European Rare Diseases Research Alliance

ERDERA
Diagnostic Research Workstream - An Overview

Holm Graessner, DRW Lead
28.05.2026

Co-funded by the European Union

ERDERA has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement N°101156595.

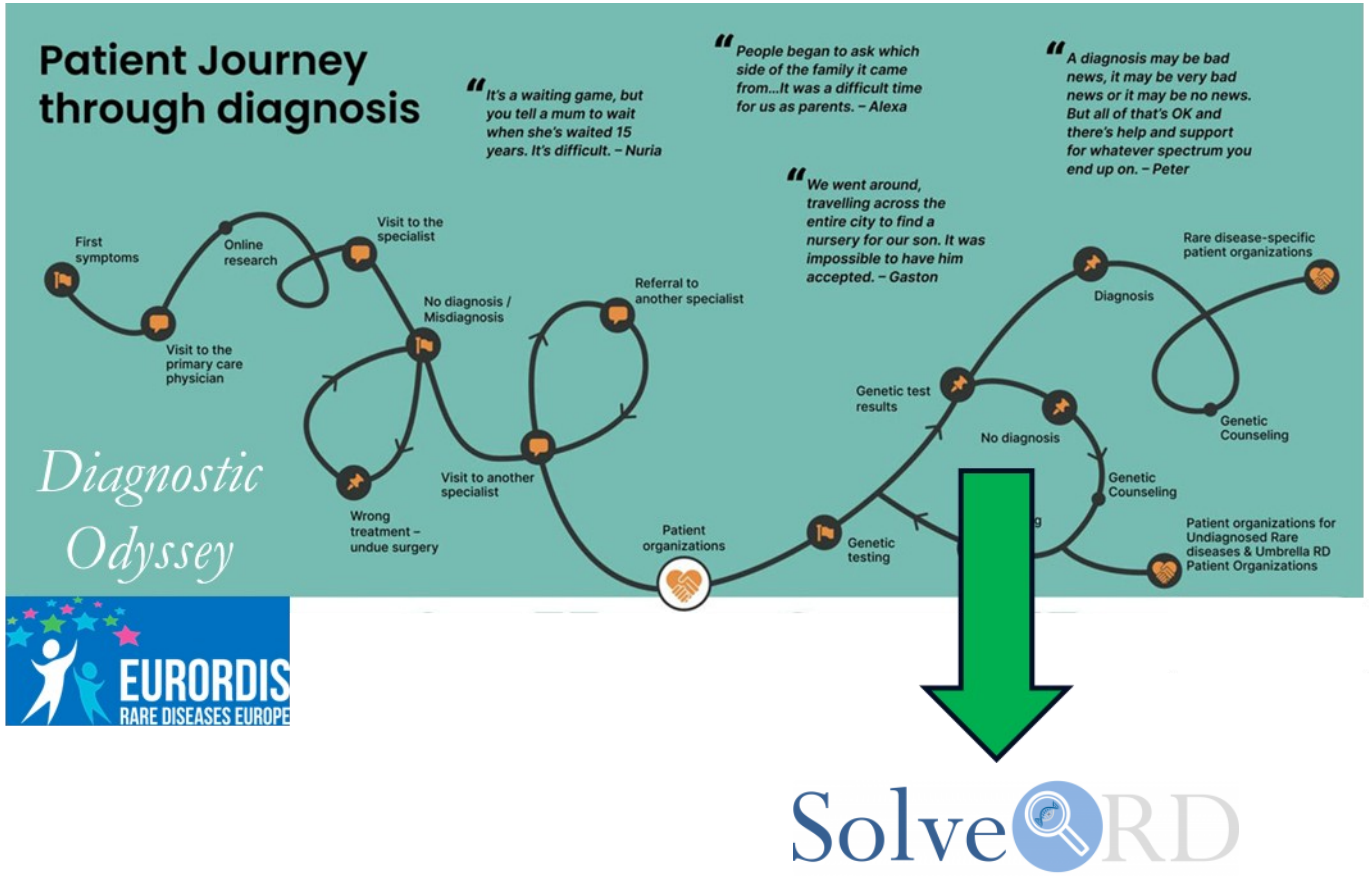
The ERDERA Diagnostic Research Workstream Webinar Series

TODAY

#	Title	Topic	Speakers	Date	Event link
1	The ERDERA Diagnostic Research Workstream – An Overview	General overview of the DRW	Holm Graessner	28 May 2026	View event
2	Data sharing, data management & ethics	DSFA, ethics, data submission, data flow, RD3	Kornelia Ellwanger, Leslie Matalonga	September 2026	Link coming soon
3	The data reanalysis approach of the Diagnostic Research Workstream	Tiered approach, DITF-DATF structure, Solvathon concept	Lisenka Vissers	October 2026	Link coming soon
4	Long-read sequencing and Optical Genome Mapping	WP8 long-read sequencing and OGM	Bart van der Sanden, Alexander Hoischen, Stephan Ossowski / Tobias Haack (tbc)	December 2026	Link coming soon
5	Results of the systematic reanalysis	Results of data reanalysis Tier 1	Sergi Beltran, Gemma Bullich, Lisenka Vissers	February 2027	Link coming soon
6	First results from our innovative reanalysis approach	Results of data reanalysis Tier 2	Sergi Beltran, Lisenka Vissers (tbc)	April 2027 (tbc)	Link coming soon
7	Scaling-up: from distributed to federated reanalysis	Distributed vs. federated approach	Sergi Beltran, Morris Swertz, Julien Thevenon (tbc)	May 2027	Link coming soon
8	Reanalysis of RNAseq data	RNAseq reanalysis results	Vicente Yépez	June 2027	Link coming soon

From Solve-RD to ERDERA‘s Diagnostic Research Workstream

Pathway to Solve-RD research



- Patients with suspected genetic RD and without a molecularly proven genetic diagnosis
- Patients for whom exome sequencing has been done
- Informed patient consent

SolveRD

Solving the Unsolved Rare Diseases

European Reference Network | Neurological Diseases (ERN-RND)

EURO-NMD | Building bridges and breaking barriers in rare neuromuscular diseases

ITHACA

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

GENTURIS

rare genetic tumour risk syndromes

SpainUDP

EpiCARE

European Reference Network for rare and complex epilepsies

rita

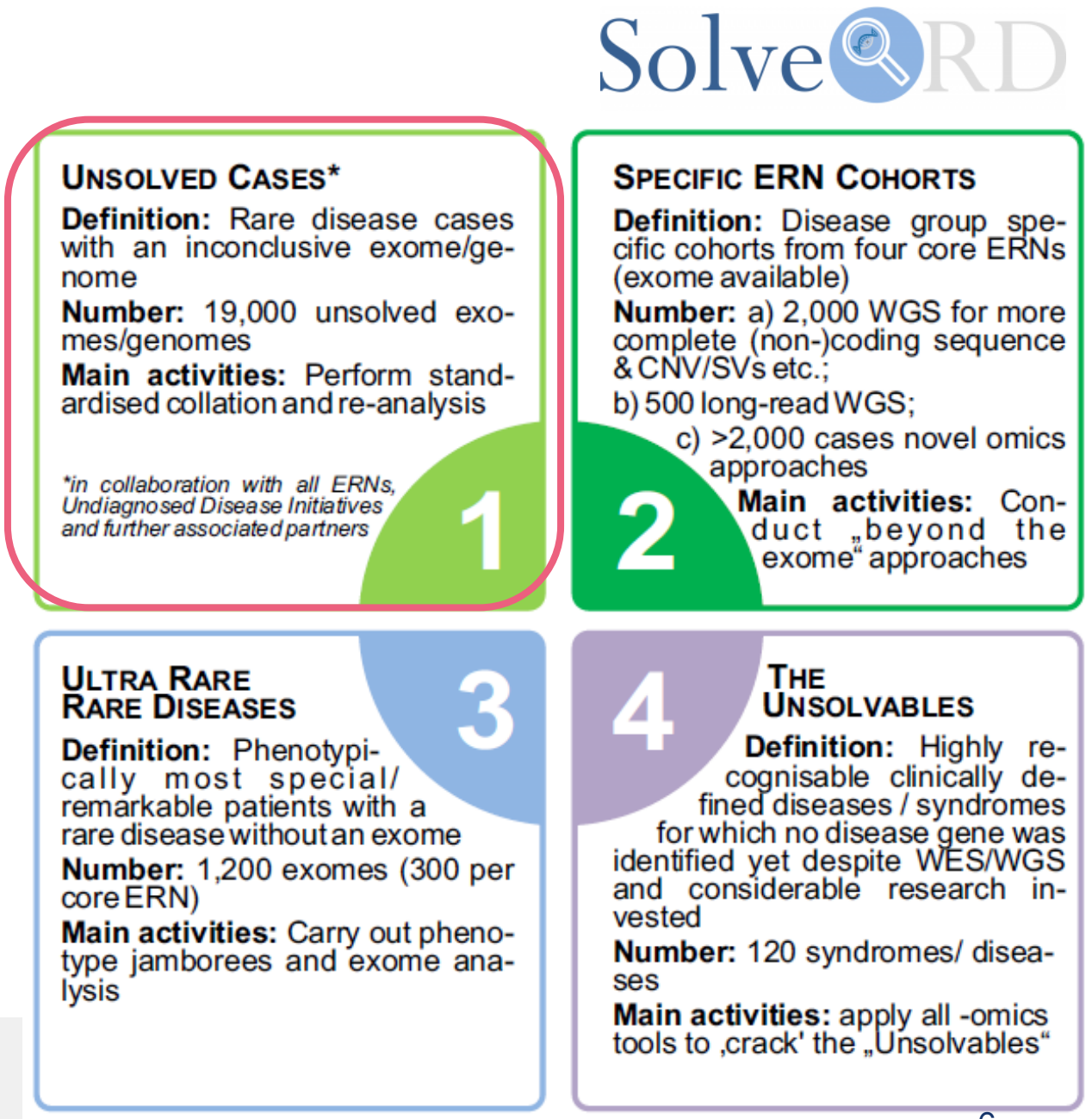
The European Reference Network that aims at improving the care of patients with Rare Immunological Disorders

Solve-RD Reanalysis

Goals:

- EU partners share data after extensive local expert analyses have proven unsuccessful
- Provide a diagnosis to as many undiagnosed patients as possible

