The LHUB-ULB at the heart of a European network of rare haematological diseases: stop or what else?

Béatrice GULBIS, M.D., PhD

Department of Clinical Chemistry

Co-coordinator EuroBloodNet

15.10.2022

Phase 1: the story

JULES BORDET INSTITUUT

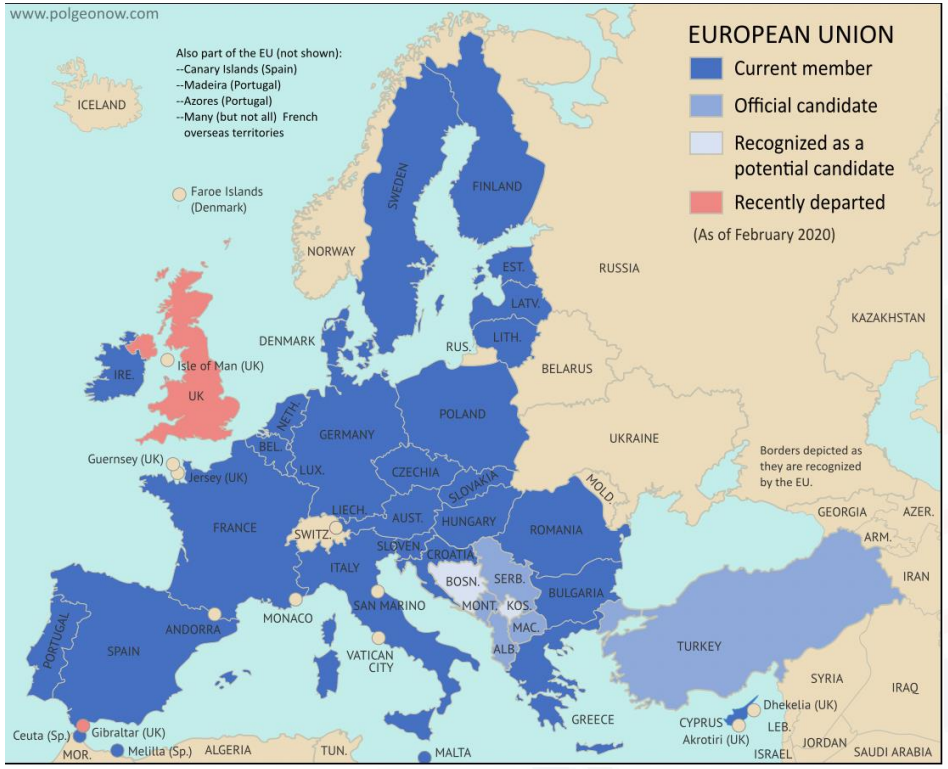
C H U | U V C BRUGMANN

Hôpital Erasme ULB

Hôpital Universitaire des Enfants Reine Fabiola
Universitair Kinderziekenhuis Koningin Fabiola

CHU Saint-Pierre
UMC Sint-Pieter

European level



JULES BORDET INSTITUUT

CHU | UVC BRUGMANN

Hôpital Erasme | ULB

Hôpital Universitaire des Enfants Reine Fabiola
Universitair Kinderziekenhuis Koningin Fabiola

