Solving the unsolved Rare Diseases

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Solving the unsolved Rare Diseases

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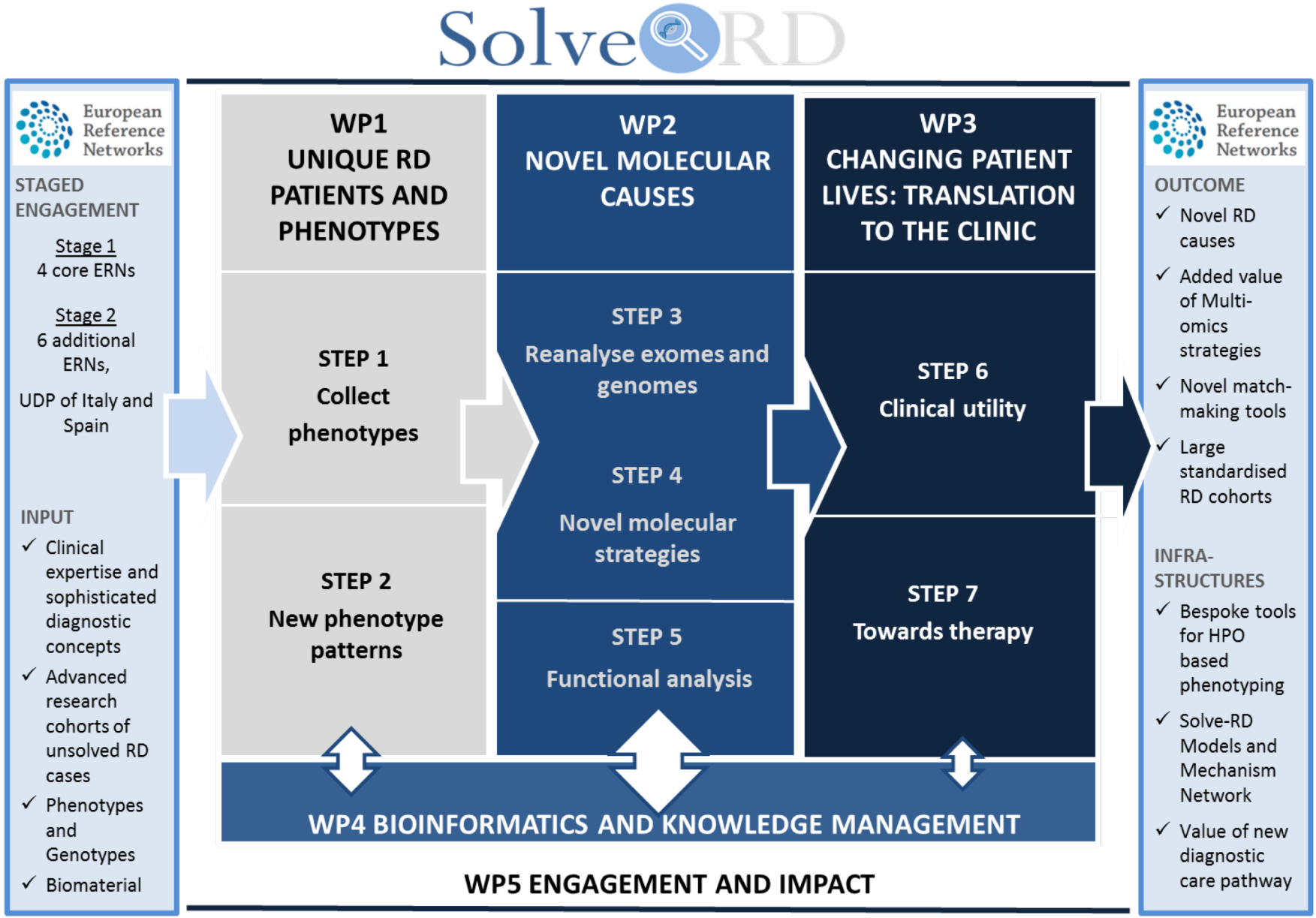
Partic-ipant Nº	Participant Organisation Name	Short Name	Country
1	Eberhard Karls Universitaet Tuebingen	EKUT	Germany
2	Stichting Katholieke Universiteit Nijmegen	RUMC	Netherland
3	University of Leicester	ULEIC	U.K.
4	University of Newcastle upon Tyne	UNEW	U.K.
5	Central Manchester University Hospitals NHS Foundation Trust	MUH	U.K.
6	Centre Hospitalier Reg Universitaire Dijon	DIJON	France
7	Fundacio Centre de Regulacio Genomica	CRG-CNAG	Spain
8	EURORDIS – European Organisation for Rare Diseases Association	EURORDIS	France
9	Institut National de la Sante et de la Recherche Medicale	INSERM	France
10	Univerzita Karlova	CUP	Czech Republic
11	European Molecular Biology Laboratory	EMBL-EBI	U.K.
12	The Jackson Laboratory Non Profit Corporation	JAX	USA
13	King's College London	KCL	U.K.
14	University College London	UCL	U.K.
15	Universiteit Antwerpen	UA	Belgium
16	Universita degli Studi della Campania Luigi Vanvitelli	Uni Naples	Italy
17	Universita degli Studi di Ferrara	UNIFE	Italy
18	Universitaetsklinikum Bonn	UHB	Germany
19	IPATIMUP – Instituto de Patologia Eimunologia Molecular da Universidade do Porto PCUP	UoP	Portugal
20	Academisch Ziekenhuis Groningen	UMCG	Netherlands
21	Charite – Universitaetsmedizin Berlin	Charité	Germany


