CoMPaSS-NMD

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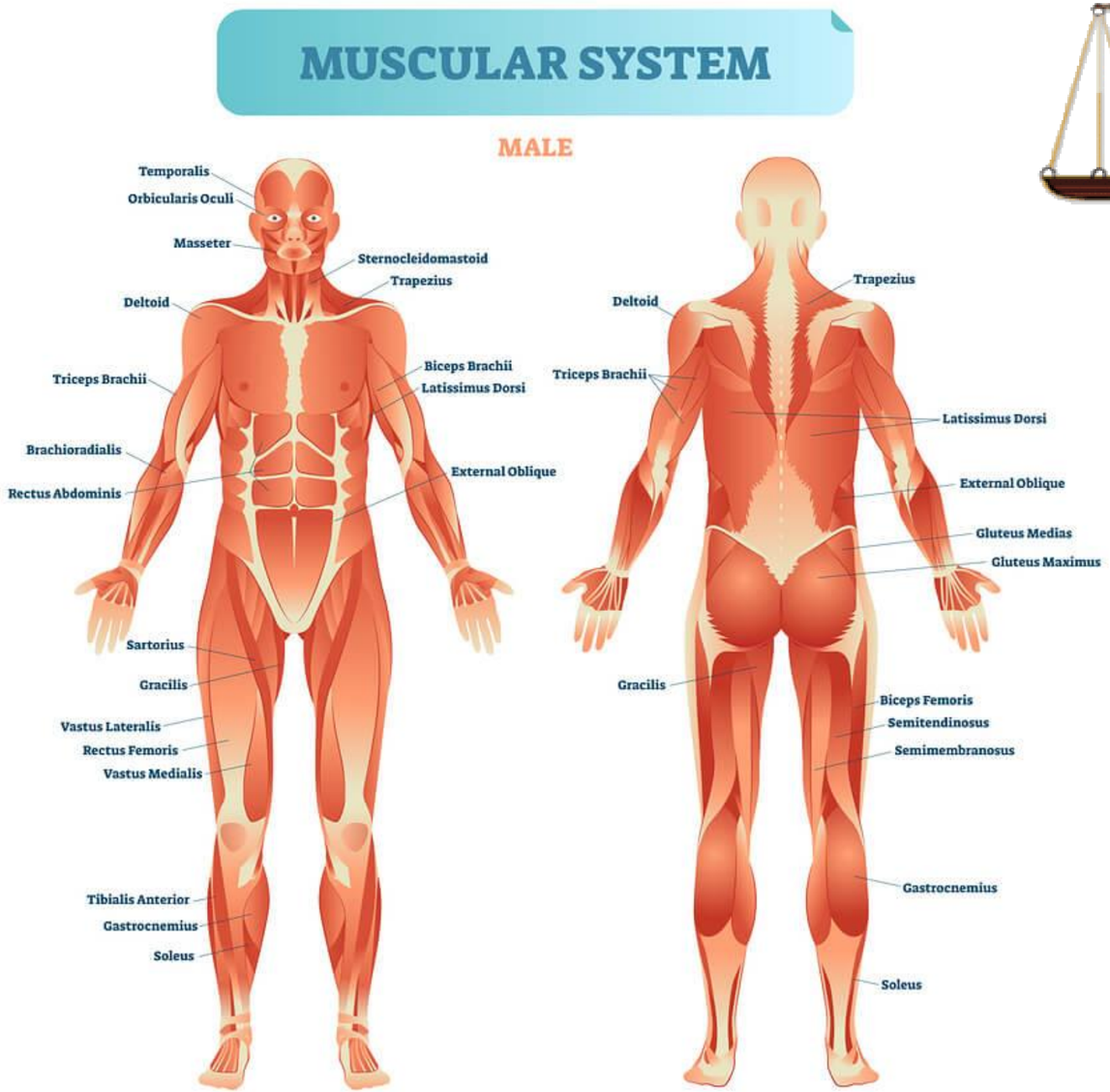
YITP in Computational Models for new Patients Stratification Strategies of Neuromuscular Disorders:

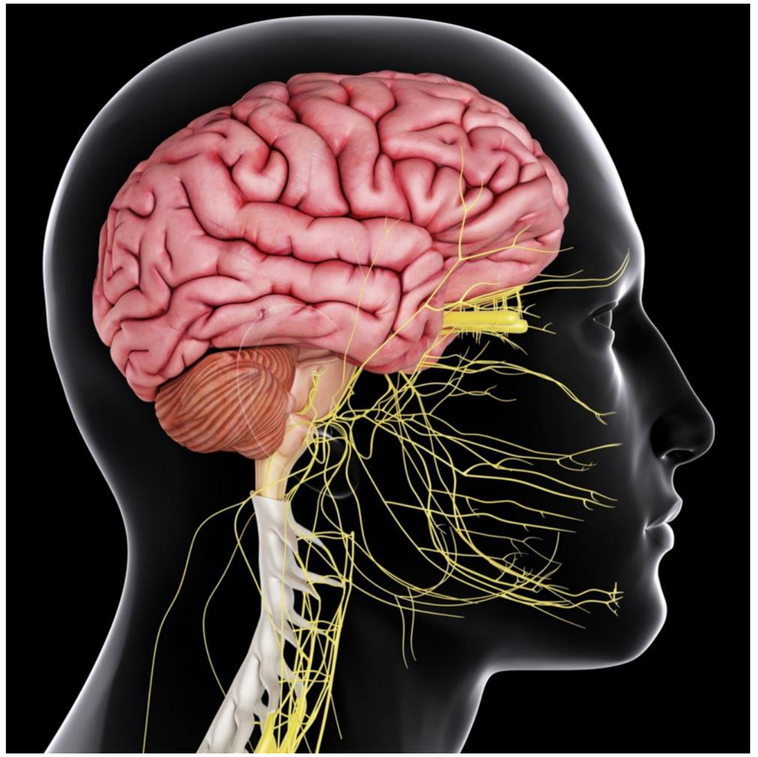
The What and Why

Filippo M. Santorelli – IRCCS Fondazione Stella Maris

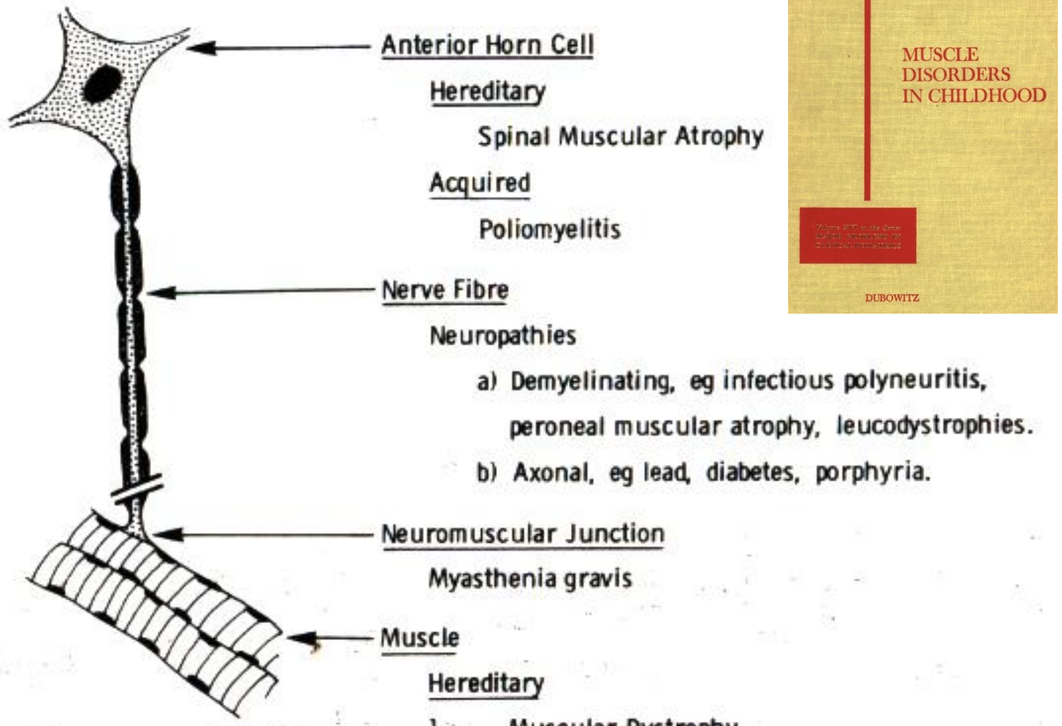
CoMPASS-NMD

Q1. What is more complex?





Human nervous system



Anterior Horn Cell

Hereditary

Spinal Muscular Atrophy

Acquired

Poliomyelitis

Nerve Fibre

Neuropathies

a) Demyelinating, eg infectious polyneuritis, peroneal muscular atrophy, leucodystrophies.

b) Axonal, eg lead, diabetes, porphyria.

