Thursdays Webinars

EuroBloodNet

" Pyruvate kinase deficiency Clinical Management: Place of Mitapivat in the guidelines and the organ damage guidance"

Speaker Dr.E.J. van Beers
Associate professor hematology
University Medical Centre Utrecht, University of Utrecht, ERN-EuroBloodNet subnetwork: Red cells.
Utrecht –the Netherlands
March 2024

Co-funded by the Health Programme of the European Union

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

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.**

Conflicts of interest and disclaimer

Advisory board: Agios

Research support: Novartis, Bayer, Agios, Mechatronics, ZonMW, H2020

About the presenter:

Associate professor hematology, Van Creveldkliniek UMCU

Co-ordinator research and trials benign hematology Eurobloodnet

Clinical trial and innovation lead U-TRIAL, UMCU

Chairman Sickle Cell Outcome Research (SCORE) group, the Netherlands

Introduction

Today:

Thursdays Webinars
EuroBloodNet

Pyruvate kinase deficiency Clinical Management: Place of Mitapivat in the guidelines and the organ damage guidance

Previously:

Thursdays Webinars
EuroBloodNet

Pyruvate Kinase Deficiency Clinical management

https://eurobloodnet.eu/education/thursdays-webinars/42/pyruvate-kinase-deficiency-clinical-management-place-of-mitapivat-in-the-guidelines-and-the-organ-damage-guidance

Thursdays Webinars
EuroBloodNet

Recommendations on Pyruvate Kinase Deficiency diagnosis

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

Outline

1. **Introduction**
2. **Diagnosis and Genetics (A1–A5):** Guidelines advise testing for PK deficiency using PKLR gene analysis or enzyme activity for diagnosis.
3. **Chronic Complications Management (B1–B10):** Recommendations include monitoring and treatment protocols for iron overload, cardiac and liver iron concentrations, and complications like pulmonary hypertension and vitamin D deficiency.
4. **Anaemia Management (C1–C6):** Highlights the consideration of splenectomy, RBC transfusions, and the importance of psychological support.
5. **Advanced Therapies (D1–D8):** Suggestions on the use of mitapivat therapy, handling non-responders, and discontinuation criteria.
6. **Special Populations (E1–E2):** Emphasizes regular haematologist monitoring and coordinated care for pregnant women or those planning pregnancy.

Diagnosis and management of pyruvate kinase deficiency: international expert guidelines

- Published in **Lancet Haematology 2024: e228–39**
- Group of international experts co-ordinated by: Hanny Al-Samkari and Rachel Grace

International experts and patients

Hanny Al-Samkari, MD
Prof Nadine Shehata, MD MSc
Kelly Lang-Robertson, MLIS
Paola Bianchi, PhD
Andreas Glenthøj, MD PhD
Prof Sujit Sheth, MD
Prof Ellis J Neufeld, MD PhD
Prof David C Rees, MBBS
Satheesh Chonat, MD
Kevin H M Kuo, MD MSc
Prof Jennifer A Rothman, MD
Prof Wilma Barcellini, MD
Eduard J van Beers, MD PhD
Dagmar Pospíšilová, MD PhD
Prof Ami J Shah, MD
Richard van Wijk, PhD
Prof Bertil Glader, MD PhD
Maria Del Mar Mañú Pereira, PhD
Oliver Andres, MD
Prof Theodosia A Kalfa, MD PhD
Stefan W Eber, MD
Prof Patrick G Gallagher, MD
Prof Janet L Kwiatkowski, MD MSCE
Prof Frédéric Galacteros, MD
Carl Lander, RN
Alejandra Watson
Riyad Elbard
Dore Peereboom
Rachael F Grace, MD MMSc

Diagnosis and management of pyruvate kinase deficiency: international expert guidelines

- Published in **Lancet Haematology 2024: e228–39**
- Group of international experts co-ordinated by: Hanny Al-Samkari and Rachel Grace

- Pyruvate kinase (PK) deficiency is the most common cause of chronic congenital non-spherocytic haemolytic anaemia worldwide.

- PK deficiency results in chronic haemolytic anaemia, with wide ranging and serious consequences affecting health, quality of life, and mortality.

- The goal of the International Guidelines was to develop evidence-based guidelines for the clinical care of patients with PK deficiency.

