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Diagnostics

The Thomas Plot

sTfR, Ferritin, RET-He and CRP:

"A New Concept in Anemia Diagnostic – Actionable Health Information"

Ralf Röddiger
Centralized Diagnostics Clinical Trials
Roche Diagnostics GmbH
Mannheim / Germany

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Agenda

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Diagnostics

- Introduction
- Iron Metabolism
- IDA, ACD, and functional Iron Deficiency
- Hematology meets Biochemistry
- The Thomas Plot

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Introduction

Anemia is a sign of an underlying pathology

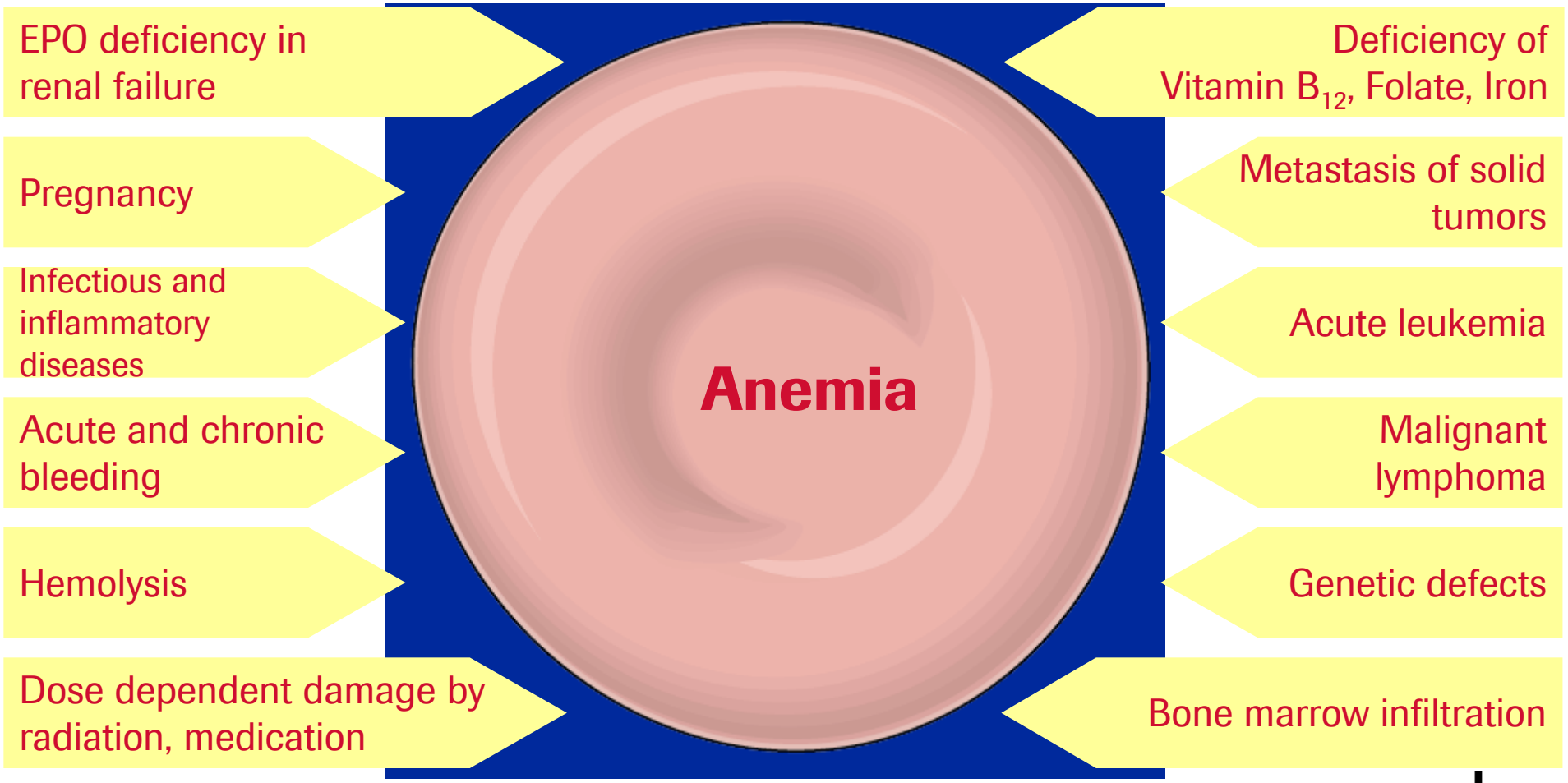
Definitions – Anemia is...

- …the result of various diseases, rather than a disease itself
- …the functional inability of the blood to supply the tissue with adequate oxygen (oxygen deficiency)
- …a reduction in the Red Blood Cells (RBC) count, the Hb-concentration and/or the hematocrit is below the lower limit of the reference range
- …if the Hb-concentration is <13 (adult men) resp. <12 g/dL* (adult women)

* acc. to WHO

Introduction – About Anemia

Anemia can be caused by numerous diseases



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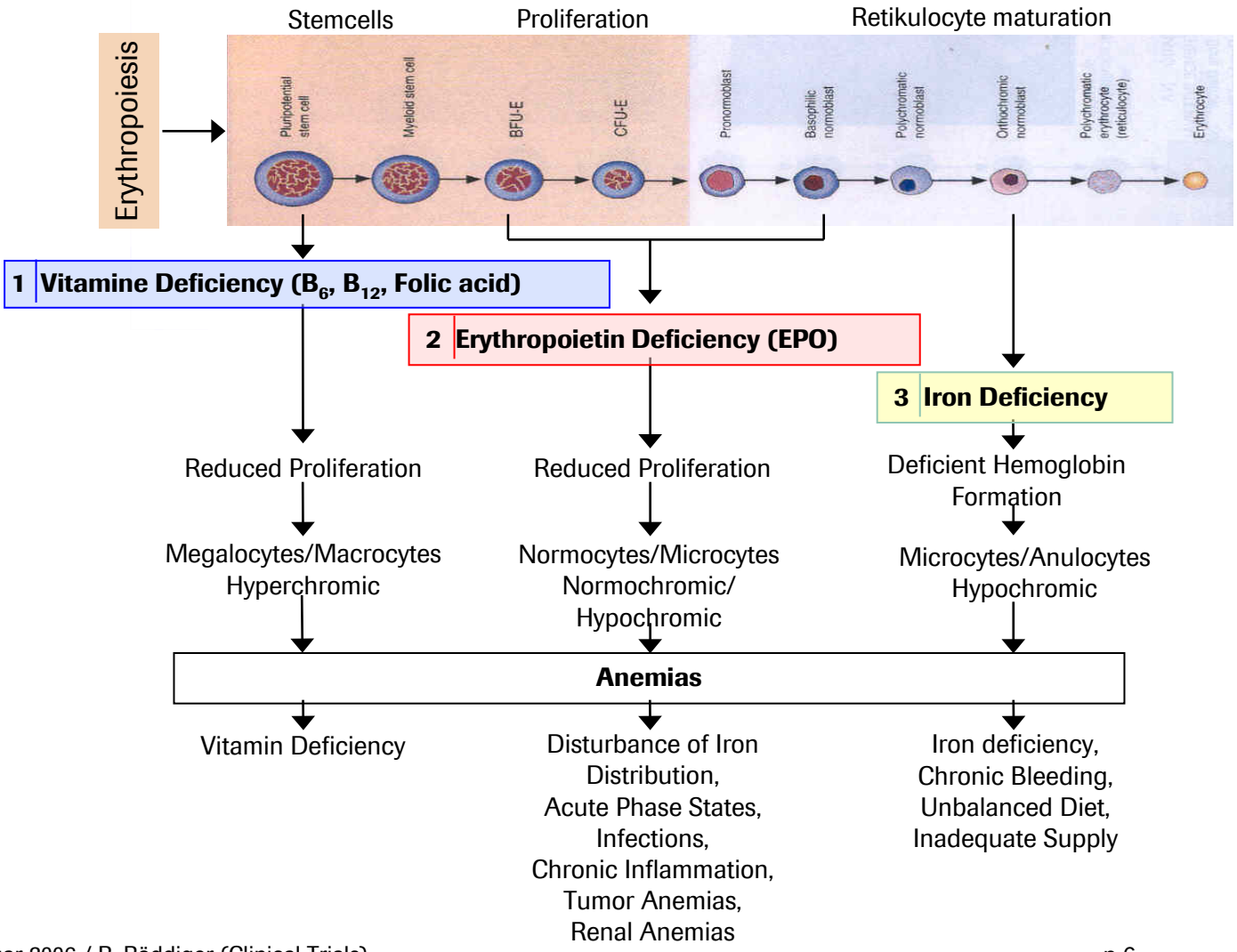
Introduction – About Anemia

Factors triggering iron metabolism and erythropoiesis



Introduction – About Anemia

Anemia is a major medical problem affecting a considerable proportion of the world's population

Diagnostics

Prevalence

- In total an estimated 30% of the world population are suffering from

Anemia !