Neuromuscular Junction

Myasthenia gravis

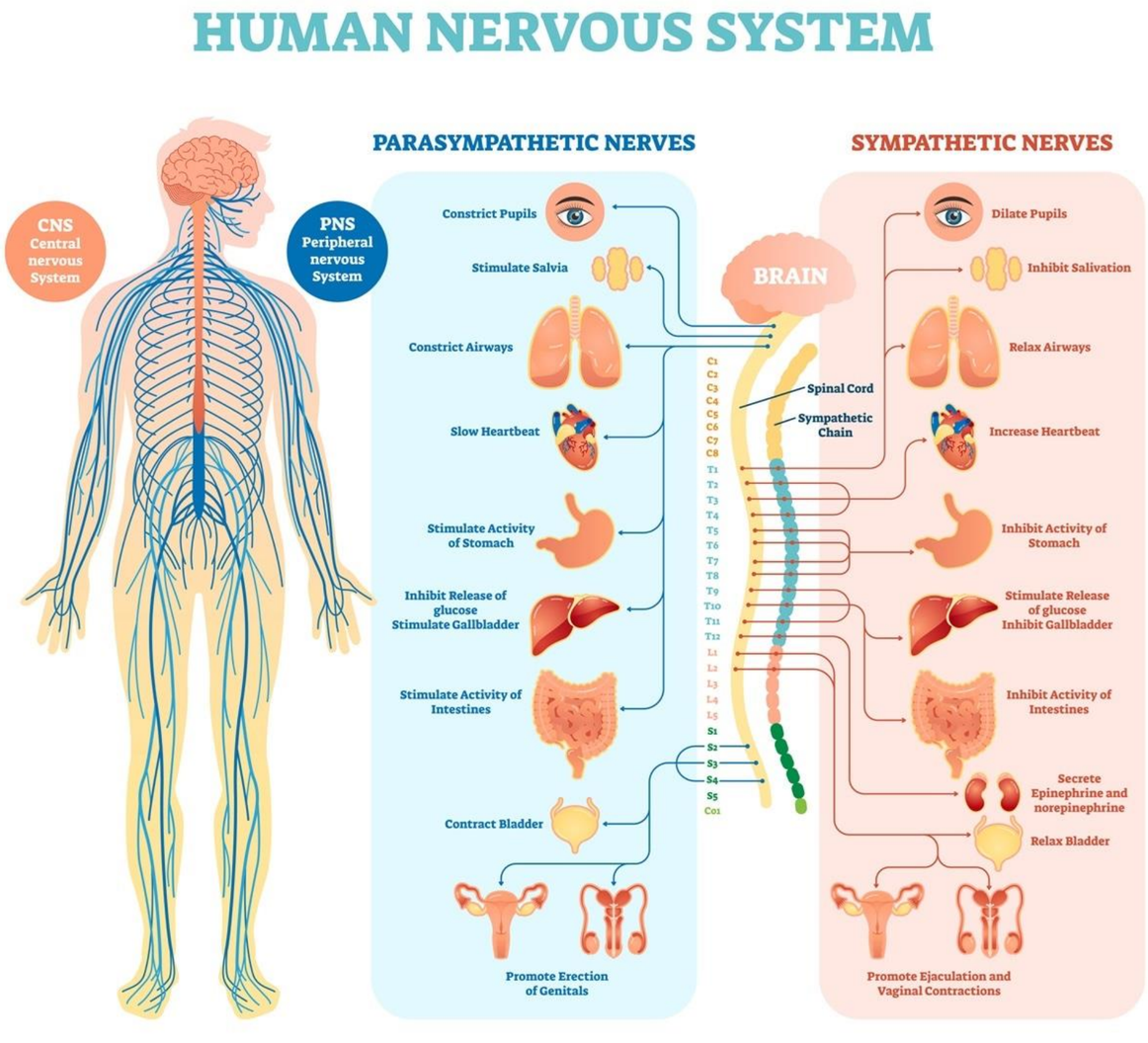
Muscle

Hereditary

1. Muscular Dystrophy
2. Dystrophia Myotonica
3. Congenital Myopathies
4. Metabolic Myopathies, eg Glycogenoses types II and V, malignant hyperpyrexia.

Acquired

1. Dermatomyositis / Polymyositis
2. Endocrine myopathies, eg thyrotoxic
3. Iatrogenic, eg steroid myopathy



The YIT initiative AGENDA

25 June 2024	**YIT Introductory part** – CoMPass-NMD: filling the gaps in inherited muscle disorders
15 July 2024	**YIT 1 (part 1)** – Electronic Structured Clinical Report Form (eSCRF)
26 August 2024	**YIT 1 (part 2)** – Electronic Structured Clinical Report Form (eSCRF)
Spring 2025	**YIT 2** – Electronic Genetic data Clinical Report Form (eGCRF)
Summer 2025	**YIT 3** – Electronic Histological data Clinical Report Form (eHCRF)
Autumn 2025	**YIT 4** – Electronic Magnetic Resonance Imaging data Clinical Report Form (eMRICRF)
Spring 2026	**YIT 5** – The CoMPaSS-NMD ATLAS

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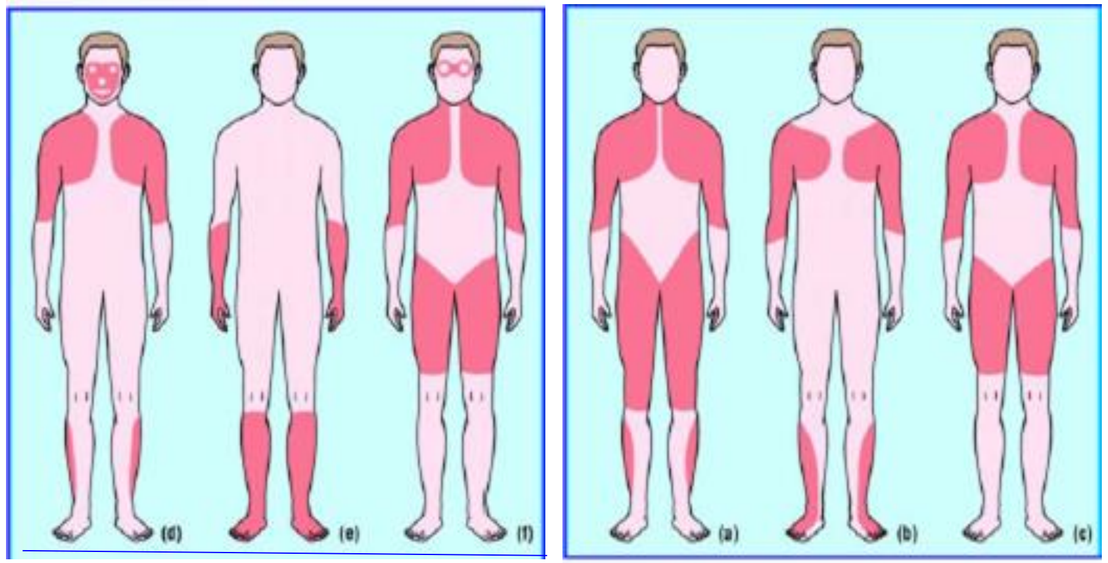
YIT Introductory part - CoMPaSS-NMD: filling the gaps in inherited muscle disorders

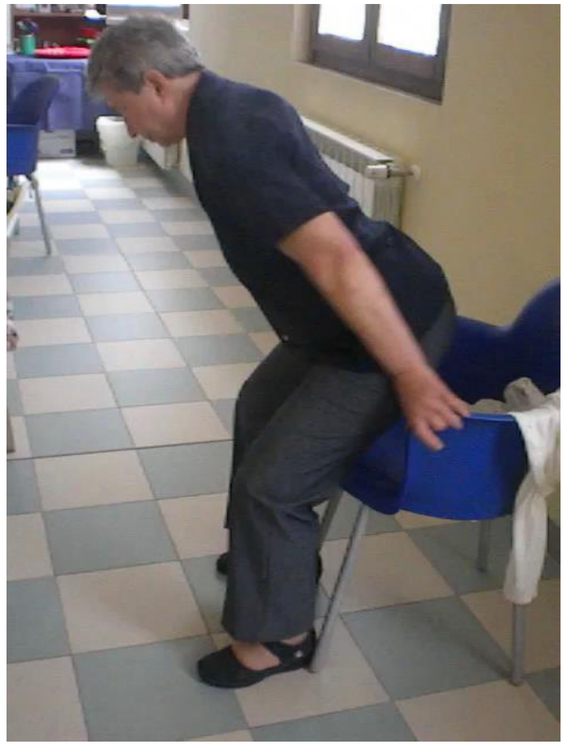
Rossella Tupler – University of Modena and Reggio Emilia
Coordinator of the CoMPaSS-NMD EU project

What are hereditary myopathies?

- Hereditary myopathies are progressive disabling disorders caused by genetic defects
- Various degree of muscle impairment
- Different progression

- The estimated prevalence of hereditary myopathies is 67.7 in 100.000, 302.507 in Europe





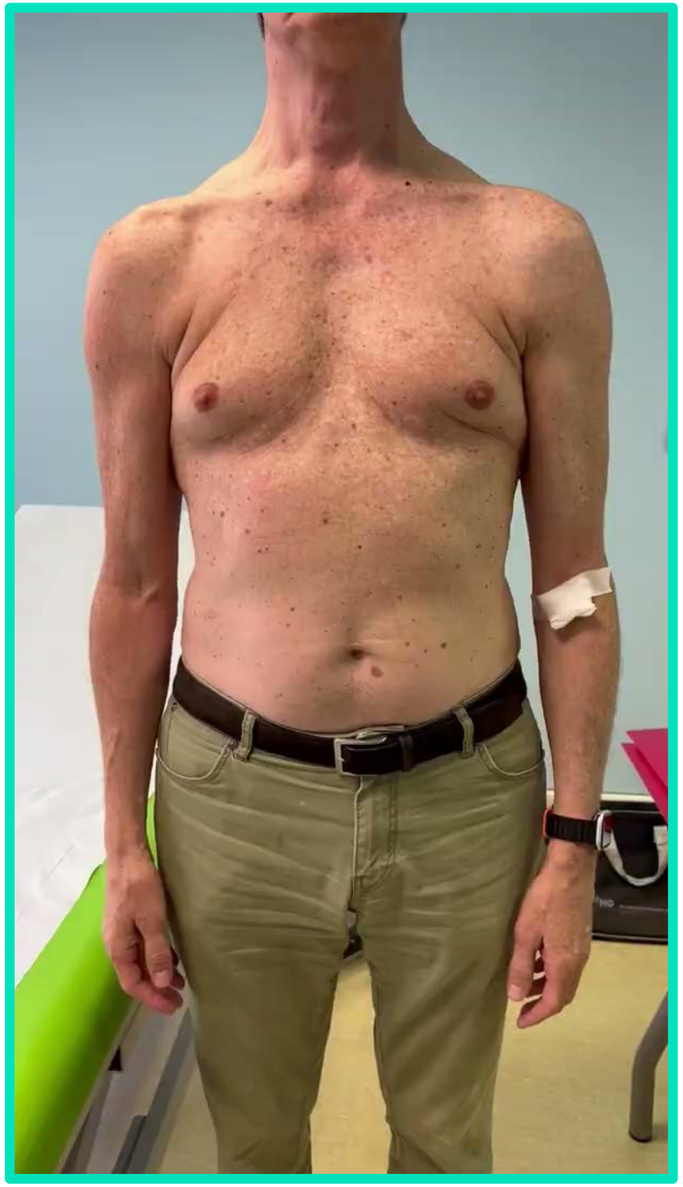
The problem

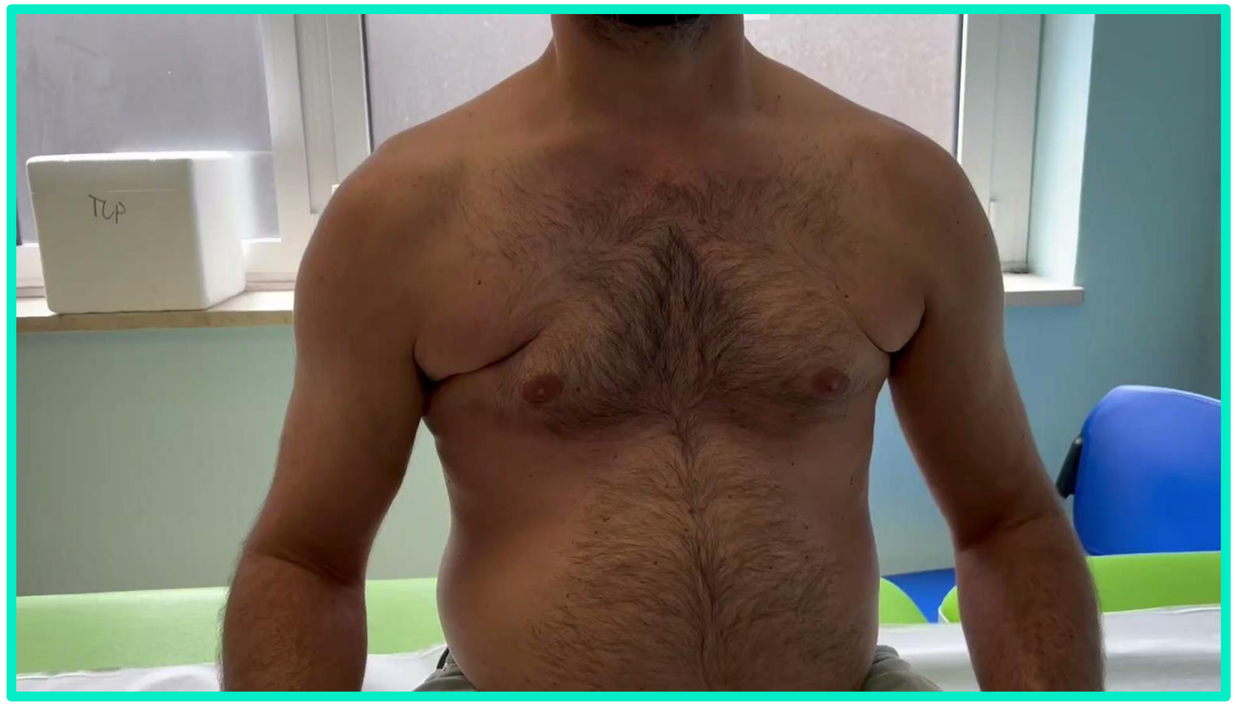
- Diagnosis of hereditary myopathies is not simple: 60% remains undiagnosed

