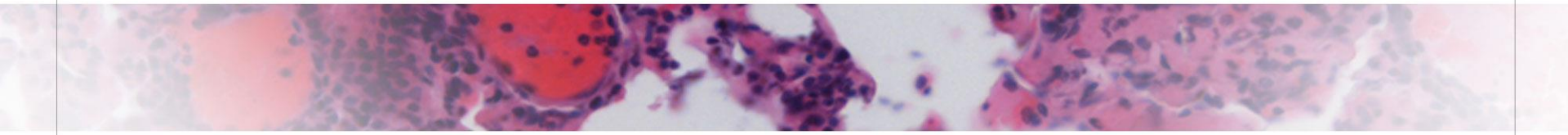
American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



uRADAR: European Patients Referral Frame to Improve Access to New Drugs and Therapies in Ultra-Rare Anemia Disorders and Severe Hereditary Spherocytosis

María del Mar Mañú Pereira

Head of the Rare Anemia Disorders Research Lab

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Vall d'Hebron

Vall d'Hebron Research Institute

Rare Anaemia Disorders European Epidemiological Platform

- To enable epidemiological and health burden surveillance of RADs in the EU to improve healthcare planning
- To enable translational and clinical research by collecting enough amount of high quality real world data to generate real world evidence for identification of reliable biomarkers for:
  - Disease progression
  - Prognosis
  - Response to treatments

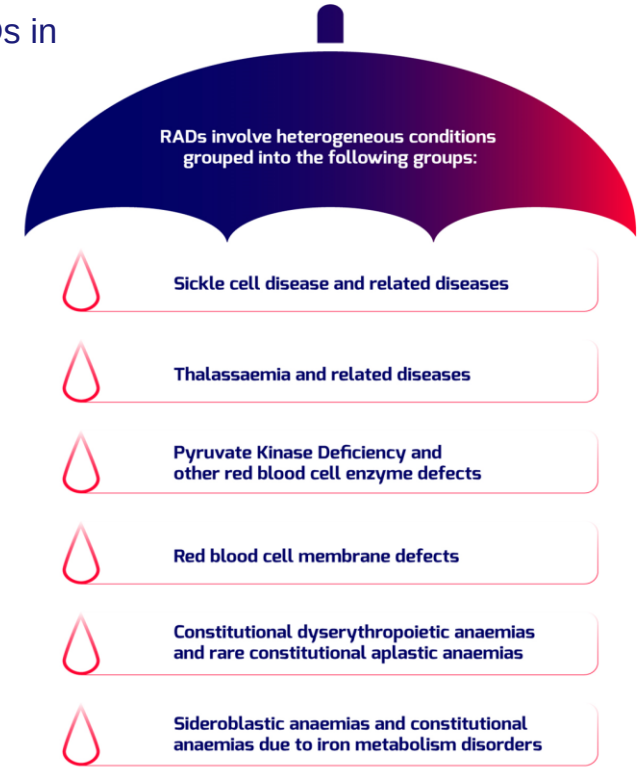
possibility to share and pool data

reach critical numbers

perform clinical trials, research projects

knowledge generation (evidence)

