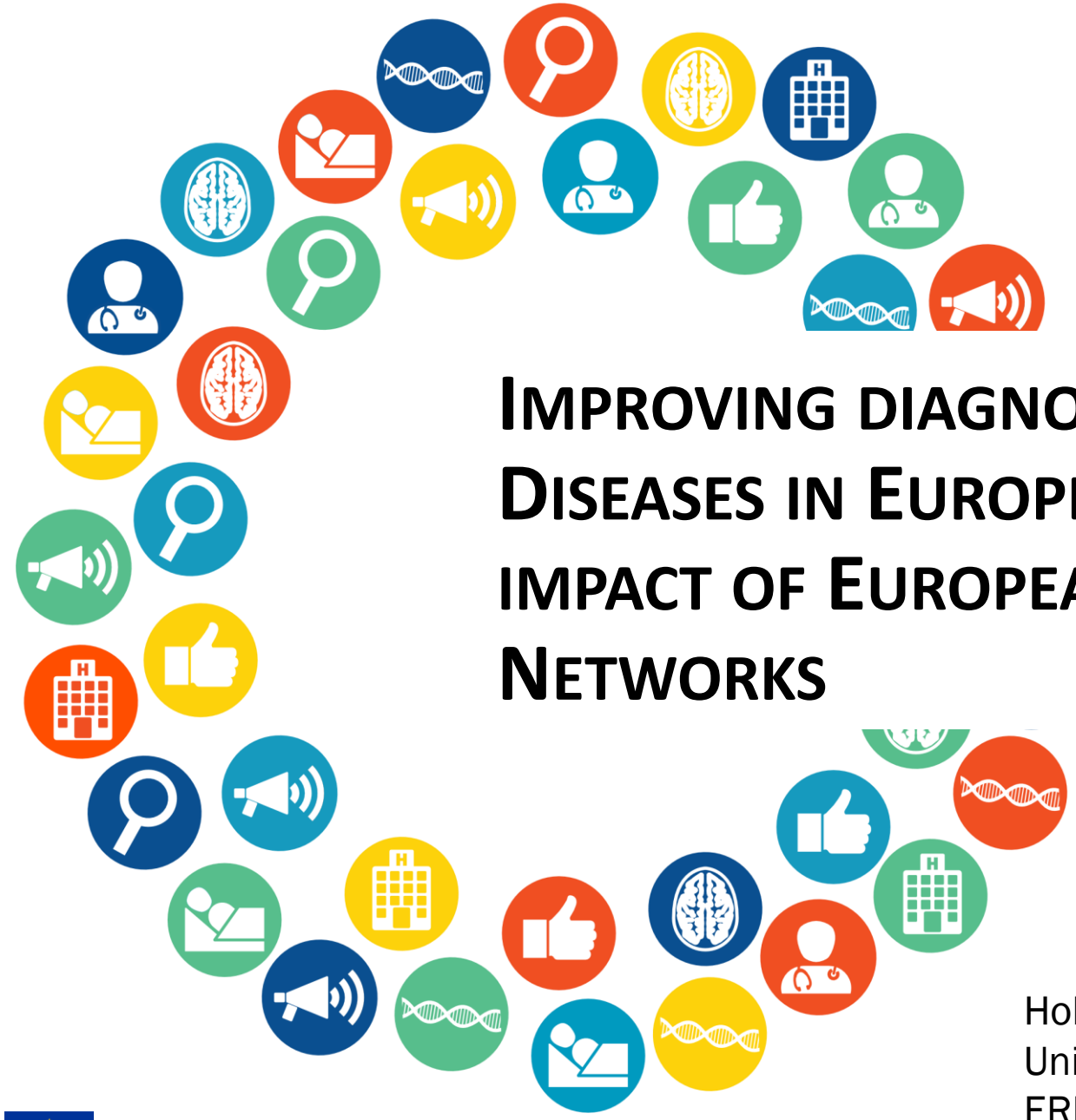
European Reference Networks



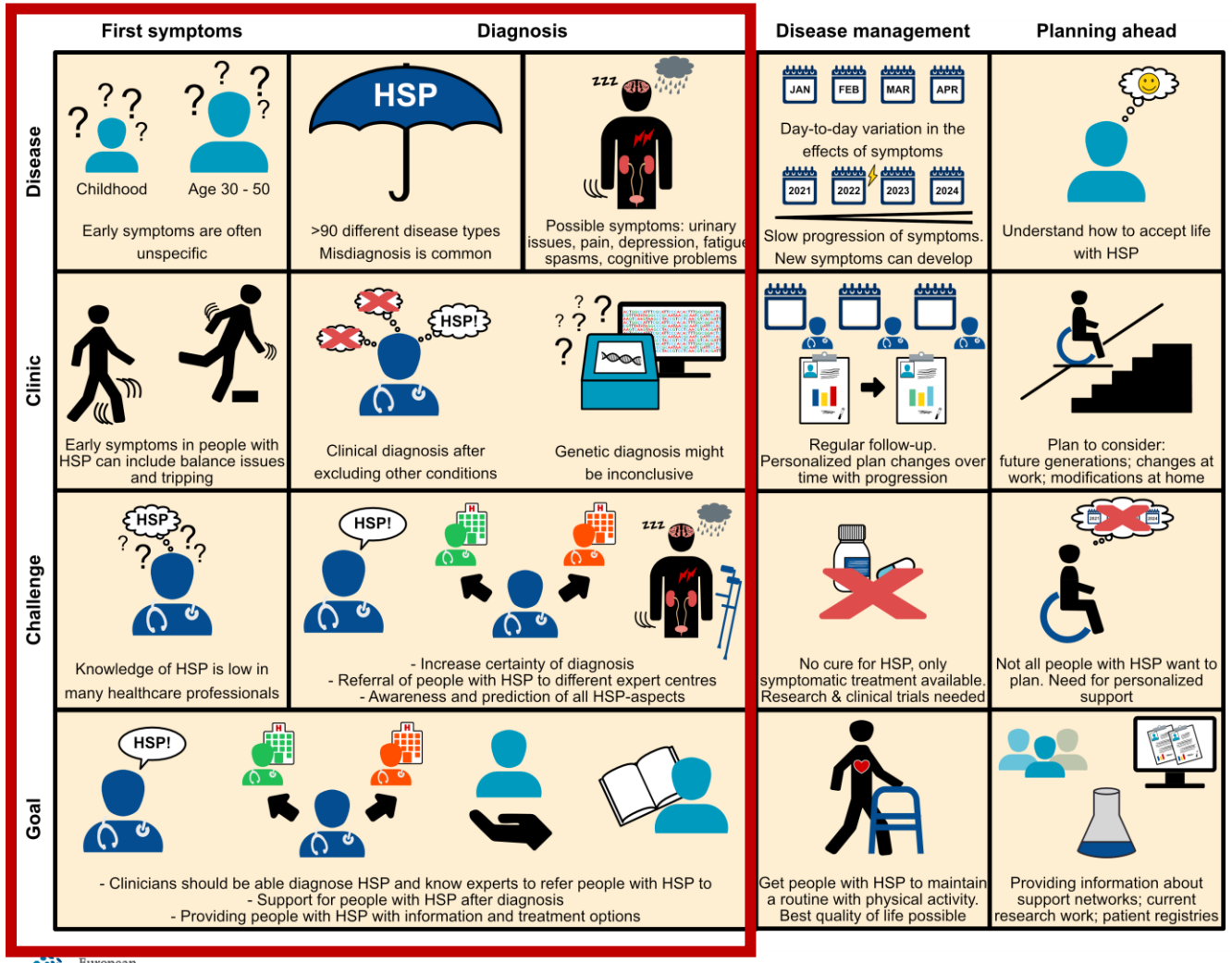
Improving diagnosis for Rare Diseases in Europe – impact of European Reference Networks

Holm Graessner
University Hospital Tübingen, Germany
ERN-RND Coordinator

European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

Co-funded by the EU

DIAGNOSIS - MAIN HEALTHCARE PROBLEM FOR RARE DISEASES