The follow-up of myopathic patients is challenging and prognosis remains uncertain

CoMPASS-NMD

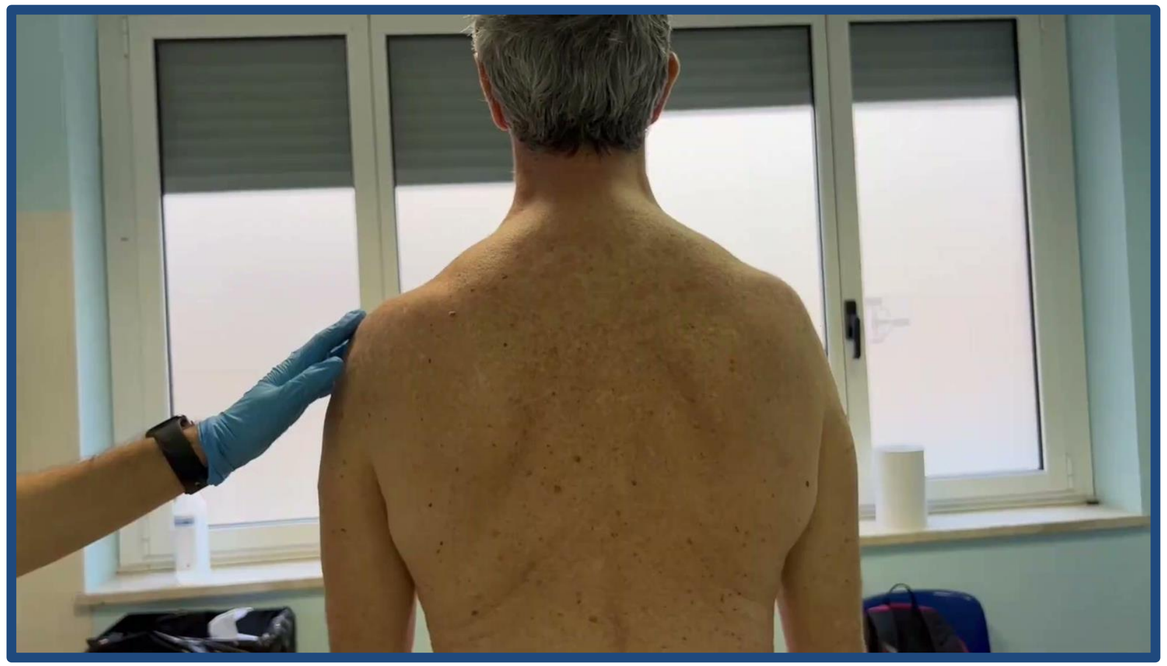
Spot the difference

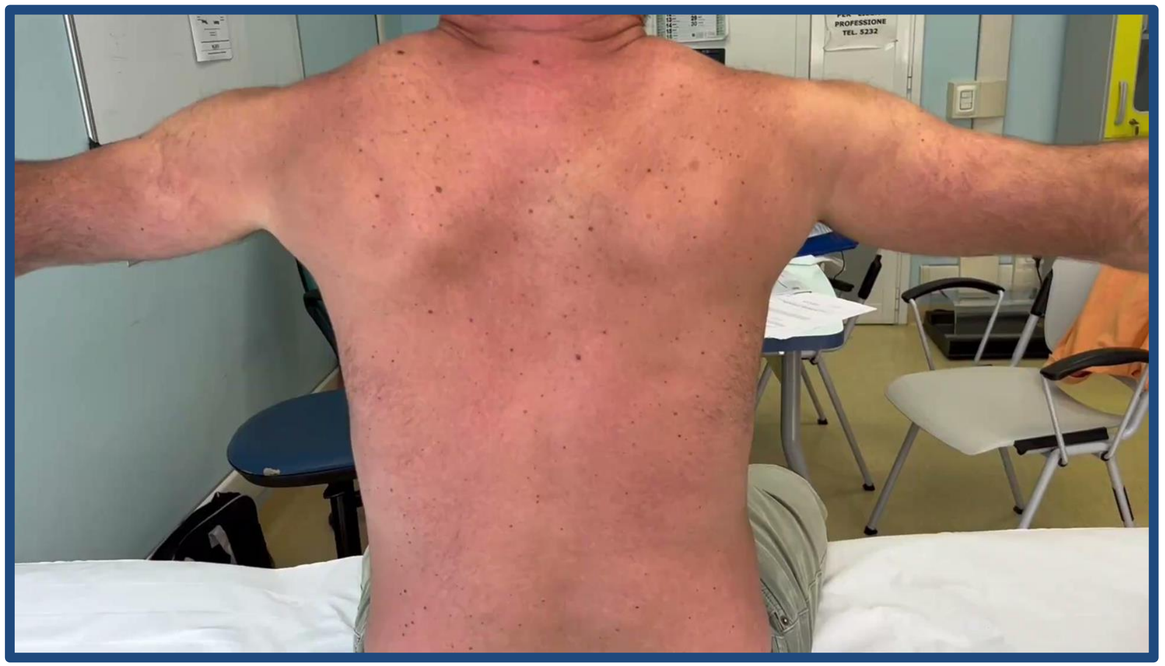




CoMPASS-NMD

Spot the difference





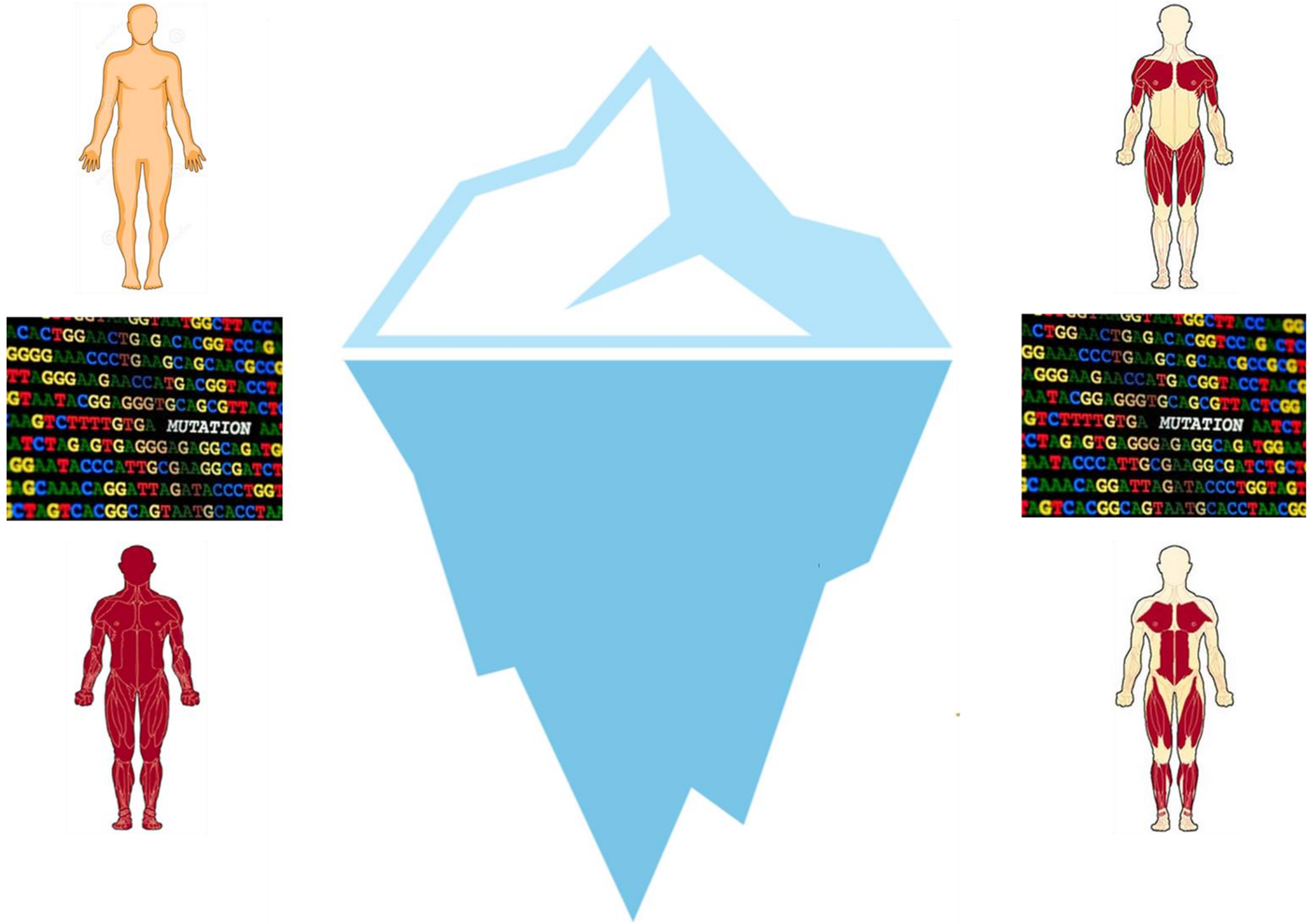
The problem, the challenge, the solution

The problem
Several efforts have been made to improve diagnosis of hereditary myopathies but still **60% remain undiagnosed with high costs for what it is called the ”diagnostic odyssey”**

The challenge is the **precise stratification of patients** to be used in clinical practice and therapeutic trials

A possible solution: CoMPaSS-NMD

Development of **innovative AI-based tools** to identify distinctive patterns from patients’ standardized clinical description, and associated genetic, imaging, histological data.



