Thursdays Webinars

EuroBloodNet

" Pyruvate Kinase Deficiency Clinical management"

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internist-hematologist
University Medical Centre Utrecht, University of Utrecht, ERN-EuroBloodNet subnetwork: Red cells.
Utrecht –the Netherlands
13 February 2020

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the Health Programme
of the European Union

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

Conflicts of interest and disclaimer

Advisory board: Agios

Research support: Novartis, Bayer, Agios, Mechatronics, ZonMW.

Content contants personal opinion of the presenter

Practical issues before starting

- ✓ **30-35min presentation (30 slides max) + 15 min Q&A session**
- ✓ **Microphones will be muted by host to avoid back noise**
- ✓ **Please, stop your video to improve internet conexion**
- ✓ **Send your questions during the presentation through the chat, they will be gathered and answered after the presentations.**

Learning objectives of the webinar

1. PK Deficiency shares the clinical picture with many other hereditary hemolytic anemia's
2. Many complications go unnoticed untill irriversible damage has been done
3. Screening for possible complications should be considered

   (there is often treatment available)

4. This is also applicable for so called "mild" transfusion independent PK Deficiency

NO learing objectives:

1. Diagnosis of PK Deficiency
2. Specific Neonatological/Paediatric aspects of PK Deficiency

Outline

1. Disclosures/ Personal info
2. Introduction
3. Organ damage
4. When to transfuse
5. When to chelate
6. When to splenectomize
7. Stem cell transplantation
8. New treatment options:
    1. Mitapivat
    2. Gene therapy
9. Acknowledgements and Q&A

THE LANCET

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The Global Burden of Disease Study 2010

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Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010

Theo Vos, Abraham D Flaxman, Mohsen Naghavi, Rafael Lozano, Catherine Michaud, Majid Ezzati, Kenji Shibuya, Joshua A Salomon, Safa Abdalla*, Victor Aboyans*, Jerry Abraham*, Ilana Ackerman*, Rakesh Aggarwal*, Stephanie Y Ahn*, Mohammed K Ali*, Miriam Alvarado*, H Ross Anderson*, Laurie M Anderson*, Kathryn G Andrews*, Charles Atkinson*, Larry M Baddour*, Adil N Bahalim*, Suzanne Barker-Collo*, Lope H Barrero*, David H Bartels*, Maria-Gloria Basáñez*, Amanda Baxter*, Michelle L Bell*, Emelia J Benjamin*, Derrick Bennett*, Eduardo Bernabé*, Kavi Bhalla*, Bishal Bhandari*, Boris Bikbov*, Aref Bin Abdulhak*, Gretchen Birbeck*, James A Black*, Hannah Blencowe*, Jed D Blore*, Fiona Blyth*, Ian Bolliger*, Audrey Bonaventure*, Soufiane Boufous*, Rupert Bourne*, Michel Boussinesq*, Tasanee Braithwaite*, Carol Brayne*, Lisa Bridgett*, Simon Brooker*, Peter Brooks*, Traolach S Brugha*, Claire Bryan-Hancock*, Chiara Bucello*, Rachelle Buchbinder*, Geoffrey Buckle*, Christine M Budke*, Michael Burch*, Peter Burney*, Roy Burstein*, Bianca Calabria*, Benjamin Campbell*, Charles E Canter*, Hélène Carabin*, Jonathan Carapetis*, Loreto Carmona*, Claudia Cella*, Fiona Charlson*, Honglei Chen*, Andrew Tai-Ann Cheng*, David Chou*, Sumeet S Chugh*, Luc E Coffeng*, Steven D Colan*, Samantha Colquhoun*, K Ellicott Colson*, John Condon*, Myles D Connor*, Leslie T Cooper*, Matthew Corriere*, Monica Cortinovis*, Karen Courville de Vaccaro*, William Couser*, Benjamin C Cowie*, Michael H Criqui*, Marita Cross*, Kaustubh C Dabhadkar*, Manu Dahiya*, Nabila Dahodwala*, James Damsere-Derry*, Goodarz Danaei*, Adrian Davis*, Diego De Leo*, Louisa Degenhardt*, Robert Dellavalle*, Allyne Delossantos*, Julie Denenberg*, Sarah Derrett*, Don C Des Jarlais*, Samath D Dharmaratne*, Mukesh Dherani*, Cesar Diaz-Torne*, Helen Dolk*, E Ray Dorsey*, Tim Driscoll*, Herbert Duber*, Beth Ebel*, Karen Edmond*, Alexis Elbaz*, Suad Eltahir Ali*, Holly Erskine*, Patricia J Erwin*, Patricia Espindola*, Stalin E Ewoigbokhan*, Farshad Farzadfar*, Valery Feigin*, David T Felson*, Alize Ferrari*, Cleusa P Ferri*, Eric M Fèvre*, Mariel M Finucane*, Seth Flaxman*, Louise Flood*, Kyle Foreman*, Mohammad H Forouzanfar*, Francis Gerry R Fowkes*, Richard Franklin*, Marlene Fransen*, Michael K Freeman*, Belinda J Gabbe*, Sherine E Gabriel*, Emmanuela Gakidou*, Hammad A Ganatra*, Bianca Garcia*, Flavio Gaspari*, Richard F Gillum*, Gerhard Gmel*, Richard Gosselin*, Rebecca Grainger*, Justina Groeger*, Francis Guillemin*, David Gunnell*, Ramyani Gupta*, Juanita Haagsma*, Holly Hagan*, Yara A Halasa*, Wayne Hall*, Diana Haring*, Josep Maria Haro*, James E Harrison*, Rasmus Havmoeller*, Roderick J Hay*, Hideki Higashi*, Catherine Hill*, Bruno Hoen*, Howard Hoffman*, Peter J Hotez*, Damian Hoy*, John J Huang*, Sydney E Ibeanusi*, Kathryn H Jacobsen*, Spencer L James*, Deborah Jarvis*, Rashmi Jasrasaria*, Sudha Jayaraman*, Nicole Johns*, Jost B Jonas*, Ganesan Karthikeyan*, Nicholas Kassebaum*, Norito 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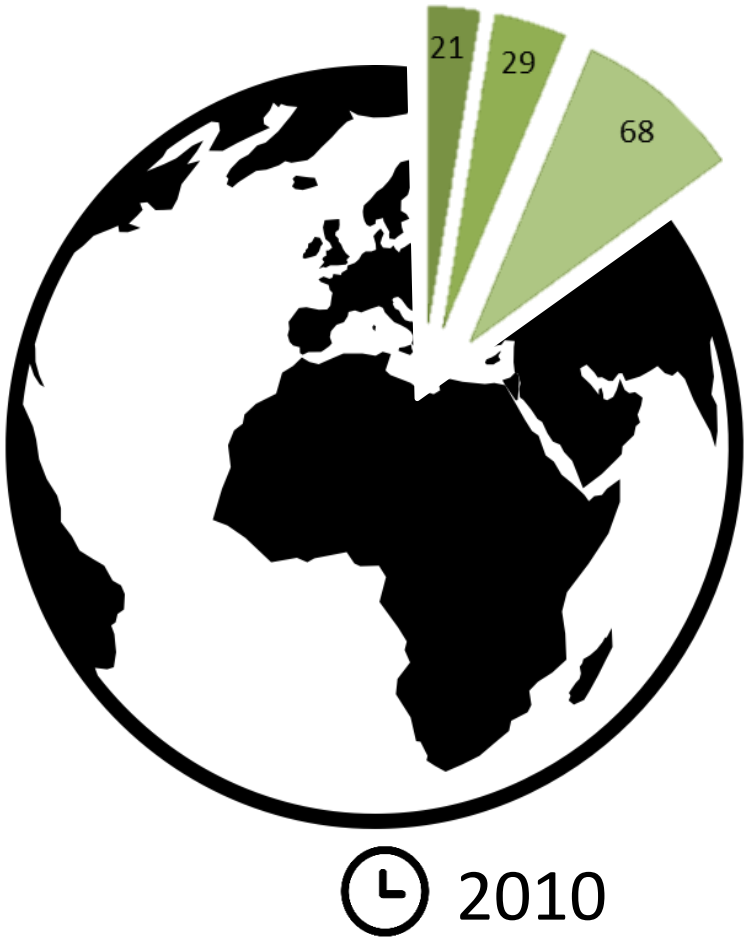
Lidia Morawska*, Rintaro Mori*, Michele E Murdoch*, Michael K Mwaniki*, Kovin Naidoo*, M Nathan Nair*, Luigi Naldi*, K M Venkat Narayan*, Paul K Nelson*, Robert G Nelson*, Michael C Nevitt*, Charles R Newton*, Sandra Nolte*, Paul Norman*, Rosana Norman*, Martin O'Donnell*, Simon O'Hanlon*, Casey Olives*, Saad B Omer*, Katrina Ortblad*, Richard Osborne*, Doruk Ozgediz*, Andrew Page*, Bishnu Pahari*, Jeyaraj Durai Pandian*, Andrea Panozo Rivero*, Scott B Patten*, Neil Pearce*, Rogelio Perez Padilla*, Fernando Perez-Ruiz*, Norberto Perico*, Konrad Pesudovs*, David Phillips*, Michael R Phillips*, Kelsey Pierce*, Sébastien Pion*, Guilherme V Polanczyk*, Suzanne Polinder*, C Arden Pope III*, Svetlana Popova*, Esteban Porrini*, Farshad Pourmalek*, Martin Prince*, Rachel L Pullan*, Kapa D Ramaiah*, Dharani Ranganathan*, Homie Razavi*, Mathilda Regan*, Jürgen T Rehm*, David B Rein*, Guiseppe Remuzzi*, Kathryn Richardson*, Frederick P Rivara*, Thomas Roberts*, Carolyn Robinson*, Felipe Rodriguez De Leòn*, Luca Ronfani*, Robin Room*, Lisa C Rosenfeld*, Lesley Rushton*, Ralph L Sacco*, Sukanta Saha*, Uchechukwu Sampson*, Lidia Sanchez-Riera*, Ella Sanman*, David C Schwebel*, James Graham Scott*, Maria Segui-Gomez*, Saeid Shahraz*, Donald S Shepard*, Hwashin Shin*, Rupak Shivakoti*, David Singh*, Gitanjali M Singh*, Jasvinder A Singh*, Jessica Singleton*, David A Sleet*, Karen Sliwa*, Emma Smith*, Jennifer L Smith*, Nicolas J C Stapelberg*, Andrew Steer*, Timothy Steiner*, Wilma A Stolk*, Lars Jacob Stovner*, Christopher Sudfeld*, Sana Syed*, Giorgio Tamburlini*, Mohammad Tavakkoli*, Hugh R Taylor*, Jennifer A Taylor*, William J Taylor*, Bernadette Thomas*, W Murray Thomson*, George D Thurston*, Imad M Tleyjeh*, Marcello Tonelli*, Jeffrey A Towbin*, Thomas Truelsen*, Miltiadis K Tsilimbaris*, Clotilde Ubeda*, Eduardo A Undurraga*, Marieke J van der Werf*, Jim van Os*, Monica S Vavilala*, N Venketasubramanian*, Mengru Wang*, Wenzhi Wang*, Kerrianne Watt*, David J Weatherall*, Martin A Weinstock*, Robert Weintraub*, Marc G Weisskopf*, Myrna M Weissman*, Richard A White*, Harvey Whiteford*, Steven T Wiersma*, James D Wilkinson*, Hywel C Williams*, Sean R M Williams*, Emma Witt*, Frederick Wolfe*, Anthony D Woolf*, Sarah Wulf*, Pon-Hsiu Yeh*, Anita K M Zaidi*, Zhi-Jie Zheng*, David Zonies*, Alan D Lopez†, Christopher J L Murray†‡

Lancet, 15 dec 2012, 4 jan 2013

Years Lived with Disability (YLD)



6,916,000,000

772,000,000

dm	21,000,000
copd	29,000,000
anemia	68,000,000

Lancet, 15 dec 2012, 4 jan 2013

Icons: C Shannon, J Cabesaz, A Coscovelnita, M Vanco.

