UNIVERSITÀ DEGLI STUDI DI UDINE
hic sunt futura

STATI GENERALI ITINERANTI
PER L'UMANIZZAZIONE DELLE CURE E IL BENESSERE ORGANIZZATIVO

Congresso scientifico

Umanizzazione delle cure: come ri-costruire la filiera della salute

COORDINAMENTO REGIONALE MALATTIE RARE FVG

ASU FC Azienda sanitaria universitaria Friuli Centrale

REGIONE AUTONOMA FRIULI VENEZIA GIULIA

STATI GENERALI ITINERANTI

PER L'UMANIZZAZIONE DELLE CURE E IL BENESSERE ORGANIZZATIVO

Umanizzazione delle cure: come ri-costruire la filiera della salute

INNOVAZIONE TECNOLOGICA E UMANIZZAZIONE NELLA RICERCA E CURA DELLE MALATTIE RARE

Maurizio Scarpa
Centro Coordinamento Regionale Malattie Rare
European Reference Network
For Inherited Metabolic Diseases, MetabERN, Udine

European Reference Network | MetabERN European Reference Network for Hereditary Metabolic Disorders

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

DISCLOSURES

- I receive unrestricted research and educational grants from Alexion, Amicus, Azafaros, BioMarin, CHIESI, Orchard, Orphazyme, Sanofi, Takeda, Ultragenix.
- The presentation reflects only my opinion on the topic.
- I do not have COI regarding the topic of my presentation

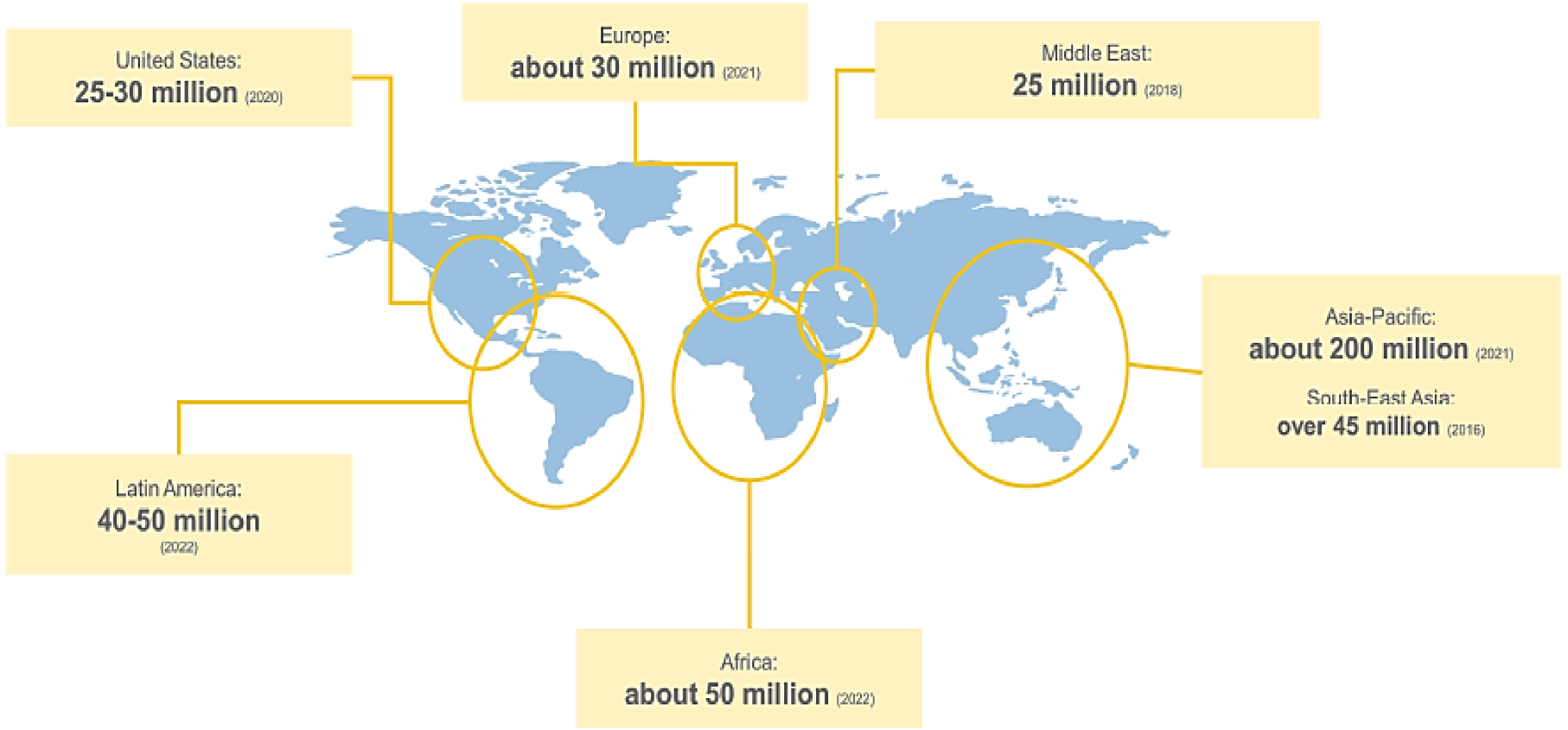
COORDINAMENTO REGIONALE
MALATTIE RARE FVG

INTRODUCTION

Humanization in the field of rare diseases encompasses a multifaceted approach aimed at centering the patient experience in diagnosis, treatment, and management.

It involves not only the clinical management of these conditions, which often lack robust research and therapeutic options, but also the emotional, psychological, and social dimensions of patient and caregiver experiences.

RD ACROSS THE WORLD



International Journal of
Environmental Research and Public Health
MDPI

Review

Enhancing Equitable Access to Rare Disease Diagnosis and Treatment around the World: A Review of Evidence, Policies, and Challenges

Takeya Adachi [1,2,3,†], Ayman W. El-Hattab [4,5,6,†], Ritu Jain [7,8,9,†], Katya A. Nogales Crespo [10,*,†], Camila I. Quirland Lazo [11,12,13,†], Maurizio Scarpa [14,15,16,†], Marshall Summar [17,18,19,20,21,†] and Duangrurdee Wattanasirichaigoon [22,23,24,25,26,27,28,29,†]

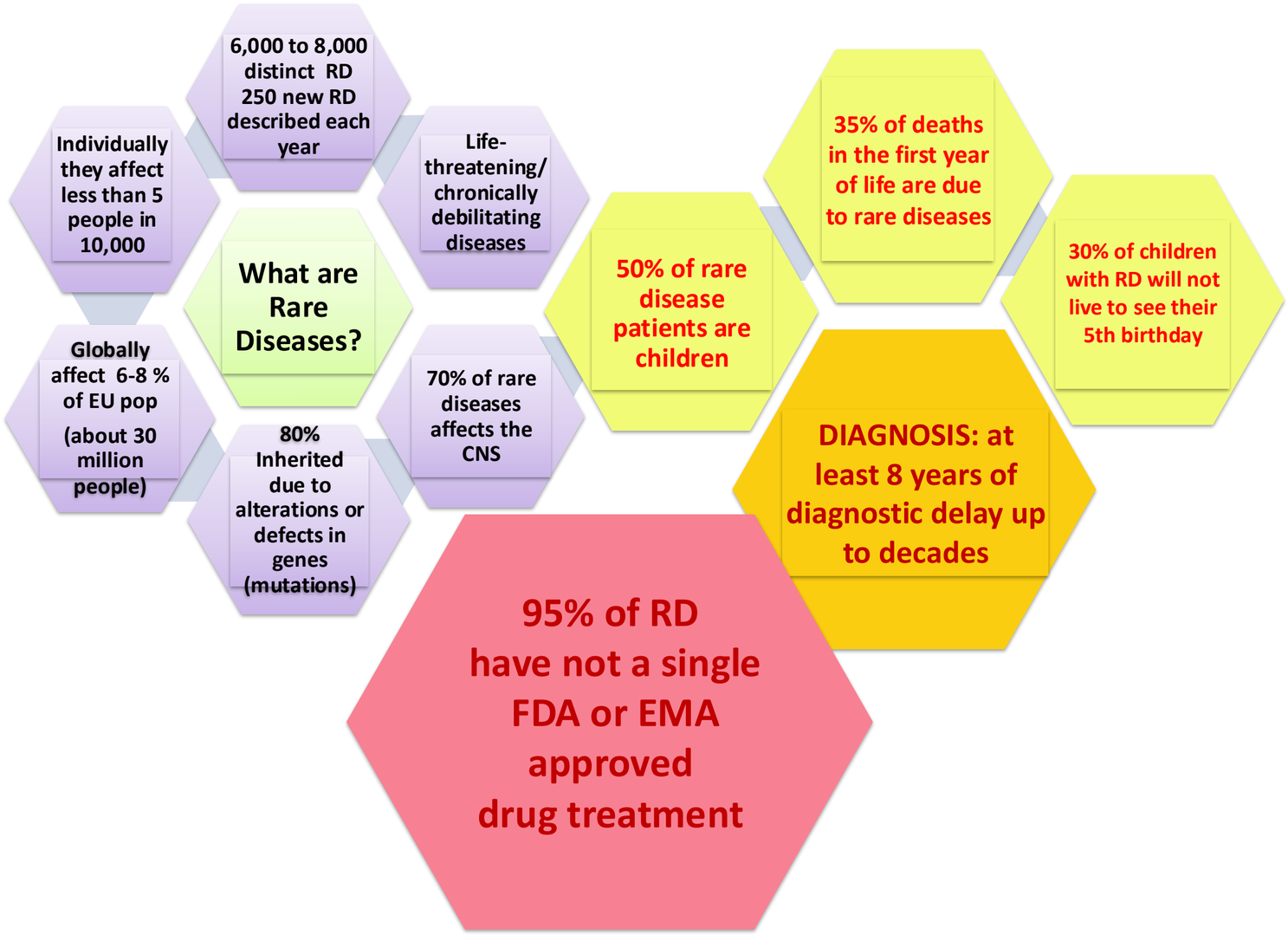
WHAT IS A RARE DISEASE?

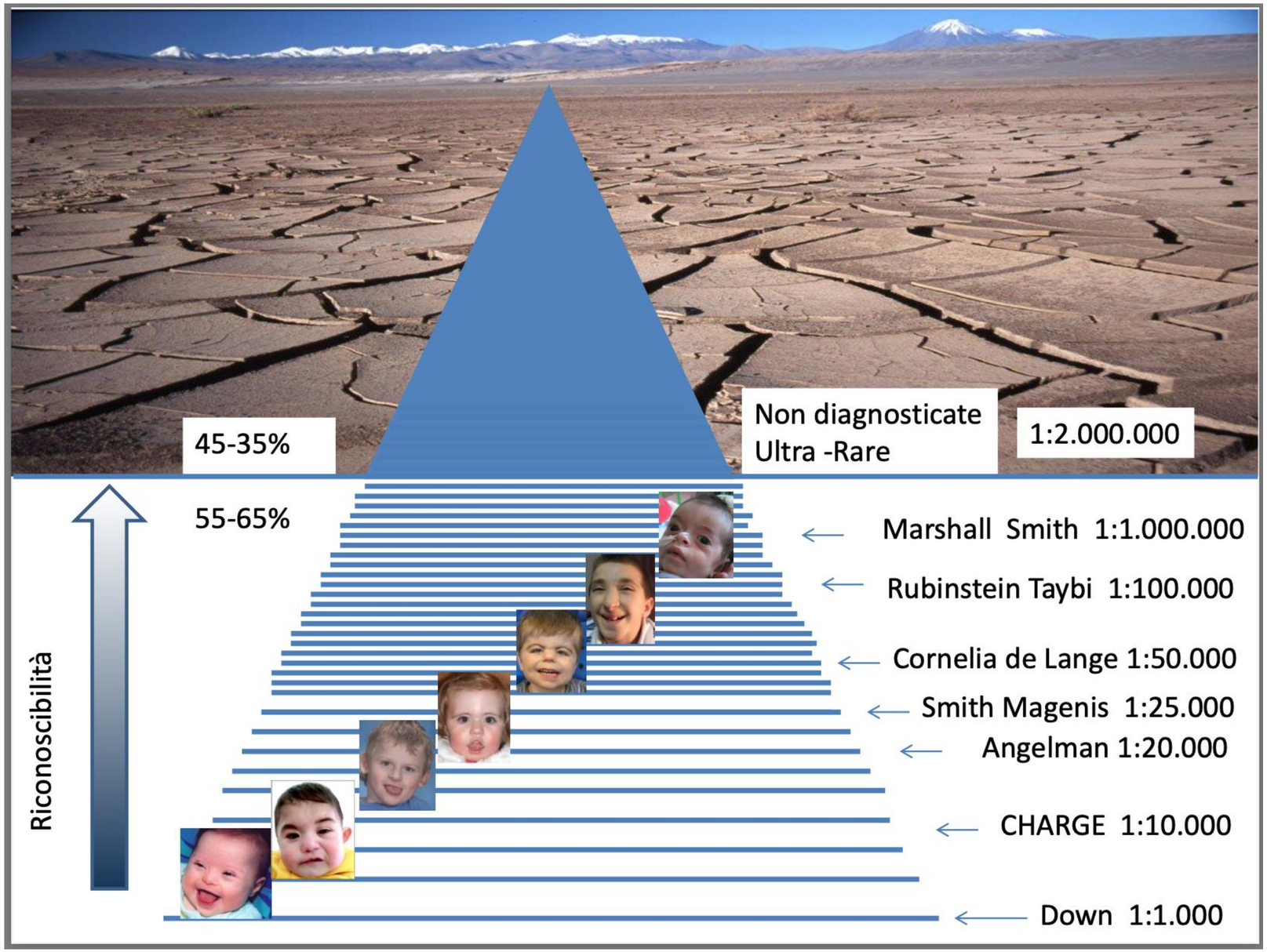
- **USA:**
  1 affected every 1.500 persons
- **Europe:**
  1 affected every 2.000 persons
- **Japan:**
  1 affected every 2.500 persons
- **Australia:**
  1 affected every 10.000 persons