CoMPaSS-NMD

The CoMPaSS-NMD Project:
Computational Models for new Patients Stratification Strategies of Neuromuscular Disorders

- targets **Hereditary Neuromuscular Diseases** (HNMDs)
- aims at creating **AI-based systems for grouping patients** on the basis of 4 types of data as a new *precision diagnostic tool* for HNMDs' patients
- will validate these methods on a cohort of patients who will be **evaluated in depth** by acquiring data with standardized methods
- **CoMPaSS-NMD** involves third level clinical centers in France (CERBM), Germany (LMUM), Finland (SFF), United Kingdom (UNEW), and Italy (UNIMORE and FSM) as well as a Department of Data Science and Engineering (SUT) in Poland, a biotech company (CEGAT) in Germany, an expert on GDP sited in Spain (TEC), an ICT provider in Switzerland (FINC) and a communication partner (DBL) in Italy.

CoMPASS-NMD

Goals

1 **Generate** a collection of robust and reliable data to develop computational tools based on validated data

2 **Create solutions that integrate different clinical data** for classifying patients with similar clinical characteristics to support clinicians, the scientific community, and HNMD patients

3 **Develop evidence-based guidelines** to improve the management of HNMD patients above the standards of care currently supported by healthcare providers

4 **Create a public platform** for collecting data from HNMD patients, the **NMD-Atlas**

Datasets

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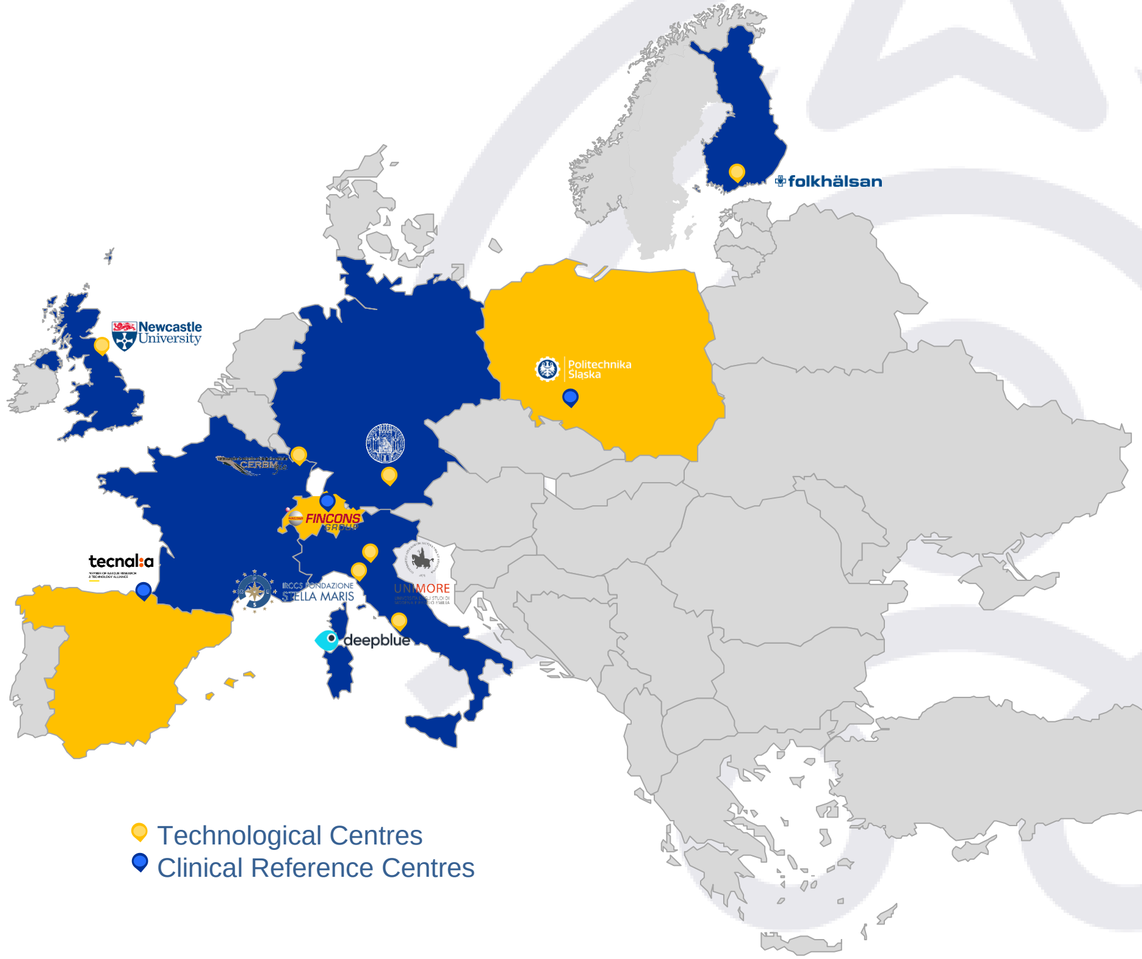
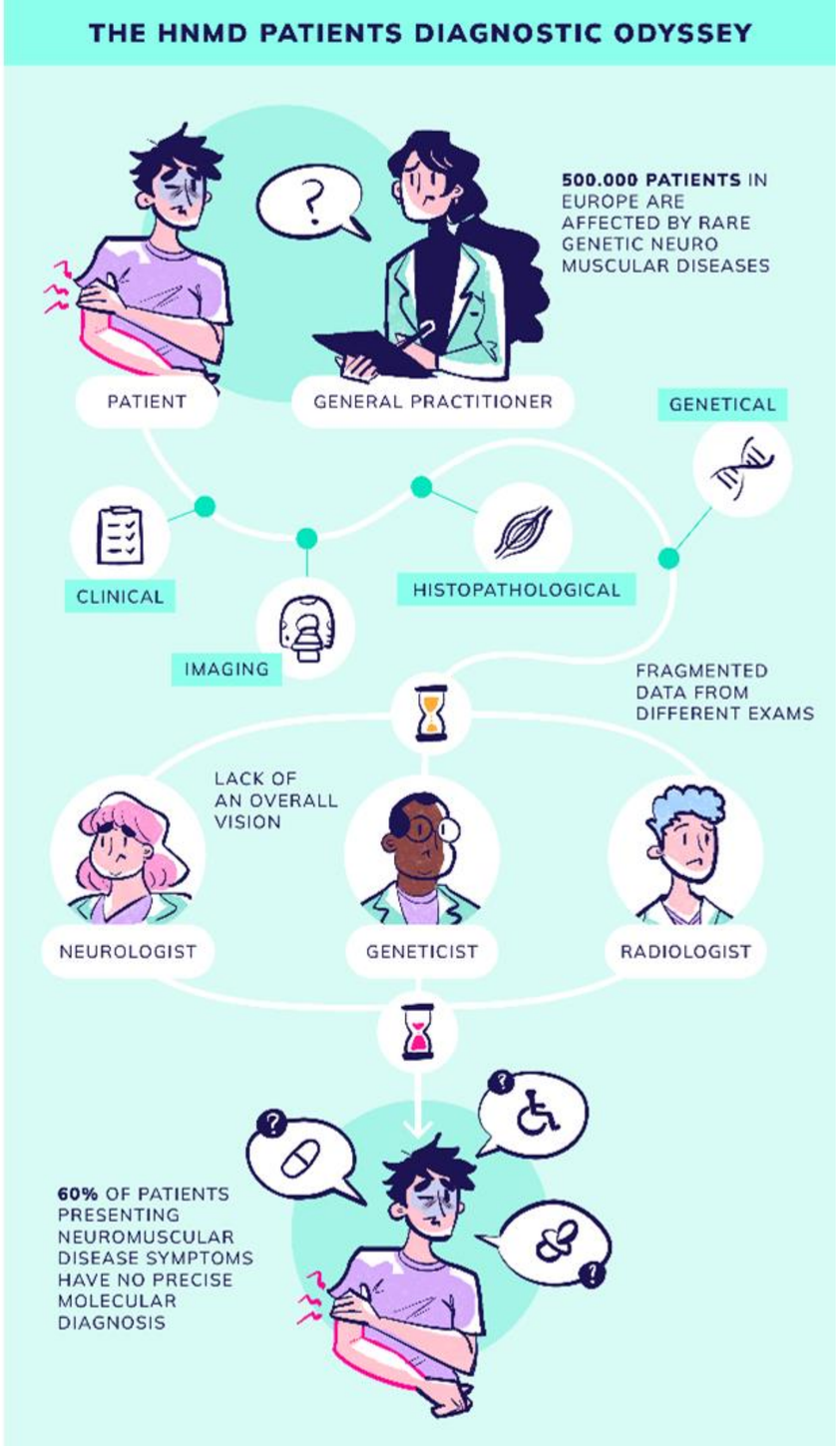
Historical datasets

A wealth of genetic and imaging data has been collected through EU-funded grants (NeurOmics, Solve-RD, MYO-SHARE/MYO-MRI). CoMPaSS-NMD aims at reusing existing data from the participating clinical centres

New data

CoMPaSS-NMD aims at generating prospective genomic, imaging and histopathological data from 500 patients.





CoMPaSS-NMD towards personalized medicine on HNMDs

HNMDs may result from complex biological interactions, mostly still unknown, and the at present, **60% of cases** do not have an **accurate molecular diagnosis**.

DNA molecular analysis has become the gold standard for diagnostics, but HNMD patients may present similar characteristics, similar changes in muscle imaging and/or muscle histology, and yet some may carry mutations in different genes and others may have no obvious harmful variants.

The lack of understanding hinders the definition of a proper prognosis, **impacts on patients' life and social participation,** with loss of independence**,** and prevents the development of efficacious treatments for most of these diseases.

