



Solve  RD

# Solving the unsolved Rare Diseases

The Solve-RD project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 779257.



# Solve-RD – solving the unsolved rare diseases

- EU funded research project
- 1.1.2018 – 31.12.2022 (5 year project)
- 22 partners from 10 countries
- Coordinated by Olaf Riess & Holm Graessner (Tübingen)
- Co-coordinated by Han Brunner (Nijmegen) and Anthony Brookes (Leicester)

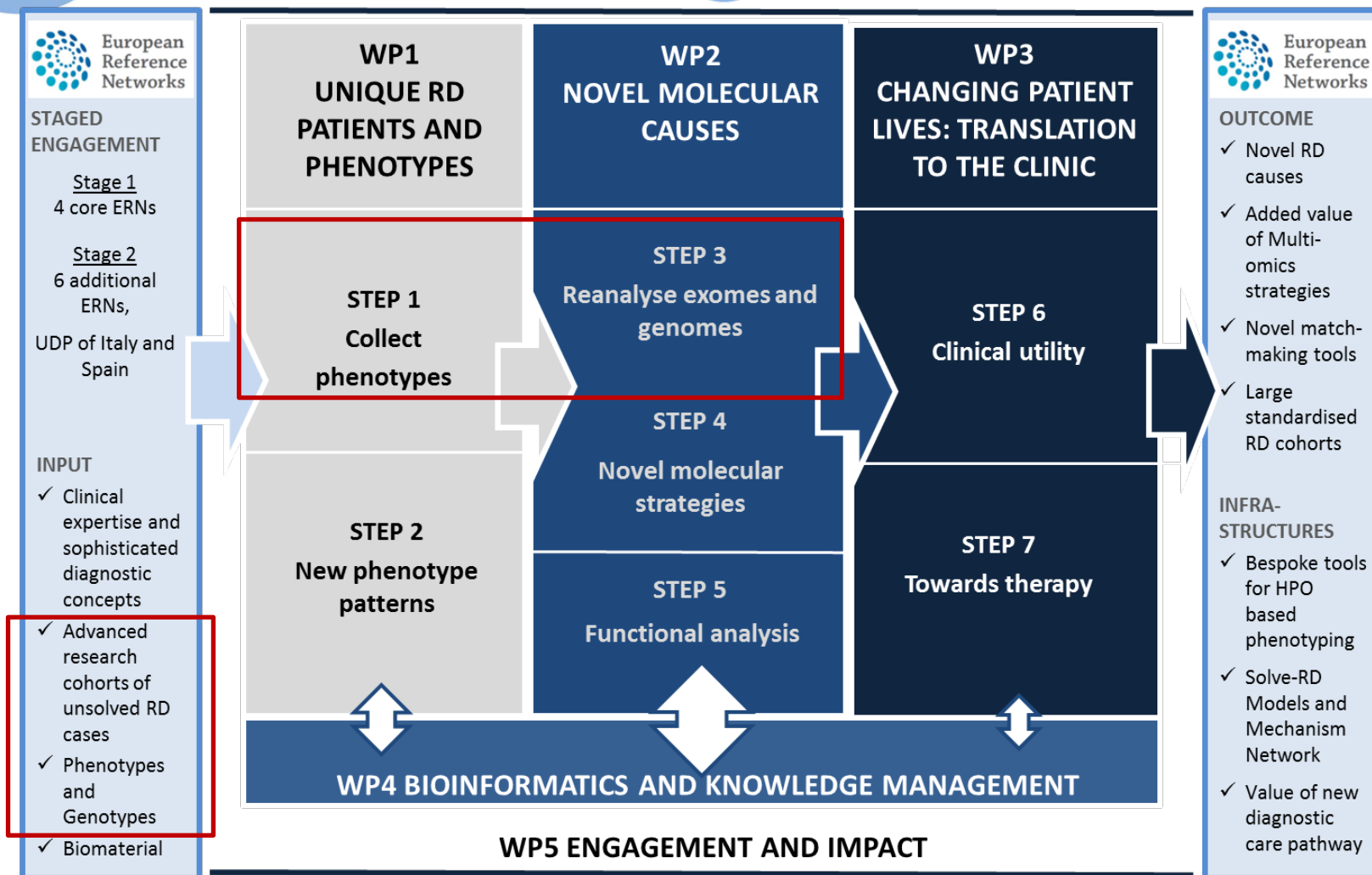


# Resources and infrastructures

- **Core group of 4 European Reference Networks:** ERN-RND, ERN-EURO-NMD, ERN-ITHACA, ERN-GENTURIS
- **Associated networks:** 6 additional ERNs and 2 Undiagnosed Patient Programmes (Italy, Spain)
- **Existing RD infrastructures:** RD-Connect/ELIXIR, Orphanet, HPO, EuroGentest, Canadian Models and Mechanisms Network
- **Patient organisations:** EURORDIS, Genetic Alliance UK



# SolveRD





# Main implementation steps (1)

## Challenge 1: Accessibility of unsolved RD cohorts with of comprehensive genetic and phenotypic data

1	Collect Phenotypes	<ul style="list-style-type: none"><li>➔ Standardized genetic and phenotypic information of more than 19,000 unsolved RD cases from advanced research cohorts of ERNs will be pooled and harmonized</li><li>➔ Identify novel ultra-rare RD entities through phenotype-jamborees in ERNs</li></ul>
2	New phenotype patterns	<ul style="list-style-type: none"><li>➔ Creation of ontology of unsolved cases allowing for new diagnostic hypotheses.</li></ul>



# Main implementation steps (2)

## Challenge 2: New and improved approaches for the discovery of novel molecular causes

3	Reanalyse exomes / genomes	<ul style="list-style-type: none"><li>→ Data mining on the variants and regions detected with Solve-RD standard analysis pipelines</li><li>→ Approaches: (i) a data driven approach, (ii) an expert driven approach.</li></ul>
