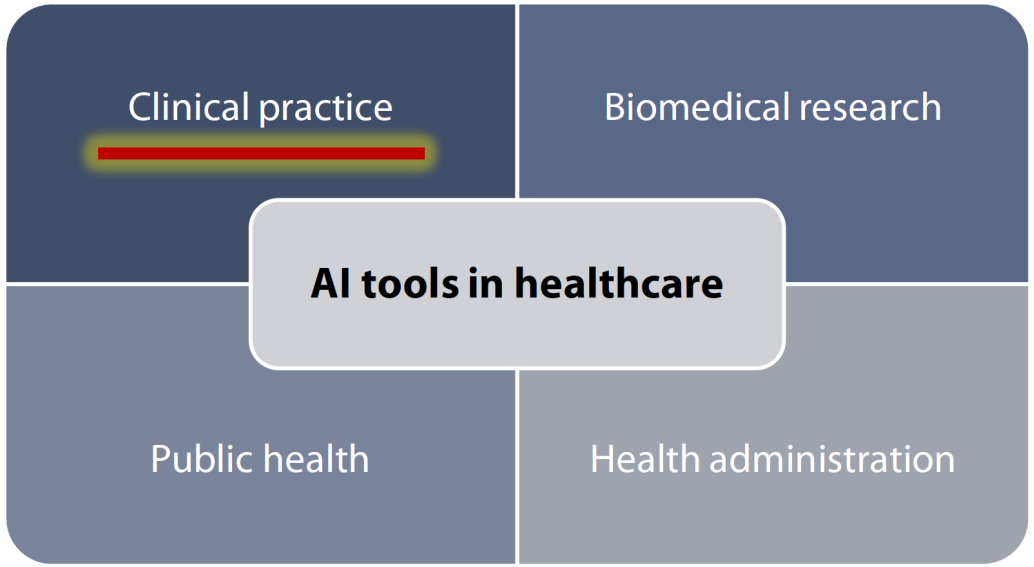




Iteration	C.I. 95%
1	77.2 – 92.7
2	74.7 – 91.2
3	68.6 – 89.3
4	64.3 – 83.6
Final	**79.1 – 92.9**

GENE	XAI score %	Corr.
SL4A1	11,79	-0,98
CAES	9,78	-0,97
VS20	6,91	-0,97
CT1	6,16	0,97
HTD4	5,94	0,96
FADD	3,83	0,95
GNE	3,35	0,97
PIGP	3,25	0,96

- Eight of the top ten genes selected by the algorithm were found in the Reactome pathway database, showing an involvement in various pathways such as **signal transduction**, gene expression (**transcription**), **protein metabolism**, **immune system**, **cell cycle and apoptosis**.
- 7 of them are involved in **protein-protein interaction** (PPI)



OPHTALMOPLASTIC SURGERY

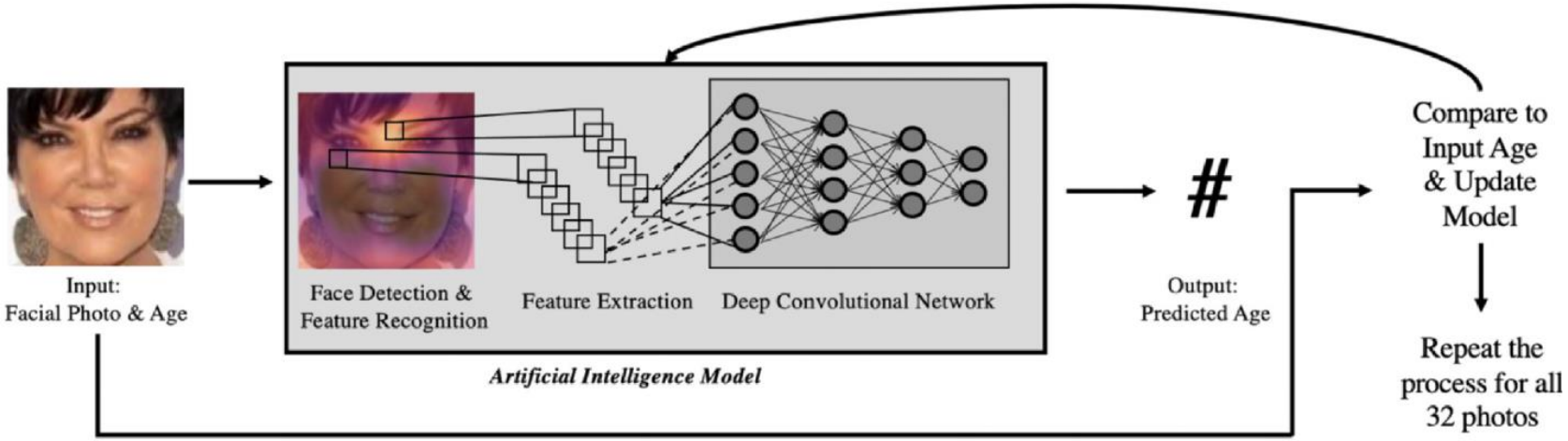
OPHTALMOPLASTIC SURGERY

How to quantify the effect of **blepharoplasty** on rejuvenation?

J Plast Reconstr Aesthet Surg. 2023 Oct:85:336-343. doi: 10.1016/j.bjps.2023.07.017.
Epub 2023 Jul 17.

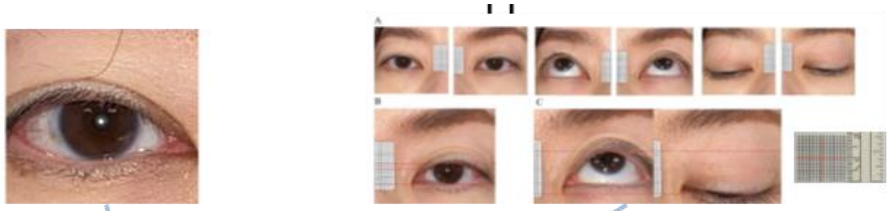
Estimating apparent age using artificial intelligence: Quantifying the effect of blepharoplasty

Kendall Goodyear [1], Persiana S Saffari [2], Mahtash Esfandiari [3], Samuel Baugh [3], Daniel B Rootman [1], Justin N Karlin [4]



OPHTALMOPLASTIC SURGERY

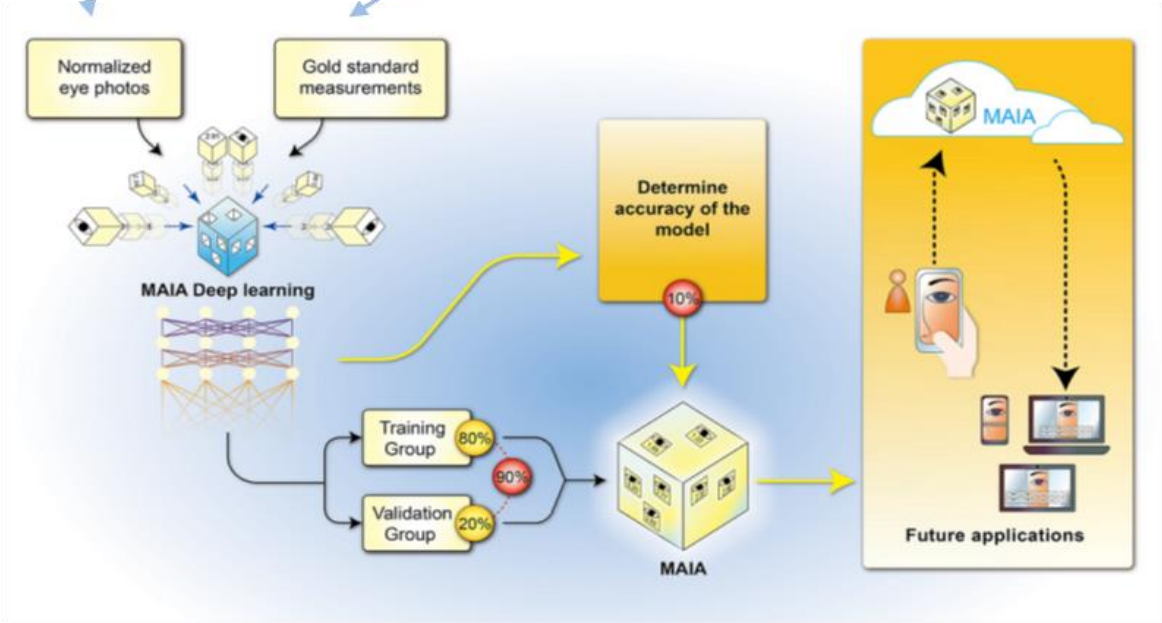
- In the evaluation and management of **ptosis** (by blepharoplasty), measurements of MRD1, MRD2, and LF are time-consuming, subjective, and prone to human error.

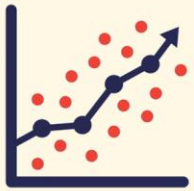


Observational Study > JMIR Mhealth Uhealth. 2021 Oct 8;9(10):e32444. doi: 10.2196/32444.