better healthcare for RADs patients

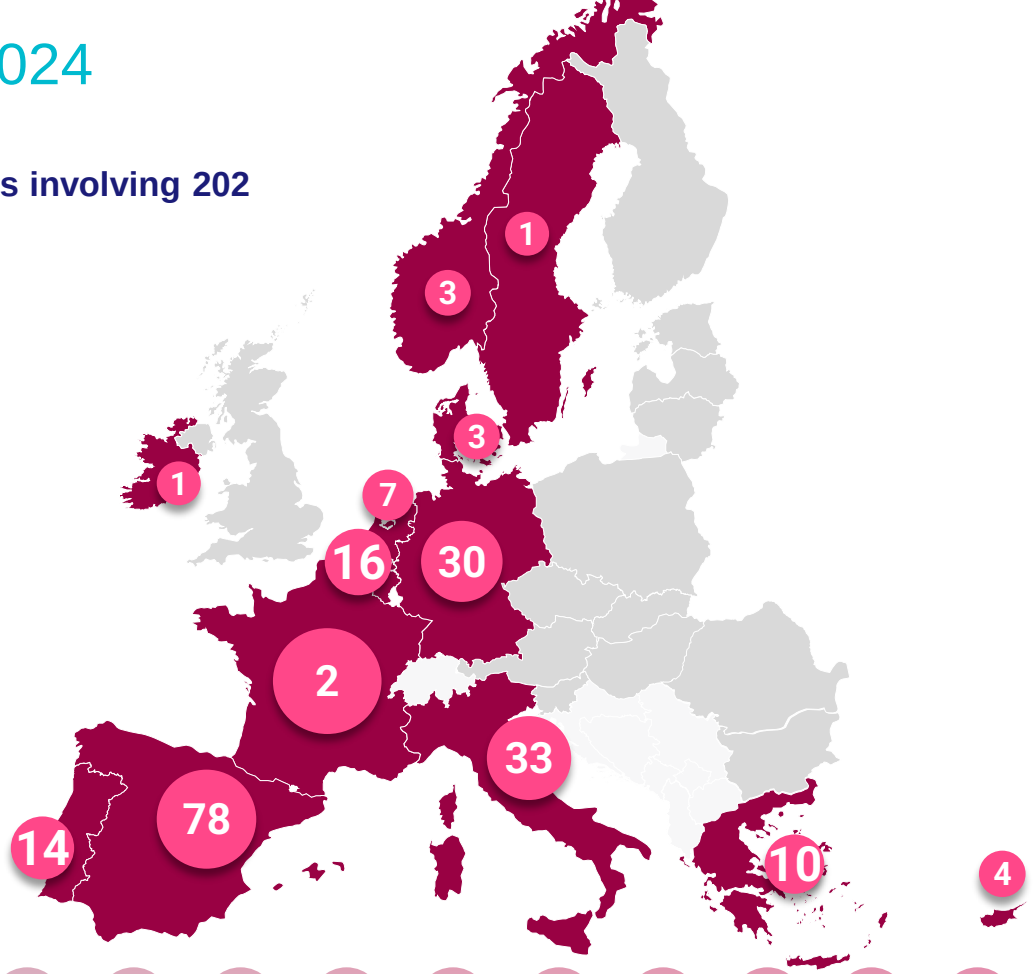


eha

Status of collaborations – 2024

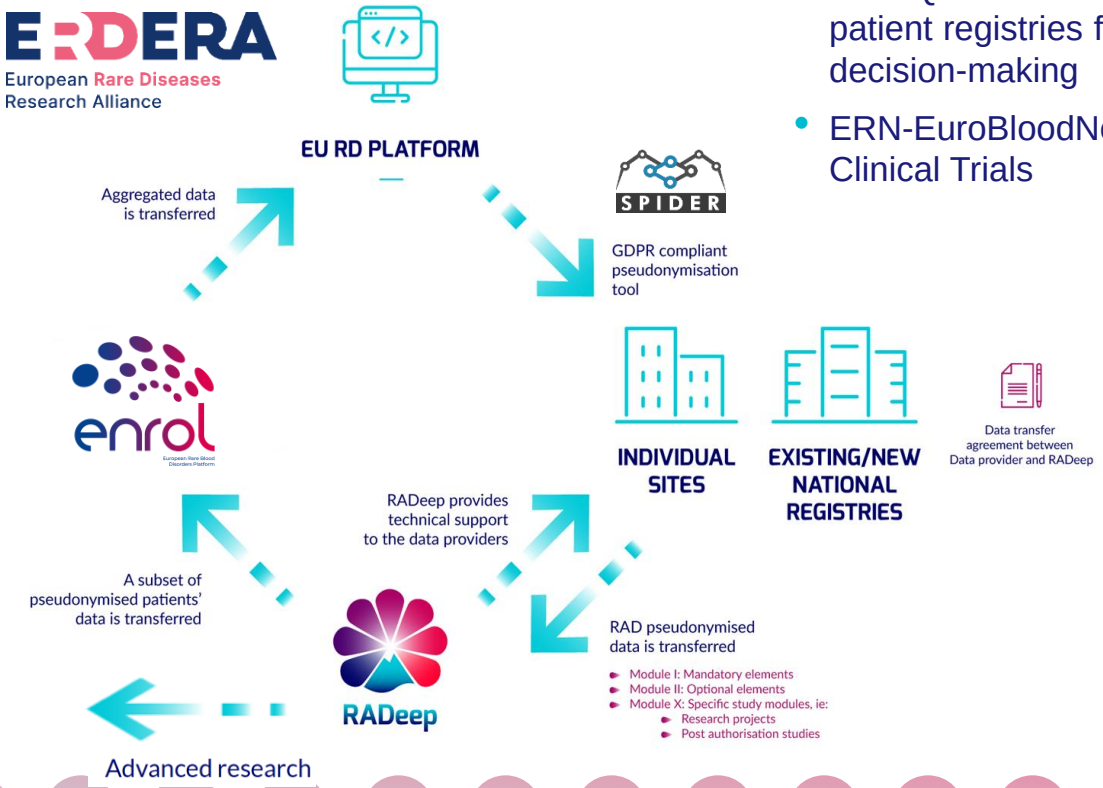
- **15 Ongoing collaboration agreements involving 202 centres in 13 EU countries:**
  12 Member States
  - Belgium
  - Cyprus
  - Denmark
  - France
  - Germany
  - Greece
  - Ireland
  - Italy
  - Portugal
  - Spain
  - Sweden
  - The Netherlands
  - + Norway

