ERN | EuroBloodNet

13th June 2025 - EHA Congress

EHA/ERN-EuroBloodNet consensus- based recommendation for the diagnosis of rare hereditary hemolytic anemia

Speaker: Richard van Wijk

European Reference Network | Hematological Diseases (ERN EuroBloodNet)

Funded by the European Union

Disclosure of Conflict of Interest

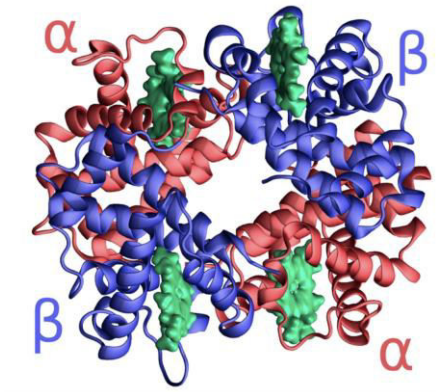
Agios Pharmaceuticals, research support

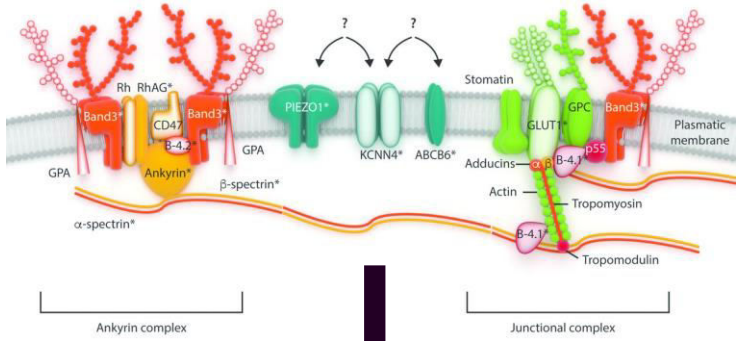
RR Mechatronics, consultancy

Highlight sentence

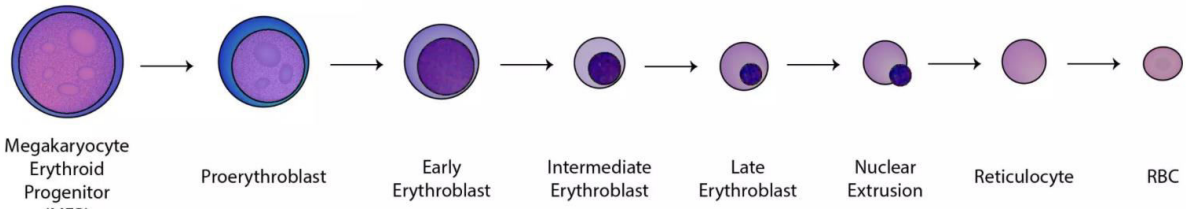
“Twenty four experts from 9 different countries are collaborating to create consensus-based recommendations for the diagnosis of rare hereditary hemolytic anemia. By addressing key questions in the field they aim to improve diagnosis and awareness of this highly heterogeneous groep of hereditary disorders“