Main issues:

- Diagnostic journey takes years
- A large fraction of RD patients are misdiagnosed (>50% of all patients)
- Major impact of misdiagnosis
- For about 50% of genetically tested patients the molecular disease cause can not be confirmed

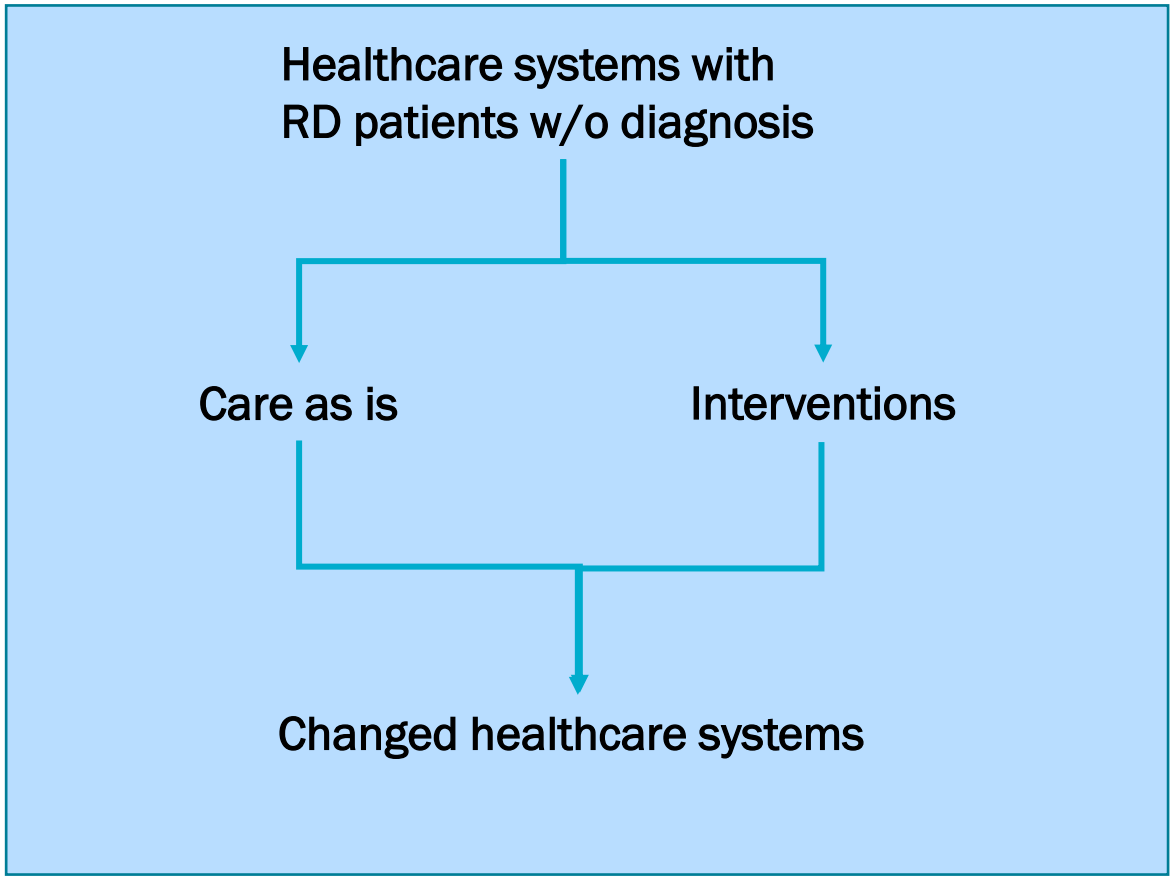
(Ref. EURORDIS: Global Rare barometer survey
On the journey to diagnosis for people living with a rare disease.)

