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)

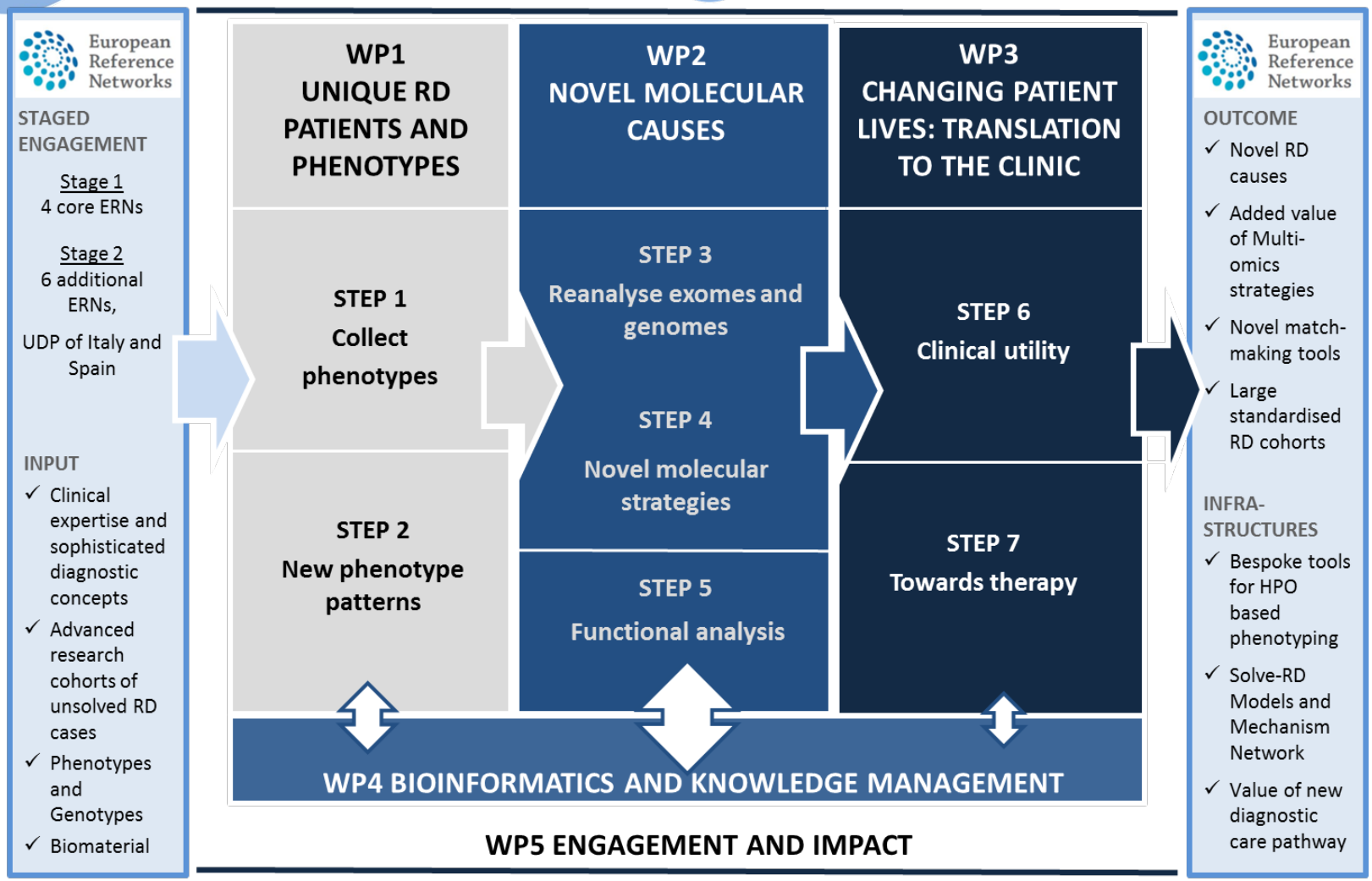
Project partners

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

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

Solve-RD


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

Main implementation steps (1)

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.

