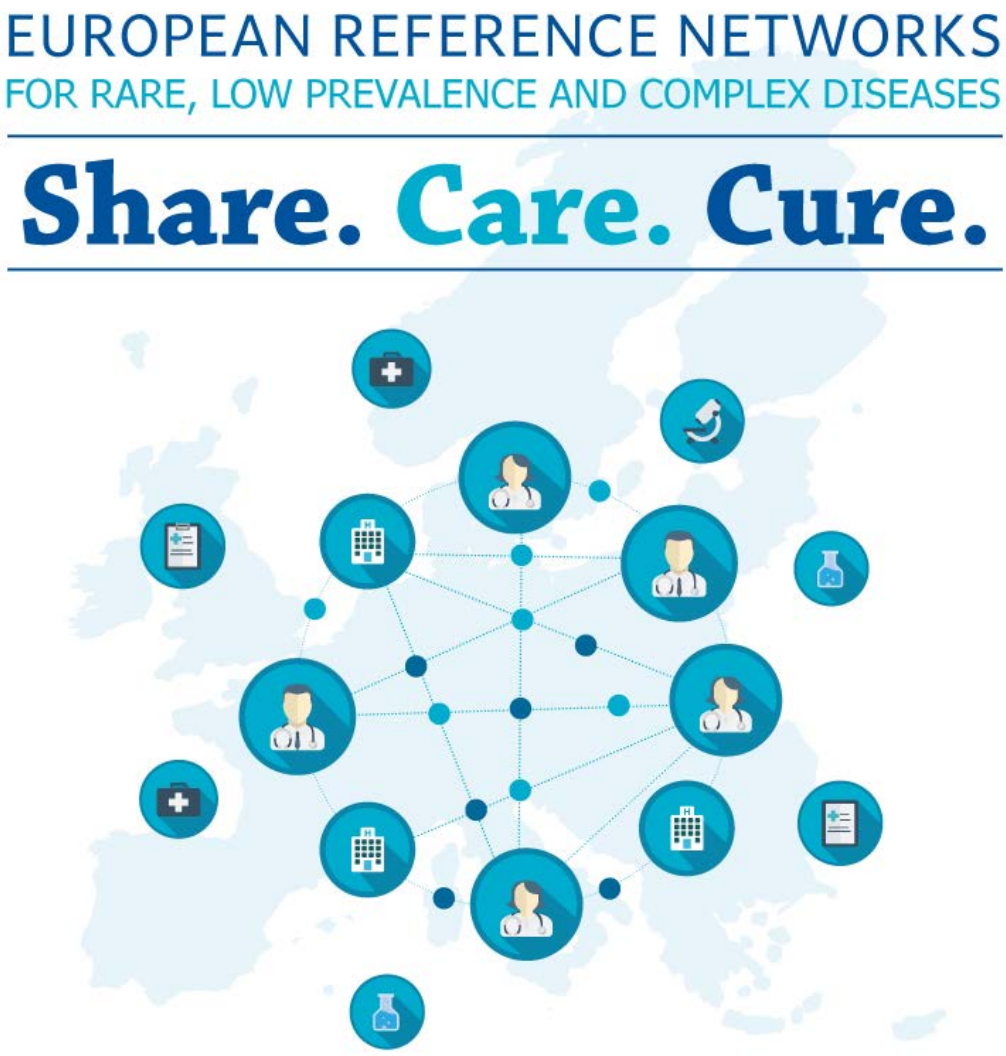
European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

European Reference Networks

5.4 ASSESSMENT OF RHD GUIDELINES AWARENESS AND IMPLEMENTATION

ERN-EuroBloodNet European Reference Network on Rare Hematological Diseases



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DOCUMENT INFORMATION

5.4 ERN-EUROBLOODNET REPORT ON THE AVAILABILITY OF HIGHLY SPECIALIZED PROCEDURES FOR RARE HEMATOLOGICAL DISEASES

Report document

ERN: **ERN-EuroBloodNet (European Reference Network on Rare Hematological Diseases)**

Call: **HP-ERN-SGA-2018**

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Short Description

Report on the first results of the assessment of implementation of ERN-EuroBloodNet endorsed recommendation "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency" in Europe.

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1. INTRODUCTION

RARE DISEASES GUIDELINES IMPLEMENTATION: GAPS AND NEEDS

"There is probably no other area in public health in which 27 national approaches could be considered to be so inefficient and ineffective as with rare diseases (RD). The reduced number of patients for these diseases and the need to mobilise resources could be only efficient if done in a coordinated European way." – European Commission COUNCIL RECOMMENDATION of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02).

It is well known that the field of RD suffers from a shortage of medical and scientific knowledge. For a long time, doctors, researchers and policy makers were unaware of RD and until very recently there was no real research or public health policy concerning issues related to the field. There is no cure for most of RD, but the appropriate treatment and medical care can improve the quality of life of those affected and extend their life expectancy.

Clinical Practice Guidelines (CPGs) and other Clinical Decision Making Tools (CDMTs) have been developed during last decades to assist practitioners and patient decisions about appropriate healthcare for specific conditions, however, given the low prevalence of RD, few of them have been addressed to the management of these conditions. Despite the efforts performed in the last years to increase the number of CPGs and CDMTs covering RDs, up to date they are still few and most of them difficult to find.

On the other hand, it is well known the important differences on the level of practical implementation of the available guidelines among Member States (MS), and even among healthcare providers in the same countries. Nevertheless, there is no a systematic procedure to evaluate their real translation into clinical practice that would help to promote those CPGs and CDMTs poorly implemented while ensuring their impact in patients' quality of life.