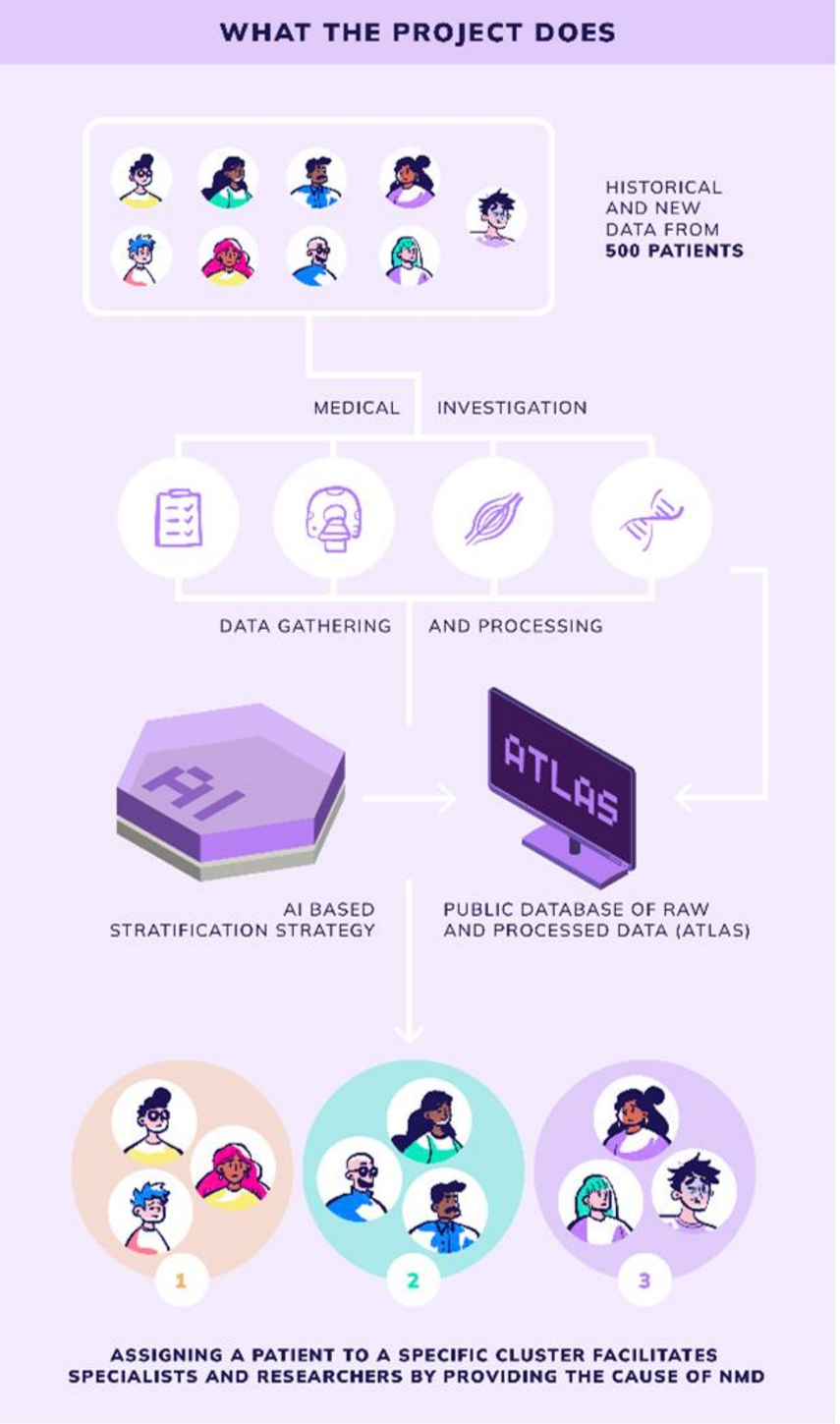
CoMPaSS-NMD

What Artificial Intelligence does in CoMPaSS-NMD?

Imagine a computer that can analyze huge amounts of information from hundreds of patients in different European centers (thanks to the so-called **Machine Learning algorithm**).

By analyzing genetic data, medical records, MRIs, and histological images**,** AI can **identify connections that might elude physicians following traditional approaches.**

AI supports medical doctors, expanding their diagnostic skills.



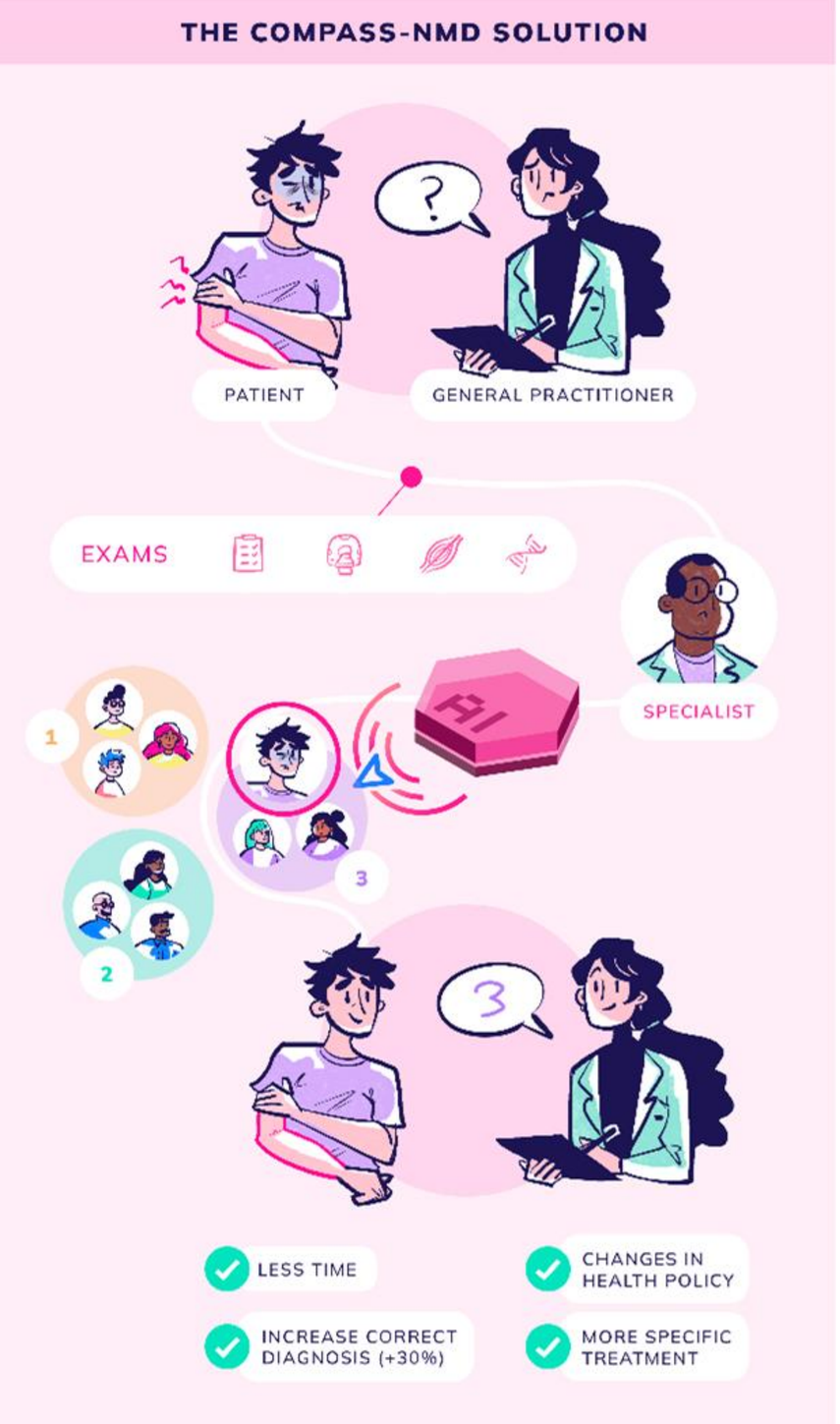
The CoMPaSS NMD approach

1) **a retrospective observational study** conducted on existing data collected from centres all over Europe: 3900 raw sequencing data files, 2000 muscle MRI, 2000 muscle biopsy specimens.

► to design Machine Learning algorithms to identify relationships between data that are not recognizable with standard analytical methods.

2) **a prospective study** involving the collection of clinical (eCRF), histological, MRI, genomic data obtained from a cohort of 500 NMD European patients still undiagnosed
►to validate the ML algorithms

Retrospective and prospective data are then analysed using **unsupervised clustering algorithms**, used to process raw, unclassified data into groups of patients to identify **common clinical patterns to constitute the CoMPaSS-NMD Atlas.**



A world with CoMPaSS

Projects results are expected to impact several stakeholders:

►**Patients:** diminishing uncertainty about their conditions and pointing them towards effective treatments

►**Specialists:** providing a new tool for the diagnosis of HNMDs

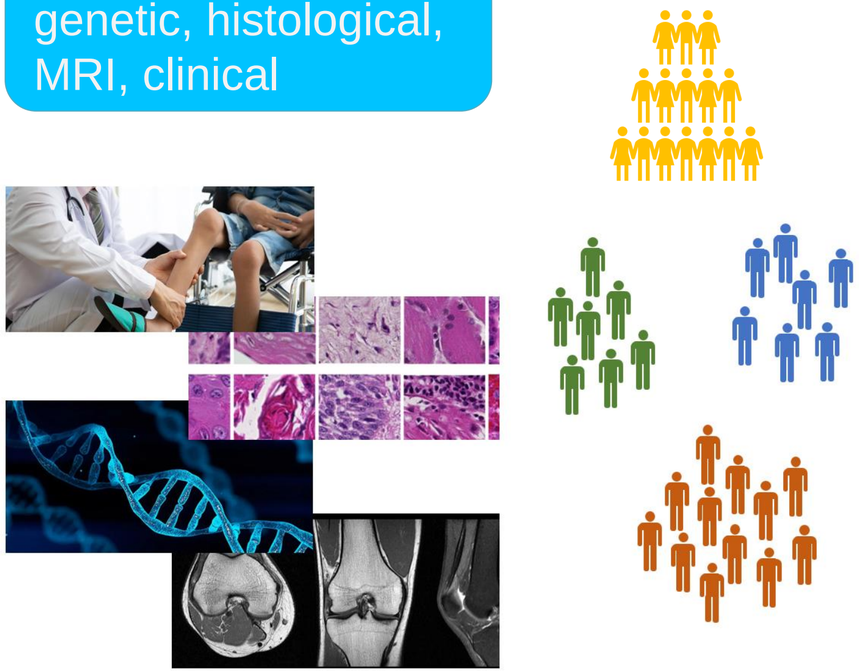
►**Pharmaceutical companies:** providing data useful to develop effective cures

►**Scientific community:** providing data to enrich all research activities related to HNMDs

►**Policy makers:** local and national health agencies/authorities will acquire new systems and interactive Guidelines to face HNMDs

Federated learning to manage private data

4 types of data: genetic, histological, MRI, clinical



Computational tools for high-dimensional **clustering** will be applied in an unsupervised learning approach using the internal structure of data to define groups of similar patients.
Classification model averaging and integration techniques for **federated learning-inspired model** building, and novel HNMD-specific descriptors of histopathological images will be implemented.