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Network Hematological Diseases (ERN EuroBloodNet)

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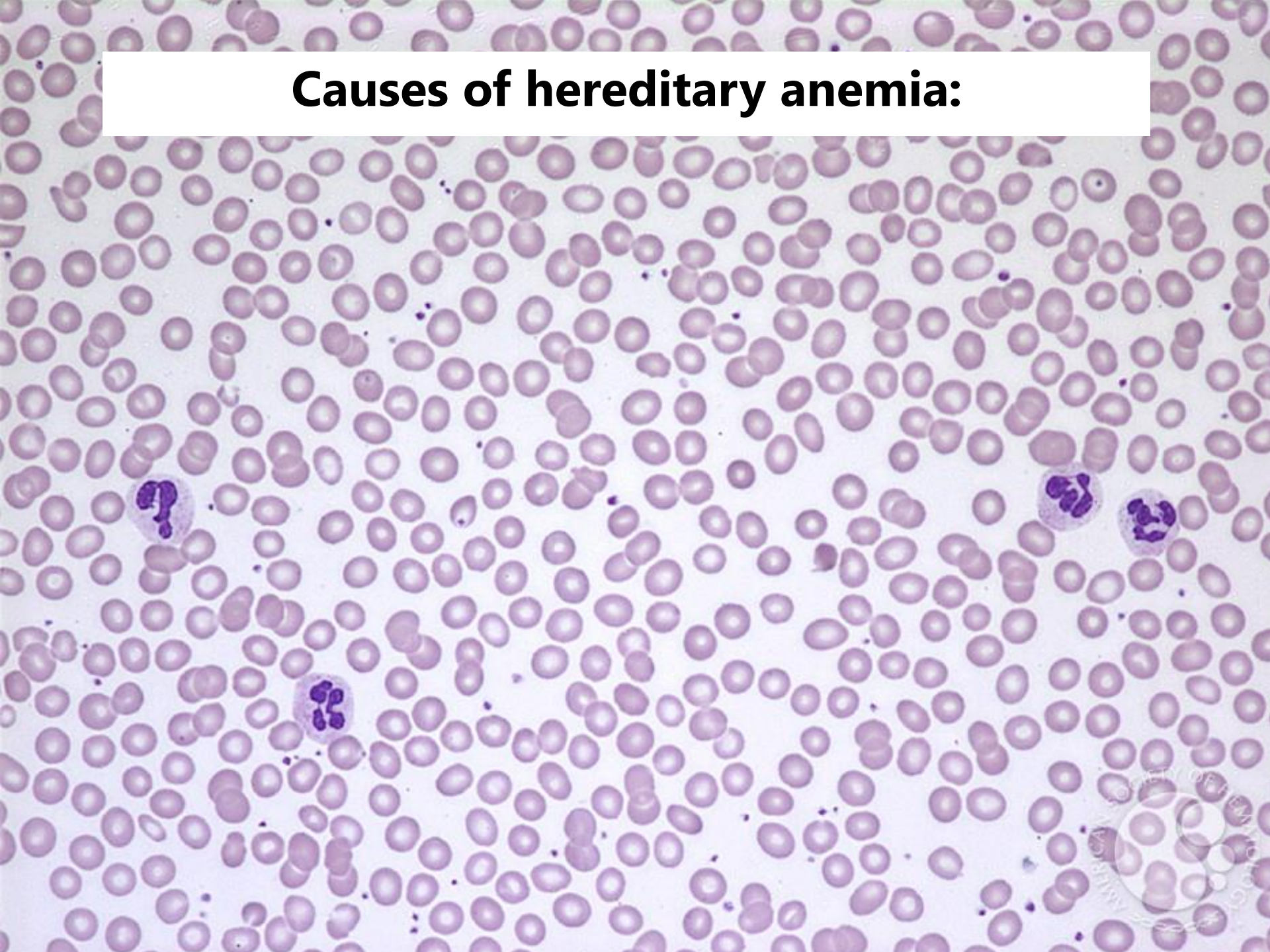
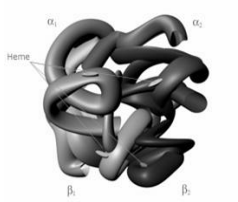
Global causes of anemia YLD:

Sex	Cause	Global	AP HI	Eurp Western	Australasia	NA HI	Eurp Central	LA Southern	Eurp Eastern	Asia East	LA Tropical	LA Central	Asia SE	Asia Central	LA Andean	NA/ME	Caribbean	Asia South	Oceania	SSA Southern	SSA East	SSA Central	SSA West
Females	Iron-deficiency anemia	1	1	8	1	11	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Males	Iron-deficiency anemia	2	2	4	2	13	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Males	Hookworm disease	3	30	11	3	12	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Females	Hookworm disease	4	28	10	4	10	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Females	Sickle cell disorders	5	6	1	7	2	7	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Females	Thalassemias	6	5	5	3	5	3	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Males	Sickle cell disorders	7	3	2	8	1	13	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Females	Malaria	8	12	12	11	9	11	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Males	Thalassemias	9	8	10	5	9	6	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Males	Malaria	10	13	13	12	8	12	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Females	Gastritis and duodenitis	30	11	11	23	10	24	22	24	27	28	18	29	23	30	29	31	27	31	31	31	29	31
Females	G6PD deficiency	31	27	20	25	21	25	29	28	31	34	27	26	27	29	31	32	22	32	32	27	32	28
Females	Maternal hemorrhage	32	29	19	27	15	26	27	25	21	29	25	27	24	25	33	30	29	20	28	29	25	32
Males	Gastritis and duodenitis	33	31	25	29	18	28	31	29	29	33	33	33	30	33	34	35	31	33	35	33	33	34
Males	G6PD deficiency	34	26	28	26	16	27	30	26	30	32	30	30	26	32	32	33	33	28	33	35	30	33
Males	Peptic ulcer disease	35	25	29	28	19	29	28	27	34	35	32	32	28	31	35	34	32	27	34	34	35	35
Females	Peptic ulcer disease																						

Causes of hereditary anemia:



Causes of hereditary hemolytic anemia (HHA)

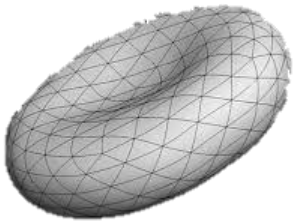


Hemoglobin disorder:

- Hemoglobinopathies
- Thalassemia's

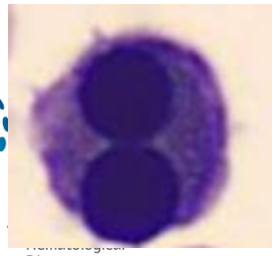
Red cell enzyme disorders (non-sperocytic HHA):

- G6PD- Deficieny
- Pyruvate Kinase Deficieny



Red cell membrane disorders :

- Spherocytosis
- Stomatocytosis



Other:

- Congenitale dyserythropoietic anemia's (CDA)

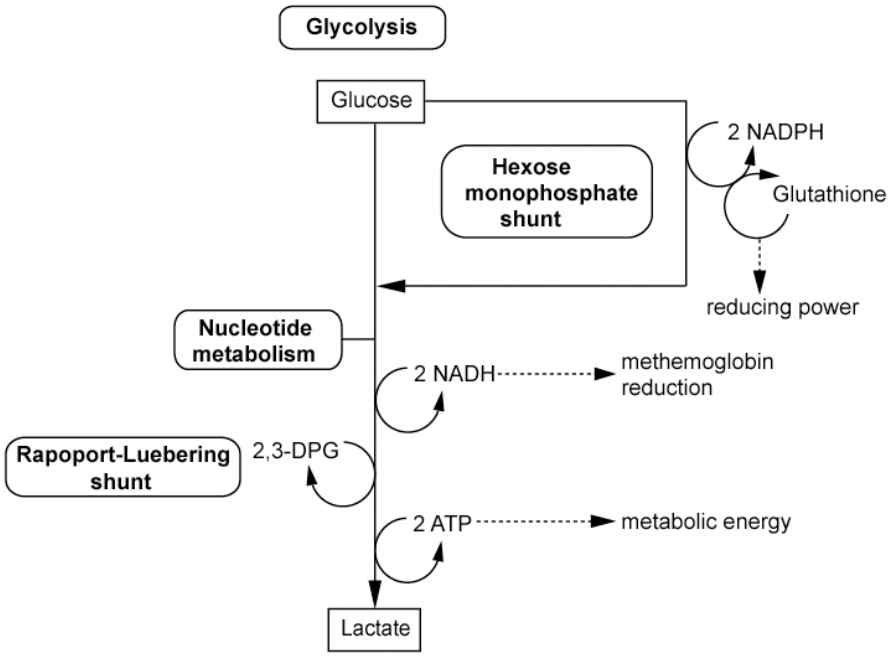
Enzymes of the red blood cell

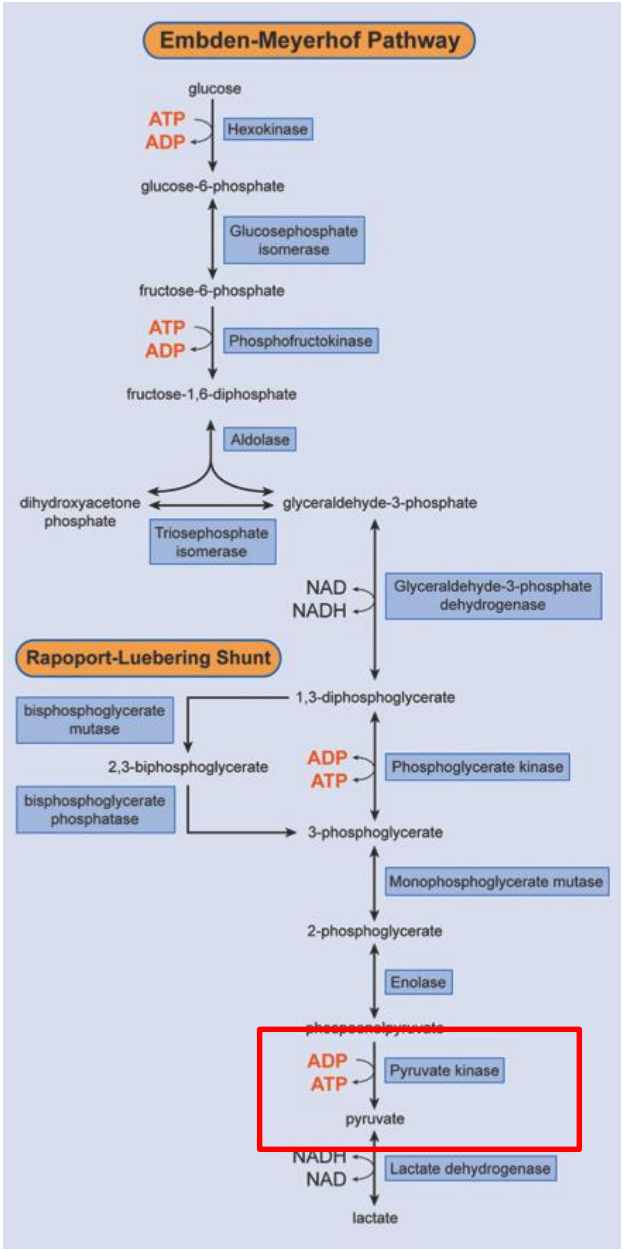
University Medical Center Utrecht

6-Phosphogluconate dehydrogenase
6-Phosphogluconolactonase
Acetylcholinesterase
Adenine phophoribosyl transferase
Adenosine deaminase
Adenylate kinase
Aldolase
AMP deaminase
Bisphosphoglycerate mutase
Carbonic anhydrase I
Carbonic anhydrase II
Catalase
Cytochrome b5 reductase
δ-ALA dehydrase
Enolase
Galactokinase
Galactose-1-P-uridyltransferase
γ-Glutamylcysteine synthetase
Glucose phosphate isomerase
Glucose-6-phosphate dehydrogenase
Gluthathione peroxidase
Gluthathione reductase
Glutathione synthetase
Glutathione-S-transferase
Glyceraldehyde 3-phosphate dehydrogenase
Glyoxalase I
Hexokinase
Hypoxanthine-guanine phosphoribosyl transferase
ITPase
Lactate dehydrogenase
NADPH diaphorase
Phosphofructokinase
Phosphoglucomutase
Phosphoglycerate kinase
Pyrimidine-5'-nucleotidase
Pyruvate kinase
Triosephosphate isomerase
Uroporphyrinogen 1 synthase

courtesy Richard van Wijk : R.vanWijk@umcutrecht.nl

Pyruvate kinase (PK)





- Key enzyme of glycolysis: sole source of energy for the red blood cell
- Catalyses the irreversible phosphoryl group transfer from phosphoenolpyruvate to ADP

  pyruvate + ATP

van Wijk. Blood (2005) courtesy Richard van Wijk : R.vanWijk@umcutrecht.nl

RARE DISEASES BIG IMPACT

Source: National Institutes of Health

The various forms of

of

Hereditary hemolytic anemia

are

rare.

Hereditary hemolytic anemia

is

common.

How

Do I

Diagnose

Hereditary hemolytic anemia?

How
Do I
Diagnose
Hereditary hemolytic anemia?