RD Diagnosis –Push and Pull factors

- European Reference Networks
- Diagnostic technology development
- Precision therapies for RD patients

- Medical need of RD patients
- Costs for healthcare systems

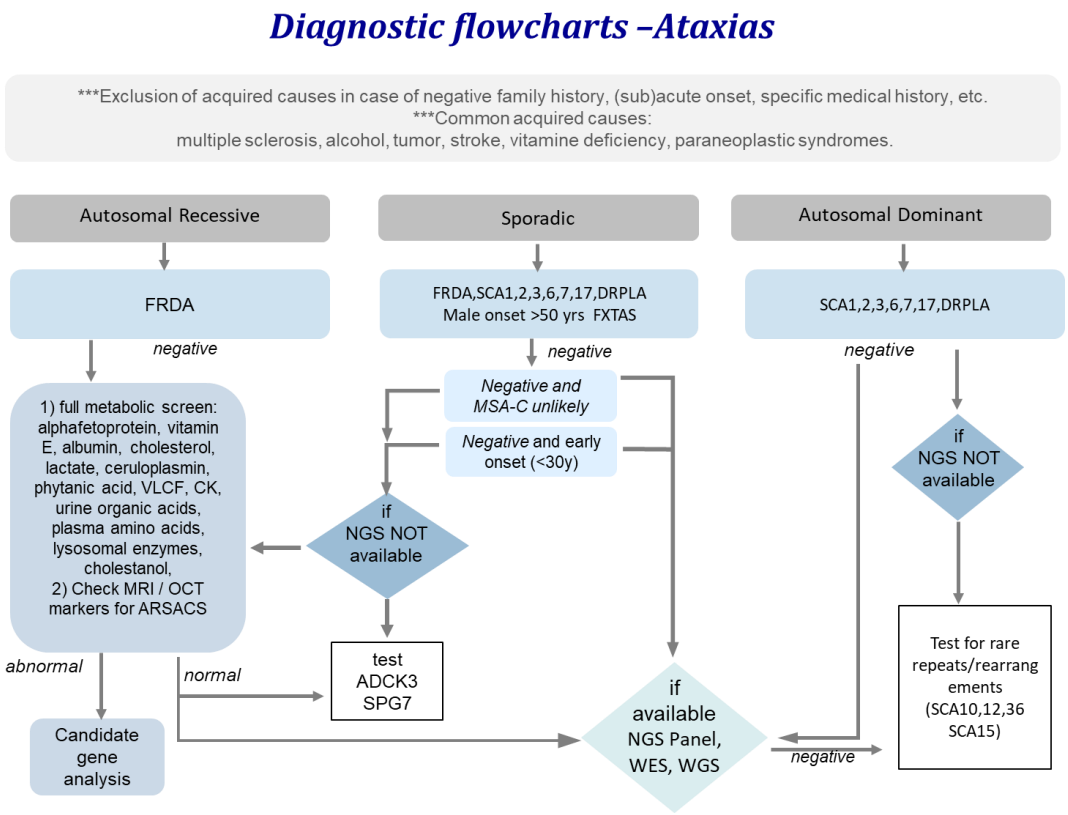
RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE



Interventions

- European Reference Networks
- Data sharing
- Novel Diagnostic Technology
- New Born Screening
- Undiagnosed Disease Programs
- Etc.

RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE

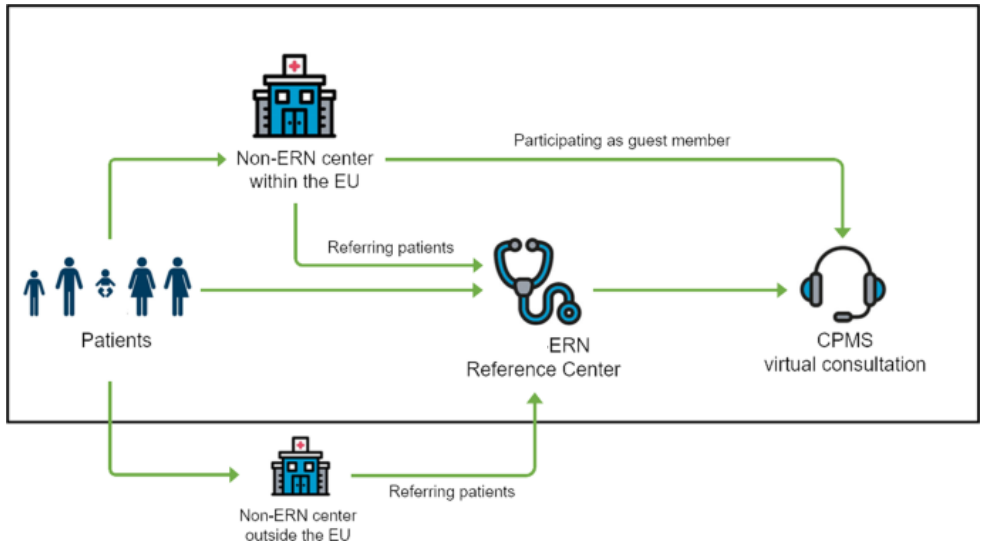


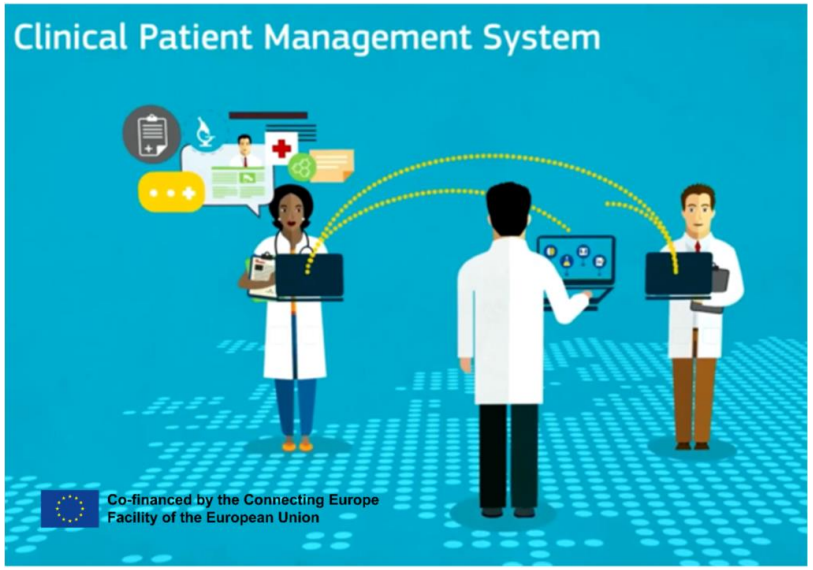
Interventions

- European Reference Networks
  - **Standards of care including care pathways, referral pathways and guidelines**
  - Cross-border diagnostic care pathways including multidisciplinary case discussions (CPMS)
  - Quality assurance for next generation sequencing
  - Collaborative research based on data sharing

RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE

Ref: Endo-ERN





Interventions

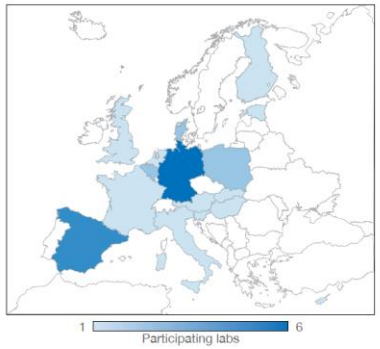
- European Reference Networks
  - Standards of care including care pathways, referral pathways and guidelines
  - **Cross-border diagnostic care pathways including multidisciplinary case discussions (CPMS)**
  - Quality assurance for next generation sequencing
  - Collaborative research based on data sharing

RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE

Quality assurance for the next-generation sequencing diagnostics of rare neurological diseases in the European Reference Network

Pilot scheme results

Participation
25 laboratories from 17 countries



Approaches to diagnosis of RNDs

The majority of participating labs employ (clinical) exome sequencing (76%)

The majority of participating analyse data using internally developed pipelines (72%)

The majority of labs do not validate the NGS findings (56%)

Interpretation

A wider variability was observed in adherence to variant interpretation standards

- Several (32%) labs did not report using an accepted variant interpretation system