Smartphone-Based Artificial Intelligence-Assisted Prediction for Eyelid Measurements: Algorithm Development and Observational Validation Study

Hung-Chang Chen [#1,2], Shin-Shi Tzeng [#1,2], Yen-Chang Hsiao [#1,2], Ruei-Feng Chen [#3], Erh-Chien Hung [#1,2], Oscar K Lee [#4,5]





Correlation up to 90%

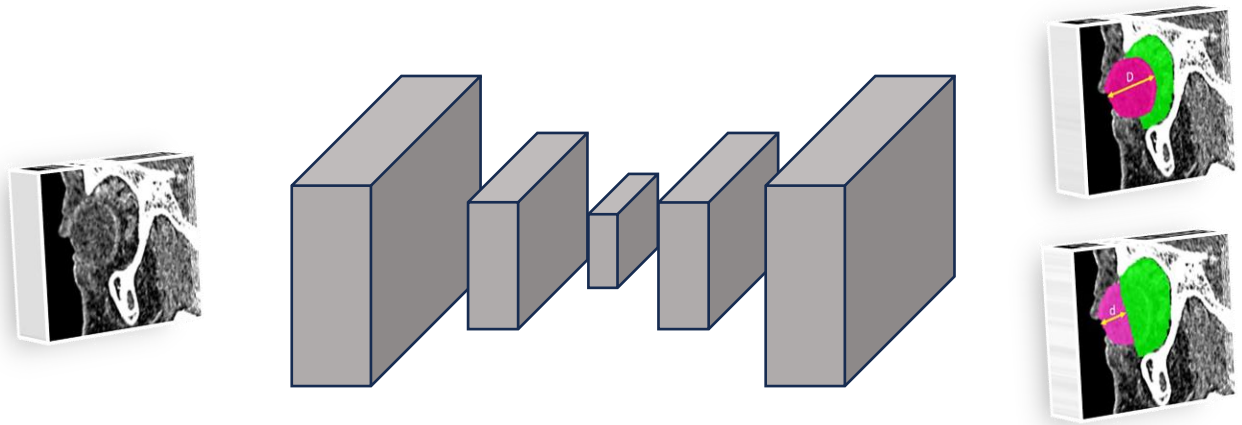
OPHTALMOPLASTIC SURGERY

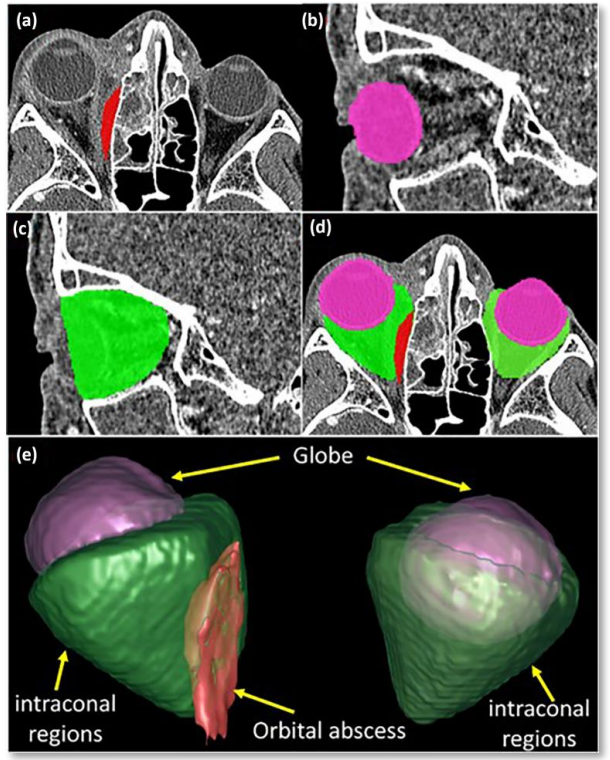
- AI to quantify **proptosis** and identify patients to be treated surgically
- Case study of 56 paediatric patients (31 of whom were surgically treated)

Ophthalmol Ther. 2023 Oct;12(5):2479-2491. doi: 10.1007/s40123-023-00754-5. Epub 2023 Jun 23.

Artificial Intelligence Automation of Proptosis Measurement: An Indicator for Pediatric Orbital Abscess Surgery

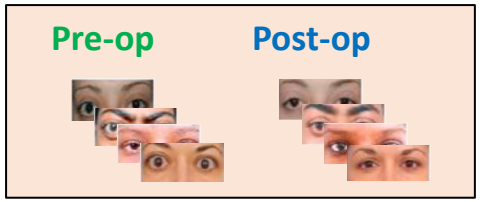
Roxana Fu [1], Andriy Bandos [2], Joseph K Leader [3 4], Samyuktha Melachuri [5], Tejus Pradeep [6], Aashim Bhatia [7], Srikala Narayanan [8], Ashley A Campbell [9], Matthew Zhang [10], José-Alain Sahel [1], Jiantao Pu [3 4]



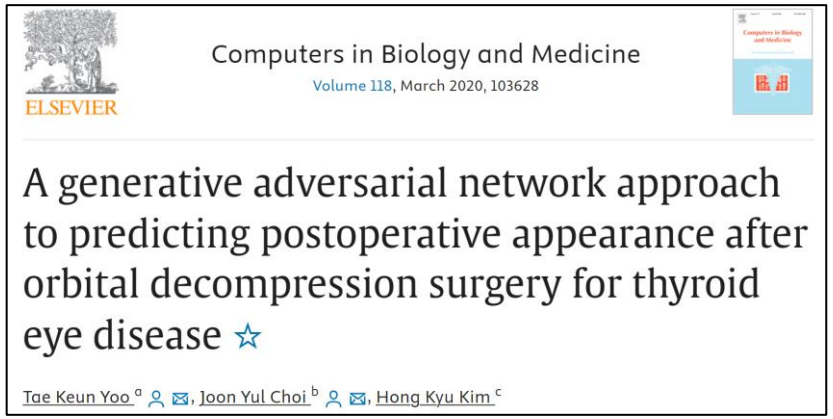


OPHTALMOPLASTIC SURGERY

- **Generative AI** to predict the aesthetic outcome of surgery
- Dataset of patients undergoing Orbital Decompression for Thyroid-Associated Ophthalmopathy (TAO)

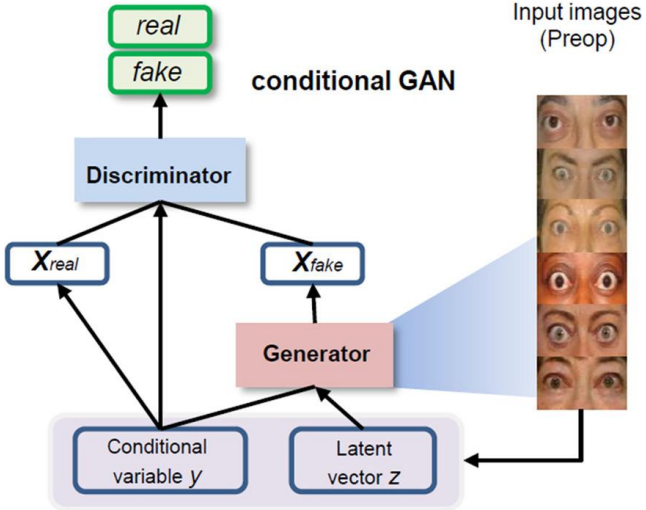


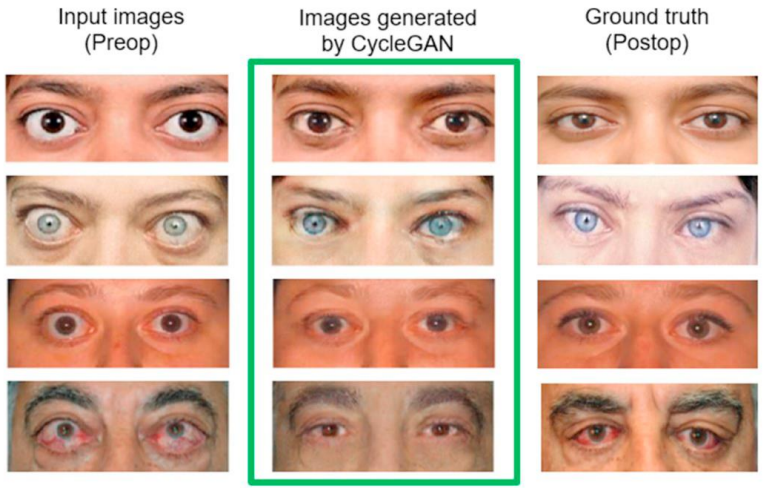
109 Pazienti

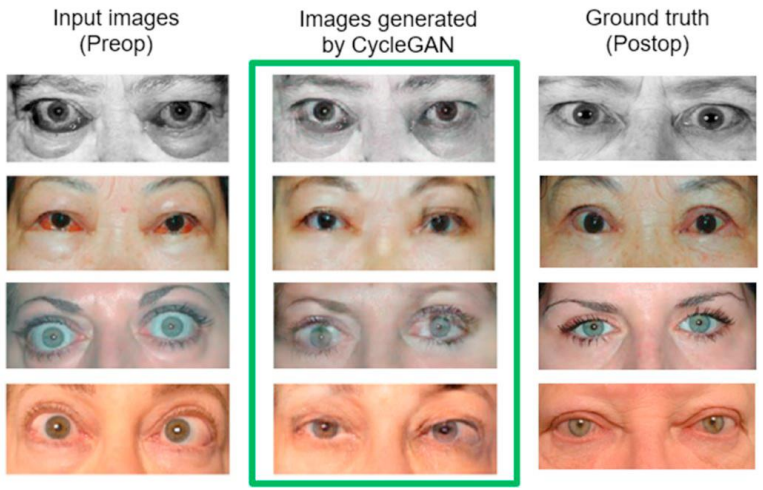

ELSEVIER
Computers in Biology and Medicine
Volume 118, March 2020, 103628

A generative adversarial network approach to predicting postoperative appearance after orbital decompression surgery for thyroid eye disease ☆

Tae Keun Yoo [a], Joon Yul Choi [b], Hong Kyu Kim [c]







OPHTALMOPLASTIC SURGERY @Unical

The Problem

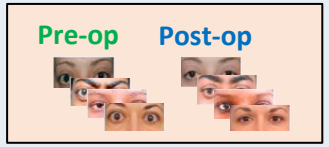
- There are no tools generated to predict Post-op
- Requires a precision, patient-tailored approach
- Lots of individual variables to consider