4	Novel molecular strategies	<ul style="list-style-type: none"><li>→ Solve unsolved diseases from unique RD cohorts provided by 4 ERNs with unique phenotypes applying novel (multi-) omics tools</li><li>→ Solve ultra-rare diseases presenting with novel phenotypes by holding phenotype-jamborees'</li><li>→ 'Solve the unsolvable syndromes' with joined power of clinical ERN and genomics experts applying all available latest -omics tools</li></ul>
5	Functional analysis	<ul style="list-style-type: none"><li>→ Validate up to 50 novel candidate genes identified by a re-sequencing those in even larger cohorts of relevant clinical samples (n=5,000)</li><li>→ Implement an innovative brokerage system which allows gene/model/pathway experts to verify pathogenicity of new genes or new disease mechanisms quickly</li></ul>



# Solve-RD cohorts

## UNSOLVED CASES\*

**Definition:** Rare disease cases with an inconclusive exome/genome

**Number:** 19,000 unsolved exomes/genomes

**Main activities:** Perform standardised collation and re-analysis

*\*in collaboration with all ERNs, Undiagnosed Disease Initiatives and further associated partners*

1

## SPECIFIC ERN COHORTS

**Definition:** Disease group specific cohorts from four core ERNs (exome available)

**Number:** a) 2,000 WGS for more complete (non-)coding sequence & CNV/SVs etc.;

b) 500 long-read WGS;

c) >2,000 cases novel omics approaches

**Main activities:** Conduct „beyond the exome“ approaches

2

## ULTRA RARE RARE DISEASES

**Definition:** Phenotypically most special/remarkable patients with a rare disease without an exome

**Number:** 1,200 exomes (300 per core ERN)

**Main activities:** Carry out phenotype jamborees and exome analysis

3

4

## THE UNSOLVABLES

**Definition:** Highly recognisable clinically defined diseases / syndromes for which no disease gene was identified yet despite WES/WGS and considerable research invested

