Grant agreement no. 769051

EpiCARE – a network for rare and complex epilepsies

HP-ERN-2016 European Reference Networks / Framework Partnership Agreement

D. 2.1. Report on key diagnostic laboratories

Work Package: WP2: Laboratory diagnostics

Due date of deliverable: 31 August 2017

Actual submission date: 26 February 2018

Start date of project: 1st March 2018 Duration: 12 months

Lead beneficiary for this deliverable: *28 EpiCARE centres*
Contributors: R.Nabbout (Hopital Enfant Malade, Necker, Paris, France) and R.Kälviäinen (Kuopio University Hospital, Kuopio, Finland)

Project co-funded by the European Commission within the HP-ERN-2016 European Reference Networks grant		
Dissemination Level		
PU	Public	x

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

Disclaimer

The content of this deliverable does not reflect the official opinion of the European Union. Responsibility for the information and views expressed herein lies entirely with the author(s).

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

Table of contents

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

1. Version log

Version	Date	Released by	Nature of Change
Version 1	9 Jan 2018	R.Nabbout (Hopital Enfant Malade, Necker, Paris, France) and R.Kälviäinen (Kuopio University Hospital, Kuopio, Finland)	First version

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

2. Definition and acronyms

Acronyms	Definitions
EU	European Union
REN	Rare Epilepsy Network
ILAE	International League against Epilepsy
TF	Task Force
MDT	Multidisciplinary team

3. Introduction

The WP-2 working group is aware of major obstacles to access the diagnosis in rare and complex epilepsies. Our goal is to shorten the odyssey of patients and families to achieve a diagnosis and further propose the best available therapies or ongoing trials. To date, the availability of advanced laboratory and genetic testing tools for rare epilepsies is heterogeneous in the different centres of our network EPICARE.

We aimed first to identify the centres where this expertise is available and to build an expert group dedicated to help in the syndrome diagnosis but also in providing the interpretation of "difficult" genetic and laboratory tests. This mapping will be available for all centres within EPICARE network at a first step to exchange better practice and help to resolve at least partly unresolved cases.

4. Activities carried out and results

4.1. Laboratory diagnostics survey

A survey of laboratory diagnostics was devised and sent to all EPICARE centres. The survey was prepared between March and June 2017 and we collected responses up till the end of February 2018.

The survey's main aim was to collect information on the available laboratory diagnosis to identify the etiology of rare epilepsies mainly for autoinmune, metabolic and genetic epilepsies. It was sent via email to each centre.

The survey allows us to pinpoint which centres are providing metabolic testing and next generation sequencing (NGS, epilepsy panels or WES). Furthermore, the result of the survey enables us to understand what kind of diagnostic testing methods are available in EpiCARE centres. The survey gives a better picture of the capacity of these diagnostic tests and whether

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

it's posible to use these facilities for patients from a different country. Therefore it will allow us to plan transborder testing when it is needed and is necessary.

We have received 26 responses from 28 EpiCARE centres, however due to the tight deadline only 20 responses were analised for this report. We endevour to collect all remaining questionnaires and create a more comprehensive report that will inform our plan to assess rare disease patients

Questions ranged from the identification of the centre to more logistic questions about the organisation of the laboratory tests that are routinely performed in each centre, detailing if the tests are done in house or through collaborations. If they are done on a diagnosis background or research background and if these tests are available for patients not treated in the centre or patients referred by the network. We also inquired if laboratory diagnostic testing is done on a public national health funds and in a given centre or as a private activity to pay by the patient or its private insurance.

Finally, we asked about comments and the top 3 requests of each centre concerning the lab and genetic testing.

We will present in the following the survey a) and detail the answers of the centres of the network b).

4.2. WP2 exploratory questionnaire

Exploratory questionnaire:
Please indicate the most adequate question. You might need to give 2 possibilities for some questions as for metabolic testing as you might have a part conducted at your institution and another part done in established collaborations.

