Deliverable 4.1
Report on the comprehensive public database of reliable guidelines

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Short description: Report on the comprehensive public database of reliable guidelines/recommendations based on results from desk research and survey conducted among members. Assessment of guidelines based on quality domains is also included

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Contents

1-Background and rationale

1.1 Guidelines for Rare Hematological Diseases, gaps and needs

Clinical practice guidelines (CPGs) are defined as "systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances". In past decades a great number of guidelines have been produced and implemented supporting the adequate provision of health care for millions of patients across the world. However, due to the low prevalence of Rare Diseases (RD), the development of high quality guidelines has usually been postponed for the prioritization of more prevalent diseases. Fortunately, the contribution of guidelines to shorten the time to diagnosis and improvement of the quality of care on RDs is now widely acknowledged, and several European countries have recently included their development as a priority in their national plans on RDs.

Another issue is the lack of findability of CPGs tackling RDs. According to “Clinical Practice Guidelines for Rare Diseases: The Orphanet Database”, there are a large number of national and international databases gathering CPGs, but generally containing very few addressing RDs, and are difficult to find amongst the mass of recommendations available for more frequent diseases. Moreover, a significant number of the guidelines produced for RDs by research networks, reference centres or other organizations are not published in international peer-reviewed journals, and thus cannot be found in biomedical literature databases.

Unfortunatelly, as for other RDs, this scenario remains when focusing on Rare hematological diseases (RHDs). A number of CPGs have been published on prevention, diagnosis, and clinical care of patients and many scientific societies have produced such guidelines at the national or European level. However there is no repository of CPGs including quality assessment, evaluation of gaps or level of implementation, updates or any system to guarantee their usefulness and impact in patients' quality of life.

Accordingly, ERN-EuroBloodNet identified as a high priority to generate a comprehensive repository of CPGs and the definition of a methodology for their classification based on quality domains and assessment of real translation into clinical practice with the final aim to, not only support guideline development when lacking, but also assess their implementation in the different EU Member States.

1.2 First year of ERN-EuroBloodNet implementation

1.2.1 Protocol for the creation of the repository of reliable guidelines and recommendations

During the first year of ERN-EuroBloodNet implementation, a protocol for the creation of the repository of reliable guidelines and recommendations on RHD was defined aiming to achieve an accurate and reliable source of information on the guidelines and recommendations followed by the ERN-EuroBloodNet members. The protocol was defined and implemented based on two complimentary approaches:

a) Creation of a list of international guidelines and recommendations

A list of international guidelines and recommendations was already created with the input of ERN-EuroBloodNet subnetworks coordinators, aiming to compile the most frequent guidelines used for the main RHD conditions.

b) Questionnaire conducted among ERN-EuroBloodNet members

A questionnaire was produced aiming to gather key essential information from the members for the identification of the guidelines/recommendations used for the less prevalent RHD.

1.2.2 Preliminary results: List of international guidelines and recommendations

A first list of international guidelines and recommendations was created with the feedback from subnetworks coordinators representing the starting point for the gathering of the most implemented guidelines at European and International levels.

A total of 69 international guidelines and recommendations were compiled for the 6 subnetworks including:

- 20 for Rare Red blood cell defects
- 13 for Bone marrow failure and hematopoietic disorders
- 10 for Rare bleeding-coagulation disorders and related diseases
- 7 for Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis
- 7 for Myeloid malignancies
- 12 for Lymphoid malignancies

2- Objectives

One of the key objectives established by ERN-EuroBloodNet is to foster best practice sharing in RHD by creating a comprehensive public repository of reliable evidence based guidelines, ranging from prevention, diagnostic tests and treatments to the organisation of patient-centred management in multidisciplinary teams.

The repository of guidelines and recommendations will serve as a central platform for sharing best practices, facilitating timely, effective and efficient translation of research results into patient oriented strategies at the individual and public health levels and provide professionals, patients, and policy makers with the best and most up to date information.

In this context and based on the first results obtained during the first year of implementation, the following goals were defined to be accomplished in the second year of ERN-EuroBloodNet:

- To expand the already initiated repository of comprehensive public database of reliable evidence-based guidelines and recommendations
- To classify guidelines and recommendations compiled based on quality domains in line with AGREE methodology.
- To assess of the level of awareness and implementation of existing guidelines.

This Deliverable presents the actions undertaken for the expansion of the ERN-EuroBloodNet repository of guidelines and recommendations and their classification based on quality domains.

The actions undertaken for the assessment of the level of awareness and implementation are reported in Deliverable 4.2 Report on guidelines implementation.

3- Methods

The actions described in this section have been undertaken under the umbrella of the ERN-EuroBloodNet Transversal Field of Action (TFA) on best practices, coordinated by Luca Malcovati for the oncological disorders, Achille Iolascon for the non-oncological disorders and Amanda Bok as ePAG representative for bleeding and coagulation disorders, together with the support from the ERN-EuroBloodNet coordination team.

3.1 Expansion of the List of international guidelines and recommendations

The first list of international guidelines and recommendations was analyzed in terms of coverage of the different diseases encompassed by the network. Given the expertise of the subnetworks coordinators, the scope of the list was well balanced through the different RHDs, nevertheless, it was agreed to conduct a revision by additional experts identified in the field in order to produce a second version as extensive and comprehensive as possible. Special efforts were focused on the gathering of more CPGs for the oncological disorders given the relatively low number compiled in the first exercise.

3.2 Definition of the ERN-EuroBloodNet task force on Guidelines

In order to initiate the actions on classification and appraisal of the CPGs compiled, a task force was created based on the identification by the subnetworks coordinators of reference experts that could be involved in the process. Given the high heterogeneity of the RHDs, it was requested to suggest at least one person for each disease or group of diseases within the specific subnetworks, in order to ensure the maximum specificity on the expertise and thus, on the results from the tasks. A total of 67 experts were identified for the definition of the Task force on Guidelines classification and assessment.

3.3 Classification of guidelines and recommendations based on Quality domains

The domains on which guidelines and recommendations compiled shall be classified were defined as follows:

Domain 1: Scope and purpose

Each document shall be classified based on the objectives and clinical questions, adopting the following items:

1. Prevention
2. Diagnosis
3. Treatment
4. Prevention and diagnosis
5. Diagnosis and treatment
6. Prevention, diagnosis, treatment

Domain 2: Patients' involvement

The composition of the guideline / recommendation development group shall be evaluated with reference to the involvement of patient advocacy organizations patients.

Domain 3: Rigour of development.

The methodology adopted to develop the guideline / recommendation shall be assessed according to the following scale.

Level A: Evidence- and consensus-based guidelines / recommendations

The guidelines / recommendations were developed adopting a grading system for strength of recommendation involving assessment of the quality of scientific evidence. The most commonly adopted systems include GRADE (Grades of Recommendation Assessment, Development and Evaluation) (http://www.gradeworkinggroup.org/) or SIGN (Scottish Intercollegiate Guidelines Network) (https://www.sign.ac.uk). Briefly, these systems involve a systematic review of the literature and synthesis of evidence with assessment of the quality of scientific evidence based on study design (i.e. randomized clinical trials, case-control or cohort studies, non-analytic studies, e.g. case reports, case series), study quality and consistency across study. Recommendations were ranked based on the strength of supporting evidence. These approaches may or may not be explicitly coupled with formal consensus development techniques (e.g. Delphi method, nominal group technique).