1 Person every 18 is affected by a rare diseases during life

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

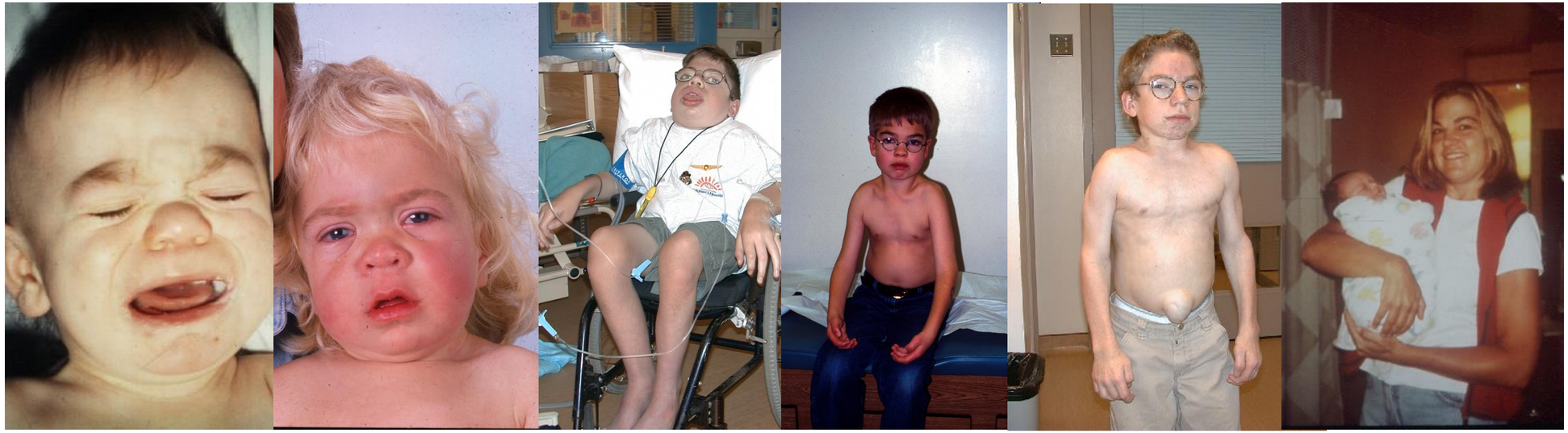
WHAT ARE RARE DISEASES?




45-35%
Non diagnosticate
Ultra -Rare
1:2.000.000
55-65%
Riconoscibilità
Marshall Smith 1:1.000.000
Rubinstein Taybi 1:100.000
Cornelia de Lange 1:50.000
Smith Magenis 1:25.000
Angelman 1:20.000
CHARGE 1:10.000
Down 1:1.000

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

THE MAJOR CLINICAL CHALLENGE: UNDERSTANDING WHY SO MANY PHENOTYPES



Neuronopathic — Non Neuronopathic

SAME GENE DEFECT, SAME PROTEIN DEFICIENCY- DIFFERENT PHENOTYPES

With Permission

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

THE COMPLEXITY OF MPSs: AN EXAMPLE

Respiratory:
upper airway obstruction
obstructive sleep apnea
restrictive lung disease
frequent infections
restrictive airway disease

Skeletal:
degenerative hip dysplasia
kyphosis or kyphoscoliosis
gibbus
joint contractures
genu valgum deformities

Cardiac:
cardiomyopathy
dysplastic valves
coronary artery disease

Gastrointestinal:
hepatosplenomegaly
umbilical & inguinal hernia
swallowing problems
diarrhea, drooling

Peripheral nervous system: Peripheral nerve entrapment (eg, carpal tunnel syndrome)

Wraith JE, Clarke JTR. In:
***Physician's Guide to the Treatment and Follow-up of Metabolic Diseases*. 2006:195–203.**

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

CNS:
hydrocephalus
atlantoaxial instability
cervical cord compression
myelopathy,
Seizures
severe behavior problems
sleep disturbance
mental retardation

Appearance:
Coarse facies

Eyes:
glaucoma
retinal dystrophy
Corneal clouding

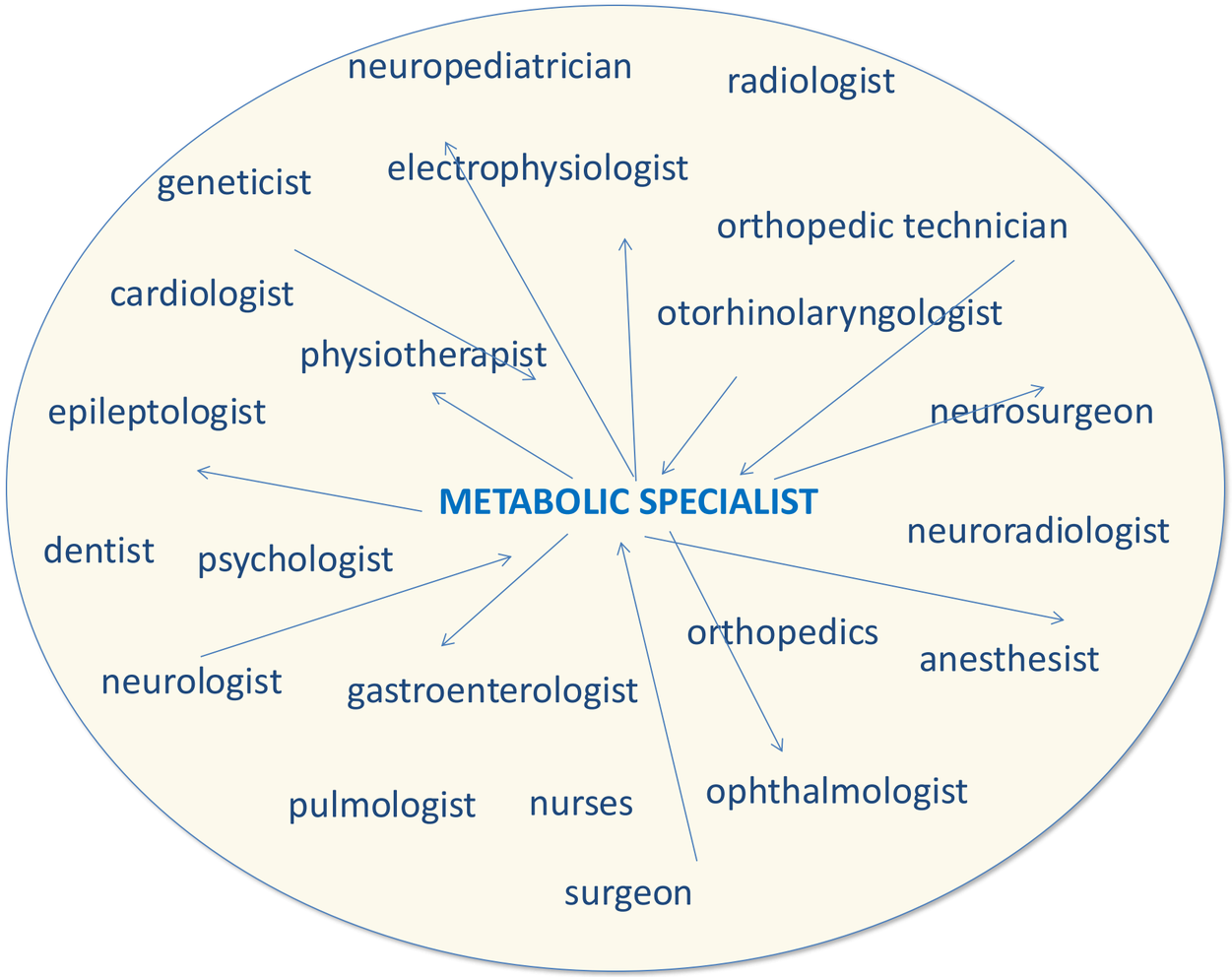
Ears:
recurrent otitis media,
sensorineural deafness

Dental:
caries, dental
abscess

1. Wraith JE, Clarke JTR. In:
Physician's Guide to the Treatment and Follow-up of Metabolic Diseases. 2006:195–203.

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

THE MULTIDISCIPLINARY TEAM FOR RD



COORDINAMENTO REGIONALE
MALATTIE RARE FVG

DEFINING HUMANIZATION IN RARE DISEASES

Humanization can be defined as a process that renders clinical practices more empathetic, personalized, and responsive to the nuanced needs of individuals affected by rare diseases.

This definition implies:

1. **Patient-Centered Care**: Prioritizing the patient's voice, tailoring treatment plans to individual circumstances, and ensuring that healthcare providers understand the specific contexts of patients' lives.

2. **Interdisciplinary Collaboration**: Fostering teamwork among diverse healthcare specialists, including geneticists, rare disease experts, psychologists, and social workers, to provide holistic care.

3. **Empathy and Relational Transparency**: Enhancing the quality of interaction between providers and patients by actively engaging in meaningful conversations that validate patient narratives and experiences

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

HUMANIZING DIAGNOSIS

1. **Comprehensive Approach to Symptoms**: Innovating diagnostic protocols to incorporate a wider range of diagnostic tools, acknowledging atypical presentations, and considering the family history and socio-environmental factors.

2. **Patient Advocacy and Education**: Empowering patients and caregivers with information tailored to their specific conditions, encouraging active participation in the diagnostic process, and enabling informed decision-making.

3. **Psychosocial Support**: Establishing a supportive framework during the diagnostic process that includes mental health resources and counseling, ensuring care teams are attuned to the psychological impact of receiving a rare disease diagnosis.

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

HUMANIZING MANAGEMENT

1. **Integrated Care Models**: Facilitating comprehensive care models that bring together clinical, psychological, social, and community resources to address the multi-dimensional challenges faced by patients and caregivers.

2. **Long-Term Follow-up and Monitoring**: Establishing continuous care pathways that incorporate regular follow-ups, allowing for ongoing assessment of disease progression and treatment efficacy, and promoting adaptive management strategies.

3. **Community and Support Networks**: Encouraging the formation of patient and caregiver networks, fostering peer support, and utilizing telehealth technologies to maintain close contact with patients throughout their care journeys.

4. **Feedback Loops for Continuous Improvement**: Creating systems for ongoing feedback from patients and caregivers about their experiences, insights, and outcomes, thus allowing healthcare systems to refine processes and interventions continually.

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

HUMANIZING TREATMENT

1. **Tailored Therapeutic Approaches**: Implementing precision medicine strategies that account for the genetic, biochemical, or physiological peculiarities of rare diseases, while allowing for treatment plans that are personalized and adjustable.

2. **Shared Decision-Making**: Incorporating shared decision-making models that respect patient autonomy and preferences, emphasizing the importance of the patient's own treatment goals alongside clinical recommendations.

3. **Accessibility of Interventions**: Ensuring that treatment options, particularly novel therapies or clinical trial opportunities, are made accessible regardless of socioeconomic or geographic status, and effectively communicating these options to patients and caregivers.