Institution name:
City
Country

How many new rare epilepsies syndromes were described in your centre?
References:
How many new genes for rare epilepsies were described in your centre?
References:

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

Please tell us the availability of the following metabolic/genetic diagnosis in your centre:
(PS: Metabolic diagnosis and guidelines will be done in collaboration with Metab ERN)

Type of test		In house	In the same institution but in another site	In another institution with inter institutions contract	In another institution without identified contract	In private labs	Research funds and not diagnosis facility	Test is reimbursed by country health authority Precise if Complete or partial	Possibility to offer this facility for external users from the same country	Possibility to offer this facility for external users from another European country
		y/n	**y/n**	**y/n**	**y/n**	**y/n**	**y/n**	**Yes, fully/Yes, partly/ No**	**y/n**	**y/n**
Metabolic testing	Classical (basic)									
	Advanced: Neurotransmitters/ Enzyme activities…									
Genetic testing	Array CGH									
	Single gene testing									
	Gene panels									
	Exome NGS									
	Genome NGS									
Auto antibodies	Specific Abs (specify)									
	Complete antibodies study									

Please add your comments and the top 3 requests you expect from this WP
Comments:
Requests:

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

The result of the survey

26 centres completed the survey, 20 survey responses were analysed.

The answers were grouped as follow:

Is Classical (basic) Metabolic testing available in your centre?

In house 16/20
In the same institution but in another site 2/20
In another institution with inter institutions contract 4/20
In another institution without identified contract 0
In private labs 0
Research funds and not diagnosis facility 0
Possibility to offer this facility for external users from the same country 12/20
Possibility to offer this facility from another European country 11/20

Is Advanced Metabolic testing (e.g. Neurotransmitters/Enzyme activities) available in your centre?

In house 14/20
In the same institution but in another site 4/20
In another institution with inter institutions contract 8/20
In another institution without identified contract 5/20
In private labs 1/20
Research funds and not diagnosis facility 2/20
Possibility to offer this facility for external users from the same country 8/20
Possibility to offer this facility from another European country 6/20

Is 'Array CGH' Genetic testing available in your centre?

In house 12/20
In the same institution but in another site 2/20
In another institution with inter institutions contract 3/20
In another institution without identified contract 3/20
In private labs 1/20
Research funds and not diagnosis facility 1/20
Possibility to offer this facility for external users from the same country 9/20
Possibility to offer this facility from another European country 6/20

Is 'single gene testing' available in your centre?

In house 16/20
In the same institution but in another site 4/20
In another institution with inter institutions contract 5/20
In another institution without identified contract 3/20
In private labs 5/20
Research funds and not diagnosis facility 2/20
Possibility to offer this facility for external users from the same country 9/20
Possibility to offer this facility from another European country 7/20

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

Is 'Gene panels' testing available in your centre?
In house 12/20
In the same institution but in another site 3/20
In another institution with inter institutions contract 3/20
In another institution without identified contract 4/20
In private labs 5/20
Research funds and not diagnosis facility 3/20
Possibility to offer this facility for external users from the same country 9/20
Possibility to offer this facility from another European country 6/20

Is 'Exome NGS' testing available in your centre?
In house 7/20
In the same institution but in another site 3/20
In another institution with inter institutions contract 5/20
In another institution without identified contract 6/20
In private labs 5/20
Research funds and not diagnosis facility 7/20
Possibility to offer this facility for external users from the same country 6/20
Possibility to offer this facility from another European country 4/20

Is 'Genome NGS' testing available in your centre?
In house 3/20
In the same institution but in another site 3/20
In another institution with inter institutions contract 3/20
In another institution without identified contract 5/20
In private labs 4/20
Research funds and not diagnosis facility 9/20
Possibility to offer this facility for external users from the same country 3/20
Possibility to offer this facility from another European country 1/20