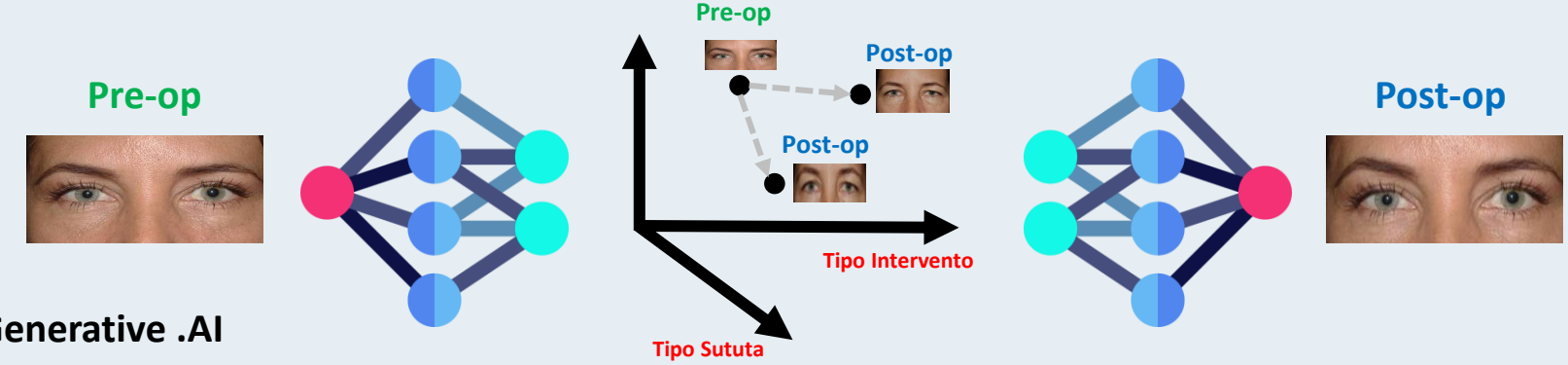
The Idea

- AI-based rendering to generate post-operative images from pre-operative photo
- Explore the results for different surgical variables

How?

1. Data Collection (smartphone + clinical data)



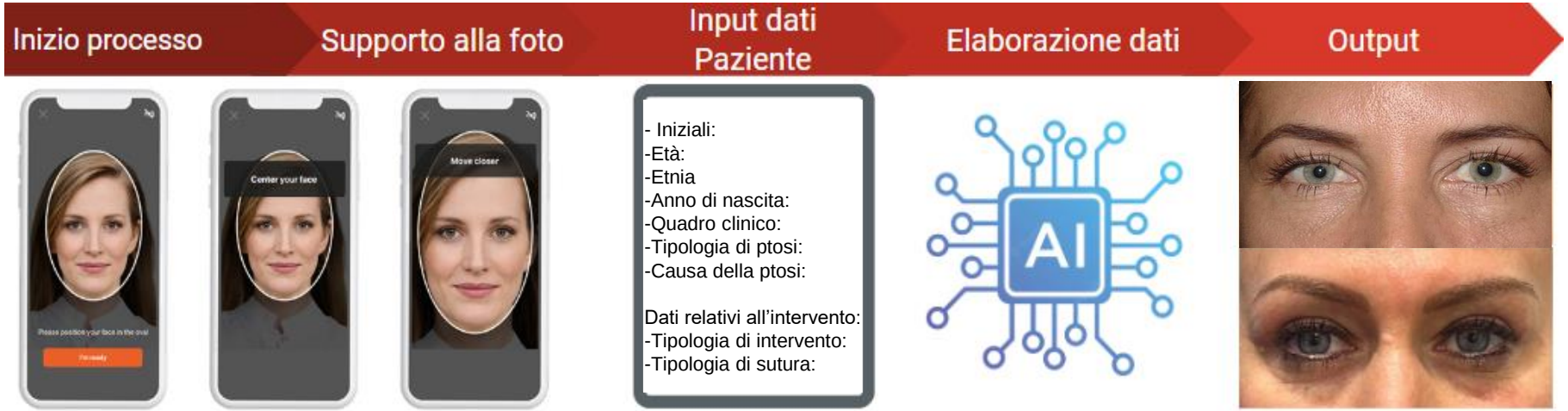


2. Generative .AI

OPHTALMOPLASTIC SURGERY @Unical

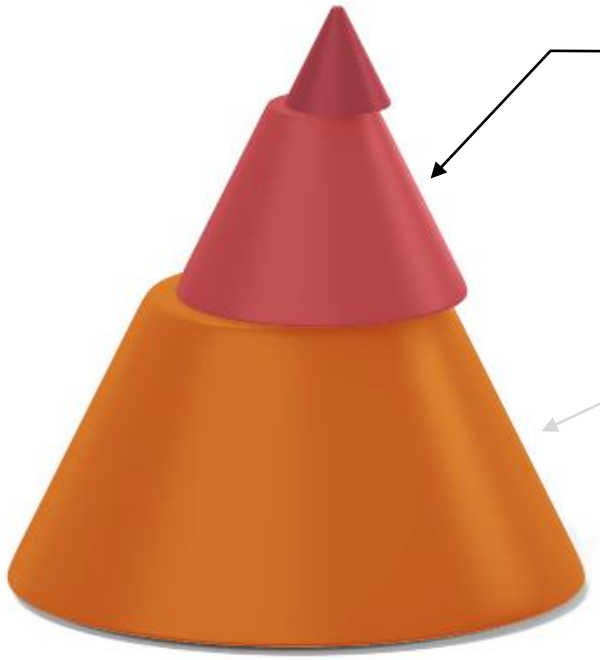
Utilities and Advantages:
To allow ophthalmoplastic surgeons to have patients who have to undergo surgery see a prediction of surgical outcomes through a rendering generated on the basis of the data provided. Each rendering will have the ability to be customized by changing the surgical variables.

Features & Functionality:
- Mobile platform
- Ability to take images with AI support to standardize photo
- Possibility to customize the intervention sheet for each individual patient
- Obtain more renderings of the surgery according to the surgical plan



AI-powered DTx

THE DIGITAL TRANSFORMATION



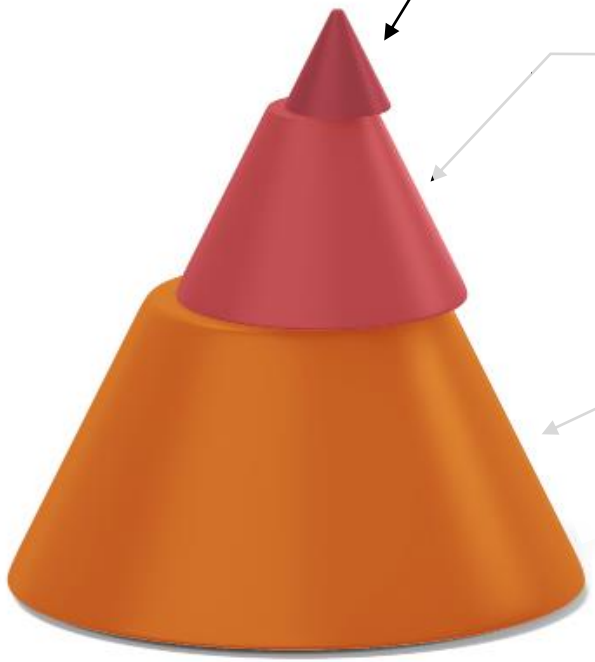
Digital Medicine

Software and hardware for clinical measurements and/or to intervene directly on health. **They require clinical efficacy trials** and are typically classified as medical devices

Digital Health

Technologies, platforms and systems that engage users for purposes related to lifestyle improvement, well-being and health. Other objectives may be to **acquire, store or transmit health data**, or to support clinical activities. To be deployed, applications in this area **do not require clinical trials**, nor regulatory supervision from any type of national or international body

THE DIGITAL TRANSFORMATION



DTx

Software that delivers therapeutic interventions to prevent, manage or treat a medical disorder or disease. **Clinical evidence and Real World Evidence are required**

Digital Medicine

Software and hardware for clinical measurements and/or to intervene directly on health. **They require clinical efficacy trials** and are typically classified as medical devices

Digital Health

Technologies, platforms and systems that engage users for purposes related to lifestyle improvement, well-being and health. Other objectives may be to **acquire, store or transmit health data**, or to support clinical activities. To be deployed, applications in this area **do not require clinical trials**, nor regulatory supervision from any type of national or international body

Lenire [FDA 03/2023]

Treating **Tinnitus** Symptoms

It uses the principle of **bimodal neuromodulation**: it provides mild electrical impulses to the tongue combined with sound reproduced through headphones to drive long-term changes or neuroplasticity in the brain to treat tinnitus.

