



IMPROVING DIAGNOSIS FOR RARE DISEASES IN EUROPE – IMPACT OF EUROPEAN REFERENCE NETWORKS

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DIAGNOSIS - MAIN HEALTHCARE PROBLEM FOR RARE DISEASES

	First symptoms	Diagnosis	Disease management	Planning ahead	
Disease	<p>Childhood Age 30 - 50</p> <p>Early symptoms are often unspecific</p>	<p>>90 different disease types Misdiagnosis is common</p>	<p>Possible symptoms: urinary issues, pain, depression, fatigue, spasms, cognitive problems.</p>	<p>Day-to-day variation in the effects of symptoms</p> <p>Slow progression of symptoms. New symptoms can develop</p>	<p>Understand how to accept life with HSP</p>
Clinic	<p>Early symptoms in people with HSP can include balance issues and tripping</p>	<p>Clinical diagnosis after excluding other conditions</p> <p>Genetic diagnosis might be inconclusive</p>	<p>Regular follow-up. Personalized plan changes over time with progression</p>	<p>Plan to consider: future generations; changes at work; modifications at home</p>	
Challenge	<p>Knowledge of HSP is low in many healthcare professionals</p>	<p>- Increase certainty of diagnosis - Referral of people with HSP to different expert centres - Awareness and prediction of all HSP-aspects</p>	<p>No cure for HSP, only symptomatic treatment available. Research & clinical trials needed</p>	<p>Not all people with HSP want to plan. Need for personalized support</p>	
Goal	<p>- Clinicians should be able diagnose HSP and know experts to refer people with HSP to - Support for people with HSP after diagnosis - Providing people with HSP with information and treatment options</p>		<p>Get people with HSP to maintain a routine with physical activity. Best quality of life possible</p>	<p>Providing information about support networks; current research work; patient registries</p>	

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.)