- Approximately half of them - more than 500 million people – have anemias caused by **Iron Deficiency**
- 20% of these have a **functional Iron Deficiency** (inadequate Iron supply of the erythropoiesis)

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Diagnostics

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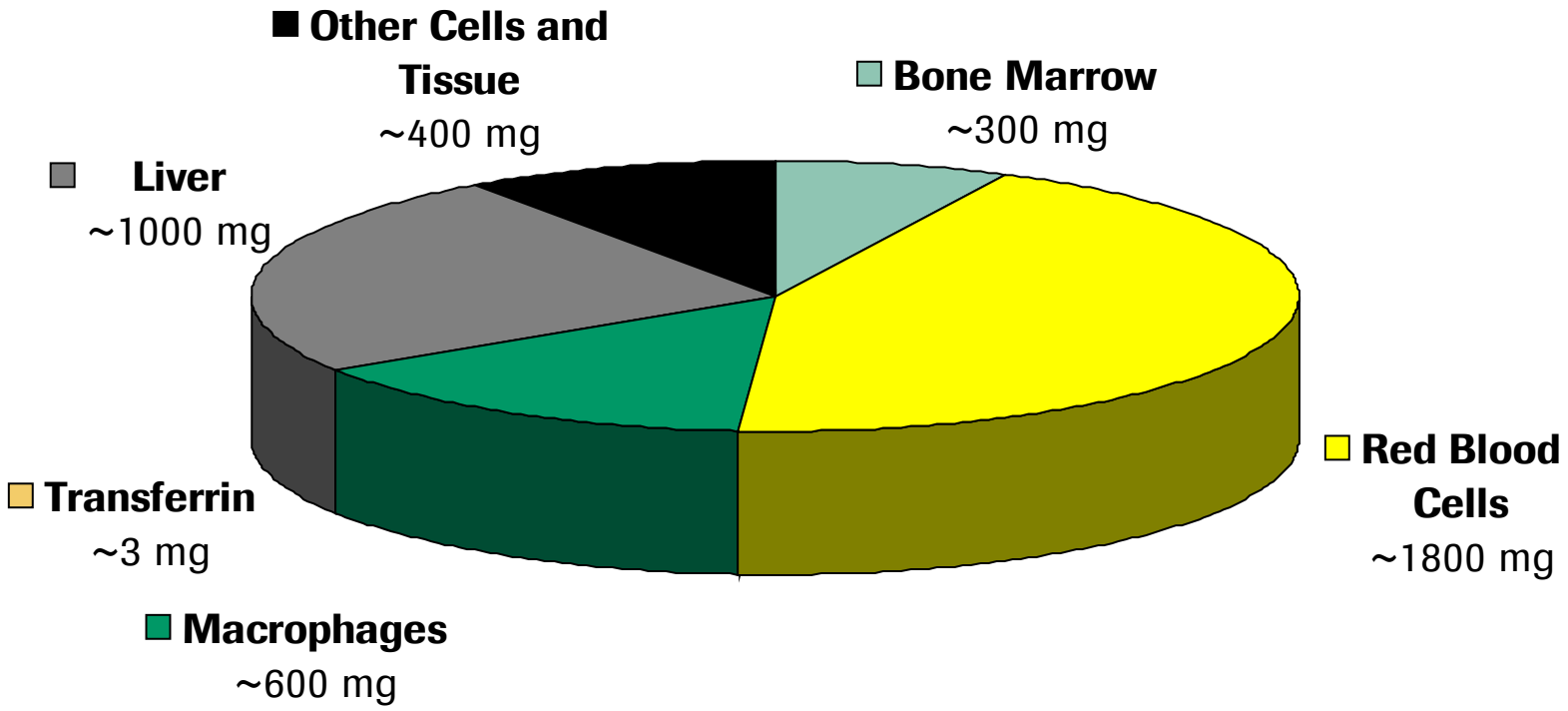
Iron Metabolism

Iron Distribution



Introduction – about Iron Metabolism

Balance of Iron Metabolism

Diagnostics

FUNCTIONAL IRON	**TRANSPORT IRON**	**STORAGE IRON**
HAEMOGLOBIN MYOGLOBIN ENZYMES	TRANSFERRIN	FERRITIN HAEMOSIDERIN
80 %	**0.1 %**	**20 %**

Iron compartments (in percent of total body iron)

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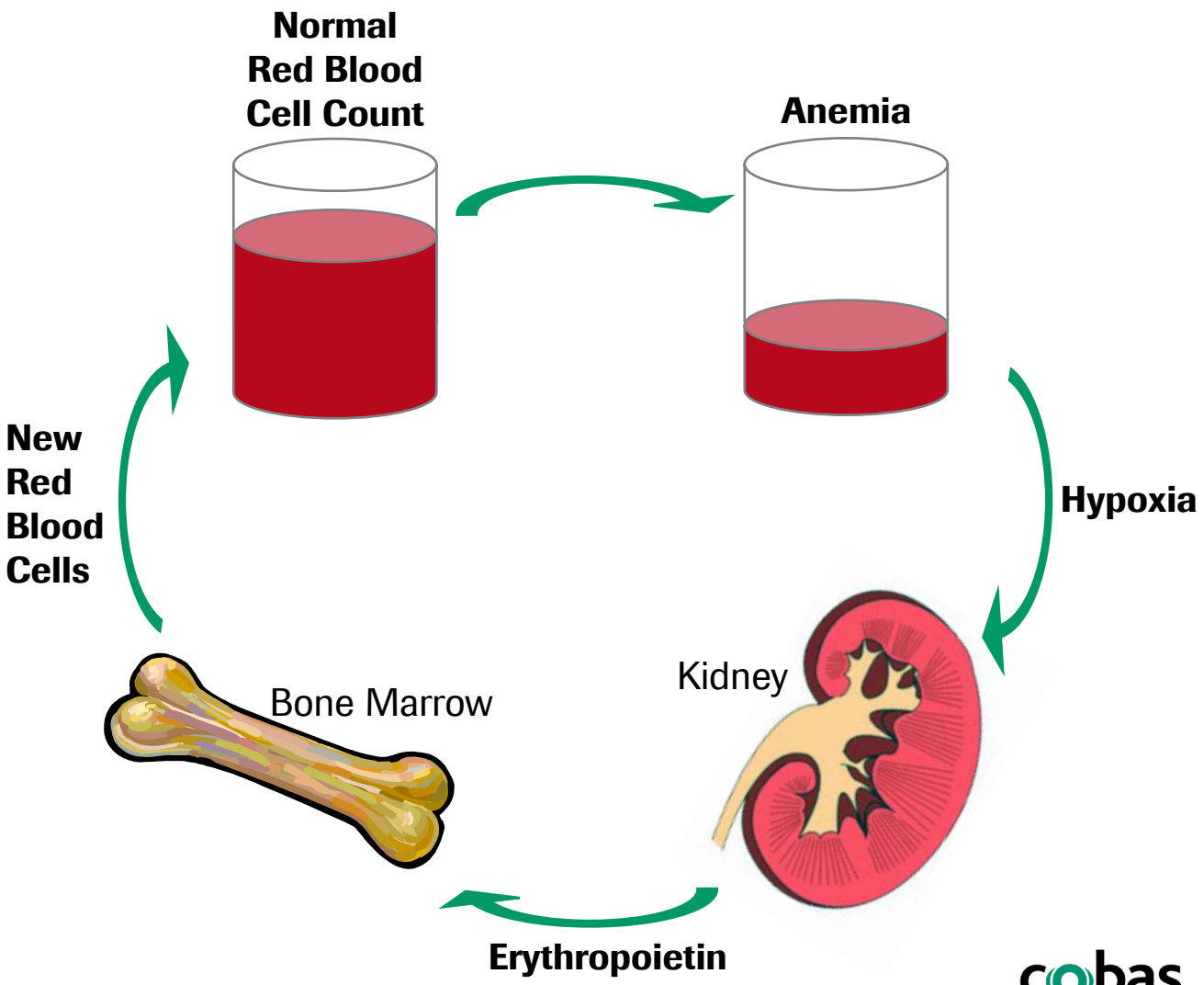
Introduction – about Iron Metabolism