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

INNOVATION DRIVERS

In the context of rare diseases, the interplay between innovation and humanization represents a complex but critical ratio affecting the acceleration of diagnosis and optimization of treatment and management. This balance can be quantitatively and qualitatively examined through several vectors, including technological advancements, patient-centric care models, and ecosystem-wide collaborations.

1. **Diagnostics**: Innovations in genomics, proteomics, and metabolomics have paved the way for rapid molecular diagnoses, enabling the identification of rare diseases that were previously undetectable. Technologies such as next-generation sequencing (NGS) have significantly reduced the time and cost associated with diagnosing rare genetic disorders, thereby accelerating early intervention.

2. **Therapeutics**: The advancement of gene therapy, CRISPR technology, and tailored small molecules represent a frontier of therapeutic innovation. These treatments often target the root causes of diseases, rather than merely alleviating symptoms. The ratio of exploratory research to successful implementation must account for the high stakes and risks associated with investigational therapies in the rare disease context.

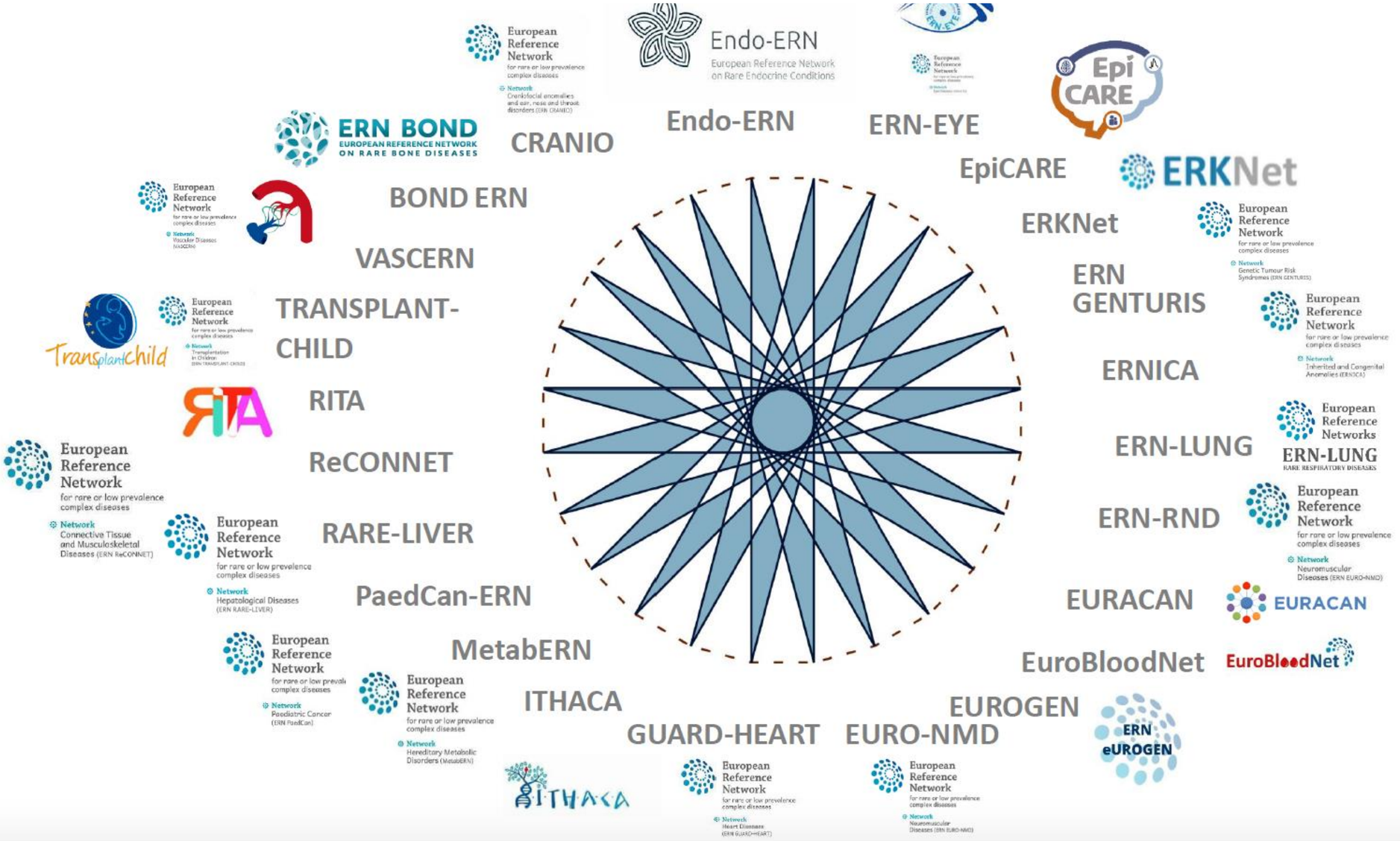
3. **Digital Health**: Wearable technologies, telemedicine, and mobile health applications are reshaping data collection and patient monitoring. These innovations facilitate remote management of disease symptoms and provide real-time data back to healthcare providers, thus enhancing treatment personalization.

The life of ERNs

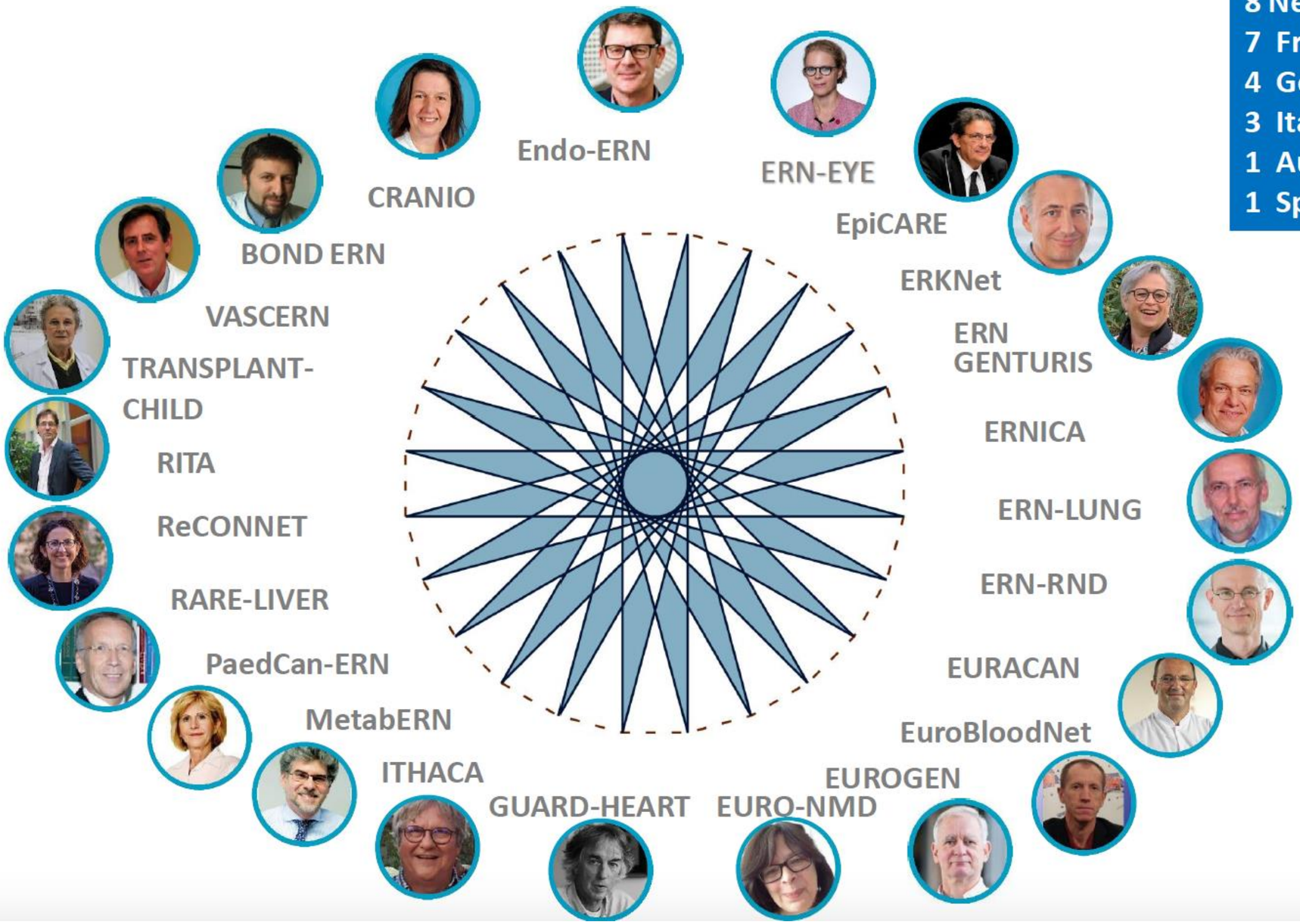
- **A long process** since **2004** with the first Rare Disease Task Force
- Council Recommandation in **2009**
- Cross Border Health DIRECTIVE **2011**/24/EU
- **2015** implementation by the commission
- **2017** launch of 24 ERNS **for 5 years = End March 2023**
- **24 ERNs – wide fields – different « natural histories » => heterogeneous entities**

2017 | 2018 | 2019 | 2020 | 2021 | 2022 | Transition phase | RENEWAL

ERNs– Thematic networks



ERN Coordinators



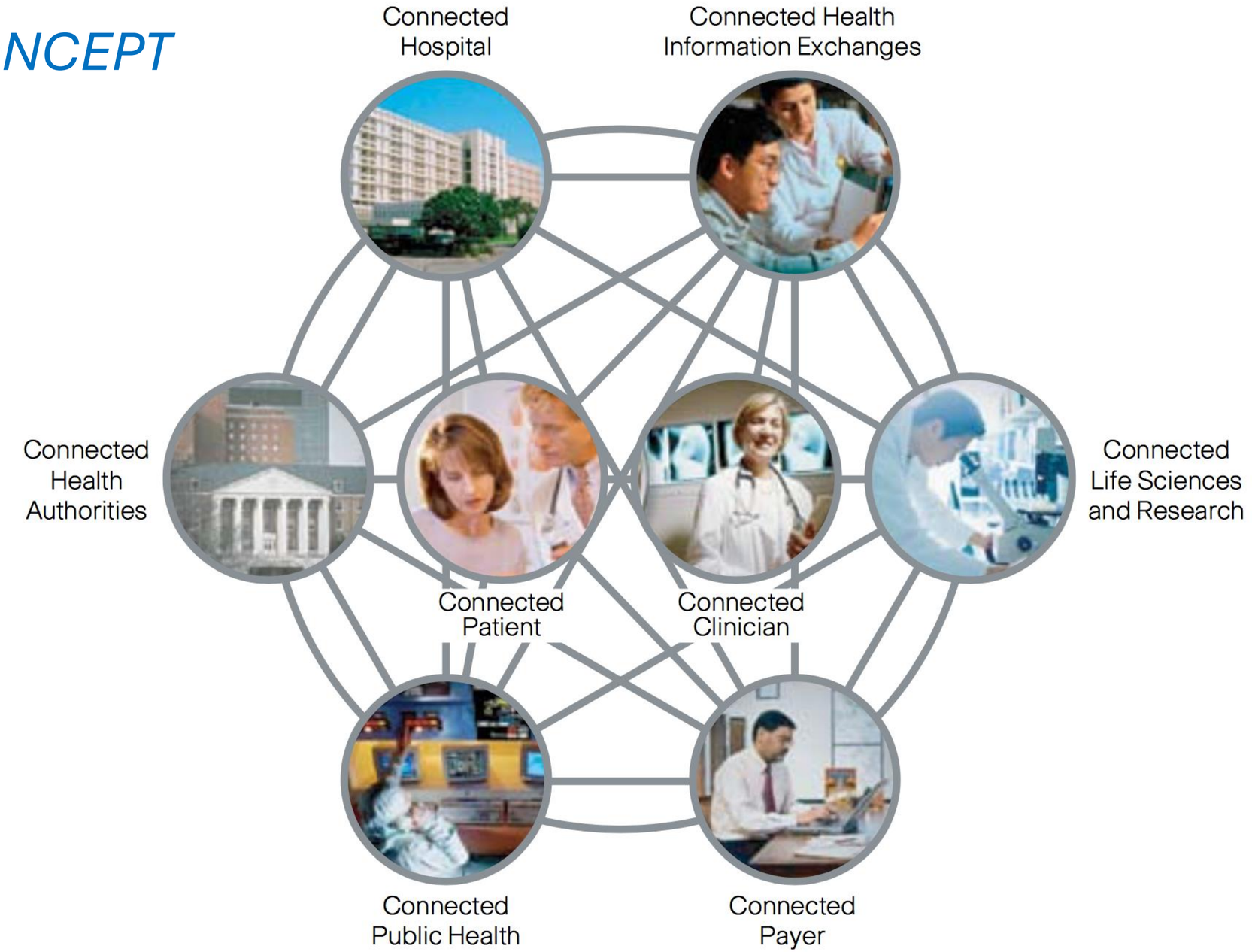
8 Netherlands
7 France
4 Germany
3 Italy
1 Austria
1 Spain