~22,500 datasets
(~13,000 families)



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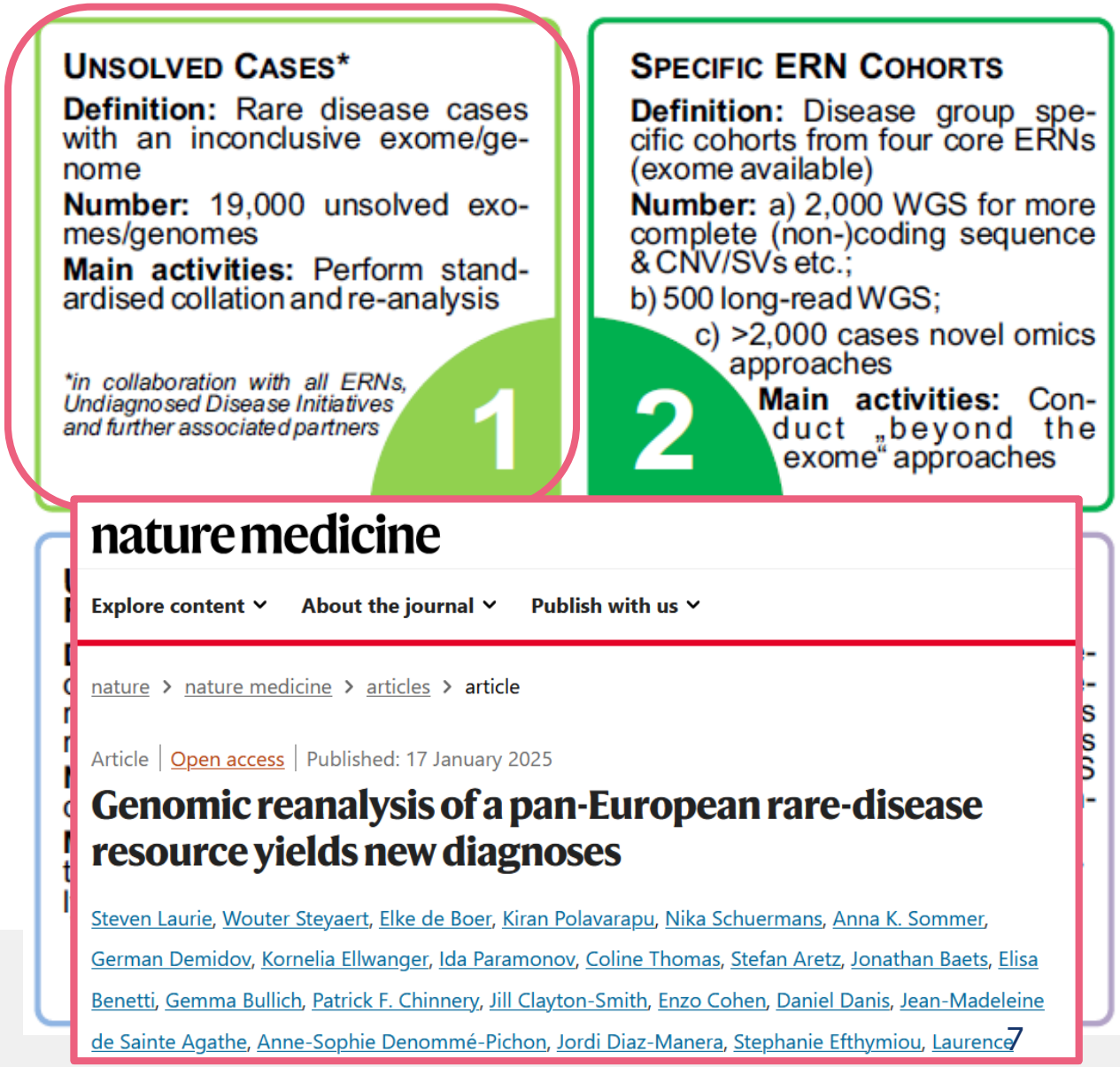