- **4,474 Patients registered**



RADeep Data driven research

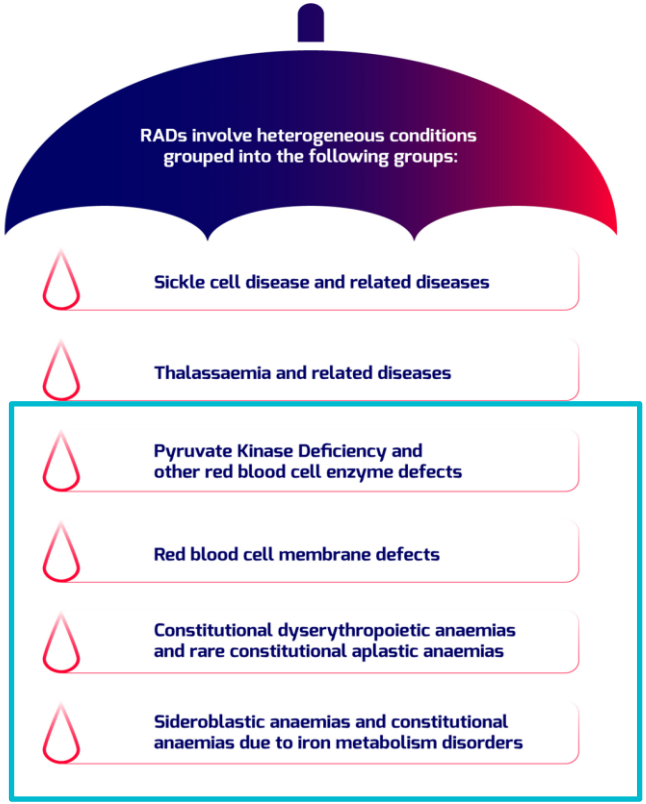
- Data driven AI models for personalized medicine and synthetic data generation in non-onco hematology



- EMA Qualification procedure: use of patient registries for regulatory decision-making
- ERN-EuroBloodNet Academic Clinical Trials

uRADAR

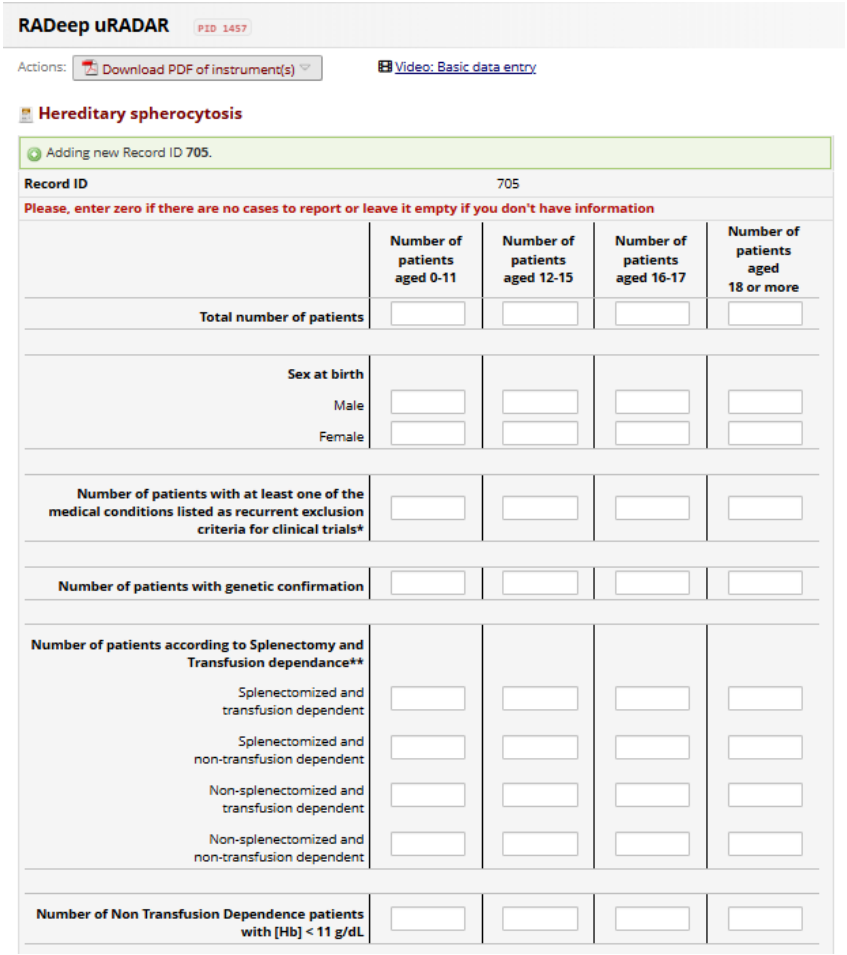
- Ultra-rare anemia disorders (uRADs) are commonly neglected from health planning and clinical research:
  - Delay in diagnosis
    - Due to clinical similarities are difficult to distinguish by standard diagnostic methods
  - Sub-optimal clinical management
  - Very few treatment options (Except PKD)
    - Mainly supportive
    - Splenectomy usually reserved for severe cases due to potential complications.
- RADeep & ERN-EuroBloodNet have joint efforts to establish the uRADAR initiative aiming to develop a referral frame for patients affected by uRADs in the European Union.
- The uRADAR ultimate goal is to enable access to clinical trials (CT), including drug repurposing