- 28% labs presented incomplete evidence to support variant's pathogenicity

- A minority of labs provided evidence codes supporting pathogenicity assertion

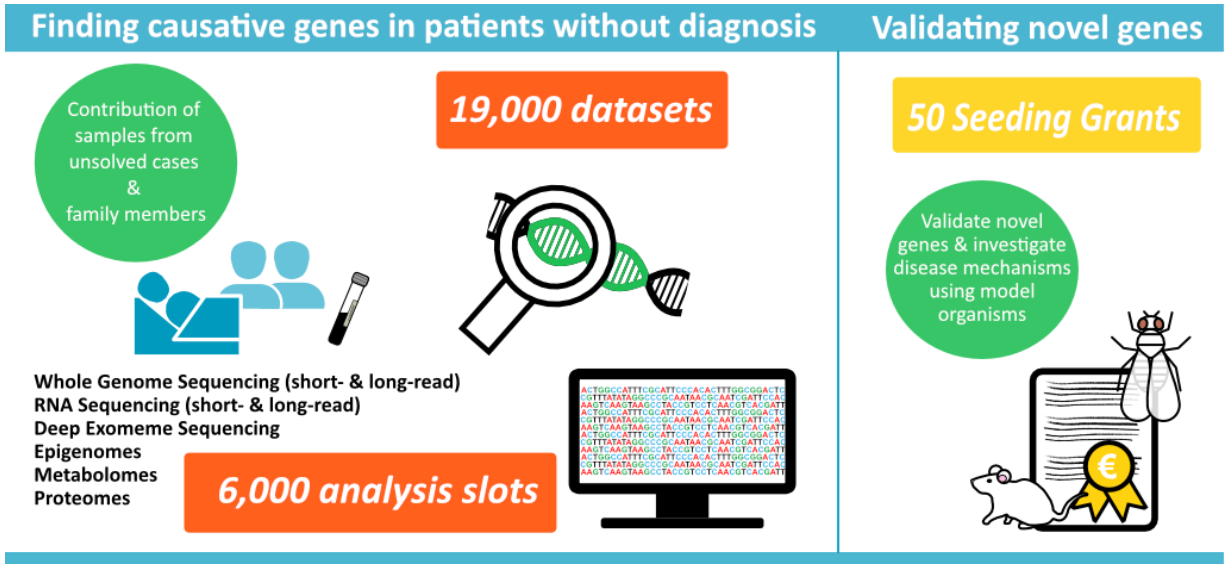
Interventions

- European Reference Networks
  - Standards of care including care pathways, referral pathways and guidelines
  - Cross-border diagnostic care pathways including multidisciplinary case discussions (CPMS)
  - **Quality assurance for Next Generation Sequencing**
  - Collaborative research based on data sharing

RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE

SolveRD

Solving the Unsolved Rare Diseases



Interventions

- European Reference Networks
  - Standards of care including care pathways, referral pathways and guidelines
  - Cross-border diagnostic care pathways including multidisciplinary case discussions (CPMS)
  - Quality assurance for next generation sequencing
  - **Collaborative research based on data sharing**

SOLVE-RD

Solve RD

Solving the Unsolved Rare Diseases

European Reference Network | Neurological Diseases (ERN-RND)

EURO-NMD | Building bridges and breaking barriers in rare neuromuscular diseases

ITHACA

ERN-ITHACA focuses on rare congenital malformation syndromes and intellectual disability

GENTURIS

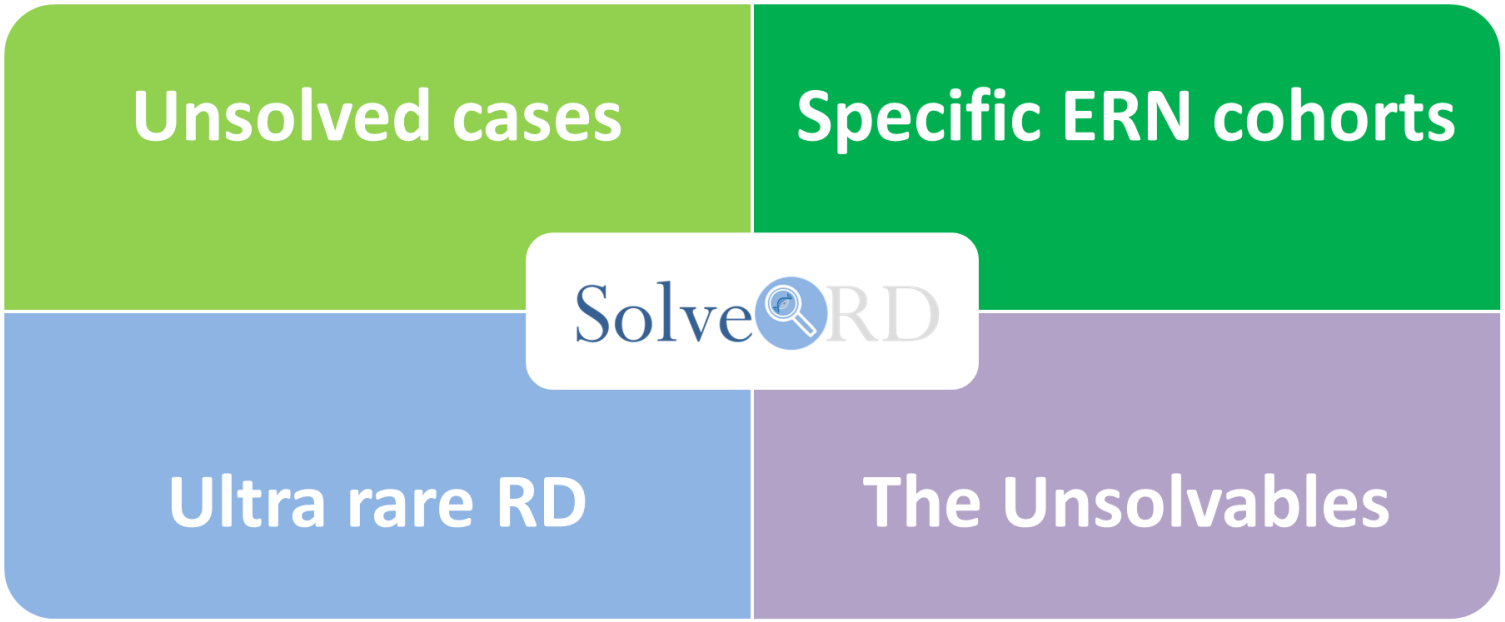
rare genetic tumour risk syndromes

EpiCARE

European Reference Network for rare and complex epilepsies

rita

The European Reference Network that aims at improving the care of patients with Rare Immunological Disorders