**Number:** 120 syndromes/ diseases

**Main activities:** apply all -omics tools to „crack“ the „Unsolvables“



# Care pathway for unsolved patients



Undiagnosed disease program – Centre for Rare Disease Tübingen

7



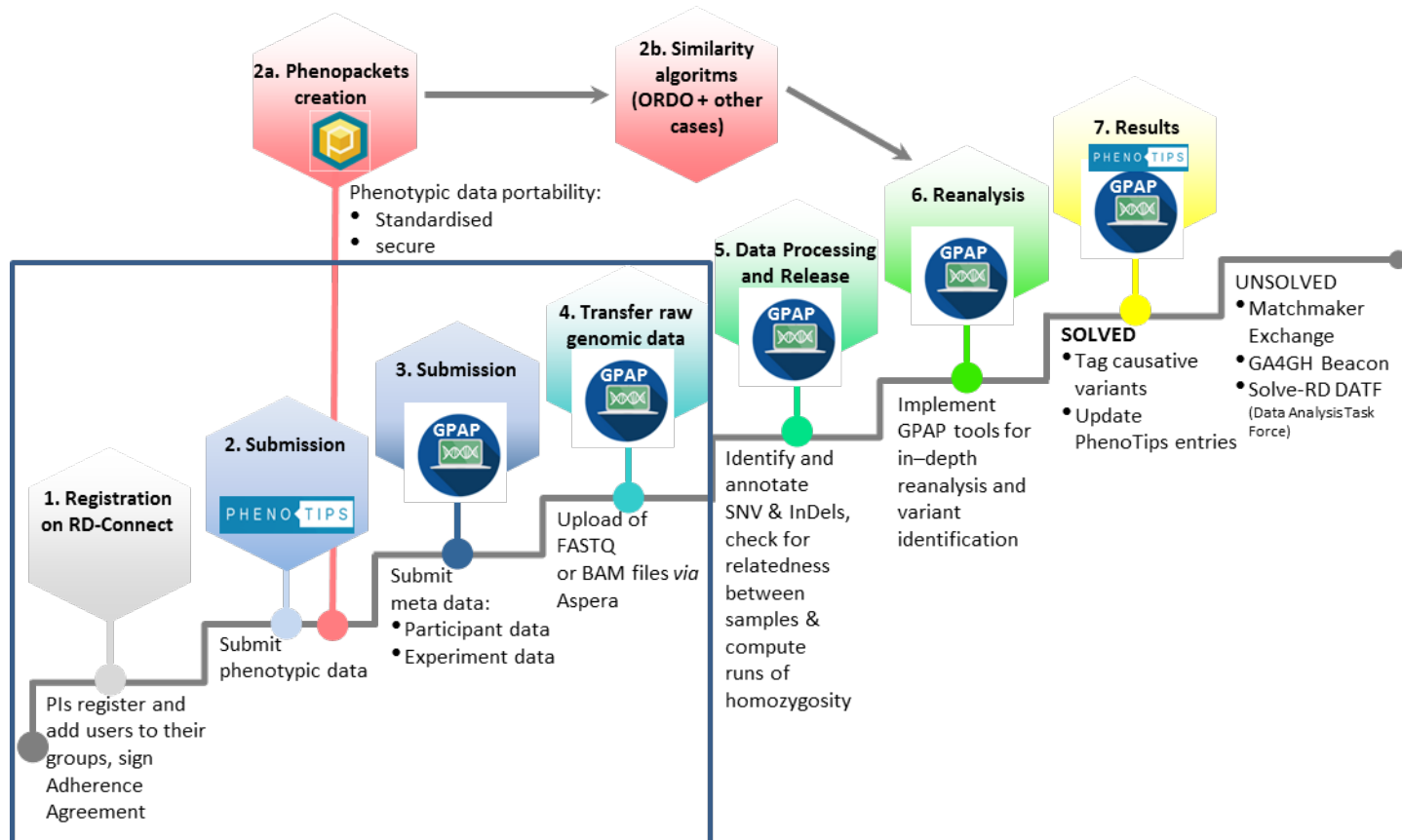
- Contact point and processes
- Diagnostic pathway
- Multidisciplinary team
- Regular case conferences
- E-consultations in Germany and Europe
- Exome/genome sequencing