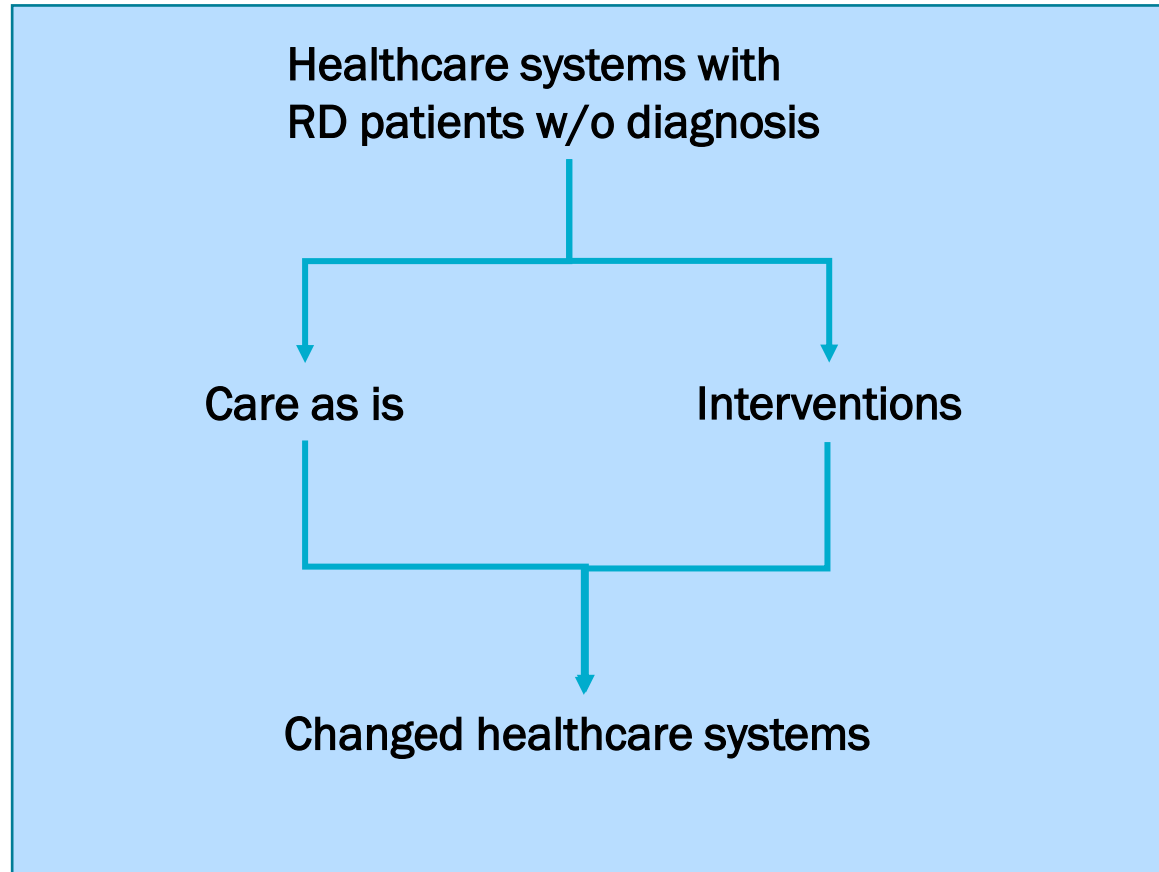
RD DIAGNOSIS – PUSH AND PULL FACTORS

- 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

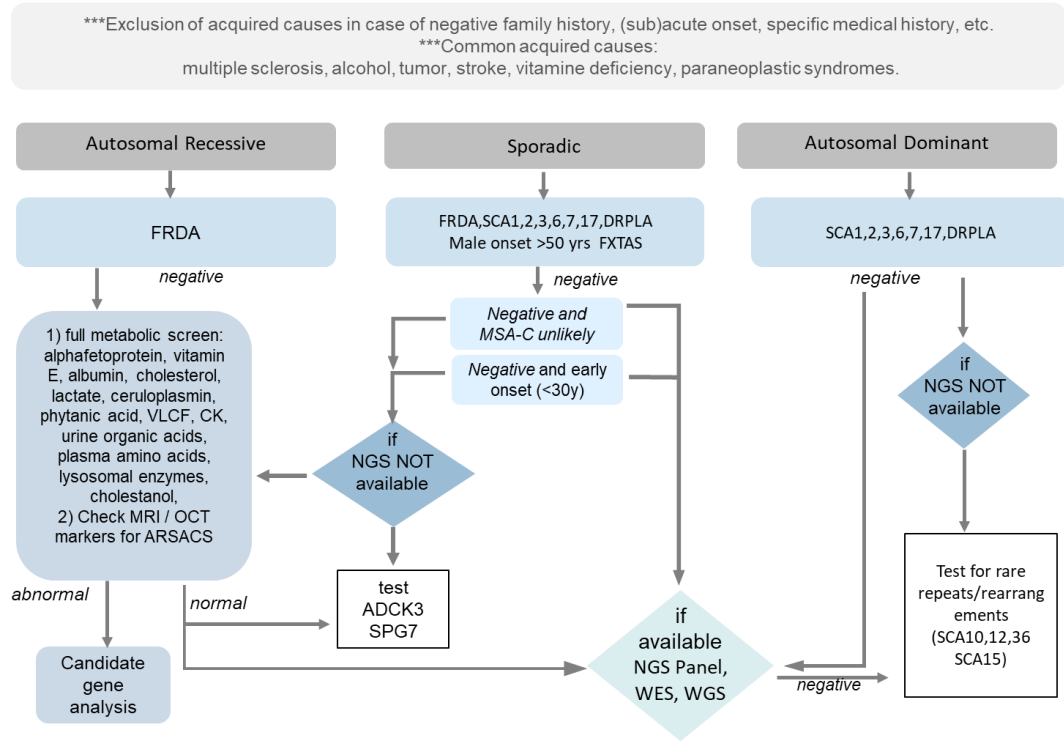


Interventions

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

RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE

Diagnostic flowcharts –Ataxias