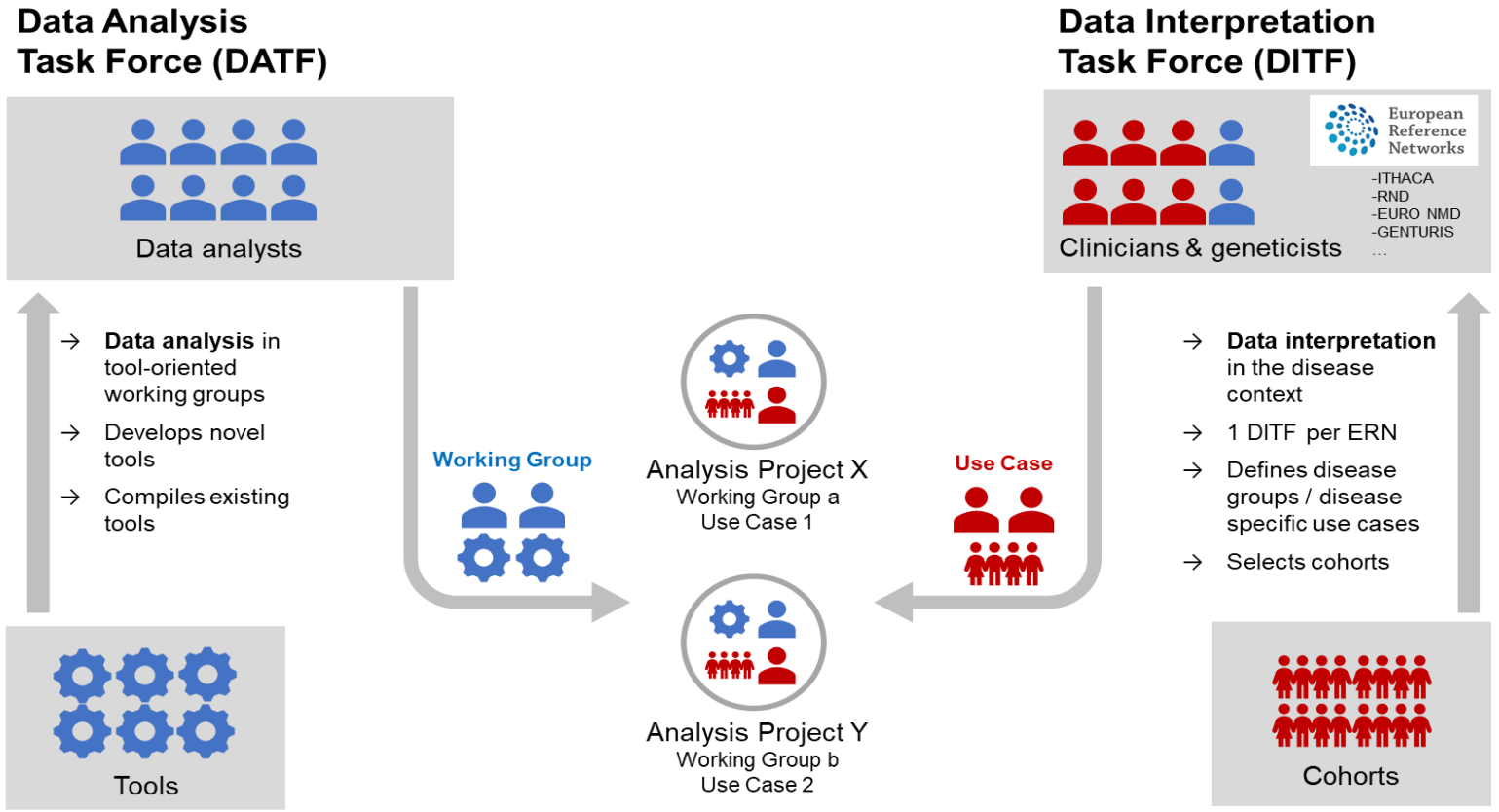
Data Sharing

Only WES and WGS datasets

~ 21.000 WES
~ 2.350 WGS
+ phenotypic data + pedigrees
+metadata

~ 620.000.000.000.000 byte
~ 620 Terabyte

SOLVE-RD



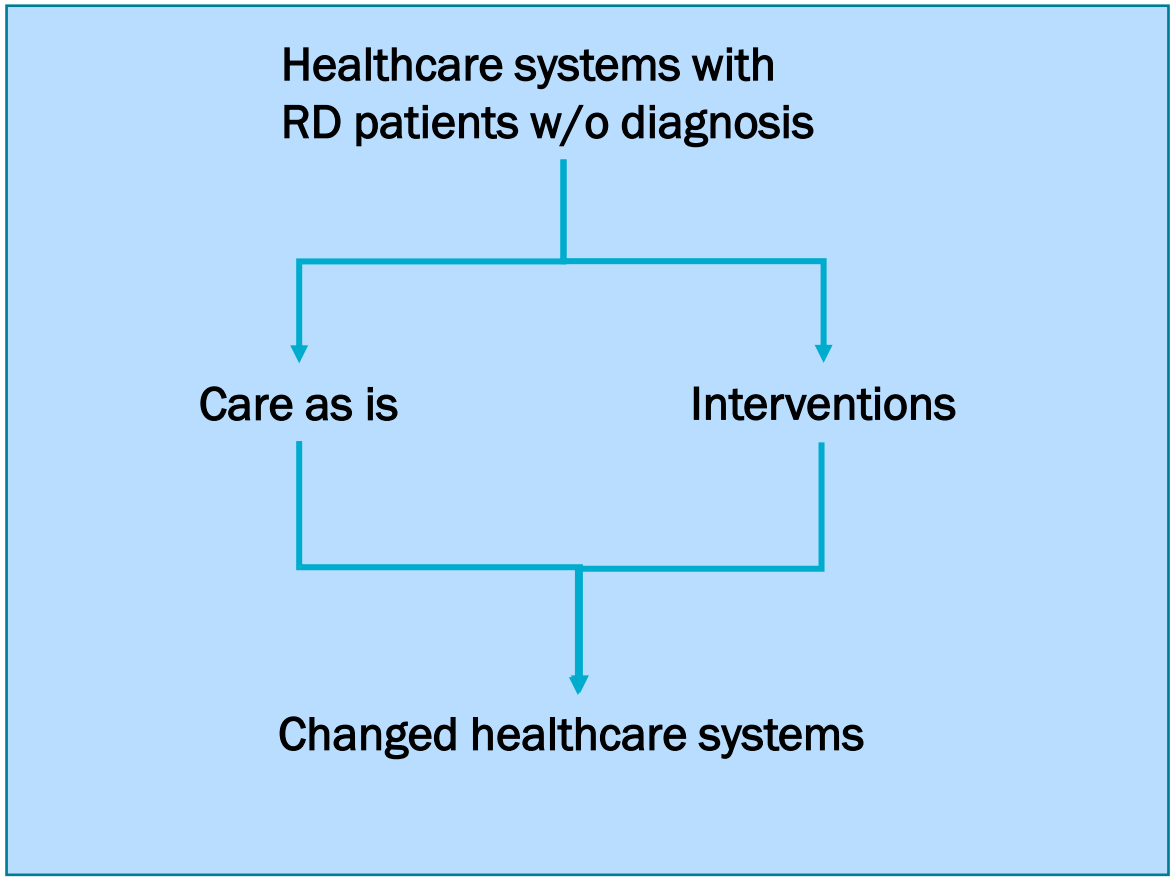
Research based

Data

Re-analysis

~ 10% additionally solved cases

RD DIAGNOSIS – TECHNOLOGY PUSH



Main issue

- For about 50% of genetically tested patients the molecular disease cause can not be confirmed

Interventions

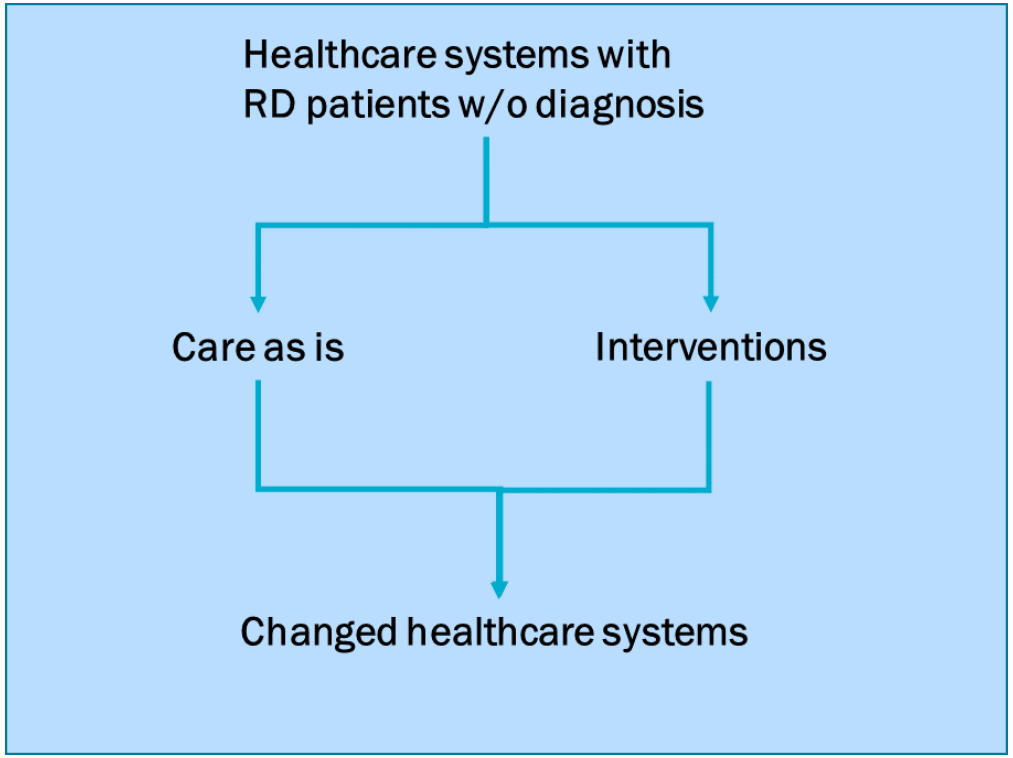
- Novel Diagnostic Technology

→ **LONG-READ SEQUENCING**

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Goal 1: All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; **all currently undiagnosable individuals will enter a globally coordinated diagnostic and RESEARCH pipeline**

RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE



How to measure the change in healthcare systems

- European Reference Network Registries
  - Interoperable for ERDRI common dataset
  - (at least) All patients seen in ERNs (1.3 million)
  - Data point for undiagnosed cases