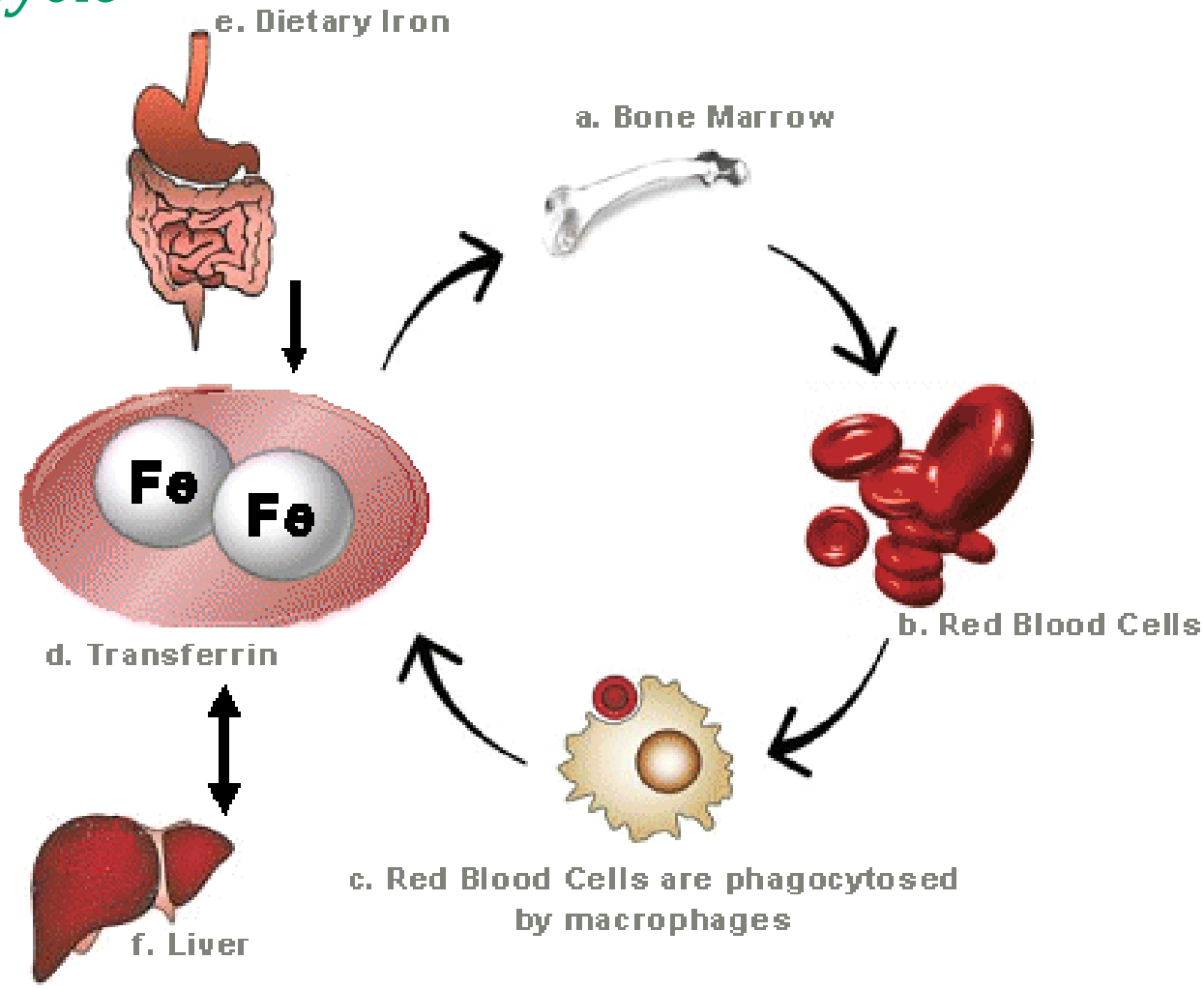
The Interaction of Iron and Erythropoietin

The production of red cells involves the coordinate interaction of two organ systems in the body.



Introduction – about Iron Metabolism

The Iron Cycle



Curr Opin Hematol 2005; 12:107-111

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IDA, ACD, and functional Iron Deficiency

Reduced Iron Supply for Erythropoiesis

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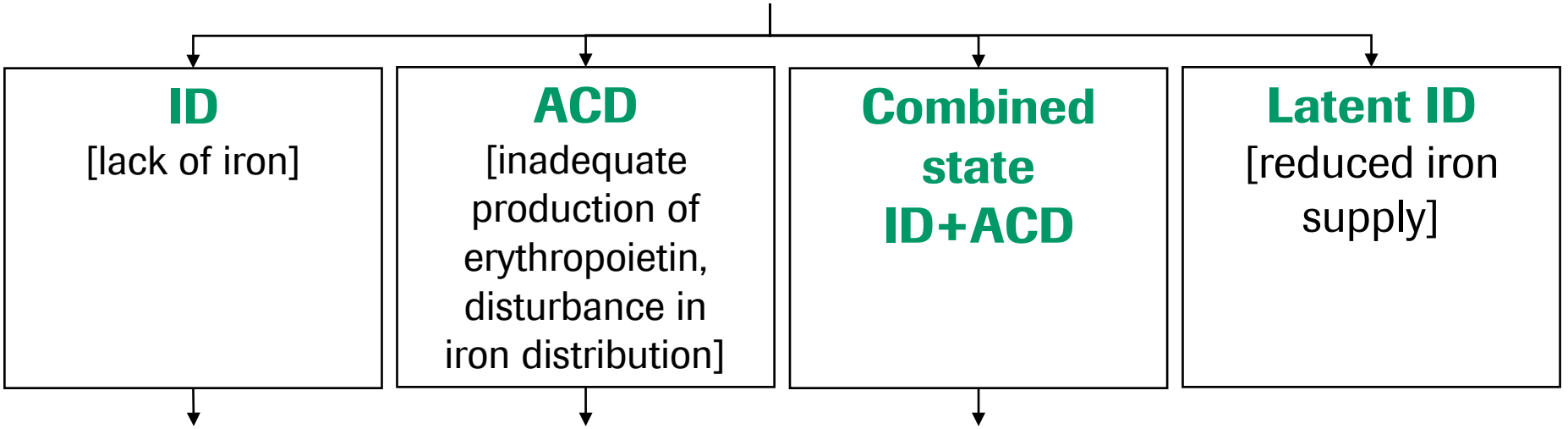

- limiting factor of erythrocyte hemoglobinization
- functional ID

- limiting factor of the proliferation of erythroid progenitor cells in the bone marrow

- limiting factor of the proliferation of erythroid progenitor cells in the bone marrow and erythrocyte hemoglobinization
- functional ID

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Introduction – Iron Deficiency

There Are Different States of Iron Deficiency

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		Iron Deficiency	Remarks
1.	Storage-Iron ê (Ferritin)	prelatent	Storage-Iron Deficiency
2.	Transferrin é	latent	Storage-Iron Deficiency + Transport-Iron Deficiency
3.	Serum-Iron ê	manifest	Storage-Iron Deficiency + Transport- Iron Deficiency + Hemoglobin- Iron Deficiency
4.	MCV, MCH ê		
5.	MCHC ê		

MCV medium cell volume
MCH absolute hemoglobin content of erythrocyte
MCHC medium hemoglobin content of erythrocyte

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Introduction – Functional Iron Deficiency

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Diagnostics

Functional Iron Deficiency is defined as

"the discrepancy between marrow iron availability and requirements"

This leads to

- **Reduced cellular Hb content in reticulocytes**
- **Reduced hemoglobinization of red blood cells**