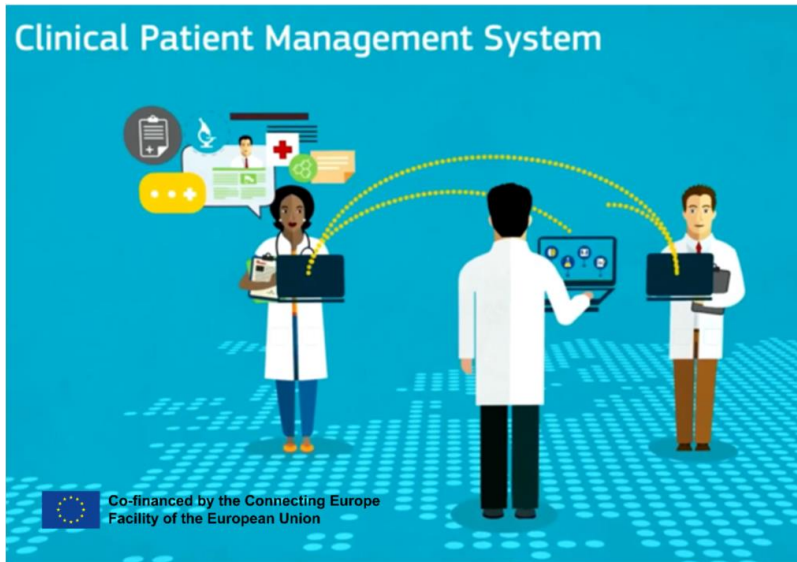
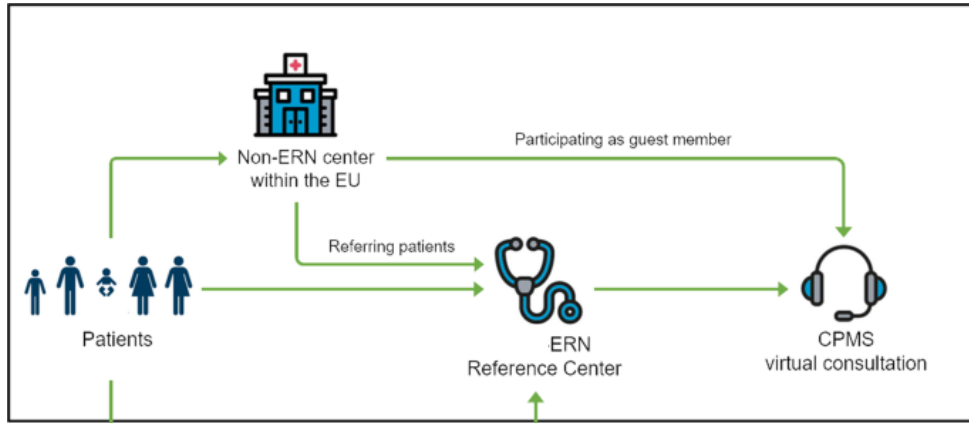


Interventions

- 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



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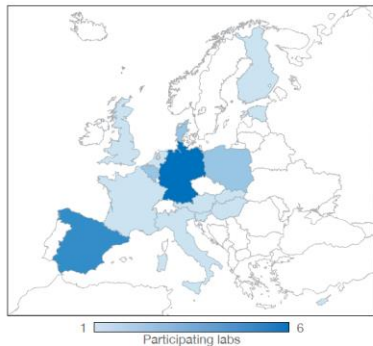
RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE

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



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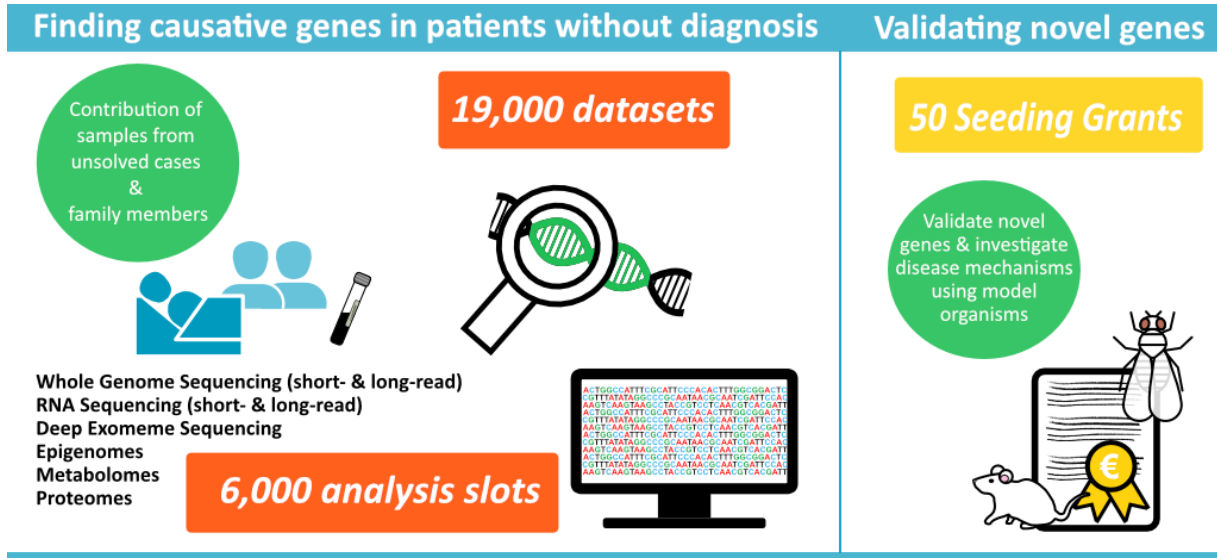
RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE

SolveORD

Solving the Unsolved Rare Diseases

Interventions

- European Reference Networks
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Solve RD

Solving the Unsolved Rare Diseases



Neurological Diseases
(ERN-RND)

