TIME TO ACT – IMPROVING RARE DISEASE DIAGNOSIS AND SOLVING THE UNSOLVED RARE DISEASE THROUGH COLLABORATION IN EUROPE

Patients with a rare disease (RD) often face a long and arduous process in order to obtain a correct diagnosis. For a large fraction of people with a RD the consequence is a years-long time to diagnosis, misdiagnosis and as a consequence delayed or even wrong treatment. In Europe, there is substantial heterogeneity with regard to access to clinical and genetic centers of expertise as well as available diagnostic technologies, and downstream analysis pipelines and methods.

These challenges can at least in part be overcome through clinical research collaboration in Europe. Therefore, in order to be able to meet

> ***IRDiRC's Goal 1:*** "All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline".

and the corresponding

- ***Rare2030 Recommendation 2:*** "All people living with a rare disease known in the medical literature will be diagnosed within six months of coming to medical attention. All people will have access to the most effective diagnostic technologies, best practices and programmes (including screening) without discrimination and regardless of where they live in Europe. All currently undiagnosable individuals will enter a European and globally coordinated diagnostic and research pipeline".

and the corresponding

- ***Call to Action of the 2022 Czech EU Council Presidency supported by 21/27 EU Member States (representing 82 % of the EU27 general population):*** *"Special consideration should also be given to evaluate the rapid development of genomics that may improve the efficacy of diagnosis shortly after birth. The novel techniques provide exciting opportunities to bring significant health and economic benefits to society and particularly to EU citizens with rare disorders, but they also raise important technical, logistic, ethical and economic issues that need to be addressed before they can be recommended as a routine part of public health policy offered on a whole population basis to asymptomatic newborns. As demonstrated by the SOLVE-RD.eu project, a combination of -omics technologies can also contribute to solving the pathogenicity in different patient cohorts and confirming a diagnosis for rare disease patients who did not receive one with other tools (e.g., molecular diagnosis)".*

we call upon all European RD stakeholders, including EU Member States, the European Commission, the Council of the European Union, the general public and private organisations active in the RD field, as well as the rare disease community at large to act NOW to seize the current once-in-a-generation opportunity to significantly improve RD diagnosis in Europe. This unique opportunity is characterized by pan-European access to diagnostic technologies in particular Whole Exome Sequencing, the just reached maturity of the European Refence Networks ecosystem, the looming opportunity

to share RD data on European-wide scale within the forthcoming European Health Data Space, the upcoming RD-Partnership as well as - with Solve-RD - the availability of a scalable transnational diagnostics research platform. Therefore, we propose the following:

1. **Ensure a clear, systematic and European-wide approach for RD diagnostics**, founded upon the ability to guide patients towards centres of expertise, in particular those participating in the European Reference Networks (ERNs), access transnational diagnostics platforms, and capture - and systematically manage - data on patients for whom a diagnosis is not forthcoming

2. **Shorten the time to accurate diagnosis** - whilst avoiding erroneous and subsequent negative consequences - through improved use and equal accessibility of currently effective and available diagnostic testing technologies and advances, such as exome and genome sequencing, as well as respective best practices, harmonisation of standards and diagnostic programmes across Europe.

3. **Enable data sharing on European-wide scale facilitated by the forthcoming European Health Data Space**, and through partnership with the European Reference Networks (ERNs) and through European initiatives such as 1+ Million Genomes (1+MG), as large datasets facilitate the discovery of new RD causes. Novel gene discovery is driven by very large datasets that cover specific disease(group)-domains, such as organised in ERNs and as shown in Solve-RD. To this end, European countries should agree on a strategy and standards for sharing core clinical details, molecular data, as well as samples for unsolved patient cases. This will enable, among other things, cross-country explorations based upon clustering of phenotype and symptoms.

4. **Improve diagnostic expertise by fostering European-scale networking of clinical and data expertise,** as implemented by the Solve-RD two-level expert review model, to ensure access to the state-of-the-art knowledge of – among other things – the spectrum of genes and variants causing monogenic rare disease. The Solve-RD two-level expert review model systematically brings together RD data analysis experts and experts with an expertise on clinical interpretation on data analysis results both on the process and infrastructure level.

5. **Scale-up the Solve-RD re-analysis framework** within the upcoming RD-Partnership – as a transnational diagnostics research platform – with its two-level expert review (involving molecular, bioinformatic and clinical disease experts) as a practical blueprint for reanalysis efforts on a European scale. The existing organisation of rare disease expertise in 24 ERNs should enable the implementation of the Solve-RD approach for the full spectrum of RD across all member states.

6. Ensure **access to new genomic technologies,** such as optical mapping and long-read genome sequencing as well as functional -omics methodologies such as transcriptomics, metabolomics and proteomics to unravel novel RD causes and novel molecular mechanisms of rare disease in a coordinated European research pipeline to reduce inequalities in accessing those technologies in Europe.

7. **Utilise the existing ERN registries** to monitor European as well as national cohorts of patients without confirmed diagnosis in terms of prevalence, percentage of patients with and without diagnosis, phenotypic characterisation of patients without diagnosis as well as respective longitudinal developments.

8. **Reduce the inequalities** regarding the identification of suitable and available treatments and therapies by promoting up to date systems and services linking them with diseases, phenotypes and biomarkers such as genes or even genetic variants.

9. **Develop optimised care pathways** as well as disease-cause tackling treatments and therapies for RDs, resulting in a situation where a genetic diagnosis is not the endpoint of clinical genetic services, but the starting point towards treatment and care.

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