5th March Eurobloodnet webinar:

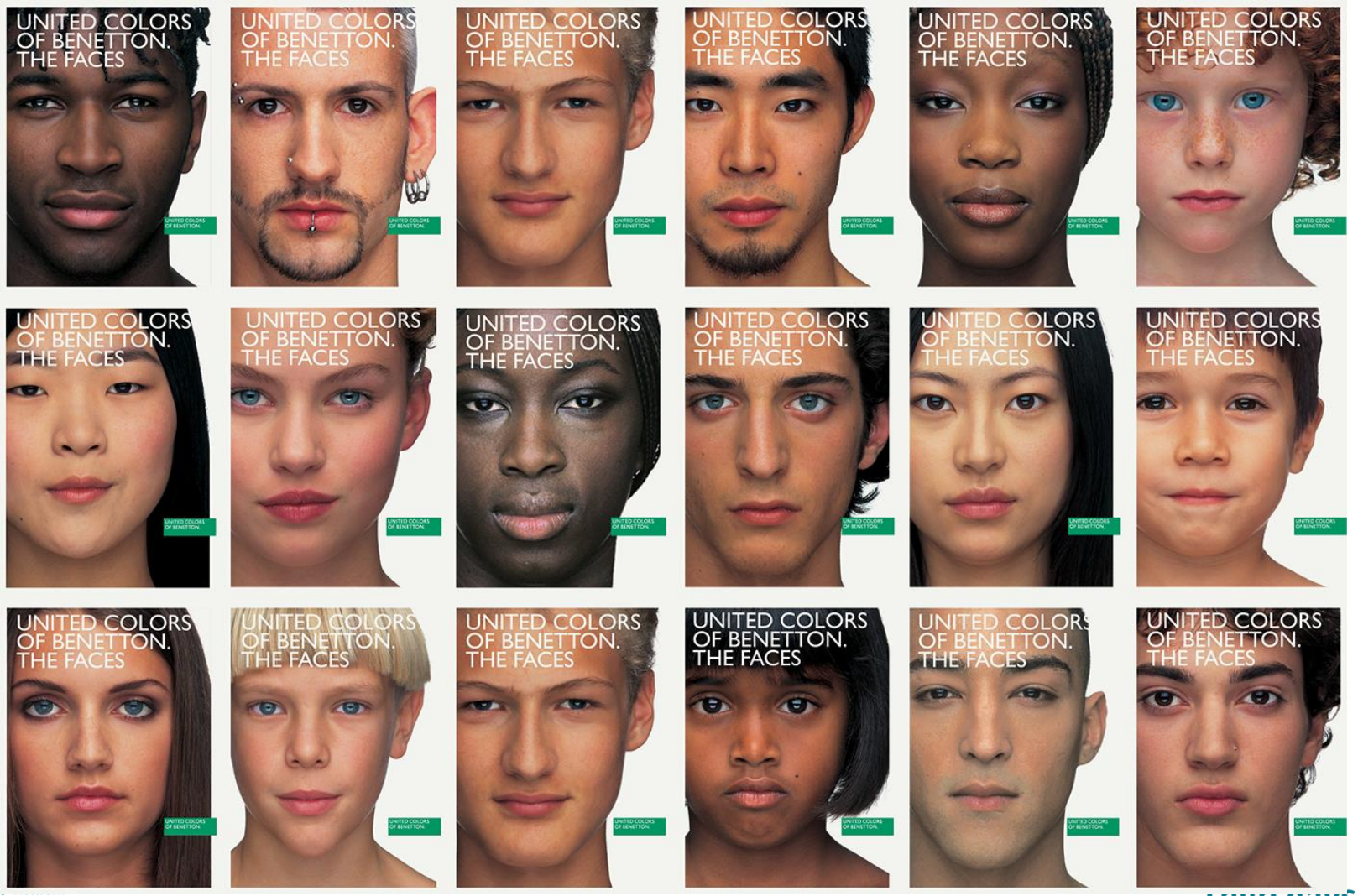
Dr Paola Bianchi: Recommendations on pyruvate kinase deficiency

https://www.eurobloodnet.eu/education/webinars/8/recommendations-on-pyruvate-kinase-deficiency-diagnosis

PK-deficiency: R.vanWijk@umcutrecht.nl (free service)

Organ damage

Patients with the same genotype have different phenotypes



Retinopathy?

Cardiac arrhythmia

Cardiomyopathy

Iron Overload

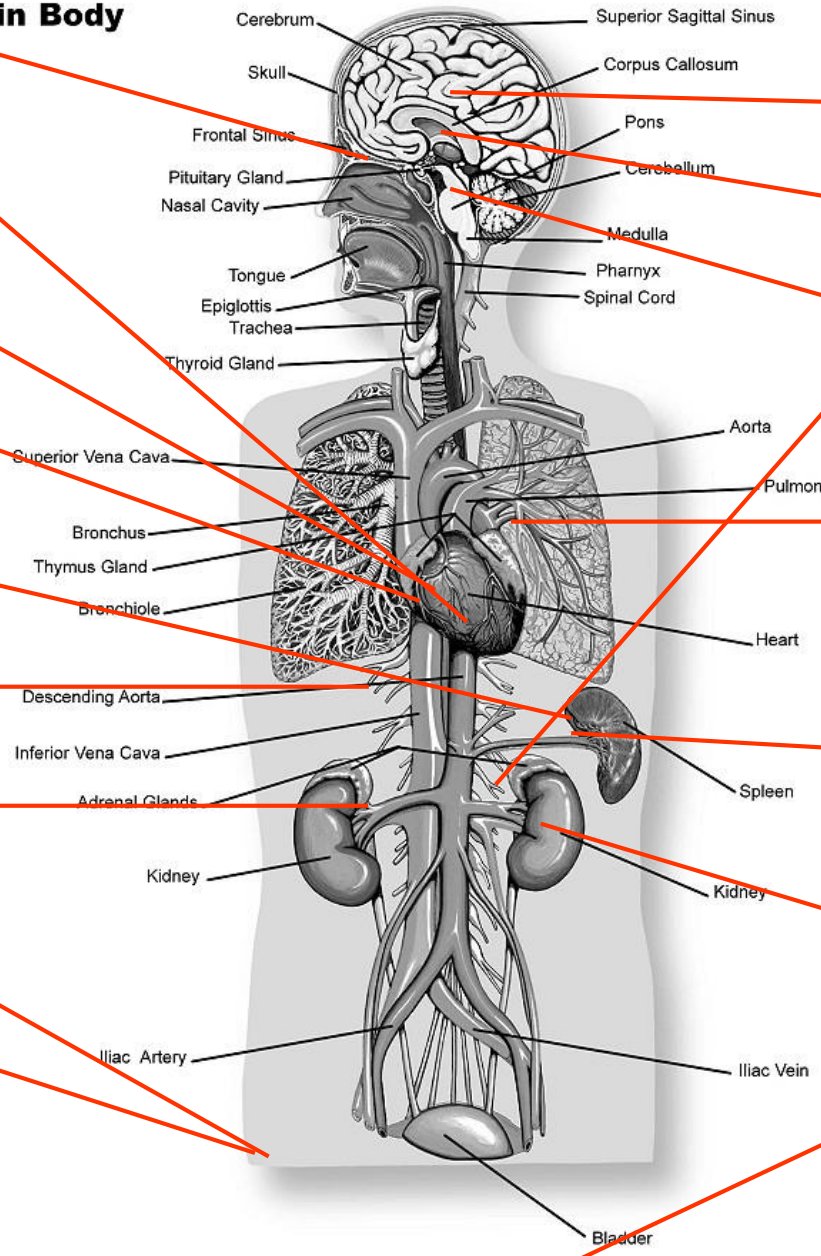
Asplenia

Gallstones

Liver cirrhosis

Osteonecrosis

Osteoporosis



Stroke?

Endocrinopathy

Hearing problems?

Pulmonary hypertension

Extra-medullary Hematopoiesis

Nefropathy

Leg ulcers

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Do all patients with

Hereditary anemia

Share the same problems?

Retinopathy?

Cardiac arrhythmia

Cardiomyopathy

Iron Overload

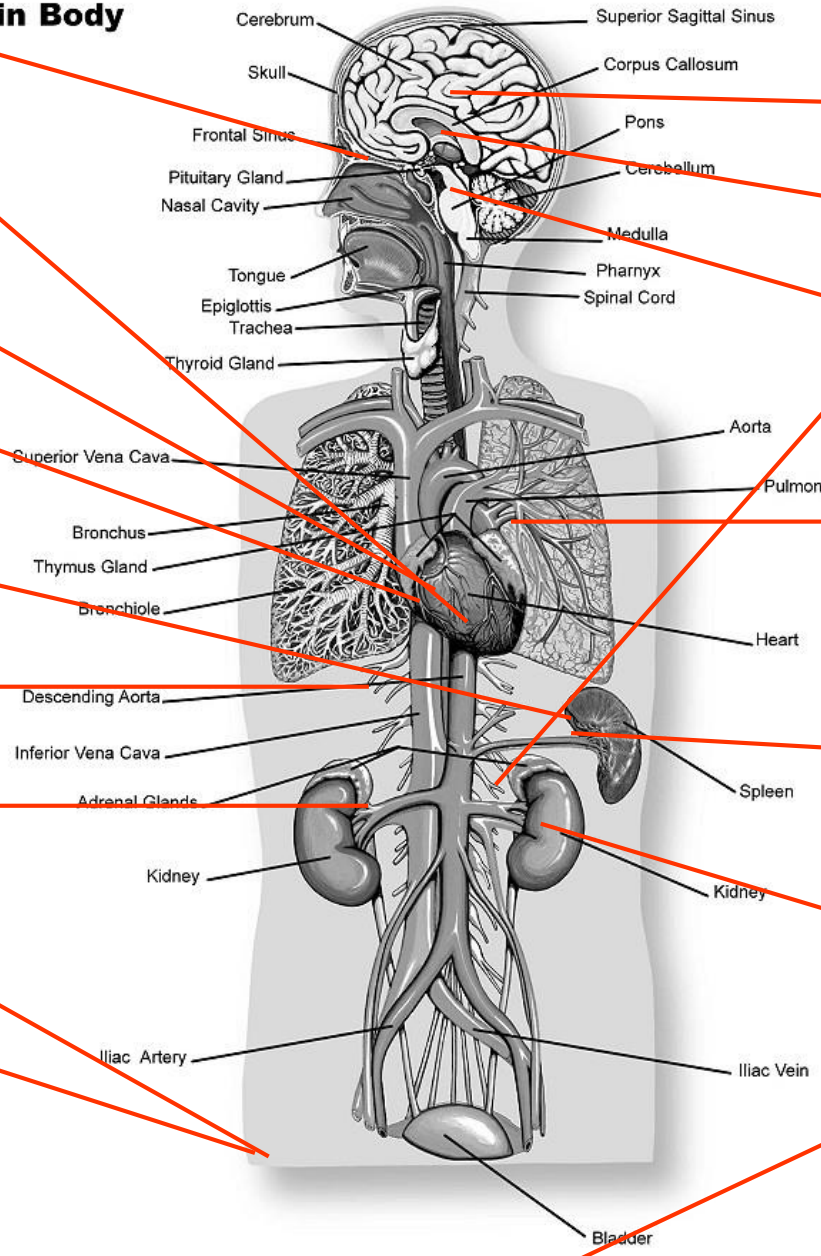
Asplenia

Gallstones

Liver cirrhosis

Osteonecrosis

Osteoporosis



Stroke

Endocrinopathy

Hearing problems?