6 Diagnosis	6.1.	Diagnosis of the rare disease	Diagnosis retained by the specialised centre	Orpha code (strongly recommended – see link) / Alpha code/ ICD-9 code/ ICD-9-CM code / ICD-10 code
	6.2.	Genetic diagnosis	Genetic diagnosis retained by the specialised centre	International classification of mutations (HGVS) (strongly recommended – see link) / HGNC / OMIM code
	6.3	Undiagnosed case	How the undiagnosed case is defined	• Phenotype (HPO) • Genotype (HGVS)
	7.1.	Agreement to be contacted for	Patient's permission exists for being contacted for research	• YES • NO

RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE

How to measure the change in healthcare systems

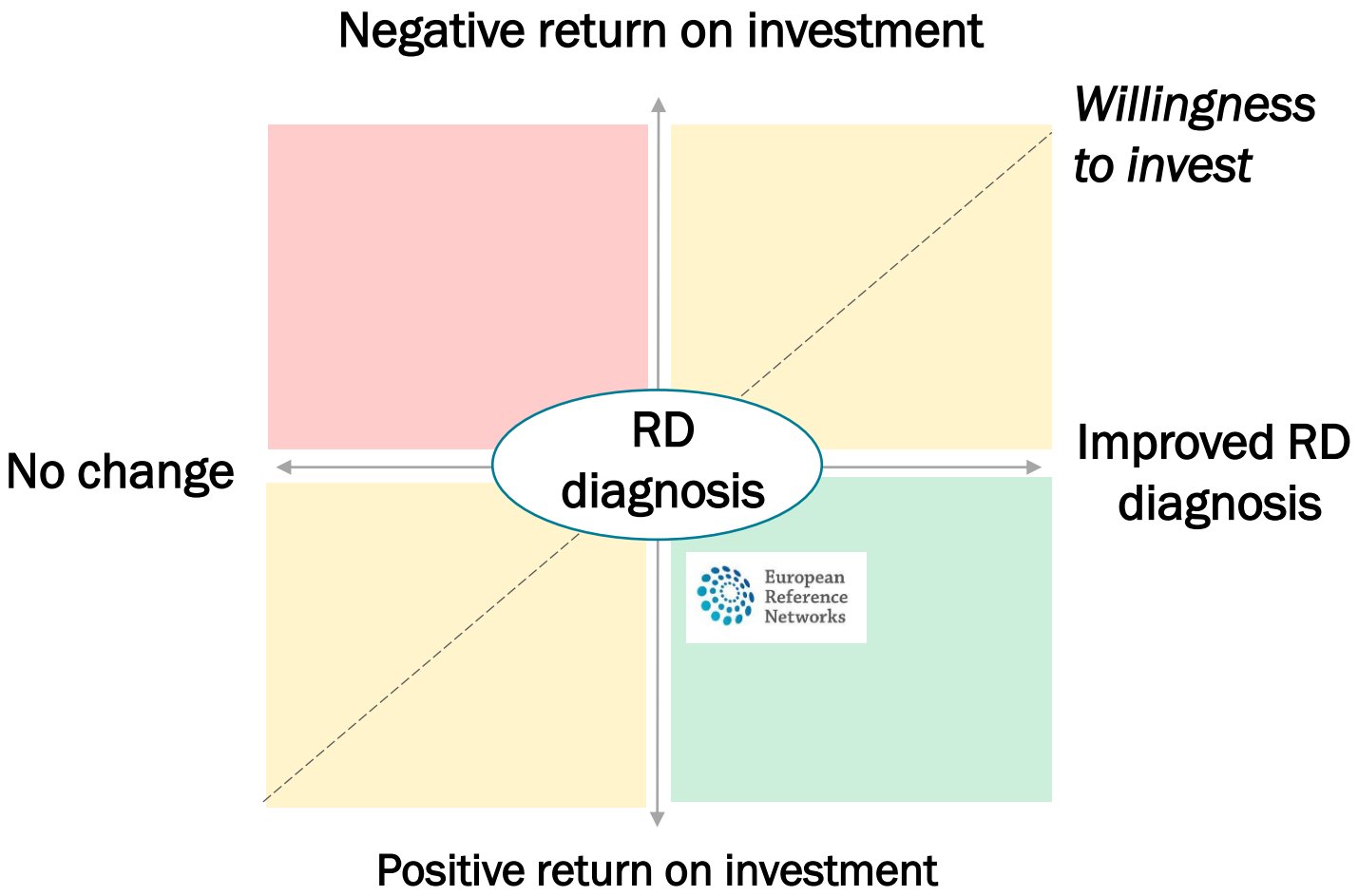
- European Reference Network Registries

6 Diagnosis	6.1.	Diagnosis of the rare disease	Diagnosis retained by the specialised centre	Orpha code (strongly recommended – see link) / Alpha code/ ICD-9 code/ ICD-9-CM code / ICD-10 code
	6.2.	Genetic diagnosis	Genetic diagnosis retained by the specialised centre	International classification of mutations (HGVS) (strongly recommended – see link) / HGNC / OMIM code
	6.3	Undiagnosed case	How the undiagnosed case is defined	• Phenotype (HPO) • Genotype (HGVS)
	7.1.	Agreement to be contacted for	Patient's permission exists for being contacted for research	• YES • NO

→ European cohort of RD patients w/o (confirmed) diagnosis

→ Member state cohorts of RD patients w/o (confirmed) diagnosis

IMPACT OF EUROPEAN REFERENCE NETWORKS ON RD DIAGNOSIS



European Reference Networks

THANK YOU!

European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

Co-funded by the EU