- These clinical guidelines were developed by use of GRADE methodology and the AGREE II framework:
  - "Recommends" means strong recommendation, and "suggest" is a weak recommendation

Diagnosis and genetics of Pyruvate Kinase (PK) Deficiency (A1–A5), the key messages:

Testing for PK Deficiency:

- Test for PK deficiency in all patients with non-immune haemolytic anaemia after exclusion of haemoglobin disorders and erythrocyte membrane disorders.

PITFALL: Patients with PK Deficiency can have normal PK activity

as both have similar

Confirmation of Diagnosis:

- Confirm a diagnosis made with PK enzyme activity measurements with PKLR gene molecular analysis.
- Confirm a diagnosis made with PKLR gene molecular analysis with PK enzyme activity measurement in patients without two known pathogenic mutations in PKLR.

Predicting Disease Severity:

- Do not use PK enzyme activity to predict disease severity or course.

Monitoring and management of chronic complications of PKD (B1–B10), the key messages:

Vitamin D Monitoring:

•Recommend annual 25-hydroxy vitamin D measurement starting at age 1 year in all patients not on regular vitamin D supplementation to detect and treat vitamin D deficiency.

Bone Mineral Density Screening:

•Recommend screening for reduced bone mineral density using dual-energy X-ray absorptiometry (DEXA) scans starting at age 18 years to diagnose and manage osteopenia and osteoporosis.

Endocrine Function Monitoring:

•Recommend age-appropriate laboratory endocrine monitoring in patients receiving regular transfusions and those not receiving regular transfusions but with iron overload, to identify and treat endocrinological complications.

Renal Function Monitoring:

•Suggest monitoring renal function in children and adults with PK deficiency, irrespective of transfusion status, for early detection of renal dysfunction

.

Monitoring and management of chronic complications of PKD (B1–B10), the key messages:

Iron Overload Screening:

•Recommend to Screen for iron overload with serum ferritin in children and adults with PK deficiency starting at age 3 years or after 12 transfusion episodes, whichever comes first, regardless of transfusion status.

Liver Iron Concentration Measurement:

•Recommend to Measure Liver Iron Concentration (LIC) using MRI in patients with consistent serum ferritin levels >500 ng/mL to detect hepatic iron overload, irrespective of transfusion status.

Cardiac Iron Overload Monitoring:

•Recommend to perform cardiac iron measurement using MRI in patients with LIC >7 mg/g dry weight to detect cardiac iron overload, regardless of transfusion status.

Iron Chelation Therapy:

•Recommend iron chelation therapy for patients aged 2 years or older with LIC >5 mg/g dry weight, irrespective of transfusion status, to reduce the risk of iron overload complications.

•Suggest iron chelation therapy for patients aged 2 years or older who have received >12 transfusions or have serum ferritin concentrations >1000 ng/mL.

Pulmonary Hypertension Screening:

•Suggest echocardiography in all patients aged 18 years or older with PK deficiency to screen for pulmonary hypertension.

Monitoring and management of chronic complications of PKD <u>not (in the main) text</u>:

Folic Acid:

•The expert panel was also not able to make evidence-based recommendations regarding the use of folic acid in PK deficiency, due to lack of evidence and diversity of clinical practice.

- •Personal opinion: Supplement or check

Proton Pump Inhibition:

•The second randomized placebo controlled trial including patients with PKD was the PPI shine again study published in may 2022.

•This trial randomized placebo versus 2dd40mg esomeprazole and found a statistical significant and clinical meaning full difference of 0.55 (−1.06 to −0.05) decrease of mg/g LIC in favor of esomprazole

- •Personal opinion: consider as adjuvans in case of intolerance or other reasons for unavailability of other chelators

Monitoring and management of chronic complications of PKD <u>not (in the main) text</u>:

Iron overload Monitoring:

The expert group discussed the clinical utility of screening for iron overload with both ferritin and transferrin saturation but concluded that the transferrin saturation would increase the sensitivity of screening but decrease specificity, particularly in infants and children and in those with hereditary hemochromatosis.

KY Fertrin. Hematology Am Soc Hematol Educ Program 2020 Dec 4; 2020(1): 478–486.