Pulmonary hypertension

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Leg ulcers

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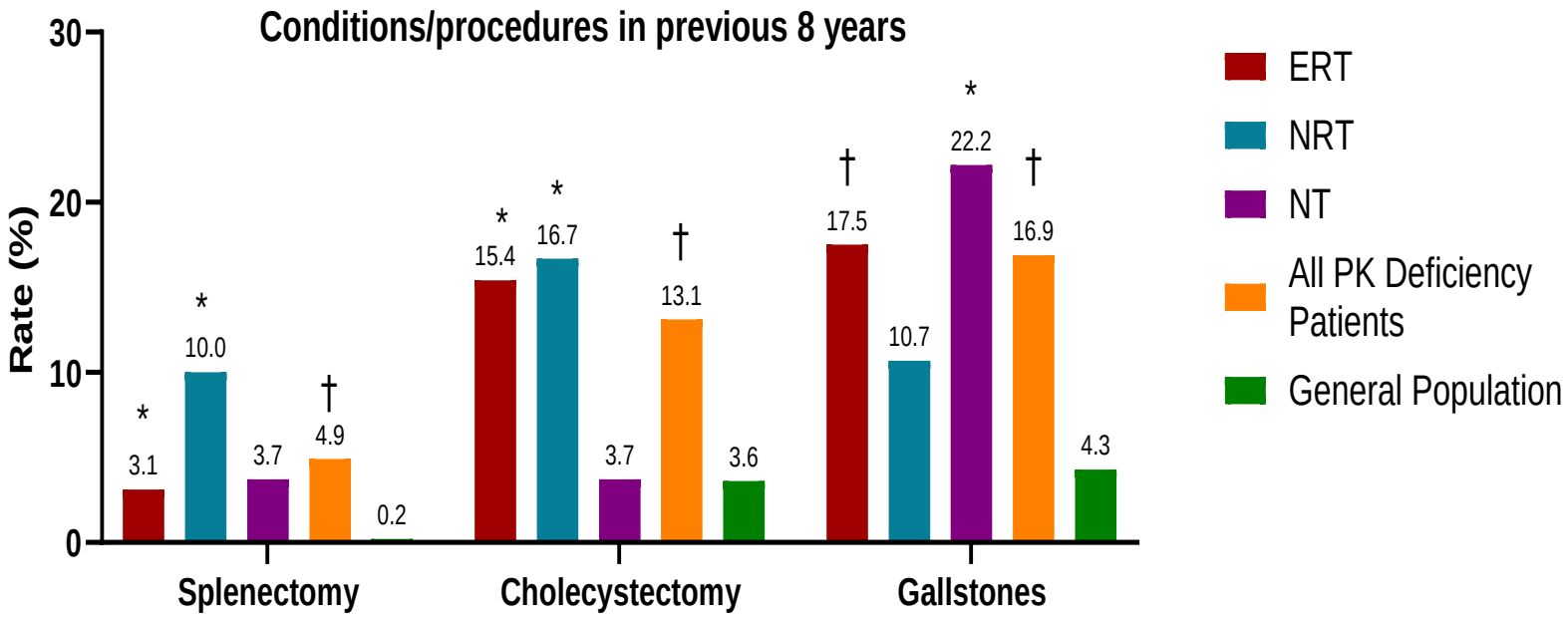
Adults with PK Deficiency Had Higher Rates of Splenectomy, Cholecystectomy and Gallstones Over the Previous 8 Years

Comparisons with the General Population

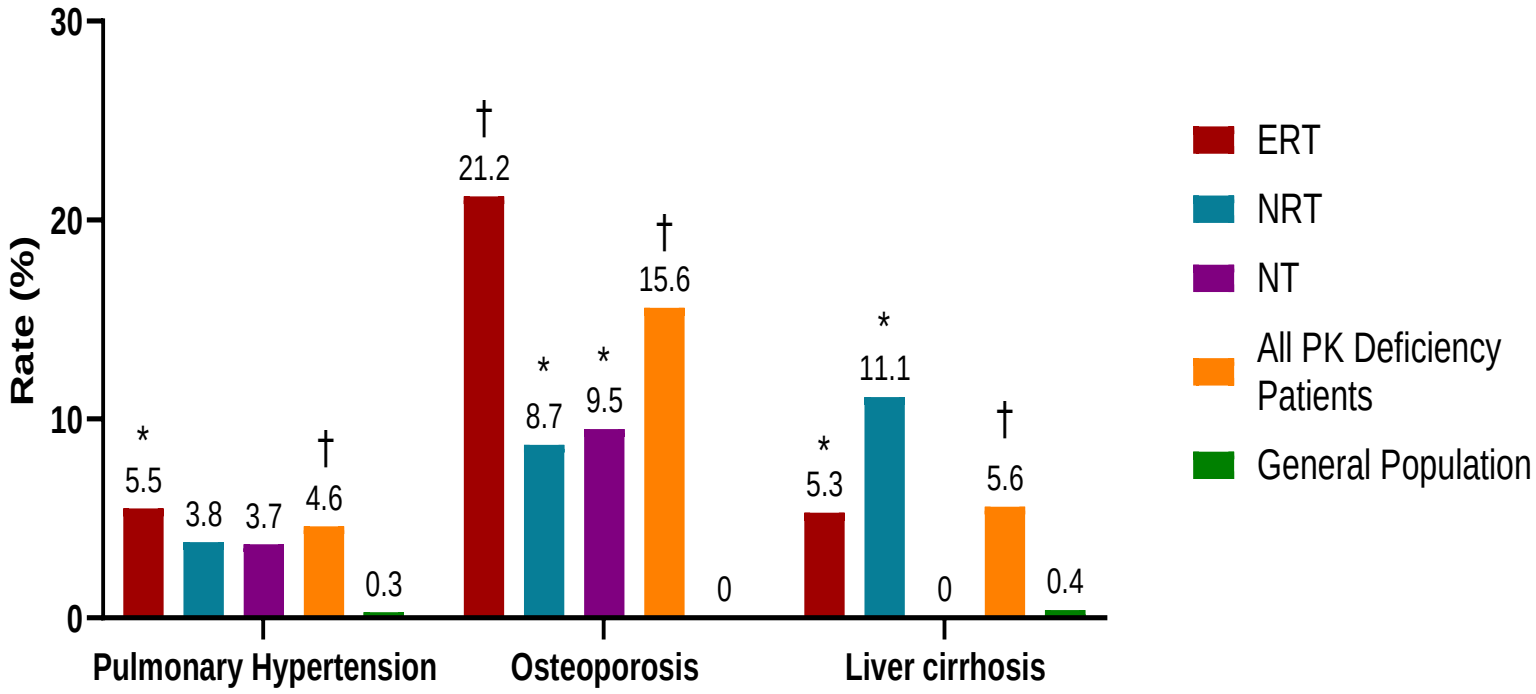


ERT: Ever Regularly Transfused; NRT: Never Regularly Transfused (but transfused at least once); NT: Never Transfused. All comparisons are based on 2-sided Fisher's exact test
***p<0.05 for PK Deficiency NHS population versus matched general population; †p<0.001 for PK Deficiency NHS population versus matched general population**

Boscoe A, Yan Y, Hedgeman E, et al.. ASH 2019, Poster #2175. (courtesy: dr. Hanny Al-Samkari, Harvard, USA)

Adults with PK Deficiency had Higher Lifetime Rates of Pulmonary Hypertension, Osteoporosis and Liver Cirrhosis

Comparisons with the General Population



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Organ damage in Hereditary Nonspherocytic Hemolytic Anemia (HNSHA)

	General population*	HNSHA# (screened for organ damage))	PK deficiency## (non-screened)
N	n.a.	30	254
Pulmonary hypertension**	3%	17%	3%
Thrombotic event	<1%	10%	11%
Iron overload (liver)	<1%	68%	48%
Microalbuminuria	7%	39%	n.r.
Renal failure	4%	3%	n.r.
Cholecystectomy	<1%	73%	40%
Osteoporosis	3%	15%	n.r.
Fractures	7%	0%	17%
Leg ulceration	<1%	7%	2%
Low testosterone	2%	14%	0%
Vitamin D deficiency	49%	50%	n.r.
IGF-1 deficiency	2%	43%	3%

n.r. not reported; IGF: insulin-like growth factor deficiency was defined as >-2 SD from healthy controls

* disease prevalence in the general Dutch population

** defined as tricuspid regurgitant jet flow velocity >2.5m/s by cardiac ultrasound.

#HNSHA: Hereditary Nonspherocytic Hemolytic Anemia. (23 PK deficiency, 4 G6PD deficiency, 2 HK deficiency, 1 GCL deficiency)

Data cited from: Straaten et al Brit J Haematol 2019.

Data cited from: Grace et al. Blood 2018

Treatment of organ damage: examples and suggestions (use Eurobloodnet expertise):

- Microalbuminuria
- Osteoporosis
- Endocrine problems
- Iron overload
- Heart failure

- Leg Ulcers

- Vitamin and Zinc deficiency
- EMH

- ACE-inhibition
- Bisphosphonates
- Suppletion
- Chelation
- Blood transfusion, specific therapy
- Topical nitroglyceride, transfusion
- Suppletion
- Blood transfusion