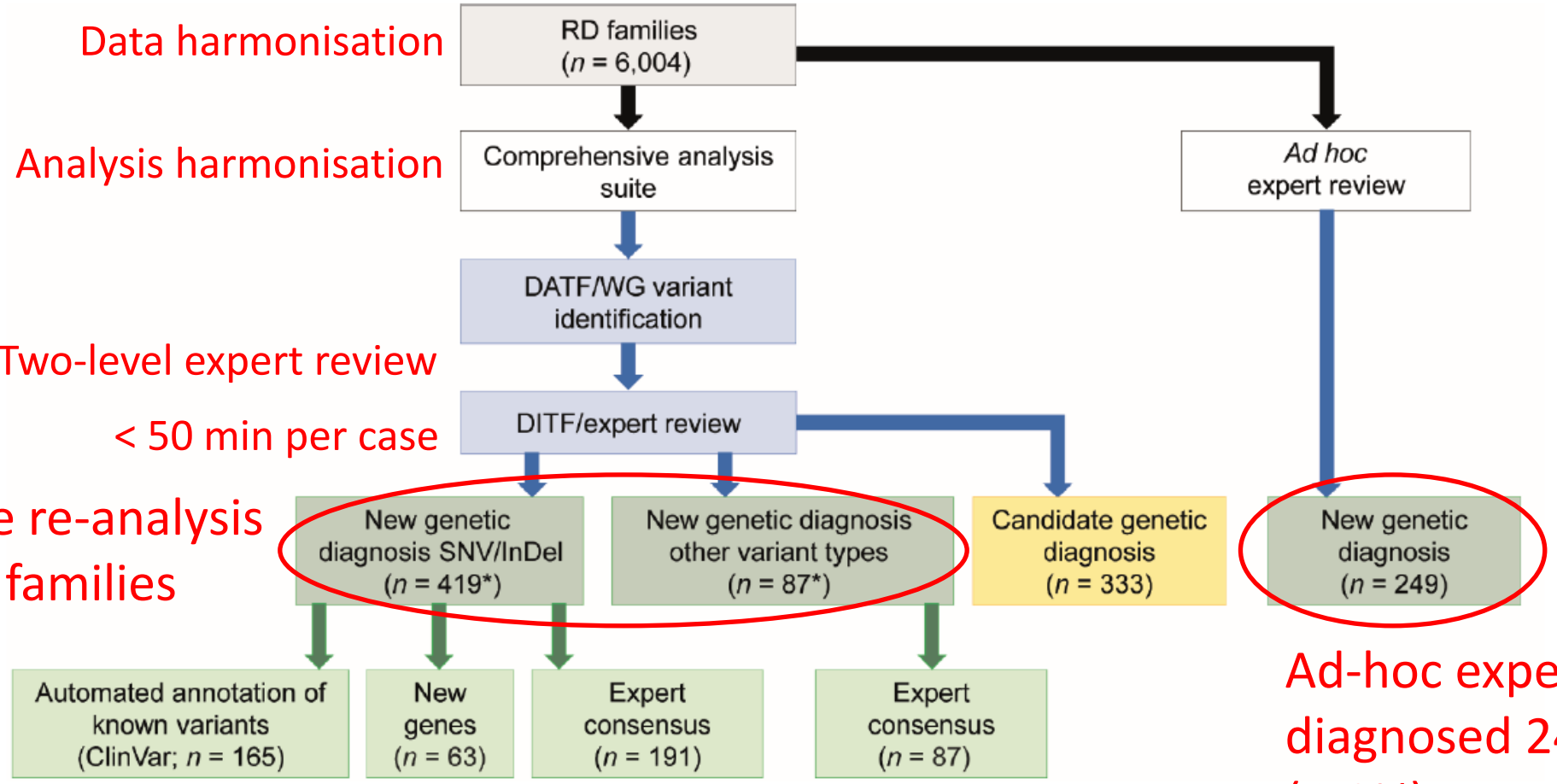
Re-analysis: yield

Data harmonisation

Analysis harmonisation

Two-level expert review

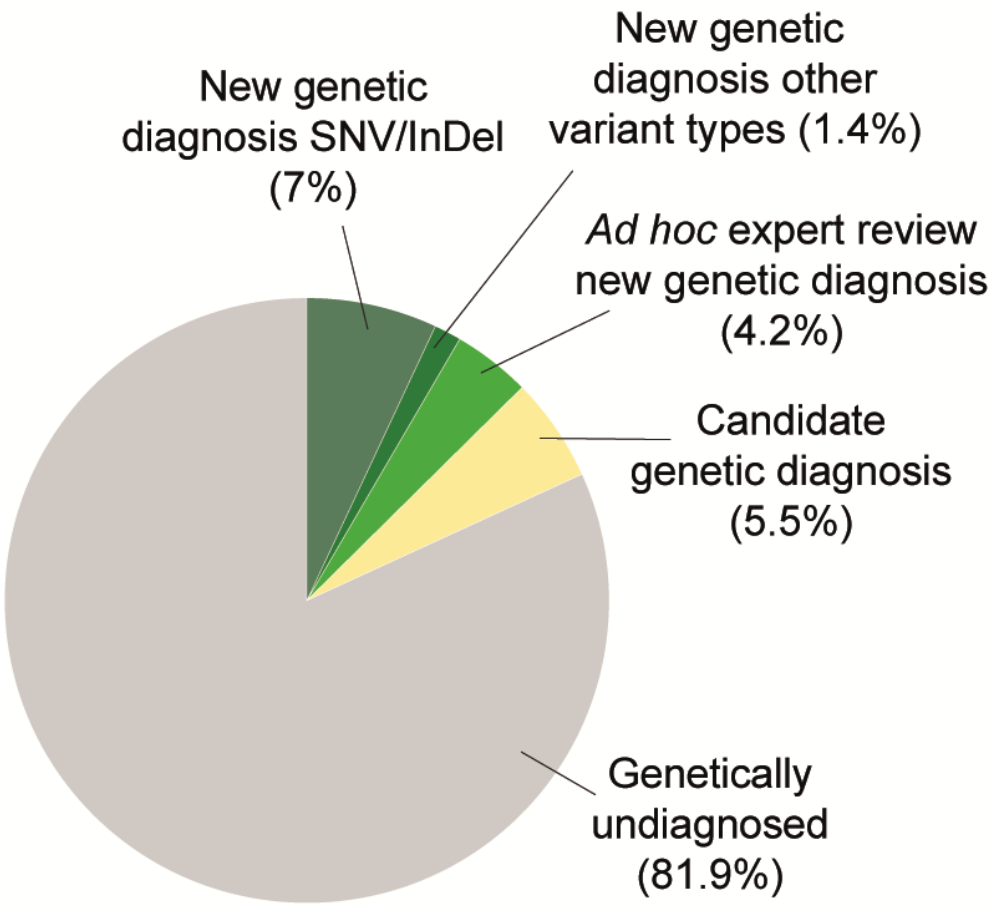
< 50 min per case

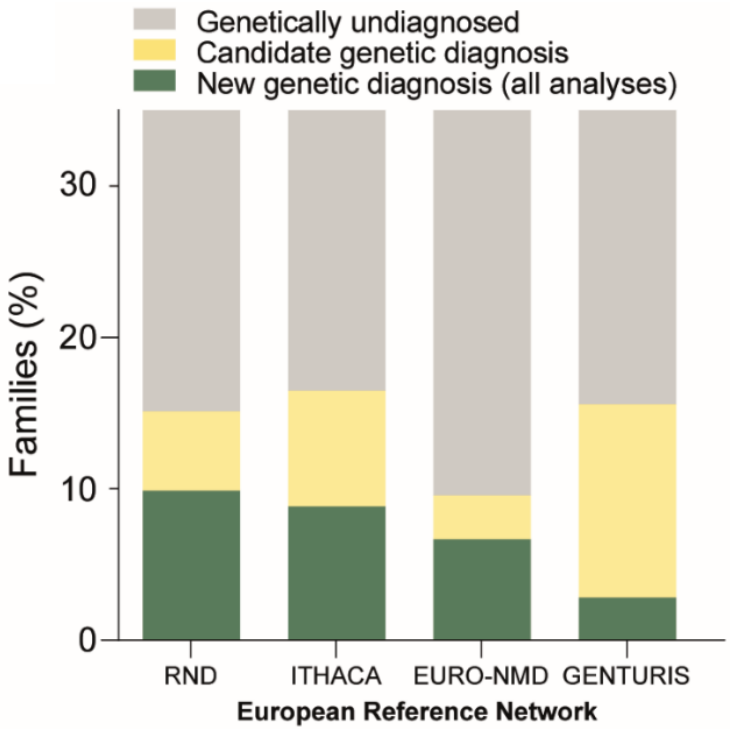


Comprehensive re-analysis diagnosed 506 families (8.4%)

Ad-hoc expert review diagnosed 249 families (4.1%)

Re-analysis: yield per ERN

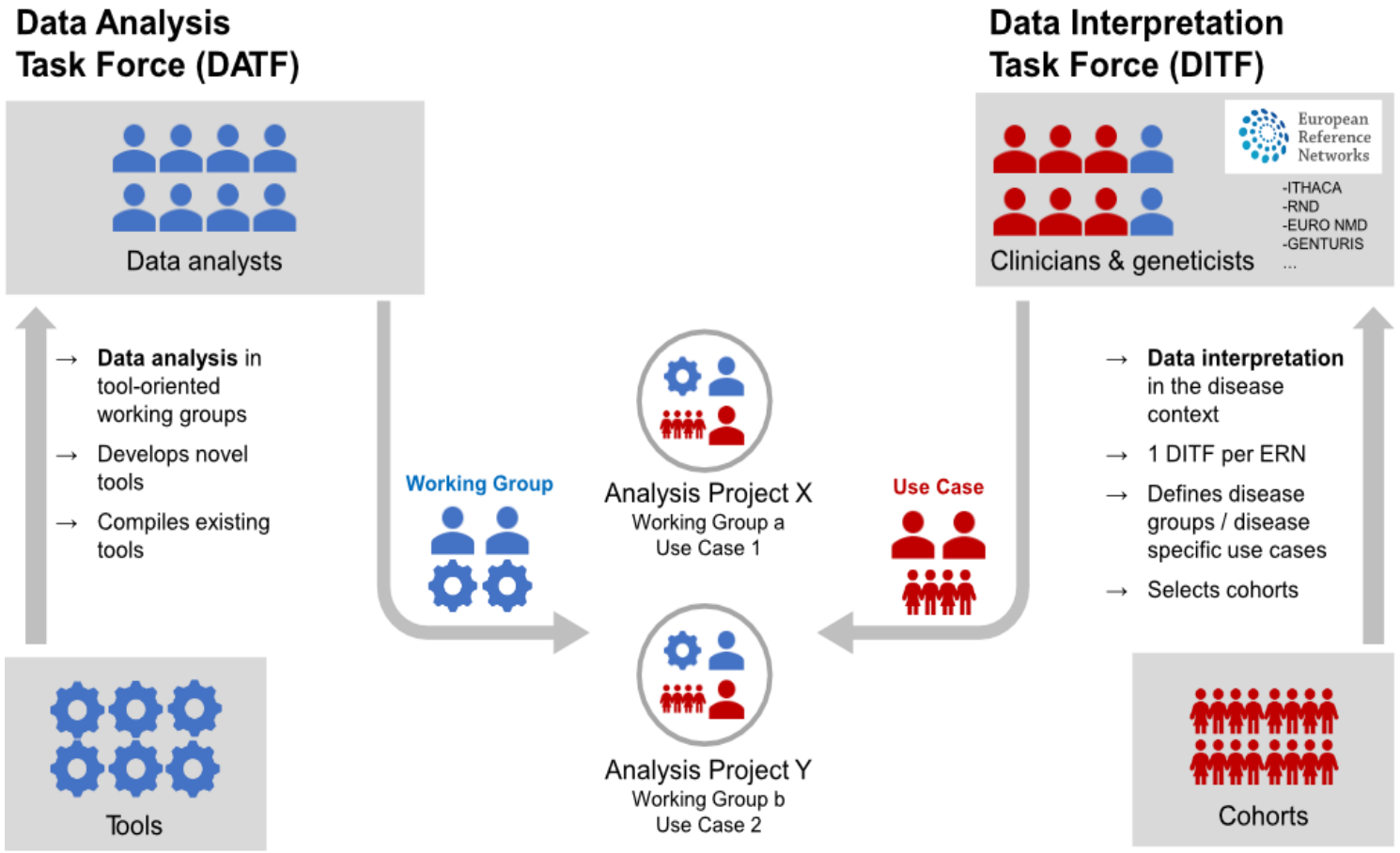




Total <u>families</u> with new diagnosis:

- Systematic re-analysis: 506
- *Ad hoc*: 249
- Candidates: 333

Joint Expert Reanalysis

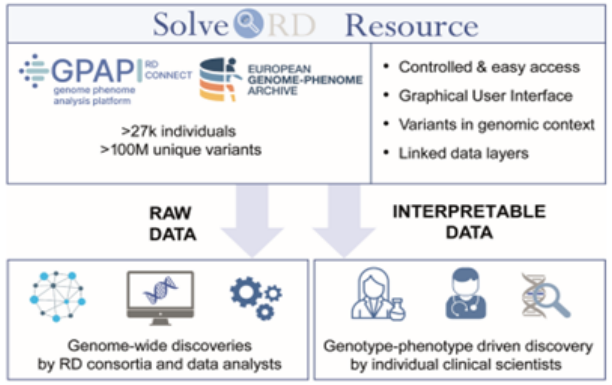


Zurek et al, 2021

From Solve-RD to ERDERA

Use case: systematic diagnostic research re-analysis

2018 - 2024



> 15% diagnoses

WES, WGS	Omics type	WES, WGS, RNAsequ, Epigenetic
Short read	Technology	Short & long read
6 ERNs	Diseases	> 15 ERNs
23.000	Numbers	> 100.000
Selected EU countries	Geographic outreach	EU + incl. underrepr.
distributed	Analysis type	Distributed and federated