BEST PRACTICES ON DIAGNOSIS

Undoubtedly, diagnosis is one of the areas most affected by the lack of sufficient scientific and medical knowledge on the RD field. Focussing on rare haematological diseases (RHD), differences in some core lab test for diagnosis have been observed across MS leading to a late diagnosis or even misdiagnosis, especially for the very rare diseases.

Pyruvate Kinase deficiency (PKD) is an example of a chronic RHD in which diagnosis can be delayed for years, can be misdiagnosis or even been labelled as haemolytic anaemia of unknown origin forever.

PYRUVATE KINASE DEFICIENCY (PKD)

PKD is a rare autosomal recessive disorder and the most frequent enzymopathy of glycolysis. Currently, 240 different mutations have been identified (www.lovd.nl/pklr). The main clinical symptom of PKD is hemolytic anemia of variable severity, from fully-compensated to life-threatening, transfusion dependent anemia.

As in other RD, real prevalence and number of patients is unknown since there is no patients' registries or exhaustive epidemiological studies. PKD prevalence has been estimated at 1-9:100,000 cases per one hundred thousand people according to ORPHANET. However, based on published literature, estimated PKD prevalence on genetic basis in the general white population was calculated to be 5: 100,000. In addition, there are other reports based on patients' registries with a lower incidence, about 1: 100,000. This discrepancy may be explained by a high number of very mild PKD patients who are not referred to Centres of Expertise, reducing the resulting prevalence.

Different from haemoglobinopathy patients, more prevalent and concentrated by ethnical and/or geographical origin, patients affected by PKD are scarcer and highly distributed. PKD diagnosis is commonly delay due to lack of adequate testing or misinterpretation and no specific drug is still available on the market. Accordingly, PKD patients could benefit for such European approach.

Diagnosis of Pyruvate Kinase deficiency (PKD) has been identified as a routine test, but not available across Europe, representing an example of a chronic RHD in which diagnosis can be delayed for years, can be misdiagnosis or even been labelled as haemolytic anaemia of unknown origin forever due to:

- Lack of knowledge of the disease
- Heterogeneous clinical phenotype
- Technical problems: Recent transfusions, WBCs/platelet contamination, increased reticulocyte number, variants displaying in vitro normal enzyme activity

In addition, there is a number of cases misdiagnosed, the main causes are:

- Hereditary Spherocytosis, it is a more common cause of chronic hemolysis
- Thalassaemia major, in cases of severe blood transfusion anemia
- Liver abnormality, anaemia is considered secondary to the liver disease

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Accordingly, there is an urgent need to promote at European level best practices for PKD diagnosis and increase its awareness among medical community; general practicioners, paediatricians and even haematologists.

ERN-EUROBLOODNET INITIATIVES TO IMPROVE PKD DIAGNOSIS

RECOMMENDATIONS ON PKD DIAGNOSIS WITH THE ENDORSEMENT OF ERN-EUROBLOODNET

In line with the need of best practice promotion on PKD diagnosis, a global PKD International Working Group was created in 2016 involving 24 experts from 20 Centers of Expertise, aiming to analyse the existing gaps in the PKD diagnosis.

Based on the conduction of a survey on key conflictive points on the diagnosis of PKD and subsequent discussions among members Expert Centers from Europe, USA, and Asia directly involved in diagnosis, a consensus was reached on recommendations for PKD diagnosis.

A high number of ERN-EuroBloodNet experts and members representatives participated in this consensus, as Paola Bianchi, Elisa Fermo, Wilma Barcellini, Tabita Maia, Maria del Mar Mañú Pereira, Eduard van Beers, and Richard van Wijk.

As final result, "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency" was published by the American Journal of Hematology under the endorsement of ERN-EuroBloodNet, with the objective to help other Centers and professionals to deliver timely and appropriate diagnosis and to increase awareness in PKD.

ASSESSMENT OF THE IMPLEMENTATION OF THE CONSENSUS RECOMMENDATIONS ON THE DIAGNOSIS OF PYRUVATE KINASE DEFICIENCY

The first Assessment of the implementation of the Consensus recommendations on the diagnosis of PKD was performed during the second year of ERN-EuroBloodNet implementation based on a mapping of centers performing PKD diagnosis and facilities.

The first mapping exercise was launched December 2018 for the gathering of basic information on patients activity (ie. number of PKD patients currently in follow-up, % genotyped, new number of patients per year) and diagnosis (ie. number of diagnosis tests, method, availability within the medical centre or externalized, implementation of *PKLR* genetic analysis).

By February 2019, a total of 41 medical centres from 10 countries completed the survey with the collection of preliminary data on number of patients in follow up and diagnosis methods used by each institution, allowing the identification of first main gaps and differences on diagnostics approaches (Deliverable 4.2 Report on guidelines implementation, February 2019, includes details the full methodology followed as well as main results).

In addition, the pilot on External Quality Assesment for PKD coordinated by Barbara De la Salle, Director of UK NEQAS Hematology showed important intra/inter variations among participating centres, all of them considered centres of reference for PKD diagnosis, not only on the results of PK activity but also on reference ranges, methods, and reporting.

Accordingly, an agreement was reached between ERN-EuroBloodNet PKD experts in April 2019 to upgrade the online application form already implemented in order to consolidate a European network of centres dealing with PKD with the main objectives to obtain epidemiological data on PKD patients and promote best practices for PKD diagnosis. This was done in collaboration with UK NEQAS Hematology and RADeep, the Rare Anaemia Disorders European Epidemiological platform.