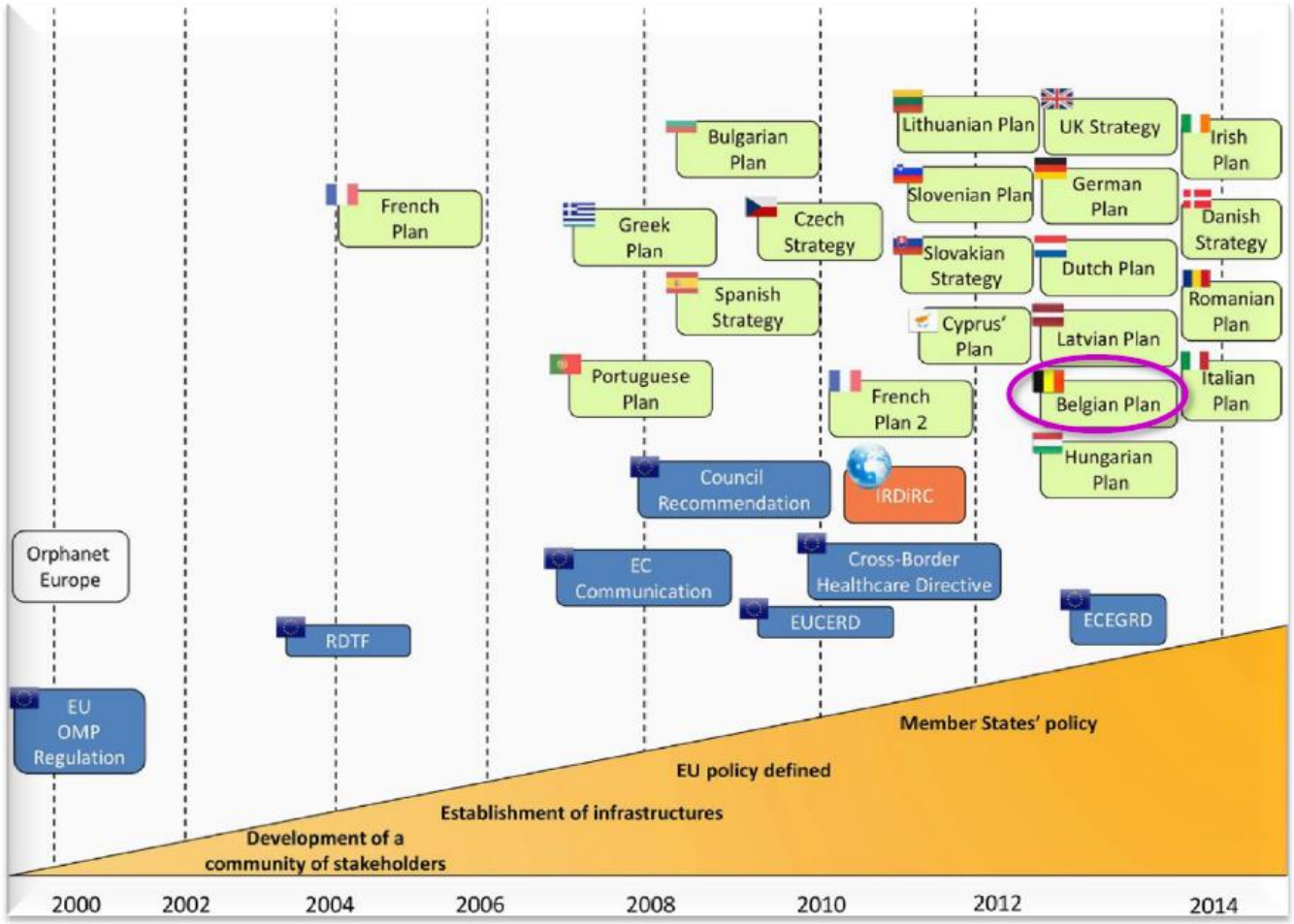
CHU Saint-Pierre
UMC Sint-Pieter

Rare or very rare diseases

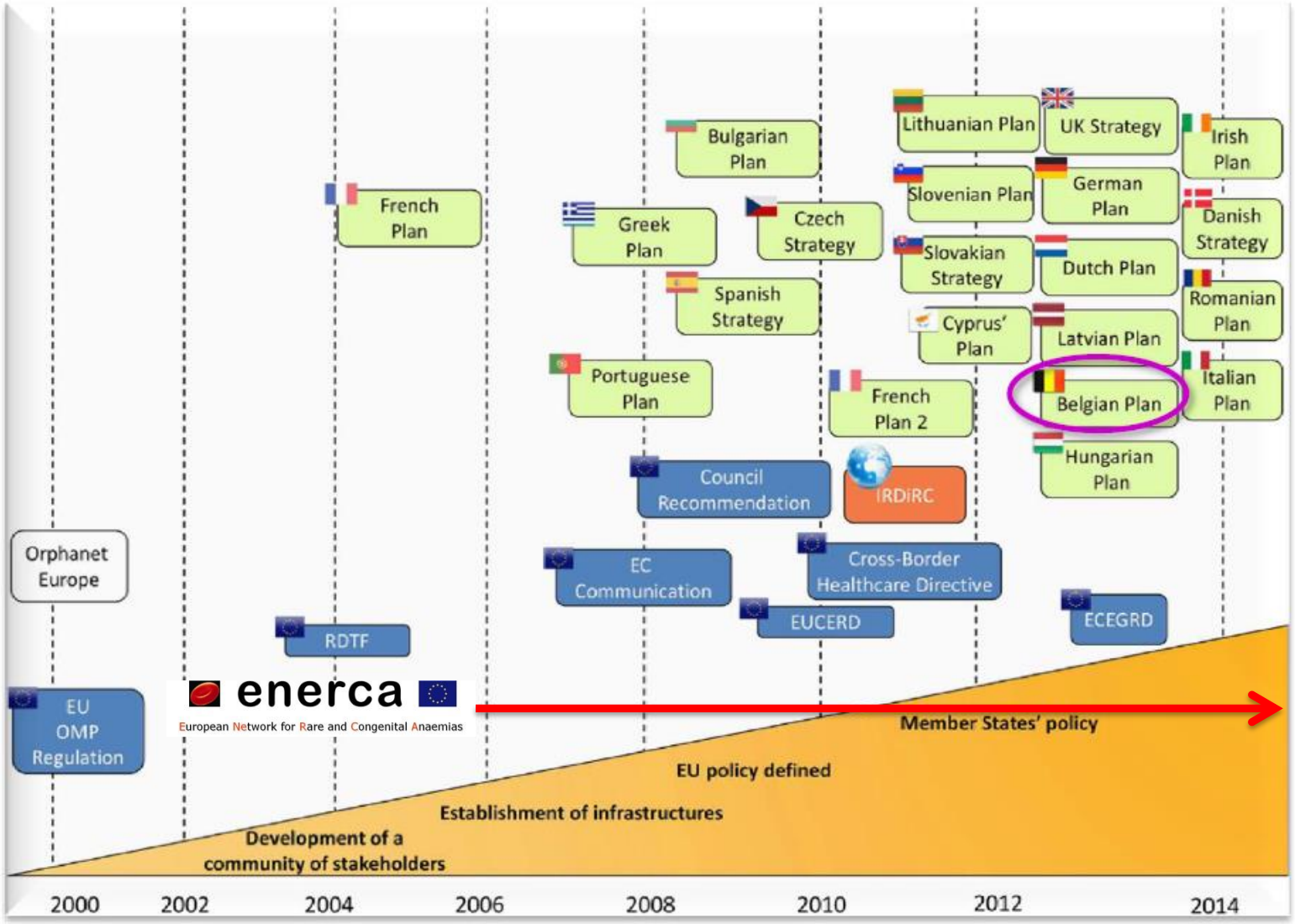
- Definition
  - Life-threatening or chronically debilitating diseases – mostly inherited
  - In Europe $\leq$ 1 person in 2,000
  - http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

- A joint action
  - To reduce the number of affected people;
  - To prevent infant and child deaths;
  - To preserve the quality of life and the socio-economic potential of patients.
  - Pooling scarce resources
  - Support the preparation of national plans
    - **Around 8,000 rare diseases affect or will affect an estimated 30 million people in the European Union**

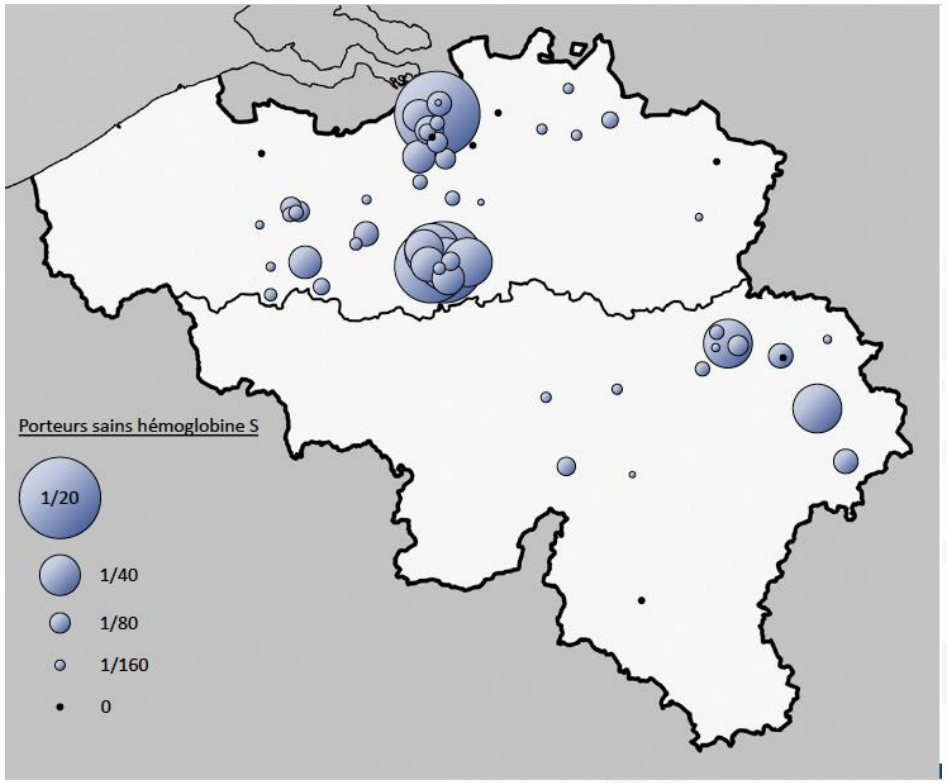
National plans (implementation for 2013 …)



European rare disease plan



Belgian level



Ketelslegers O. et al. Belg J Hematol 2015;6(4):135-41

Plan belge pour les Maladies Rares

Laurette ONKELINX,

Ministre des Affaires sociales et de la Santé publique

Bruxelles,
décembre 2013

.be

Belgian rare diseases plan

Why?