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Introduction – About ACD

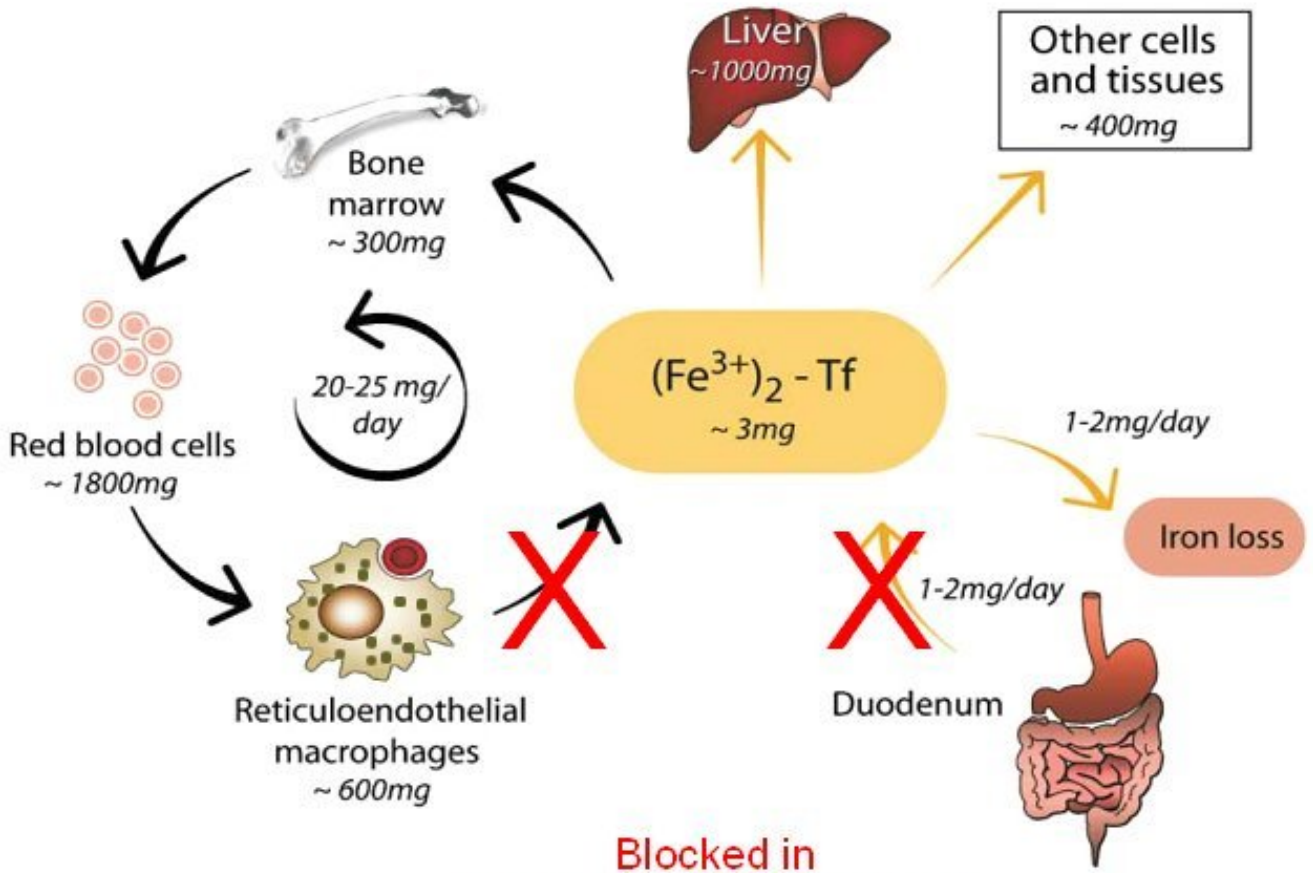
Chronic inflammation and the acute-phase-response interact with hematopoietic System

ACD is characterized by

- Inadequate production of Erythropoietin (kidneys!)
- Reduced proliferation of erythroid progenitor cells in the bone marrow
- Disturbance of normal Iron distribution
  - Iron re-distribution
    - Sufficient Iron in stores but not available for Hb synthesis
      - Impaired erythropoiesis

Introduction – About ACD

Major pathways of iron transfer in anemia of chronic disease



Hentze . . . Andrews, Cell 117: 285 (2004)

Iron uptake in the duodenum and release from macrophages is blocked, thereby decreasing delivery of iron to the erythropoiesis.

Introduction – About ACD

Chronic inflammation and infections also inhibit the mobilization of stored Iron and lead to ACD

Diagnostics

The process is driven by_

- Increased production of pro-inflammatory cytokines such as IL-1, IL-6, TNF-alpha, and IL-gamma

- Increased concentration of CRP and other acute phase proteins such as Ferritin (!) in the blood

Consequence:_

- Patients with CRP >50 mg/L need around 30% higher EPO doses than patients with CRP <50 mg/L *)

*) acc. to OPTA Working Group (Optimal Treatment of Renal Anemia)

Introduction – About IDA

The proper assignment of the different phases of IDA especially in patients with chronic diseases represents a diagnostic challenge.

Clinical Interest

- Early detection of sub-clinical Iron Deficiency (ID) to prevent systemic complications of IDA
- Identification of manifest or classic Iron Deficient Anemia
- Differential diagnosis of Anemia often seen in
  - Infection / Inflammation
  - Renal failure
  - Cancer
  - Heart failure
  - ….

Anemia of Chronic Disease (ACD)

to distinguish ACD from combined states of functional ID+ACD

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Biochemistry

Traditional biochemistry parameters have some limitations especially in the presence of Acute Phase Reactions (APR)

Analyte	Level in ID	Remarks
Ferritin	**Decreased**	▪ **Acute Phase Protein** ▪ **APR: increased**
Transferrin	**Elevated**	▪ **Acute Phase Protein** ▪ **APR: decreased**
Serum-Fe	**Decreased**	▪ **Extreme diurnal variation** ▪ **Further decrease in stress situations and APR**
Total Iron Binding Capacity (TIBC)	**Decreased**	**Very specific but poor sensitivity**
Transferrin Saturation (Tf-Sat)	**Decreased**	**Cannot distinguish between functional ID and ACD**
Ferritin Index (sTfR/log Ferritin)	**Elevated**	**Very sensitive discriminator between classic and functional ID**

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Hematology

The Hb content of Reticulocytes is a strong and early marker of the effectiveness of the Erythropoiesis

Diagnostics

Two hematological markers give information about the erythropoietic condition:

- **Hemoglobinzation of Red Cells (% HYPO)**
  The fraction of hypochromic red cells is a late indicator of an Iron restricted erythropoiesis (lifespan of red cells ~ 120 days!) and underlying functional ID

- **Hemoglobin content of Reticulocytes (CHr/RET-He)**
  Very early marker of impaired erythropoiesis and functional ID
  (~ 1-2 days in the circulation)

CHr – Bayer ADVIA
RET-He - Sysmex

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Hematology meets Biochemistry

Hematological and Biochemical Parameters complement each other in the differential diagnosis

Diagnostics

Hematological and biochemical markers together inform about_

The status of available Iron, the Iron need and the activity of Erythropoiesis

- **Hematology (RET-He):**
  ACTIVITY of the bone marrow / erythropoiesis

- **Biochemistry (Ferritin-Index):**
  SUPPLY of the bone marrow / erythropoiesis with Iron

- **Hematology and Biochemistry:**

Combination provides accurate information about different phases of ID/functional ID in Anemia

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Hematology meets Biochemistry

Combination of sTfR, Ferritin (=Ferritin Index), RET-He, and CRP in a diagnostic plot …

…leads to

The Thomas Plot *)

*) named after Prof. Lothar Thomas, Krankenhaus Nordwest, Frankfurt/Germany

The Thomas Plot

Serum levels of analytes that differentiate Anemia of Chronic disease from Iron-Deficiency Anemia

Analyte	ACD	IDA	ACD + IDA
Iron	Reduced ↓	Reduced ↓	Reduced ↓
Transferrin	Reduced to normal → ↓	Increased ↑	Reduced ↓
Transferrin saturation	Reduced ↓	Reduced ↓	Reduced ↓
Ferritin	Normal to increased → ↓	Reduced ↓	Reduced to normal ↓ →
sTfR	Normal →	Increased ↑	Normal to increased → ↑
Ferritin Index (sTfR/log Ferritin)	Low ↓	High ↑	High ↑
Cytokine levels	Increased ↑	Normal →	Increased ↑

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All involved analytes play their specific role

Ret-He	Hemoglobin contents of reticulocytes for very early assessment of **erythropoietic response**
sTfR	Soluble Transferrin Receptor for the assessment of the **erythropoietic activity**
Ferritin	For assessment of current total **inventory of storage Iron**
sTfR/ log Ferritin	For assessment of the **iron supply for erythropoiesis**
CRP	Indicator of non-specific disturbance of Iron metabolism caused by **acute phase processes**