Level B: Consensus-based guidelines / recommendations

The guidelines / recommendations were developed based on consensus among experts adopting formal consensus development techniques without including a systematic review of the literature and synthesis of evidence and a grading for strength of recommendation. Formal consensus development techniques include the Delphi method or nominal group technique. Briefly, these communication techniques are aimed at providing an unbiased and independent process of consensus within a panel of experts through the use of questionnaires and structured face-to-face meetings addressing key clinical questions relevant to the guideline / recommendation purpose.

Level C: Expert opinion

The guidelines / recommendations were entirely based on opinion by a variable number of experts without systematic review of the literature and formal consensus development techniques.

Subnetworks coordinators were requested to coordinate the action on their area of expertise. For this task, TFA on best practices coordinators and Coordination team circulated subnetworks-specific Assessment templates, including:

- Objective and Instructions: with the definition of the levels for each of the three domains
- Assessment template: list of guidelines and recommendations including disease coverage and template for completing the three domains
- Subnetwork task force: list of experts per disease identified as potential contributors for the task

4- Results

4.1 Expansion of the List of international guidelines and recommendations

The list of international guidelines and recommendations was successfully reviewed and expanded including a total of 117 CPGs for the six subnetworks. See Figure1.

The complete list of guidelines compiled is available in Annex I (see 4.2 Classification of guidelines based on Quality domains).

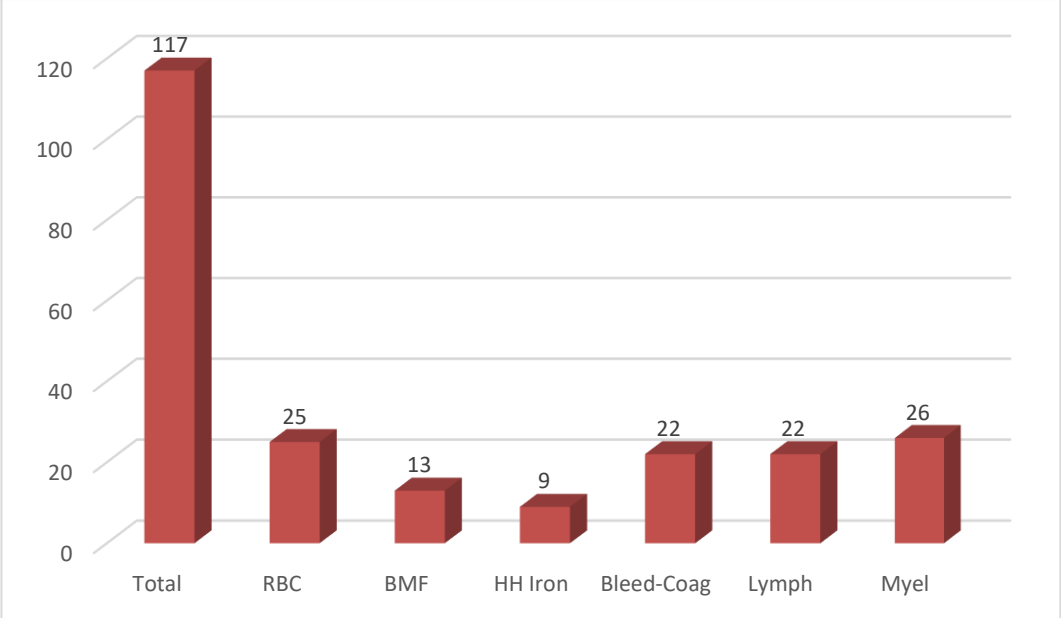

Fig 1. List of international guidelines/recommendations compiled for RHD (RBC: Red blood cell diseases subnetwork, BMF: Bone marrow failures subnetwork, HH-Iron: Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork, Bleed-Coag: Bleeding and coagulation subnetworks, Lymph: Lymphoid malignancies subnetwork, Myel: Myeloid malignancies subnetwork.

Similar numbers of guidelines and recommendations are found for the different subnetworks, with the clear exception of the Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork. The last encompasses a great number of very rare disorders and where especial efforts have to be focused on the promotion of the existing CPGs and development of new ones.

4.2 Classification of guidelines based on Quality domains

10 ERN-EuroBloodNet experts participated in the classification of guidelines and recommendations compiled based on quality domains for four subnetworks: Red blood cell, bone marrow failures, HH iron and myeloid malignancies. The task is still ongoing for the Bleeding and coagulation disorders and Lymphoid malignancies.

The updated list of guidelines and recommendations including their classification in quality domains, experts who participated in the action and their comments is available in **Annex I Classification of RHD guidelines/recommendations based on Quality Domains.**

Some of the guidelines and recommendations were not classified since they are important documents for the management of the disorders in some aspect, but do not fulfill the requirements to be classified based on the methodology established. Accordingly, a total of 24 guidelines/recommendations for RBC, 13 for BMF, 6 for HH-Iron and 26 for Myeloid were taken into consideration for the analysis and thus, classified based on quality domains.

Proportion (%) of guidelines and recommendations has been according to the scope and purpose, participation of patients for its development or not, and rigour of development.

According to the scope and purpose, results are shown in figures 2 - 6.