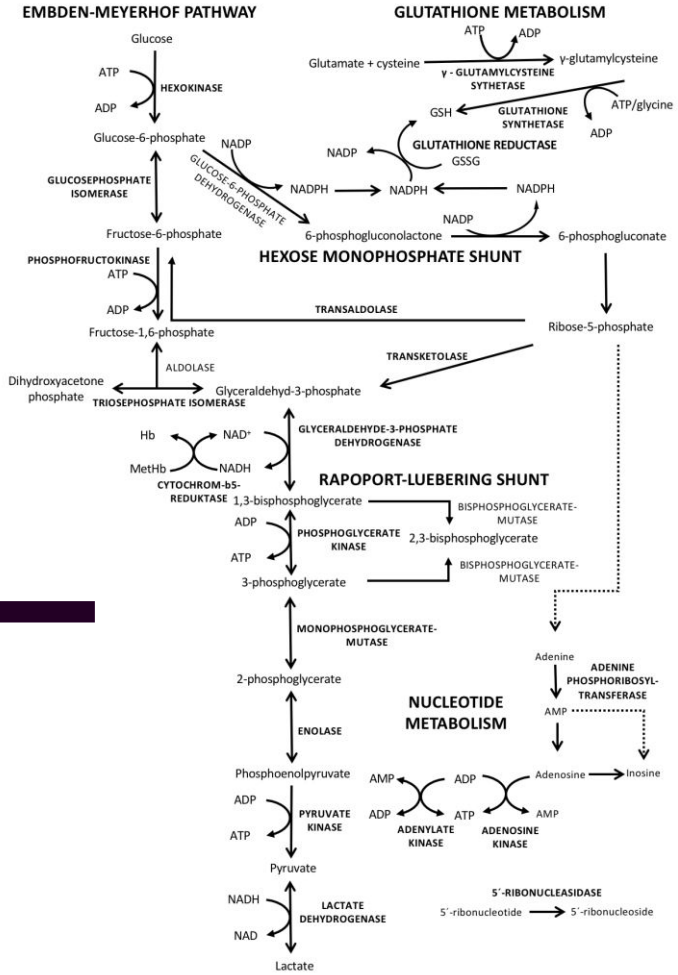
Rare hereditary hemolytic anemia





Decreased RBC survival





Why is this guideline needed?

The diagnosis of hereditary hemolytic anemia can be quite challenging due to:

- The many different underlying causes (i.e. >30 different underlying causes/genes)
- The highly heterogeneous presentation on both the laboratory and clinical level;
- The rarity of many of the underlying causes which causes a lack of awareness.

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Why is this guideline needed?

- Proper differential diagnosis is important to provide patients with the appropriate care (e.g. splenectomy can be indicated in some forms but is contraindicated in others)
- Current developments, in particular the focus on metabolic activation of pyruvate kinase as a novel form of therapy for a number of hereditary hemolytic anemias, and new gene therapy approaches

An EHA/EBN consensus guideline is urgently needed, and will include a diagnostic flow chart and will take into account state-of-the art diagnostic techniques

The team

24 Experts

- 12 Laboratory

- 8 clinical (5 adult / 3 pediatric)

- 4 patient representatives

16 female / 8 male

9 countries (1 non-EU)

EHA/EBN member

Marije Bartels

Paola Bianchi

Lydie da Costa

Maria del Mar Mañú Pereira

Noémi Roy

Roberta Russo

Patricia Aguilar Martinez

Immacolata Andolfo

Eduard van Beers

Celeste Bento

Angelo Loris Brunetta

Elmas Citak

Rafaella Colombatti

Jonathan Cottignies

Elisa Fermo

Beatrice Gulbis

Achille Iolascon

Kevin Kuo

Dore Peereboom

Silverio Perrotta

Veronique Picard

Minke Rab

Richard van Wijk

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Key questions to be addressed