- Improving the care and quality of life of people with a rare disease in Belgium

  - **Concerns approximately 800,000 Belgians? (Rare diseases epidemiology 2010 report).**

Belgian rare diseases plan

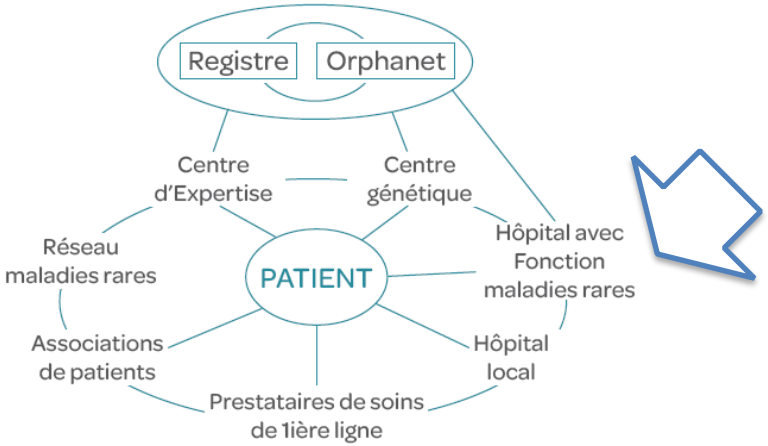
- Budget
  - 15.7 millions euros (2014)
  - Strategic plan
    - Diagnosis and patient information
      - Improved test reimbursement
      - Definition of new standards for the 8 human genetics centers
      - Creation of a call centre available 24 hours a day
      - Optimization of the exchange of expertise at European level

Belgian rare diseases plan

- Care optimization project
  - Gives the 21 reference centres 5 years to comply with the requirements of the **centres of expertise**
  - Provides for the creation of haemophilia treatment centres.
  - Hospitals may be approved for the new **"rare diseases" function**.
  - Innovative treatments will benefit from accelerated reimbursement.
- A third axis has been deployed around knowledge of rare diseases
  - Establishment of a **central registry** (via the 8 genetics centres).

And within our University?

- Hospitals may be approved for the new **"rare diseases" function**.
  - CUB Hôpital Erasme= « **Fonction maladies rares »**



PAR RECOMMANDE

DATE DE NOTIFICATION : 30 OCT. 2018

LE MINISTRE-PRESIDENT DE LA COMMUNAUTE FRANCAISE

Agrément A/406

* * *

AVIQ/BES/DSH/CC/VD/07.2018/Cl. Univ. De Bruxelles -Erasme/A/406 / Maladies rares

Vu le décret du 30 mars 1983 sur l'organisation des établissements de soins dans la Communauté française ;

Vu l'Arrêté de l'Exécutif de la Communauté française du 5 novembre 1987 déterminant les modalités d'agrément, de fermeture et la procédure de recours pour les hôpitaux, services hospitaliers, services médico-techniques lourds, sections, fonctions, initiatives d'habitation protégée et associations d'institutions et de services psychiatriques, notamment l'article 4 ;

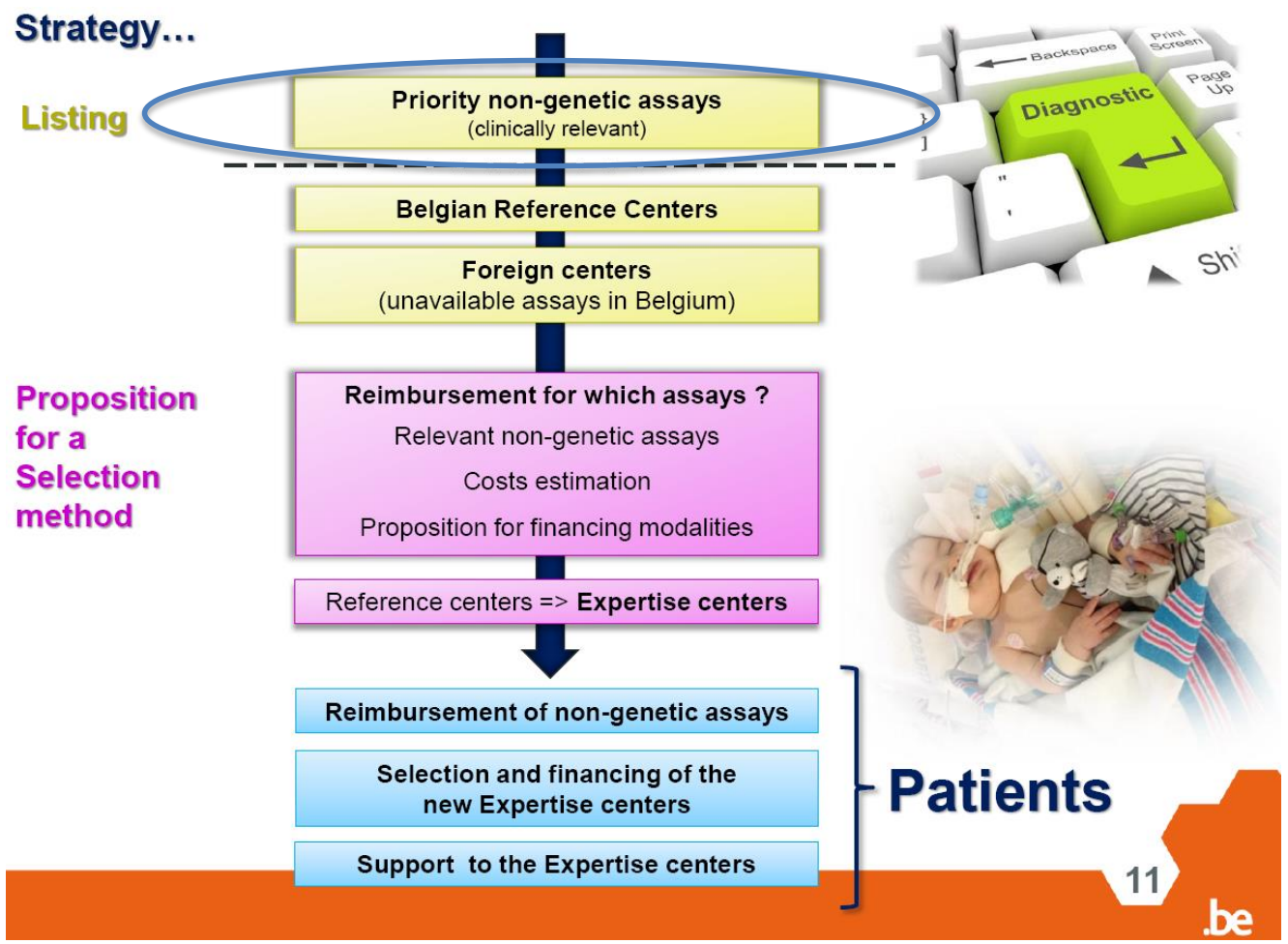
Vu la loi coordonnée du 10 juillet 2008 sur les hôpitaux et autres établissements de soins ;

Vu l'arrêté royal du 25 avril 2014 rendant certaines dispositions de la loi du 10 juillet 2008 coordonnée sur les hôpitaux et autres établissements de soins applicables à la fonction « Maladies rares » ;

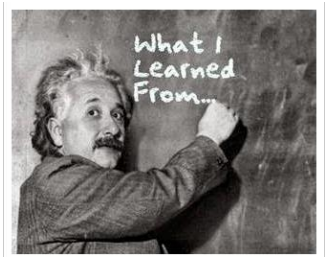
Vu l'arrêté royal du 25 avril 2014 fixant les normes auxquelles une fonction « maladies rares » doit répondre pour être agréée et le rester ;