THE ERN CONCEPT: PAVING A NEW COLLABORATIVE BASE FOR THE DEVELOPMENT OF THERAPIES

- ERNs are patients centered and respond to patients´need. Diagnostics and new therapies are a primary need.
- More efficiently bring the results of research and innovation to the patient
- Programme to implement a research and innovation pipeline, from bench to bedside
- Integrative programme linking major EU and national initiatives – R&D, research infrastructures, registries
- Bridging to ERNs to help implementing research results and taking lessons learned from the clinic back to the bench

© Image Source :http://ec.europa.eu/research/health/pdf/rare-diseases-how-europe-meeting-challenges_en.pdf

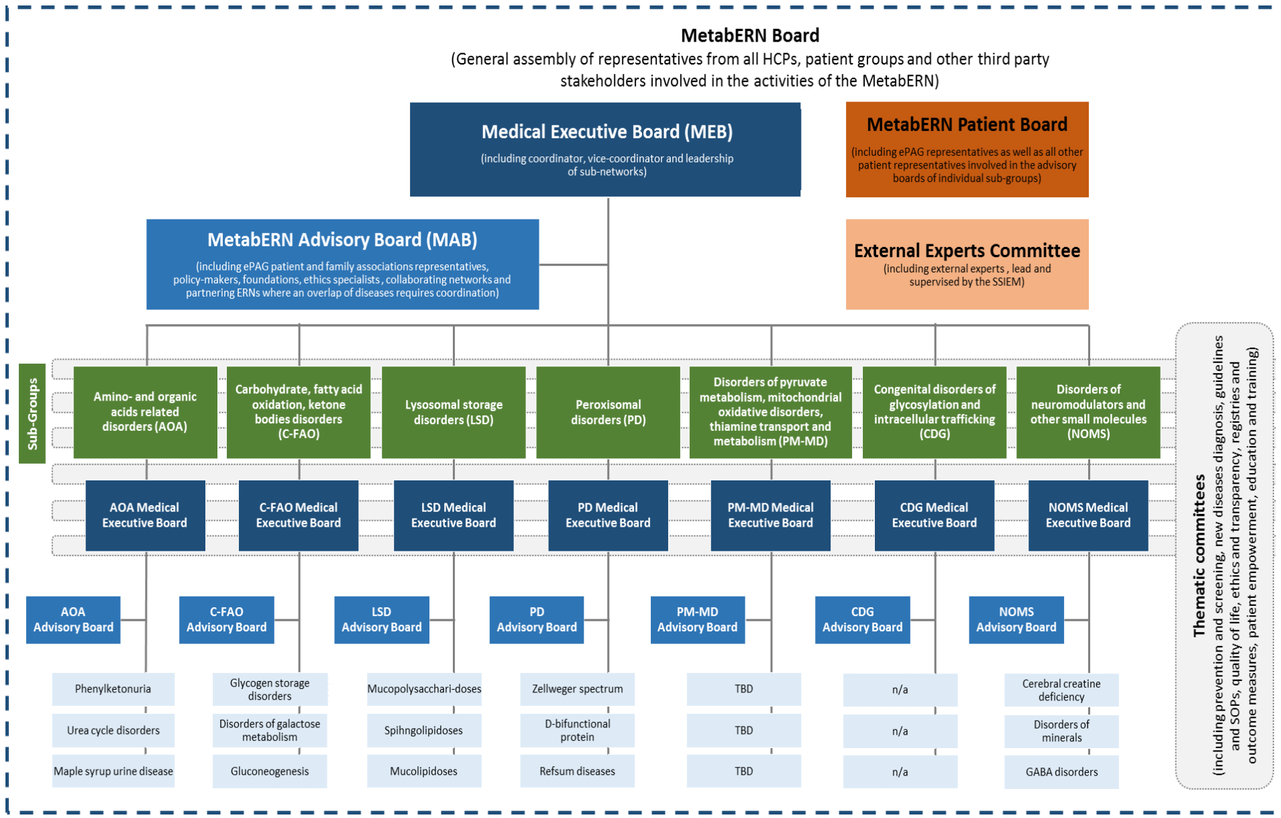
THE ERN CONCEPT



MetabERN MEMBERS

78 HCPs from 23 countries

94 HCPs from 27 countries with the inclusion of the new full Members in January 2022)
44 Patient Organizations
1475 IMDs to treat



Advertisements

MetabERN: How we share, how we care

- Increase **awareness** amongst general public and Health care professionals, health authorities and relevant stakeholders on inherited metabolic disease (IMDs)
- Dissemination of new and revision of existing health information, **scientific publications**

Prevention

- Facilitate and harmonise the **newborn screening** in EU
- Use of the Unified-IMD registry to study the **natural history** of asymptomatic and symptomatic state of diseases

Screening

- Enhance speedy **diagnosis** by promotion of diagnostic expert consultation (CPMS) and training sessions
- Improve access to the best diagnostics (biochemical/genetic) and to **genome-wide genetic investigations** through active collaboration with Orphanet and ERNDIM

Diagnosis

- Revise/develop of **Care pathways & Guidelines**
- Facilitate **Clinical Trials/Research** (defining research priorities and disseminating research-related information)
- **Create big databases with patients data**
- Improve the Regulatory process for medicines
- Participate in the production of White papers and Recommendations

Treatment & Facilitation of access to the best diagnostics

- Assess the effectiveness and efficiency of clinical processes
- Develop a common programme on **Transition from childhood to adulthood**

Follow up

- Participate in and provide input and insights from patients and HCPs in **Education of patients**
- **Instruct general practicioners** on how to follow patients
- Promote the MetabERN Education website (https://metab.ern-net.eu/) dedicated to **capacity-building, education & training.**

Education and Training needs

- Share the **'Quality of Life'** surveys and outcomes measurement
- Facilitate the provision of social care services

Social framework

- Continue collaboration with **other ERNs** through the ERN-Coordinators Platform (on a strategic level) and through on-going consultations with overlapping networks (at a practical level)

Inclusiveness

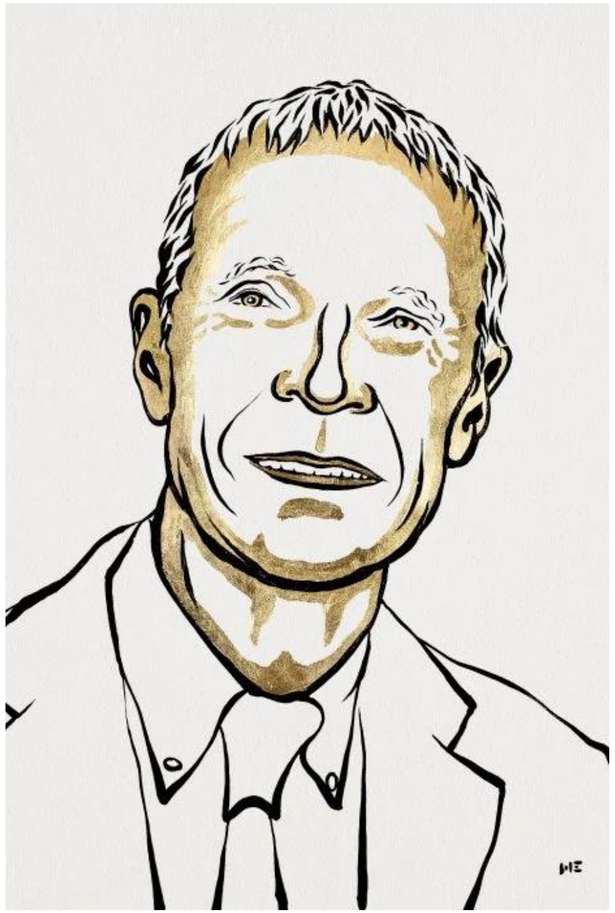
Patient Empowerment

Recent achievements to start the journey:

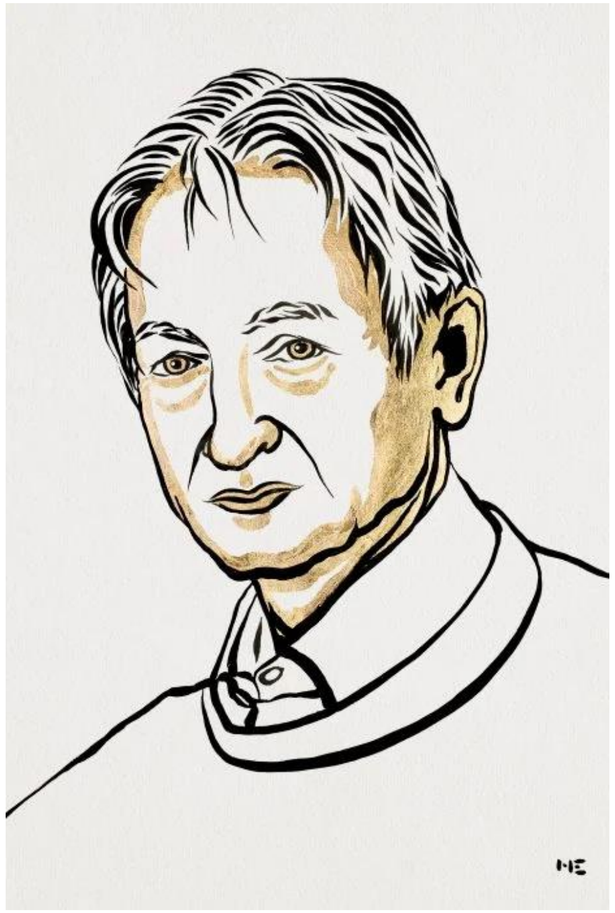
- A dedicated group on **patient empowerment** has been established
- The **Patient Board governance structure** is up and running including the Patient Executive Committee (PEC). The PEC is the voice of all patient representatives involved in the subnetworks and Work Packages in order to improve their involvement and enable their feedback to be heard by HCPs.
- Patients have been involved in addressing their **specific needs, preferences and priorities** (Survey, feedback systems, etc.)

ALL WITH ONE GOAL IN MIND: OUR PAT

THE NOBEL PRIZE IN PHYSICS 2024



John J. Hopfield

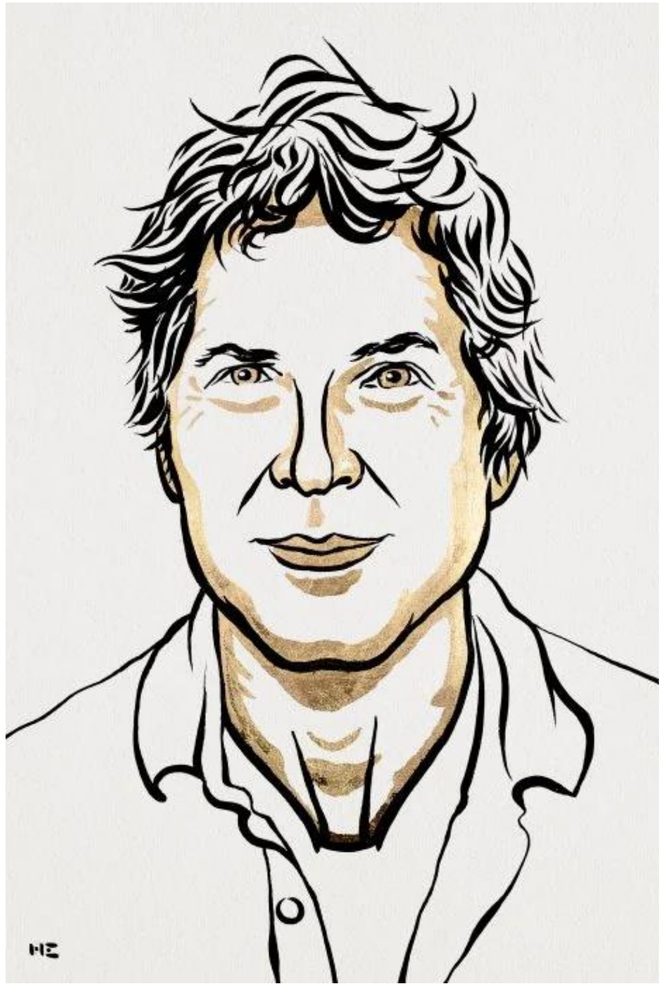


Geoffrey E. Hinton

"For foundational discoveries and inventions that enable machine learning with artificial neural networks"