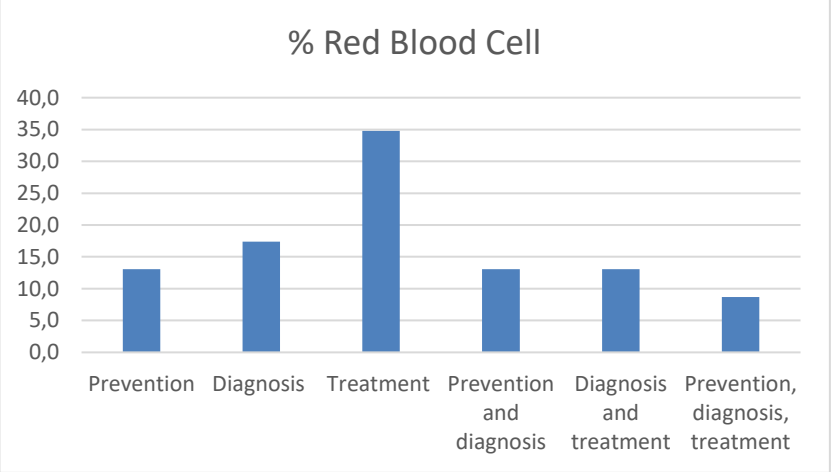

Fig 2. RBC CPGs based on scope and purpose

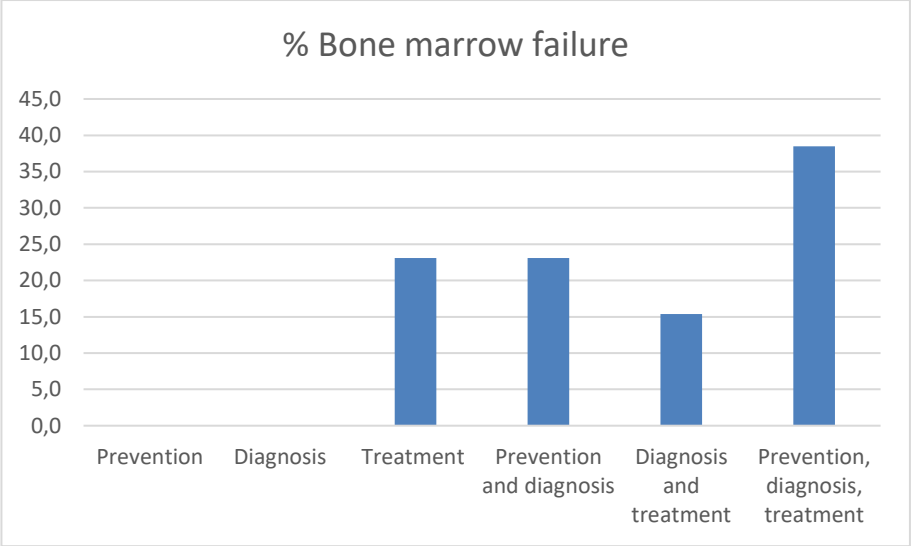

Fig 3. BMF CPGs based on scope and purpose

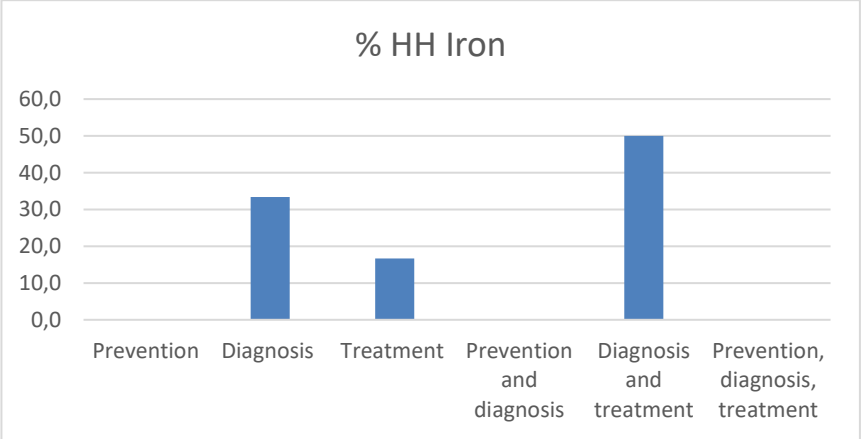

Fig 4. HH Iron CPGs based on scope and purpose

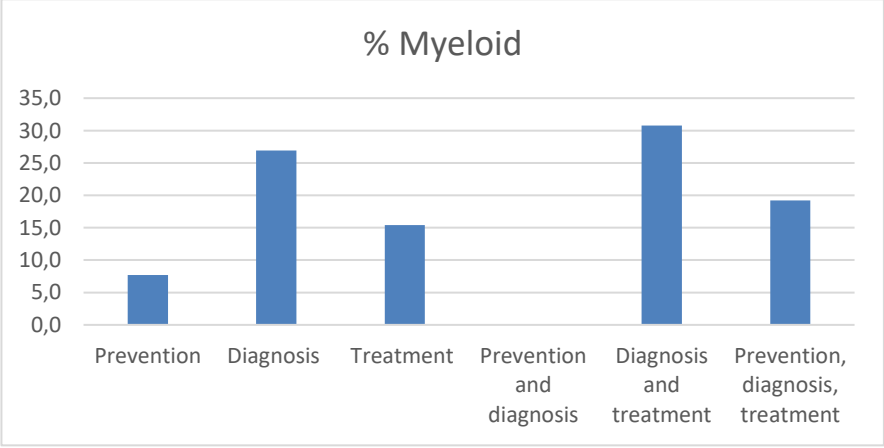

Fig 5. Myeloid CPGs based on scope and purpose

Guidelines and recommendations gathered for RBC cover either prevention, diagnosis, treatment or a combination of them, highlighting the high number of CPGs covering treatment from the total compiled for the subnetwork, including a total of 34,8% only for treatment, 13% for diagnosis and treatment and 8,7 for the three areas.

Attending to BMF it is remarkable the almost 40% of the CPGs compiled have a total scope ranging from prevention to treatment. Importantly, from the HH-iron subnetwork, half of the CPGs cover diagnosis and treatment, while none is found for prevention probably due to its ultra low prevalence.

In myeloid disorders the majority of CPGs are focussed clearly on diagnosis and treatment or a combination of both, which in total addresses more than the 70% of the CPGs found on myeloid disorders. The percentage is specially low for the CPGs focussed only in prevention, which represents only the 7% of the guidelines and recommendations.

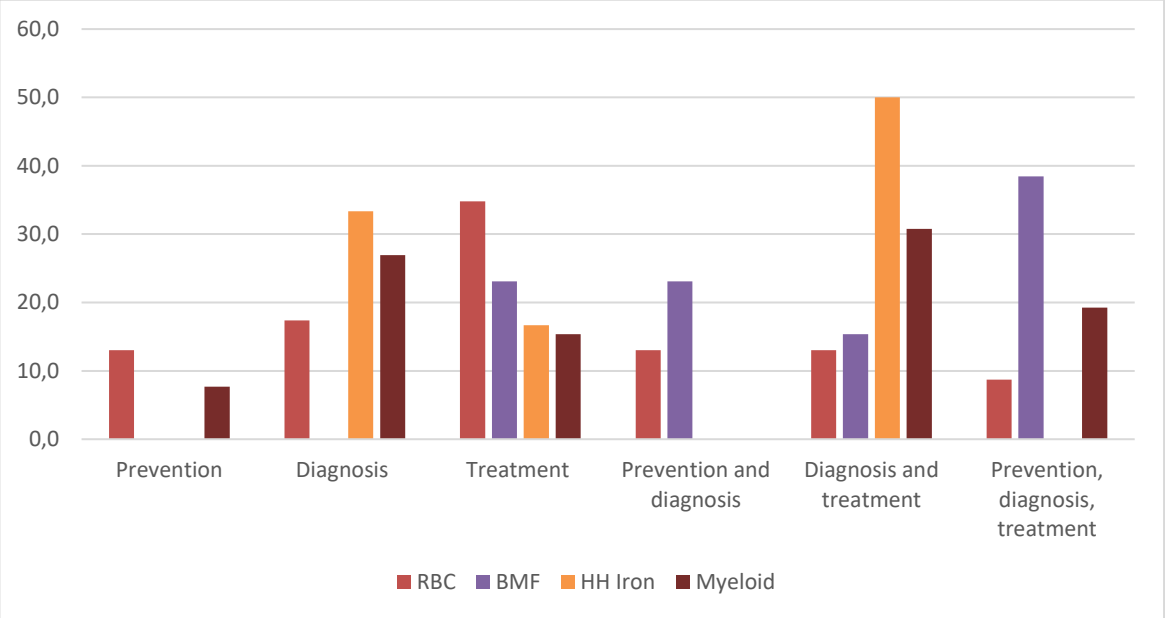

Fig 6. Comparison among subnetworks on % Guidelines/recommendations based scope and purpose

Regarding patients' involvement, it is very remarkable the low participation of patients in the development of guidelines/recommendations, especially for BMF and Myeloid disorders with a total lack of patients' participation, and RBC area, where patients only have participated in 10% of them. In contrast, important also to highlight that patients were present in half of the CPGs compiled for the HH-iron area. Figure 7.