EURO-NMD

Building bridges and breaking barriers
in rare neuromuscular diseases



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



European Reference Network for rare and complex epilepsies




GENTURIS

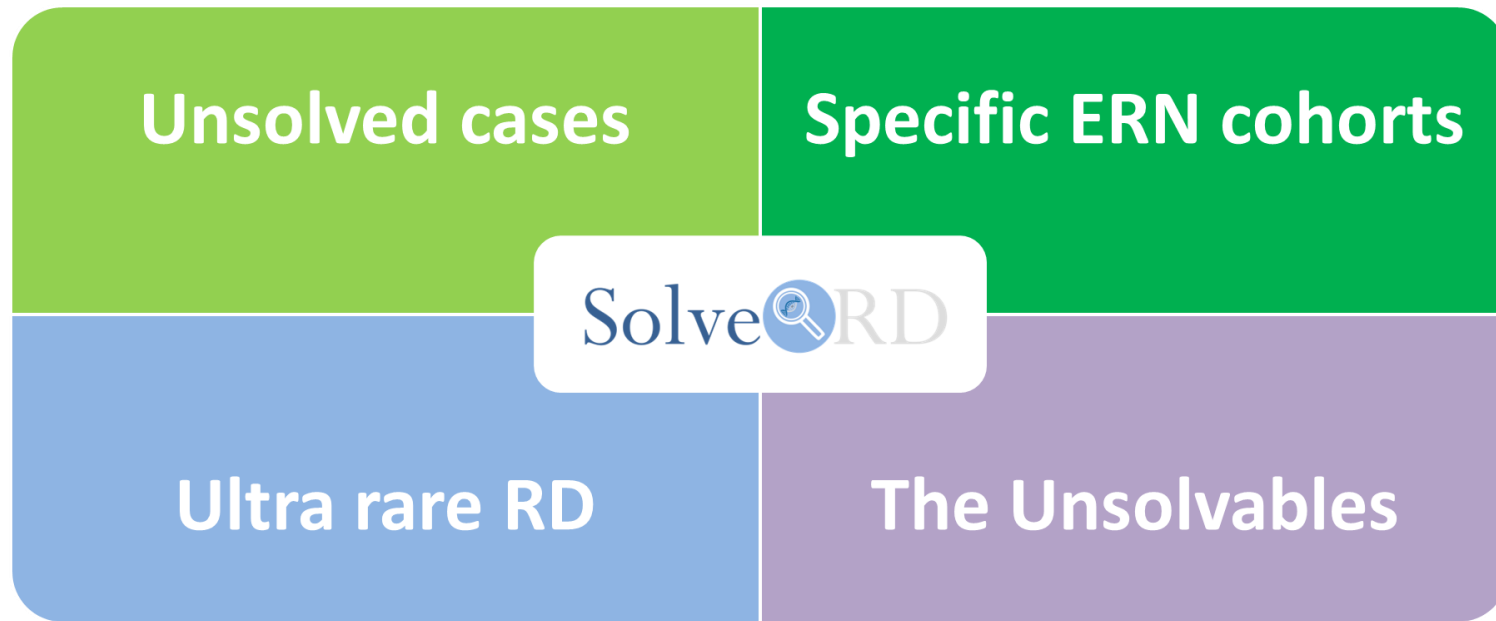
rare genetic tumour risk syndromes



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



 Solve-RD partner and collaborator institutions



Data Sharing

Only WES and WGS datasets

~ 21.000 WES

~ 2.350 WGS

+ phenotypic data + pedigrees

+metadata

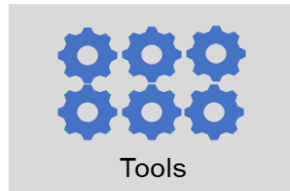
~ 620.000.000.000.000 byte

~ 620 Terabyte

Data Analysis Task Force (DATF)



- Data analysis in tool-oriented working groups
- Develops novel tools
- Compiles existing tools



Working Group



Use Case

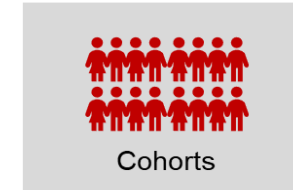


Data Interpretation Task Force (DITF)



- ITHACA
- RND
- EURO NMD
- GENTURIS
- ...

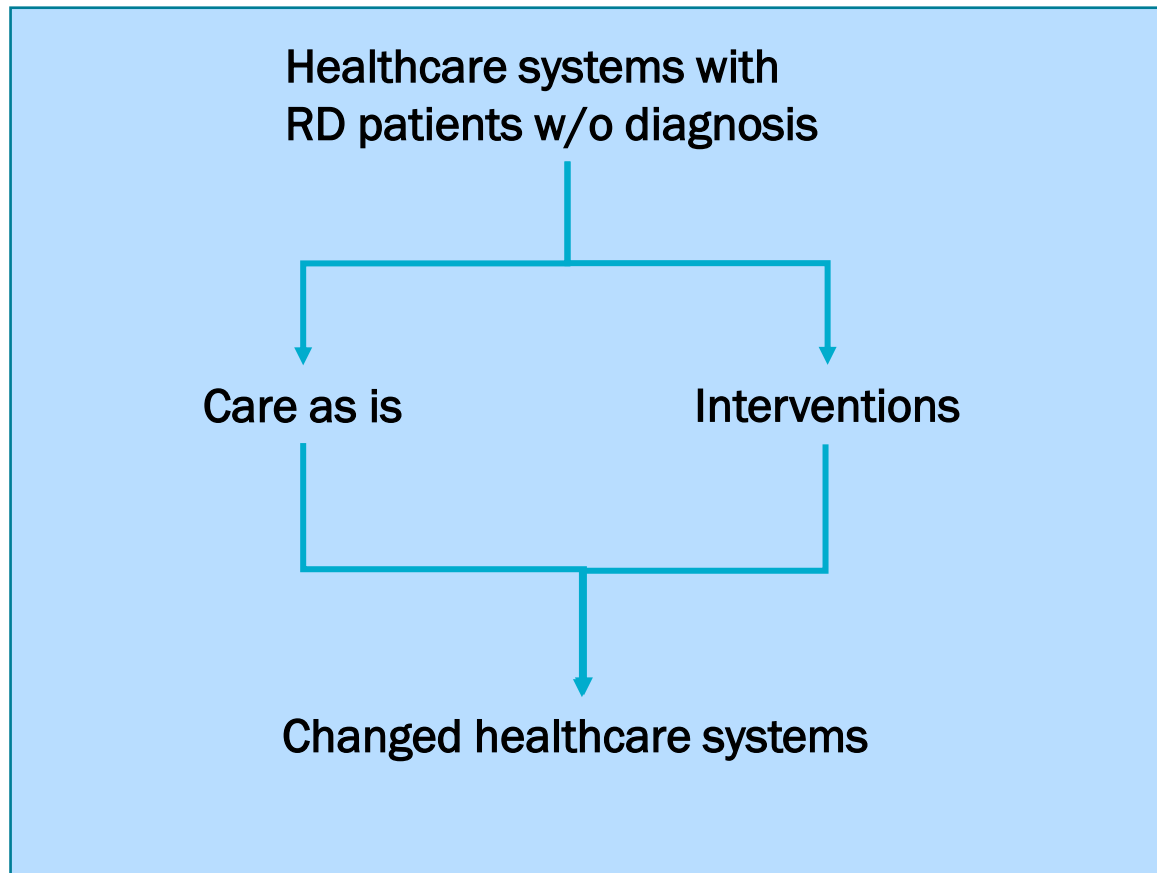
- Data interpretation in the disease context
- 1 DITF per ERN
- Defines disease groups / disease specific use cases
- Selects cohorts