A space for clinical laboratories

- Project conduct by Sciensano



Message

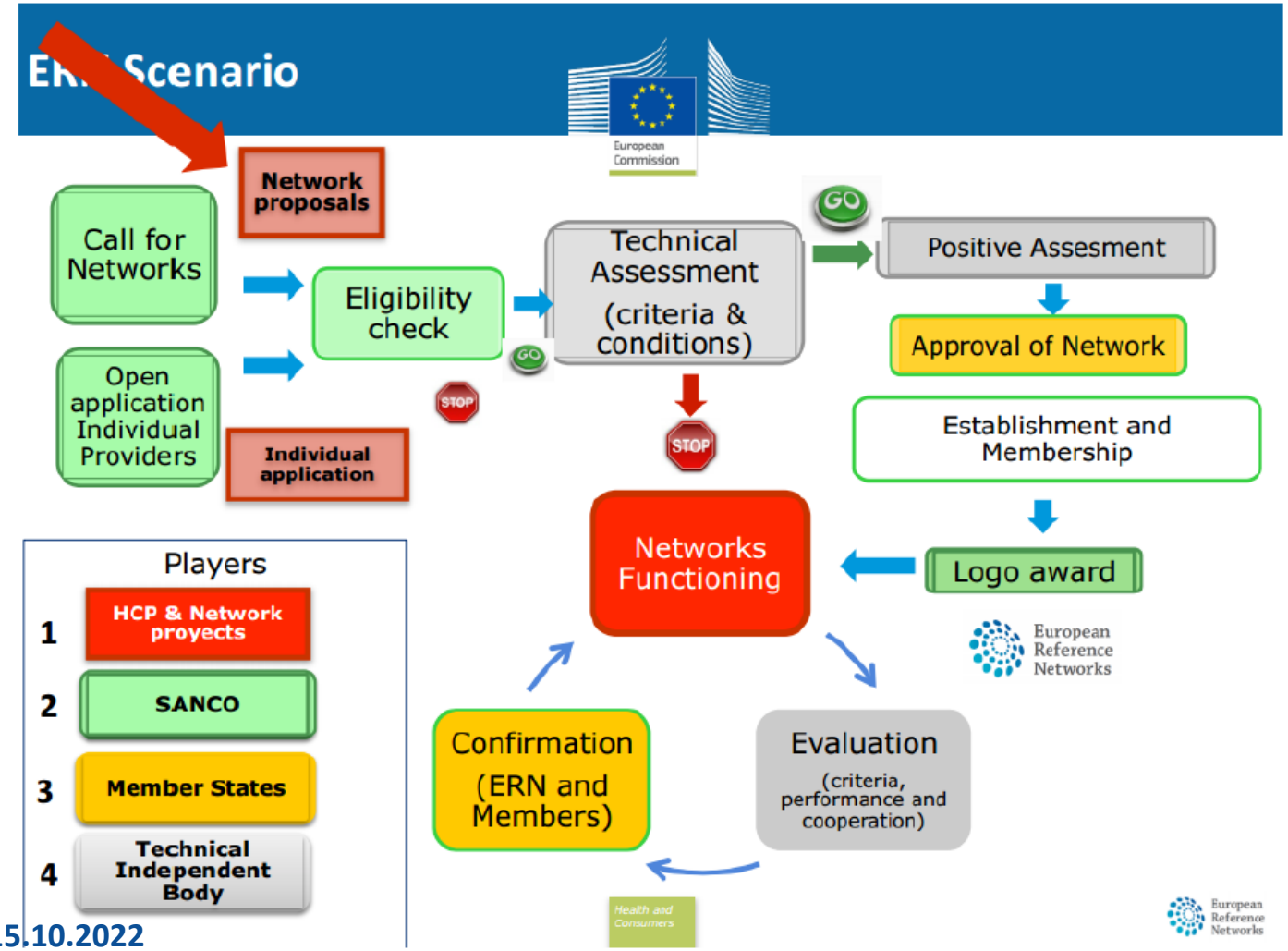


- Complexity of European Union in health care policies, strategies
  - From European Commission to EU countries, and back
  - Calendar…
- Rare or very rare diseases
  - Clinical laboratories have been included in the frame

Phase 2: concretization

European level

➢ European Commission – Call for European Reference networks



24 European Reference Networks

First launch 2017 > 2022

Second grant 2022 - 2027

European level - 24 Networks

- The first ERNs were launched in March 2017,
  - involving more than 900 highly-specialised healthcare units from over 300 hospitals in 26 EU countries. 24 ERNs are working on a range of thematic issues including bone disorders, childhood cancer and immunodeficiency.
  - ERN members per network
  - ERN members per country
- **Legislation**
  - Directive 2011/24/EU on patients' rights in cross-border healthcare
  - Commission delegated decision (annex) defining the criteria and conditions that healthcare providers and the ERNs should fulfil
  - Commission implementing decision (annex) defining criteria for establishing and evaluating ERNs

ERN for rare and very rare haematological diseases

EuroBloodNet

Adults

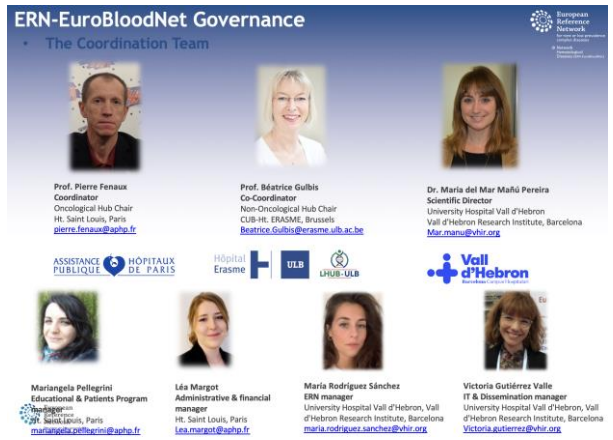
Oncological diseases Hub
Coordinated by Prof Fenaux
(AP-HP, Hôpital St Louis, Paris)

Myeloid malignancies
Lymphoid malignancies

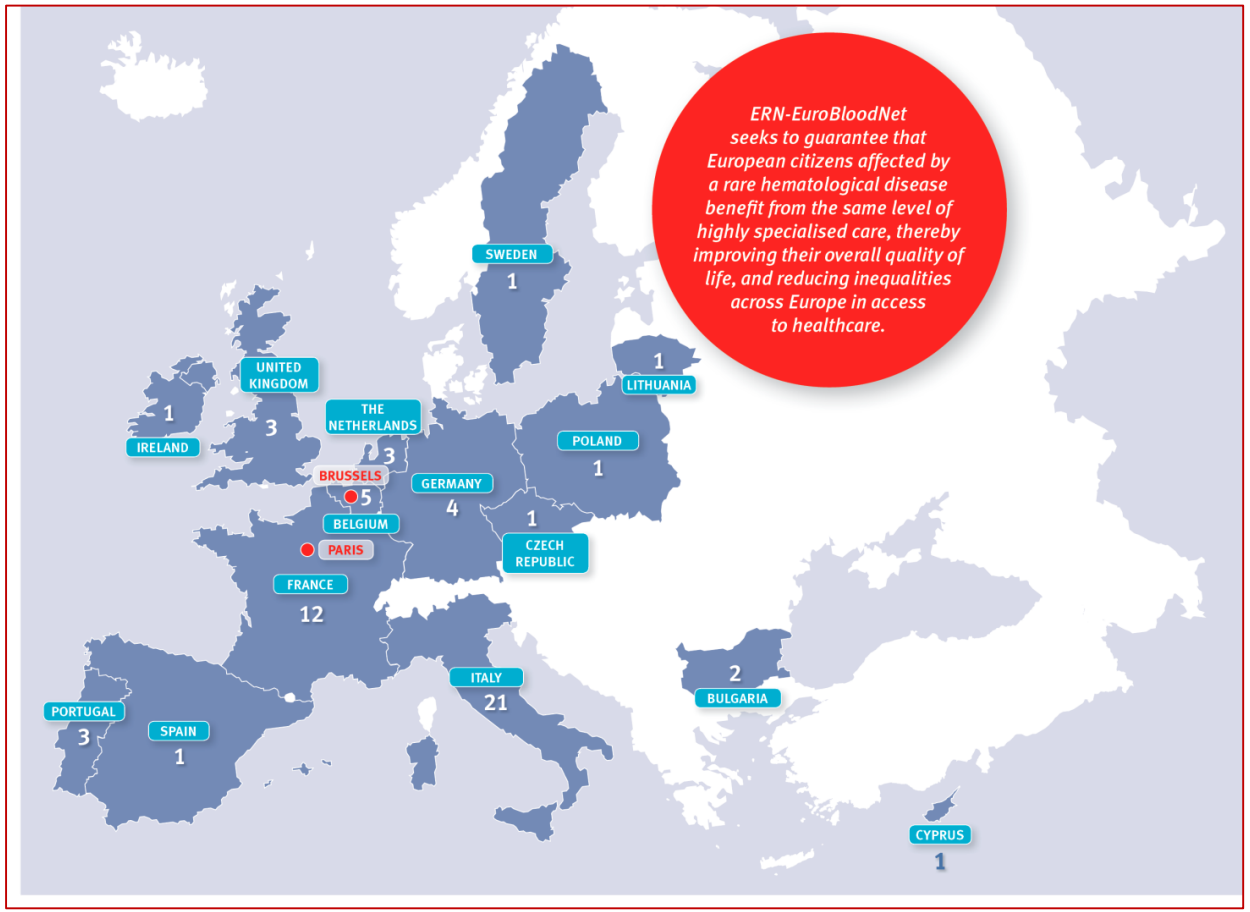
Non -oncological diseases Hub
Coordinated by Prof Gulbis
(CUB Hôp. Erasme - LHUB-ULB, Brussels)