Clinical trial on **112 patients** and RWE of 204 users, with 79.4% improvement

The frequencies of the sounds played by the headphones must be **customized**

Tinnitracks [non-FDA]

Treating **Tinnitus** Symptoms

Filter music based on the specific tinnitus frequency

Clinical trial on **98 patients**, with 65% improvement

The application filters the music played **in real time**, optimizing it according to the frequency of tinnitus

CognICA [FDA 10/2021]

Assessment of **cognitive functions**

Implement a rapid test, based on displaying images at a rapid pace on the iPad screen and asking you to identify them as animals or non-animals

Clinical trial on **91 patients**, with 94% accuracy

The classification of the patient, based on response speed and accuracy, takes place with a **regression system**

FDA clears AI-powered digital test for early dementia

A self-administered, artificial intelligence (AI) platform for cognitive assessment in multiple sclerosis (MS)

Seyed-Mahdi Khaligh-Razavi[1,2*], Maryam Sadeghi[3], Mahdiyeh Khanbagi[2], Chris Kalafatis[1,4,5] and Seyed Massood Nabavi[2]

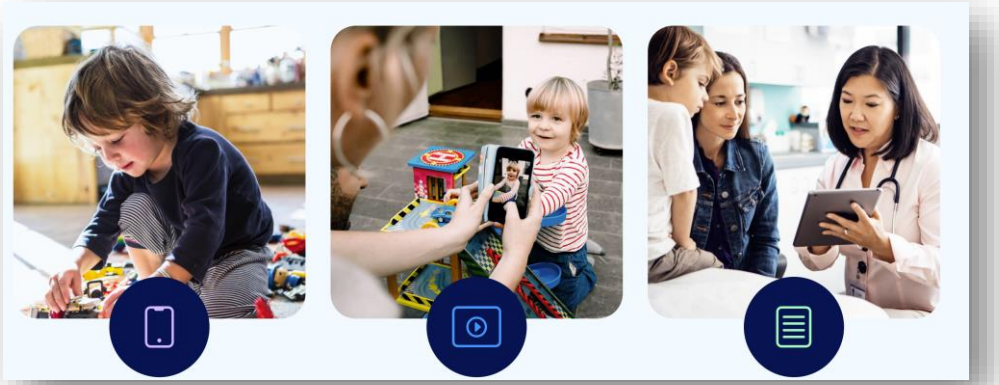
CanvasDx [FDA 06/2021]

Early diagnosis of **autism spectrum disorders**

An app collects behavioral data, videos and feedaback from healthcare professionals

Clinical trial on **425 children**

The application classifies the various cases through a machine learning algorithm (**gradient boosted decision tree algorithm**)



Cognoa's AI-based autism diagnosis aid gets FDA de novo clearance

Canvas Dx can be used by physicians for autism diagnosis in children aged 18 months to 72 months.

MedRhythm [FDA Breakthrough Device Designation 2020]

Walking in stroke patients

Use of rhythmic auditory stimulation, to facilitate walking and the ability to synchronize movements

Clinical trial on **11 patients**

The application analyzes the cadence and quality of walking and **dynamically adapts** auditory stimuli

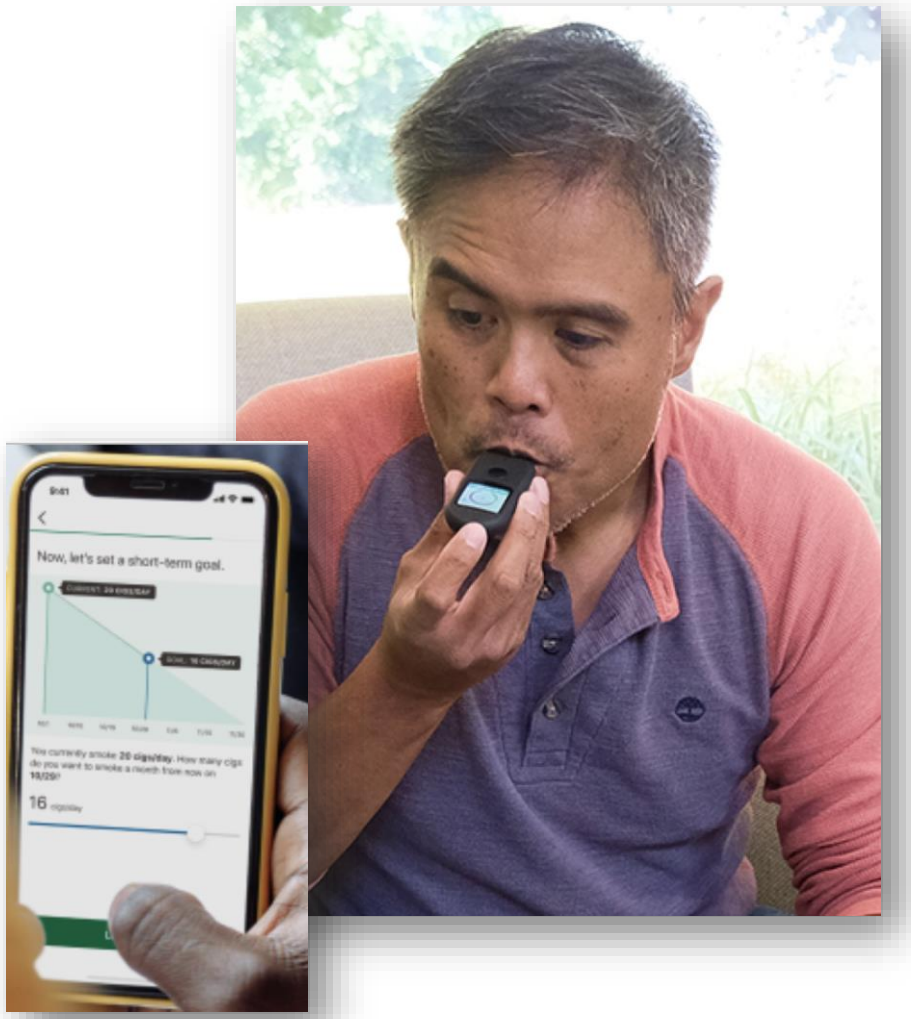
Pivot Breathe [FDA 10/2017]

Tobacco **addiction**

Coaching app that uses a sensor to read carbon monoxide levels in the breath

Clinical trial on **319 patients**, 35% success

The virtual coaching system is **adaptive** and personalizes the experience based on the user's characteristics



RhythmAnalytics [FDA 5/2019]

Identification of **cardiac arthymia**

System that allows you to detect and analyze cardiographic traces, and other data collected with sensors

Testing on **120,000 episodes**, with superior reliability to expert panels

The artimia identification system is based on **anomaly identification** mechanisms, trained on millions of cases

Biofourmis' RhythmAnalytics™ Platform Receives FDA Clearance for AI-Based Automated Interpretation of Cardiac Arrhythmias

A cloud-based, deep learning software platform can aid healthcare professionals in detecting over 15 types of cardiac arrhythmias using ambulatory ECG monitoring recordings.

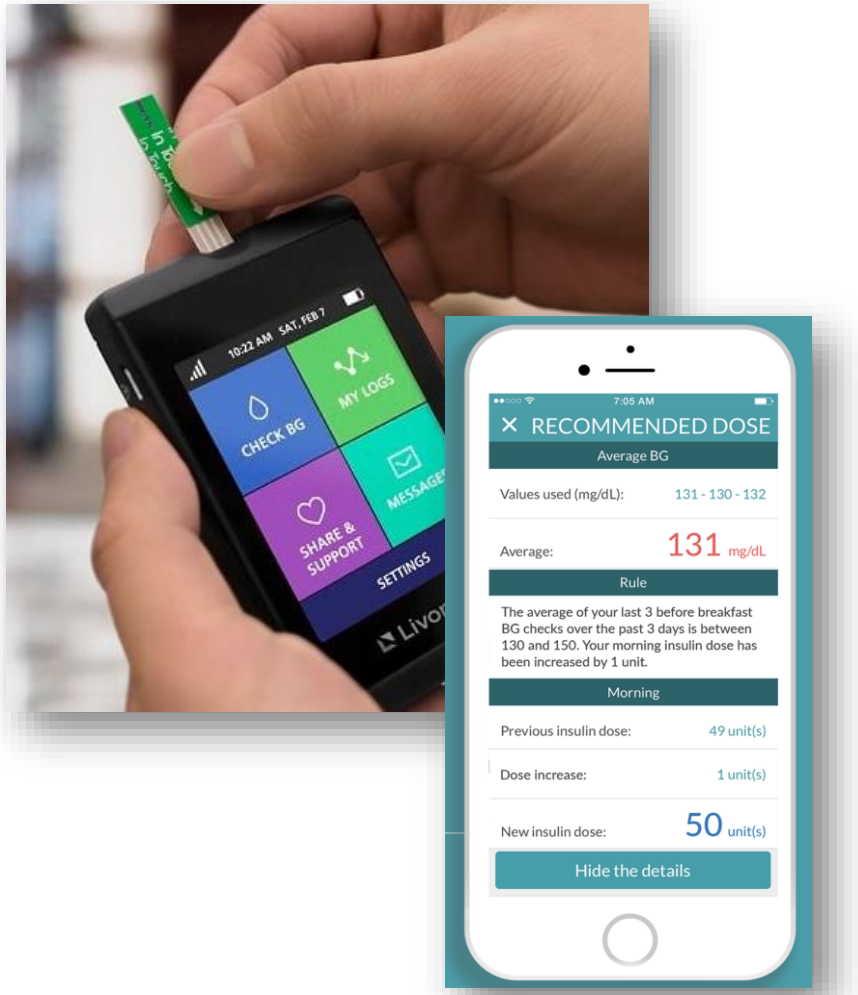
Insulia [FDA 7/2021]

Treatment of **type II diabetes**

Integrated system of sensors and personalized recommendation, about the correct dosage of insulin

Clinical trial involving **191 patients**

Expert system that encodes domain knowledge, between recorded values and recommended doses



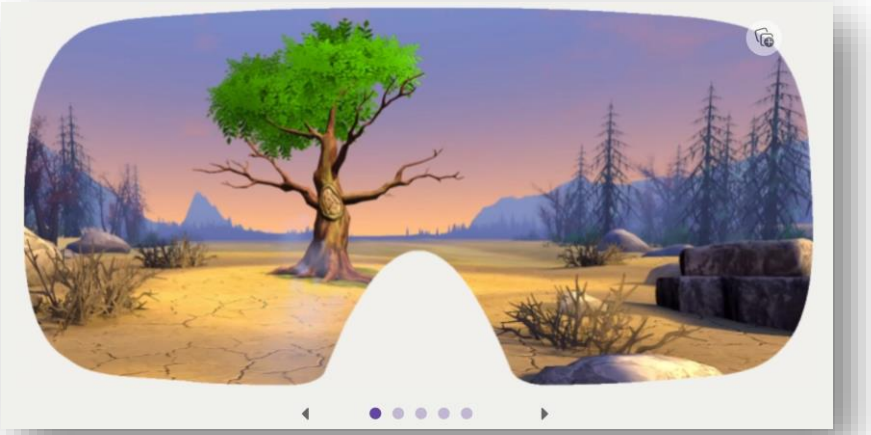
RelieVRx [FDA 7/2021]