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

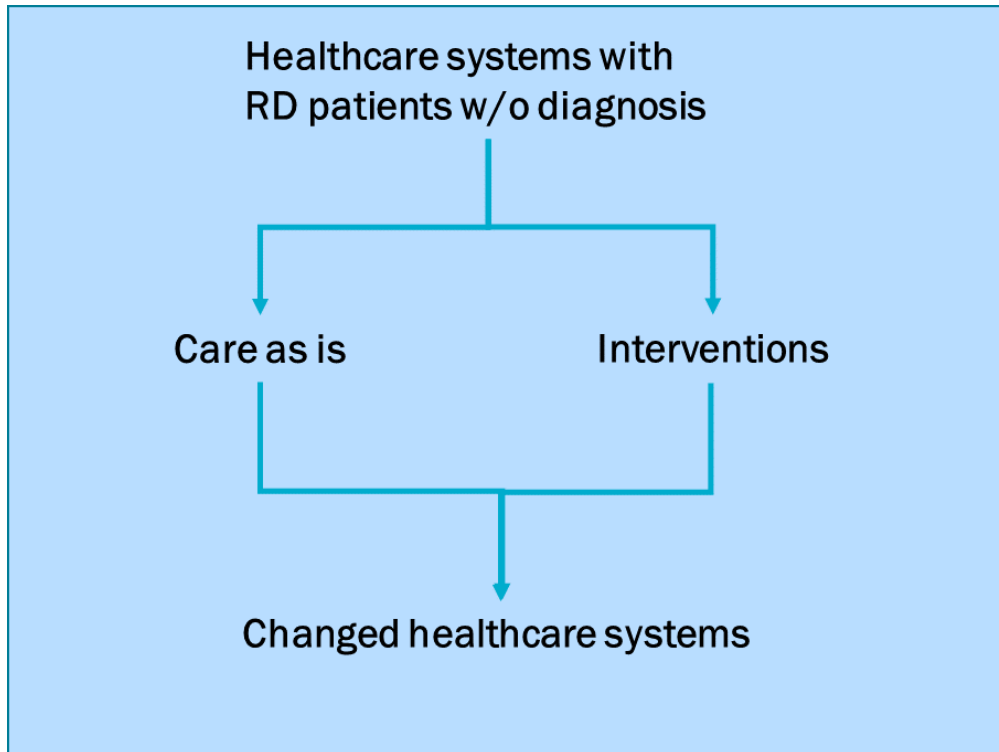
Interventions

- Novel Diagnostic Technology
→ **LONG-READ SEQUENCING**



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	<ul style="list-style-type: none"> • Phenotype (HPO) • Genotype (HGVS)
	7.1.	Agreement to be contacted for	Patient's permission exists for being contacted for research	<ul style="list-style-type: none"> • YES • NO