Organ damage

in

Hemolytic anemia including PKD

is

underdiagnosed

and

prevalent

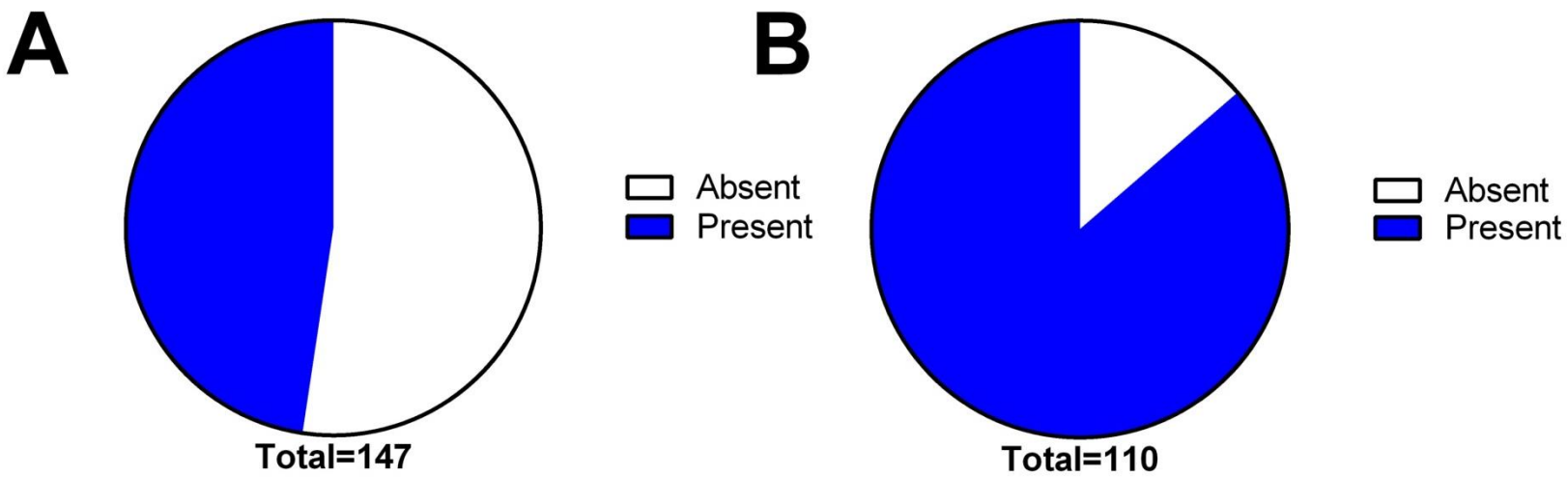
How to

recognise iron overload

in

your patients

Iron overload in Pyruvate kinase deficiency

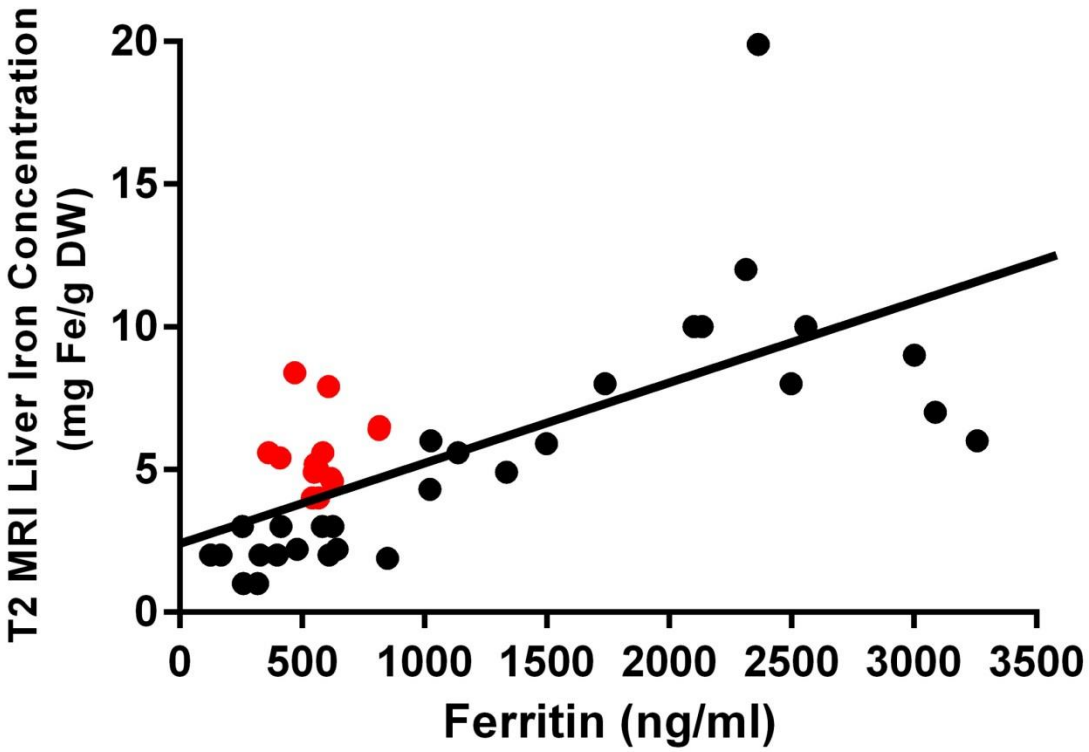


A. Ferritin based

B. MRI based

van Beers et al. Haematologica 2019

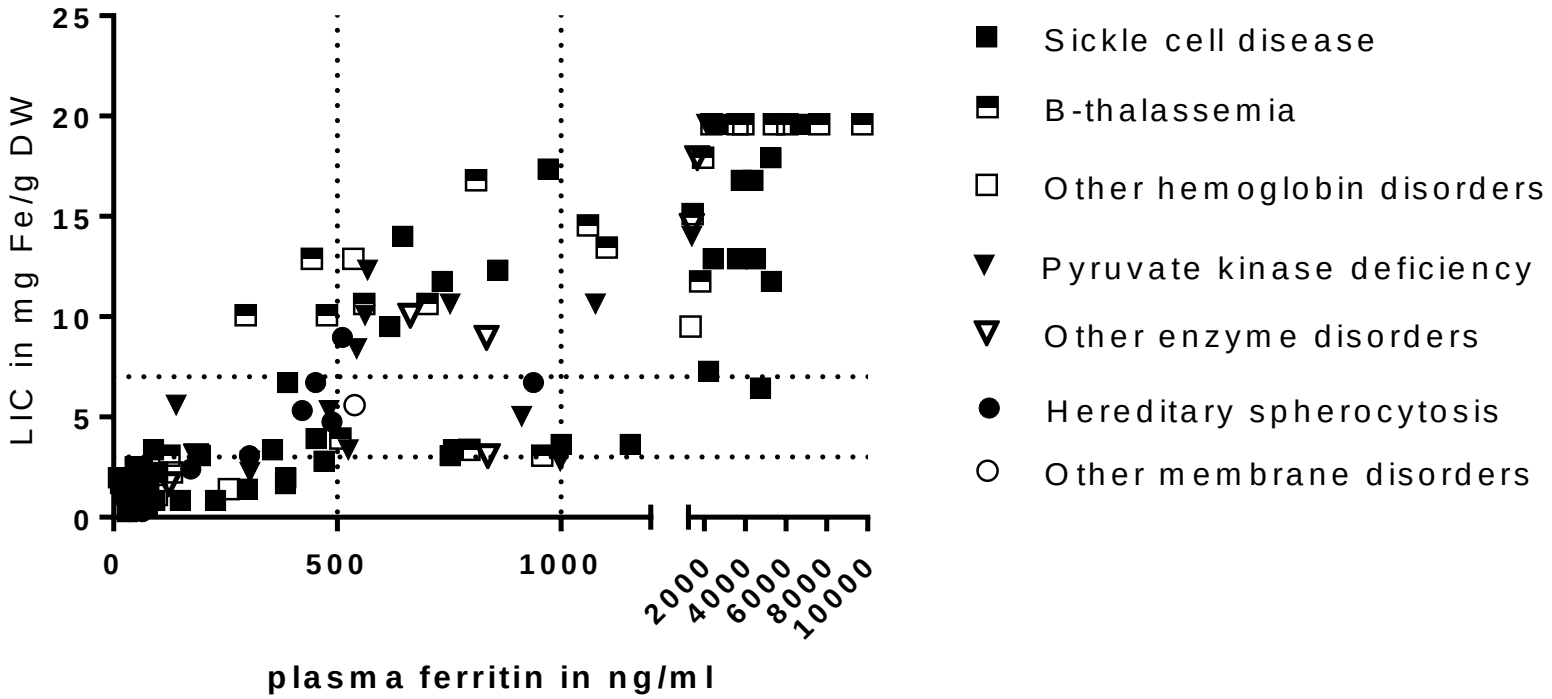
Ferritin versus LIC in PK Deficiency



B. MRI based

van Beers et al. Haematologica 2019

Ferritin versus LIC per disease category



Van Straaten et al. Am J Hematol 2019

Sensitivity of ferritin combined with transferrin saturation to predict iron overload.

Table 3: predictive value of ferritin, TSAT and LIC

	ferritin ≥1000		**ferritin ≥500**		**ferritin ≥500 or TSAT≥45**	
Total *N=112*	LIC≥3	LIC≥7	LIC≥3	LIC≥7	LIC≥3 *N=51*	LIC≥7
Sensitivity	41%	58%	76%	92%	87%	100%

"At a ferritin cut off of 500 ng/mL, the sensitivity for LIC >3 mg/g DW was 90% and the specificity was 67%"

PKD –NHS study:

"In patients with a transferrin saturation >45% or a ferritin >500 ng/ml, the sensitivity to predict LIC >3 mg/g DW was 92%"

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Van Straaten et al. Am J Hematol 2019

Van Beers et al. Haematologica 2019

UMC Utrecht Van Creveldkliniek

Consider to diagnose

iron overload

by

MRI

in all with

TSAT>45%

or

Ferritin>500

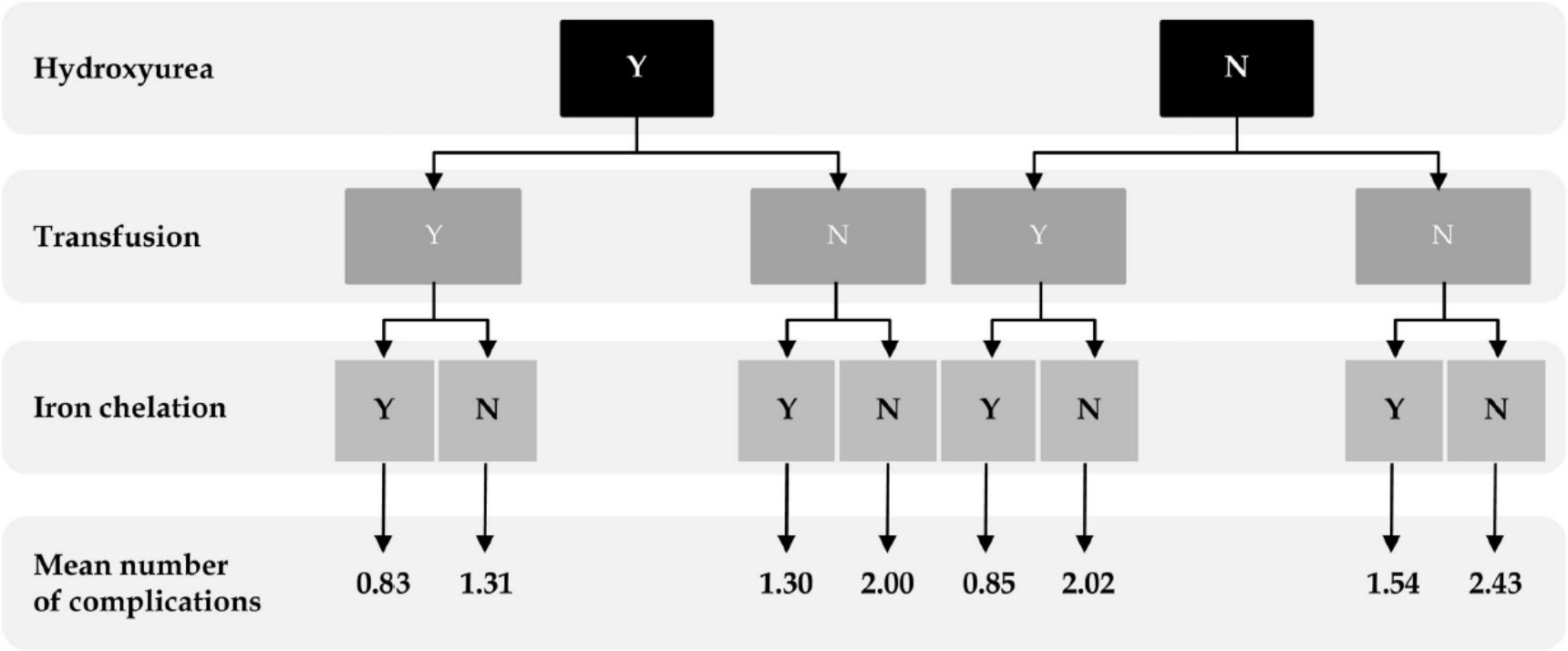
When to

Transfuse

Considerations when to transfuse in PK deficiency

- Controversial topic
- Traditionally: very tolerant to anemia…
- But 2-3 dpg levels are comparable to SCD e.g.
- Aging patient with complications differs from younger patient without complications
- Depends on “needs” or “activity” of patient
- Good chelation is available; iron overload is not a major decision driver
- Antibody formation no major issue when extended matching is performed
- No specific target hemoglobin. *(e.g. do not use Thalassemia targets)*

Organ damage and treatment in thalassemia intermedia



Taher et al. Blood 2010

Considering to

transfuse

is a

personalized medicine

shared decision

When to

Splenectomize

Consider

splenectomy

if patient is

transfusion-dependent

or

severely anemic

Iolascon et al. Haematologica 2017

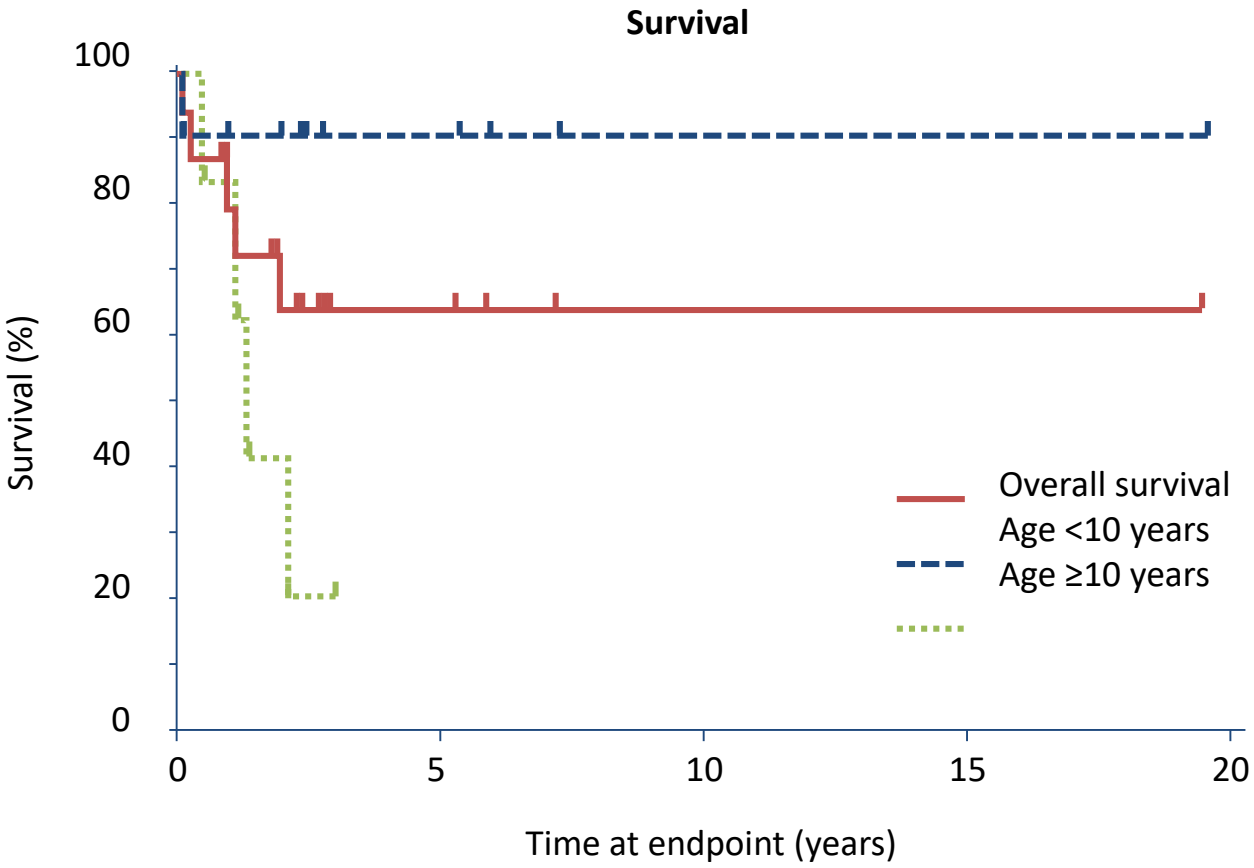
Stem cell transplantation in pyruvate kinase deficiency

Results of stem cell transplantation in PK-deficiency

	Survivor	Non-survivor	*P* value
Age in years	7.5 – 3.0 (0.8-41)	17.4 – 15.2 (6-39)	0.036*
Asian hospital	8/11 (73%)	0/5	0.026*
Splenectomy performed	3/11 (27%)	4/5 (80%)	0.106
Mena Hb (g/dL) (N=13)	6.0 – 5.5 (4,5-7,9)	7.1 – 6.9 (6.0-8.1)	0.112
Pre-transplant ferritin (ng/ml) (n=12)	804 – 771 (206-1650)	2167 – 675 (596-7026)	0.432
Myeloablation	6/11 (55%)	4/5 (80%)	0.588
Graft type			0.507
MSD	2/11 (18%)	0/5	
MUD	6/11 (55%)	3/5 (60%)	
CORD	2/11 (18%)	0/5	
MFD	1/11 (9%	2/5 (40%)	
Transplant source			0.333
Bone marrow	4/11 (36%)	4/5 (80%)	
Peripheral blood	5/11 (45%)	1/5 (20%)	
Cord blood	2/11 (18%)	0/5	
GvHD			0.015*
None	7/11 (64%)	0/5	
Grade 1	1/11 (9%)	0/5	
Grade 2	1/11 (9%)	0/5	
Grade 3	0/11	1/5 (20%)	
Grade 4	2/11 (18)	4/5 (80%	

Straaten et al. *Haematologica* 2018

Results of stem cell transplantation in PK-deficiency



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Strate

UMC Utrecht
Van Creveldkliniek

Stem cell transplantation

can be

curative treatment,

in

pyruvate kinase deficiency,

but…

New treatment options?