Is 'Complete antibodies study' available in your centre?
In house 10/20
In the same institution but in another site 1/20
In another institution with inter institutions contract 7/20
In another institution without identified contract 6/20
In private labs 4/20
Research funds and not diagnosis facility 2/20
Possibility to offer this facility for external users from the same country 7/20
Possibility to offer this facility from another European country 5/20

Is 'specific antibodies testing' available in your centre?
In house 8/20
In the same institution but in another site 1/20
In another institution with inter institutions contract 6/20

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

In another institution without identified contract 6/20
In private labs 5/20
Research funds and not diagnosis facility 2/20
Possibility to offer this facility for external users from the same country 5/20
Possibility to offer this facility from another European country 4/20

Test is reimbursed by the country's health authority
Classical (basic) metabolic testing 19/20 fully- 1/20 partially
Advanced metabolic testing (Neurotransmitters/Enzyme activities…) 19/20 fully-1/20 partially
Array CGH (genetic testing) 18/20 fully- 2/20 partly
Single gene testing 19/20 fully – 1/20 partially
Gene panels testing 16/20 fully – 3/20 partially – 1/20 not reimbursed
Exome NGS testing 12/20 fully – 3/20 partially – 5/20 not reimbursed
Genome NGS testing 11/20 fully – 4/20 partially – 5/20 not reimbursed
Specific Antibodies test 16/20 fully – 3/20 partially – 1/20 not reimbursed Yes, fully
Complete antibodies study 14/20 fully – 3/20 partially – 3/20 not reimbursed Yes, fully

What would be your top 3 requests you expect from the laboratory diagnostics WP?
The centre requests were mainly on the availability of gene panels for evaluation of rare epilepsies and the reimbursement facilities. The second most requested issue was about guidelines for genetic testing and sharing the analysis of difficult cases with experts.

Finally the participation in research projects on unsolved cases.

4.3. Discussion of the results of the survey:

This survey showed a large heterogeneity between centres and countries with two centres having few possibilities to work on etiology diagnosis. The network should help to support these centres in obtaining additional facilities.

The NGS panels for the rare Epilepsie seems to be to date a major need for etiological diagnosis.

This survey highlighted the possibility of sharing ressources, however, this should be discussed further in the network in order to establish referral guidelines in order to have the best results for the patient and the best cost-benefit result.

These results will be discussed at the anual meeting in March 2018. Actions will be addressed in the action plan for year 2.

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

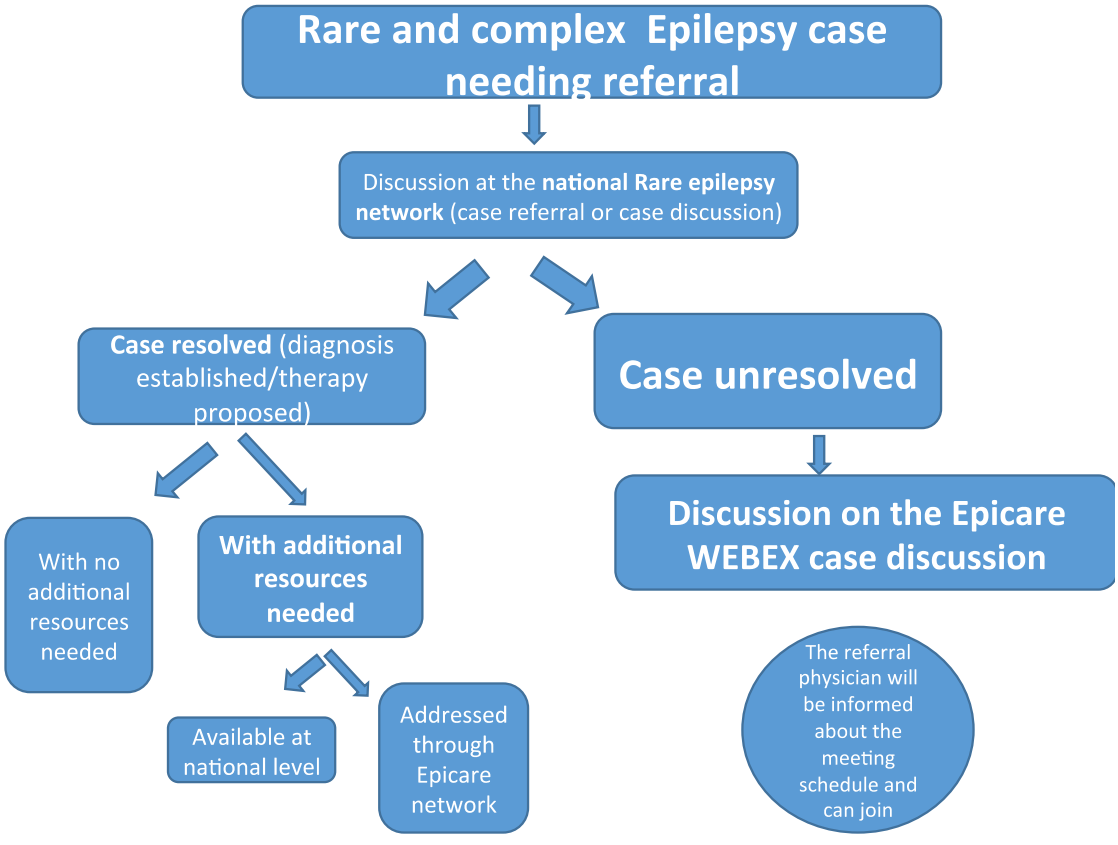
4.4. Activities carried out between September-December 2017