Treatment for **chronic pain reduction**

It includes a VR headset and a device that amplifies the sound of the user's breathing to assist in breathing exercises. Use the principles of cognitive behavioral therapy (digital CBT)

Clinical trial on **188 patients**, efficacy on 65%

Use of **immersive environment**, with strong characteristics of human-machine interaction



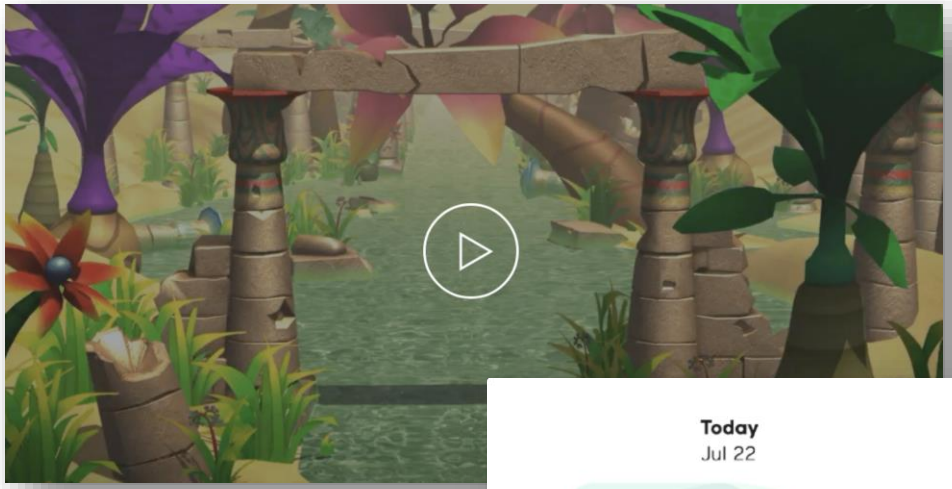
EndeavorRx [FDA 6/2020]

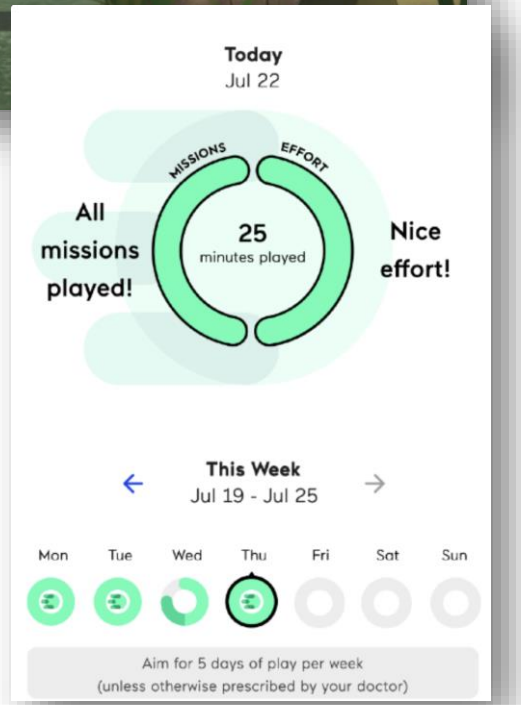
Improved **attention** in children 8-12 years

Video game that develops specific cognitive areas, which require particular stress in children with attention deficit hyperactivity disorder (ADHD)

Clinical trial on **600 children**, success on 73%

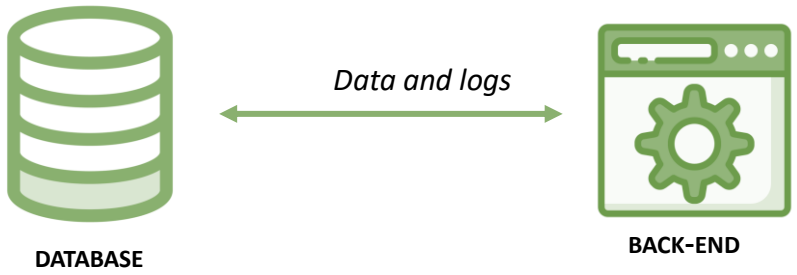
Videogames are among the most classic development environments for artificial intelligence technologies