Rare red blood cell defects
Bone marrow failure and rare haematopoietic disorders
Rare bleeding-coagulation disorders and related diseas.
Haemochromatosis and rare hereditary iron metabolism disorders

Adults
Paediatrics



ERN EuroBloodNet challenge : Management of a network formed by 66 HCPs (2017 – 2022) – UK HCPs …



Cross-border health

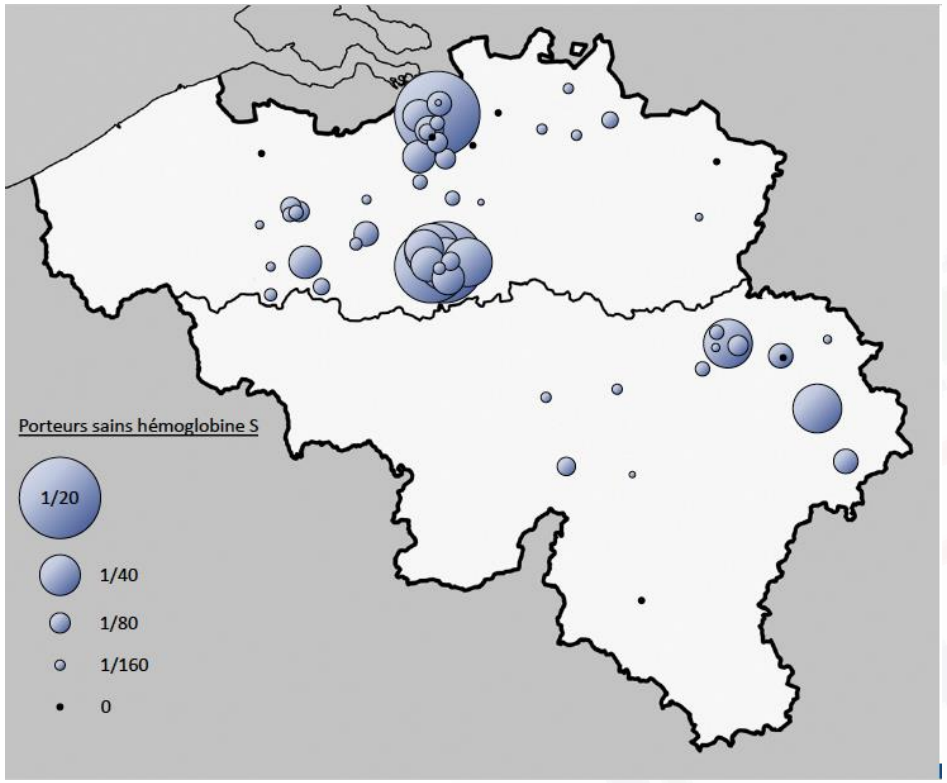
Best practices

Continuing medical education

Telemedicine

Clinical trials and research

Belgian level

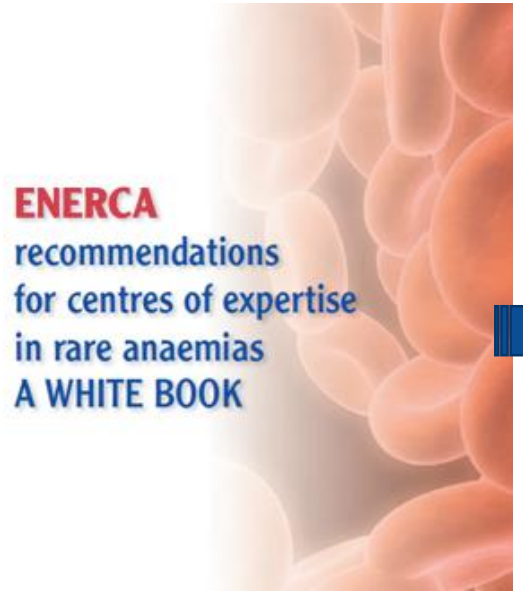


Ketelslegers O. et al. Belg J Hematol 2015;6(4):135-41

Health care providers

2	BE	CUB-Hôpital Erasme	Béatrice Gulbis	Florence Roufosse
3	BE	Jules Bordet Institute	Dominique Bron	Sebastian Wittnebel
4	BE	Universitair Ziekenhuis Antwerpen	Philip Maes	Alain Gadisseur
5	BE	University Hospital Leuven	Kathelijne Peerlinck	Chris Van Geet
6	BE	University Hospital Liège	Yves Beguin	Frédéric Baron
7	BE	University Hospitals Saint-Luc	Cedric Hermans	Catherine Lambert

From Belgium to Europe



ARRETE :

Article 1er : L'agrément provisoire octroyé aux Cliniques Universitaires de Bruxelles – Hôpital Erasme (A/406) pour une fonction « maladies rares », est renouvelé pour une durée d'un an (2 périodes de six mois), prenant cours du 23 novembre 2017 au 22 novembre 2018.