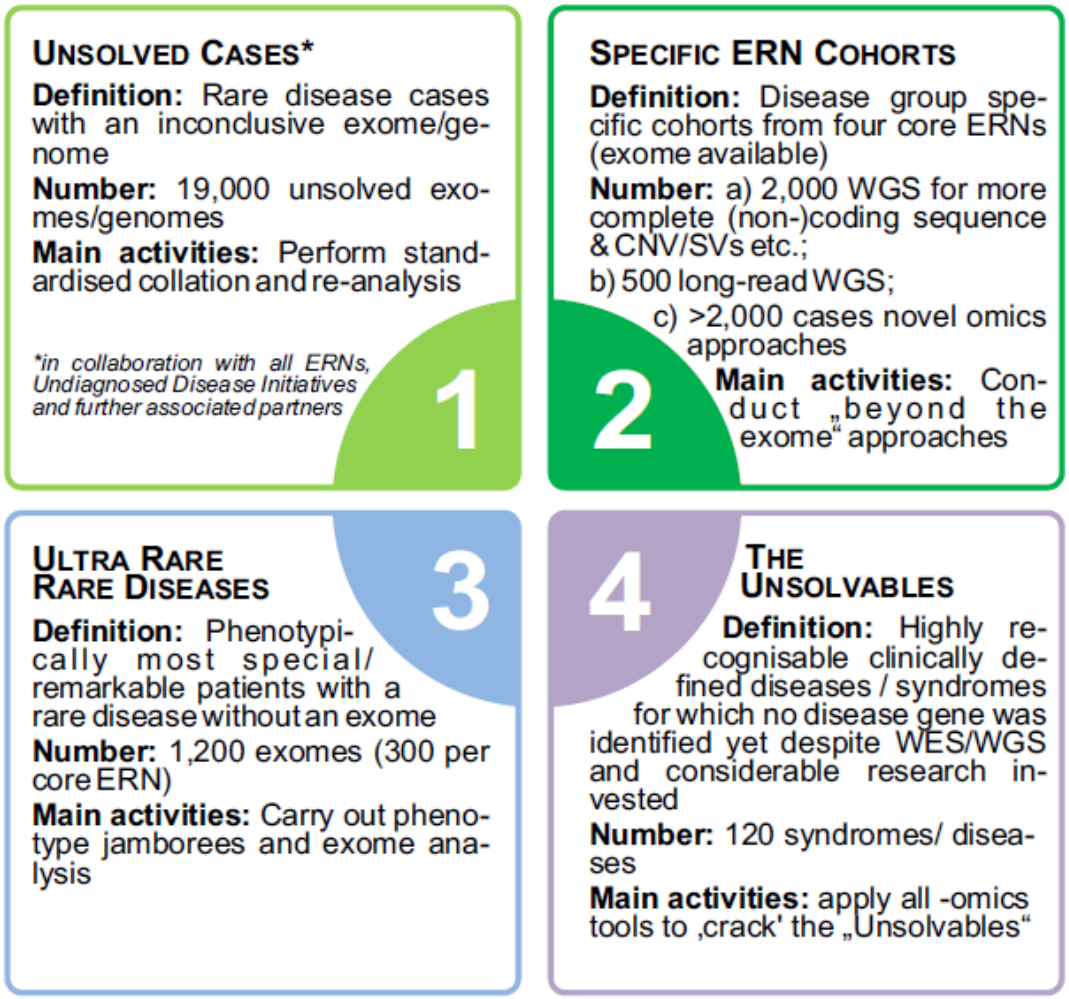
Main implementation steps (2)

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

Main implementation steps (3)

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

Solve-RD cohorts



Unsolved cases – re-analysis

- 1st Data freeze: 30 September 2019
- Embargo: 12 months commencing data release in November 2019