Monitoring and management of chronic complications of PKD not (in the main) text:

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%

Dutch SCORE study:

"In patients with a ferritin **>500 ng/ml,** the ability to correctly identify those with **LIC >3 mg/g DW was 76%"**

"In patients with a ferritin **>500 ng/ml or TSAT >45%,** the ability to correctly identify those with

LIC >3 mg/g DW was 87%"

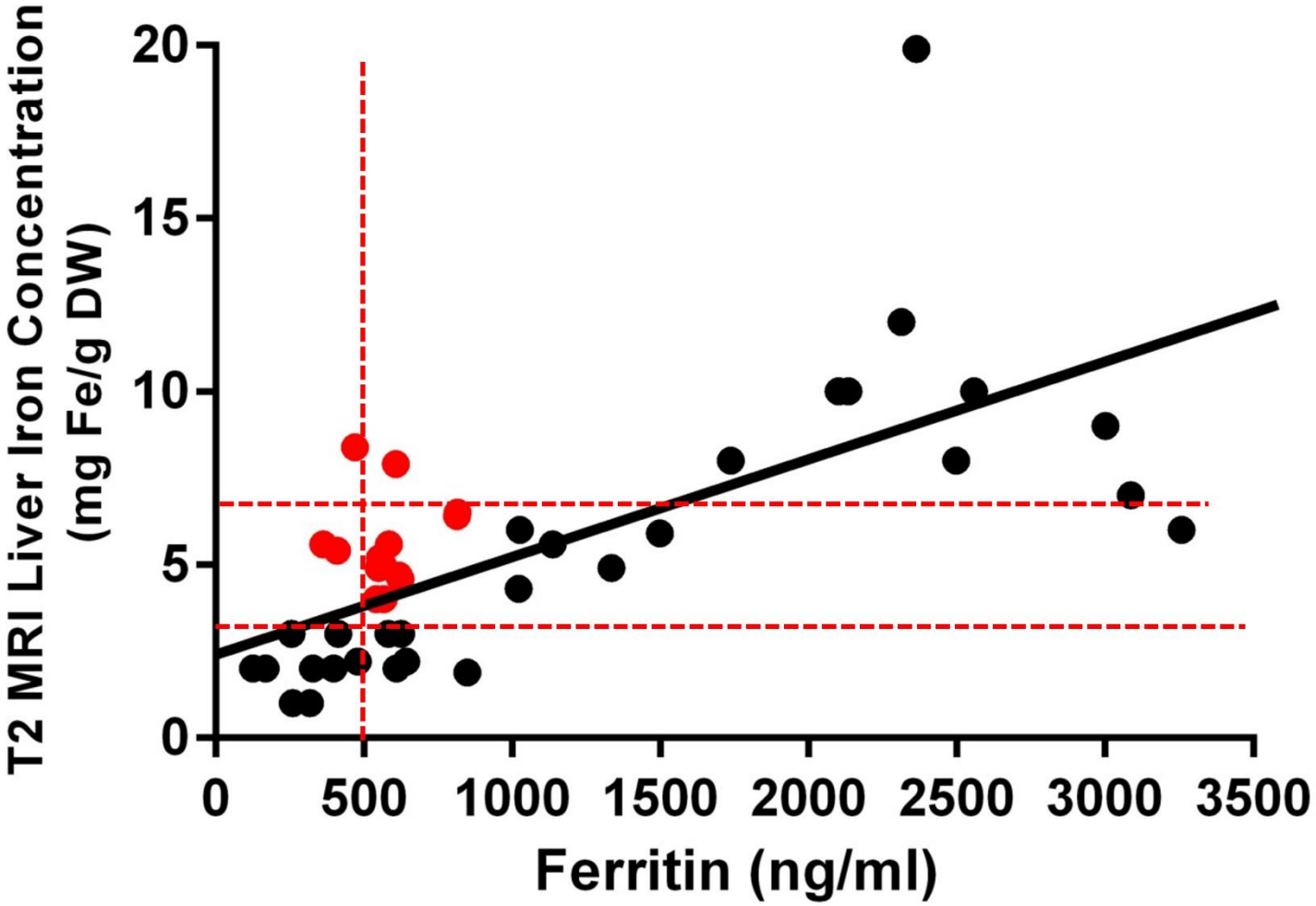
European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Van Straaten et al. Am J Hematol 2019