► to increment the diagnostic rate of HNMDs by 30% and foster effective actions by European national health systems

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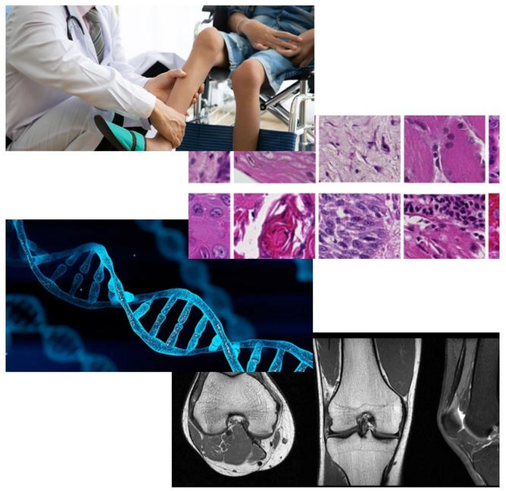
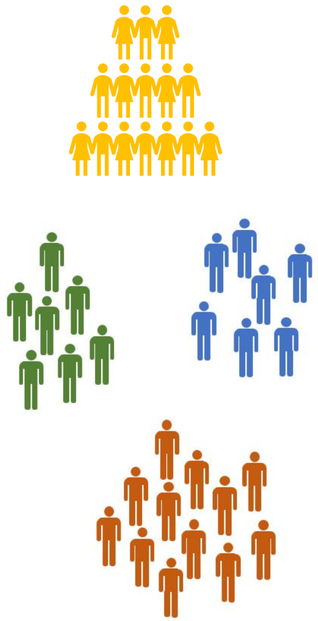
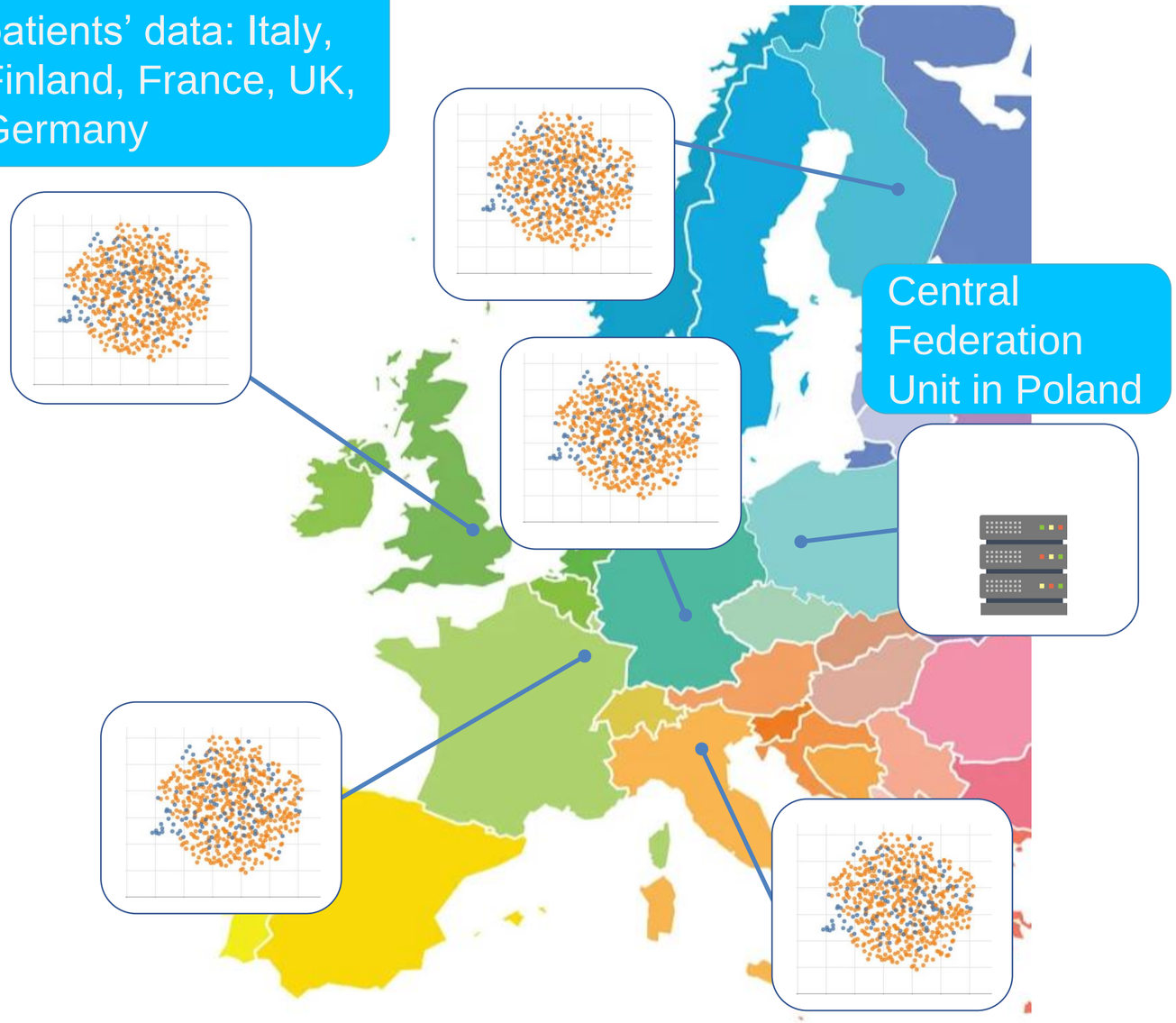
Data Description

4 types of data: genetic, histological, MRI, clinical





5 collections of patients' data: Italy, Finland, France, UK, Germany



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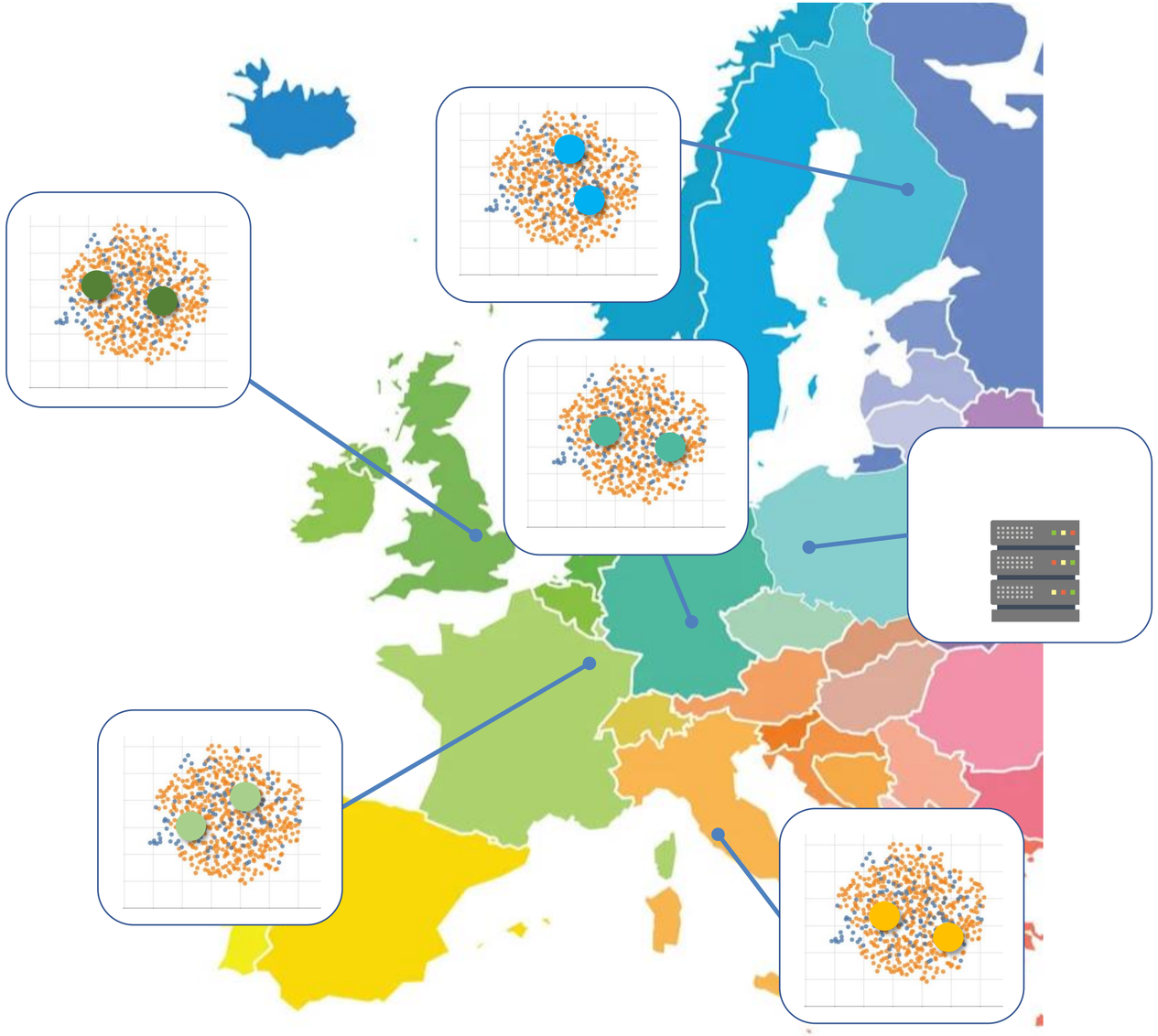
Federated Clustering

Local clustering iterations are executed in each of the centres (without transferring personal data)



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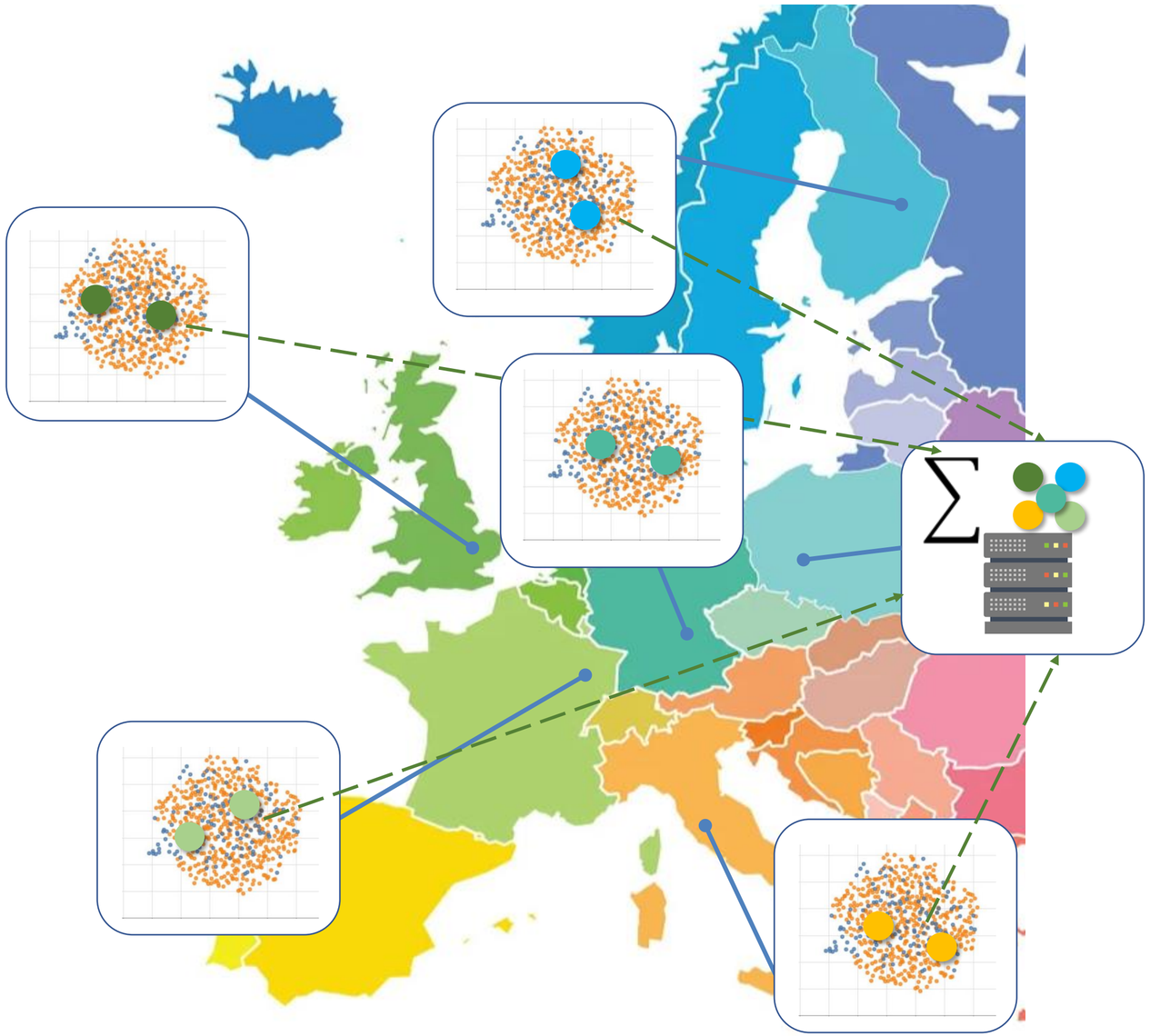
Federated Clustering