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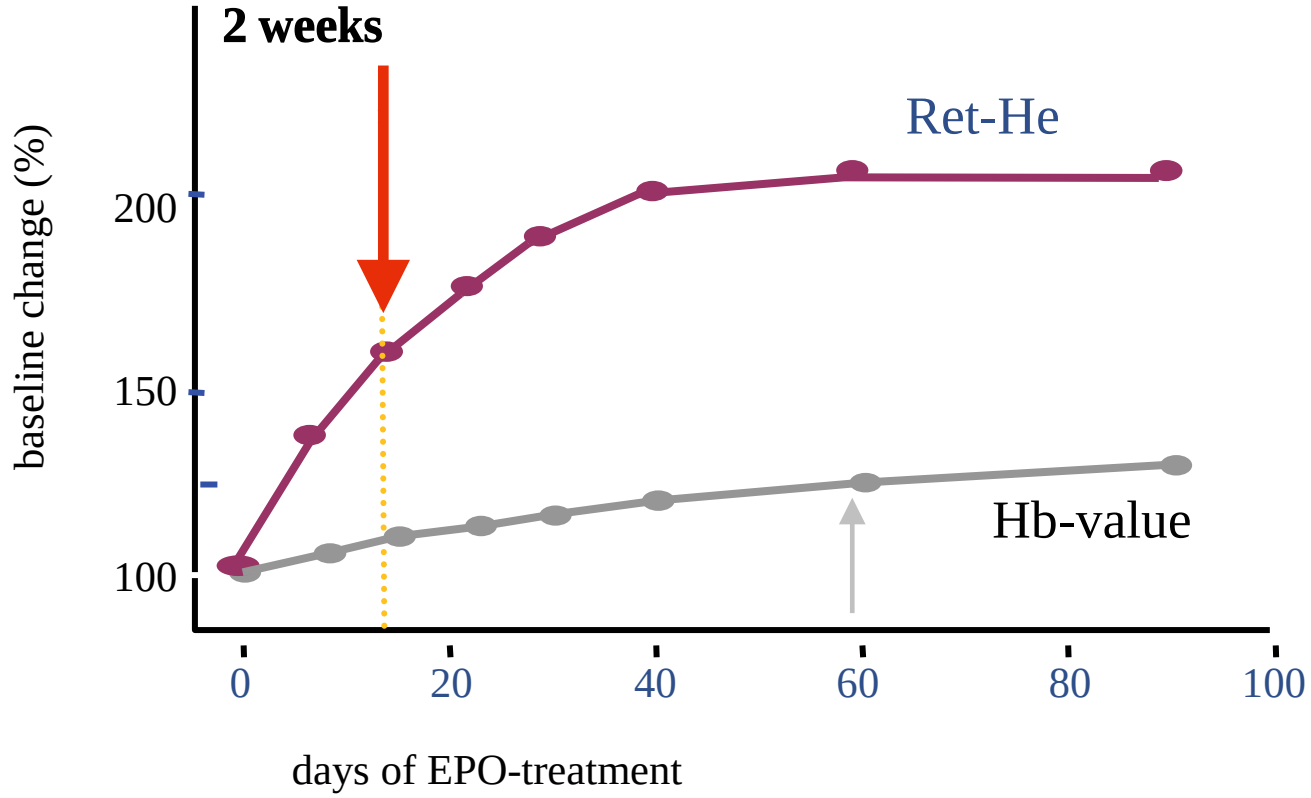
Therapeutic response and monitoring

Therapy monitoring – Ret-He is an indicator of Iron demand and an earlier indicator of treatment response than Hb



Roche Diagnostics Anemia Product Portfolio

Extensive Routine Portfolio for the Serum Work Area

Diagnostics

	Stand alone systems			MODULAR *ANALYTICS*
	RD/Hit	Integra	Elecsys	E170 + P-Module
Serum Iron	ü	ü		P
Transferrin	ü	ü		P
sTfR	ü	ü		P
Ceruloplasmin	ü	ü		P
Haptoglobin	ü	ü		P
UIBC	ü	ü		P
Ferritin	ü	ü	ü	P/E
(RBC) Folate			ü	E
Vitamin B12			ü	E
Ret-He	Sysmex			

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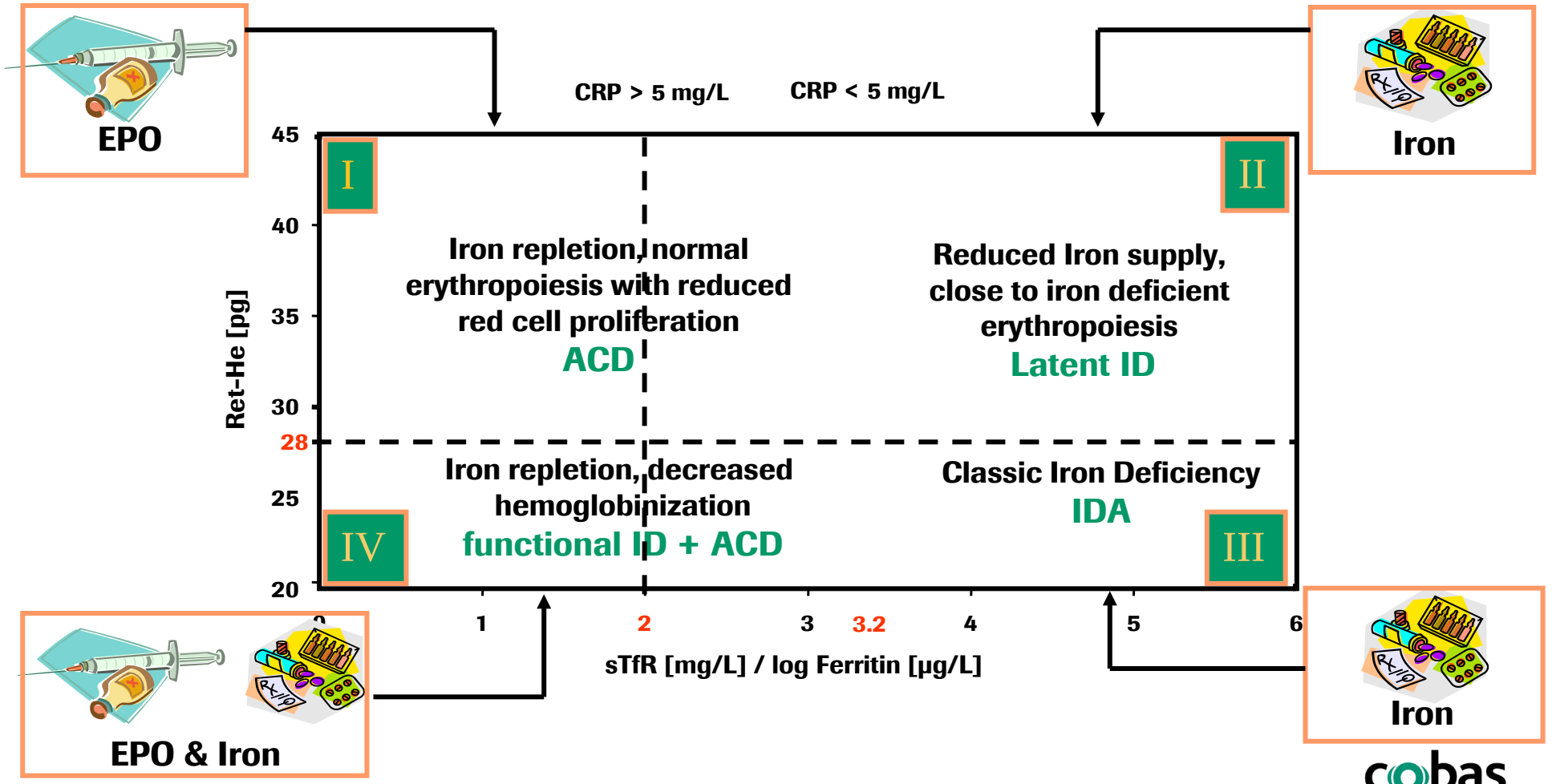
Iron deficiency can be classified in four conditions – each requiring specific treatment