SolveRD
European Reference Networks
STAGED ENGAGEMENT
Stage 1
4 core ERNs
Stage 2
6 additional ERNs,
UDP of Italy and Spain
INPUT
✓ Clinical expertise and sophisticated diagnostic concepts
✓ Advanced research cohorts of unsolved RD cases
✓ Phenotypes and Genotypes
✓ Biomaterial
WP1 UNIQUE RD PATIENTS AND PHENOTYPES
WP2 NOVEL MOLECULAR CAUSES
WP3 CHANGING PATIENT LIVES: TRANSLATION TO THE CLINIC
STEP 1 Collect phenotypes
STEP 2 New phenotype patterns
STEP 3 Reanalyse exomes and genomes
STEP 4 Novel molecular strategies
STEP 5 Functional analysis
STEP 6 Clinical utility
STEP 7 Towards therapy
WP4 BIOINFORMATICS AND KNOWLEDGE MANAGEMENT
WP5 ENGAGEMENT AND IMPACT
European Reference Networks
OUTCOME
✓ Novel RD causes
✓ Added value of Multi-omics strategies
✓ Novel match-making tools
✓ Large standardised RD cohorts
INFRA-STRUCTURES
✓ Bespoke tools for HPO based phenotyping
✓ Solve-RD Models and Mechanism Network
✓ Value of new diagnostic care pathway

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

Main implementation steps

Challenge 1: Accessibility of unsolved RD cohorts with of comprehensive genetic and phenotypic data		
1	Collect Phenotypes	➔ Standardized genetic and phenotypic information of more than 19,000 unsolved RD cases from advanced research cohorts of ERNs will be pooled and harmonized ➔ Identify novel ultra-rare RD entities through phenotype-jamborees in ERNs
2	New phenotype patterns	➔ Creation of ontology of unsolved cases allowing for new diagnostic hypotheses.

Main implementation steps

Challenge 2: New and improved approaches for the discovery of novel molecular causes		
3	Reanalyse exomes / genomes	➔ Data mining on the variants and regions detected with Solve-RD standard analysis pipelines ➔ Approaches: (i) a data driven approach, (ii) an expert driven approach.
4	Novel molecular strategies	➔ Solve unsolved diseases from unique RD cohorts provided by 4 ERNs with unique phenotypes applying novel (multi-) omics tools ➔ Solve ultra-rare diseases presenting with novel phenotypes by holding phenotype-jamborees‘ ➔ ‚Solve the unsolvable syndromes‘ with joined power of clinical ERN and genomics experts applying all available latest -omics tools
5	Functional analysis	➔ Validate up to 50 novel candidate genes identified by a re-sequencing those in even larger cohorts of relevant clinical samples (n=5,000) ➔ Implement an innovative brokerage system which allows gene/model/pathway experts to verify pathogenicity of new genes or new disease mechanisms quickly

Main implementation steps

Challenge 3: Translate discoveries to impacting clinical practice		
6	Clinical utility	➔ Communication of (gen)omics test results to patients in an evidence-based manner ➔ Cost-effectiveness of –omics technologies in a diagnostic setting
7	Towards therapy	➔ Patient registration in registries and biobanks ➔ Treatabolome

Numbers

- Re-analysis of 19.000 exomes of unsolved cases
- 800 ultra-rare RD patients presenting new phenotypes that will undergo WES/WGS
- WGS for 2.000 cases to achieve a more complete coding sequence
- Long-read genomes for 500 cases with smartly chosen phenotypes such as anticipated repeat expansion disorders (SBMA; DM1 and DM2)
- Novel omics approaches (transcriptome, epigenome, proteome, metabolome, deep WES, deep molecular phenotyping) for more than 2.000 cases
- Multiomics approaches for 120 „unsolvable syndromes“