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2. OBJECTIVES

Following the results achieved during the first mapping of centers performing PKD diagnosis and facilities for accurate diagnosis and genetic characterization conducted from December 2018 to February 2019, the present deliverable describes the procedures and results obtained from the upgrade of the online form aiming to:

- Assess in detail the implementation of the Consensus recommendations on the diagnosis of pyruvate kinase deficiency based on the gathering of exhaustive data on how expert centers perform PKD diagnosis
- Obtain a first approach of PKD epidemiological data across EU-MS for the identification of diagnostics gaps based on lower actual number of patients versus expected
- Consolidate the European Network of centers performing PKD diagnosis

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3. TASKS

TASK 1. DESIGN OF THE QUESTIONNAIRE

The questionnaire to assess recommendations on PKD diagnosis was created by ERN-EuroBloodNet/RADeep experts on PKD diagnosis Paola Bianchi (IT) and Maria del Mar Mañú Pereira (ES) and validated by Celeste Bento (PT), Barbara de la Salle (UK-NEQAS), Serge Pissard (FR) and Richard van Wijk (NL). It includes the following main sections:

CENTRE DATA

Includes general information of the medical centre but also of the departments dealing with PKD. It includes information on:

- Age coverage for follow-up
- Agreement for transition to adulthood if not covered in the own centre
- Phenotyping and genotyping facilities

PKD PATIENTS ACTIVITY

Includes yearly data on number of patients in follow-up stratified by age (<18 years or >18 years) and main criteria for PKD patients' severity; Splenectomy yes / no and Regular transfusion yes / no. In addition, information on number of PKD patients genotyped is requested.

PKD DIAGNOSIS ACTIVITY

Part A PK enzyme activity and PKD Diagnosis activity – Part B PKLR genetic analysis has been developed based on the publication:

Bianchi P, Fermo E, Glader B, Kanno H, Agarwal A, Barcellini W, Eber S, Hoyer JD, Kuter DJ, Maia TM, Mañu-Pereira MDM, Kalfa TA, Pissard S, Segovia JC, van Beers, Gallagher PG, Rees DC, van Wijk R; with the endorsement of EuroBloodNet, the European Reference Network in Rare Hematological Diseases. Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency. Am J Hematol. 2019 Jan;94(1):149-161.

PKD Diagnosis activity – Part A PK enzyme activity

Includes information on PKD enzyme assay performance including number of assays per year, new PKD diagnosis per year, total number of PKD diagnosis over the last 25 years, method for sample preparation and enzyme assay, reference ranges, sample storage and transport conditions, units for reporting results and interpretation, laboratory work flow for hemolytic anemia, turn-around time. Figure 4.

In the case that the medical centre do not perform the PKD assay in the own centre, information on extern centre and process is also requested.

PKD population frequency is expected to be globally similar independently to the European country. Comparison between diagnosis rates among countries and number of patients in follow-up will also give use inestimable information on PKD management and diagnosis efficiency at the national level.

PKD Diagnosis activity – Part B PKLR genetic analysis

Includes availability for PKLR genetic analysis, method, gene coverage, identification of PKD patients lacking of one (or even two) of the two expected mutations in PKLR, time-around time, additional genetic testing.

GENETIC COUNSELLING AND PRENATAL DIAGNOSIS

Includes two simple questions to assess availability of genetic counselling and prenatal diagnosis for PKD. It also includes the possibility to inform on collaborating centres with a collaboration agreement for these porpoises

COMMENTS AND PRIVACY

Includes a free text box for additional comments and permission to publish the data marked with "blue web".

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TASK 2. LAUNCH OF THE ONLINE APPLICATION FORM

The on-line application form was programmed at RADeep website for an easy provision of data by the respondent.

Online forms include multiple sections which are only visible depending on the answer selected by the responder. In addition, the different sections are accessible through the always-displayed menu at the right, allowing the access to the sections of interest in an easy way.

The online forms were designed in line with the design of RADeep website. Some parts of the form are shown in Figs 1-6:

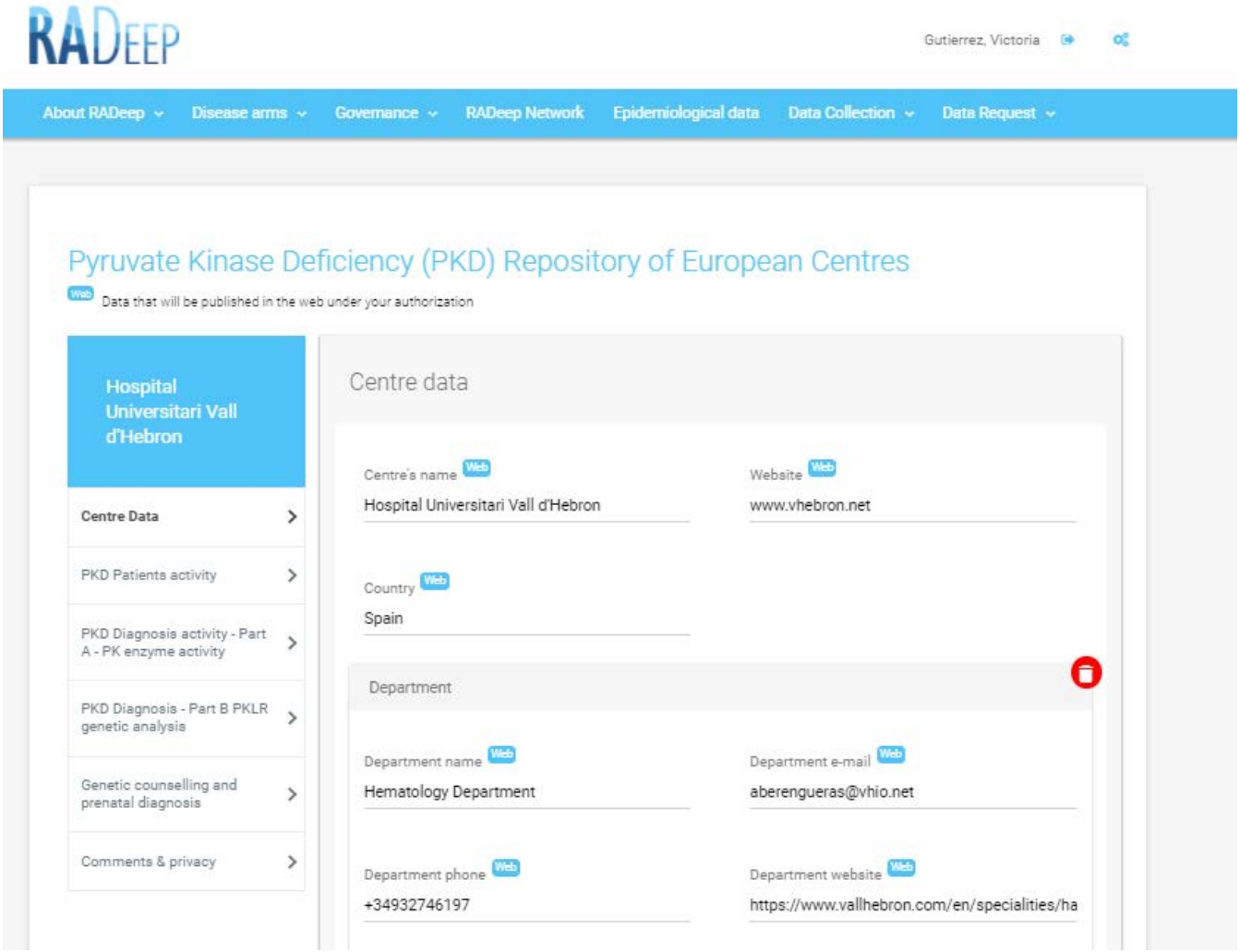

Fig 1. Part of the centre data section of the online form

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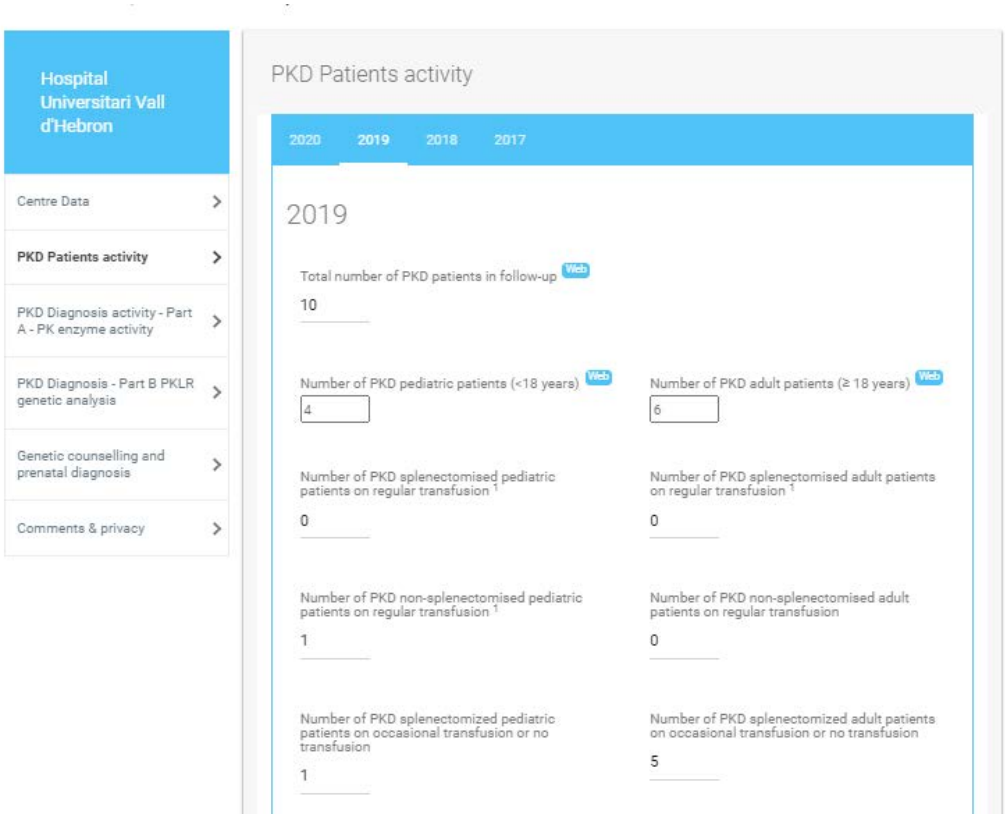