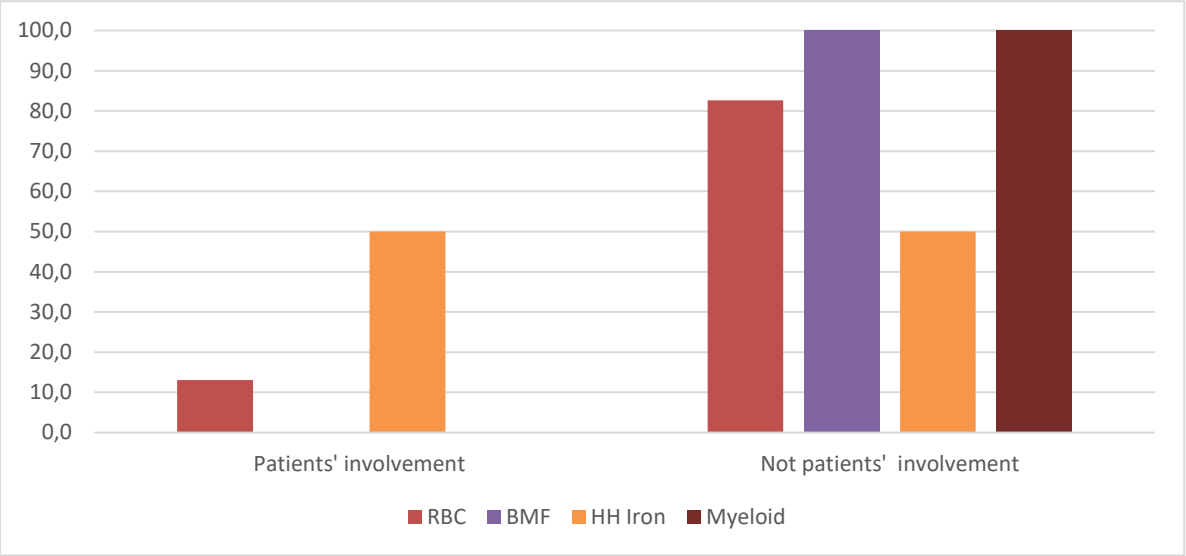

Fig 7. % Guidelines/recommendations based on patients' participation

Lastly, results regarding CPG classification attending to the rigour of development is shown in Figure 8. Myeloid and RBC guidelines and recommendations classified attending to the rigour of development have followed a similar pattern where approximately half of them has been classified as level A and B, and only 8% and 4% respectively has been classified as C. These results contrast importantly with the CPGs for BMF, where almost 80% of them has been classified as C and the other 20% as B. Better results have been found for the HH-iron subnetwork where more than the 60% of guidelines have been classified as level A and 30% as C.

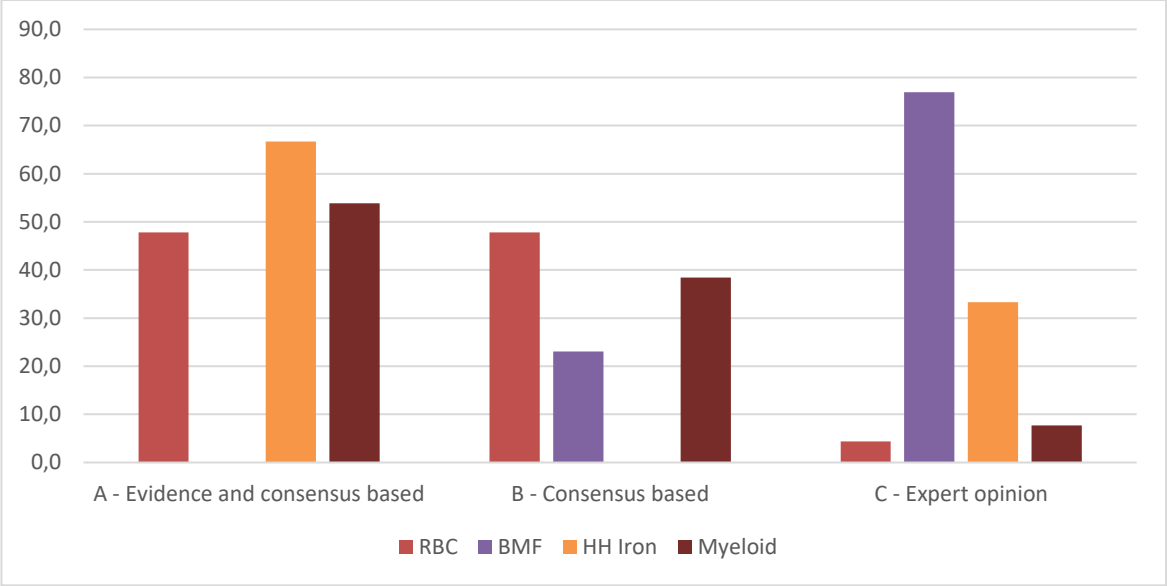

Fig. 8 % Guidelines/ recommendations based on rigour of development

5- Conclusions and next steps

The strategy followed for the creation of the repository of reliable guidelines and recommendations has led to the identification of the most common used guidelines/recommendations at EU level for the most frequent RHD and to their classification according to quality domains in line with the Appraisal of Guidelines, REsearch and Evaluation (AGREE).

The classification of guidelines and recommendations based on quality domains has not been intended to be an exhaustive analysis of quality but a first practical classification for further analysis of gaps. The exercise has shed light on the current coverage of CPGs for four of the subnetworks while allowing the identification unbalances among the different scopes and purposes. In addition, a clear need of patients' involvement in the generation of CPGs have been revealed, especially in the Myeloid, bone marrow failures and red blood cell disorders areas, where their involvement have been null or nearly null in the CPGs assessed. The analysis of the classification attending the rigour of development has also provided very valuable information of the grade of evidence used for their creation, while allowing the identification of areas where additional efforts are needed to increase the CPGs available as level A, for instance, on the bone marrow failures area.

Once the classification of CPGs on quality domains is completed, the action will allow the generation of the full picture of guidelines/recommendations available for RHD at EU level, and thus, the identification of areas needing for best practices promotion in collaboration with the European Hematology Association (EHA).

In addition, the repository will be publicly available on ERN-EuroBloodNet website allowing both non-experts and experts in RHD to benefit from an exhaustive database with reliable and updated guidelines. This will promote the delivery of highly specialised procedures and treatments and the harmonisation of care delivery across EU.

Next steps also envisage the expansion of the repository for the coverage of national guidelines, recommendations or experts' opinion. Following the success of the strategy implemented, it was agreed to follow the same procedure as for the gathering of international ones and request the action of the task force on guidelines.