DRIVE PK *New England Journal of Medicine* Publication

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Mitapivat in Pyruvate Kinase Deficiency

Rachael F. Grace, M.D., Christian Rose, M.D.,* D. Mark Layton, M.B., B.S., Frédéric Galactéros, M.D., Wilma Barcellini, M.D., D. Holmes Morton, M.D., Eduard J. van Beers, M.D., Hassan Yaish, M.D., Yaddanapudi Ravindranath, M.D., Kevin H.M. Kuo, M.D., Sujit Sheth, M.D., Janet L. Kwiatkowski, M.D., M.S.C.E., Ann J. Barbier, M.D., Ph.D., Susan Bodie, Pharm.D., Bruce Silver, M.D., Lei Hua, Ph.D., Charles Kung, Ph.D., Peter Hawkins, Ph.D., Marie-Hélène Jouvin, M.D., Chris Bowden, M.D., and Bertil Glader, M.D., Ph.D.

ABSTRACT

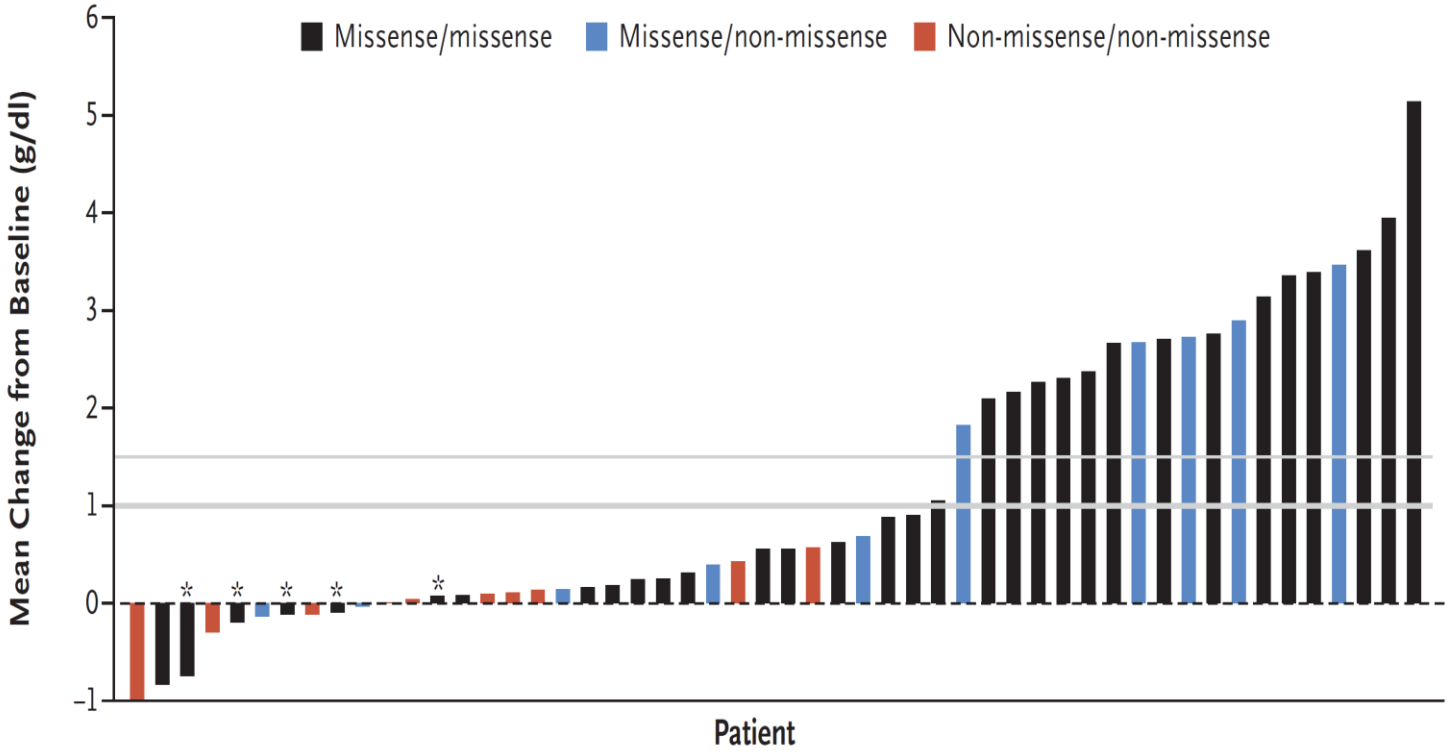
N ENGL J MED 381;10 NEJM.ORG SEPTEMBER 5, 2019

Characteristic	Mitapivat, 50 mg Twice Daily (N=27)	Mitapivat, 300 mg Twice Daily (N=25)	All Patients (N=52)
Sex — no. (%)			
Female	9 (33)	11 (44)	20 (38)
Male	18 (67)	14 (56)	32 (62)
Median age (range) — yr	28 (18–58)	40 (20–61)	34 (18–61)
Race — no. (%)†			
White	22 (81)	21 (84)	43 (83)
Asian	2 (7)	1 (4)	3 (6)
Not reported	2 (7)	1 (4)	3 (6)
Other	1 (4)	2 (8)	3 (6)
PKLR mutation type — no. (%)			
Missense/missense	15 (56)	17 (68)	32 (62)
Missense/non-missense	6 (22)	4 (16)	10 (19)
Non-missense/non-missense	6 (22)	4 (16)	10 (19)
Median hemoglobin (range) — g/dl	9.6 (6.9–12.3)	8.6 (6.5–12.0)	8.9 (6.5–12.3)
Splenectomy — no. (%)‡	23 (85)	20 (80)	43 (83)
Cholecystectomy — no. (%)	19 (70)	19 (76)	38 (73)
Chelation therapy before enrollment — no. (%)	14 (52)	11 (44)	25 (48)
Median ferritin (range) — ng/ml	723 (41–3254)	775 (346–2518)	764 (41–3254)
Osteoporosis — no. (%)	5 (19)	3 (12)	8 (15)
Completion of 24-wk core period — no. (%)§	21 (78)	22 (88)	43 (83)

Grace RF,, et al. *New England Journal of Medicine.* 2019; 381(10):933-944

Average Change in Hemoglobin by *PKLR* Genotype

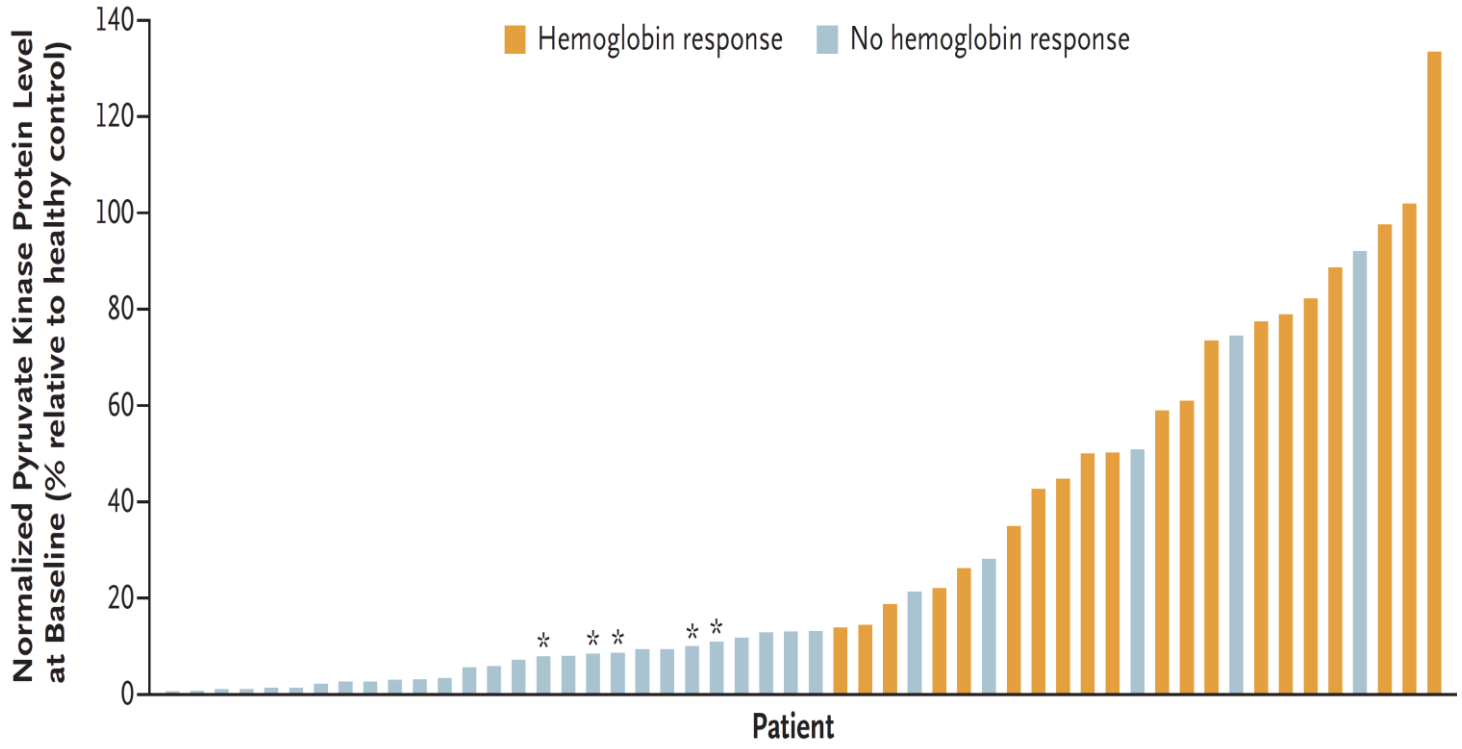
- 50% (26/52) of patients had an increase from baseline of more than 1.0 g/dL in Hemoglobin (Hb) level
  - Mean maximum increase in the Hb was 3.4 g/dL (range 1.1 – 5.8 g/dL)
  - Median time until first observed increase of >1.0 g/dL in Hb was 10 days (range 7 to 187 days)
  - All patients who had an average hemoglobin increase from baseline of >1.0 g/dL had at least one missense *PKLR* mutation



*Patients homozygous for R479H.

Grace RF,, et al. *New England Journal of Medicine.* 2019; 381(10):933-944

Average Change in Hemoglobin by PK-R Protein Level



*Patients homozygous for R479H.