Fig 2. Part of the PKD patients activity of the online form

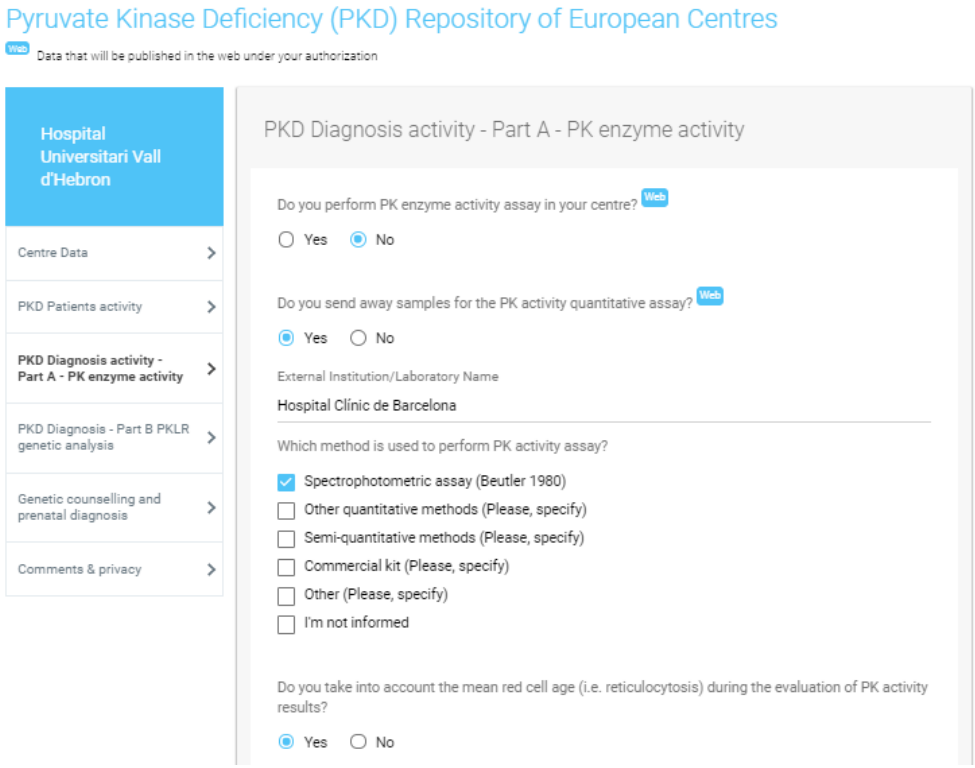

Fig 3. Part of the PKD diagnosis activity Part A section of the online form

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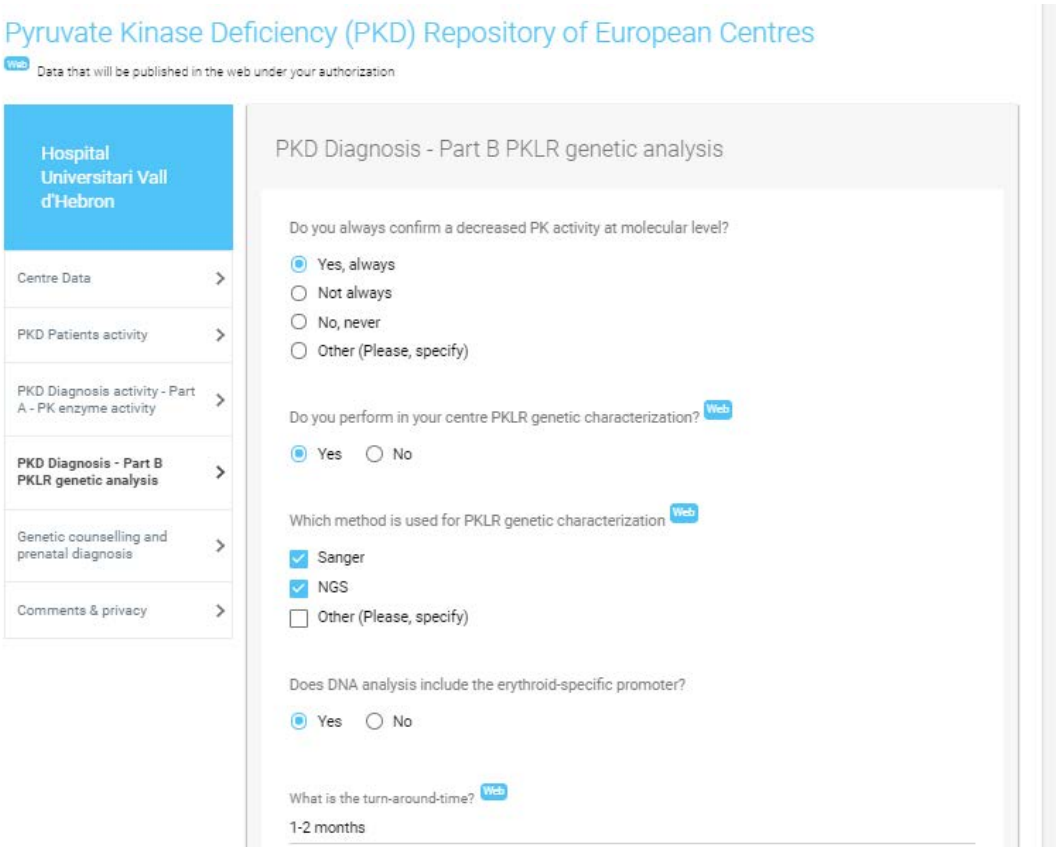