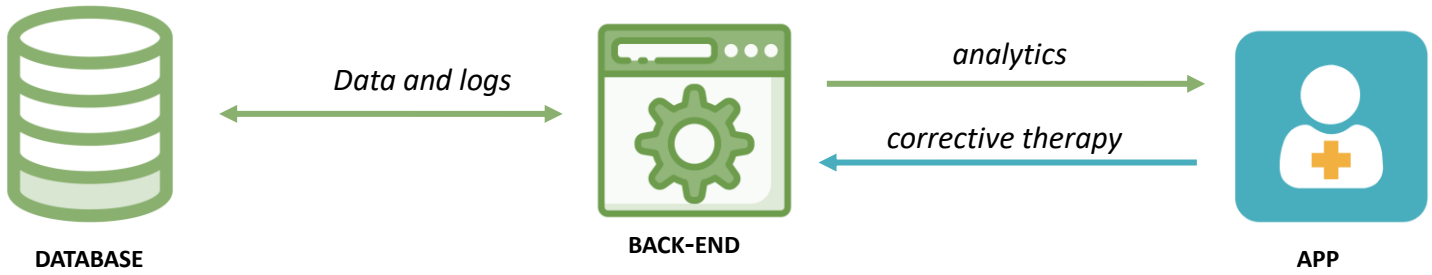


Further opportunities

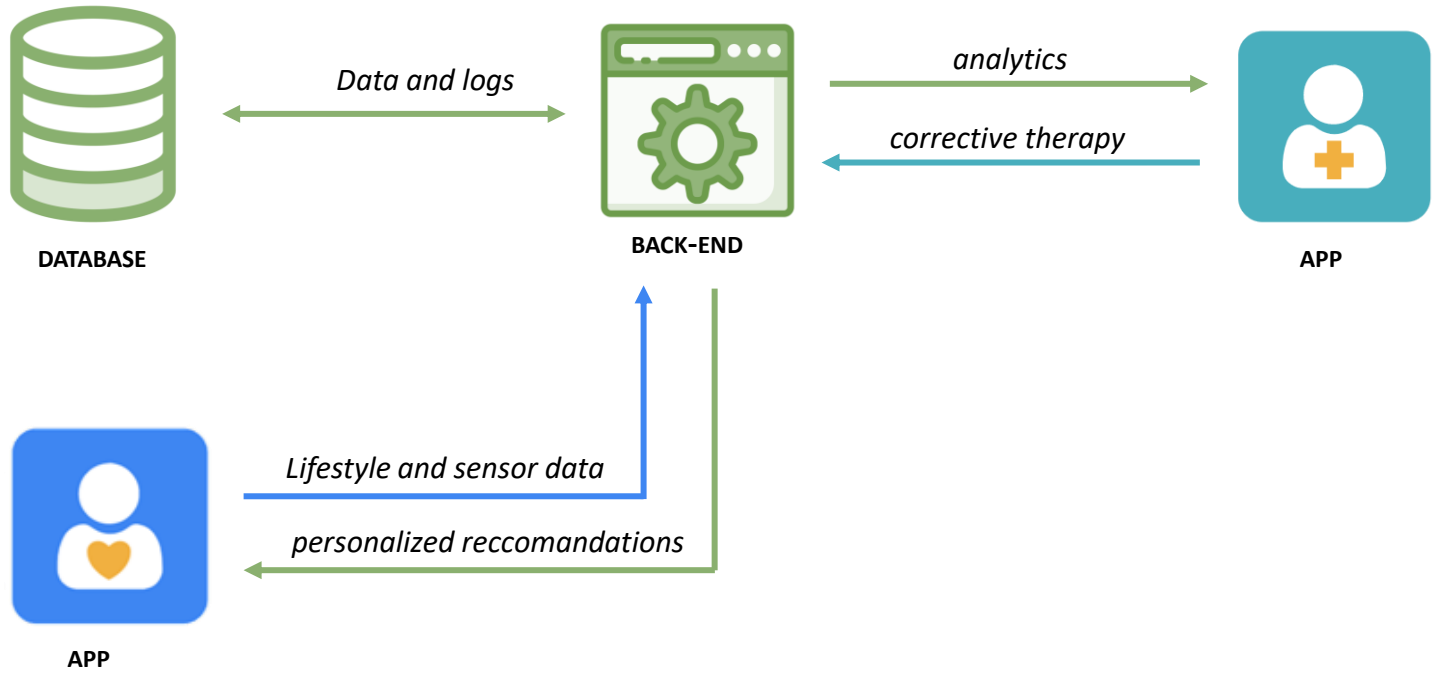
AI IN DIGITAL DEVICES



AI IN DIGITAL DEVICES



AI IN DIGITAL DEVICES



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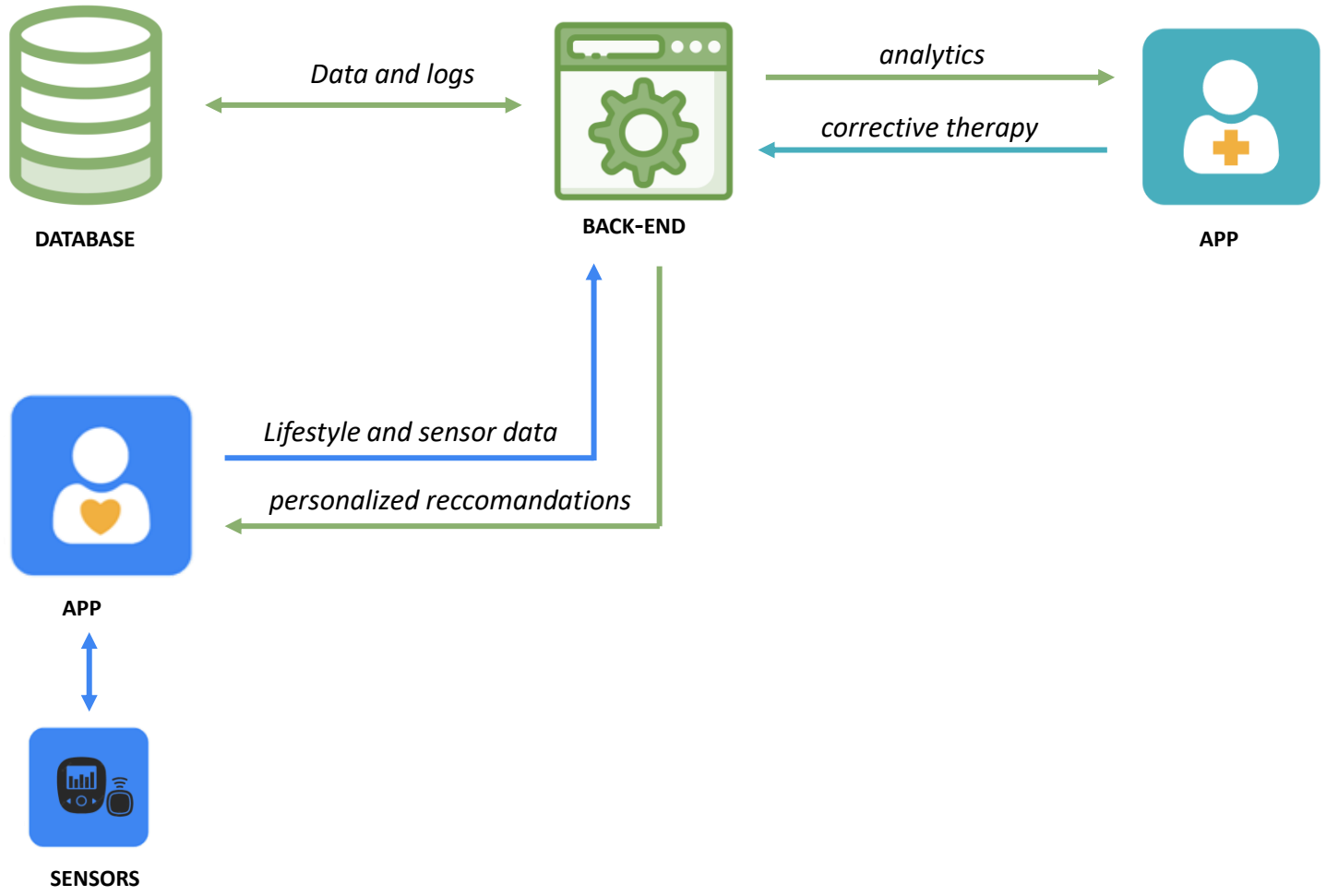

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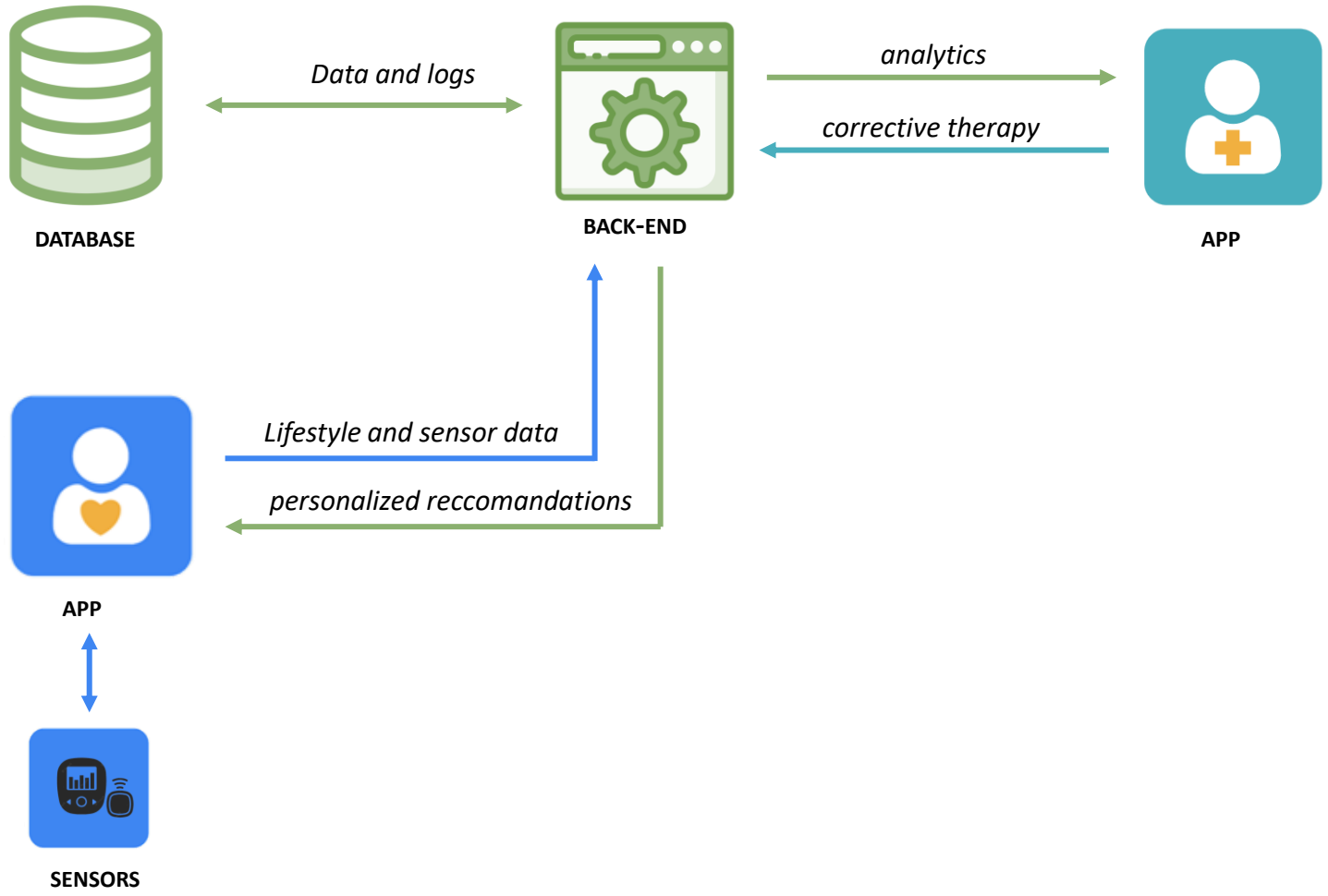
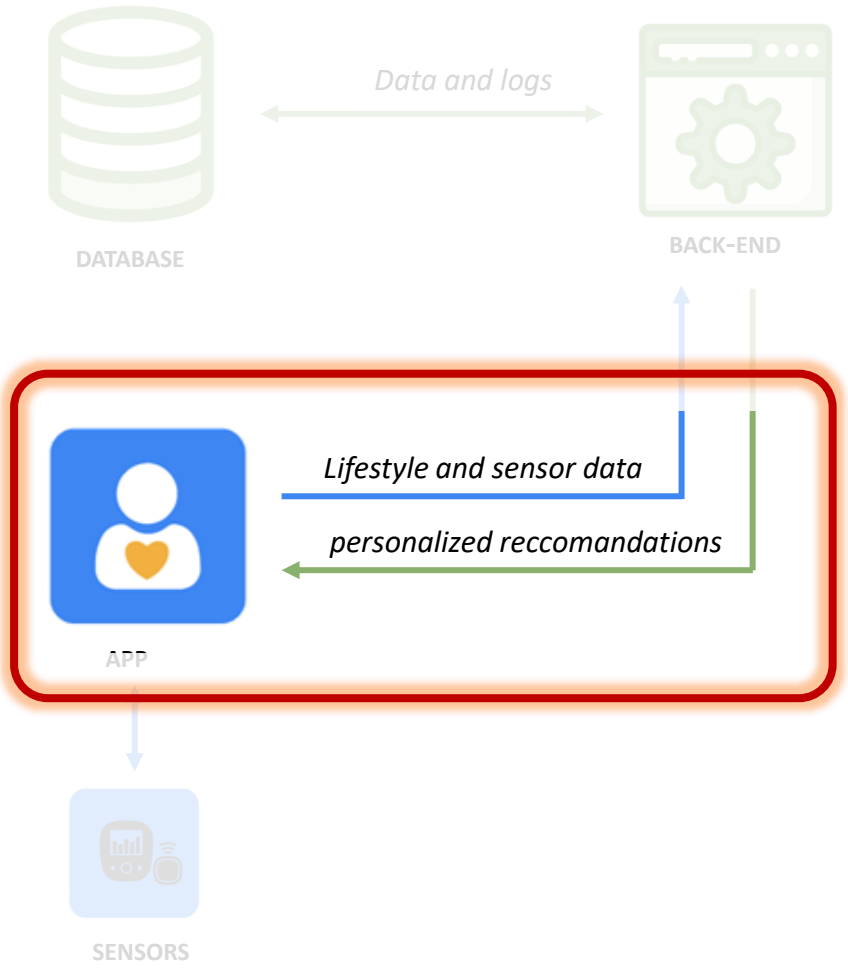
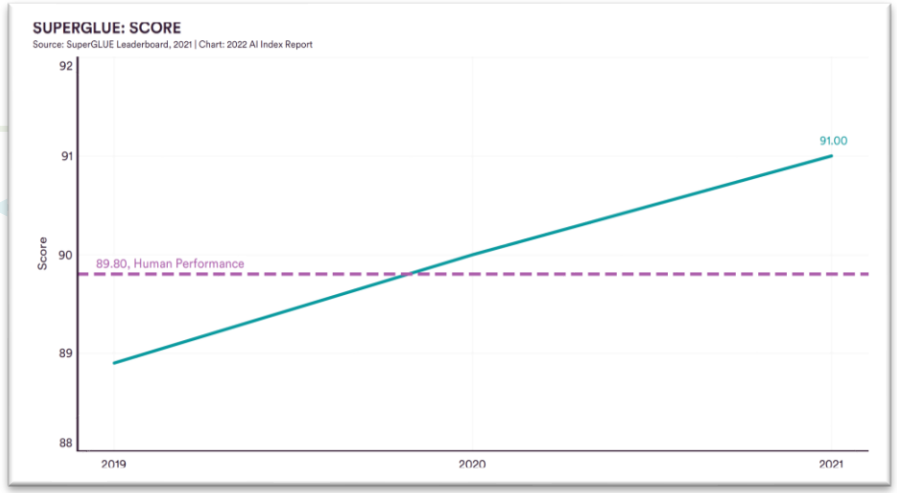