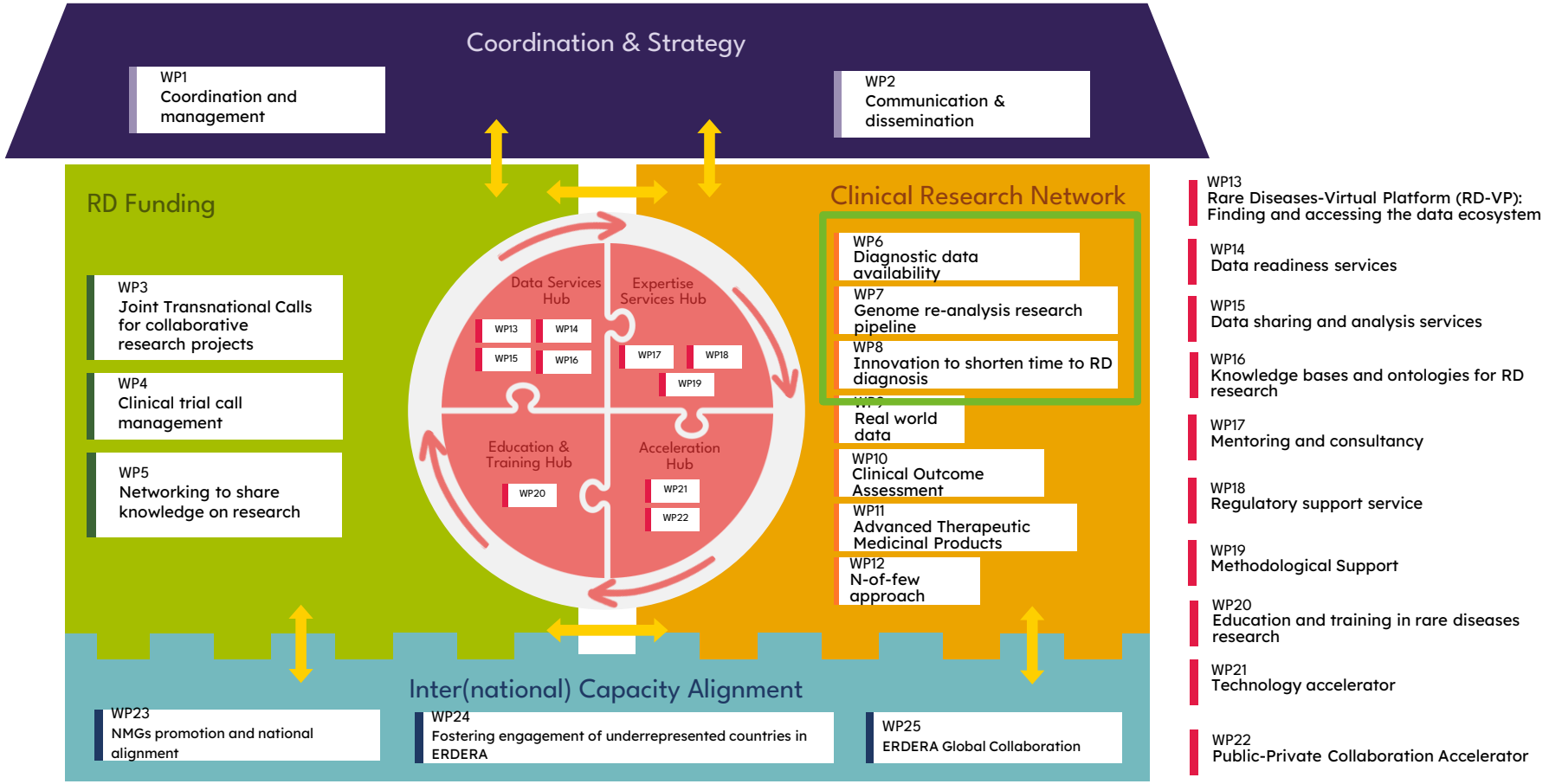
2024 - 2031

> ? % diagnoses

Diagnostic Research Workstream

ERDERA
European Rare Diseases Research Alliance

Diagnostic Research Workstream of ERDERA



WP13
Rare Diseases-Virtual Platform (RD-VP): Finding and accessing the data ecosystem

WP14
Data readiness services

WP15
Data sharing and analysis services

WP16
Knowledge bases and ontologies for RD research

WP17
Mentoring and consultancy

WP18
Regulatory support service

WP19
Methodological Support

WP20
Education and training in rare diseases research

WP21
Technology accelerator

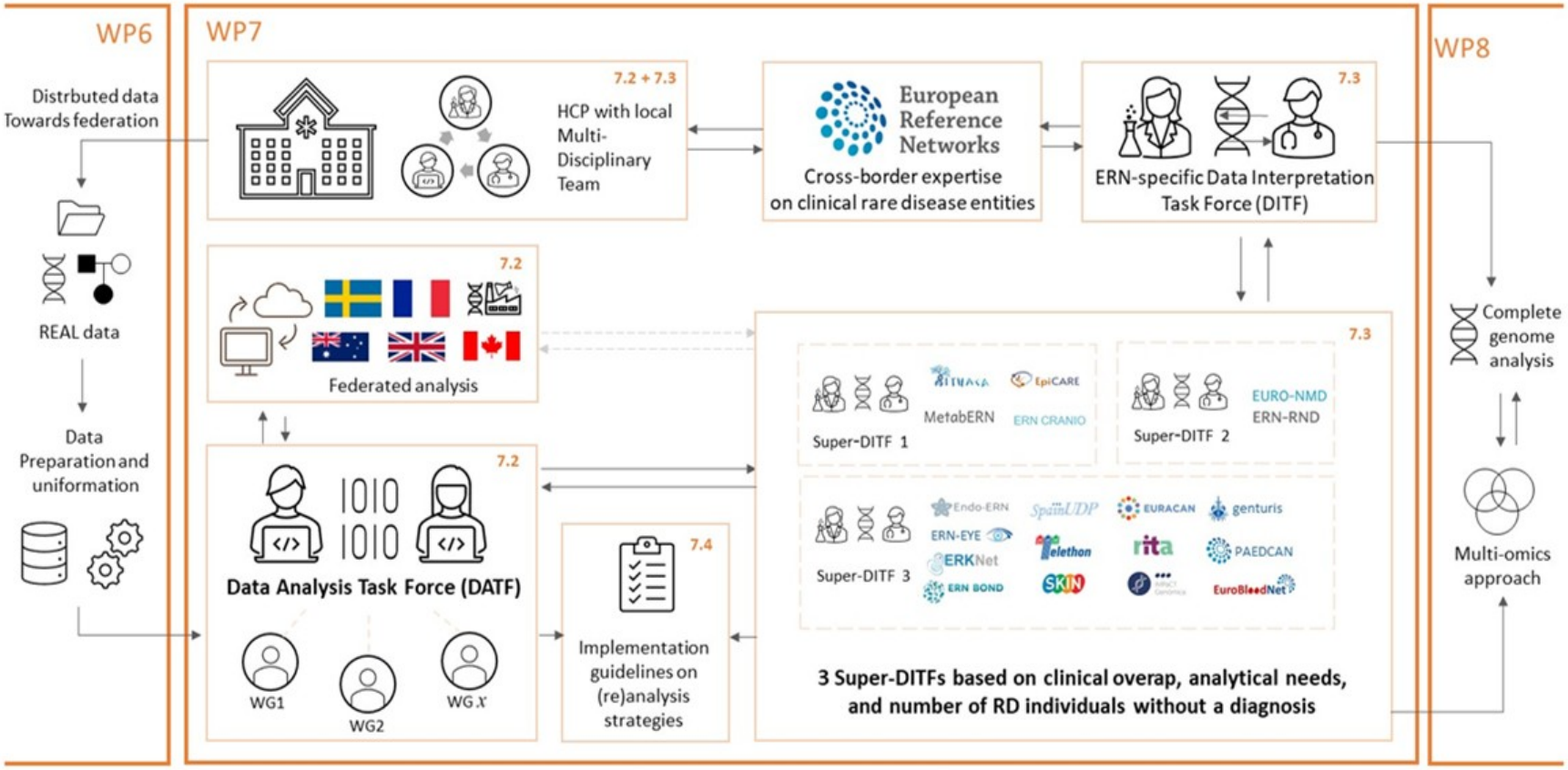
WP22
Public-Private Collaboration Accelerator

DRW Work Packages

Data Availability

Genome Re-Analysis Research Pipeline

Innovation to shorten time to RD diagnosis



WP6
Data Availability

WP6 Objectives and Governance

1. Expand diagnostic data availability and collation effort
2. Implement data standardization and quality criteria for other omics data besides WES and WGS
3. Operationalise results return workflow and facilitate collaborative variant interpretation

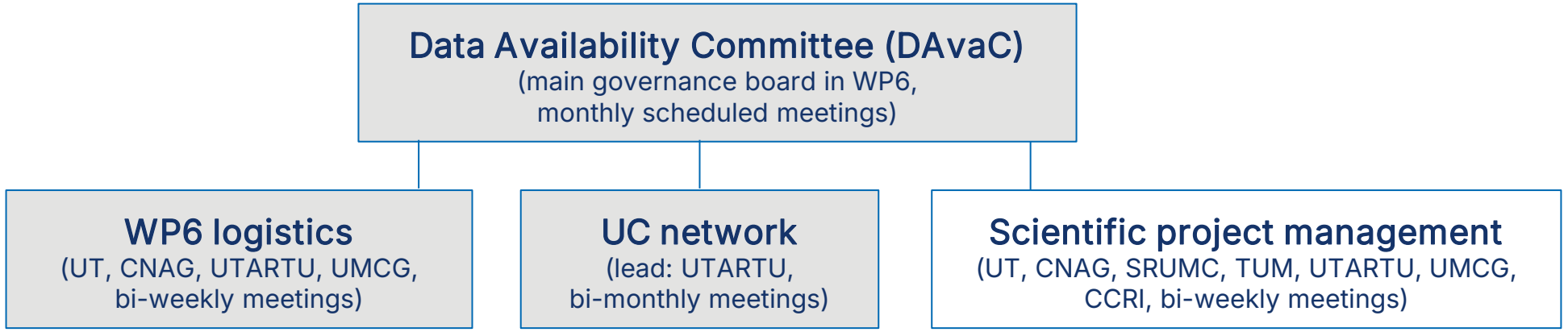
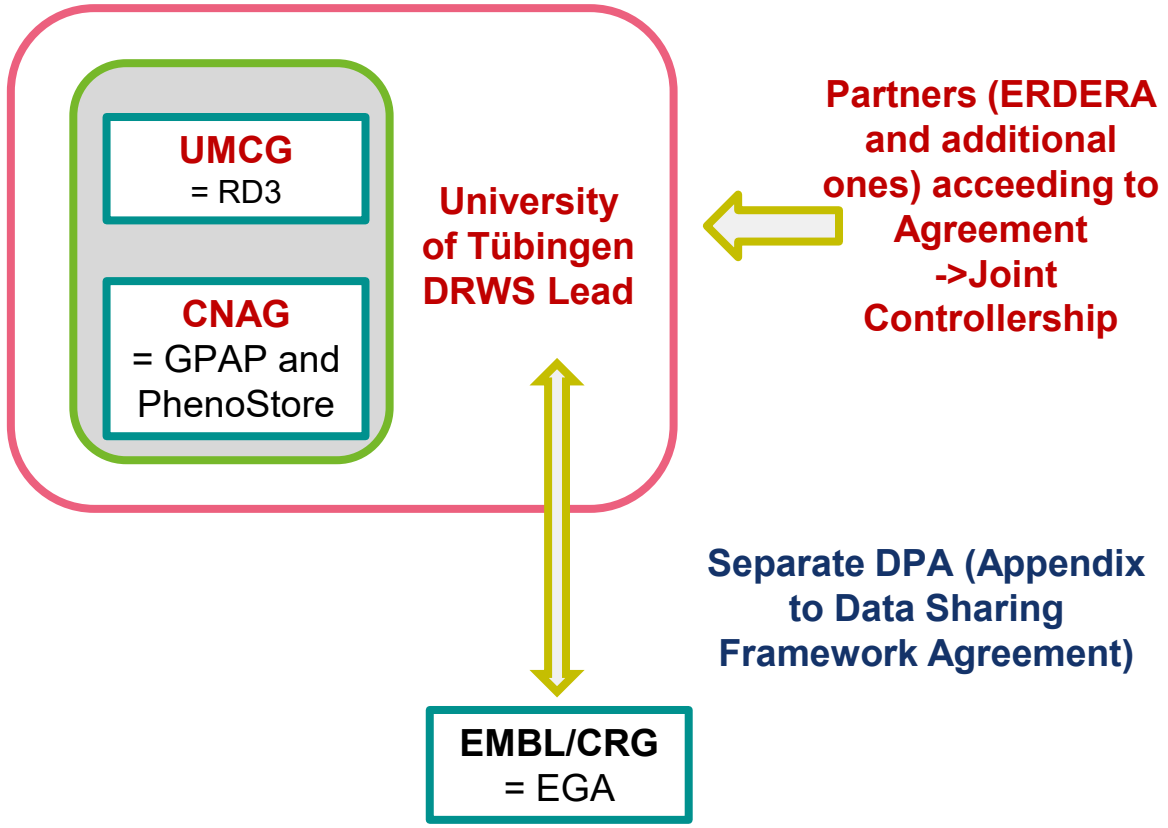