uRADAR: ultra-rare anemia disorders

Orpha	Disease or Disease group for collection of EpiData	Orpha	Include	Proof of diagnosis
766	Pyruvate kinase deficiency			Enzyme test or gene analysis
712	Glucophosphate isomerase deficiency			Enzyme test or gene analysis
	Glucose-6-phosphate dehydrogenase deficiency	466026	Class A glucose-6-phosphate dehydrogenase deficiency (<20%) - chronic (Class1)	Enzyme test or gene analysis
			Class B glucose-6-phosphate dehydrogenase deficiency (<45%) - acute, triggered	Enzyme test or gene analysis
98369	Rare constitutional hemolytic anemia due to an enzyme disorder (Other than PKD, GPI, G6PD)	714	Hemolytic anemia due to diphosphoglycerate mutase deficiency	Enzyme test or gene analysis
		90031	Non-spherocytic hemolytic anemia due to hexokinase deficiency	Enzyme test or gene analysis
		248305	Hemolytic anemia due to glyceraldehyde-3-phosphate dehydrogenase deficiency	Enzyme test or gene analysis
		35120	Hemolytic anemia due to pyrimidine 5' nucleotidase deficiency	Enzyme test or gene analysis
		86817	Hemolytic anemia due to adenylate kinase deficiency	Enzyme test or gene analysis
		99138	Hemolytic anemia due to erythrocyte adenosine deaminase overproduction	Enzyme test or gene analysis
		79277	Congenital erythropoietic porphyria	Enzyme test or gene analysis
		32	Glutathione synthetase deficiency	Enzyme test or gene analysis
		33574	Gamma-glutamylcysteine synthetase deficiency	Enzyme test or gene analysis
		90030	Hemolytic anemia due to glutathione reductase deficiency	Enzyme test or gene analysis
		99135	6-phosphogluconate dehydrogenase deficiency	Enzyme test or gene analysis
		371	Glycogen storage disease due to muscle phosphofructokinase deficiency	Enzyme test or gene analysis
		868	Triose phosphate-isomerase deficiency	Enzyme test or gene analysis
		57	Glycogen storage disease due to aldolase A deficiency	Enzyme test or gene analysis
		713	Glycogen storage disease due to phosphoglycerate kinase 1 deficiency	Enzyme test or gene analysis
822	Hereditary spherocytosis			Functional analysis or gene analysis
288	Hereditary elliptocytosis			Functional analysis or gene analysis
3203	Overhydrated hereditary stomatocytosis			Functional analysis and gene analysis
3202	Dehydrated hereditary stomatocytosis			Functional analysis and gene analysis
2882	Sitosterolemia			Functional analysis or gene analysis
98869	Congenital dyserythropoietic anemia type I			Gene analysis
98873	Congenital dyserythropoietic anemia type II			Gene analysis
98870	Congenital dyserythropoietic anemia type III			Gene analysis
293825	Congenital dyserythropoietic anemia type IV			Gene analysis
1195	Congenital atransferrinemia			Gene analysis
48818	Aceruloplasminemia			Gene analysis
83642	Microcytic anemia with liver iron overload			Gene analysis: DMT1
209981	IRIDA syndrome			Gene analysis
300298	Severe congenital hypochromic anemia with ringed sideroblasts			Gene analysis: STEAP3/TSAP6
	Hereditary methemoglobinemia due to NADH-cytochrome b5 reductase defect or hemoglobin variant	621	Hereditary methemoglobinemia (NADH-cytochrome b5 reductase defect)	Enzyme test or gene analysis
		330041	Hemoglobin M disease (hemoglobin variant)	Gene analysis
49827	Thiamine-responsive megaloblastic anemia syndrome			Gene analysis: SLC19A2
98362	Constitutional sideroblastic anemia (Other than Thiamine-responsive megaloblastic anemia syndrome)	699	Pearson syndrome	Gene analysis: SLC19A2 large-scale mtDNA deletion
		2598	Mitochondrial myopathy and sideroblastic anemia	Gene analysis: PUS1
		2802	X-linked sideroblastic anemia and spinocerebellar ataxia	Gene analysis: ABCB7
		75563	X-linked sideroblastic anemia	Gene analysis: ALAS2 gene
		255132	Adult-onset autosomal recessive sideroblastic anemia	Gene analysis: GLRX5
		260305	Autosomal recessive sideroblastic anemia	Gene analysis: SLC25A38
		369861	Congenital sideroblastic anemia-B-cell immunodeficiency-periodic fever-developmental delay syndrome	Enzyme test or gene analysis: TRNT1
	Unstable hemoglobinopathy	99139	Unstable hemoglobin disease	Gene analysis
		231226	Dominant beta thalassemia	Gene analysis

uRADAR: Data collection



RADeep uRADAR PID 1457

Actions: Download PDF of instrument(s) Video: Basic data entry

Hereditary spherocytosis

Adding new Record ID **705**.

