The main ambitions of Solve-RD are (i) to solve large numbers of rare disease (RD), for which a molecular cause is not known yet, by sophisticated combined Omics approaches, and (ii) to improve diagnostics of RD patients through contribution to, participation in and implementation of a “genetic knowledge web” which is based on shared knowledge about genes, genomic variants and phenotypes. Solve-RD will pursue a clear visionary and integrated “beyond the exome” approach and will demonstrate strategies to identify disease causes in unsolved genetic RD patients as currently about 50% of all RD causes remain unclear.

Through its integrated approach focusing on identifying disease-causing mutations in patients who received WES with a negative or an inconclusive molecular diagnosis, Solve-RD will significantly increase the diagnostic yield from 50% to >70% by developing novel strategies using novel molecular approaches.

- EU-funding: 15 Mio. EUR under Horizon 2020
- Project duration: five years (1.1.2018 - 31.12.2022)
- Involves 4 European Reference Networks (ERNs) - the core ERNs: ERN-RND, ERN-EURO-NMD, ERN-ITACA, ERN-GENTURIS
- Consortium comprises 21 partner from 10 countries:
  - Leading clinicians, geneticists and translational researchers of 4 core ERNs
  - RD research and diagnostic infrastructures (RD-Connect, Orphanet/ORDO, Human Phenotype Ontology [HPO], EuroGentest)
  - Patient organisations (EURORDIS, GenAttract Alliance)
  - Leading experts in the field of ‘omics technologies, bioinformatics and knowledge management

Key Deliverables

- Novel disease causing genes
- Novel validated disease causing genes will be transferred to routine diagnostics
- Novel diagnostic approaches
- Applied in Solve-RD cohorts and scrutinised for clinical utility in Solve-RD
- Ontology of unsolved rare diseases
- Ontology sustainable and ready for uptake of further unsolved RD
- Collection of phenotypic and genomic data from unsolved patients
- High quality FAIR quality data sustainably stored at RD-Connect and EGA
- Evidence based methodology to communicate (gen)omics results
- Methodology has been approved by a few ERNs and will need to be adapted by further ERNs
- Trial-ready cohorts in registries and biobanks
- Registries and biobanks are existing and will need to be exploited for trial design

Implementation Steps

1. **STEP 1**
   - Adapt tools for ‘omics-based collection of phenotypes of unsolved RD cases
   - Standardised methodology to communicate (gen)omics test results to patients in an evidence-based manner
   - Communication of (gen)omics test results in a diagnostics setting

2. **STEP 2**
   - Create an ontology of unsolved RD cases
   - Utilise novel algorithms to compare phenotypes from unsolved RD with phenotypes from solved RD and RD models
   - Implement Solve-RD Models
   - “beyond the exome” approaches
   - Standardised collation of data and re-analysis with state-of-the art variant calling pipeline
   - “Unsolvables” approach

3. **STEP 3**
   - Definition: Unsolvable RD cases with an inconclusive exome
   - Numbers: at least 19,000 cases from ERNs and beyond
   - Main activity: standardisation of data and re-analysis with state-of-the art variant calling pipeline
   - Expected diagnostic efficiency: 3.5% of all cases

4. **STEP 4**
   - Definition: Disease groups specific cohorts from four core ERNs
   - Numbers: 2,000 cases WGS to achieve a more complete (non-)coding sequence, structural variants (SVs) etc.; 500 cases long-read WGS; 750 cases deep WES; 800 cases short-read and 80 cases long-read transcriptomics
   - ‘Unsolvables’ approach: ‘beyond the exome’ approaches
   - Expected diagnostic efficiency: 20-30% of all cases. 10% by moving from WES to WGS, 10-20% by adding transcriptomics, and at least 10% estimate by other omics technologies and moving to long read WGS.

5. **STEP 5**
   - Definition: Ultra-rare RD cases
   - Numbers: 800 cases
   - Main activity: Novel disease causing genes
   - Expected diagnostic efficiency: 50% of all cases; high yield due to exquisite phenotype selection

6. **STEP 6**
   - Definition: The Unsolvable RD cases
   - Numbers: At least 120 cases
   - Main activity: Combination of all available omics tools to ‘crack’ the „Unsolvable“
   - Expected diagnostic efficiency: see cohort 2

Challenges

1. **Challenge 1**
   - Accessibility of unsolved RD cohorts with comprehensive genetic and phenotypic data
   - WP1

2. **Challenge 2**
   - New and improved approaches for the discovery of novel molecular causes
   - WP2

3. **Challenge 3**
   - Translate discoveries to impacting clinical practice
   - WP3

Partners

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<tr>
<th>No.</th>
<th>Partners</th>
<th>City, Country</th>
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<tbody>
<tr>
<td>1</td>
<td>University of Antwerp, Institute of Biomedical Sciences and Department of Medical Genetics</td>
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<td>Universita degli Studi di Ferrara, Institute of Neurology and Institute of Child Health</td>
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<tr>
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<td>University of Maastricht, Institute of Neurology and Institute of Child Health</td>
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<td>9</td>
<td>University of Cambridge, Cambridge Institute of Medical Research, and Institute of Child Health</td>
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