A deeper patients' involvement will be also promoted in next steps as cornerstone for guaranteeing their voice is heard in both, guidelines development and implementation based on their personal experience. ePAGs will also contribute to define priorities in guidelines production and/or adaptation to different populations. Important efforts will be dedicated to promote the incorporation of more ePAGs in the network for those conditions without representation, which are also the most lacking of clinical guidelines and/or recommendations.

In addition, ERN-EuroBloodNet is one of the members of the "ERN Working Group on Knowledge Generation" and will work together with other ERNs with the common goal of producing unique guidelines at the EU level by the best experts in the field, following a concrete methodology and validated at the national level.

Annex I

Classification of RHD guidelines/recommendations based on Quality Domains

List of ERN-EuroBloodNet experts who performed the Guidelines/Recommendation classification based on Quality Domains

By alphabetic order:

Paola Bianchi, Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Italy

Domenica Cappellini, Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Italy

Raffaella Colombatti, AO Padua, Italy

Pierre Fenaux, Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, France

Béatrice Gulbis, CUB-Hôpital Erasme, Brussels

Achille Iolascon, AOU Federico II, Italy

Luca Malcovati, Foundation IRCCS Polyclinic San Matteo, Italy

Regis Peffault de la Tour, Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, France

Graça Porto, Centro Hospitalar do Porto, EPE, Portugal

Dorine Swinkels, Radboud University Medical Center Nijmegen, Netherlands

Red Blood Cell defects subnetwork			Rare Red blood cell defects									Domains		
nº	Title of the guideline	Link	Haemoglobinopathy	SCD	Thal	Hereditary erythroenzymopathies	PKD	G6PD	Hereditary RBC membrane defects	Hereditary Spherocytosis	Congenital Erythrocytosis	Scope and Purpose	Patients' involvement	Rigour of development
1	Guidelines for the diagnosis and management of hereditary spherocytosis – 2011 update	https://www.ncbi.nlm.nih.gov/pubmed/22055020								X		5. Diagnosis and treatment	Yes	A - Evidence and consensus based
2	ICSH guidelines for the laboratory diagnosis of nonimmune hereditary red cell membrane disorders	https://www.ncbi.nlm.nih.gov/pubmed/25790109							x			2. Diagnosis	No	A - Evidence and consensus based
3	Standards for the clinical care of children and adults with thalassaemia in the UK	http://ukts.org/standards/Standards-2016final.pdf			x							3. Treatment	Yes	B - Consensus based
4	Recommendations regarding splenectomy in hereditary hemolytic anemias.	https://www.ncbi.nlm.nih.gov/pubmed/28550188	x			x			x			3. Treatment	No	A - Evidence and consensus based
5	Management of Non-Transfusion-Dependent Thalassemia: A Practical Guide	https://www.ncbi.nlm.nih.gov/pubmed/25255924			x							3. Treatment	No	C - Expert opinion
6	EMQN Best Practice Guidelines for molecular and haematology methods for carrier identification and prenatal diagnosis of the haemoglobinopathies	https://www.ncbi.nlm.nih.gov/pubmed/25052315	x									4. Prevention and diagnosis	No	B - Consensus based
7	Significant haemoglobinopathies: guidelines for screening and diagnosis	http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2009.08054.x/abstract	x									4. Prevention and diagnosis	Yes	B - Consensus based
8	NHS SCT Handbook for Newborn Laboratories	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/656094	x									1. Prevention	No	B - Consensus based
9	Antenatal Laboratory Handbook SCD Thal	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/585126	x									1. Prevention	No	B - Consensus based
10	Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014	https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-		x								3. Treatment	No	B - Consensus based
11	ENERCA clinical recommendations for disease management and prevention of complications of sickle cell disease in children	https://www.ncbi.nlm.nih.gov/pubmed/20981677		x								3. Treatment	No	B - Consensus based
12	Recommended methods for the characterization of red cell pyruvate kinase variants	https://www.ncbi.nlm.nih.gov/pubmed/41566					x					2. Diagnosis	No	B - Consensus based
13	Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype.	https://www.ncbi.nlm.nih.gov/pubmed/?term=Clinical+Pharmacogenetics+Implementat						x				5. Diagnosis and treatment	No	A - Evidence and consensus based
14	Preterm Neonates: Beyond the Guidelines for Neonatal Hyperbilirubinemia	https://www.ncbi.nlm.nih.gov/pubmed/27235216	?			x			x					
15	Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis	https://www.ncbi.nlm.nih.gov/pubmed/?term=Guidelines+for+the+diagnosis%2C+inves									x	5. Diagnosis and treatment	No	A - Evidence and consensus based
16	Prevention and Diagnosis of Haemoglobinopathies: A Short Guide for Health Professionals and Laboratory Scientists (2016)	http://thalassaemia.org.cy/publications/tif-publications/prevention-and-			x							2. Diagnosis	No	B - Consensus based

Red Blood Cell defects subnetwork			Rare Red blood cell defects									Domains		
nº	Title of the guideline	Link	Haemoglobinopathy	SCD	Thal	Hereditary erythroenzymopathies	PKD	G6PD	Hereditary RBC membrane defects	Hereditary Spherocytosis	Congenital Erythrocytosis	Scope and Purpose	Patients' involvement	Rigour of development
17	Guidelines for the management of non transfusion dependent thalassaemia (NTDT) 2ND edition	https://www.ncbi.nlm.nih.gov/pubmed/24672826			x							6. Prevention, diagnosis, treatment	No	A - Evidence and consensus based
18	A guide for haemoglobinopathy nurse	http://thalassaemia.org.cy/publications/tif-publications/a-guide-for-the-	x									3. Treatment	No	A - Evidence and consensus based
19	Prevention of Thalassaemias and other Haemoglobin Disorders, Vol 1, 2nd Edition (2013)	https://www.ncbi.nlm.nih.gov/pubmed/24672827	x									1. Prevention	No	A - Evidence and consensus based
20	A Short Guide to the Management of Transfusion Dependent Thalassaemia	http://thalassaemia.org.cy/publications/tif-publications/a-short-guide-to-the-			x							3. Treatment	No	A - Evidence and consensus based
21	Emergency Management of Thalassaemia (2012)	https://www.ncbi.nlm.nih.gov/pubmed/24672825			x							3. Treatment	No	B - Consensus based
22	Guidelines for the Management of Transfusion Dependent Thalassaemia, 3rd Edition (2014)	https://www.ncbi.nlm.nih.gov/pubmed/25610943			x							6. Prevention, diagnosis, treatment	No	A - Evidence and consensus based
23	Prevention of Thalassaemias and Other Haemoglobin Disorders, Vol. 2: Laboratory Protocols (2012)	https://www.ncbi.nlm.nih.gov/pubmed/24672828	x									4. Prevention and diagnosis	No	A - Evidence and consensus based
24	Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency. (2019)	https://www.ncbi.nlm.nih.gov/pubmed/30358897					x					2. Diagnosis	No	B - Consensus based
25	Newborn screening for sickle cell disease in Europe: recommendations from a Pan-European Consensus Conference	https://www.ncbi.nlm.nih.gov/pubmed/?term=30334577		x								4. Prevention and diagnosis	No	B - Consensus based