Record ID 705

Please, enter zero if there are no cases to report or leave it empty if you don't have information

	Number of patients aged 0-11	Number of patients aged 12-15	Number of patients aged 16-17	Number of patients aged 18 or more
Total number of patients				
Sex at birth				
Male				
Female				
Number of patients with at least one of the medical conditions listed as recurrent exclusion criteria for clinical trials*				
Number of patients with genetic confirmation				
Number of patients according to Splenectomy and Transfusion dependance**				
Splenectomized and transfusion dependent				
Splenectomized and non-transfusion dependent				
Non-splenectomized and transfusion dependent				
Non-splenectomized and non-transfusion dependent				
Number of Non Transfusion Dependence patients with [Hb] < 11 g/dL				

The RADeep uRADAR module for standardized collection of uRADs data was developed in a REDcap web application.

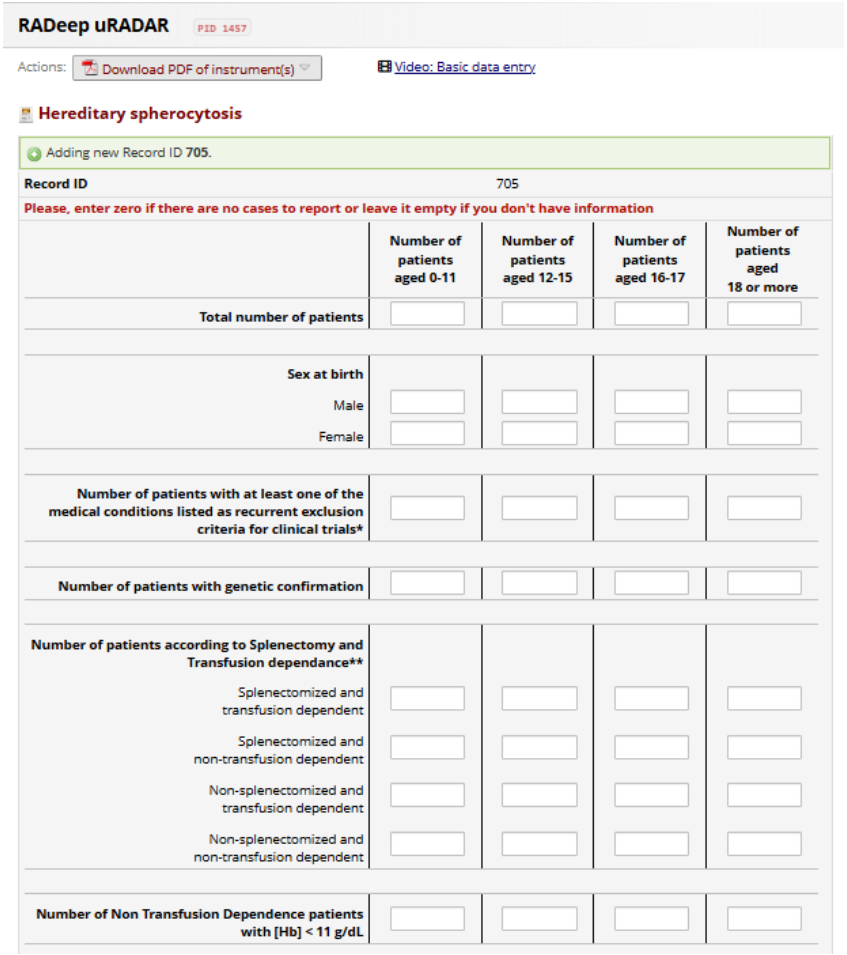
We gathered disaggregated data by age ranges (0-11, 12-15, 16-17 and ≥18 yo) on:

- Sex at birth (Male, Female)
- Genetic confirmation
- Number of patients with at least one of the medical conditions listed as recurrent exclusion criteria for clinical trials
- Therapeutic intervention: splenectomy and/or blood transfusion dependence
- Anemia is considered as Hb <11g/dL in NTD patients.

Transfusion dependent ≥3 separate events in the last 12 months

Severity based on therapeutic intervention and anemia is analyzed for >12yo.

uRADAR: Data collection



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Splenectomized and non-transfusion dependent				
Non-splenectomized and transfusion dependent				
Non-splenectomized and non-transfusion dependent				
Number of Non Transfusion Dependence patients with [Hb] < 11 g/dL				

Number of patients with at least one of the medical conditions listed as recurrent exclusion criteria for clinical trials*