Local clustering iterations are executed in each of the centres

Resulting cluster centroids are sent to the server and aggregated



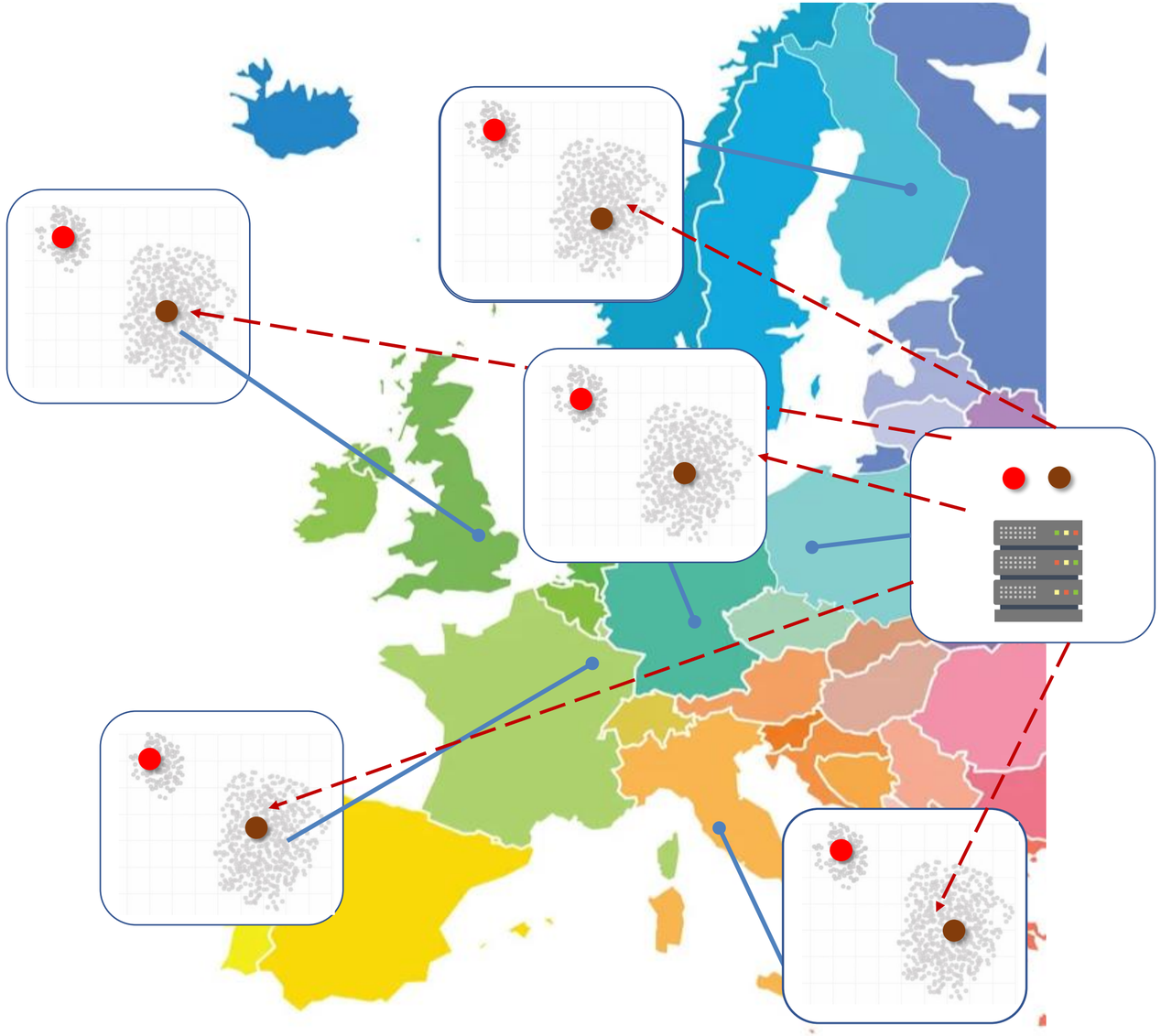
CoMPASS-NMD

Federated Clustering

Local clustering iterations are executed in each of the centres

Resulting cluster centroids are sent to the server and aggregated

Global centroids are distributed back to the local centres



CoMPASS-NMD

Federated Clustering

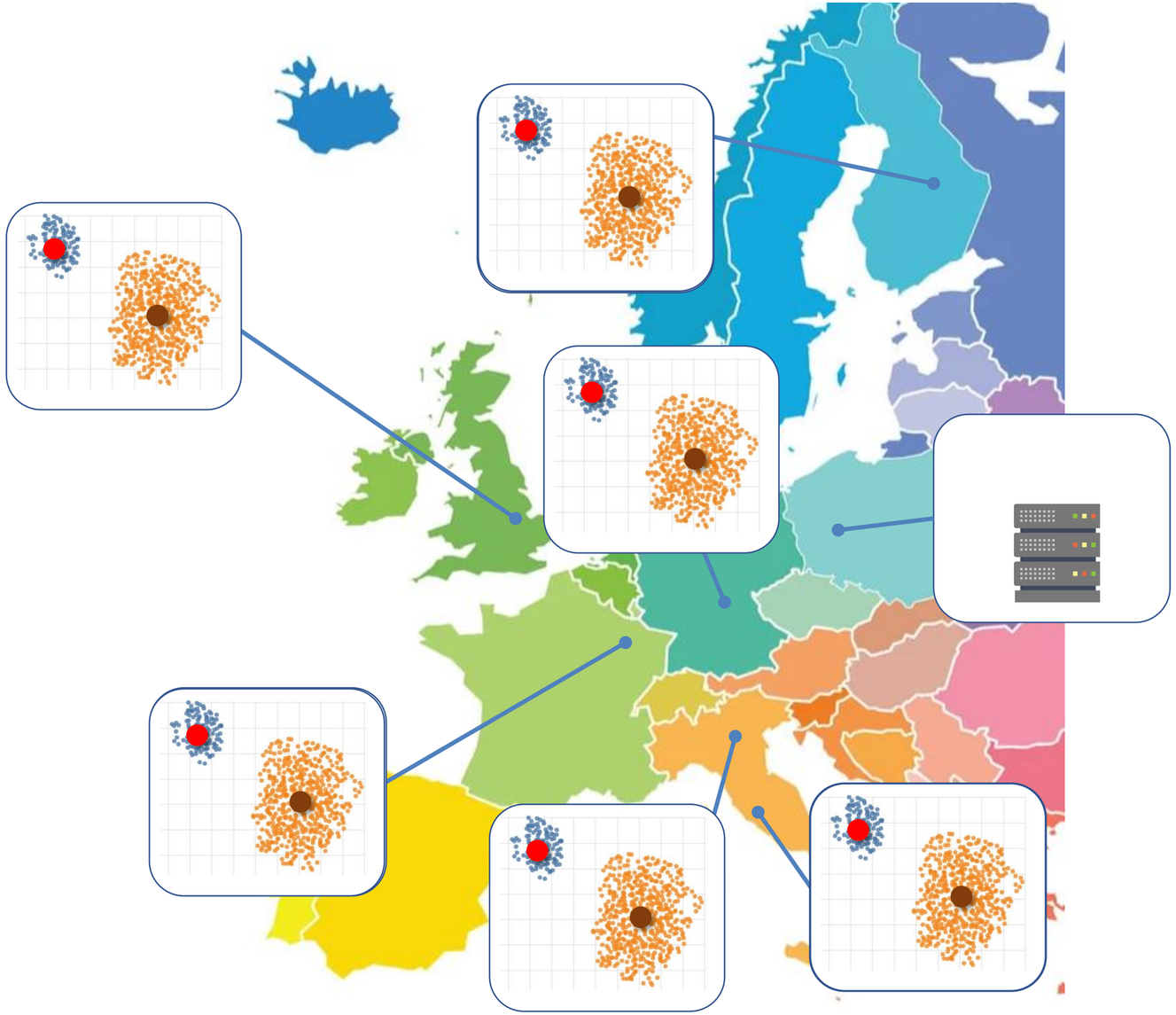
Multiple training iterations

Local clustering iterations are executed in each of the centres

Resulting cluster centroids are sent to the server and aggregated

Global centroids are distributed back to the local centres

Training continues until a convergence criteria is met and global model is built



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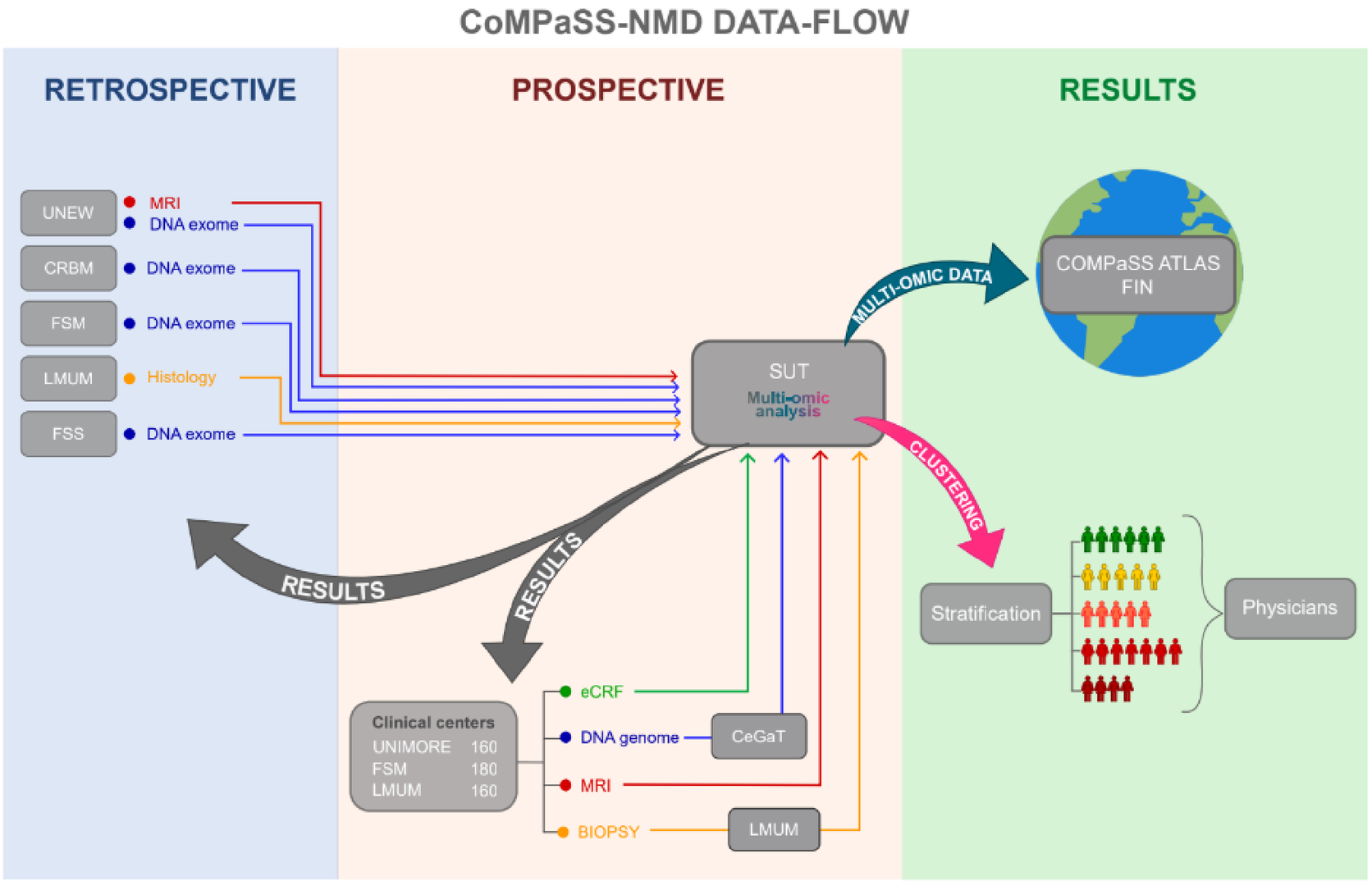
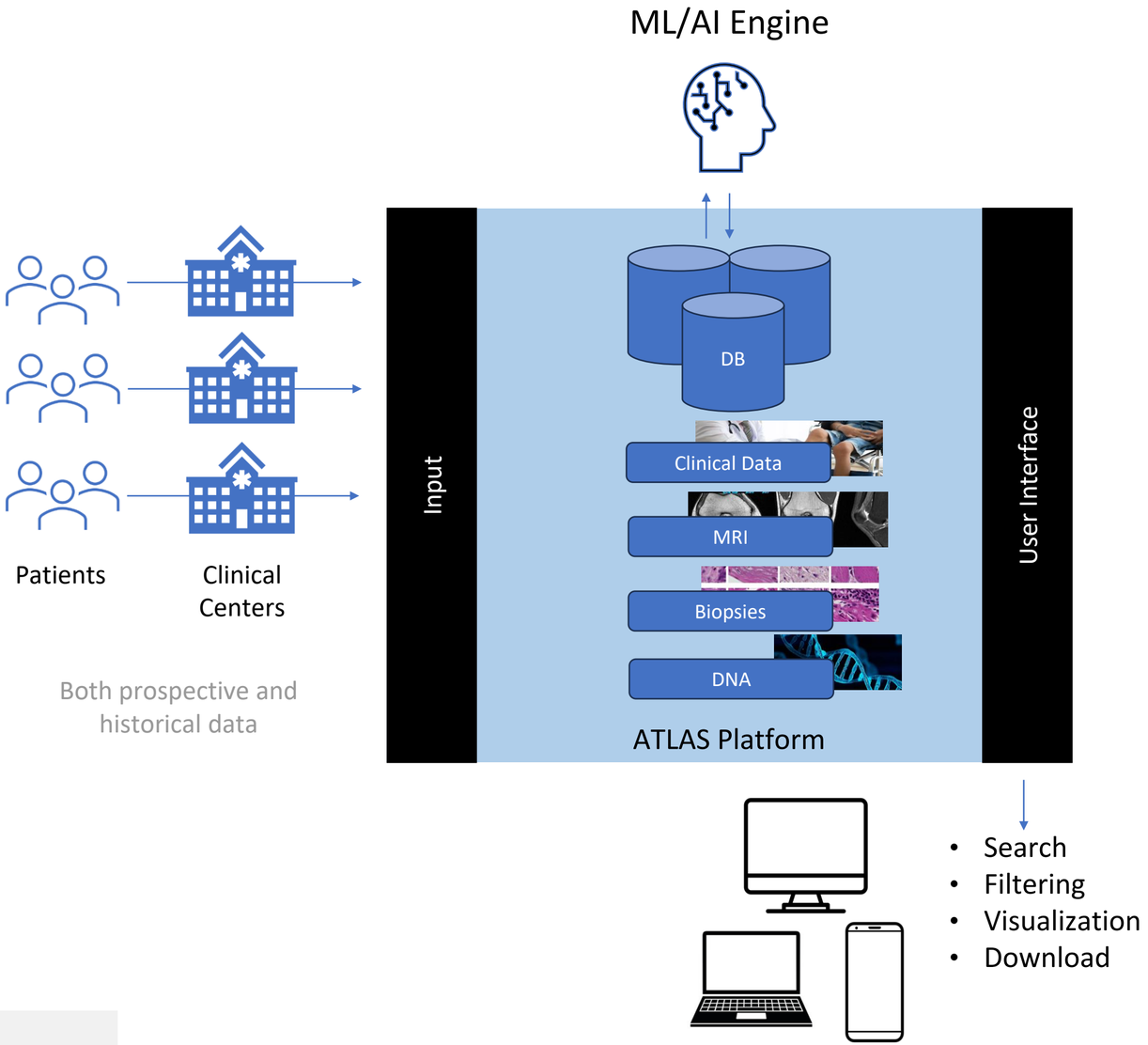
The data flow



ATLAS: a public database



CoMPaSS-NMD Neuromuscular Genome Atlas is an open repository of the genetic, imaging, and histopathological data of **patients from six clinical centers in five countries.**

The CoMPaSS-NMD Atlas supports **a more precise definition of HNMDs** by setting up a **landmark muscle genomic program**.

The platform acts as a common data portal, in which data can be centrally analyzed, searched for, and filtered, **to facilitate discovery and inspection of patients' data available in clinical centers.**

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Data analysis - innovative approach