Diagnostics

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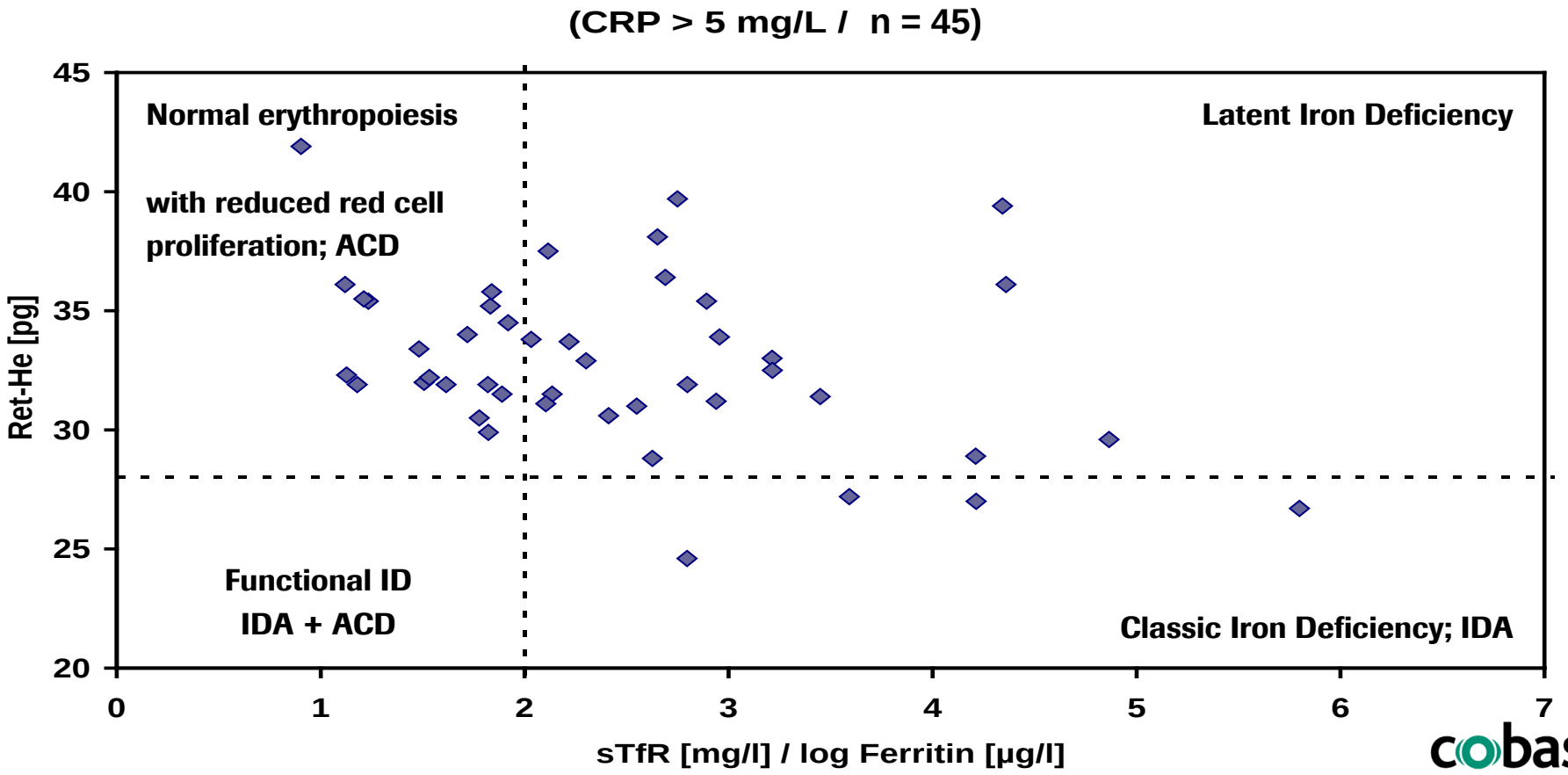
Iron deficiency can be classified in four conditions – each requiring specific treatment

Diagnostics

Prevalence in renal Dialysis Patients



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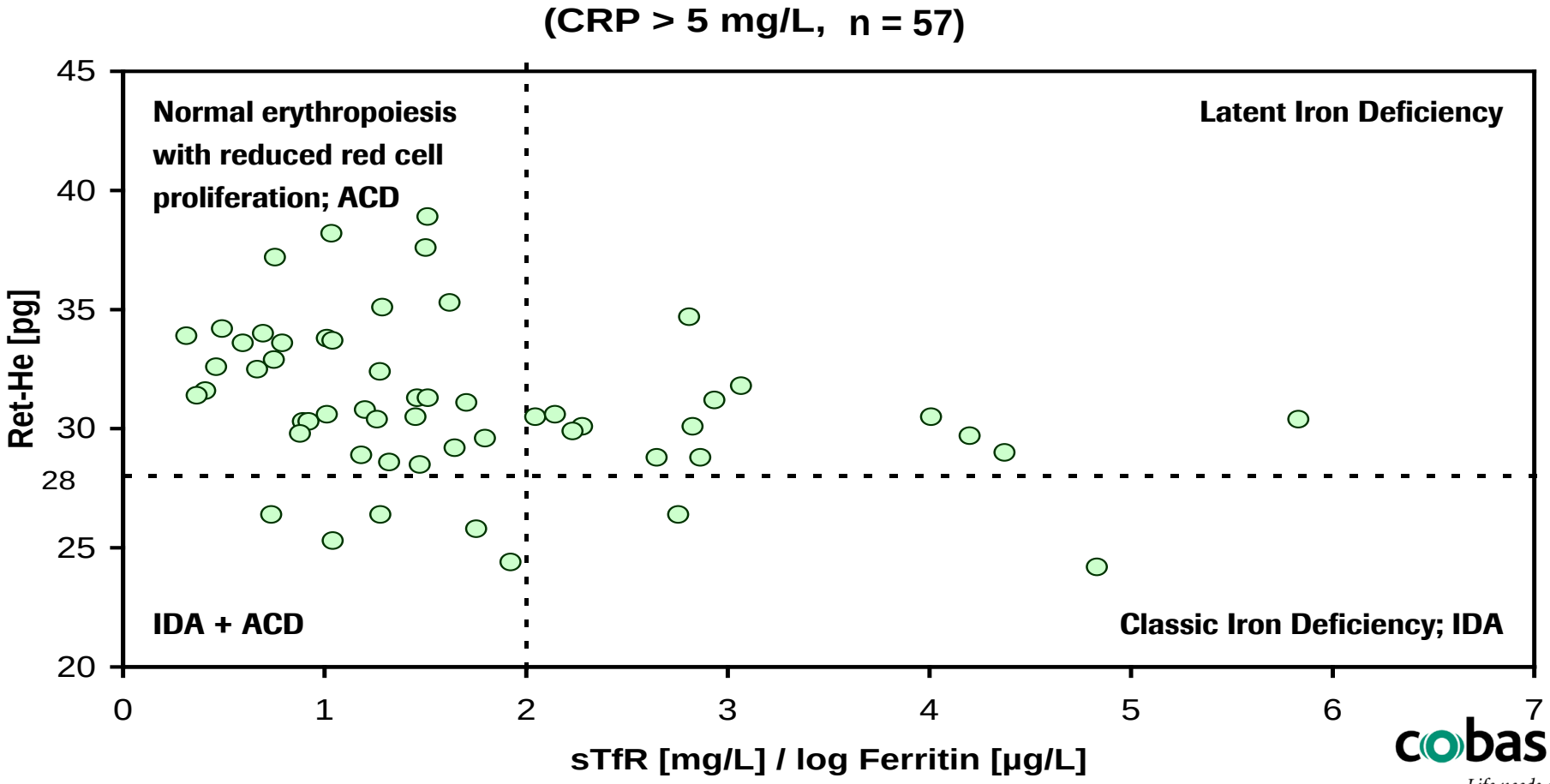
Iron deficiency can be classified in four conditions – each requiring specific treatment

Prevalence in Tumor Patients



The Thomas Plot

The Thomas Plot supports optimal management of ID Anemia and cost-effectiveness of r-HuEPO treatment – Example: Dialysis Patients

Diagnostics

Factors that may counteract the positive action of EPO therapy*)

- Inadequate hemodialysis dose
- Absolute and functional Iron deficiency
- Inflammation and infection

▶ Every single factor on its own could lead to a substantial decrease in Hb **OR** an increase in EPO dosage of up to 100%

Optimal management of Iron Deficiency leads to:

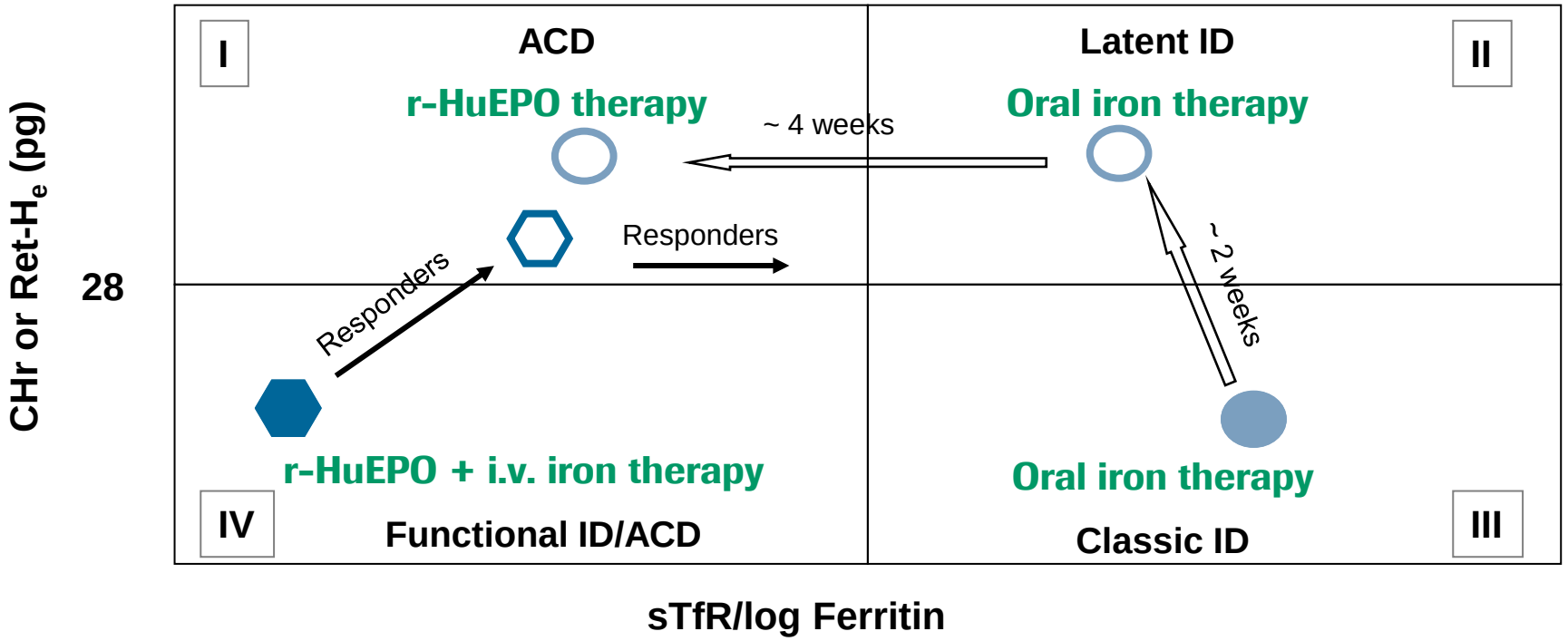
▶ a substantial reduction in EPO dosage of about 20 – 60%