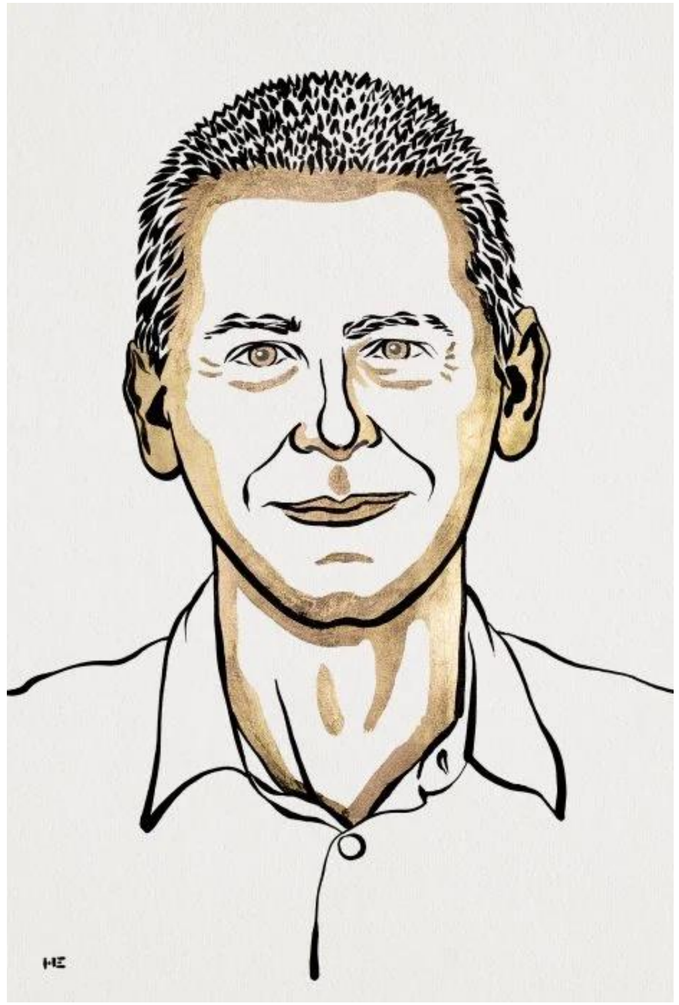
https://www.nobelprize.org/prizes/lists/all-nobel-prizes/

THE NOBEL PRIZE IN CHEMISTRY 2024



David Baker

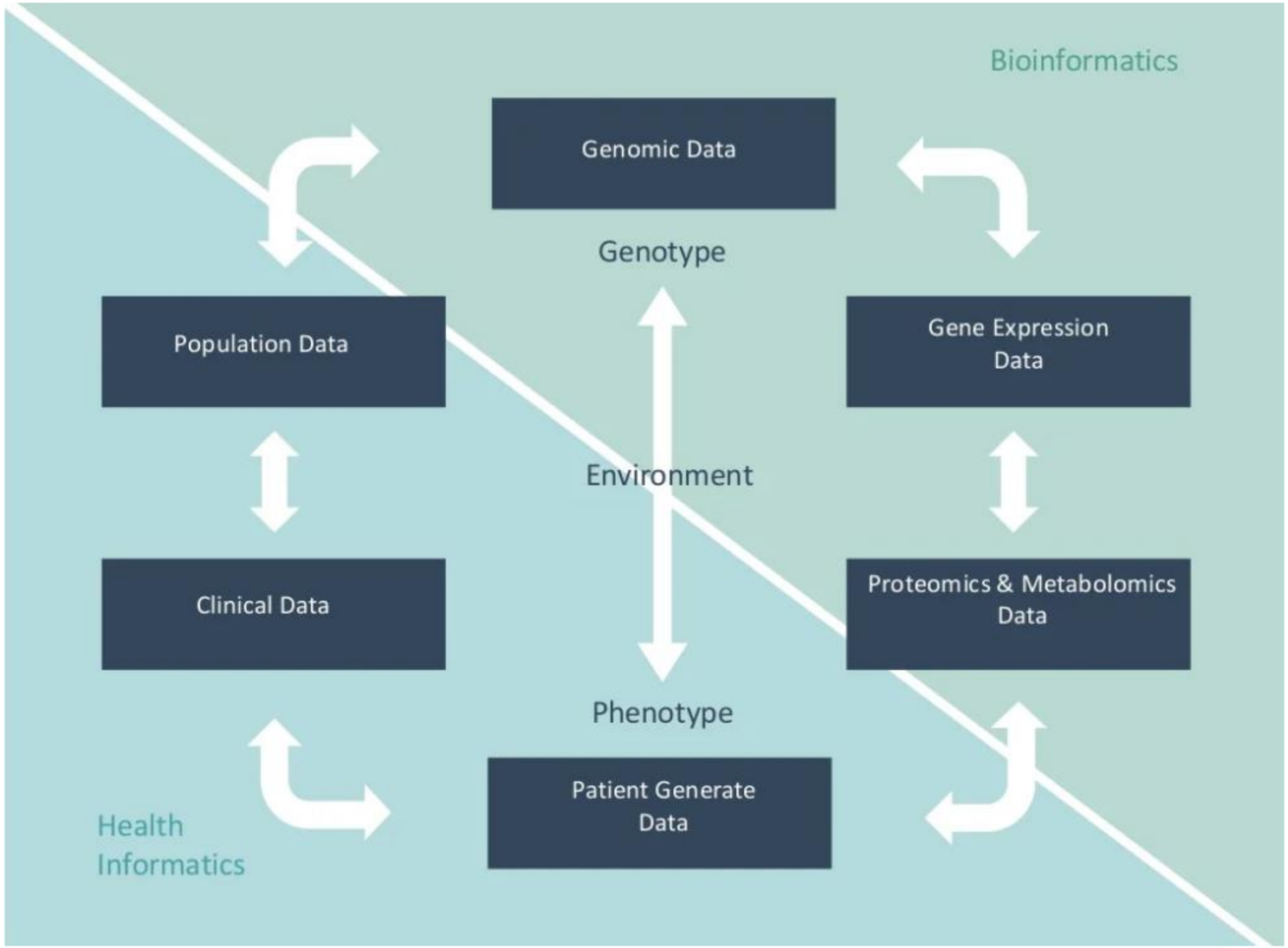
Demis Hassabis



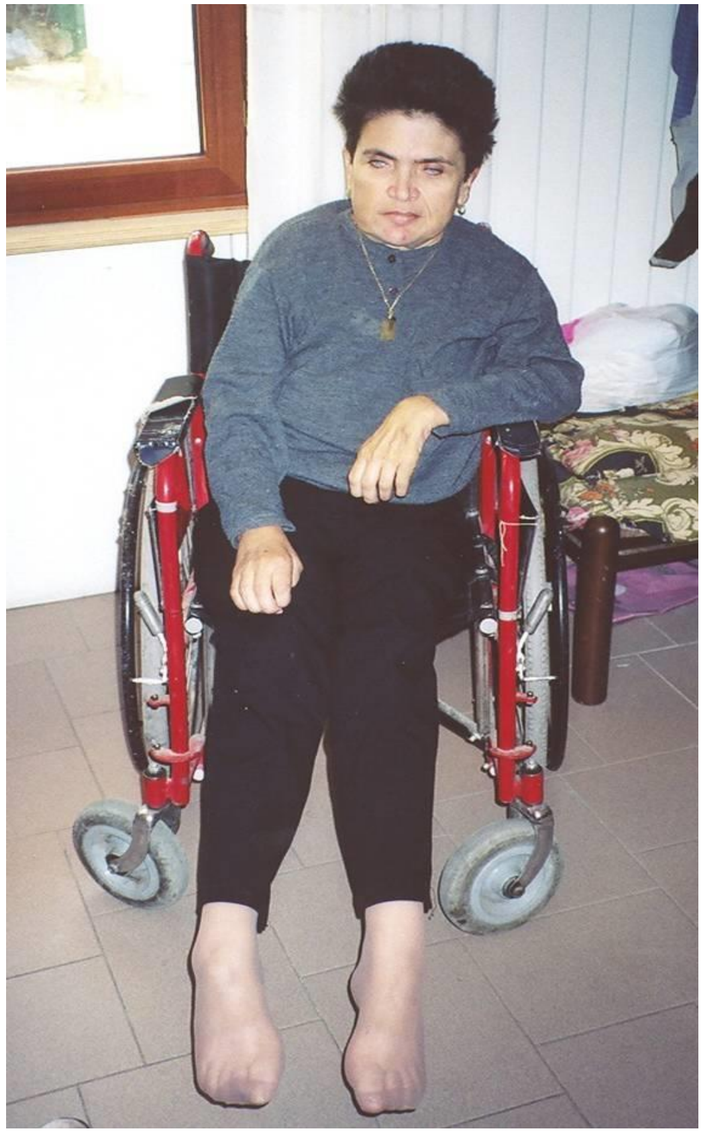
John M. Jumper

"for computational protein design"

"for protein structure prediction"



Adapted from https://doi.org/10.1038/s41525-021-00176-x



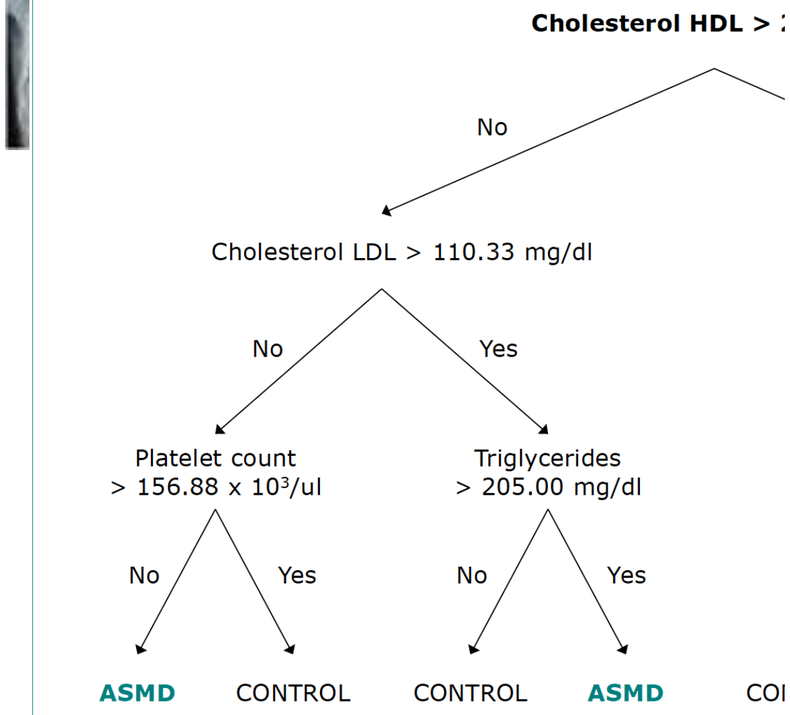
WHY DO WE STILL NEED AUGMENTED INTELLIGENCE?

With Permission

Courtesy G. Coppa

ASMD/Niemann Pick A-B

Figure 2: ASMD decision tree rules



ASMD, acid sphingomyelinase deficiency; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

CONCLUSIONS

- The ASMD decision tree highlighted 4 laboratory measurements (HDL cholesterol, LDL cholesterol, triglycerides, platelets) and 1 clinical manifestation (hydrocephalus) and provided cut off values for laboratory parameters.
- In the training cohorts, it distinguished ASMD vs. matched controls, with a sensitivity of ~78% and a specificity >99%.
- In the validation cohorts, both, the ASMD decision tree and the clinical algorithm, distinguished ASMD vs. controls with a sensitivity of 40% but the ASMD decision tree showed higher specificity (>99% vs 98.5%).
- The ASMD decision tree was also able to discriminate between ASMD and NPD-C and GD patients.
- Given the limited number of ASMD patients available in the validation cohort, further assessment in another independent EHR database is advisable.
- The proposed ML-based approach to develop a rare disease diagnostic algorithm is interpretable and potentially easy-to-use for screening of EHRs to flag potential patients.

M.Scarpa et al. Tailored diagnostic decision tree resulting from machine learning to improve early diagnosis of ASMD with ID **20672 SSIEM 2024** sponsored by SANOFI

USE OF GPT-4 TO DIAGNOSE COMPLEX CLINICAL CASES

•**Case Selection:** 38 complex clinical case challenges. Each case included a medical history and a poll with six diagnostic options.