Grace RF,, et al. *New England Journal of Medicine.* 2019; 381(10):933-944

Gene therapy

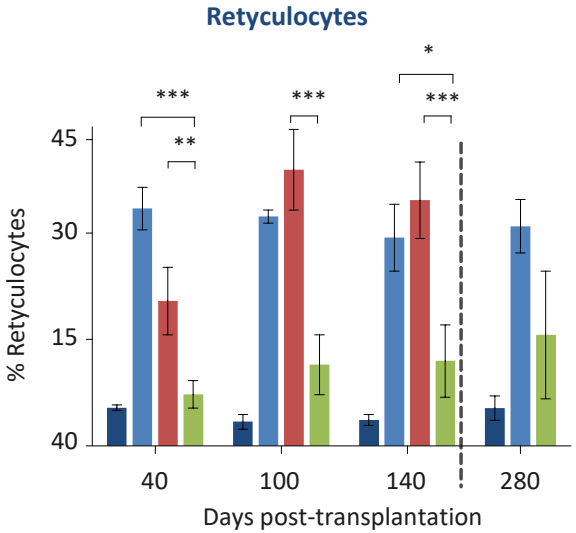
in

pyruvate kinase deficiency

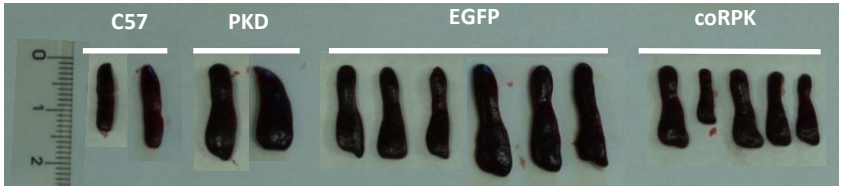
Courtesy: dr. J.C. Segovia
jc.segovia@ciemat.es

Efficacy of PK deficiency gene therapy in mouse model

- Improved hematological parameters:
  - Reb blood cell counts
  - Hemoglobin
  - Hematocrit
  - Retyculocytosis
  - Erythrocyte half-life
  - Erythropoietin levels
  - Erythroid differentiation



- Organs
  - Spleen
  - Liver
    - Iron deposits
    - Extramedullary hematopoiesis



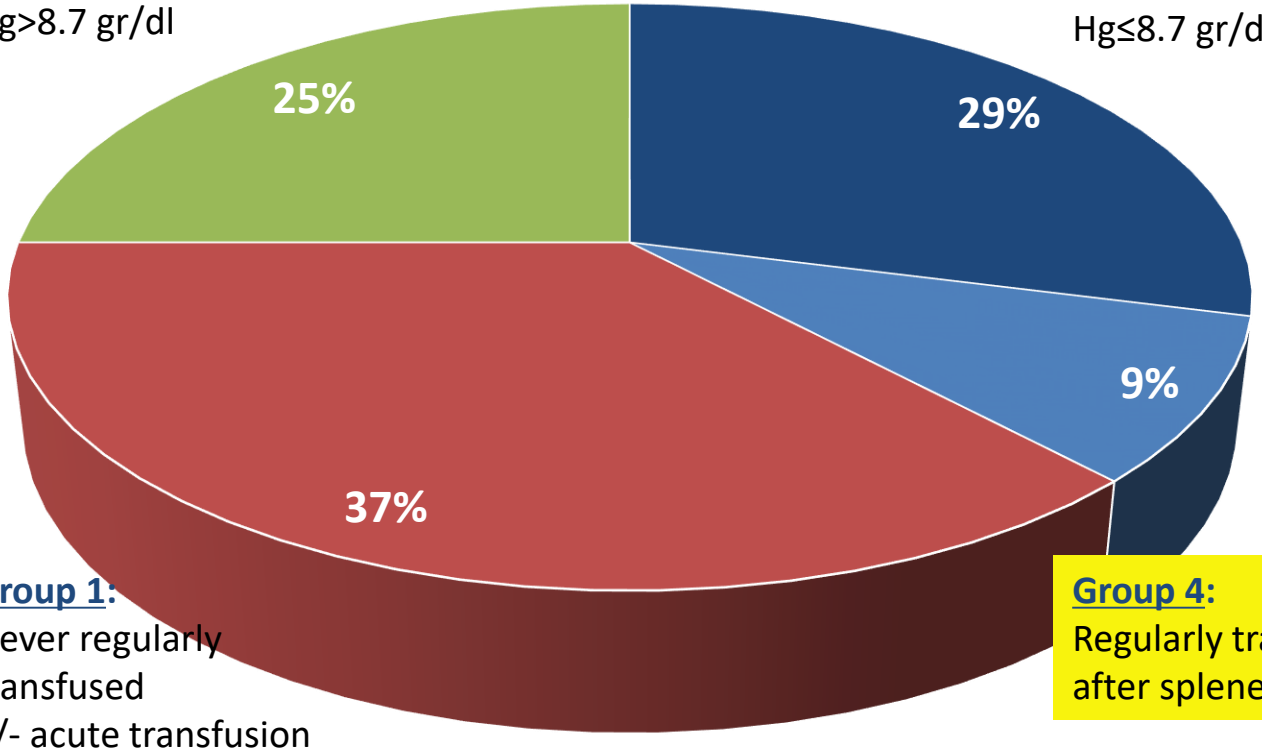
Meza et al. Mol Ther 2009 Courtesy: dr. J.C. Segovia

jc.segovia@ciemat.es

Who are the patients eligible for being enrolled?

Group 2:
Regularly transfused before splenectomy
Less anemic
Hg>8.7 gr/dl

Group 3:
Regularly transfused before splenectomy
Less anemic
Hg≤8.7 gr/dl



Group 1:
Never regularly transfused
+/- acute transfusion

Group 4:
Regularly transfused after splenectomy

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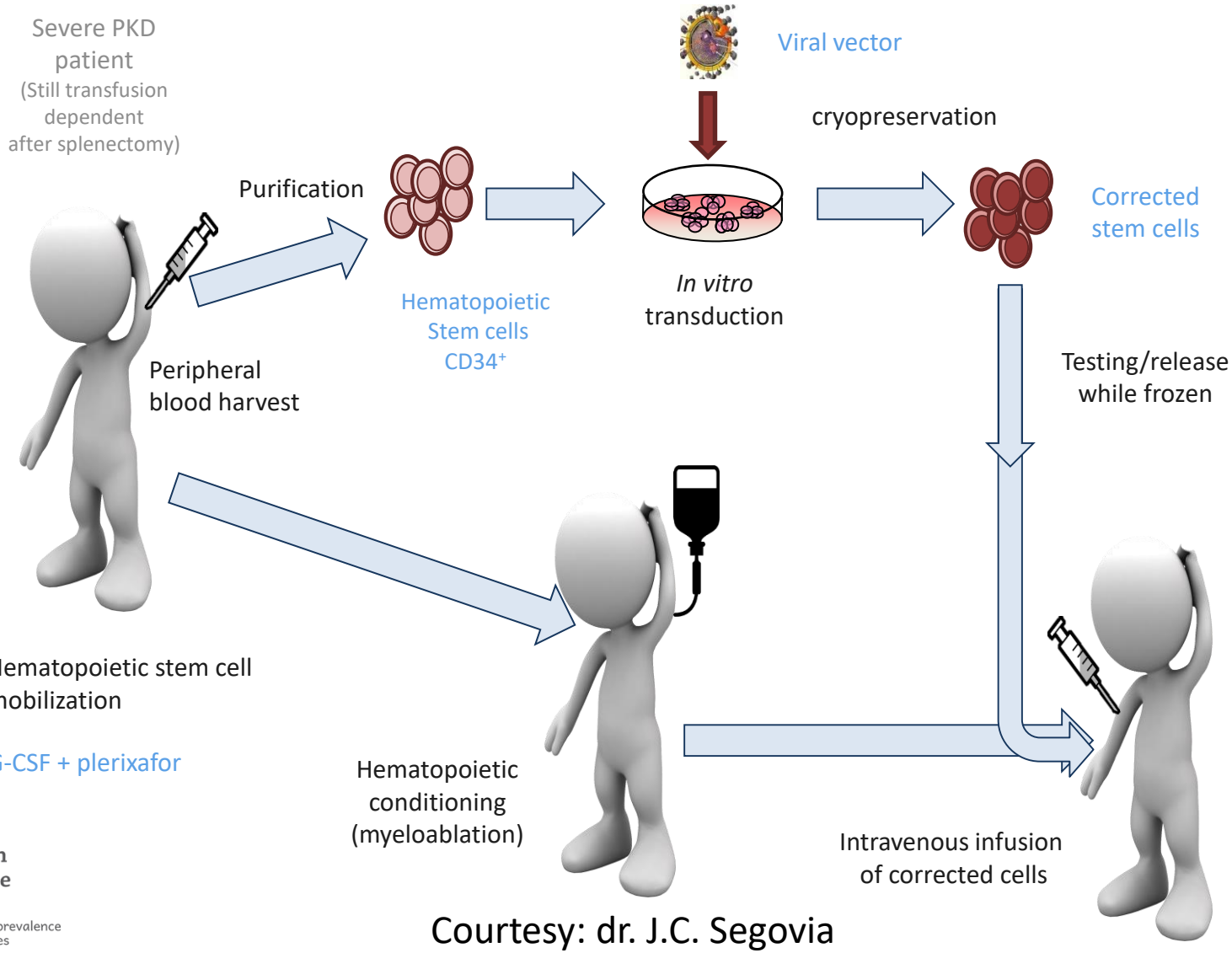
Courtesy: dr. J.C. Segovia
jc.segovia@ciemat.es

Overview of the clinical protocol



Courtesy: dr. J.C. Segovia

jc.segovia@ciemat.es

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Thursdays Webinars

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dr. Hanny Al-Samkari, Harvard, USA
dr. J.C. Segovia Ciemat-Ciberer Madrid Spain
(Q&A gene therapy: jc.segovia@ciemat.es)

Questions: e.j.vanbeers-3@umcutrecht.nl

Take Home

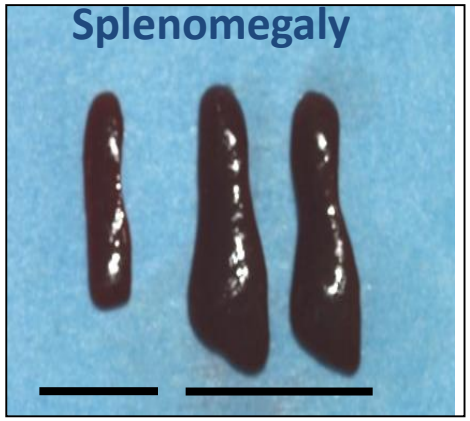
1. PK Deficiency shares the clinical picture with many other hereditary hemolytic anemia's
2. Many complications go unnoticed untill irriversible damage has been done
3. Screening for possible complications should be considered

   (there is often treatment available)

4. This is also applicable for so called "mild" transfusion independent PK Deficiency

Supplemental slides

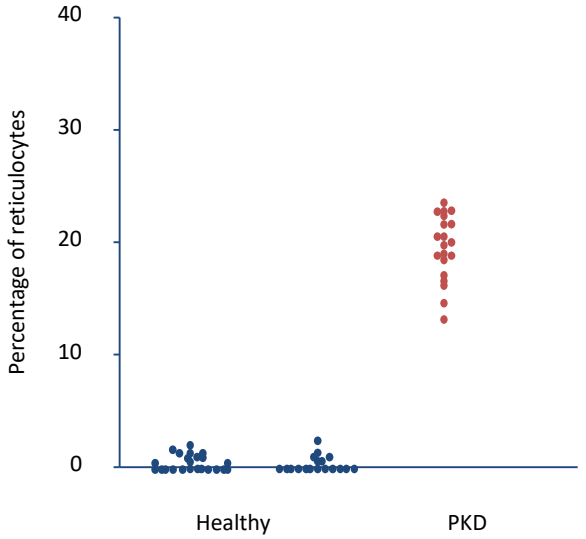
Pyruvate kinase deficiency mouse model



Anemia

Erythrocyte parameters	Mouse strain	
	Healthy mouse	PKD mouse
RBC	10,5 x 10^{12}/L	6,39 x 10^{12}/L
HGB	13,8 g/dL	9,7 g/dl
HCT	46,2%	38,9%

Reticulocytosis



Min-Oo, G. et al., *Nature Genetics* 2003 (4): 257-63

Towards a gene therapy clinical trial for PKD

rocket pharma

Orphan Drug Designation

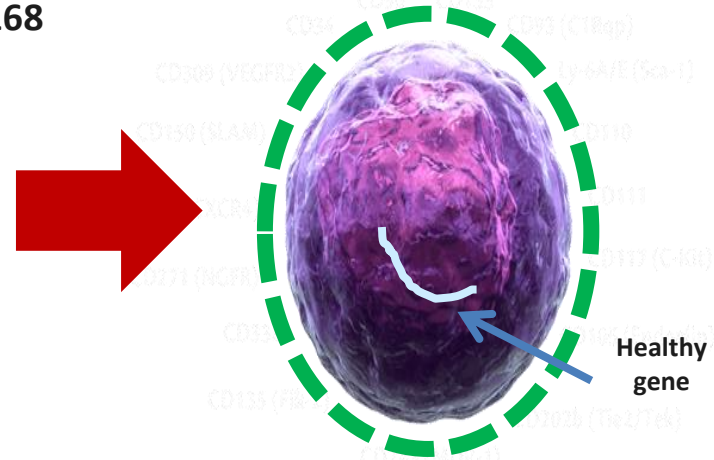
EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