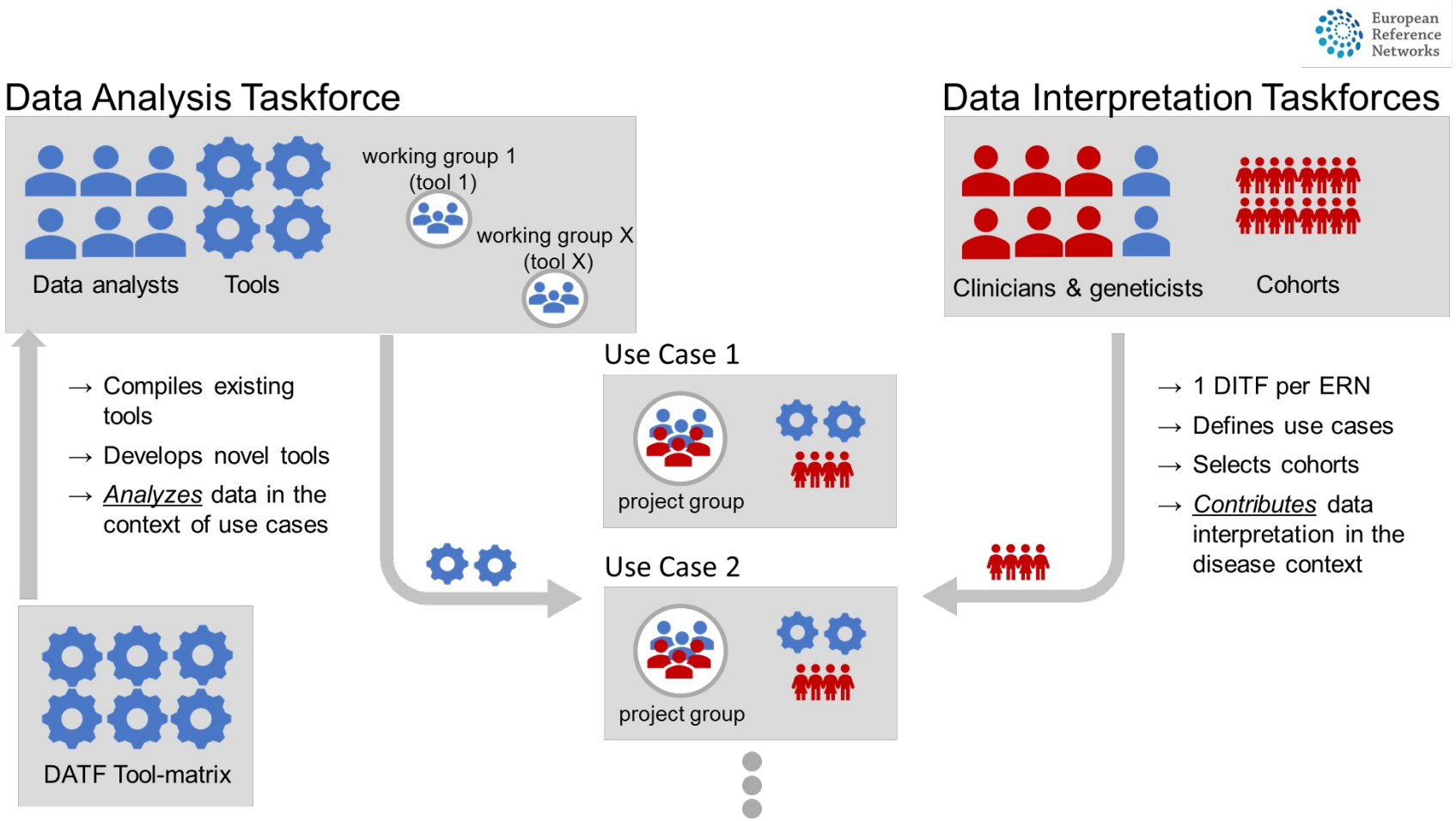
Status upload of unsolved exomes/genomes:

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

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

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

Data Analysis Organisation



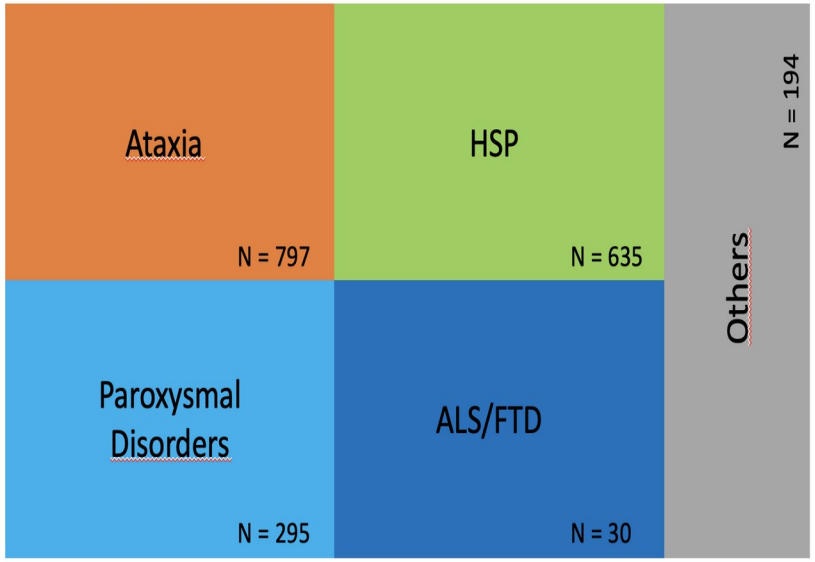
5 Working Groups

1. Relatedness and Runs of Homozigosity (lead: EKUT)
2. SNV and InDel standard filtering (lead: CNAG-CRG)
3. CNV analysis (lead: CNAG-CRG)
4. De novo trio analysis (lead: RUMC)
5. Meta-analysis (lead: RUMC)

4 DITFs

1. Euro-NMD: lead - Ana Topf
2. ERN-RND: lead - Rebecca Schüle-Freyer, Matthis Synofzik
3. GENTURIS: lead - Richarda de Voer
4. ITHACA: lead - Lisenka Visser
5. EpiCare

DITF: ERN-RND



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 DATF, transparency, accountability, harmonization of efforts

Specific ERN Solve-RD - Solving the unsolved Rare Diseases cohorts

	Available in Solve-RD			Novel experimental data 'beyond the exome'												
					WGS		RNAseq						Deep molecular phenotyping			
	WES available	WGS available	Cohort highlights	New WES	Short read	Long read	Short read	Long read	Epigenome	Metabolome	Proteome	Deep-WES	Peptide arrays	Histo-logy	Immune -seq	Description in STEP
Rare neurological disease (ERN-RND)	3,725	235														STEP3
Hereditary ataxias	835	10	RNA pathology important, brain tissue, fibroblasts, iPSCs, PBMCs		250	100	30B;60F; 30I;60P	30B								STEP4b1; 4b2
Hereditary spastic paraplegias (HSP)	1,210	75	Fibroblasts, iPSCs, PBMCs		300		60F;30I; 60P									STEP4b1; 4b2
Paroxysmal movement disorders	165	NA	Fibroblasts, iPSCs		70		25F;25I									STEP4b1; 4b2
Frontotemporal dementia	1,515	150	Brain tissue, fibroblasts, iPSCs, PBMCs		100		40B;30P	30B								STEP4b1; 4b2
200 new ultra-rare RD entity cases				300(50trios)												STEP4a
20 unsolvable syndromes/disorders						60 (20trios)	20		20	20	20	20				STEP4b6
Neuromuscular disease (ERN-NMD)	3,958	674														STEP3
Congenital muscular dystrophies & congenital myopathies (CMD/CM)	416	15	Muscle tissue		100		50				30					STEP4b1; 4b2; 4b4
Limb girdle muscular dystrophies (LGMD) & adult onset myopathies	1,014	73	Muscle tissue		100	50	50	20			30					STEP4b1; 4b2; 4b4
Congenital myasthenic syndromes (CMS) & muscle channelopathies	488	16	Muscle tissue		100		50				25					STEP4b1; 4b2; 4b4
Inherited Peripheral Neuropathies	1,377	300	Muscle tissue		100		50				30					STEP4b1; 4b2; 4b4
Mitochondrial diseases	663	270	Muscle tissue		100		50				25					STEP4b1; 4b2; 4b4
200 new ultra-rare RD entity cases				300(50trios)												STEP4a
50 unsolvable syndromes/disorders						150 (50trios)	50		50	50	50	50				STEP4b6
ITHACA	4,750	500														STEP3
Unexplained ID	4,750	500	Collaboration to access >20,000 cases (DNA from ASID consortium)		640(200 trios,40 recessive)				150 (50 trios)	150						STEP4b1; 4b3; 4b4
200 new ultra-rare RD entity cases				300(50 trios)												STEP4a
50 unsolvable syndromes/disorders						150 (50trios)	50		50	50	50	50				STEP4b6
GENTURIS	720	30														STEP3
Rare hereditary colorectal cancer and polyposis syndromes	500	NA	Fresh colon mucosa (tumor/normal)				100 (50 tumor/ normal)					450	200	250	200	STEP4b1; 4b2; 4b5
Rare hereditary diffuse gastric cancer	100	30	Fresh tumor material						90 (45 tumor/ normal)			150				STEP4b1; 4b2; 4b5
Rare pheochromocytomas and paragangliomas	120		Fresh tumor material		80 (40 tumor-normal)				120 (60 tumor/ normal)			150				STEP4b1; 4b2; 4b5
200 new ultra-rare RD entity cases				300(50trios)												STEP4a
Other collaborators	3,000	Other ERNs & undiagnosed disease networks														
TOTAL EXOMES/GENOMES (n)	16,153	2,848	TOTAL NEW OMICS	1,200	1,940	510	920	80	480	270	260	870	200	250	200	