Figure: WP6 governance structure

Expand diagnostic data availability and collation effort

- Implemented **Data Sharing Framework Agreement** as a core enabler for secure and compliant transnational data sharing



Expand diagnostic data availability and collation effort

- Implemented **Data Sharing Framework Agreement** as a core enabler for secure and compliant transnational data sharing
- >44 centres have joined the **joint controllership**, including all key data-contributing centres active in the first two project years; partner accession remains ongoing (incl. Non-ERDERA partners)
- **Implemented option to access data** for partners under the agreement based on study proposals. Access is carefully governed to ensure data protection and **full compliance with the Data Sharing Framework**

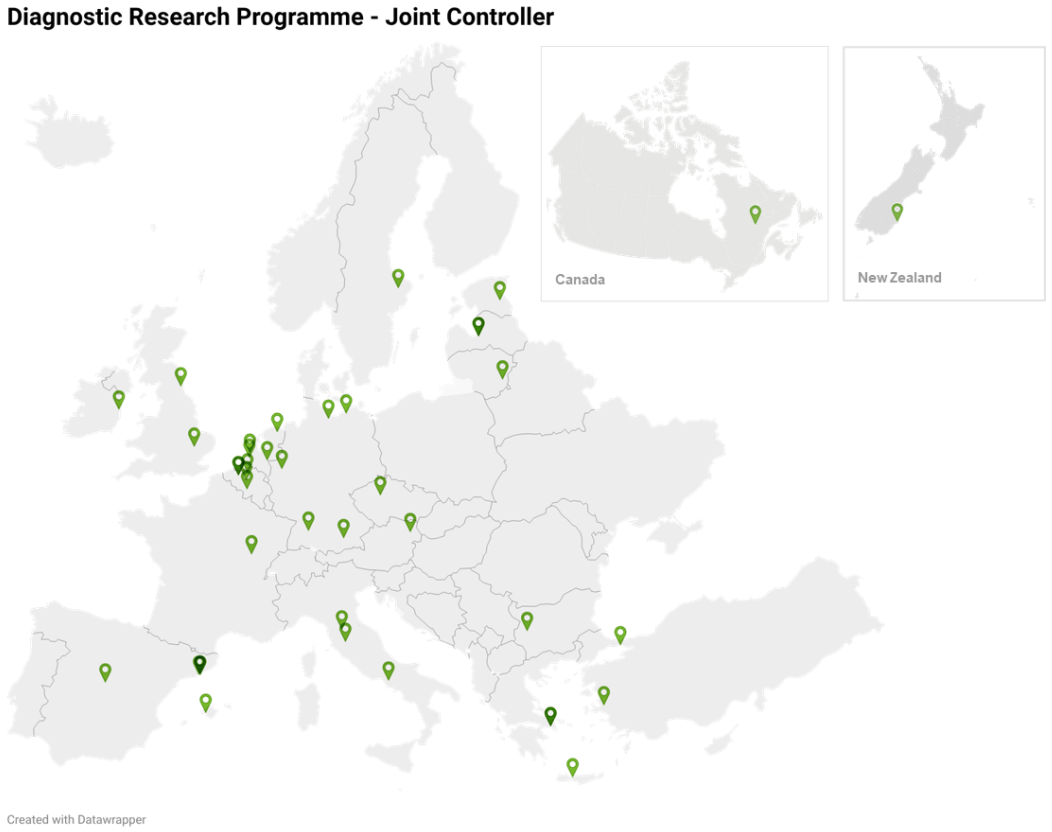
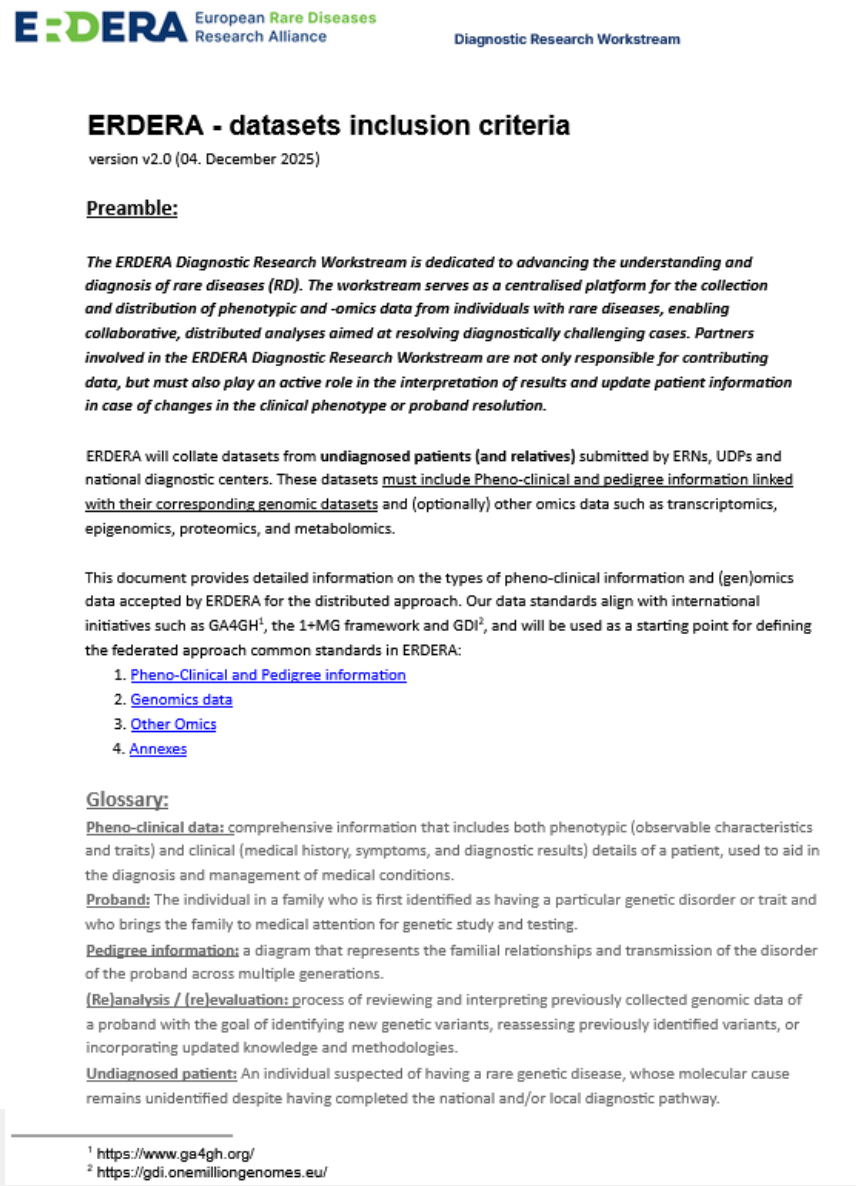


Figure: Institutions and countries that have signed the Data Sharing Framework Agreement as of 03/2026

Data Standardization & quality criteria

- Data standards for WES, WGS and **RNAseq** based submission and re-analysis (developed and) adopted and approved by the Data Availability Committee (DAvaC)
- Adoption of data standards for **LR-WGS and OGM** submission in progress
- Established results return workflow and **collaborative variant interpretation**



ERDERA European Rare Diseases Research Alliance — Diagnostic Research Workstream

ERDERA - datasets inclusion criteria

version v2.0 (04. December 2025)

Preamble:

The ERDERA Diagnostic Research Workstream is dedicated to advancing the understanding and diagnosis of rare diseases (RD). The workstream serves as a centralised platform for the collection and distribution of phenotypic and -omics data from individuals with rare diseases, enabling collaborative, distributed analyses aimed at resolving diagnostically challenging cases. Partners involved in the ERDERA Diagnostic Research Workstream are not only responsible for contributing data, but must also play an active role in the interpretation of results and update patient information in case of changes in the clinical phenotype or proband resolution.

ERDERA will collate datasets from **undiagnosed patients (and relatives)** submitted by ERNs, UDPs and national diagnostic centers. These datasets must include Pheno-clinical and pedigree information linked with their corresponding genomic datasets and (optionally) other omics data such as transcriptomics, epigenomics, proteomics, and metabolomics.

This document provides detailed information on the types of pheno-clinical information and (gen)omics data accepted by ERDERA for the distributed approach. Our data standards align with international initiatives such as GA4GH[1], the 1+MG framework and GDI[2], and will be used as a starting point for defining the federated approach common standards in ERDERA:

1. Pheno-Clinical and Pedigree information
2. Genomics data
3. Other Omics
4. Annexes

Glossary:

Pheno-clinical data: comprehensive information that includes both phenotypic (observable characteristics and traits) and clinical (medical history, symptoms, and diagnostic results) details of a patient, used to aid in the diagnosis and management of medical conditions.

Proband: The individual in a family who is first identified as having a particular genetic disorder or trait and who brings the family to medical attention for genetic study and testing.

Pedigree information: a diagram that represents the familial relationships and transmission of the disorder of the proband across multiple generations.

(Re)analysis / (re)evaluation: process of reviewing and interpreting previously collected genomic data of a proband with the goal of identifying new genetic variants, reassessing previously identified variants, or incorporating updated knowledge and methodologies.

Undiagnosed patient: An individual suspected of having a rare genetic disease, whose molecular cause remains unidentified despite having completed the national and/or local diagnostic pathway.