# Data workflow in Solve-RD

## Data Workflow and WP1



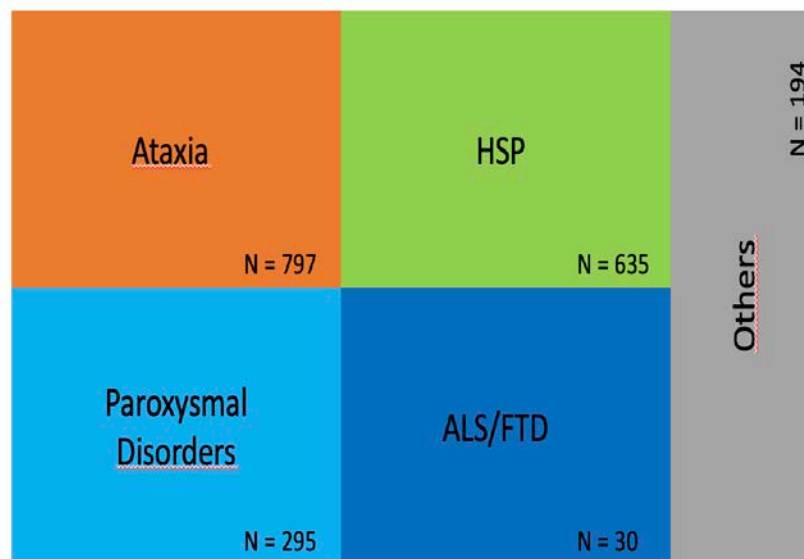


# Status upload of unsolved exomes/genomes:

- Status October 2019: **8612 data sets uploaded**

ERN	uploaded data sets by October 2019
ITHACA	4165
RND	3011
NMD	1119
Genturis	317
	<b>8612</b>

- Deliverable D1.7: Pooling of clinical, phenotypic and experimental data from **19.000 unsolved RD cases**



upload by Sept 30, 2019

## A. Reanalysis of exomes (cohort 1)

→ 4 complementary analyses approaches:

- (i) *family-by-family-based*
- (ii) *gene-based*
- (iii) *cohort-based*
- (iv) *strategy-based*

→ all orchestrated via specific **project templates** = basis for collaboration within DITF, between DITF and DATEF, transparency, accountability, harmonization of efforts



- HPOs
- ORDO-IDs



# ORDO used for unsolved cases – for example

- Adult-onset autosomal dominant leukodystrophy
- Ataxia neuropathy spectrum
- Ataxia with dementia
- Autosomal dominant cerebellar ataxia
- Autosomal dominant spastic ataxia
- Autosomal recessive cerebellar ataxia
- Autosomal recessive spastic ataxia
- Complex hereditary spastic paraplegia



# ORDO used for solved cases – for example

- Autosomal recessive spastic paraplegia type 21 - *SPG21 gene*
- Autosomal recessive spastic paraplegia type 15 - *ZFYVE26 gene*



# Summary

- 1) Solve-RD clinical and research centres are situated at the end of the diagnostic care pathway of a patient → transition from care at ERN centres to research → “beyond the exome”
- 2) The “rareness” of the disease has been indicated by expert clinicians
- 3) Unsolved RD cases are coded with more general terms
- 4) Solved cases are coded with mutation level terms
- 5) As a result of Solve-RD, the introduction of new ORPHA codes will be necessary that reflect the identification of novel disease causing genes
- 6) Solve-RD does not primarily deal with coding issues that are linked to the diagnostic care pathway



For more information visit [www.solve-rd.eu](http://www.solve-rd.eu)

Follow us on Twitter!



@Solve\_RD