UMC Utrecht Van Creveldkliniek

Ferritin and LIC in PKD-NHS



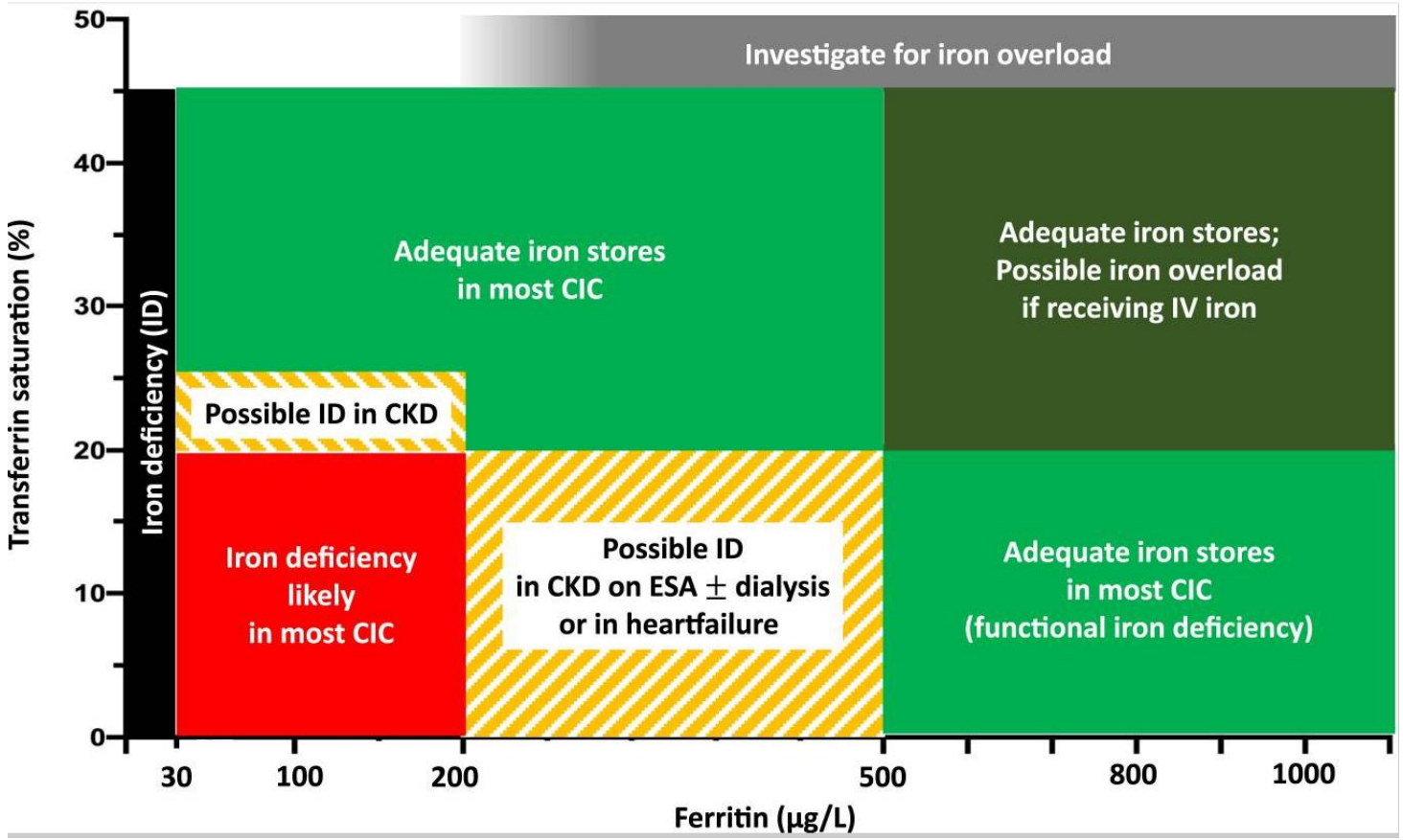
Van Beers et al. Haematologica 2019

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

UMC Utrecht
Van Creveldkliniek

Monitoring and management of chronic complications of PKD <u>not (in the main) text</u>:

Iron overload Monitoring:



KY Fertrin. Hematology Am Soc Hematol Educ Program 2020 Dec 4; 2020(1): 478–486.