Fig 4. Part of the PKD diagnosis activity Part B section of the online form

Fig 5. Genetic counselling and prenatal diagnosis section of the online form

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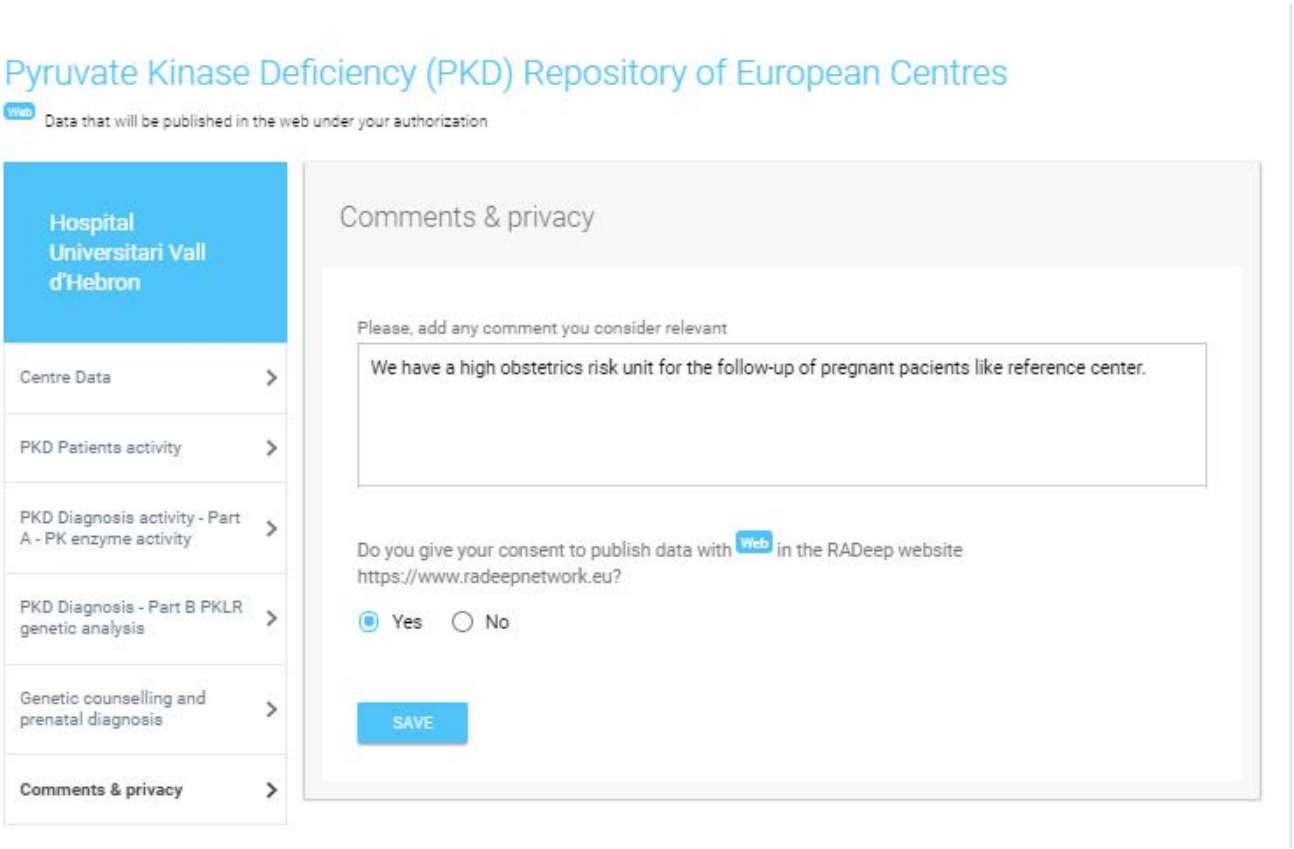

Fig 6. Comments and privacy section of the online form

The upgraded on-line application form was launched for a first internal testing. Once validated, invitations with protected user/password accounts were sent to PKD experts to complete / expand the form.

The on-line form was disseminated through national scientific associations working groups on red blood cell in order to obtain a comprehensive picture of the European centres dealing with PKD. In addition, a dedicated wave of contacts to centers with partial data completed was reinforced from July to September 2020 aiming to get as highest number of responses as possible.

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4. RESULTS

FIRST RESULTS FROM THE MAPPING OF CENTERS PERFORMING PKD DIAGNOSIS AND FACILITIES FOR ACCURATE DIAGNOSIS AND GENETIC CHARACTERIZATION

To date September 2020 a total of 49 medical centers from 11 countries have answered the expanded online mapping exercise.

A total of 297 PKD patients in follow-up has been gathered from the 49 medical centres. Up to 690 PKD diagnosis have been performed in these centres over the last 25 years. National PKD frequency based on a) number of patients in follow-up and b) number of PKD diagnosis, was calculated for the 11 countries based on total population for year 2019. Expected number of PKD patients was calculated for each participating country and for the total population in EU based on higher frequency observed for patients diagnosed and in follow up, Netherlands (Fig. 7). Relations among the actual data gathered vs the expected were calculated (Fig.8).