▶ a reduction in the number of low or non-responders

*) acc. to OPTA Working Group (Optimal Treatment of Renal Anemia)

Therapeutic implications of the Thomas-Plot

Response to the treatment of anemia



Anemia

Assessment of results two and four weeks after starting rHuEPO therapy

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Diagnostics

Parameter	Result	Treatment
Ferritin index vector	> 0.6 < 0.6	Adequate rHuEPO dosage. Increase rHuEPO dosage.
Ret-Hb	> 28 pg or increase of > 2 pg < 28 pg or increase < 2 pg	No functional ID. Functional ID, supplement i.v. iron.
Ferritin index	< 3.2 > 3.2	Adequate iron stores. Inadequate iron stores, supplement i.v. iron.
Hemoglobin (Hb)	Increase > 1 g/dL Increase < 1 g/dL	Adequate response. Inadequate response, supplement rHuEPO until week 4. If no Hb elevation increase rHuEPO dosage or stop rHuEPO therapy.

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Is basically valid for all ID states, but some limitation due to physiological / path physiological reasons

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Remarks

- Valid for anemic patients with Iron Deficiency of all origin
- Ferritin index cut-offs as shown in this presentation only valid for Roche Diagnostics reagents

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Recent Progress in Laboratory Diagnostics

Iron Deficiency, Erythropoietic Status in Anemia, rHuEPO Therapy: New Diagnostic Approaches – The "Thomas-Plot"

Thomas L
Thomas C
Lehmann P
Roeddiger R
Brugnara C

Iron Deficiency, Erythropoietic Status in Anemia, rHuEPO Therapy: New Diagnostic Approaches – The "Thomas-Plot"

Thomas L, Thomas C, Lehmann P, Roeddiger R, Brugnara C

New diagnostic approaches in iron deficiency and evaluation of erythropoietic status

The diagnosis of iron deficiency (ID) is particularly challenging in patients with acute or chronic inflammatory conditions. Most of the biochemical markers for iron metabolism are affected by acute-phase reaction and represent the storage and functional iron pool in an inadequate way. Recently, a novel approach based on hematologic indices was presented which provides important new insights into the proper identification of ID, both in iron repleted and in iron depleted states in the presence and absence of acute-phase response [1-5].
The issue of functional ID (iron supply for erythropoiesis does not meet iron demand) has received a great deal of attention by treating patients on chronic renal dialysis and tumor patients [6-10]. It is well known that in many of these patients biochemical markers for iron metabolism are non-informative: serum ferritin concentrations in the range of 200-800 µg/L are frequently seen in patients who have functional ID and respond to iron therapy. It was shown that the hemoglobin content of reticulocytes (Ret-Hb) is valuable in identifying ID/functional ID as well as determining when iron therapy is needed [1, 11-13].
Using the Ret-Hb as a gold standard to define functional ID [1,5], the cut-off values for ferritin, sTfR and sTfR/log ferritin (ferritin index) [14, 15] in patients with and without acute-phase response (based on CRP cut-off of 5 mg/L) can be assessed [1]. Functional ID was defined as a Ret-Hb < 28 pg, based on the distribution of these values in healthy controls. The biochemical markers performed significantly better in the absence of inflammation: the cut-off for the ferritin index is 3.2 for ID without acute phase reaction (APR) and 2.0 for ID combined with anemia of chronic disease (ACD), anemia of infection, chronic inflammation, endstage renal failure and cancer-related anemia [1]. The relationship between Ret-Hb and the ferritin index is described in a simple plot (Fig. 1) [1]. Four quadrants can be identified based on the respective cut-off values for Ret-Hb and the ferritin index.

The quadrants shown in these plots correspond to different hypo- or normo- regenerative erythropoietic states [1]:

1. Normal erythropoiesis with repleted iron stores (iron status in ACD)
2. Normal erythropoiesis with depleted iron stores but not yet in an iron-deficient erythropoietic state (latent iron deficiency)
3. Hypoproliferative erythropoiesis, depletion of storage and functional iron compounds (classic iron deficiency), decreased hemoglobinization of red cells
4. Hypoproliferative erythropoiesis, functional ID in iron-repleted stores (functional ID in patients with ACD), decreased hemoglobinization of red cells.

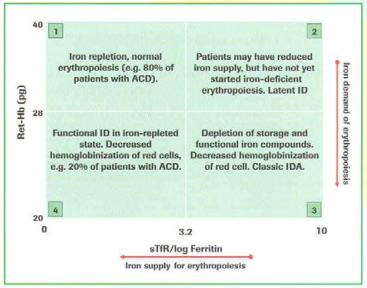

Figure 1: Thomas-Plot plot for identifying the different erythropoietic states of advancing ID combining the best biochemical marker for iron supply (sTfR/log ferritin ratio, ferritin index) with Ret-Hb, the real-time hematologic indicator for iron demand of erythropoiesis (CHr, Ret-He). The plot is also used for evaluating the erythropoietic state prior to commencing rHuEPO therapy. A Ret-Hb of < 28 pg indicates functional iron deficiency. In patients with CRP values of < 5 mg/L, a ferritin index of > 3.2 indicates depleted iron stores, and a ferritin index of < 3.2 indicates repleted iron stores. In patients with inflammatory diseases (CRP > 5 mg/L), the cut-off value for the ferritin index is 2.0.

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Diagnostics

Advantages of the diagnostic plot in the diagnosis of ID

In comparison to the traditionally used biochemical markers of iron metabolism and the complete blood count the plot offers the following advantages:

1. Early stages of ID are detected in real time before the development of microcytosis and hypochromia.
2. Functional ID can be diagnosed in conditions of hypoproliferative erythropoiesis and apparently normal iron stores (anemia of infection and chronic inflammation, endstage renal failure and cancer-related anemia).
3. The plot identifies major categories of erythropoietic states.

Therapeutic implications of the diagnostic plot

Therapeutic implications of the diagnostic plot are to differentiate anemic patients into those who should be administered iron, rHuEPO, or a combination of rHuEPO and iron [4].

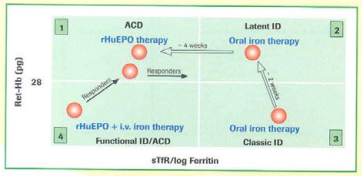

Figure 2: Therapeutic implications of the Thomas-Plot Response to the treatment of Anemia.

Monitoring response to iron administration

We recommend, the clinician provides iron supplementation to anemic patients with data points in quadrants 2 and 3 (Fig. 2). Patients with adequate oral iron supplementation usually respond with a shift in their data points from quadrant 3 to quadrant 2 within two weeks, and to quadrant 1 after 4 to 20 weeks.

rHuEPO therapy

The use of rHuEPO has led to the understanding that an adequate iron supply is critical to obtaining a therapeutic response and functional ID is seen in individuals with apparently normal iron stores. The marked expansion in erythroid mass induced by rHuEPO is of a magnitude to transiently deplete otherwise normal body iron stores and leads to the production of reticulocytes and erythrocytes that are indistinguishable from those produced in iron-deficiency anemia [6, 16, 17].
Using the diagnostic plot we recommend anemic patients with data points in quadrants 1 and 4 are administered to rHuEPO therapy. To optimize rHuEPO therapy with proper laboratory management the following procedure is recommended (Fig. 2) [18]:

1. Classification of patients into two different categories of erythropoietic state (quadrant 1 or 4) in accordance with Fig. 1 as the preliminary investigation.
2. Monitoring rHuEPO therapy in accordance with the modified diagnostic plot (Fig. 3) at week 2, 4, 8 and 12 after starting therapy. The aim is real-time detection of blunted response to rHuEPO (inadequate expansion in erythroid mass and development of functional ID). Changes in rHuEPO dose or use of intravenous iron can restore optimal response to rHuEPO.