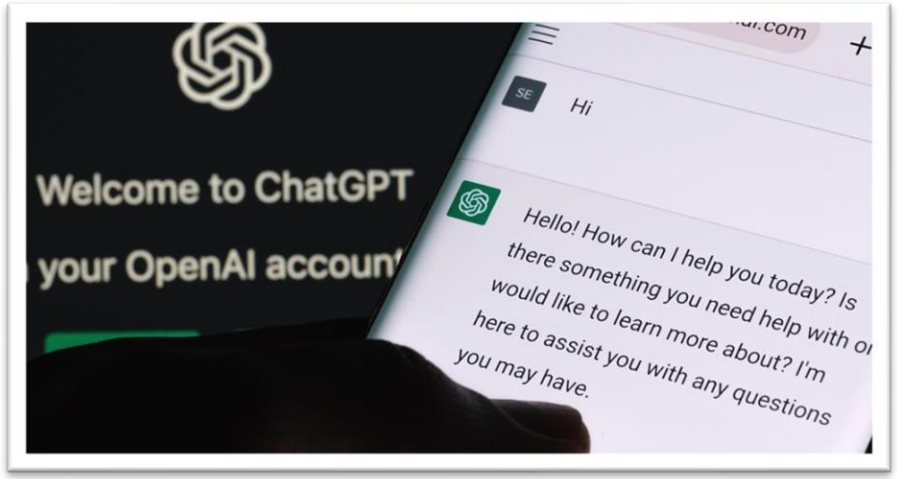
AI

- Chatbot
- Sensing
- Planning
- Reasoning
- Regressione
- Anomaly Detection
- Raccomandazioni