- Succesful HSCT or gene therapy;
- Karnofsky Index < 50 in adults or Lansky < 50 in children;
- Pulmonary hypertension requiring more than 1 therapeutic agent;
- Poorly controlled hypertension refractory to medical management;
- Heart failure NYHA C or D;
- Severe liver fibrosis (F3 or more), liver chirrosis, active HVB or HCV infection;
- Iron overload CTCAE v5.0 G4;
- Active hematologic or solid organ malignancy (not including non-melanoma skin cancer or another carcinoma in situ);
- End stage renal disease or requirement for chronic dialysis;
- Intellectual disability or other mental health diagnosis that prevents from giving consent

uRADAR: Results

- Data from 5,623 patients from 82 centers (13 EU countries, Norway and United Kingdom) has been collected
  - 3,146 (56%) Hereditary Spherocytosis (HS)
  - 1,175 (21%) G6PD
  - 1,302 (23%) uRAD.
- The cohort has a balanced age and sex distribution, except for X-linked diseases.
- Patients with genetic confirmation:

Age	Total	Total	Adult Total	Adult Total	Pediatric Total	Pediatric Total
Disease Group	**Number of patients**	**% Genetic confirmation**	**Number of patients**	**% Genetic confirmation**	**Number of patients**	**% Genetic confirmation**
HS	3146	25%	1529	30%	1617	21%
G6PD	1175	31%	387	52%	788	21%
uRADs	**1302**	**78%**	**851**	**83%**	**451**	**68%**
TOTAL	5623	39%	2767	49%	2856	29%

- We collected 21 patients with sitosterolemia, 175 unstable hemoglobinopathies and 60 with congenital methemoglobinemia. These numbers are higher than expected suggesting an under-representation of these diseases in available literature.

uRADAR: Results

Disease	Pediatric and Adult	Pediatric and Adult Severity	Pediatric Exclusion Criteria %	Adult Exclusion Criteria %	Pediatric and Adult Exclusion Criteria %	[Hb] < 11 g/dL Ped %	[Hb] < 11 g/dL Adult %	[Hb] < 11 g/dL Ped+Adult %	Ped Splenectomized + TD	Adult Splenectomized + TD	Total Splenectomized + TD	Total Non Splenectomized + NTD
Pyruvate kinase deficiency	415	330	1,2%	5,4%	3,3%	33,1%	54,5%	43,9%	6,2%	12,0%	10,34%	52%
Glucophosphate isomerase deficiency	10	8	0,0%	0,0%	0,0%	60,0%	33,3%	50,0%	0,0%	0,0%	0,00%	40%
Glucose-6-phosphate dehydrogenase deficiency	1175	701	0,4%	4,9%	2,0%	29,2%	23,3%	27,1%	0,0%	0,0%	0,00%	98%
Rare constitutional hemolytic anemia due to an enzyme disorder (Other than PKD, GPI, G6PD)	36	27	0,0%	10,5%	7,4%	37,5%	36,8%	37,0%	0,0%	5,3%	5,00%	60%

RBC enzyme defects:

- 1,600 patients: 1,175 G6PD deficiency, 415 PKD and 46 Other.
- Even G6PD deficiency is a non-severe disease in most cases, we detected 27,1% anemic patients.
- In PKD 48% required therapeutic intervention. 54,5% adults were anemic and 10,3% remained TD after splenectomy, twice as reported for other ultra-rare enzyme defects.

uRADAR: Results

Disease	Pediatric and Adult	Pediatric and Adult Severity	Pediatric Exclusion Criteria %	Adult Exclusion Criteria %	Pediatric and Adult Exclusion Criteria %	[Hb] < 11 g/dL Ped %	[Hb] < 11 g/dL Adult %	[Hb] < 11 g/dL Ped+Adult %	Pediatric Splenectomized + TD	Adult Splenectomized + TD	Total Splenectomized + TD	Total Non Splenectomized + NTD
Hereditary spherocytosis	3146	1749	0,9%	7,5%	3,7%	28,4%	15,5%	23,0%	0,0%	0,4%	0,27%	54%
Hereditary elliptocytosis	162	121	0,0%	5,8%	2,5%	23,2%	32,7%	27,3%	0,0%	0,0%	0,00%	91%
Overhydrated hereditary stomatocytosis	17	15	0,0%	0,0%	0,0%	50,0%	36,4%	40,0%	0,0%	0,0%	0,00%	92%
Dehydrated hereditary stomatocytosis	122	88	0,0%	6,1%	4,5%	36,4%	21,2%	25,0%	0,0%	0,0%	0,00%	85%
Sitosterolemia	21	14	25,0%	0,0%	7,1%	0,0%	20,0%	14,3%	0,0%	0,0%	0,00%	100%

Membranopathies:

- 3,468 patients: 3,146 HS, 162 Hereditary elliptocytosis-HE, 122 dehydrated hereditary stomatocytosis-DHS and 38 Other
- In the HS group 46% required therapeutic intervention and 23,0% were anemic. Only 3 patients (0,27%) remained TD after splenectomy.
- HE is usually not severe, nevertheless 9% required therapeutic intervention and 27,3% were anemic.
- In DHS, 15% required therapeutic intervention and 25,0% were anemic.