Bone Marrow Failure subnetwork			Bone marrow failure (BMF) and rare haematopoietic disorders							Domains		
nº	Title of the guideline/recommendation	Link	Congenital dyserythropoietic anemia	Blackfan-Diamond anemia	Aplastic anemia	PNH	GATA2 syndrome	Fanconi Anemia	Transient erythroblastopenia of childhood	Scope and Purpose	Patients' involvement	Rigour of development
1	Diagnosis and management of congenital dyserythropoietic anemias	https://www.ncbi.nlm.nih.gov/pubmed/26653117	x							6. Prevention, diagnosis, treatment	No	C - Expert opinion
2	Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference	https://www.ncbi.nlm.nih.gov/pubmed/18671700		x						6. Prevention, diagnosis, treatment	No	C - Expert opinion
3	How I treat Diamond-Blackfan anemia	https://www.ncbi.nlm.nih.gov/pubmed/?term=How+I+treat+Diamond-Blackfan+anemia		x						6. Prevention, diagnosis, treatment	No	C - Expert opinion
4	Guidelines for the diagnosis and management of adult aplastic anaemia	https://www.ncbi.nlm.nih.gov/pubmed/26568159			x					5. Diagnosis and treatment	No	B - Consensus based
5	How I manage patients with Fanconi anaemia	https://www.ncbi.nlm.nih.gov/pubmed/28474441						x		6. Prevention, diagnosis, treatment	No	C - Expert opinion
6	How I treat MDS and AML in Fanconi anemia	https://www.ncbi.nlm.nih.gov/pubmed/?term=How+I+treat+MDS+and+AML+in+Fanconi+anemia						x		6. Prevention, diagnosis, treatment	No	C - Expert opinion
7	Paroxysmal nocturnal hemoglobinuria	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4215311/				x				5. Diagnosis and treatment	No	C - Expert opinion
8	Paroxysmal Nocturnal Hemoglobinuria	https://www.intechopen.com/books/anemia/paroxysmal-nocturnal-hemoglobinuria				x				4. Prevention and diagnosis	No	C - Expert opinion
9	Haematopoietic and immune defects associated with GATA2 mutation	https://www.ncbi.nlm.nih.gov/pubmed/25707267					x			4. Prevention and diagnosis	No	C - Expert opinion
10	GATA2 deficiency andrelated myeloid neoplasms	https://www.ncbi.nlm.nih.gov/pubmed/28637621					x			4. Prevention and diagnosis	No	C - Expert opinion
11	Transplantation for bone marrow failure: current issues	https://www.ncbi.nlm.nih.gov/pubmed/27913467			x					3. Treatment	No	C - Expert opinion
12	Recommendations on hematopoietic stem cell transplantation for inherited bone marrow failure syndromes	https://www.ncbi.nlm.nih.gov/pubmed/26052913			x					3. Treatment	No	B - Consensus based
4 RBC	Recommendations regarding splenectomy in hereditary hemolytic anemias.	https://www.ncbi.nlm.nih.gov/pubmed/28550188	x							3. Treatment	No	B - Consensus based

HH-Iron subnetwork			Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis					Domains			Additional comment
nº	Title of the guideline/recommendation	Link	non-HFE related hereditary hemochromatosis: (HH types 2A, 2B, 3 and 4A,4B), TFH1-Related Hemochromatosis (type V), Hereditary Hyperferritinemia Cataract Syndrome	HFE-related hereditary hemochromatosis with established severe clinical expression or due to very rare mutations in HFE	Low iron availability for erythropoiesis: Iron Refractory Iron deficiency Anemia (IRIDA), Aceruloplasminemia (ACP)	Rare defects in iron acquisition and transport: Atransferrinemia, Microcytic anemia with iron loading (DMT1), Sideroblastic anemia (STEAP3)	Defects in heme synthesis or Fe-S cluster biogenesis: Sideroblastic anemias (SLC25A38, GLRX5; HSPA9), XLSA with ataxia (ABCB7), XLSA (ALAS2)	Scope and Purpose	Patients' involvement	Rigour of development	Comment
1	The quality of hereditary haemochromatosis guidelines: a comparative analysis	https://www.ncbi.nlm.nih.gov/pubmed/25441394		x							Important as a tool to question the need for more extended evidence; it uses AGREE II to evaluate the evidence from the European ASL and American ASLD guidelines
2	European Association For The Study Of The Liver. EASL clinical practice guidelines for HFE hemochromatosis.	https://www.ncbi.nlm.nih.gov/pubmed/20471131		x				5. Diagnosis and treatment	Yes	A - Evidence and consensus based	
3	American Association for the Study of Liver Diseases.Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases	https://www.ncbi.nlm.nih.gov/pubmed/21452290		x				5. Diagnosis and treatment	No	A - Evidence and consensus based	Some divergences with the European guidelines (namely on the value of the H63D variant).
4	EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH)	https://www.ncbi.nlm.nih.gov/pubmed/26153218		x				2. Diagnosis	No	A - Evidence and consensus based	The most updated guidelines on genetic testing
5	Reassessing the Safety Concerns of Utilizing Blood Donations from Patients with Hemochromatosis. Hepatology	https://www.ncbi.nlm.nih.gov/pubmed/28902419		x							These are not guidelines but important as recommendation
6	Molecular diagnosis of hemochromatosis	https://www.ncbi.nlm.nih.gov/pubmed/23530886	x					2. Diagnosis	No	C - Expert opinion	Expert opinion" based recommendations and "in house recommendations"
7	Practice guidelines for the diagnosis and management of microcytic anemias due to genetic disorders of iron metabolism or heme synthesis	https://www.ncbi.nlm.nih.gov/pubmed/24665134			x	x	x	5. Diagnosis and treatment	Yes	A - Evidence and consensus based	Only guideline available on this topic. It does not cover SA due to HSPA9-variants since this latter disorder is described after the publication of the guidelines
8	Therapeutic recommendations in HFE hemochromatosis for p.Cys282Tyr (C282Y/C282Y) homozygous genotype	https://www.ncbi.nlm.nih.gov/pubmed/29589198		x				3. Treatment	Yes	C - Expert opinion	
9	Key-interventions derived from three evidence based guidelines for management and follow-up of patients with HFE haemochromatosis.	https://www.ncbi.nlm.nih.gov/pubmed/27733158		x							Development of Key-interventions (KI's) by team from Belgium and the Netherlands to measure and improve the quality of care delivered to patients diagnosed with HH.