[1] https://www.ga4gh.org/
[2] https://gdi.onemilliongenomes.eu/

Dataset inclusion criteria

Expand diagnostic data availability and collation effort

- Data sharing of **> 10,000 WES/WGS** in year 1; Additional >**29,000 WES/WGS/omics submissions** for ERDERA Year 2 in progress
- Successful deposition of the first Year 1 datasets at the **EGA**, establishing the basis for controlled sharing of raw genomic data among joint controllers
- Expanding **Network of Underrepresented Countries (Ucs)** in the Diagnostic Research Programme. Regular webinars to address specific needs: Ethics/GDPR, sample processing, and AI-driven diagnosis

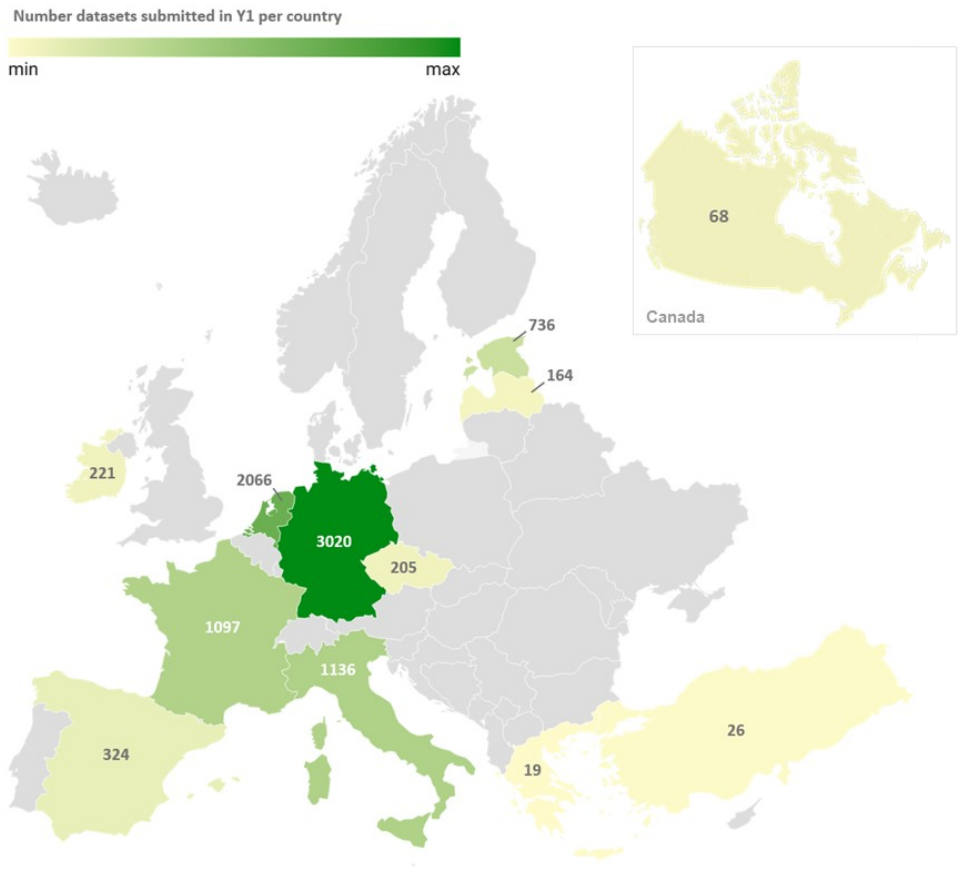


Figure: WES/WGS dataset submission numbers per country in year 1

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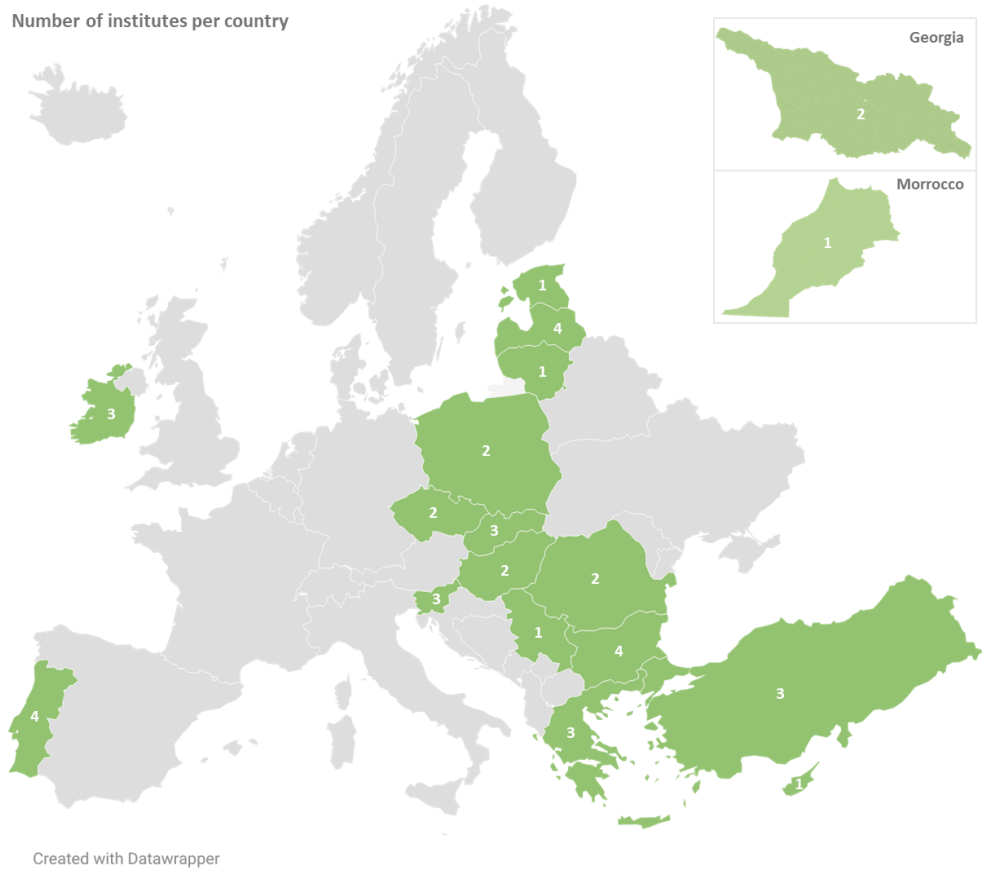


Figure: WP6 network of Underrepresented Countries (UCs) as of 10/2025

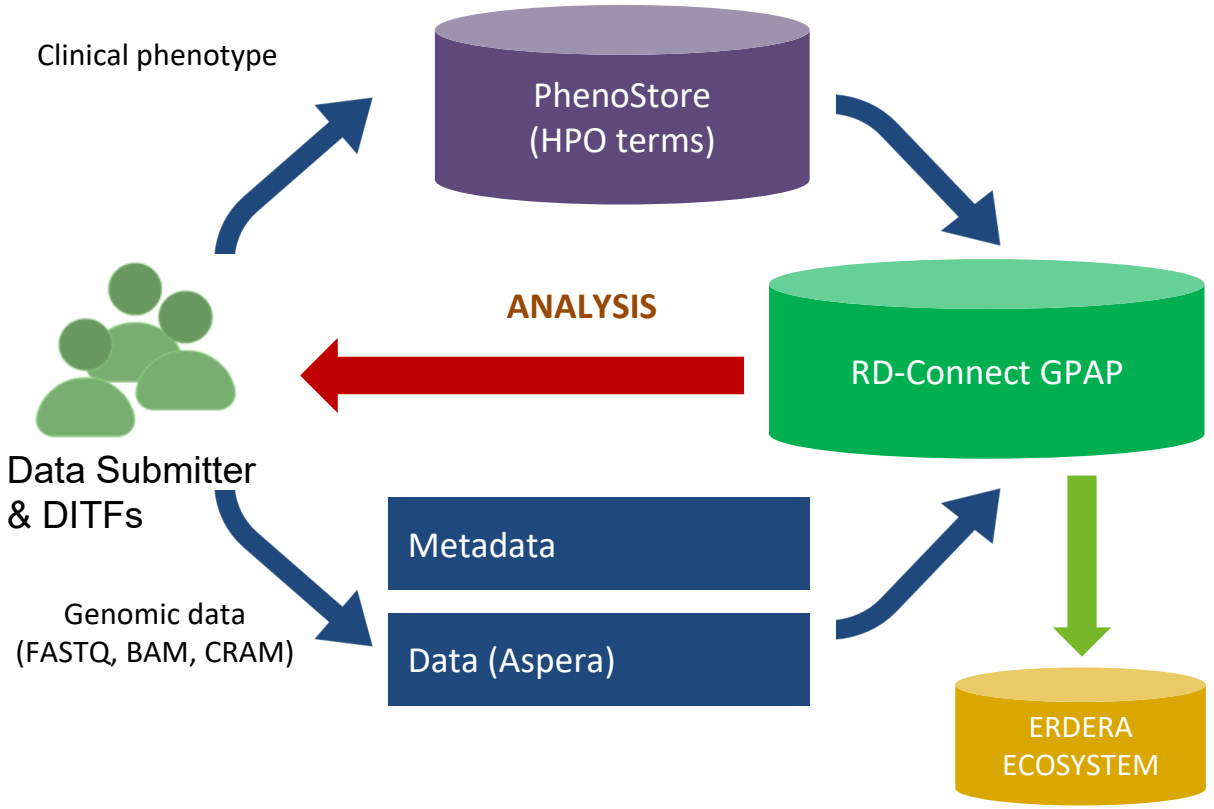
Current Submission Workflow

distributed approach

WES/WGS (for re-analysis)