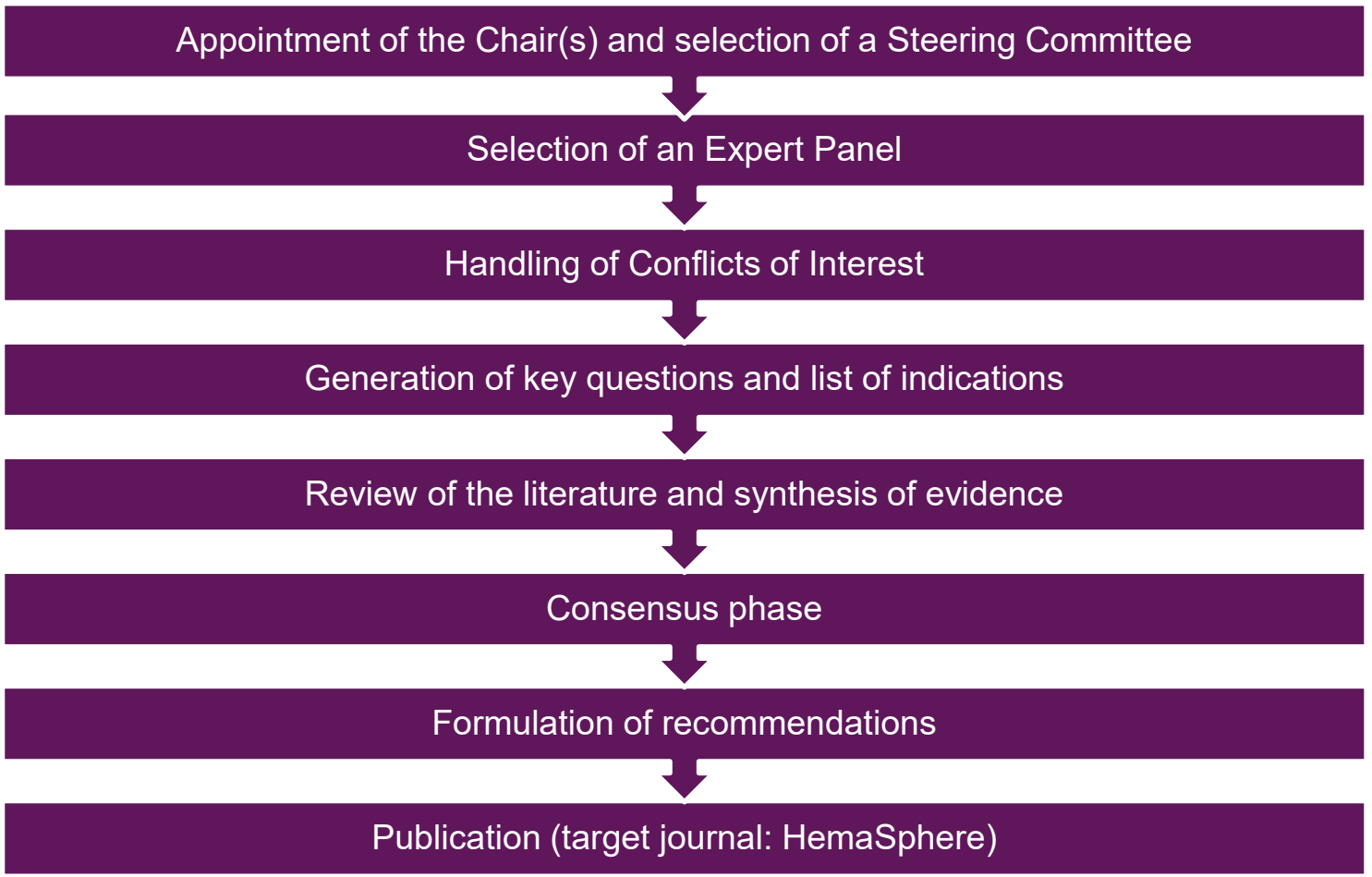
- Which disorders are considered a cause of hereditary hemolytic anemia and what is their prevalence?
- What are the key clinical and hematological diagnostic aspects in diagnosing patients with hereditary hemolytic anemia?
- Which diagnostic laboratory tests are used in the diagnosis of hereditary hemolytic anemia?
- What are the recommendations for proper diagnosis of hereditary hemolytic anemia in adults and neonates?
- How to interpret the co-inheritance of genetic variants in other genes to the clinical expression of hereditary hemolytic anemia?
- What are the recommendations for interpretation and/or functional validation of VUS detected by NGS?
- What is the preferred moment for collecting blood for diagnostic purposes in transfused patients?

Five working group topics

The EHA/EBN Guideline will provide:

- Topic 1: Diagnostic flowchart/algorithm (led by Andreas Glenthøj)
- Topic 2: Overview of preferred diagnostic tests (led by Lydie da Costa)
- Topic 3: Recommendations on the interpretation of Variants of Unknown clinical Significance (VUS) (led by Noémi Roy)
- Topic 4: Special section on diagnosis in the neonate (led by Marije Bartels)
- Topic 5: Special section on genotype-to-phenotype correlations (led by Roberta Russo)