EU/3/14/1330

FDA

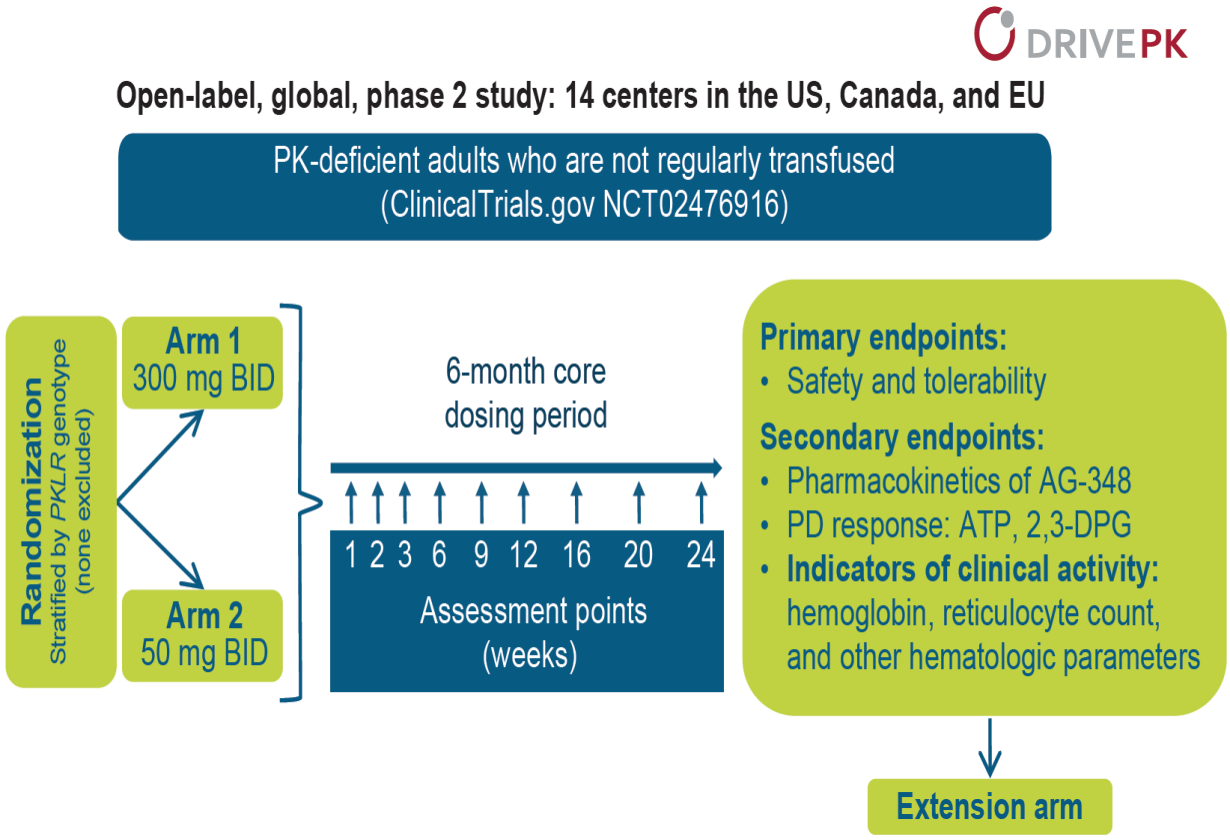
DRU-2016-5168

HEMATOPOIETIC STEM CELLS CORRECTED BY THE THERAPEUTIC VECTOR



DRIVE PK: Phase 2, Open Label, Randomized Study of Safety and Efficacy in Patients with PK Deficiency

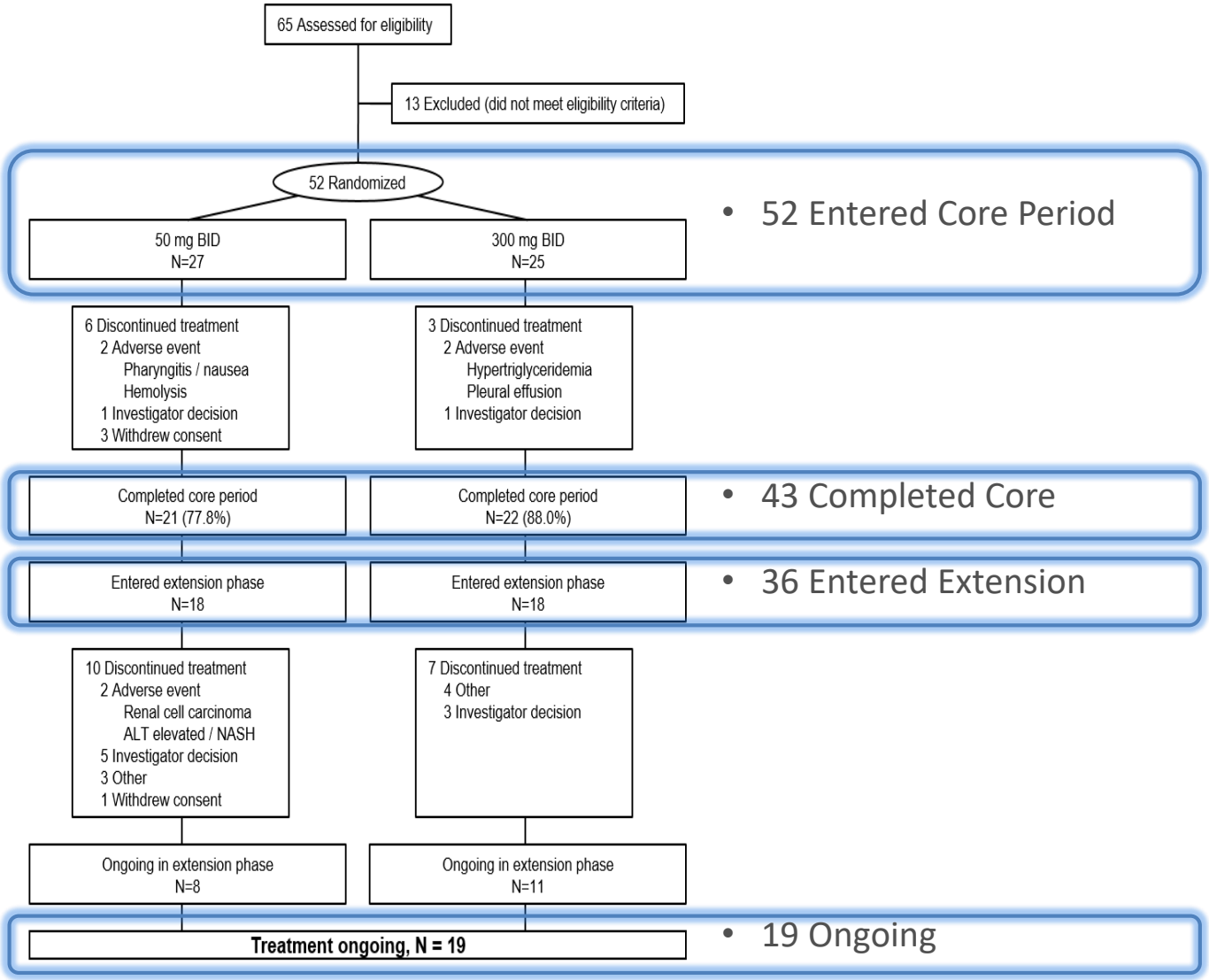
Study design



Not regularly transfused = no more than 3 units of red blood cells transfused in the 12 months prior to the first day of study dosing and no transfusions within 4 months of the first day of study dosing
All patients provided written informed consent
2,3-DPG = 2,3-diphosphoglycerate; BID = twice daily; PD = pharmacodynamic

Grace RF, Rose, C, Layton DM, et al. Safety and Efficacy of Mitapivat in Pyruvate Kinase Deficiency. *New England Journal of Medicine.* 2019; 381(10):933-944

Patient Disposition by Randomized Dose



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Network Hematological Diseases (ERN EuroBloodNet)

Safety Findings

- The vast majority of AEs were:
  - CTCAE Grade 1 or 2
  - Non-serious events
  - Transient
  - Self-limiting
- No clinically meaningful trends in BMD (total hip, total lumbar spine, and femoral neck) were evident over median of 17 months
- Changes from baseline in sex hormone levels, the result of off-target aromatase inhibition, were observed in males, with most values of testosterone and estradiol remaining within the normal range
- Interpretation of sex hormone data in females was confounded by variability in menopausal status and hormonal contraception use, and is the subject of further investigation

Grace RF, Rose, C, Layton DM, et al. Safety and Efficacy of Mitapivat in Pyruvate Kinase Deficiency. *New England Journal of Medicine.* 2019; 381(10):933-944

Most Common Adverse Events

- The most common adverse events were transient and generally resolved within 7 days for patients with headache (92%), insomnia (47%), and nausea (78%)

Incidence of Treatment-Emergent Adverse Events by Randomized Dose

	Core Period			Core Period + Extension Phase
Most common adverse events occurring in ≥15% of the overall population — no. of patients (%)	Mitapivat 50 mg Twice Daily N=27	Mitapivat 300 mg Twice Daily N=25	All Patients N=52	All Patients N=52
Headache	9 (33)	14 (56)	23 (44)*	24(46)
Insomnia	5 (19)	16 (64)	21 (40)†	22 (42)
Nausea	10 (37)	10 (40)	20 (38)	21 (40)
Nasopharyngitis	7 (26)	2 (8)	9 (17)	16 (31)
Hot flush	2 (7)	7 (28)	9 (17)‡	9 (17)
Arthralgia	5 (19)	3 (12)	8 (15)	9 (17)
Fatigue	4 (15)	4 (16)	8 (15)	9 (17)
Vomiting	2 (7)	5 (20)	7 (13)	9 (17)
Diarrhea	3 (11)	3 (12)	6 (12)	9 (17)
Influenza	6 (22)	1 (4)	7 (13)	9 (17)
Cough	4 (15)	4 (16)	8 (15)	8 (15)
Dizziness	5 (19)	2 (8)	7 (13)	8 (15)
Oropharyngeal pain	3 (11)	4 (16)	7 (13)	8 (15)
Pyrexia	1 (4)	5 (20)	6 (12)	8 (15)

*Headache was transient and generally resolved within several days. †Insomnia typically occurred within 14 days of initiating mitapivat, was self-resolving (generally <7 days) and was not unexpected on the basis of off-target antagonistic or inverse agonist activity against the histamine H3 receptor. ‡Hot flush events were transient and generally reported within the first 7 days of treatment and resolved without treatment within 3 days. Events did not correspond to changes in hormone levels or correlate with age or sex.

Grace RF, Rose, C, Layton DM, et al. Safety and Efficacy of Mitapivat in Pyruvate Kinase Deficiency. *New England Journal of Medicine.* 2019; 381(10):933-944

Table 4. Multivariate analysis for determinants of complication rate

Complication/parameter	RR	95% CI	*P*
EMH			
Age > 35 y	0.85	0.46-1.58	.610
Ferritin ≥ 1000 μg/L	0.85	0.51-1.44	.548
Splenectomy	0.44	0.26-0.73	.001*
Transfusion	0.06	0.03-0.09	< .001*
Hydroxyurea	0.52	0.30-0.91	.022*
PHT			
Age > 35 y	2.59	1.08-6.19	.032*
Splenectomy	4.11	1.99-8.47	< .001*
Transfusion	0.33	0.18-0.58	< .001*
Hydroxyurea	0.42	0.20-0.90	.025*
Iron chelation	0.53	0.29-0.95	.032*
HF			
Splenectomy	2.88	0.99-8.32	.051
Transfusion	0.06	0.02-0.17	< .001*
Hydroxyurea	1.84	0.98-3.47	.057
Iron chelation	0.45	0.18-1.12	.086
Thrombosis			
Age > 35 y	2.60	1.39-4.87	.003*
Female	1.27	0.74-2.19	.387
Hb ≥ 90 g/L	0.41	0.23-0.71	.001*
Ferritin ≥ 1000 μg/L	1.86	1.09-3.16	.023*
Splenectomy	6.59	3.09-14.05	< .001*
Transfusion	0.28	0.16-0.48	< .001*
Hydroxyurea	0.56	0.28-1.10	.090
Iron chelation	0.97	0.56-1.68	.912
Cholelithiasis			
Age > 35 y	2.76	1.56-4.87	< .001*
Female	1.96	1.18-3.25	.010*
Splenectomy	5.19	2.72-9.90	< .001*
Transfusion	0.36	0.21-0.62	< .001*
Hydroxyurea	0.55	0.29-1.02	.058
Iron chelation	0.30	0.18-0.51	< .001*

Taher et al. Blood 2010