

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:

DIAGNOSTIC ORIENTATION AND EXPERT ADVICE

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

MASSIVE SEQUENCING TECHNIQUES

REANALYSIS OF PREVIOUS GENOMIC DATA

It is offered by our Bioinformatic platform

WES, WGS and others. Search for new genomic alterations as the cause of disease

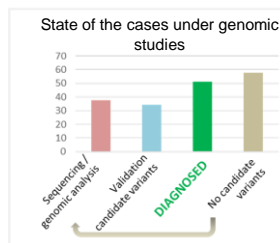


Results and Conclusions

- 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?

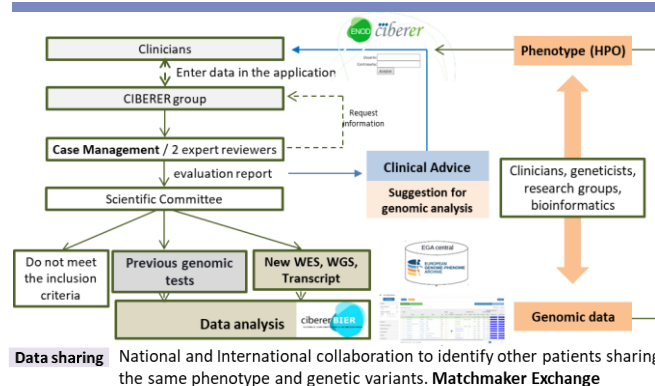
- Open to **all rare diseases**. Open to patients from all hospitals in Spain
- Referred by a **PHYSICIAN** through close cooperation with **CIBERER'S RESEARCHERS**
- Collaboration with **FEDER**, the **Spanish Federation of Rare Diseases** and **Undiagnosed Patients Association** to unravel diagnosis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

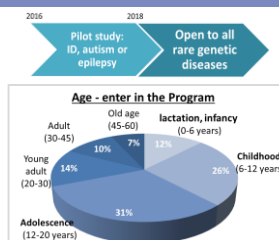
ENoD workflow



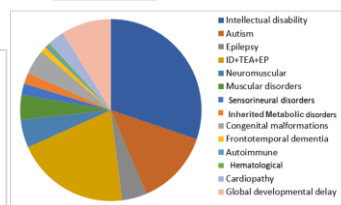
Participant's Role

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

Reaching diagnosis

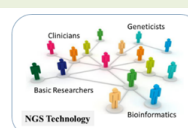


Rare diseases



CONCLUSIONS ENoD Program

Collaborative approach to diagnosis



in-depth phenotyping

in-depth genomic analysis

Data sharing