

# The CIBERER Program for Undiagnosed Rare Diseases (ENOD)

## A collaborative and multidisciplinary approach to diagnosis

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Over 80% of rare diseases have a genetic cause. Achievement of a genetic diagnosis is essential for the correct management of patients and families. **Many clinical cases have not identified the molecular origin of the disease (approx. 40%)** after applying the established diagnostic protocols. These **UNDIAGNOSED PATIENTS** are located on the frontier of the translational process between research and the clinical practice. They need to **enter a globally coordinated diagnostic and research pipeline.**

### What is CIBERER? Centre for Biomedical Network Research on Rare Diseases

Spanish Consortium created and belonging to the Carlos III Institute of Health (ISCIII)



A team of up **700 BASIC BIOMEDICAL SCIENTISTS AND CLINICAL INVESTIGATORS** organized in **57 research groups, 20 clinical linked/associated groups from 28 Spanish institutions** Universities, Research Centres, Hospitals. Collaborating with industry, national and international administrations, and **PATIENTS ASSOCIATIONS.**

### ENOD CIBERER Undiagnosed program, ENoD

Multidisciplinary team. Cross-cutting approach

- It incorporates **scientific support** to the diagnostic process. Deep / up-to-date knowledge of pathologies
- Based on a **network of expert evaluators**, scientific committee and a Case and Program Manager
- Application of **latest diagnostic technologies** (WGS, Transcriptome) Support by a Bioinformatics Platform

### Objectives of the program

- To contribute to the **precise molecular diagnosis of unsolved clinical cases** after exclude a known cause
- Search for **new genomic alterations** not described so far as cause of disease
- Contribute to the **advancement of knowledge**

### What does the program offer?

It manages undiagnosed cases referred to the program with the following purposes:



Cases are assessed by CIBERER's clinicians and geneticists specialized in the field. They advise on possible actions to achieve the precise molecular diagnosis

It is offered by our Bioinformatic platform

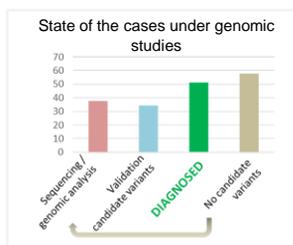


### Results and Conclusions

- Up to **40 investigators** from **22 centers** have referred patients to the program and **72 experts** collaborated with the clinical evaluation
- More than 350 cases** have been incorporated in the platform and have been evaluated. 120 cases did not meet criteria
- Almost 75% are children and adolescence. **Most of the submitted conditions are congenital or of pediatric onset.** Represented a broad range of rare diseases but are enriched in intellectual disability, autism because of the firsts patients accepted in the program
- Close collaboration to unravel diagnosis of unsolved cases with **Patients Associations.**



- DIAGNOSTIC RATE** of the undiagnosed program allows achieving diagnosis in a **25% of cases** so far
- Re-analysis** of previous inconclusive genomic data get a diagnostic rate of 18%.
- Relevance of establishment of a **collaborative approach to diagnosis**
- Essential to optimize tools and resources for the development of **genomic medicine**



### How do patients access the program?

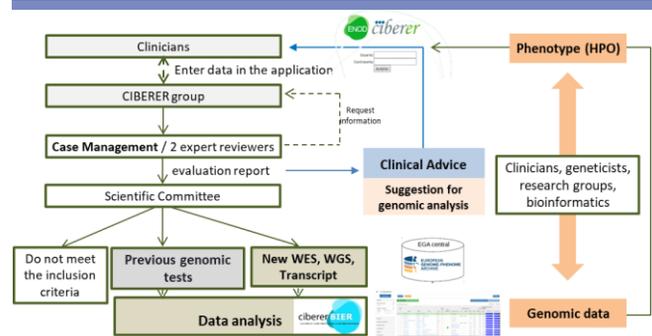
- Open to **all rare diseases.** Open to patients from all hospitals in Spain
- Referred by a **PHYSICIAN** through close cooperation with **CIBERER'S RESEARCHERS**
- Collaboration with **FEDER**, the **Spanish Federation of Rare Diseases and Undiagnosed Patients Association** to unravel diagnosis of unsolved cases

### ENoD platform: recovery clinical data. Phenotyping



- An online application to register all the **clinical information** available
- It allows **data entry and sharing** among the researchers and practitioners involved
- The data is codified to ensure confidentiality.** The access is restricted and controlled **in-depth phenotyping** Using the standard terminology **Human Phenotype Ontology (HPO)** It incorporates more than 13,000 terms and their definitions (English and Spanish)

### ENoD workflow

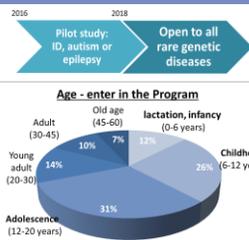


**Data sharing** National and International collaboration to identify other patients sharing the same phenotype and genetic variants. **Matchmaker Exchange**

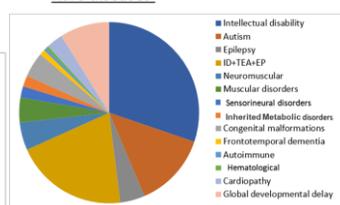
### Participant's Role

Clinicians	Geneticists	CIBERER's Researches	Bioinformatics
<ul style="list-style-type: none"> <li>Recruit patients into the program</li> <li>Correct phenotyping of the patients (HPO)</li> <li>Order complementary tests</li> <li>Communication with the patient</li> </ul>	<ul style="list-style-type: none"> <li>Interpretation and filtering of variants after sequencing</li> <li>Contribute knowledge about the genetics of the disease</li> </ul>	<ul style="list-style-type: none"> <li>Contribute knowledge about physiopathology of the disease</li> <li>In vitro and in vivo functional studies</li> <li>Validation of new genes</li> </ul>	<ul style="list-style-type: none"> <li>NGS Data analysis</li> <li>Data sharing (EGA, Beacons)</li> <li>Development of new tools to aid gene discovery</li> </ul>

Reaching diagnosis

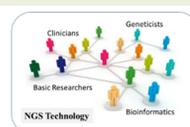


### Rare diseases



### CONCLUSIONS ENoD Program

Collaborative approach to diagnosis



in-depth phenotyping

in-depth genomic analysis

Data sharing