Art. 2 : La fonction visée à l'article 1er du présent arrêté prend en charge les maladies rares ou groupes de maladies rares suivants :

1. Drépanocytose et autres pathologies héréditaires du globule rouge ;
2. Pneumopathies interstitielles diffuses ;
3. Hypertension artérielle pulmonaire ;
4. Maladies rares cardiologiques ;
5. Maladies rares ophtalmologiques ;
6. Porphyries ;
7. Maladies rares neuromusculaires ;
8. Ataxies héréditaires :

3) Point 12_Table in page 11 "Multidisciplinary team" Up to 16 Health care professionals have to be defined: position, training and number of patients/procedures by year (for assure expertise)

Health care provider
Reference centre

Healthcare professional	Training and qualifications	Nº procedures/patients per year
Haematologist	Expertise in haemoglobinopathies > 3 years	50
Pediatrician or Hematologist with proven pediatric experience	Expertise in haemoglobinopathies > 3 years	50
Transfusion Medicine expert	Expertise in chronic transfusion > 3 years	20
Pediatrician/Haematologist	Expertise in Bone marrow transplant in haemoglobinopathies > 3 years	2
Nurse	Expertise in haemoglobinopathies > 3 years	33
Laboratory specialist	Expertise in haemoglobinopathies > 3 years	150
Radiologist	Expertise in haemoglobinopathies > 3 years	30
Genetic counsellor	Expertise in haemoglobinopathies >	20

Belgian registry for sickle cell disease

From Belgian to European network

From sickle cell disease to rare haemolytic anaemias

Clinical trials
and
research

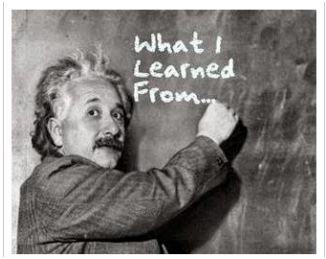
EuroBloodNet

RADeep

Diagnosis, follow-up >>
Laboratory data

Promotors : A. Ferster , B. Gulbis
Project Manager : S. Wambacq

Message



- Recognition as a reference centre within the European Reference Networks and at the national level
  - An additional asset at Belgian and European levels for patients and medical teams
    - Health care pathways
    - Participation in training
    - Participation in European registries (Belgian registry for sickle cell disease)
    - …
  - The laboratory is an effective contributor

Phase 3: benefits of a European initiative for the laboratory

JULES BORDET INSTITUUT

C H U | U V C B R U G M A N N

Hôpital Erasme | ULB

Hôpital Universitaire des Enfants Reine Fabiola
Universitair Kinderziekenhuis Koningin Fabiola

CHU Saint-Pierre
UMC Sint-Pieter

From Europe to Belgium Laboratory NRCs

UZ Antwerpen

- Bepaling van α-aminoadipinezuur semialdehyde (α-AASA) en δ1-piperideïne-6-carboxylaat (P6C) in urine

UZ Gent

- Doseren van erytrocytaire plasmalogenen
- Cytogenetische stralingsgevoeligheidstest
- Bepaling van pterinen in urine

Cliniques universitaires St Luc

- Doseren van intra-leukocytaire cysteine
- Bepaling van δ1-piperideïne-6-carboxylaat (P6C) in plasma
- Bepaling van 5-methyltetrahydrofolaat (MTHF) in CSV

LHUB-ULB

- Doseren van plasma porfobilinogeen
- Fractionering van plasma porfyrinen (bevestigingstest)
- **Spectrofluorometrische bepaling van plasma porfyrinen**
- **Doseren van vrije erytrocytaire protoporfyrinen (FEP-test)**
- Vervormbaarheid van rode bloedcellen (RB) door ektacytometrie & scheidingstest van RB membraaneiwitten door SDS-PAGE
- Immunologisch doseren van complementbfactor B
- Immunologisch doseren van complementbfactor Bb
- Immunologisch doseren van complementbfactor D
- Immunologisch doseren van complementbfactor P

UZ Leuven

- **Spectrofluorometrische bepaling van plasma porfyrinen**
- **Doseren van vrije erytrocytaire protoporfyrinen (FEP-test)**

CHU Liège

- Doseren van de B6 vitameren in plasma
- Bepaling van DHPR activiteit in DBS

Ring test establishment

Since 2017, inter-laboratory quality control (ring test) for the diagnosis of RBC membranes disorders

- Monitor the quality of analytical results
- Identify assays that need improvement
- Propose standardisation of methods & interpretation

Involved collaborators:

- LHUB-ULB, Brussels

- Hospital Clinic Provincial, Barcelona

- Policlinico di Milano

- UMC, Utrecht

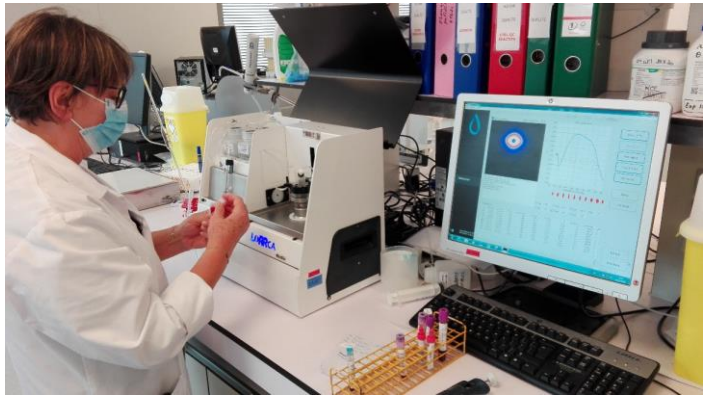
Ring test focused on :

- Eosine-5-maleimide binding (EMA test)
- Osmotic gradient ektacytometry
- SDS-PAGE *

*Only LHUB-ULB and Policlinico di Milano

NRC: Diagnosis of RBC membranopathy

Belgian Rare Diseases Plan in Clinical Pathology (Sciensano)
LHUB-ULB-> December 2019 :



- National Reference Center :
  - Osmotic gradient ektacytometry
  - Separation of RBC membrane proteins by SDS-PAGE

Sciensano missions :

- Selection, financing and follow-up of the NRC of medical biology
- **Provision of external quality assurance schemes**

Vandevelde, Nathalie M., et al. “Belgian Rare Diseases Plan in Clinical Pathology: Identification of Key Biochemical Diagnostic Tests and Establishment of Reference Laboratories and Financing Conditions. *Orphanet Journal of Rare Diseases*, vol. 16, no. 1, BioMed Central, 2021, pp. 1–16.

Ring test evolution
Coordination by sciensano

- Quality control of the national reference centres included in the INAMI-RIZIV envelop
  - ➢ Ring test for red blood cell membranes extended
  - ➢ Included in the Belgian QC Toolkit
  - ➢ Improvement of diagnostic testing
    - ➢ Standardization/harmonization of the reported results
    - ➢ A try to standardize of a screening test , i.e., eosin-5'-maleimide binding test

Involved collaborators:

- LHUB-ULB, Brusse
- Hospital Clinic Provincial, Barcelona
- Policlinico di Milano
- UMC, Utrecht
- CHU Hôpital Robert Debré, Paris
- CHU Bicêtre, Le Kremlin Bicêtre
- Rigshospitalet, Copenhagen
- CEING, Napoli

EMA-binding test (Ring test)

LHUB-ULB-> Hematology department

	Polyclinic of Milan	UMC, Utrecht	LHUB-ULB
Instrument	BD FACSCANTO ii	BD Canto	BC Navios
Criteria	<11% of decrease in fluorescence	Low <89% Uncertain 89-92% Normal >92%	<19% of decrease in fluorescence

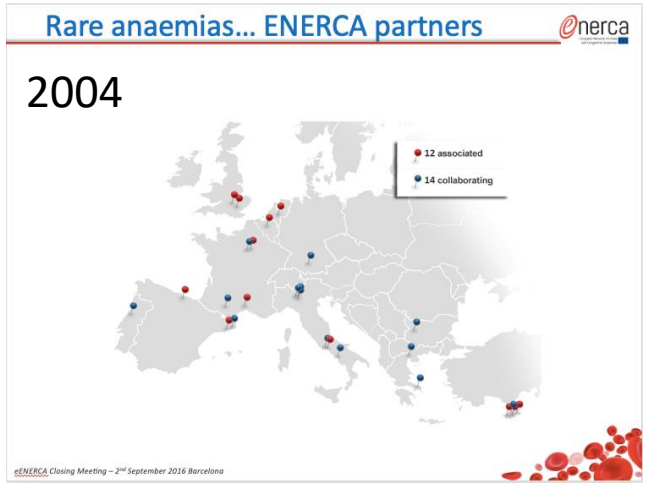
Andreas Birkedal Glenthøj (Herlev-Gentofte Hospital/Rigshospitalet)

- Replacing of fresh blood samples (healthy controls) with commercially available fluorescent beads as controls

- Standardisation of the method
- Permitting inter-laboratory comparison

Glenthøj, Andreas, et al. “Improving the EMA Binding Test by Using Commercially Available Fluorescent Beads.” Frontiers in Physiology, vol. 11, Frontiers, 2020, p. 1163.