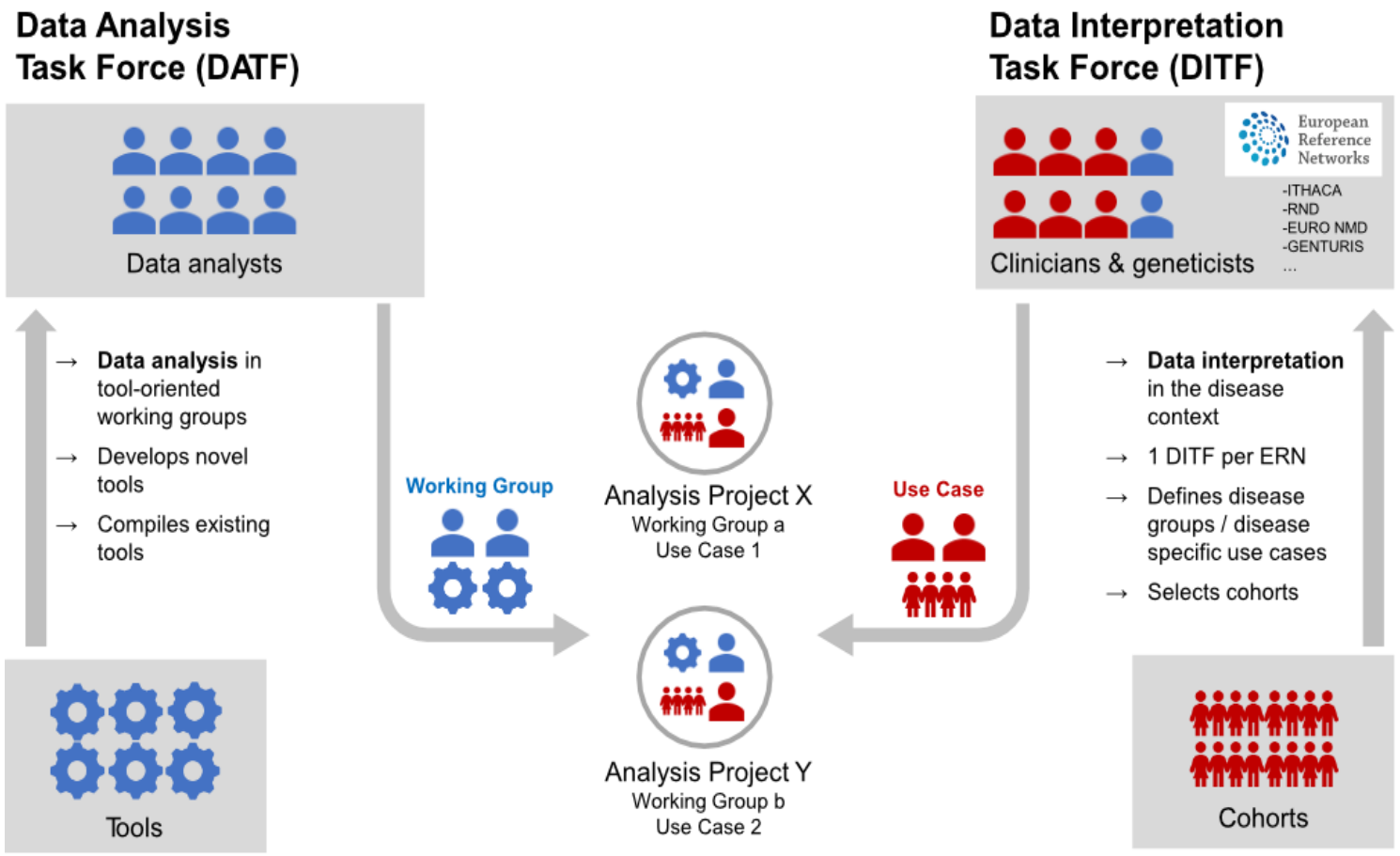
1. Pheno-clinical information will be collated through GPAP-PhenoStore using standards and ontologies.
2. Genomic information from srWES and srWGS:
    - metadata will be collated in GPAP
    - Files submitted through Aspera

Processes for submission of RNAseq and LR-WGS data are currently in progress



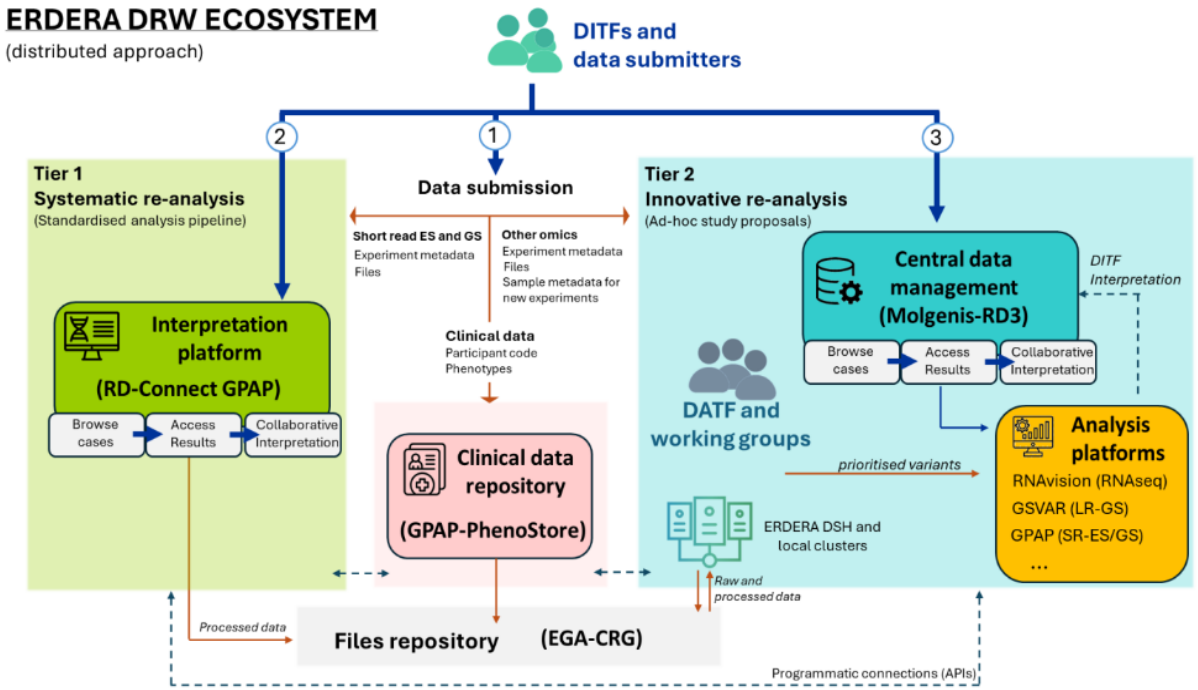
WP7
Genome Re-Analysis Research Pipeline

Joint Expert Reanalysis – DATF and DITFs



Reanalysis Workflow (for unsolved exome and genome datasets)

- **Submission** of data of diagnostically unsolved patients
- Central **re-annotation and re-analysis for WES/WGS** pipeline via CNAG (DRAGEN v4.4.6)
- **Additional analysis tailored to variant type** in analysis hubs – DATF Working Groups
- **Case based interpretation** by submitting centres in GPAP
- **Group based interpretation** led by ERN led/informed DITF
- **Availability of result data** via EGA (CRG)
- **Flagship publication** of results via ERDERA
- **DITF specific publications** via DITFs and DATF WG



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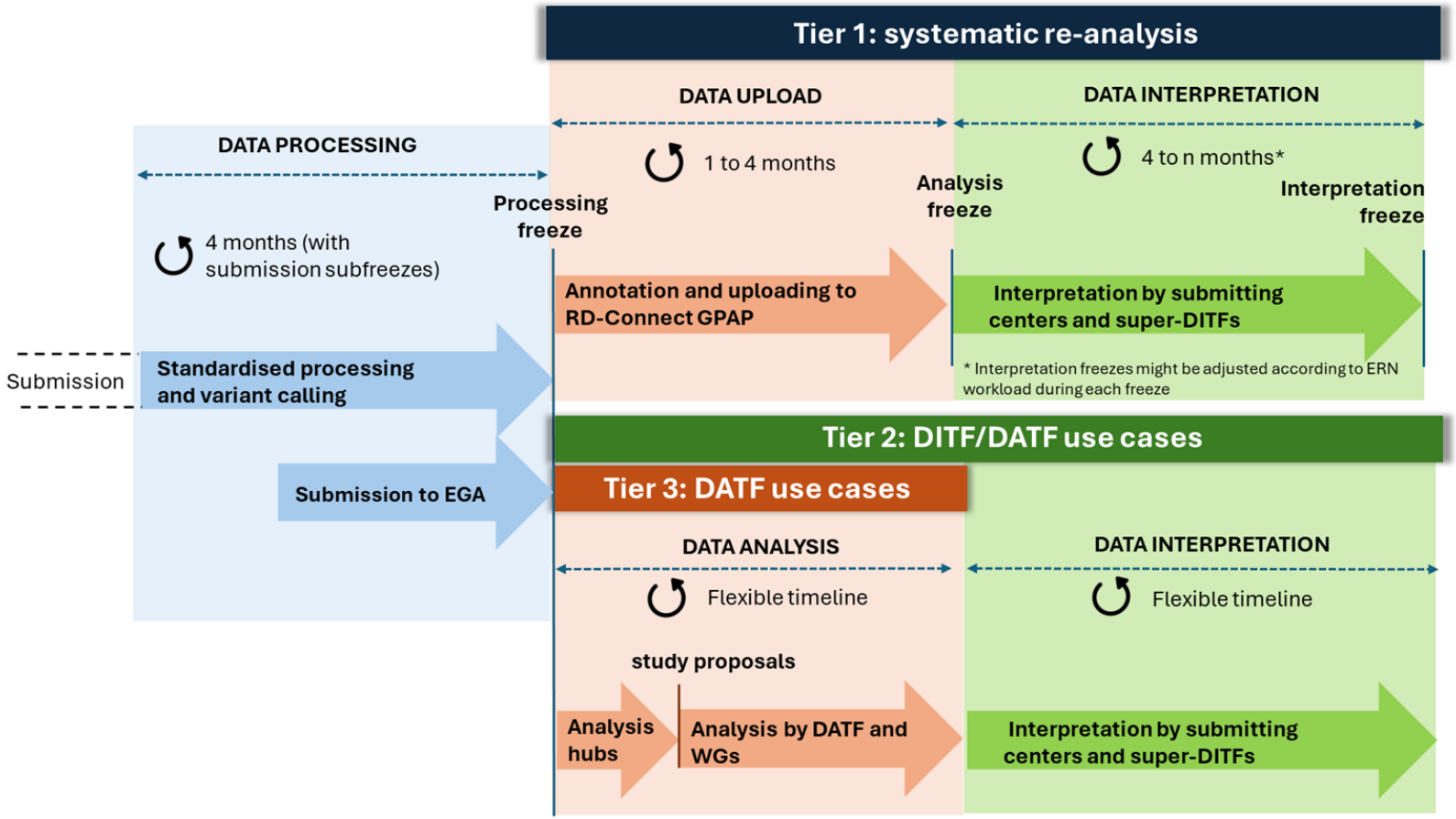