RD DIAGNOSIS – HEALTHCARE SYSTEM PERSPECTIVE

How to measure the change in healthcare systems

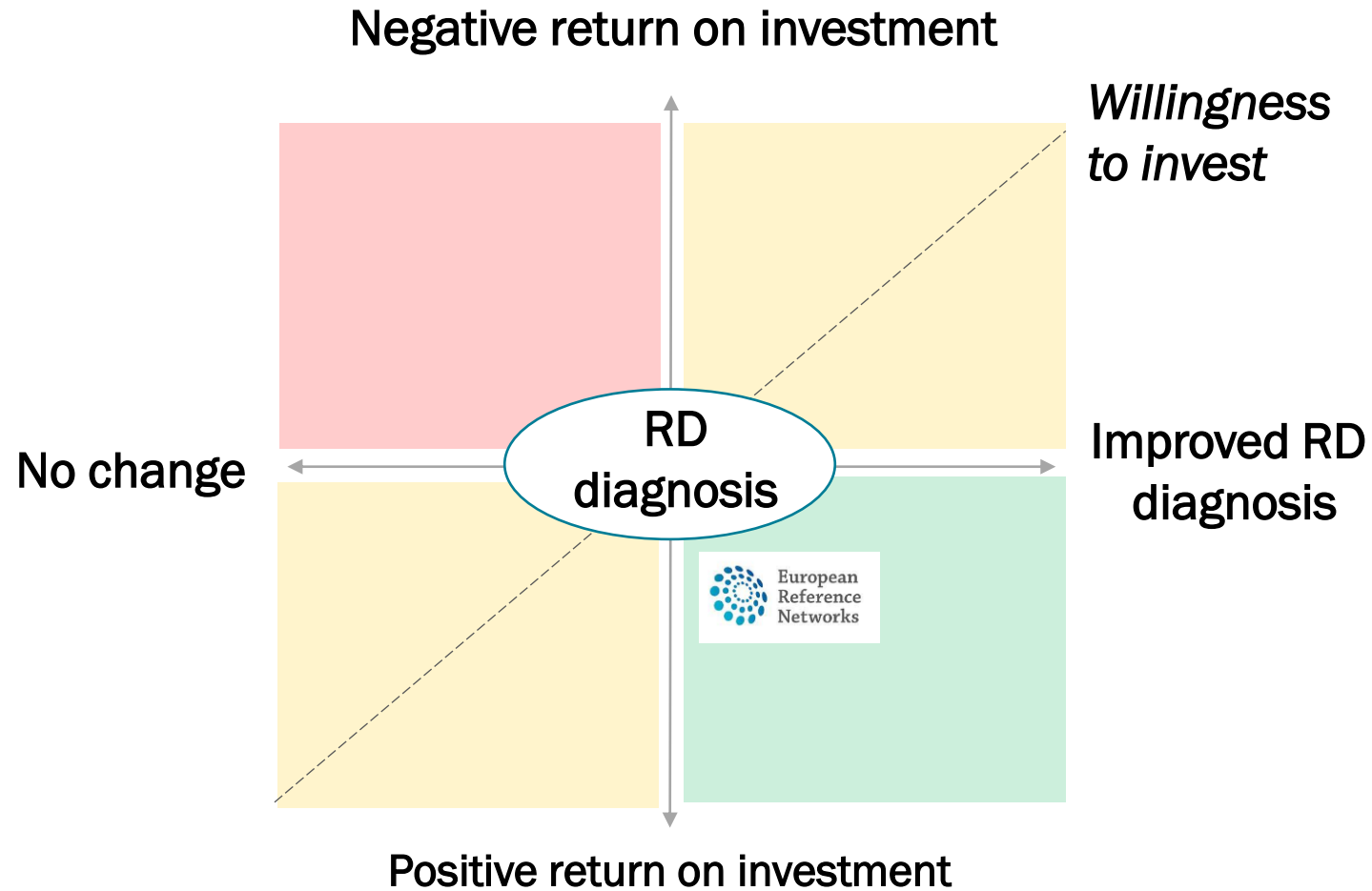
- European Reference Network Registries

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→ 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





THANK YOU!