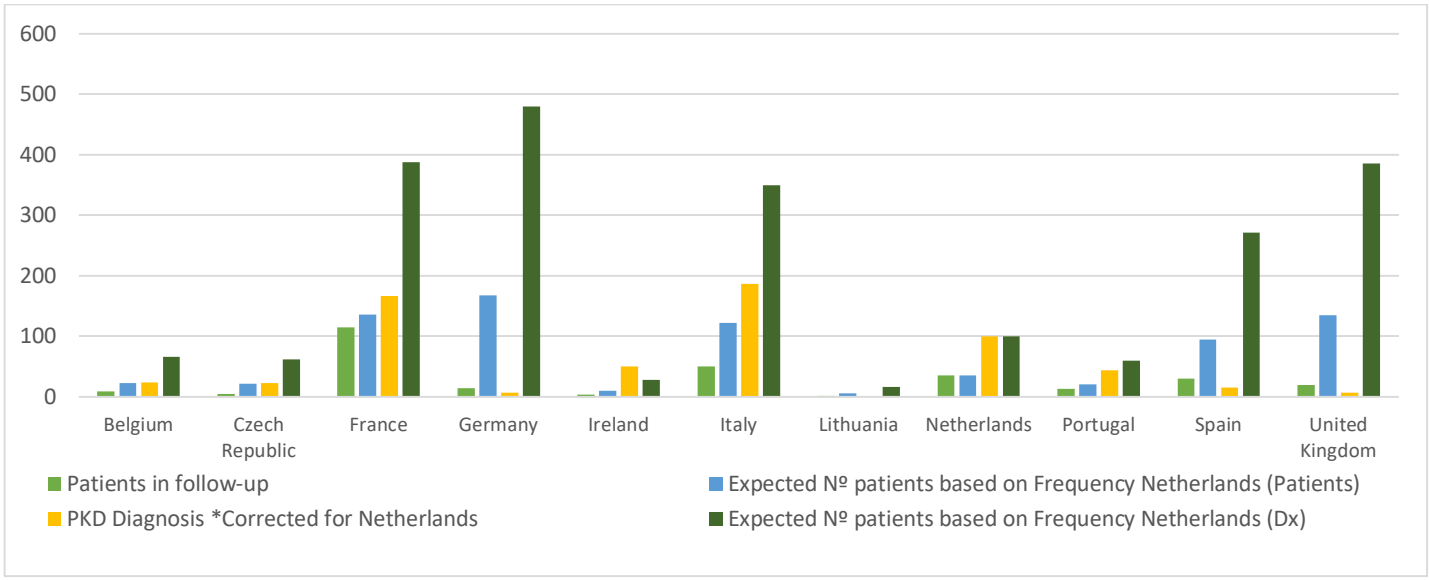

Fig. 7 National PKD frequency based on number of patients in follow-up and number of PKD diagnosis observed and expected numbers based on Netherlands frequency.

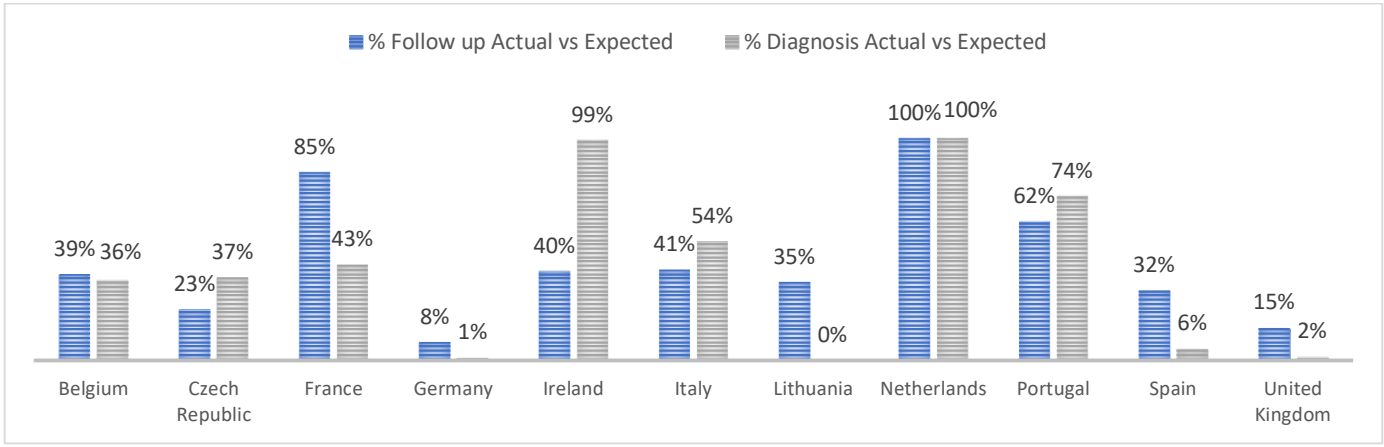

Fig. 8 Relations among the actual data gathered vs the expected

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PKD population frequency is expected to be globally similar independently to the EU country, thus, through this preliminary results, major gaps in diagnosis are identified, as in Germany, Lithuania, Spain or UK.

Only eight of the medical centres presented more than 10 patients in follow-up, accounting for 202 of the 297 patients registered and based in France, Italy, Netherlands, Portugal, Spain and United Kingdom. However, when adjusting the number of patients in follow-up according to the total population of the country, the highest values are found in Netherlands, France and Portugal, and the lowest in Germany, United Kingdom and Czech Republic.

Higher numbers of patients in follow-up in comparison to diagnosis could be explained by the organization of National health systems based on centralization of mild-moderate cases to reference centers, as France.

Important differences can be appreciated from analysis performed last year, remarking the increase of the estimated frequency in follow up (18%) and diagnosis (64%), which can be explained for the efforts devoted to increase participation, adding robustness to the analysis.