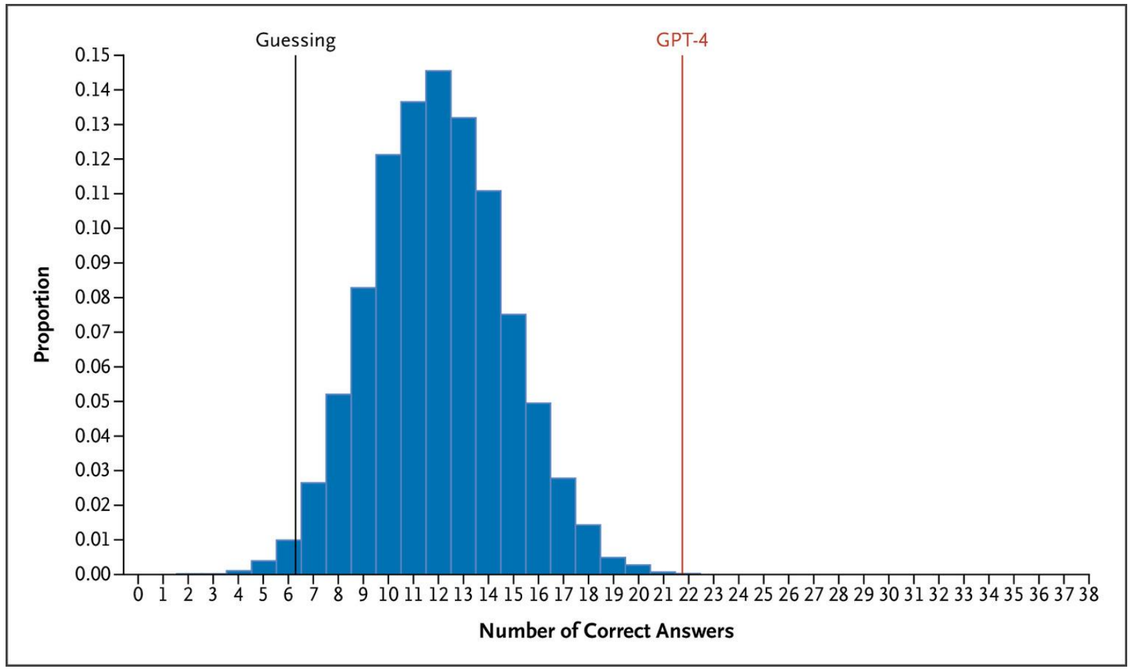
•**Human Reader Simulation:** Data from 248,614 answers by online medical-journal readers were used to simulate 10,000 sets of answers, creating a pseudopopulation for comparison.

Results

•**Case Demographics:** Cases covered various medical fields, with the majority in infectious diseases (39.5%). Patients ranged from newborns to 89 years old, with 37% being female.

•**GPT-4 Performance:**

- •GPT-4 correctly diagnosed 21.8 cases on average (57%).
- •The simulated medical-journal readers, averaged 13.7 correct diagnoses (36%).



Use of GPT-4 to Diagnose Complex Clinical Cases Alexander V. Eriksen, NEJIM AI **DOI: 10.1056/AIp2300031**

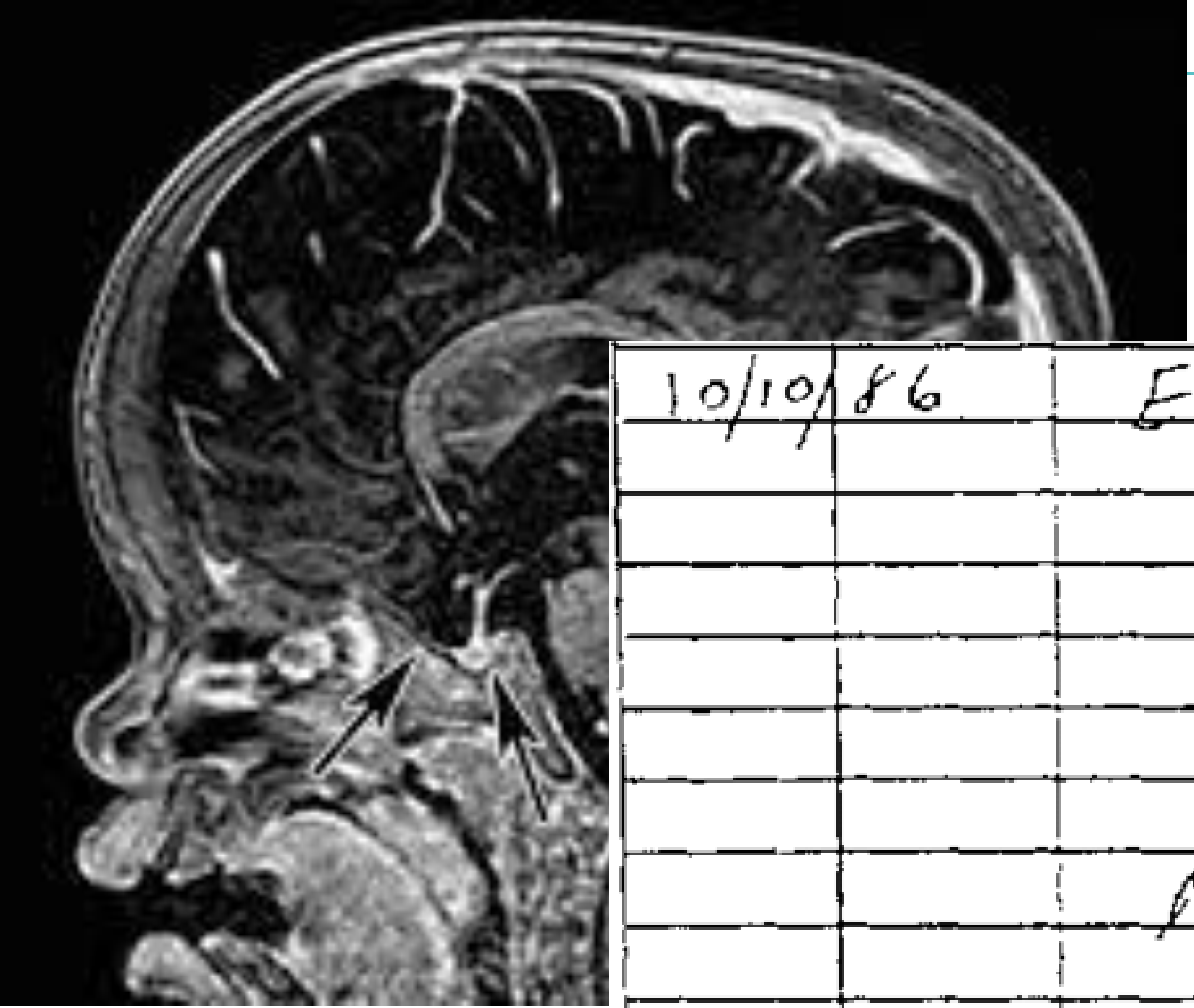
MARRVEL Ai

AI-MARRVEL (AIM) improved the rate of accurate genetic diagnosis, doubling the number of solved cases as compared with benchmarked methods, across three distinct real-world cohorts.

To better identify diagnosable cases from the unsolved pools accumulated over time, a confidence metric has been designed on which AIM achieved a **precision rate of 98% and identified 57% of diagnosable cases out of a collection of 871 cases.**

Furthermore, AIM's performance improved after being fine-tuned for targeted settings including recessive disorders and trio analysis. Finally, AIM demonstrated potential for novel disease gene discovery by correctly predicting two newly reported disease genes from the Undiagnosed Diseases Network.

AI-MARRVEL — A Knowledge-Driven AI System for Diagnosing Mendelian Disorders Dongxue Mao, NEJM AI 2024;1(5)



Blood test data	AUC	Optimal cut-off value	Univariate analysis				Multivariate analysis		
				Number of patients	30-day survival (%)	p	Odds ratio for 30-day mortality	95%CI	p
C-reactive protein	0.6752	5.4 mg/dL	≧5.4	385	29.4%	<0.0001	1.86	1.30 – 2.67	0.0007
			<5.4	376	55.5%		1		
Albumin	0.6275	2.8 g/dL	≧2.8	294	56.0%	<0.0001	1		0.0006
			<2.8	467	33.7%		1.9	1.31 – 2.76	
Total bilirubin	0.5909	1.3 mg/dL	≧1.3	151	23.8%	<0.0001	1.55	0.93 – 2.62	0.0953
			<1.3	610	46.8%		1		
Aspartate aminotransferase (AST)	0.5783	47 IU/L	≧47	218	47.3%	<0.0001			

SUMMARY

As a Clinical Data Analyst over 5 years of experienced in providing over view of data- base, contributing data management activities and tracking quality of data.

SKILLS

Process Improvement, Data Collection, Data Management Activities.

CE

yst

2011 – April 2016

nd communicated quality and utilization metrics for the hospital, partment chairs, and physician faculty to educate and align medical litor, and governmental guidelines.

ospitalists, specialists, and residents emphasizing action steps to bridge

orts to solve priority performance issues across silos.

ships with clinicians, care management, administrators, and vendor ccess.

takeaways, benchmarking Case Mix Index, Length of Stay, ty, Costs, and Denials.

gement project activities according to Training Manuals and SOPs.

team meetings and partnered with the Clinical Research Associates to bject data and other project-related issues.

yst

2011

ansion of duties listed below at Pfizer Inc., GR&D

10/10/86 | ENT:

Pt c Aspergillosis by path

Tolerating Amphotericin B well

except for nausea c [illegible]

C: 1.7

Pt c retro headache c visual

blurring c [illegible]

PE: [illegible] PERRLA

HEENT: TM's clear & mobile

Nose: ⊖ lesions

⊖ bleed

HP/NP: ⊖ ⊖ slight frontal sinus tenderness

LX – clear TVC mobile

Will [illegible] scan, neurology

[illegible]

[illegible]

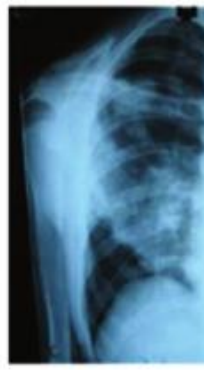
Imp: stable

Plan: – continue Amphotericin B

– plan as per

LE RADIOLOGY CONSULTING

entification



Card Number: 2435/98
Age: 45
Sex: Male
Maritial Status: Married
Occupation: Merchant
Address: Yirgalem

tient Clinical History

cough,fever and night sweating of 02 months. Hx of signific

eatment (if given)

antibiotics and analgesic.

