The CIBERER Program for Undiagnosed Rare Diseases (ENOD)  
A collaborative and multidisciplinary approach to diagnosis

Morte B.*, Rovira E., Pérez-Florido J., Carmona R., Aquino V., Herreras E., Dopazo J, Pérez-Jurado L.A.  
Center for Biomedical Network Research on Rare Diseases (CIBERER): www.ciberer.es, Spain. *bmorte@ciberer.es

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 to 700 BASIC BIO MEDICAL 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.

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 experts/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:

- MASSIVE SEQUENCING TECHNIQUES  
- REANALYSIS OF PREVIOUS GENOMIC DATA

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

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 undisagnosed 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  
  - Testify patients into the program  
  - Correct phenotyping of the patients (HPO)  
  - Order complementary tests  
  - Communicate with the patient

- Geneticians  
  - Interpretation and filtering of variants after sequencing  
  - Contribute knowledge about the genetics of the disease

- CIBERER’s Researchers  
  - Contribute knowledge about pathophysiology of the disease in order to develop new functional studies.

- Bioinformatics
  - ENoD database analysis  
  - Data sharing (HPO, Genotype, Phenotype)

- Development of new tools to aid gene discovery

Rare diseases

CONCLUSIONS ENoD Program

Collaborative approach to diagnosis

- in-depth phenotyping

in-depth genomic analysis

Data sharing