Myeloid malignancies subnetwork			Myeloid malignancies									Domains			Additional comment
nº	Title of the guideline	Link	Myelodysplastic syndrome (MDS)	Acute myeloid leukemia (AML)	Acute promyelocytic leukemia	Chronic myelomonocytic leukemia (CMML)	Chronic Myeloid Leukemia (CML)	Myeloproliferative neoplasm (MPN)	Myelofibrosis	Systemic mastocytosis	Histiocytosis	Scope and Purpose	Patients' involvement	Rigour of development	Comment
1	Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet	https://www.ncbi.nlm.nih.gov/pubmed/23980065	x									5. Diagnosis and treatment	No	A	Systematic review of the literature but no grading system for strength of recommendation
2	Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel.	https://www.ncbi.nlm.nih.gov/pubmed?term=27895058		x								5. Diagnosis and treatment	No	B	
3	NCCN Guidelines Insights: Myeloproliferative Neoplasms, Version 2.2018.	https://www.ncbi.nlm.nih.gov/pubmed/28982745						x				5. Diagnosis and treatment	No	A	Systematic review of the literature but no grading system for strength of recommendation
4	Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet	https://www.ncbi.nlm.nih.gov/pubmed/18812465			x							5. Diagnosis and treatment	No	B	
5	Diagnosis and management of mastocytosis: an emerging challenge in applied hematology	https://www.ncbi.nlm.nih.gov/pubmed/26637707								x		5. Diagnosis and treatment	No	C	
6	Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel.	https://www.ncbi.nlm.nih.gov/pubmed/28096091	x			x						3. Treatment	No	A	
7	Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party.	https://www.ncbi.nlm.nih.gov/pubmed/29330221		x								2. Diagnosis	No	B	
8	Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report.	https://www.ncbi.nlm.nih.gov/pubmed/23838352						x	x			2. Diagnosis	No	B	
9	Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project.	https://www.ncbi.nlm.nih.gov/pubmed/23591792						x				2. Diagnosis	No	B	
10	Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet.	https://www.ncbi.nlm.nih.gov/pubmed/21205761						x	x			5. Diagnosis and treatment	No	B	Systematic review of the literature but no grading system for strength of recommendation
11	An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults.	https://www.ncbi.nlm.nih.gov/pubmed/25624319				x						2. Diagnosis	No	B	
12	European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013.	https://www.ncbi.nlm.nih.gov/pubmed/23803709					x					5. Diagnosis and treatment	No	B	Systematic review of the literature but no grading system for strength of recommendation
13	European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia	https://www.ncbi.nlm.nih.gov/pubmed/27121688					x					5. Diagnosis and treatment	No	B	Systematic review of the literature but no grading system for strength of recommendation
14	Which patients with myelofibrosis should receive ruxolitinib therapy? ELN-SIE evidence-based recommendations	https://www.ncbi.nlm.nih.gov/pubmed/27740634							x			3. Treatment	No	A	
15	Harmonemia: a universal strategy for flow cytometry immunophenotyping-A European LeukemiaNet WP10 study	https://www.ncbi.nlm.nih.gov/pubmed/26922887										2. Diagnosis	No	A	Project aimed at harmonizing diagnostic protocols adopting the highest quality experimental methodology. Current methodology assessment scale not applicable.

Myeloid malignancies subnetwork			Myeloid malignancies									Domains			Additional comment
nº	Title of the guideline	Link	Myelodysplastic syndrome (MDS)	Acute myeloid leukemia (AML)	Acute promyelocytic leukemia	Chronic myelomonocytic leukemia (CMML)	Chronic Myeloid Leukemia (CML)	Myeloproliferative neoplasm (MPN)	Myelofibrosis	Systemic mastocytosis	Histiocytosis	Scope and Purpose	Patients' involvement	Rigour of development	Comment
16	The EBMT-ELN working group recommendations on the prophylaxis and treatment of GvHD: a change-control analysis.	https://www.ncbi.nlm.nih.gov/pubmed/27892949										6. Prevention, diagnosis, treatment	No	C	Survey aimed at evaluating how effectively the information in the recommendations had reached the centres, studying the attitudes of the centres and the impact of the recommendations on centre policies.
17	Management of viral hepatitis in patients with haematological malignancy and in patients undergoing haemopoietic stem cell transplantation: recommendations of the 5th European Conference on Infections in Leukaemia (ECIL-5)	https://www.ncbi.nlm.nih.gov/pubmed/27599653										6. Prevention, diagnosis, treatment	No	A	
18	ECIL guidelines for treatment of Pneumocystis jirovecii pneumonia in non-HIV-infected haematology patients	https://www.ncbi.nlm.nih.gov/pubmed/27550993										3. Treatment	No	A	
19	ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients.	https://www.ncbi.nlm.nih.gov/pubmed/27550992										1. Prevention	No	A	
20	ECIL guidelines for the diagnosis of Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients	https://www.ncbi.nlm.nih.gov/pubmed/27550991										2. Diagnosis	No	A	
21	Pneumocystis jirovecii pneumonia: still a concern in patients with haematological malignancies and stem cell transplant recipients	https://www.ncbi.nlm.nih.gov/pubmed/27550990										6. Prevention, diagnosis, treatment	No	A	
22	Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines.	https://www.ncbi.nlm.nih.gov/pubmed/27365460										6. Prevention, diagnosis, treatment	No	A	
23	ECIL guidelines for the prevention, diagnosis and treatment of BK polyomavirus-associated haemorrhagic cystitis in haematopoietic stem cell transplant recipients	https://www.ncbi.nlm.nih.gov/pubmed/29190347										6. Prevention, diagnosis, treatment	No	A	
24	Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines	https://www.ncbi.nlm.nih.gov/pubmed/29079323										1. Prevention	No	A	
25	ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients	https://www.ncbi.nlm.nih.gov/pubmed/28011902										3. Treatment	No	A	
26	Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials.	https://www.ncbi.nlm.nih.gov/pubmed/30404811										2. Diagnosis	No	B	

Bleeding-coagulation subnetwork			Rare bleeding-coagulation disorders					
nº	Title of the guideline	Link	Haemophilia A and B (including female carriers)	The rarer congenital deficiencies of other coagulation factors (such as fibrinogen and factors II, V, VII, X, XI and XIII)	Von Willebrand disease	Rare hemorrhagic disorder due to a platelet anomaly	thrombotic thrombocytopenic purpura	Rare thrombotic disorder due to a platelet anomaly
1	WFH Guidelines: Guidelines for the management of haemophilia	http://www.haemophiliacentral.org/Guidelines.aspx	x					
2	Guideline on the management of haemophilia in the fetus and neonate	http://www.haemophiliacentral.org/Guidelines.aspx	x					
3	Practice Guidelines for the Molecular Diagnosis of Haemophilia A	http://www.haemophiliacentral.org/Guidelines.aspx	x					
4	Practice Guidelines for the Molecular Diagnosis of Haemophilia B	http://www.haemophiliacentral.org/Guidelines.aspx	x					
5	A United Kingdom Haemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A	http://www.haemophiliacentral.org/Guidelines.aspx	x					
6	Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO) guideline approved by the British Committee for Standards in Haematology	http://www.haemophiliacentral.org/Guidelines.aspx	x	x	x	x		
7	A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO	http://www.haemophiliacentral.org/Guidelines.aspx				x		x
8	The molecular analysis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organisation Haemophilia Genetics Laboratory Network	http://www.haemophiliacentral.org/Guidelines.aspx			x			
9	Management of von Willebrand's disease: a guideline from the UK Haemophilia Centre Doctors' Organisation	http://www.haemophiliacentral.org/Guidelines.aspx			x			
10	The diagnosis of von Willebrand's disease: a guideline from the UK Haemophilia Centre Doctors' Organisation	http://www.haemophiliacentral.org/Guidelines.aspx			x			
11	Emergency and out of hours care for patients with bleeding disorders – Standards of care for assessment and treatment	http://www.haemophiliacentral.org/Guidelines.aspx	x	x	x	x		
12	A framework for genetic service provision for haemophilia and other inherited bleeding disorders	http://www.haemophiliacentral.org/Guidelines.aspx	x	x	x	x		
13	UKHCDO guidelines on the management of HCV in patients with hereditary bleeding disorders 2011.	http://www.haemophiliacentral.org/Guidelines.aspx	x	x	x	?		
14	Guideline on the diagnosis and management of chronic liver disease in haemophilia	http://www.haemophiliacentral.org/Guidelines.aspx	x					
15	The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation	http://www.haemophiliacentral.org/Guidelines.aspx	x					
16	The obstetric and gynaecological management of women with inherited bleeding disorders-review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization	http://www.haemophiliacentral.org/Guidelines.aspx	x	x	x	x		
17	The rare coagulation disorders--review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation	http://www.haemophiliacentral.org/Guidelines.aspx	x	x	x			