levant Lab.Information

ESR 100mm/hr
Bc 7500
50%
40%
=05%
05%

evious related imaging findings

no

nsulting Physician Impression

Pulmonary TB R/O Bronchogenic Carcinoma

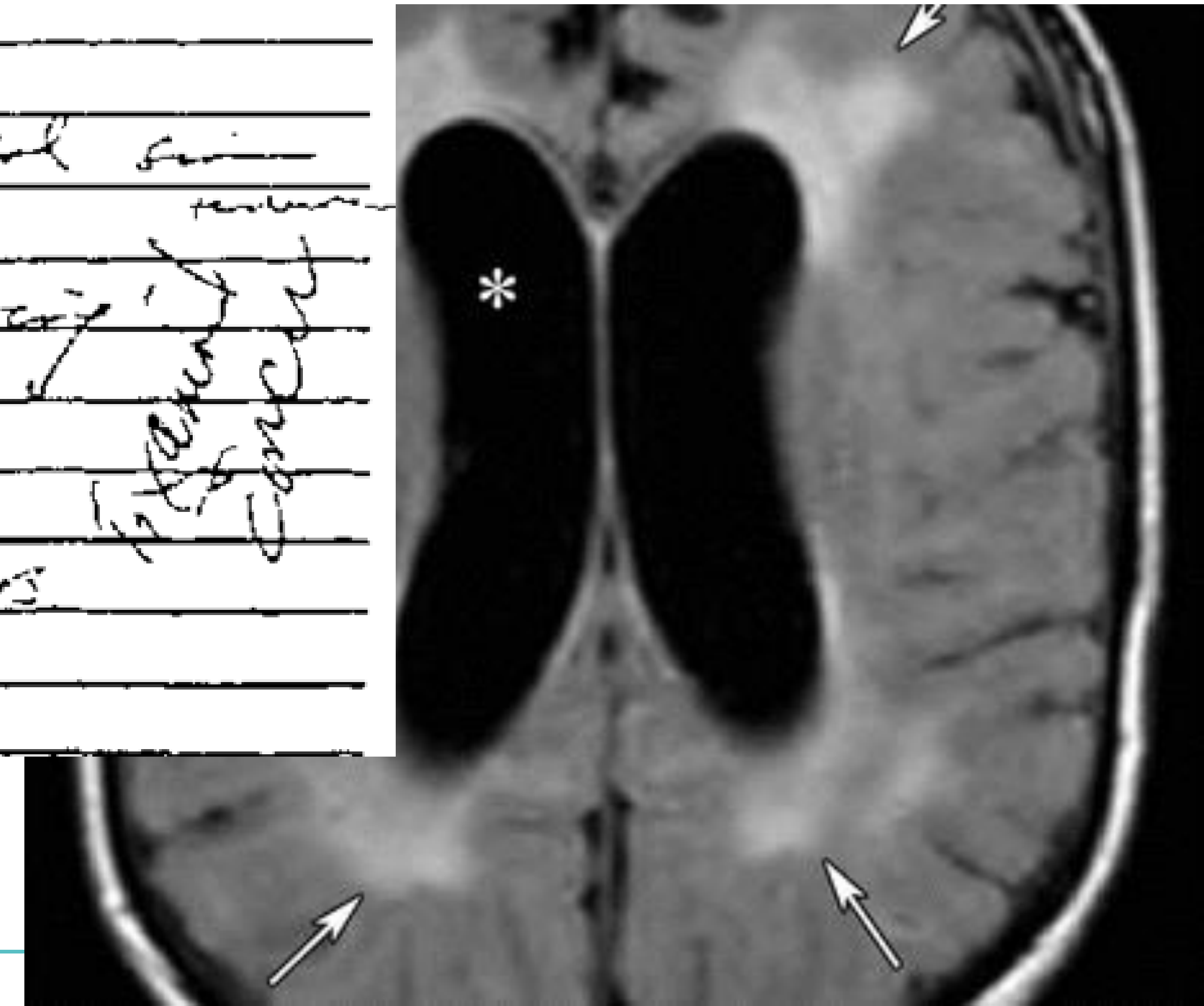
ffering Physician:Dr Zelalem Assefa

te of Consultation :09/03/06

Fasting insulin (μU/mL)	11.8±8.7	10.7±6.5	−1.1	0.248
HbA1c (%)	5.7±0.8	5.7±0.6	0.0	0.006*

Notes: Values are presented as mean ± SD. Wilcoxon signed-rank test was use for analysis. *$P<0.05$.

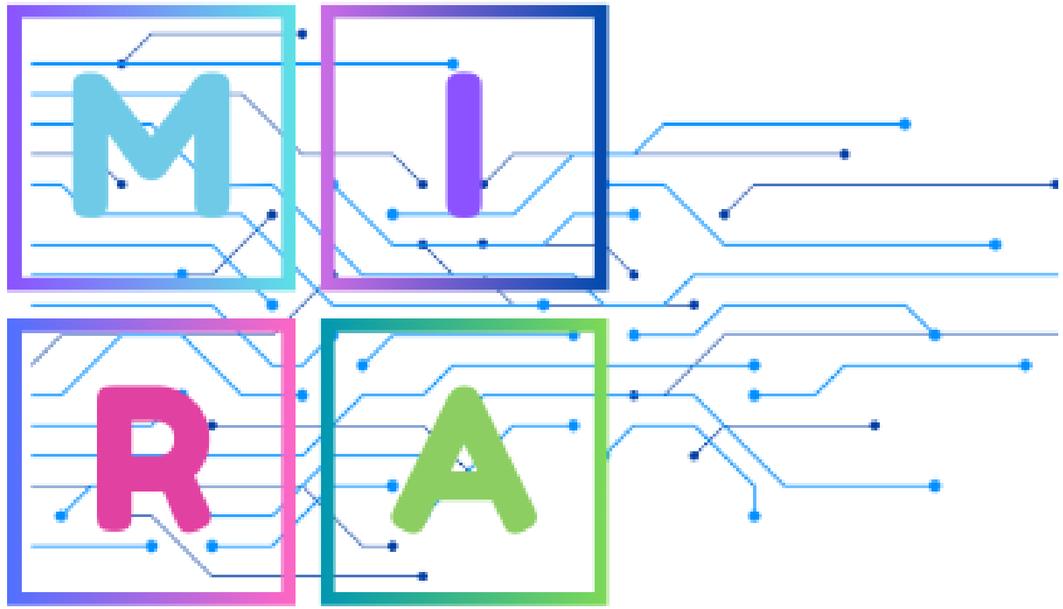
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase alanin



COORDINAMENTO REGIONALE
MALATTIE RARE FVG

ASU FC
Azienda sanitaria universitaria Friuli Centrale
REGIONE AUTONOMA FRIULI VENEZIA GIULIA

UNIVERSITÀ DEGLI STUDI DI UDINE
hic sunt futura



SISSA
ma per seguir virtute e canoscenza

AREA SCIENCE PARK

1. Shorten the path to RD diagnosis by applying advanced digital technologies that allow suspicion/identification of RD from the analysis of textual reports and images

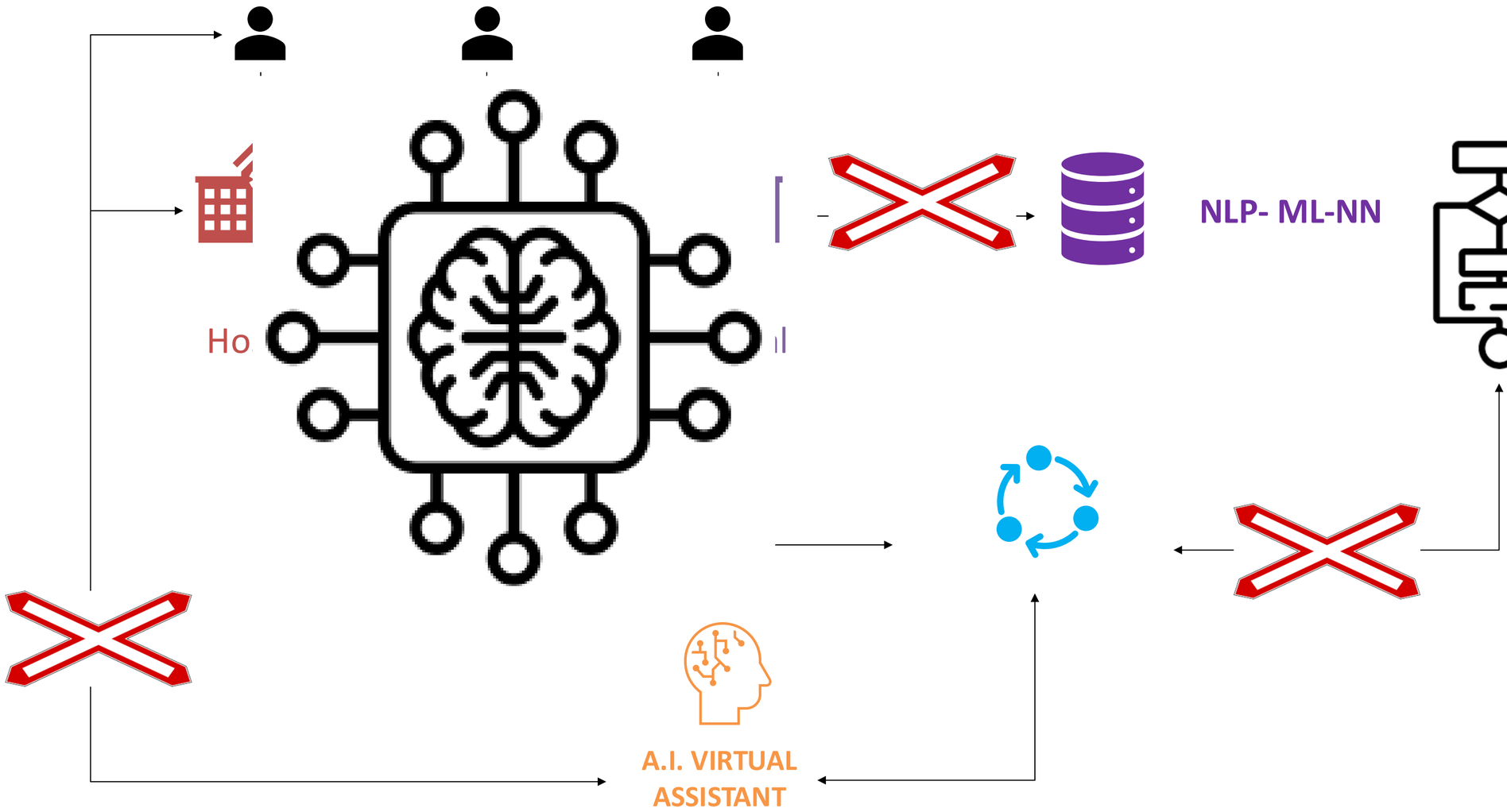
2. Develop a standard format for data extraction: Define a standardized data export format and technical implementation plan based on an analysis of the current state of electronic health records (EHRs) in the Friuli Venezia Giulia (FVG) Region.

3. Create a digital ecosystem for data management: Develop an advanced data management platform that allows secure data ingestion, integration, curation, sharing, and analysis, following the FAIR principles (Findable, Accessible, Interoperable, Reusable).

4. Apply natural language processing (NLP) techniques: Use supervised and unsupervised NLP approaches to automatically extract information from textual clinical reports and encode it in standard terminologies.

5. Integrate the computational ecosystem with a new high-performance computing center in Udine: Replicate and integrate the data management platform with the new supercomputing infrastructure being developed.

6- Ensuring the protection and privacy of health data used in the project through anonymization and cybersecurity solutions.



ASU FC
Azienda sanitaria universitaria Friuli Centrale
REGIONE AUTONOMA FRIULI VENEZIA GIULIA

UNIVERSITÀ DEGLI STUDI DI UDINE
hic sunt futura

ma per seguir virtute e canoscenza
SISSA

AREA SCIENCE PARK

- Structured data in hospital database.
- Common elements for data.
- Sharing of EHR between hospitals or other databases through an interoperability platform.

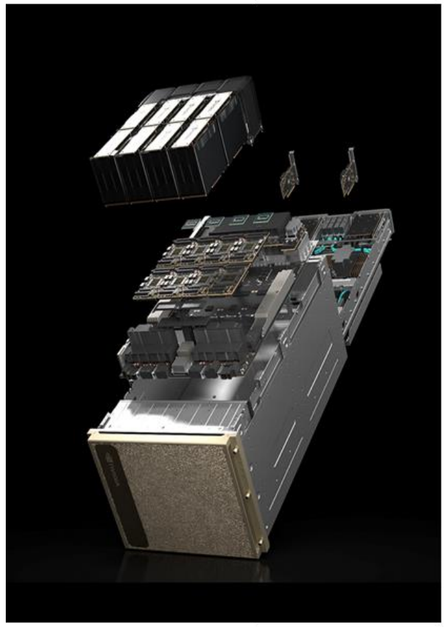
- Automatic input of data in registry.
- Structured data in registry database.
- Sharing of EHR between registries through an interoperablity platform.
- A.I. Analysis.