From Belgium to Europe



DE GRUYTER

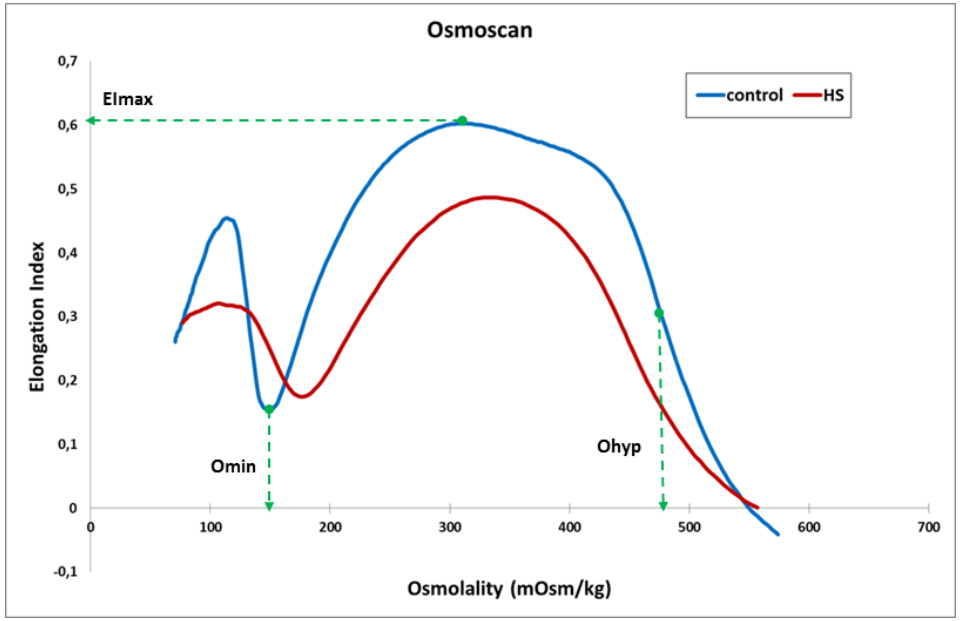
Clin Chem Lab Med 2016; aop

Elena Lazarova*, Béatrice Gulbis, Brigitte van Oirschot and Richard van Wijk

Next-generation osmotic gradient ektacytometry for the diagnosis of hereditary spherocytosis: interlaboratory method validation and experience

Osmotic gradient ektacytometry (Ring test)

Typical shifts in the deformability curve are obtained



Osmoscan: Reference Values -> Different expression/criteria

	Polyclinic of Milan	UMC, Utrecht	LHUB-ULB
	LoRRca	LoRRca	LoRRca
O min	116-140	134-157	<18
O hyper	406-472	445-497	>-8.0
EKTA area	142-166	153-178	>-18.0
EI max	0,585-0,625	0,596-0,613	>-13.5

Osmoscan app (Andreas Birkedal Glenthøj)

- Analyzing Osmoscan CSV-files to compare curves (R Shiny)

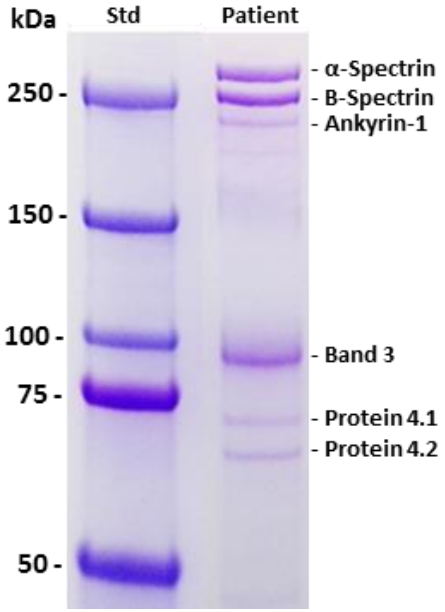
➢ Inter-laboratory comparison of ektacytometry Osmoscan curves

Lazarova, Elena, et al. “Next-Generation Osmotic Gradient Ektacytometry for the Diagnosis of Hereditary Spherocytosis: Interlaboratory Method Validation and Experience.” Clinical Chemistry and Laboratory Medicine (CCLM), vol. 55, no. 3, De Gruyter, 2017, pp. 394–402.

SDS-PAGE (Ring test)

- Specialized testing for selected cases

Membrane protein analysis by electrophoresis SDS-PAGE



Modified Fairbanks Coomassie stain development (2020; Akiki P.)

- **Linear gradient** : 4-15% ; Mini-Protean TGX Precast
- **Running Buffer** : TAE 1x, SDS 0.2%, pH 7.4
- **Migration** : 140 min; 100 volts (constant)

- Rapid (precast gels, ↘ migration time,…)
- ↘ Inter-assay variability
- Better resolution for Spectrin/Ankyrin
- Reference values

SDS-PAGE	Polyclinic of Milan	LHUB-ULB
Spec. A/B	/	0,89-0,95
Spec./B3	0,95-1,17	0,95-1,18
Ank/4.1	/	1,01-1,49
Ank/B3	0,14-0,21	0,18-0,28
4.2/B3	0,15-0,20	0,15-0,19
4.1/4.2	0,93-1,16	0,94-1,25
B3/4.1	/	4,37-6,36
Sp + Ank /B3	/	1,15-1,44
4.1/Band 3	0,15-0,22	0,15-0,22
4.2/Band 3	0,15-0,20	0,15-0,19

- Proposed common reference values/criteria for protein band ratios (LHUB-ULB/Polyclinic of Milan)

In preparation : **Philippe Akiki** *et al*. Precast commercial polyacrylamide gels for separation of erythrocyte membrane proteins: an application for the diagnosis of hereditary spherocytosis. Department of Clinical Chemistry, LHUB-ULB, Université Libre de Bruxelles (ULB) 322, Rue Haute, 1000 Brussels, Belgium.