Knowledge discovery process

Three modalities/omics (ES, MRI, histopathology),

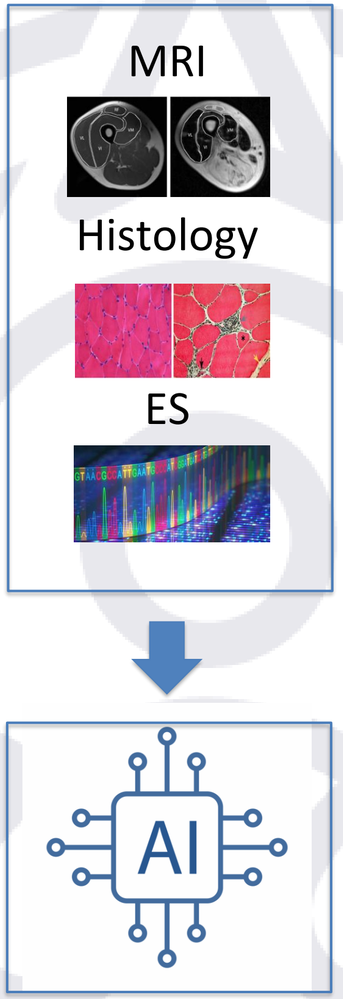
Three clinical centres (Helsinki, Newcastle, Strasbourg),

Historical data, partially disjoint patient groups,

Unsupervised deep learning based local data clustering & cross-centre and cross-modality cluster projection.

Supervised local patient classification system, single modality cluster-specific signature identification & cross-centre and cross-modality signature integration

Results: patient stratification and genetic, imaging and histopathological signatures of patient clusters.



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Data analysis - innovative approach

Discovery implementation and validation

Three modalities (ES, MRI, histopathology),

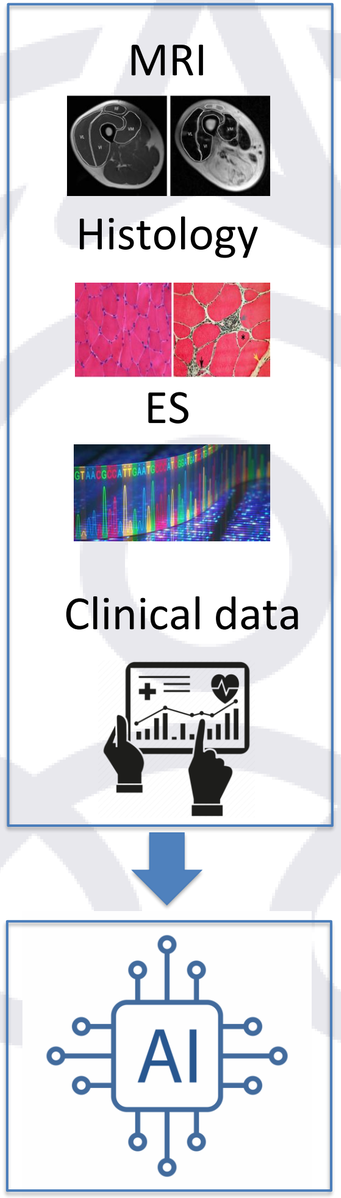
Three clinical centres (Modena, Munich, Pisa),

New data, complemented by standardised clinical description, 500 patients

Fine tuning and validation of multi-omic classification system,

XAI-based identification of the cluster-specific clinical profiles.

Result: standardised clinical (phenotyping) profiling of patient clusters.



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Young Investigator Training (YIT) initiative

Electronic Structured Clinical Report Form (eSCRF)

Part 1

15 July 2024

SAVE THE DATE

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15 July 2024 | 15:00 CEST | 1 hour | Online

CoMPaSS-NMD

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