AI IN DIGITAL DEVICES





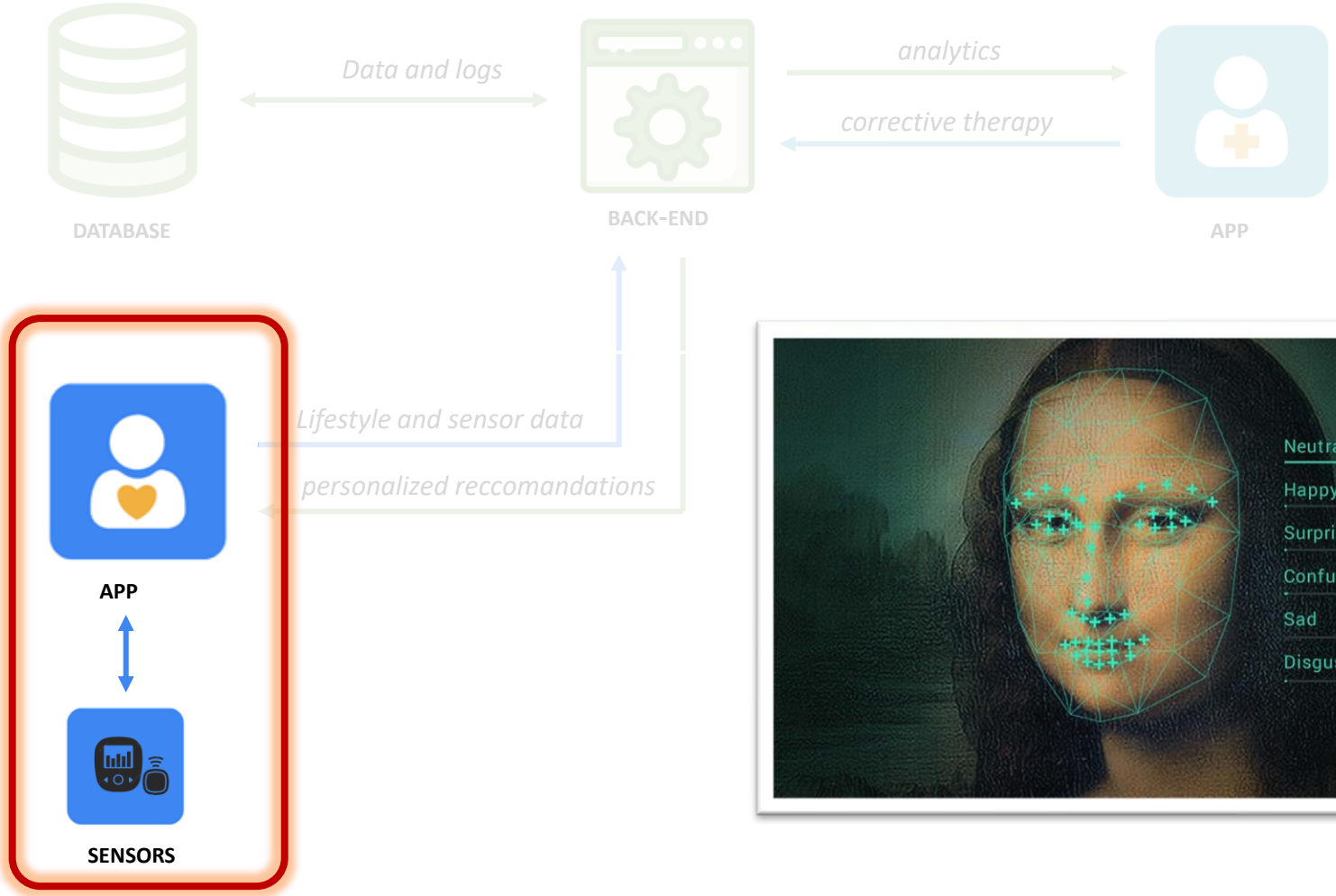


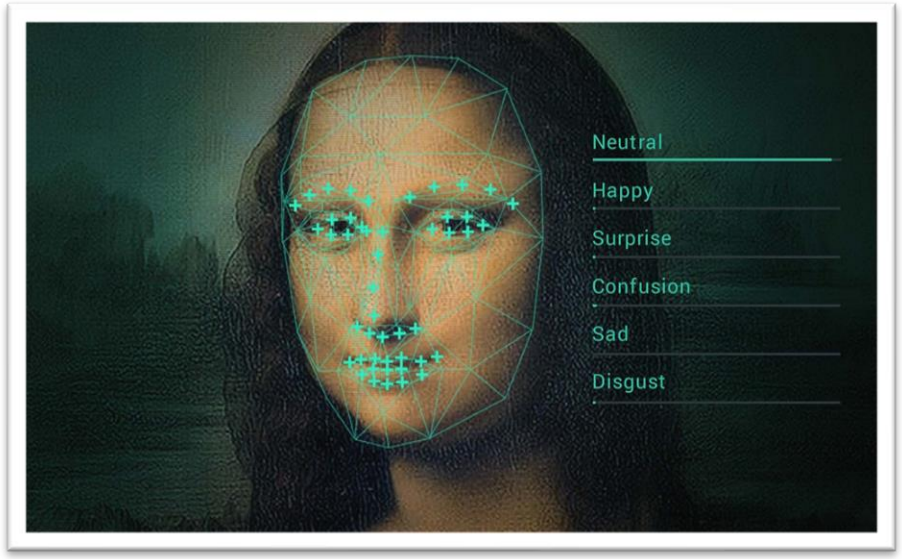
AI

Chatbot

Raccomandazioni

AI IN DIGITAL DEVICES

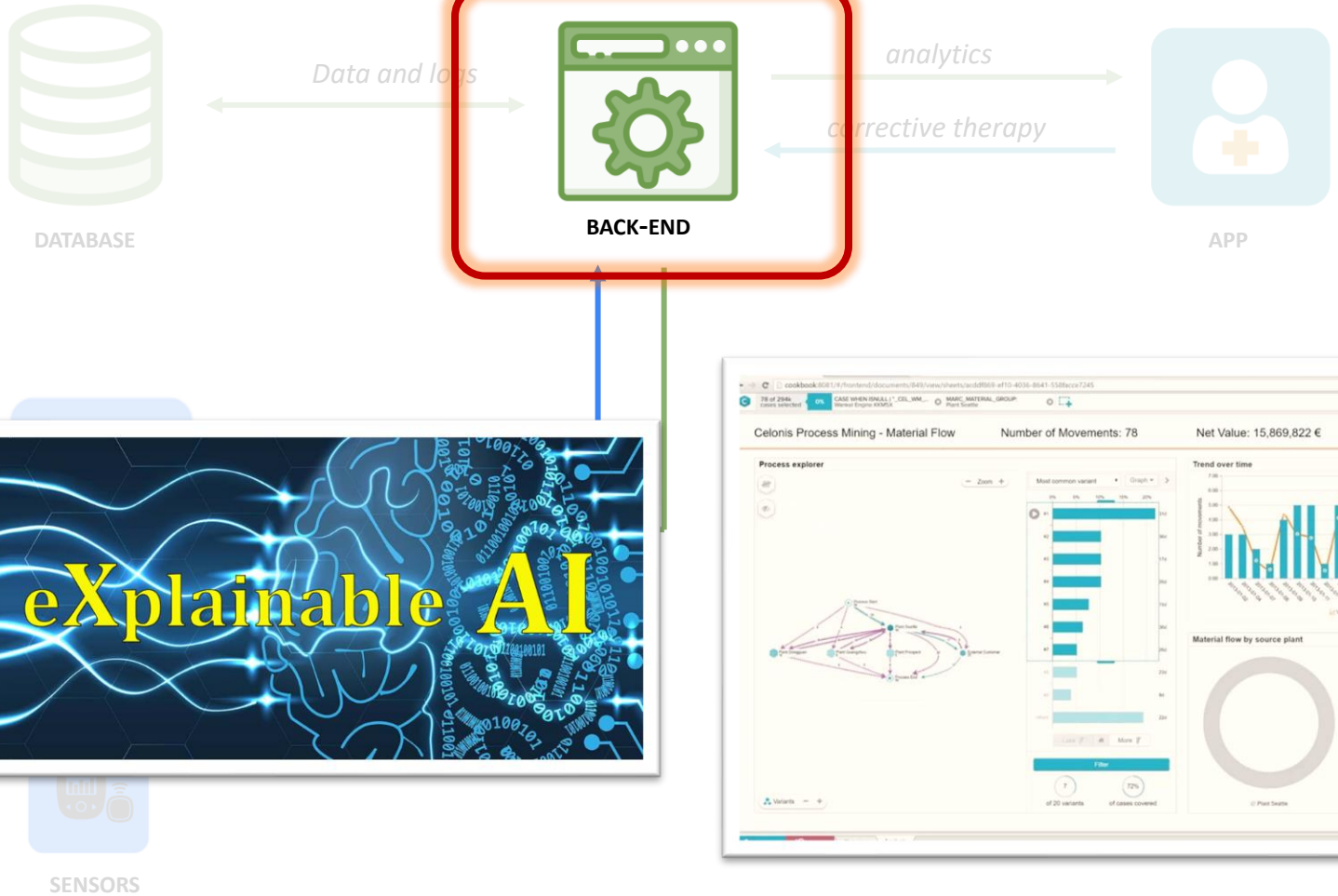




AI

Sensing

AI IN DIGITAL DEVICES



AI

- Planning
- Reasoning
- Regressione
- Anomaly Detection
- Raccomandazioni

AI regulations in digital medicine

REGULATIONS

Artificial Intelligence

for

Medical Devices

REGULATIONS

*[..] AI system shall be considered **high-risk** where both of the following conditions are fulfilled:*

- *the AI system is intended to be used as a **safety component** of a product, or is itself a product, covered by the Union **harmonisation legislation listed in Annex II**;*
- *the product whose safety component is the AI system, or the AI system itself as a product, is **required to undergo a third-party conformity assessment** with a view to the placing on the market or putting into service of that product pursuant to the Union harmonisation legislation listed in Annex II.*

*In addition to the high-risk AI systems referred to in paragraph 1, **AI systems referred to in Annex III shall also be considered high-risk***

LEGISLATION ON MEDICAL DEVICES

Regulation (EU) ***2017/745*** *of the European Parliament and of the Council of 5 April 2017 on medical devices*

MDR

The Medical Devices Regulation applies since 26 May 2021

Regulation (EU) ***2017/746*** *of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices*

IVDR

The In Vitro Diagnostic Devices Regulation applies since 26 May 2022

MDR GENERAL ARCHITECTURE

- In the European Union (EU) MEDICAL DEVICES must undergo a **conformity assessment** to demonstrate they meet legal requirements to ensure they are safe and perform as intended.
- They are regulated at EU Member State level, but the **European Medicines Agency** (EMA) is involved in the regulatory process.
- **Manufacturers can place a CE** (Conformité Européenne) **mark** on a medical device once it has passed a conformity assessment.
- **The conformity assessment usually involves an audit** of the manufacturer's quality system and, depending on the type of device, a review of technical documentation from the manufacturer on the safety and performance of the device.
- EU Member States designate **accredited notified bodies** to conduct conformity assessments. For certain high-risk devices, notified bodies shall request the opinion of specific expert panels before issuing the certificate of conformity. These expert panels benefit from EMA's technical and scientific support.

MDR AND AI

Classification rule 11

Software *intended to provide information which is used to* ***take decisions with diagnosis or therapeutic purposes is classified as class IIa****, except if such decisions have an impact that may cause:*

- ***Death or an irreversible deterioration of a person's state of health, in which case it is in class III****; or*
- ***Serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb****.*

Software intended to monitor physiological processes is classified as class IIa*, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that* ***it could result in immediate danger to the patient, in which case it is classified as class IIb****.*

All other software are classified as class I*.*

MDR AND AI

Classification rule 11

Dificulties in defining appropriate classification for medical devices

MDCG 2019-11

Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR

October 2019

MDR AND AI

Classification rule 11

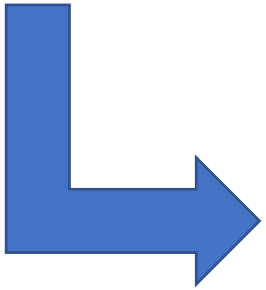
Dificulties in defining appropriate classification for medical devices

MDCG 2019-11

Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR

October 2019

- AI systems are often black box and implement various functionalities
- Guidelines for softwares made of different modules
- Examples and pratical guidance



MDR classes are related to risk categories

IMDRF International Medical Device Regulators Forum

FURTHER ISSUES WITH DTx

- Although in some European countries several procedures have been set up for the marketing authorization and reimbursement of DTx, these are just individual and **uncoordinated initiatives**.

- **The European regulatory system concerning DTx is still immature** and specific regulations aimed at evaluating these tools and ensuring the safety of the devices and the integrity of the data collected are lacking.

- It is necessary to define **specific indications for DTx approval**, taking into account their peculiar characteristics, such as the rapidity of digital evolution and the issues concerning patients' privacy and data security

A FEW EXCEPETIONS

- A specific fast-track regulatory process for digital health applications (**DiGA**, Digitale Gesundheitsanwendungen) was launched

- **Physicians can prescribe digital health applications** (including several DTx) that can then be reimbursed by health insurance companies

- The **National Institute for Health and Care Excellence** (NICE) established an Office for Digital Health to accelerate efforts to deliver innovation to the health and care system

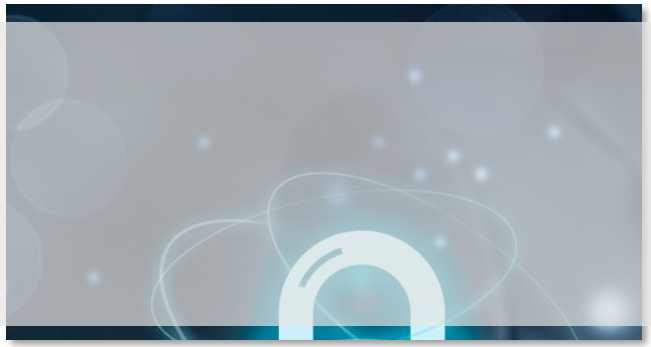
- The Office launched a project, the **Innovative Devices Access Pathway** (IDAP), to design and scope an innovative access pathway for selected medical and digital health technologies

But also challenges

SOLUTION SECURITY

As with any device that handles patient data, **privacy and security** are crucial, especially those with frequent software updates or connections to other electronic health record devices or systems.

BALANCING DATASETS



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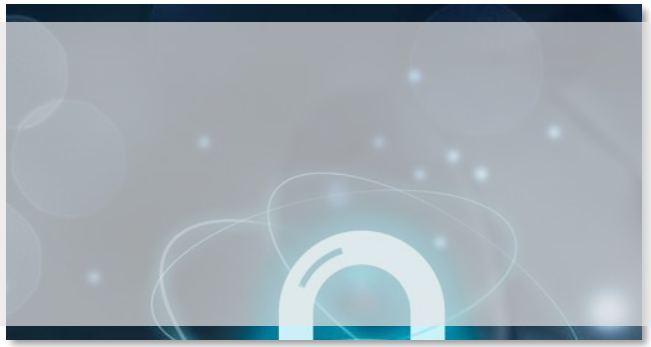
It is very complex to evaluate the effectiveness of machine learning algorithms in **different patient populations**. Training datasets must be well defined, and address bias issue.

COST-EFFECTIVE TECHNIQUES AND TOOLS



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FURTHER RISKS OF AI

Patient harm due to AI errors

- Noise and artefacts in AI's input or data shifts between training and real-world can cause false diagnosis and/or incorrect scheduling or prioritization

Keep human in the loop, and implement approaches that continuously improve over time

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Misuse of medical AI tools

- Lack of AI training of medical staff can cause incorrect usage of tools, resulting in incorrect medical assessment and decision making (again with potential harm)

Invest on education, training and res-skilling programs, targeted to digital medicine

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Associazione Italiana per l'Intelligenza Artificiale

Thank You!