Bleeding-coagulation subnetwork			Rare bleeding-coagulation disorders					
nº	**Title of the guideline**	**Link**	**Haemophilia A and B (including female carriers)**	**The rarer congenital deficiencies of other coagulation factors (such as fibrinogen and factors II, V, VII, X, XI and XIII)**	**Von Willebrand disease**	**Rare hemorrhagic disorder due to a platelet anomaly**	**thrombotic thrombocytopenic purpura**	**Rare thrombotic disorder due to a platelet anomaly**
18	Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia: A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guideline.	https://www.ncbi.nlm.nih.gov/pubmed/28370924	x					
19	Primary prophylaxis in haemophilia care: Guideline update 2016	https://www.ncbi.nlm.nih.gov/pubmed/28363466	x					
20	European principles of inhibitor management in patients with haemophilia.	https://www.ncbi.nlm.nih.gov/pubmed/29703220	x					
21	Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies.	https://www.ncbi.nlm.nih.gov/pubmed/22624596					x	
22	Diagnostic and treatment guidelines for thrombotic thrombocytopenic purpura (TTP) 2017 in Japan	https://www.ncbi.nlm.nih.gov/pubmed/28550351					x	

Lymphoid malignancies subnetwork			Lymphoid malignancies										
nº	Title of the guideline	Link	Acute lymphoblastic leukemia (ALL)	Marginal zone lymphomas	mantle cell lymphoma	peripheral T-cell lymphoma	Hairy cell leukaemia	Light chain Amyloidosis (AL amyloidosis)	Diffuse large B-cell lymphoma (DLBCL)	Follicular lymphoma	Chronic Lymphocytic Leukemia (CLL)	Hodgkin lymphoma	Waldenström macroglobulinemia
1	ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)	https://www.ncbi.nlm.nih.gov/pubmed/23175624							x	x	x		
2	ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma	https://www.ncbi.nlm.nih.gov/pubmed/?term=ESMO+Consensus+conferences%3A+guidelines+on+malignant+lymphoma+		x	x	x							
3	Hairy cell leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	https://www.ncbi.nlm.nih.gov/pubmed/?term=Hairy+cell+leukaemia%3A+ESMO+Clinical+Practice+Guidelines+for+diagnos					x						
4	AL amyloidosis: from molecular mechanisms to targeted therapies	https://www.ncbi.nlm.nih.gov/pubmed/29222231						x					
5	Update on nodal and splenic marginal zone lymphoma	https://www.ncbi.nlm.nih.gov/pubmed/29222281		x									
6	Acute lymphoblastic leukemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up	https://www.ncbi.nlm.nih.gov/pubmed/?term=Acute+lymphoblastic+leukemia+in+adult+patients%3A+ESMO+clinical+pract	x										
7	Acute lymphoblastic leukemia: Version 2.2015	https://www.ncbi.nlm.nih.gov/pubmed/26483064	x										
8	Gastric marginal zone lymphoam of MALT type: ESMO clinical practice guidelines for diagnosis, treatment and follow-up	https://www.ncbi.nlm.nih.gov/pubmed/24078657		x									
9	Guidelines on the management of AL amyloidosis	https://www.ncbi.nlm.nih.gov/pubmed/25303672						x					
10	Hodgkin´s lymphoma: ESMO clinical practice guidelines on diagnosis, treatment and follow up	https://www.ncbi.nlm.nih.gov/pubmed/25185243										x	
11	Hodgkin lymphoma, Version 1.2017	https://www.ncbi.nlm.nih.gov/pubmed/28476741										x	
12	Hodgkin´s lymphoma in adults: diagnosis, treatment and follow-up	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3608228/										x	
13	Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome	https://www.ncbi.nlm.nih.gov/pubmed/?term=Guideline+for+the+diagnosis%2C+treatment+and+response+criteria+for+Bi											x

Lymphoid malignancies subnetwork			Lymphoid malignancies										
nº	Title of the guideline	Link	Acute lymphoblastic leukemia (ALL)	Marginal zone lymphomas	mantle cell lymphoma	peripheral T-cell lymphoma	Hairy cell leukaemia	Light chain Amyloidosis (AL amyloidosis)	Diffuse large B-cell lymphoma (DLBCL)	Follicular lymphoma	Chronic Lymphocytic Leukemia (CLL)	Hodgkin lymphoma	Waldenström macroglobulinemia
14	Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop	https://www.ncbi.nlm.nih.gov/pubmed/23150997											x
15	Guidelines for Diagnosis, Indications for Treatment, Response Assessment and Supportive Management of Chronic Lymphocytic Leukemia	https://www.ncbi.nlm.nih.gov/pubmed/?term=Guidelines+for+Diagnosis%2C+Indications+for+Treatment%2C+Response+A									x		
16	Investigation and management of IgM and Waldenström-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel	https://www.ncbi.nlm.nih.gov/pubmed?term=Investigation%20and%20management%20of%20IgM%20and%20Waldenstr											x
17	Treatment recommendations from the Eighth International Workshop on Waldenström's Macroglobulinemia	https://www.ncbi.nlm.nih.gov/pubmed/?term=Treatment+recommendations+from+the+Eighth+International+Workshop+											x
18	A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: an European Research Initiative on CLL study.	https://www.ncbi.nlm.nih.gov/pubmed/26639181									x		
19	Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: updated ERIC recommendations.	https://www.ncbi.nlm.nih.gov/pubmed/28439111									x		
20	High-risk chronic lymphocytic leukemia in the era of pathway inhibitors: integrating molecular and cellular therapies.	https://www.ncbi.nlm.nih.gov/pubmed/29997221									x		
21	Reproducible diagnosis of chronic lymphocytic leukemia by flow cytometry: An European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation project	https://www.ncbi.nlm.nih.gov/pubmed/29024461									x		
22	ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia-update on methodological approaches and results interpretation.	https://www.ncbi.nlm.nih.gov/pubmed/29467486									x		