Recommendations on standard management of anemia in PK Deficiency (C1–C6)

- **Splenectomy Consideration**:
- Discuss the personalized risks and benefits of splenectomy for children over 5 years and adults requiring regular or frequent RBC transfusions or experiencing symptomatic anemia.
- **RBC Transfusions for Young Children**:
- Initiate regular RBC transfusions for children under 5 with symptomatic anemia or anemia affecting growth and development to improve symptoms and support growth.
- **RBC Transfusions for Older Children and Adults**:
- Recommend regular RBC transfusions for children aged 5 and older and adults with symptomatic anemia who have had a splenectomy, are unsuitable for, or refuse splenectomy to improve anemia symptoms.
- **Transfusion Criteria**:
- Base RBC transfusions on symptoms and complications of anemia rather than a universal hemoglobin threshold.
- **Splenectomy and Cholecystectomy**:
- Consider cholecystectomy alongside splenectomy in patients with PK deficiency, especially those with known gallstones or biliary sludge.
- **Psychological Support**:
- Offer appropriate psychological support to children and adults with PK deficiency and their families or caregivers

Recommendations on targeted and advanced therapies in PK Deficiency (D1–D8)

Initiating Mitapivat Therapy (high):

•Start mitapivat therapy in adult patients with PK deficiency who are anemic, not regularly receiving transfusions, and without two non-missense mutations, regardless of splenectomy status, to improve hemoglobin levels and quality of life.

Determining Non-Responsiveness to Mitapivat (high):

•Consider patients non-responsive to mitapivat only after at least 3 months of treatment at an optimal or maximum dose for those not receiving regular transfusions.

Mitapivat for Regularly Transfused Adults:

•Begin mitapivat therapy in adult patients with PK deficiency receiving regular transfusions and without two non-missense mutations to reduce transfusion burden.

Discontinuing Mitapivat for Non-Responders:

•Stop mitapivat therapy and return to supportive care in patients who do not respond to treatment, irrespective of their transfusion status.

recommendations on targeted and advanced therapies in PK Deficiency (D1–D8)

- **Exploring Alternatives for Non-Responders**:
- Consider alternative treatments or clinical trials for patients not responding to mitapivat, regardless of transfusion status.
- **Criteria for Continuing Mitapivat in Transfused Patients**:
- Continue mitapivat therapy in transfused patients only if there's at least a 33% reduction in transfusion requirement, unless significant improvements in iron status, health outcomes, or other disease parameters are observed.
- **Mitapivat Before Splenectomy in Transfused Adults**:
- Recommend a trial of mitapivat therapy before considering splenectomy in adults receiving regular transfusions who have not undergone the procedure.
- **Using PK Deficiency-Specific HRQoL Measures**:
- Suggest using PK deficiency-specific quality of life measures as success indicators in trials of mitapivat, especially when improvements in transfusion burden or hemoglobin levels are not met by numerical cutoffs