4.4.1. Patient referral pathway

An ad hoc task force (WPII TF) was formed by members from: Hopital Enfants Malades, Necker, Paris, Kuopio University Hospital, Finland, University Medical Centre Utrecht, Netherland and Paracelsus Medical University, Salzburg, Austria. The TF started to build up a **rare epilepsy care pathway** at a National and European level. The core idea is to encourage countries to organize discussions at a national level and we will propose a collaboration with individual reference centres for countries without a reference centre to mimic the "national" discussion of cases before raising it to the EPICARE network MDT meetings. This "twinning"-collaboration will be based on language and previous collaborations. The TF met in September and in December 2017.

The first case discussion will be performed in March after the training on the Clinical Patient Management System (CPMS).

Figure 1. Draft care pathway



"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"

4.4.2. Initiation of collaboration with Orphanet to work on the phenotype characteristics of rare epilepsies (*December 2017*)

The goal of this collaboration is to better delineate rare epilepsies and to disseminate the knowledge on the phenotype of the rare epilepsies syndromes.

This action was also supported by a meeting in December 2017 with the American Rare Epilepsy Network (REN) to harmonize our definitions under the auspices of the nosology task force of the ILAE (request ongoing).

4.4.3. Initiation of the collaboration with the metabolic ERN to establish the common work on rare epilepsies with metabolic etiology (January 2018)

Proposal of a task force with the Research Work Package (Professor Renzo Guerrini) and with the following institutes: Meyer Institute, Florence, Italy, Hospices civils de Lyon, France, Bambino Gesù, Italy, Hopital Enfant Malade, Necker, Paris, Kuopio University Hospital, Finland, Hospice civils de Lyon, France to establish expert MDT discussions for difficult genetic and metabolic/autoimmune laboratory findings during Year 2.

5 Conclusions

Activities in the first year focused on mapping the laboratory and genetic and genetic diagnosis facilities in the centres of the network. We established the care pathway that we will adopt for case discussions and an expert task force to prioritize and advise on prposed genetic testing and results analysis for unresolved cases. This workplan is ready for implementation for Year 2.

The collaboration with Orphanet and the REN (USA) will be a first step toward the harmonisation of rare epilepsies description and dissemination.

"This project has received funding from the European Union's HP-ERN-2016 European Reference Networks / Framework Partnership Agreement Grant under the Grant Agreement No 769051"