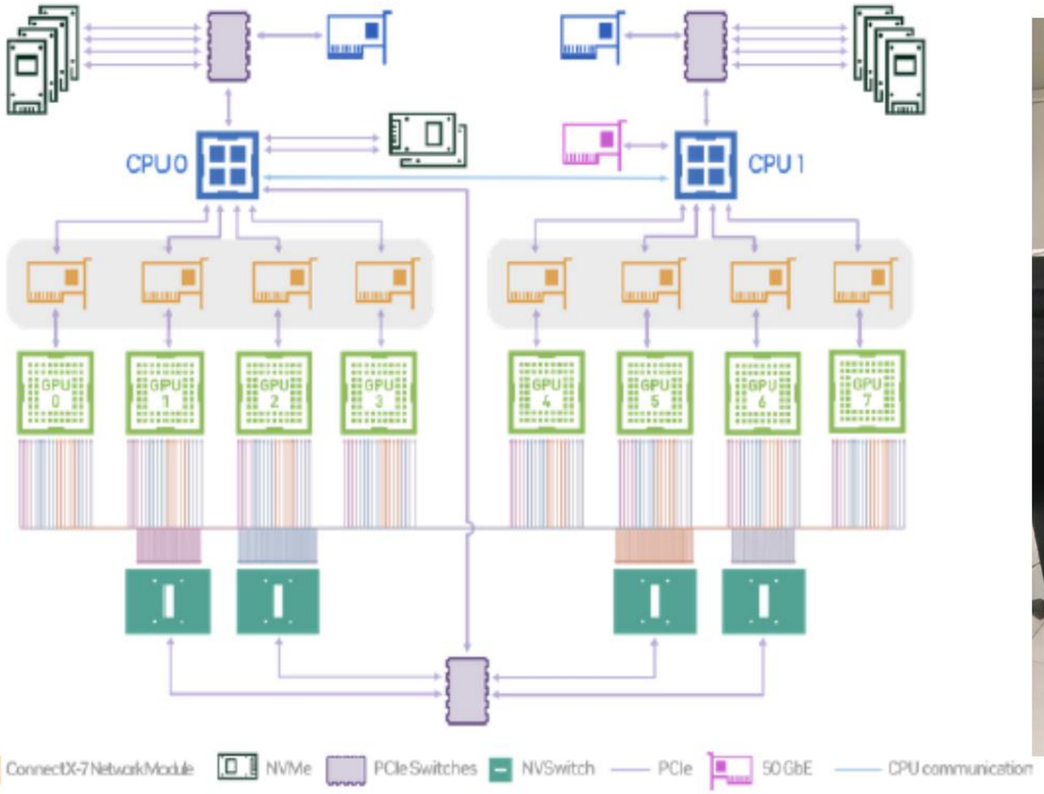
MIRA

ASU FC
Azienda sanitaria universitaria Friuli Centrale

REGIONE AUTONOMA FRIULI VENEZIA GIULIA

UNIVERSITÀ DEGLI STUDI DI UDINE
hic sunt futura

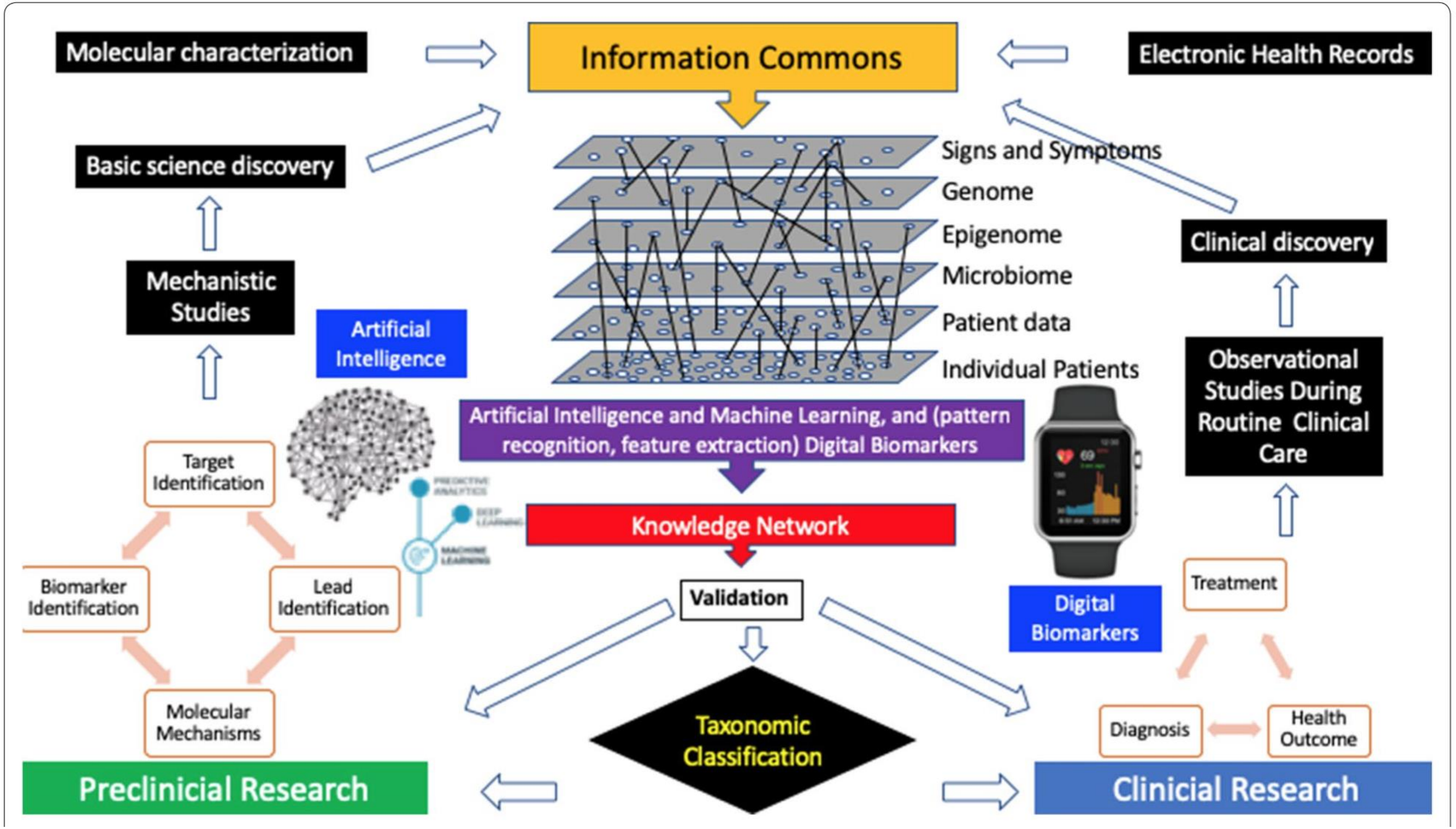




8 GPU NVIDIA H100 with 640 Gigabyte of total GPU memory

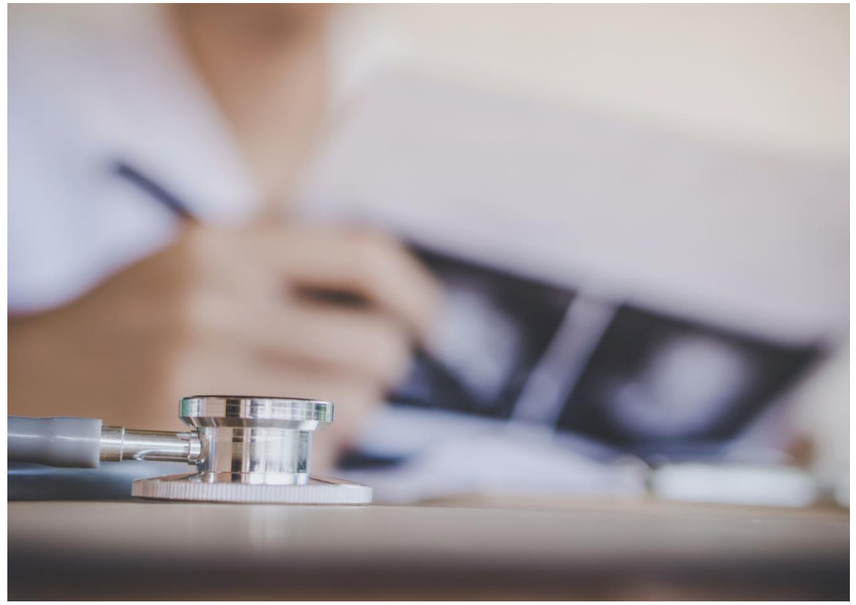
Dual Intel Xeon Platinum 8480C processors, 112 cores, and 2 TB System Memory

Speaker's personal experience



Seyhan and Carini *J Transl Med (2019) 17:114*

TELEMEDICINE AS A TOOL FOR THE MANAGEMENT OF THE RD PATIENTS



Doctors and patient communicate via smartphone

- Digital technology is increasingly entering doctor-patient communication:
- Physicians use email
  - 80% of specialists
  - 85% of general practitioners
- Physiscians use WhatsApp
- 57% of specialists
- 64% of general practitioners.

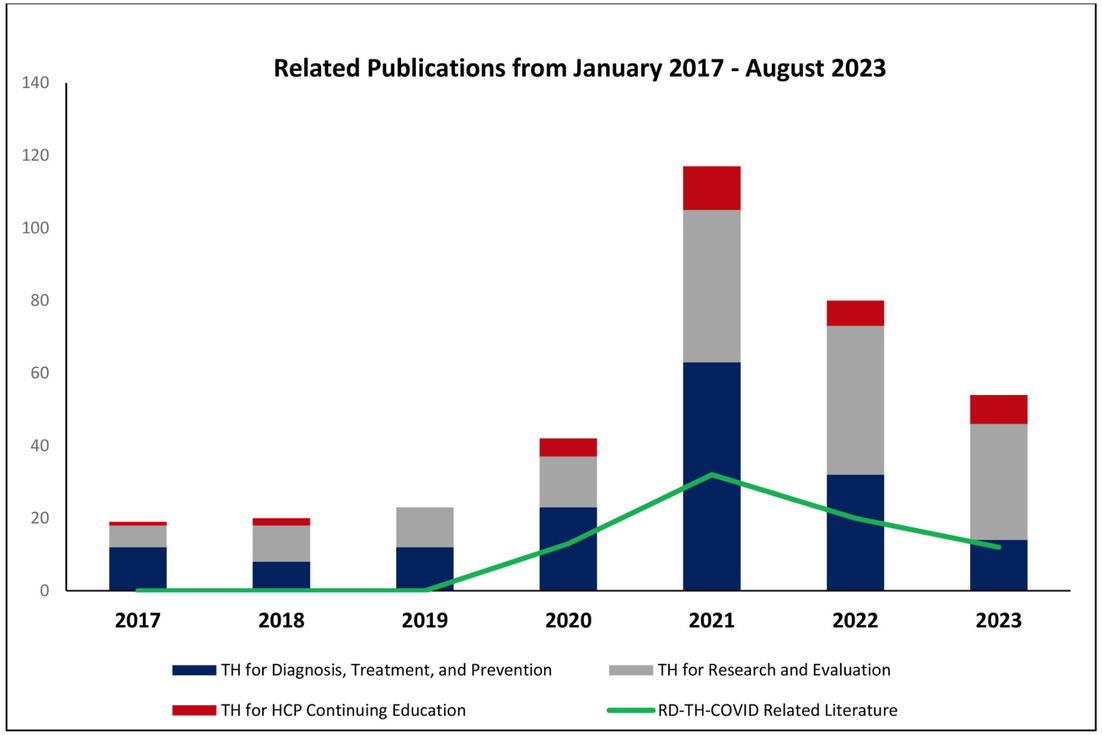
Health research on the internet:

- 38% seek information on diseases, symptoms, and treatments;
- 37% look for information on proper lifestyles and nutrition;
- 29% search for information on medications and therapies;
- 15% look for information on vaccinations online (1 in 4 women).

IRDiRC: International Rare Diseases Research Consortium; RD: Rare Disease; TH: Telehealth

https://medicoepaziente.it/2019/sanita-digitale-in-italia-medici-e-pazienti-sempre-piu-connessi/

TELEHEALTH FOR RARE DISEASE CARE, RESEARCH, AND EDUCATION ACROSS THE GLOBE



- The IRDiRC Telehealth (TH) Task Force explored the use of TH for improving diagnosis, care, research, and education for rare diseases (RDs). The Task Force reviewed related literature published from January 2017 to August 2023.
- One of the major benefits of TH for RDs lies in its capacity to surmount geographical barriers, which helps in overcoming the constraints posed by limited numbers and geographical dispersion of specialists. This was evident during the pandemic.
- TH, through which clinical research can be decentralized, can also facilitate and enhance RD research by decreasing burden, expanding access, and enhancing efficiency.
- This will be especially beneficial when coupled with the adoption of digital health technologies, such as mobile health (mHealth) and wearable devices for remote monitoring (i.e., surveillance of outpatient data transmitted through devices), along with big data solutions.
- TH has also been shown to be an effective means for RD education and peer mentoring, enabling local health care providers (HCPs) to care for RD patients, which indirectly ensures that RD patients get the expertise and multidisciplinary care they need.

Chen FH *et al.* Eur J Med Genet. 2024 Oct 5;72:104977.

COORDINAMENTO REGIONALE
MALATTIE RARE FVG

CONCLUSION

- Humanization within the rare diseases landscape goes beyond simplistic notions of empathy; it entails a systematic reorientation of clinical practices, policies and patients interactions.
- Humanization goes toward a model of care that fundamentally acknowledges the individuality of patients and caregivers.
- By recognizing and integrating the diverse dimensions of the patient experience ranging from clinical symptoms to emotional and social implication, stakeholders can enhance the quality of care and promote better health outcomes in the rare disease community.
- Humanization is centered at the answer to the patients´s unmet needs: early diagnoses, better management and access to therapies are mandatory.
- New technolgies also based on artificial intelligence will be instrumental to optimize a humanized and personalize care of the patients.