Newborn screening for sickle cell disease

bjh research paper

Newborn screening for sickle cell disease in Europe: recommendations from a Pan-European Consensus Conference

Stephan Lobitz,[1,2] Paul Telfer,[3] Elena Cela,[4] Bichr Allaf,[5] Michael Angastiniotis,[6] Carolina Backman Johansson,[7] Catherine Badens,[8] Celeste Bento,[9] Marelle J. Bouva,[10] Duran Canatan,[11] Matthew Charlton,[12] Cathy Coppinger,[12] Yvonne Daniel,[12] Marianne de Montalembert,[13] Patrick Ducoroy,[14] Elena Dulin,[4] Ralph Fingerhut,[15] Claudia Frömmel,[16] Marina García-Morin,[4] Béatrice Gulbis,[17] Ute Holtkamp,[18] Baba Inusa,[19] John James,[20] Marina Kleanthous,[21] Jeannette Klein,[22] Joachim B. Kunz,[23] Lisa Langabeer,[24] Claudine Lapoumérioulie,[25] Ana Marcao,[26] José L. Marín Soria,[27] Corrina McMahon,[24] Kwaku Ohene-Frempong,[28] Jean-Marc Périni,[29] Frédéric B. Piel,[30] Giovanna Russo,[31] Laura Sainati,[32] Markus Schmugge,[33] Allison Streetly,[34,35] Leon Tshilolo,[36] Charles Turner,[37] Donatella Venturelli,[38] Laura Vilarinho,[26] Rachel Yahyaoui,[39] and Jacques Elion,[25] Raffaella Colombatti[32] with the endorsement of EuroBloodNet, the European Reference Network in Rare Haematological Diseases

Summary

Sickle Cell Disease (SCD) is an increasing global health problem and presents significant challenges to European health care systems. Newborn screening (NBS) for SCD enables early initiation of preventive measures and has contributed to a reduction in childhood mortality from SCD. Policies and methodologies for NBS vary in different countries, and this might have consequences for the quality of care and clinical outcomes for SCD across Europe. A two-day Pan-European consensus conference was held in Berlin in April 2017 in order to appraise the current status of NBS for SCD and to develop consensus-based statements on indications and methodology for NBS for SCD in Europe. More than 50 SCD experts from 13 European countries participated in the conference. This paper aims to summarise the discussions and present consensus recommendations which can be used to support the development of NBS programmes in European countries where they do not yet exist, and to review existing programmes.

Keywords: sickle cell disease, sickle cell anaemia, haemoglobinopathies, newborn screening, prevention.

Direction/Service : *Direction Santé*
Rédacteur/trice de la note : *Tatiana Pereira*
Personne de contact lors du CA : *Ingrid Morales*
Portable : *0478/44.07.14*

ONE OFFICE DE LA NAISSANCE ET DE L'ENFANCE

Bruxelles, le 6 mai 2022

Note au Conseil d'administration

Objet : Projet d'Arrêté modifiant l'Arrêté du Gouvernement de la Communauté française du 9 janvier 2020 en matière de dépistage d'anomalies congénitales en Communauté française. Introduction du dépistage de la drépanocytose.

Aperçu

L'Administration propose un projet d'arrêté modificatif visant à intégrer la drépanocytose dans le programme de dépistage des anomalies congénitales. Le budget nécessaire est détaillé dans le point budget. Une augmentation du budget devra être négociée dans le cadre des demandes 2023.

Le projet d'arrêté modificatif est annexé à la présente note.

Artificial intelligence

GENOMED4ALL

GenoMed4ALL

N° de convention de subvention: 101017549

Date de début 1 Janvier 2021

Date de fin 31 Decembre 2024

Financé au titre de
H2020-EU.3.1.
H2020-EU.3.1.5.

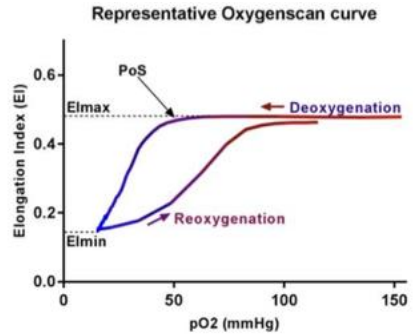
Budget total
€ 9 999 063,75

Contribution de l'UE
€ 9 999 063,75

Coordonné par
UNIVERSIDAD POLITECNICA DE MADRID
Espagne

LABORATOIRE HOSPITALIER UNIVERSITAIRE DE BRUXELLES
LHUB-ULB
UNIVERSITAIR LABORATORIUM BRUSSEL

- Sickle cell disease
  - Clinical data
  - Proteomics
  - Genomics
  - …
  - One goal: To allocate SCD patients to an **sickling risk profile** based on **genomic profile and Point of sickling** (LoRRca Oxygenscan)



Training and preceptorship

ERN-EUROBLOODNET EXCHANGE PROGRAM

2nd educational program on Rare Haemolytic Anaemia in Laboratories

HCP CUB-Hôpital Erasme / LHUB-ULB, Brussels, Belgium

Coordinated by Prof. Béatrice Gulbis

December 19 – 22, 2022

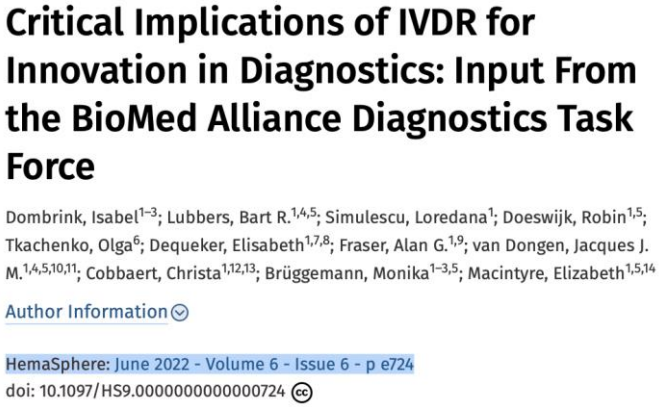
Educational objectives

1. Acquire the theoretical and practical basis for the use of diagnostic tools and follow-up of patients with suspected hereditary hemolytic anemia.
2. Know the diagnostic and monitoring tools, their limitations and the interpretation of the results.
3. Be able to propose a change in his/her own laboratory, to make adaptations or to propose that analyses in a particular field be sent to a reference centre.
4. Propose a rational approach/algorithm to a hemolytic anemia based on national/international recommendation.

Teachers: *Alina FERSTER, Samantha BENGHIAT, Martin COLLARD, Xavier PEYRASSOL, Anne Sophie ADAM, Sara BENYAICH, Béatrice GULBIS*

Directives, rules, regulations

- In Vitro Directive Regulation (IVDR) and effect on diagnosis and follow-up of rare and very rare disorders



Critical Implications of IVDR for Innovation in Diagnostics: Input From the BioMed Alliance Diagnostics Task Force

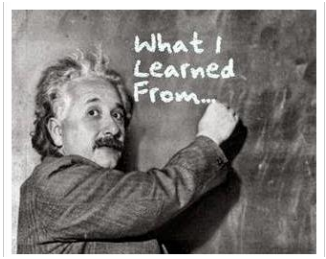
Dombrink, Isabel[1–3]; Lubbers, Bart R.[1,4,5]; Simulescu, Loredana[1]; Doeswijk, Robin[1,5]; Tkachenko, Olga[6]; Dequeker, Elisabeth[1,7,8]; Fraser, Alan G.[1,9]; van Dongen, Jacques J. M.[1,4,5,10,11]; Cobbaert, Christa[1,12,13]; Brüggemann, Monika[1–3,5]; Macintyre, Elizabeth[1,5,14]

Author Information

HemaSphere: June 2022 - Volume 6 - Issue 6 - p e724
doi: 10.1097/HS9.0000000000000724

  - *« …Appropriate concerted action should allow us to avoid the IVDR complicating innovation and instead support it from its early development steps onwards. »*

Message



- Collaboration is a key element to progress and allow patient to be taken care of in optimal conditions.
- This refers to our vocation within the LHUB-ULB that is to play a leading role in providing excellent care accessible to all.

But probably the most important …

- **All 24 ERNs united to help Ukrainian people with rare diseases**

www.erncare4ua.eu

But probably the most important …

Thank you to all the collaborators