B = brain tissue; F = fibroblast; I = iPSCs

RND cohorts

Available in Solve-RD				Novel experimental data 'beyond the exome'											
	WES available	WGS available	Cohort highlights	New WES	WGS		RNAseq		Epigenome	Metabolome	Proteome	Deep-WES	Deep molecular phenotyping			Description in STEP
					Short read	Long read	Short read	Long read					Peptidearrays	Histology	Immune-seq	
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200 new ultra-rare RD entity cases				300 (50trios)												STEP4a

Current use cases: ERN-RND

1. **de novo trio WGS**: candidate families will be submitted until Sept 30, 2019 ➔ expected: 41 ataxia, 49 HSP families

2. **Structural and non-coding variants by WGS+RNAseq**: expected 15 ataxia, 15 HSP families; submission deadline June 1st 2020
   Aut-dom WGS: 33 ataxia families, 50 HSP families; 3 affected family members (no unaffected!); submission deadline January 31st 2020

3. **Repeat-expansions and retractions by long range WGS**: 33 ataxia families, preferentially negative cases from aut-dom WGS project. Need to check SOP (DNA) fragmentation, will determine the timeline

4. **Somatic brain mutations in FTD brains:** discovery cohort (brain + blood), followed by validation cohort (blood only). Collaborate with outside partners to increase numbers. Target: 33 brain+blood pairs.

Leveraging long-read WGS for unravelling novel ataxia genes

Ataxias: a unique target cohort for long-range WGS

Background

- >25% of all autosomal-dominant and >50% of all autosomal-recessive ataxia patients remain unsolved *despite advanced WES analysis!*
- ataxias are unique: **repeat-expansions represent the most frequent disease cause**

1. 75% of all known *autosomal-dominant* ataxia cases are caused by repeat-expansions (exonic/coding: SCA1,2,3,7 and 17; non-coding: SCA8,12, 14)

2. 50% of all known *autosomal-recessive* ataxia cases are caused by repeat-expansions

distinguishes ataxias from almost all other neurological diseases (e.g. AD, PD, dystonias, HSP,….)

There is thus strong promise that a substantial share of repeat-expansion disorders are still to be found in the large share of still unsolved WES-negative ataxia cases

