Deliverable

D5.3 Unsolved cases from associated ERNs and undiagnosed disease programmes analysed through RD-Connect	
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Explanation according to GA Annex I:

Unsolved cases from associated ERNs and undiagnosed disease programmes analysed through RD-Connect.

Abstract:

At the clinical core of the Solve-RD project, there are four European Reference Networks (ERNs) that contributed 1000s of unsolved rare disease cohorts. During the implementation period of the project, two further ERNs have joined the Solve-RD network as associated ERNs: ERN EpiCare which focuses on Rare and Complex Epilepsies, and ERN RITA which focuses on Rare Immunodeficiency, Autoinflammatory and Autoimmune diseases. Together they have submitted 2,273 new datasets for re-analysis, which have been processed through the standard analysis workflow in the RD-Connect GPAP (GPAP), and secondary analyses at CNAG, EKUT, and RadboudUMC, within the DATF Working Groups.

Introduction:

The incorporation of ERNs EpiCare and RITA has allowed them to participate in many Solve-RD activities, with a focus on the re-analysis of exome and genome data, and associated clinical and phenotypic information from their rare disease patients and relatives.

This report describes the processing of unsolved cases that were submitted to Solve-RD for reanalysis, by these two associate ERNs, and subsequently made available through the GPAP and to partners at EKUT and RUMC, for downstream analyses and interpretation.

Report:

As part of the Solve-RD data submission to the RD-Connect GPAP, the user needs to indicate to which ERN the data should be assigned. As each ERN focuses on specific disease types, the patients they typically manage have a restricted number of phenotypic characteristics that are associated with their specific condition. To facilitate the efficient collation of phenotypic descriptions of affected individuals, the RD-Connect GPAP provides disease-specific templates within its PhenoStore module. These templates provide rapid access to the phenotypic terms most likely to be informative for the specific disease.

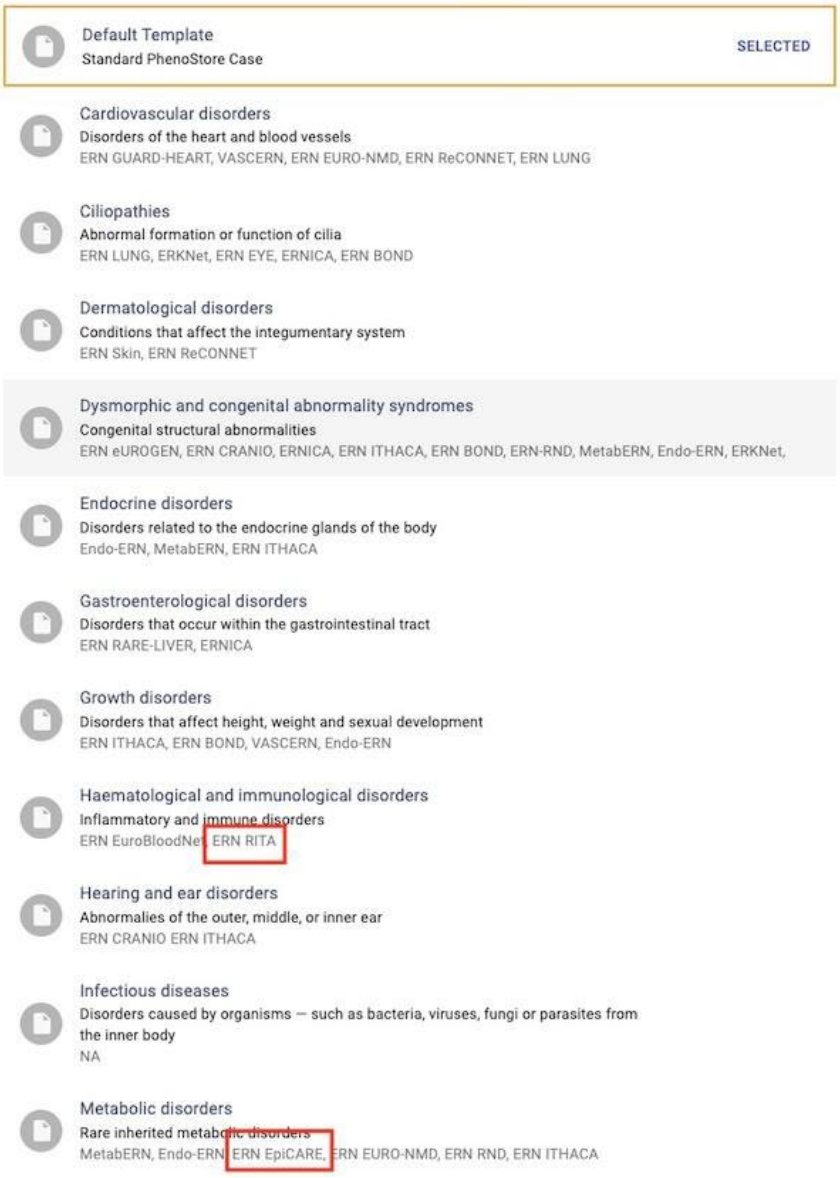
Following the incorporation of ERNs EpiCare and RITA, the RD-Connect GPAP development team at CNAG worked together with clinical experts from the new ERNs to define which groups of phenotypic terms were most commonly used to describe their patients, and developed templates tailored to their needs (see Figure 1 and D5.1 Bespoke Phenotips frontends for associated ERNs and undiagnosed disease programmes). Thus, four new templates were developed specifically for these two associated ERNs: Hematological and Immunological disorders, Metabolic disorders, Neurology and neurodevelopmental disorders and Psychiatric disorders.