uRADAR: Results

Disease	Total Pediatric and Adult	Total Pediatric and Adult Severity	Total Pediatric Exclusion Criteria %	Total Adult Exclusion Criteria %	Total Pediatric and Adult Exclusion Criteria %	[Hb] < 11 g/dL Ped %	[Hb] < 11 g/dL Adult %	[Hb] < 11 g/dL Ped+Adult %	Ped Splenectomized + TD	Adult Splenectomized + TD	Total Splenectomized + TD	Total Non Splenectomized + NTD
Congenital dyserythropoietic anemia type I	46	37	0,0%	0,0%	0,0%	85,7%	43,3%	51,4%	0,0%	0,0%	0,00%	72%
Congenital dyserythropoietic anemia type II	104	79	5,6%	16,4%	13,9%	50,0%	65,6%	62,0%	15,4%	8,2%	9,46%	49%
Congenital dyserythropoietic anemia type III	2	2	0,0%	0,0%	0,0%	0,0%	50,0%	50,0%	0,0%	0,0%	0,00%	50%
Congenital dyserythropoietic anemia type IV	2	2	0,0%	0,0%	0,0%	100,0%	0,0%	50,0%	0,0%	0,0%	0,00%	0%
Congenital atransferrinemia	2	2	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,00%	100%
Aceruloplasminemia	11	10	0,0%	10,0%	10,0%	0,0%	20,0%	20,0%	0,0%	0,0%	0,00%	100%
Microcytic anemia with liver iron overload	2	2	0,0%	0,0%	0,0%	100,0%	0,0%	100,0%	0,0%	0,0%	0,0%	0,0%
IRIDA syndrome	31	29	0,0%	0,0%	0,0%	70,0%	63,2%	65,5%	33,3%	0,0%	4,55%	91%
Severe congenital hypochromic anemia with ringed sideroblasts	11	11	0,0%	11,1%	9,1%	50,0%	77,8%	72,7%	0,0%	0,0%	0,00%	80%
Hereditary methemoglobinemia due to NADH-cytochrome b5 reductase defect or hemoglobin variant	60	45	0,0%	0,0%	0,0%	5,3%	0,0%	2,2%	0,0%	0,0%	0,00%	100%
Thiamine-responsive megaloblastic anemia syndrome	17	10	0,0%	0,0%	0,0%	16,7%	59,0%	80,0%	0,0%	0,0%	0,00%	100%
Constitutional sideroblastic anemia (Other than Thiamine-responsive ...)	56	39	16,7%	12,1%	12,8%	50,0%	27,3%	30,8%	0,0%	9,1%	8,82%	71%
Unstable hemoglobinopathy	175	144	15,0%	4,8%	7,6%	42,5%	21,2%	27,1%	18,2%	1,9%	3%	77%

- CDAs: 154 patients. 45% required therapeutic intervention. 18% were anemic. 6,4% remained TD after splenectomy.
- Ultra-rare iron defects: 46 patients. 6% required therapeutic intervention. 6,3% were anemic. 2,9% remained TD after splenectomy.
- Sideroblastic anemias: 84 patients. 24% required therapeutic intervention. 5,3% were anemic. 6% remained TD after splenectomy.
- Unstable hemoglobinopathy: 175 patients. 23% required therapeutic intervention. 27,1% were anemic. 3,0% remained TD after splenectomy.

uRADAR: Conclusions

Disease	Total Pediatric and Adult	Total Pediatric and Adult Severity	Total Pediatric Exclusion Criteria %	Total Adult Exclusion Criteria %	Total Pediatric and Adult Exclusion Criteria %	[Hb] < 11 g/dL Ped %	[Hb] < 11 g/dL Adult %	[Hb] < 11 g/dL Ped+Adult %	Ped Splenectomized + TD	Adult Splenectomized + TD	Total Splenectomized + TD	Total Non Splenectomized + NTD
Spherocytosis	3146	1749	0,9%	7,5%	3,7%	28,4%	15,5%	23,0%	0,0%	0,4%	0,27%	54%
G6PD	1175	701	0,4%	4,9%	2,0%	29,2%	23,3%	27,1%	0,0%	0,0%	0,00%	98%
uRADs	1302	1015	2,8%	6,2%	4,9%	34,6%	39,6%	37,7%	6,4%	4,9%	5,20%	70%

- Numbers collected for some uRADs are higher than expected suggesting an under-representation of these diseases in available literature.
- Analyzing by age ranges, we noted patients were constantly diagnosed and followed during pediatric care, however about 2/3 are lost during follow-up at adult age.
- 30% of uRADs required a therapeutic intervention, still 39,6 % of adults with an uRAD are anemic, 6,2% would be excluded from a CT, partially due to disease progression and suboptimal management.
- Hereditary Spherocytosis: 46% required therapeutic intervention and 23.0% were anemic, 7,5% would be excluded from a CT
  - ERN-EuroBloodNet SATISFY Phase 2 Trial (NCT05935202).