Ataxias: a unique target cohort for long-range WGS

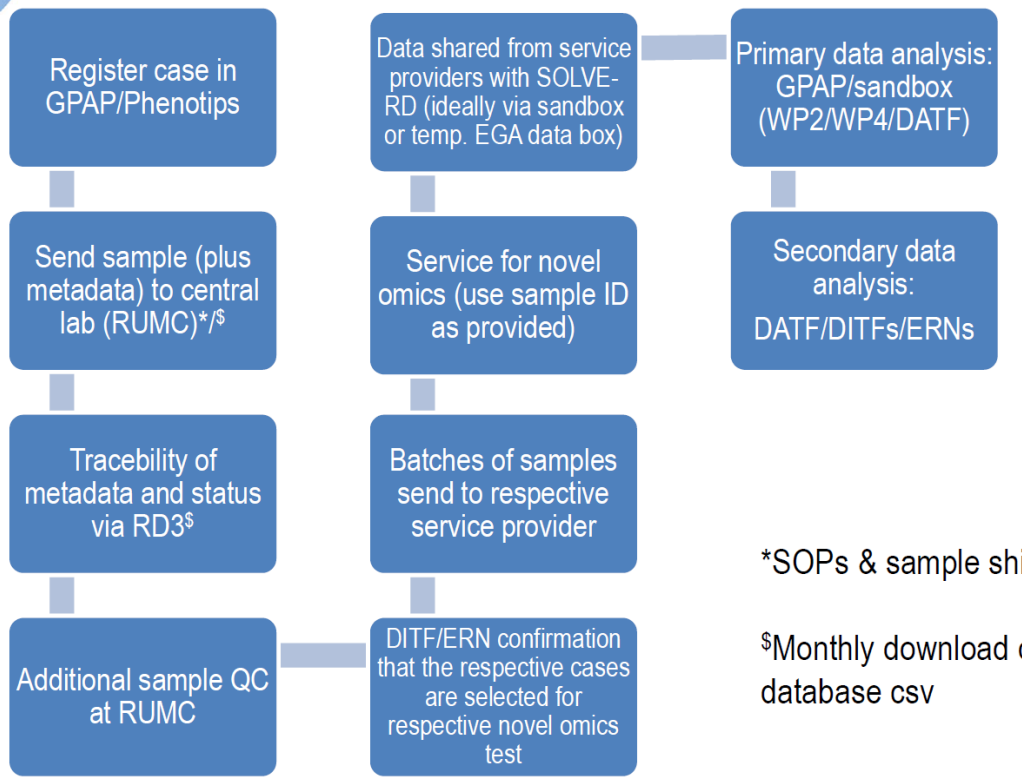
SOLVE-RD project

- goal: demonstrate the power of long-range WGS to unravel novel repeat-expansion diseases
- method: long-range WGS from 33 family „triplets“ from autosomal-dominant ataxia families

- **stringently enriched for novel repeat-expansion disorders:**
    - only families where DNA from >2 affected + >2 non-affected family members are available
    - families must be negative not only on WES, but also on short-read WGS

Sample flow

Sample flow for SOLVE-RD novel omics:



*SOPs & sample shipment sheet

$Monthly download of Nijmegen database csv

Ultra Rare RD

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

Initial ideas:

- Ultra-rare patients seen by the entire ERN (some >100,000 cases)
- Selection by phenotype jamborees virtual/in person
- Usually no previous WES done yet (for majority)
- Last SC: WGS instead of WES

- Solving rare disease, not 'unsolved cases with known disease (e.g. last 20% Kabuki or similar)'

Ultra Rare RD

- ERN-RND – call for ultra-rare cohorts/families
- Definition of what “ultra-rare” means for ERN-RND
- Submitting centres
  - University Medical Center Groningen
  - University Hospital Tuebingen,
  - University of Antwerp
  - UC London
  - Semmelweis University Budapest
  - ICM (Institut du Cerveau et de la Moelle épinière) Paris
  - University Hospital in Krakow
  - Hospital Sant Joan de Déu, Barcelona
  - Institute of Neurogenetics, Lübeck
  - Radboud university medical center, Nijmegen
  - Vall d’Hebron University Hospital, Barcelona
- 12 Cohorts, 51 families
- Status: peer review has been finalised
- Sample shipment will be initiated soon

RDMM-Europe

- 50 catalyst grants à 20.000 EUR open to ERNs and associated partners
- Database implemented – same software as Canadian RDMM
- Activities:
  - Invitation to European researchers (via ERNs and beyond) to register at European RDMM database from September 2018 on
  - Pilot matchmaking in December 2018
  - Full operation from January 2020 on
- Collaboration with the Canadian RDMM Network

WP3 - Treatabolome

- Congenital myasthenic syndromes

  Thompson R[1], Bonne G[2], Missier P[3], Lochmüller H[4,5,6,7].

  Targeted therapies for congenital myasthenic syndromes: systematic review and steps towards a treatabolome.

  Emerg Top Life Sci. 2019 Mar;3(1):19-37. doi: 10.1042/ETLS20180100. Epub 2019 Jan 28.

- Charcot-Marie-Tooth (Matt Jennings, Angela Lochmuller, Rita Horvath - Cambridge)
- Genetic forms of Parkinson (Katja Lohman – Lubeck)
- Early Onset Ataxias (David Gómez Andrés - Barcelona , Matthis Synofizik - Tübingen)
- Channelopathies (Jean-François Desaphy and Bertrand Fontaine - Bari, Paris)
- Laminopathies (Gisèle Bonne, Rabah Ben Yaou, Antonio Atalaia - Paris)

Planned 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“

For more information visit www.solve-rd.eu

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