Super-DITF/DITF Structure

Leads Super DITF 1
Lisenka Vissers
Holger Lerche/Christian Boßelmann

- ITHACA
- MetabERN
- EpiCARE
- ERN CRANIO

Leads Super DITF 2
Ana Topf/ Volker Straub
Bart Dermaut/ Dimitri Hemelsoet

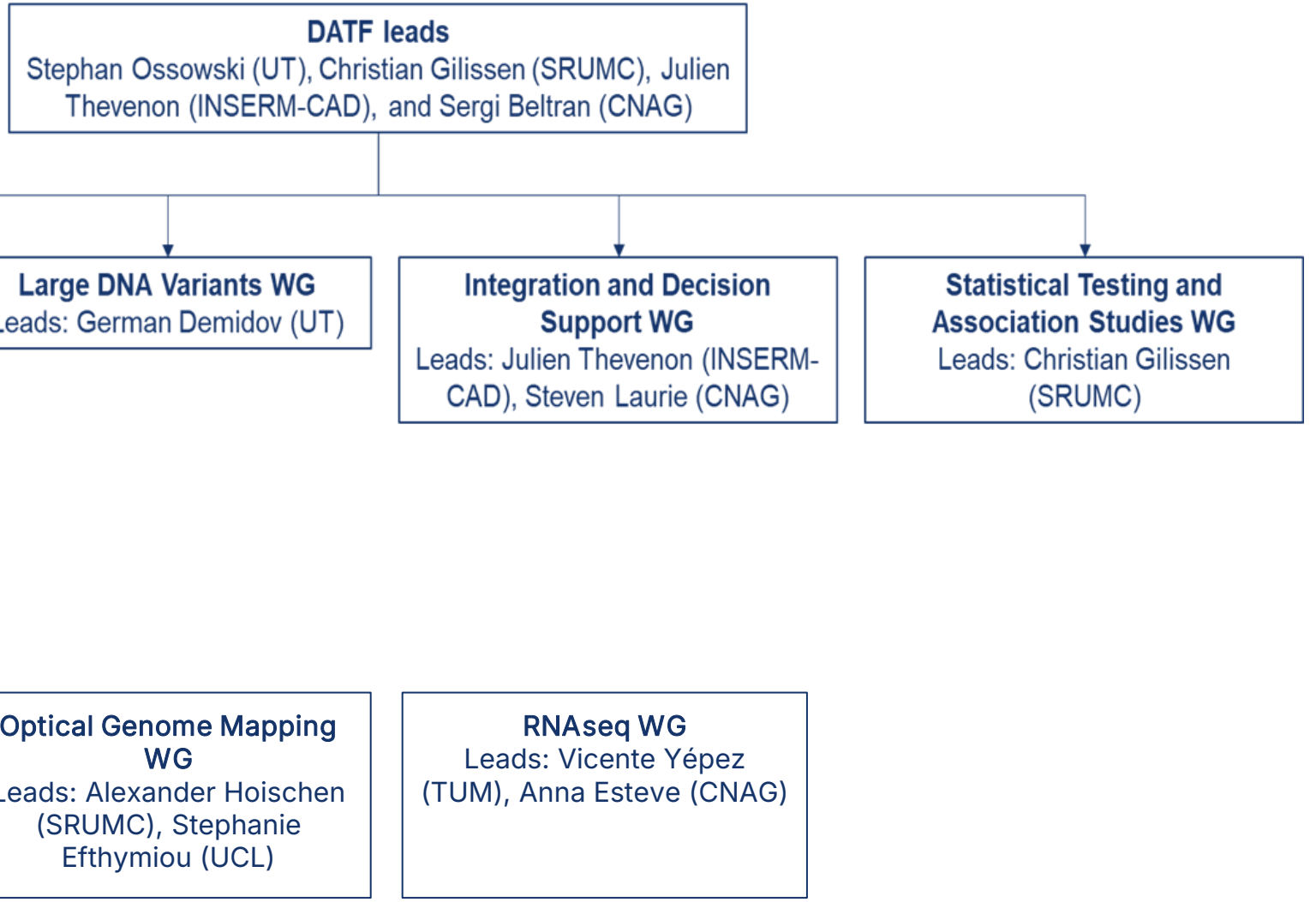
- EURO-NMD
- ERN-RND

Leads Super DITF 3
Richarda de Voer
Beatriz Martinez Delgado

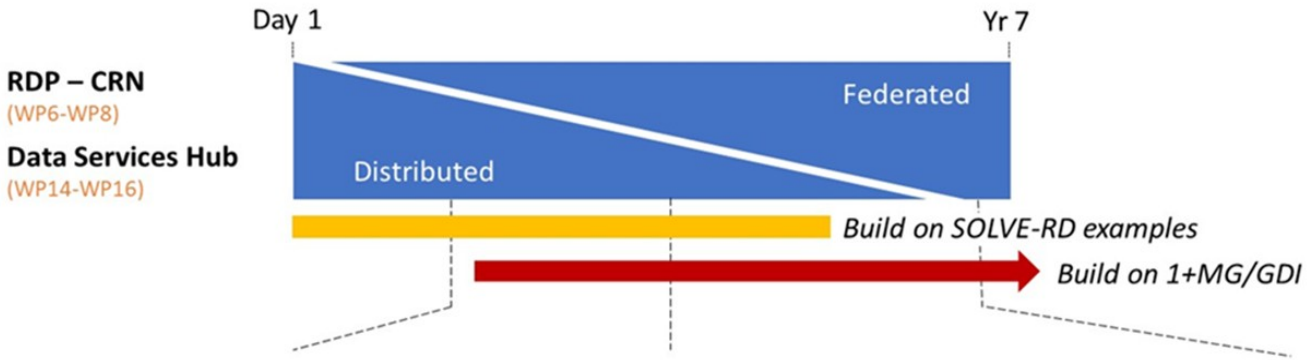
- Endo-ERN
- ERKNet
- ERN BOND
- SpaïnUDP
- EuroBloodNet
- ERN GENTURIS
- ERN-EYE

- EURACAN
- IMPaCT Genómica
- Telethon
- rita
- PAEDCAN
- SKIN

DATF - WGs


DATF leads
Stephan Ossowski (UT), Christian Gilissen (SRUMC), Julien Thevenon (INSERM-CAD), and Sergi Beltran (CNAG)
WP7
Small DNA Variants WG
Leads: Gemma Bullich (CNAG), Lennart Johansson (UMCG)
Large DNA Variants WG
Leads: German Demidov (UT)
Integration and Decision Support WG
Leads: Julien Thevenon (INSERM-CAD), Steven Laurie (CNAG)
Statistical Testing and Association Studies WG
Leads: Christian Gilissen (SRUMC)
Mt DNA Variants sub-WG
Lead: Ida Paramonov (CNAG)
Mosaic Variants sub-WG
Lead: Jessika Nordin (UU)
WP8
Long-Read Sequencing WG
Leads: Alexander Hoischen (SRUMC), Stephan Ossowksi (UT), Tobias Haack (UT)
Optical Genome Mapping WG
Leads: Alexander Hoischen (SRUMC), Stephanie Efthymiou (UCL)
RNAseq WG
Leads: Vicente Yépez (TUM), Anna Esteve (CNAG)

From distributed to federated reanalysis



Accelerate diagnosis through Distributed approach (Phase I)
→ Upload phenotype + data
→ Coordinated analysis
→ Coordinated interpretation together with submitters for feedback to patients

For: local HCPs without infrastructure or bioinformatic support

Accelerate diagnosis through Distributed approach (Phase II)
→ Provide analytical tools & interpretation guidelines
→ Local analysis
→ Local interpretation
→ Share results with ERDERA

For: local HCPs without infrastructure or bioinformatic support

Accelerate diagnosis through Federated approach
→ Access to data in other centres
→ Local & federated interpretation
→ Share results with ERDERA

For: National programs and industry from the start, and allowing for scalability to local HCPs later in project

CRN: Analysis + interpretation incl. tool development
Data Hub: compute services and data platforms

CRN: Analytical + interpretation support incl. tool development
Data Hub: Operational/Deployment aspects
Intrastructure for Data Access: 1+MG / GDI

WP8
Innovation to shorten time to RD diagnosis

WP8 - Innovations to Shorten Time to Diagnosis

Cutting-edge genomics and integrated multi-omics approaches to accelerate the diagnosis of rare diseases

Key activities

- Conducting novel **lrWGS and OGM and comprehensive analyses** for challenging rare disease cases from Underrepresented Countries (UC).
- Developing RNAseq- and **integrated multi-omics methods** to improve the analysis and interpretation of genetic variation.
- Facilitating the **adoption of innovative approaches across Europe**, strengthening diagnostic solidarity and capacity.
- Organizing **dedicated training sessions and Solvathons** focused on RNAseq, lrWGS and OGM data interpretation and diagnosing undiagnosed cases.

WP8 - Opportunities for centers from Underrepresented Countries (UCs)

Submit biosamples for the generation of novel data for analysis together with experts in the field

Long-read genome sequencing

PacBio	160 samples	Radboudumc, Nijmegen, Netherlands
Oxford Nanopore Technologies	160 samples	University of Tübingen, Tübingen, Germany

Optical genome mapping

bionano genomics	200 samples	Radboudumc, Nijmegen, Netherlands

Centers from UCs interested in submitting samples for lrWGS and/or OGM data generation?
Complete the linked template and submit it to Bart van der Sanden (Radboudumc, the Netherlands) to see if your samples/cases qualify for lrGS/OGM data generation.

Links and contacts

Resources

- Dataset inclusion criteria (standards, formats and minimum quality criteria for data submission)
- Data submission toolkit (incl. links to dedicated submission guidelines)
- Data Sharing Framework Agreement
- RD-Connect GPAP registration

Questions or comments?

Please contact us!

ERDERA-diagnostic-research@med.uni-tuebingen.de

help@rd-connect.eu

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Thank you!

For further information get in touch with us:
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