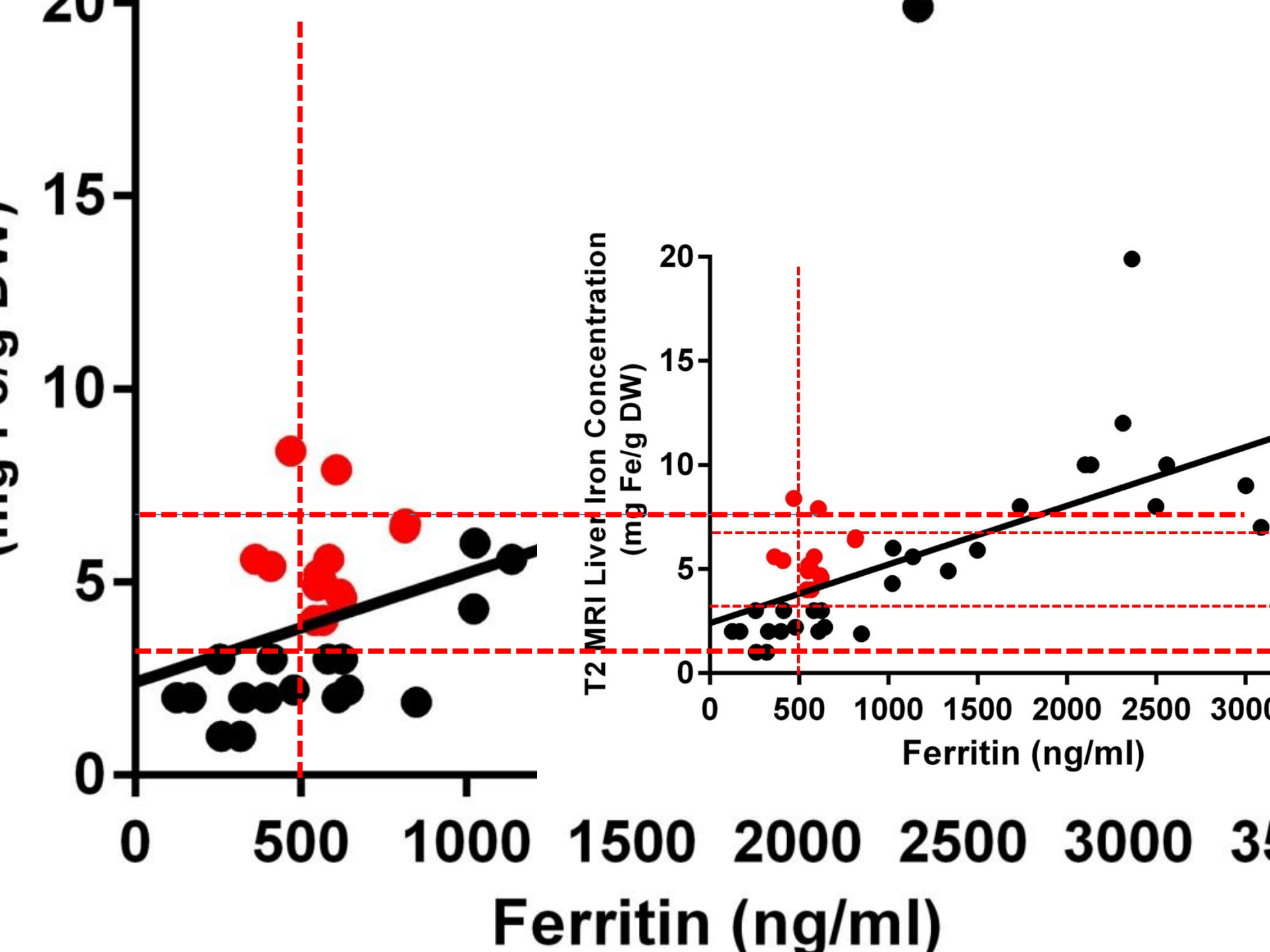
.

Recommendations for special populations in PK Deficiency (E1–E2)

Regular Haematologist Monitoring:
•Ensure children and adults with PK deficiency are regularly monitored by a haematologist, regardless of their transfusion status.
Care for Pregnant Women:
•Refer women with PK deficiency, whether pregnant or planning pregnancy, to a multidisciplinary fetomaternal team that includes a haematologist, obstetrician, neonatologist, and other relevant specialists to minimize maternal and fetal complications
.

Q@ A and acknowledgements

Hanny Al-Samkari, MD
Prof Nadine Shehata, MD MSc
Kelly Lang-Robertson, MLIS
Paola Bianchi, PhD
Andreas Glenthøj, MD PhD
Prof Sujit Sheth, MD
Prof Ellis J Neufeld, MD PhD
Prof David C Rees, MBBS
Satheesh Chonat, MD
Kevin H M Kuo, MD MSc
Prof Jennifer A Rothman, MD
Prof Wilma Barcellini, MD
Eduard J van Beers, MD PhD
Dagmar Pospíšilová, MD PhD
Prof Ami J Shah, MD
Richard van Wijk, PhD
Prof Bertil Glader, MD PhD
Maria Del Mar Mañú Pereira, PhD
Oliver Andres, MD
Prof Theodosia A Kalfa, MD PhD
Stefan W Eber, MD
Prof Patrick G Gallagher, MD
Prof Janet L Kwiatkowski, MD MSCE
Prof Frédéric Galacteros, MD
Carl Lander, RN
Alejandra Watson
Riyad Elbard
Dore Peereboom
Rachael F Grace, MD MMSc


T2 MRI Liver Iron Concentration (mg Fe/g DW)
0
5
10
15
20
0
500
1000
1500
2000
2500
3000
Ferritin (ng/ml)