Regarding dianostic facilities, from the 49 medical centres only 10 performs both PKD assay and PKLR gene analysis, 3 medical centres in Italy, 2 in Netherlands and Czech Republic, and 1 in France, Belgium and Portugal. This highlights the lack of facilities for PKD diagnosis even in countries where expert centres for follow-up are already identified. Data on diagnostic facilities by country is shown in Fig. 9.

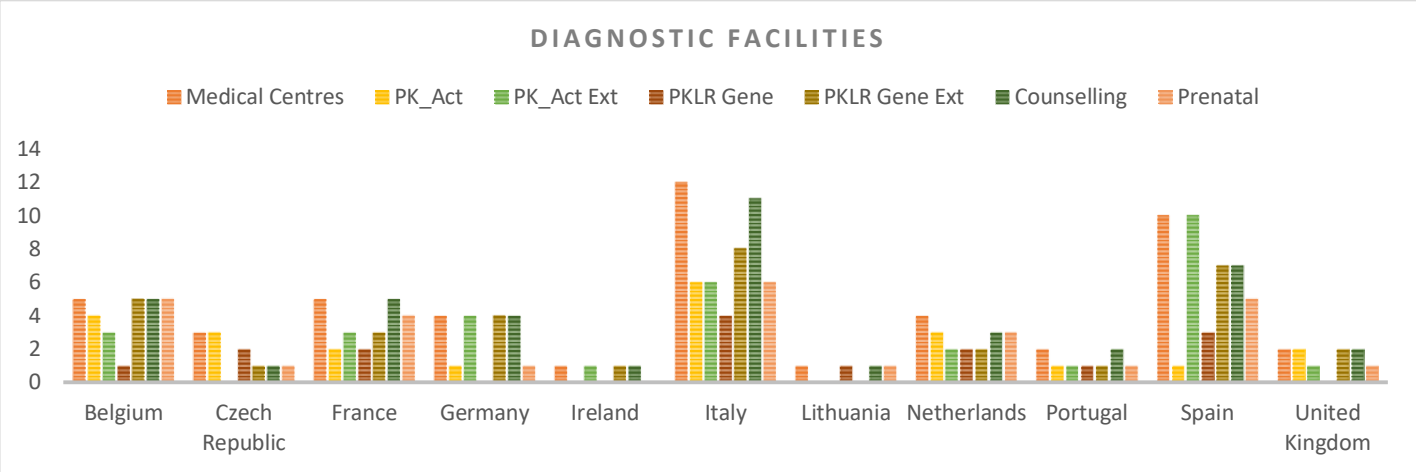

Fig 9. Data on diagnostic facilities by country

23 of the 49 medical centres perform PK Activity test in their own centres (46,9%), 7 of them also externalized the PK activity. 9 of them (39,13%) perform PK activity by spectrophotometric assay, reference method by Beutler 1980, and in 14 cases specific method was not reported. 31 of the medical centres externalize the PK activity (63,3%), 16 of them (51,6%) reported not be informed on the method used by the external laboratory.

To the question “If you do not perform PK activity assay nor in your centre neither externalized please specify the reason” 4 medical centres answered “We only perform DNA analysis of PKLR”. However, 2 of them are likely to be misunderstood the question since they also reported that they performed PK activity. To the question “Do you always confirm a decreased PK activity at molecular level?” 38 medical centres answered yes (77,5%), but only 16 centres (32,7%) perform PKLR gene analysis.

42 of the medical centres offers genetic counselling for PKD (85,7%), however only 28 (57,1%) offer prenatal diagnosis.

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5. CONCLUSIONS AND NEXT STEPS

As much important as identifying the medical centres concentrating patients and offering PKD diagnosis facilities is the identification of the GAPs. PKD patients are likely to be undiagnosed and/or misdiagnosed, probably due to the lack of facilities or expertise in a given country. In some countries, most of them are likely to not being genotyped due to economical shortages in the national health systems.

The synergy of ERN-EuroBloodNet, UK-NEQAS and RADeep PKD team has allowed the upgrade of the PKD survey with the inclusion of key indicators from the recommendation "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency" that has recently being published by the American Journal of Hematology under the endorsement of ERN-EuroBloodNet, allowing a first analysis of the level of implementation of the Recommendations while identifying centers performing PKD diagnosis and facilities.

The analysis of data provided from the 49 centers has allowed the first estimation of number of patients diagnosed and in follow up expected to be found in each country while assessing a ratio of the number of patients identified vs the estimations. Those countries with a low ratio percentage may be presenting important gaps for diagnosis and therefore, having high rates of under/missdiagnosed PKD patients. In order to confirm the hypothesis and dissipate potential bias in the data gathered, these countries become target to be further analysed in the next steps, ie. by approaching new additional centers that may deal with PKD patients.

Future actions foreseen also include to reinforce the contact with those centers providing partial data in their forms in order to allow a much comprehensive analysis on the diagnostic methods available while removing some incongruences found during this first assessment.

The continues expansion and update of the inventory on medical centres and diagnosis facilities is possible thanks to the implementation of the online form in order to update information from already listed centres or add new centres. Moreover the list of centers and facilities are easily searchable through the on-line application, creting a repository of medical centres dealing with PKD that will enable general practitioners, pediatricians or even hematologists to find experts on the disease to ask for advice and/or request appropriate diagnosis. This will impact in both a reduction of the number of PKD patients non-diagnosed or misdiagnosed and an increase on the number of PKD patients with a genetic diagnosis.

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https://ec.europa.eu/health/ern_en

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