Framework and methodology



Framework and methodology – list of diseases

Disease group	Disorders expected to yield evidence	Orpha_Code	Ultra rare disorders, not expected to yield evidence	Orpha_Code
Membranopathies	Hereditary spherocytosis	822	Overhydrated hereditary stomatocytosis	3203
	Hereditary elliptocytosis	288	Dehydrated hereditary stomatocytosis/Gardos channellopathy (KCNN4)	3202
	Dehydrated hereditary stomatocytosis/Piezo1	3202	Sitosterolemia	2882
			Familial Pseudohyperkalemia (FP),	90044
			Cryohydrocytosis	398088
			Southeast Asian Ovalocytosis	98868
Enzymopathies	Pyruvate kinase deficiency	766	Glucose-6-phosphate dehydrogenase deficiency, class A, associated with chronic hemolysis	466026
	Glucose-6-phosphate dehydrogenase deficiency, class B (<45% residual activity), associated with acute hemolytic anemia activity vs DNA/screening tests (fluorescent spot test)		Glucose-6-phosphate dehydrogenase deficiency, class C (>60% residual activity), associated with acute hemolytic anemia	
			Glucophosphate isomerase deficiency	712
			Non-spherocytic hemolytic anemia due to hexokinase deficiency	90031
			Hemolytic anemia due to glyceraldehyde-3-phosphate dehydrogenase deficiency	248305
			Hemolytic anemia due to pyrimidine 5' nucleotidase deficiency	35120
			Hemolytic anemia due to adenylate kinase deficiency	86817
			Hemolytic anemia due to erythrocyte adenosine deaminase overproduction	99138
			Glutathione synthetase deficiency	32
			Gamma-glutamylcysteine synthetase deficiency	33574
			Hemolytic anemia due to glutathione reductase deficiency	90030
			6-phosphogluconate dehydrogenase deficiency	99135
			Glycogen storage disease due to muscle phosphofructokinase deficiency	371
			Triose phosphate-isomerase deficiency	868
			Glycogen storage disease due to aldolase A deficiency	57
			Glycogen storage disease due to phosphoglycerate kinase 1 deficiency	713
Congenital dyserythropoietic anemias	Congenital dyserythropoietic anemia type I	98869	Congenital dyserythropoietic anemia type III	98870
	Congenital dyserythropoietic anemia type II	98873	Congenital dyserythropoietic anemia type III	293825
			Unstable hemoglobinopathies	99139

- 32 different disorders

Framework and methodology – PICO questions

1. What is the best approach to diagnose a patient with hereditary spherocytosis, in terms of clinical, hematological and laboratory tests?

Population: individuals of all ages (newborn, children, adult, splenectomized) with non-immune hemolytic anemia, i.e. positive for markers of hemolysis (e.g. reticulocytosis, bilirubinemia, decreased haptoglobin, Coombs-negative)
Intervention: Diagnostic tests for membranopathies:

- 1.1: Osmotic gradient ektacytometry
- 1.2: Osmotic fragility test
- 1.3: Cryohemolysis test
- 1.4: Acidified Glycerol Lysis Test
- 1.5: Hematology analyser parameters (e.g. % hyperchromic cells)
- 1.6: DNA diagnosis (e.g. targeted NGS panel, WES)
- 1.7: RBC peripheral blood morphology

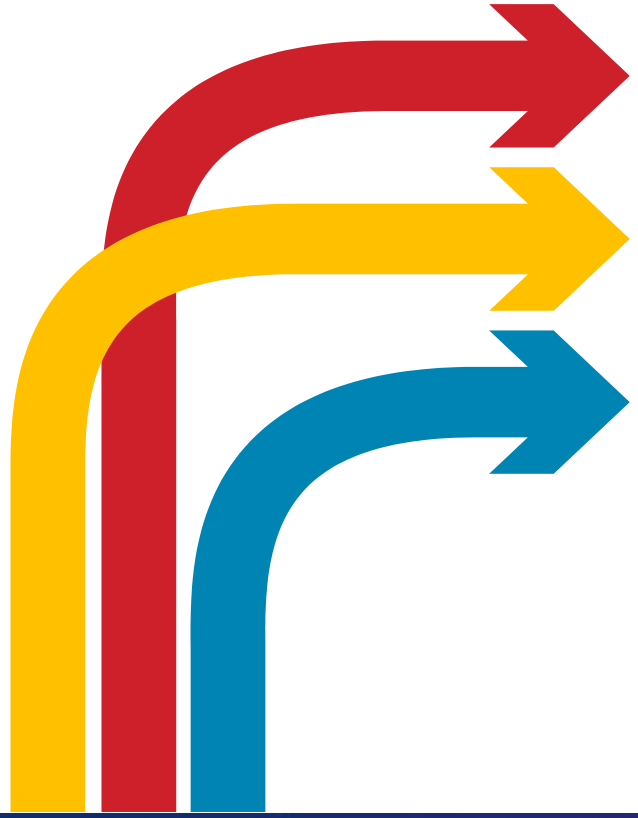
Comparison: EMA binding test
Outcome: True positive, true negative, false positive, false negative, sensitivity, specificity of tests involved in diagnosis

2. Pyruvate kinase deficiency

3. Glucose-6-phosphate dehydrogenase deficiency, class A

4. Congenital dyserythropoietic anemia, type II

Framework and methodology – synthesis of evidence & literature review



Start oct. 2025
End oct. 2026

B?

C?

THANK YOU!

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