3831 Satisfy: A Eurobloodnet Multicenter, Single-Arm Phase 2 Trial of Mitapivat in Adult Patients with Erythrocyte Membranopathies and Congenital Dyserythropoietic Anemia Type II – Results from the 8-Week Dose-Escalation Period
Monday, December 9, 2024, 6:00 PM-8:00 PM

- Erythrocyte membranopathies; hereditary spherocytosis (HS) and dehydrated hereditary stomatocytosis (DHSt)
- Congenital dyserythropoietic anemia type II (CDA II)

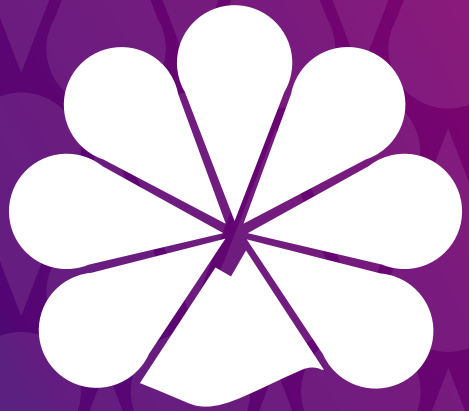
uRADAR Task Force

Country	Member	Centre	Role
ES	María del Mar Mañú Pereira	Vall d'Hebron Barcelona Hospital Campus	Coordination - Principal Investigator
IT	Paola Bianchi	Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milan	Coordination - Principal Investigator
ES	Anna Collado	Vall d'Hebron Barcelona Hospital Campus	Coordination - Clinical Researcher
ES	Maria A. Rodríguez-Sánchez	Vall d'Hebron Barcelona Hospital Campus	Coordination - Data Manager
ES	Sara Reidel	Vall d'Hebron Barcelona Hospital Campus	Coordination - BioStatistician
BE	Béatrice Gulbis	CUB-Hôpital Erasme	Coordination - National Coordinator
BE	Laurence Dedeken	CUB-Hôpital Erasme	National Coordinator
CZ	Dagmar Pospíšilová	Faculty Hospital of Palacky University Olomouc	National Coordinator
CZ	Monika Horváthová	Faculty Hospital of Palacky University Olomouc	National Coordinator
CZ	Pavla Kořalková	Faculty Hospital of Palacky University Olomouc	National Coordinator
DK	Andreas Glenthøj	Copenhagen University Hospital – Rigshospitalet	National Coordinator
FR	Frédéric Galacteros	Assistance Publique-Hôpitaux de Paris, Hôpital Henri-Mondor	National Coordinator
FR	Patricia Aguilar-Martinez	CHU de Montpellier	National Coordinator
DE	Joachim Kunz	Universitätsklinikum Heidelberg	National Coordinator
DE	Andreas Kulozik	Universitätsklinikum Heidelberg	National Coordinator
ES	Elena Cela	Hospital General Universitario Gregorio Marañón	National Coordinator
ES	Marta Morado Arias	Hospital Universitary La Paz	National Coordinator
PT	Celeste Bento	Centro Hospitalar e Universitário de Coimbra, EPE	National Coordinator
NL	Richard van Wijk	University Medical Center Utrecht	National Coordinator
NL	Minke Rab	Erasmus MC: University Medical Center Rotterdam & University Medical Center Utrecht	National Coordinator
NL	Eduard van Beers	University Medical Center Utrecht	National Coordinator
UK	Noémi Roy	Oxford University Hospitals NHS Foundation Trust	National Coordinator
UK	Emma Drasar	Whittington NHS Trust and University College Hospital London	National Coordinator
UK	Ana Ortuño	Whittington NHS Trust and University College Hospital London	National Coordinator

Laboratory of Rare Anemia Disorders

Team Members

- María del Mar Mañú Pereira, MSc, PhD – Head – Principal Investigator
- Anna Collado Gimbert, MD, Clinical PhD Researcher
- *Open position, MD, Clinical PhD Researcher – new hiring*
- Amira Idrizovic, MSc, PhD Researcher
- Sara Reidel, MSc, Biostatistician, PhD Researcher
- Núria Torquet, Data Scientist
- Ángela Menárguez, MD, Clinical Researcher
- Gisela Muraca, MSc, Laboratory Specialist
- Ferran Balbastre, BSc, Technician
- Victoria Gutierrez Valle, MSc, ERN-EuroBloodNet Scientific manager
- *Open position- new, ERN-EuroBloodNet Scientific manager*
- *Open position - replacement, Registries Data Manager*
- Raquel Mosull, BEc, Registries Project Manager
- *Open position - replacement, Registries Project Assistant*
- Claire Diot Lefebvre, MA, Operations Manager
- *Open position - replacement, Project Manager*
- Daiana López, BCom, Dissemination Manager
- Patricia González, FP2 Admin, Financial Admin Manager
- Maria Victoria Cerezo, Innovation Manager
- Carles Garcia, MSc, PhD ENROL Project Manager.



RADeep

Thanks!

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Vall d'Hebron

Vall d'Hebron Research Institute

www.radeepnetwork.eu