New Index Case Submisson

The following templates are based on Genomics England Clinical Data Models. Please, mind that displayed ERNs are only suggestions to recommend clinical scientists the best template to enter their case

Choose a Template:

21 Templates Available



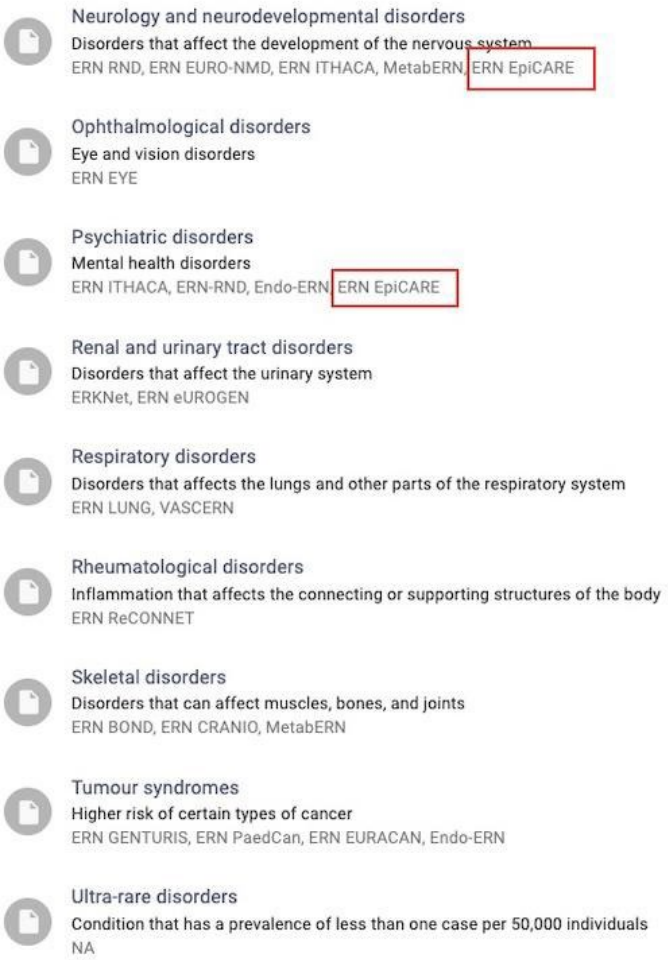


Figure 1: Available custom template in PhenoStore, highlighting those newly developed for ERNs EpiCare and RITA.

Data submission and analysis within Solve-RD was divided into four Data Freezes, where each dataset contained phenotypic and clinical data, experiment metadata and sequencing data. The new ERNs were incorporated towards the end of the second data freeze period, and thus submitted data to Data Freezes 3 and 4. Combined, ERNs RITA and EpiCare submitted 2,273 datasets for reanalysis, as indicated in Table 1.

*Table 1: Number of reanalysis datasets submitted by ERNs EpiCare and RITA. *262 ERN RITA datasets were submitted at the end of data freeze 2 but analysed as part of data freeze 3.*

ERN	Data Freeze	Number of datasets
ERN EpiCare	Data Freeze 3	1,665
ERN EpiCare	Data Freeze 4	45
ERN RITA	Data Freeze 3	560*
ERN RITA	Data Freeze 4	3
Total		**2,273**

All reanalysis datasets were submitted to the GPAP and processed with the standard analysis pipeline to harmonise the output. These datasets from data freeze 3 have also undergone comprehensive secondary analyses and interpretation within the various DATF working groups, including transfer of processed data to partners at EKUT and RUMC for further bespoke analyses.

Solve-RD users, who have submitted data to Data Freeze 4 or have submitted data under an ERN other than ERN-ITHACA, -RND, Euro-NMD, -Genturis, -EpiCare or -RITA, can benefit from the data being processed by the standard RD-Connect GPAP pipelines and made available in the RD-Connect GPAP for additional analysis, even though they have not been further re-analysed within the frame of the Solve-RD project.

Conclusion:

The incorporation of the ERNs RITA and EpicCare under the umbrella of the Solve-RD project has proven to be highly successful., resulting in the re-analysis of a further 2,273 datasets from unsolved families, leading to the resolution of many diagnostic odysseys. This indicates how the infrastructure and RD-REAL framework built by Solve-RD can be extended further across Europe to incorporate the remaining ERNs.