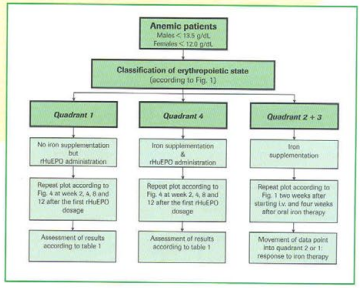

Figure 3: Classification of erythropoietic state.

The following conditions are defined for optimum response to rHuEPO 2 and 4 weeks after the first rHuEPO dosage (Fig. 4):

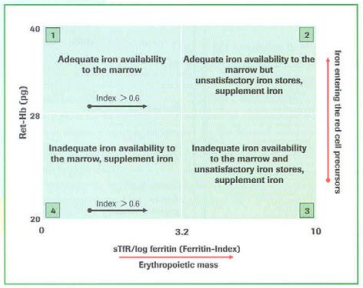

Figure 4: Thomas-Plot for monitoring expansion of erythroid mass, iron entering red cell precursors, and adequate iron stores in patients under rHuEPO therapy. Two weeks after the first rHuEPO dosage the increase in ferritin index vector of > 0.60 indicates effectiveness of rHuEPO, increase in Ret-Hb by > 2 pg or Ret-Hb values of > 28 pg excludes functional iron deficiency, and a ferritin index of < 3.2 demonstrates adequate iron supply from the stores for new red cell production.

1. Increase in ferritin index of > 0.6 as indicator of adequate expansion of erythroid mass.
2. Increase in Ret-Hb of > 2 pg or a permanent Ret-Hb > 28 pg as indicator of adequate amount of iron entering the red cell precursors; a Ret-Hb < 28 pg characterizes functional ID.
3. No increase in the ferritin index to > 3.2, the threshold value at which marrow iron availability is limited.
4. Increase in Hb concentration > 1 g/dL.

At week 8 and 12 indicators of adequate iron supply to the marrow are Ret-Hb > 28 pg and a ferritin index < 3.2.
A continuous increase in the Hb concentration indicates adequate rHuEPO dosage. Iron and rHuEPO should be adapted according to the latest results.

Parameter	Result	Treatment
Ferritin index vector	> 0.6	Adequate rHuEPO dosage.
	< 0.6	Increase rHuEPO dosage.
Ret-Hb	> 28 pg or increase of > 2 pg	No functional ID
	< 28 pg or increase < 2 pg	Functional ID, supplement i.v. iron.
Ferritin index	< 3.2	Adequate iron stores
	> 3.2	Inadequate iron stores, supplement i.v. iron.
Hemoglobin (Hb)	Increase > 1 g/dL	Adequate response.
	Increase < 1 g/dL	Inadequate response, supplement rHuEPO until week 4. If no Hb elevation increase rHuEPO dosage or stop rHuEPO therapy.

Table 1: Assessment of results two and four weeks after starting rHuEPO therapy.

Further considerations to be taken into account

The following limitations should be considered in order to effectively use the plot:

1. An increase of erythroid precursor cell mass (hemolytic syndrome, myelodysplastic syndrome, pregnancy) may shift data points from quadrant 1 to quadrant 2. This is caused by an increase in sTfR which correlates with erythroid precursor mass.
2. Patients with β-thalassemia trait may have data points in quadrant 4 even though they do not have functional iron deficiency.
3. A ferritin index cut-off of 2.0 in patients with APR should only be used in cases where CRP has been persistently elevated for at least 2 weeks, since changes in iron stores and erythroid precursor mass caused by APR need this time to affect the ferritin index.
4. Iron-supplemented patients with ACD may have data points in quadrants 2 or 3, but near the ferritin index cut-off. In these cases the iron supplementation may increase erythrocyte maturation and elevate sTfR, mostly within the reference range.
5. In cancer patients with chemotherapy-induced anemia and HYPO in the 5 to 25% range, Ret-Hb may have inadequately high values.
6. A low reticulocyte count may cause large variations in the calculation of Ret-Hb as hematology analyzers only measure fixed red cell counts (sum of erythrocytes and reticulocytes) in the sample.
7. The 95% confidence intervals for Ret-Hb of 28 pg and ferritin indices of 3.2 and 2.0 are 27-29 pg, 3.0-3.4 and 1.9-2.1, respectively. Samples with data points in quadrants 2 and 3 but within the confidence intervals of the ferritin index should be assessed clinically as belonging to erythropoietic status 1 and 4, respectively.

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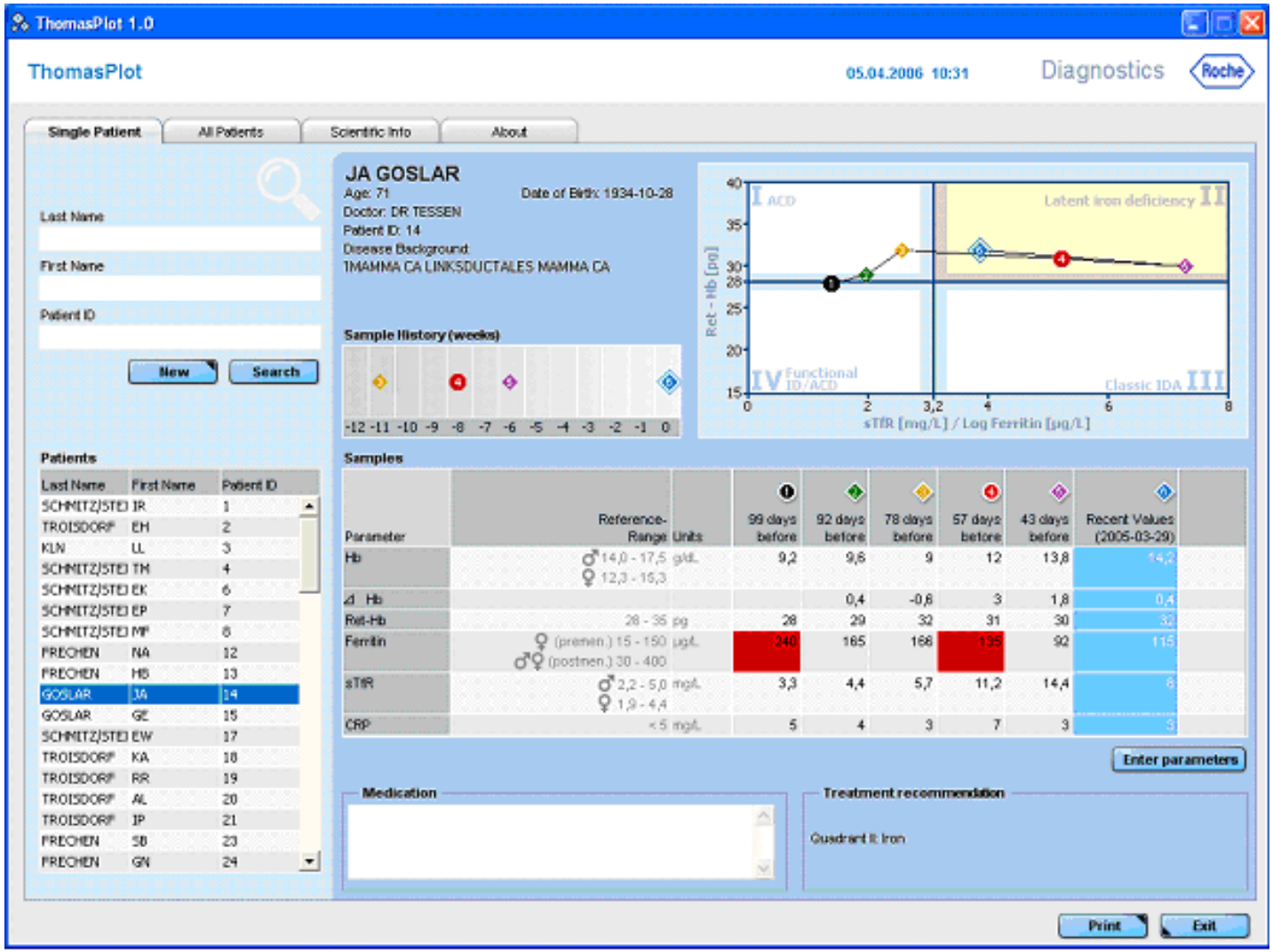
The Thomas Plot

A patented software gives instant graphical information



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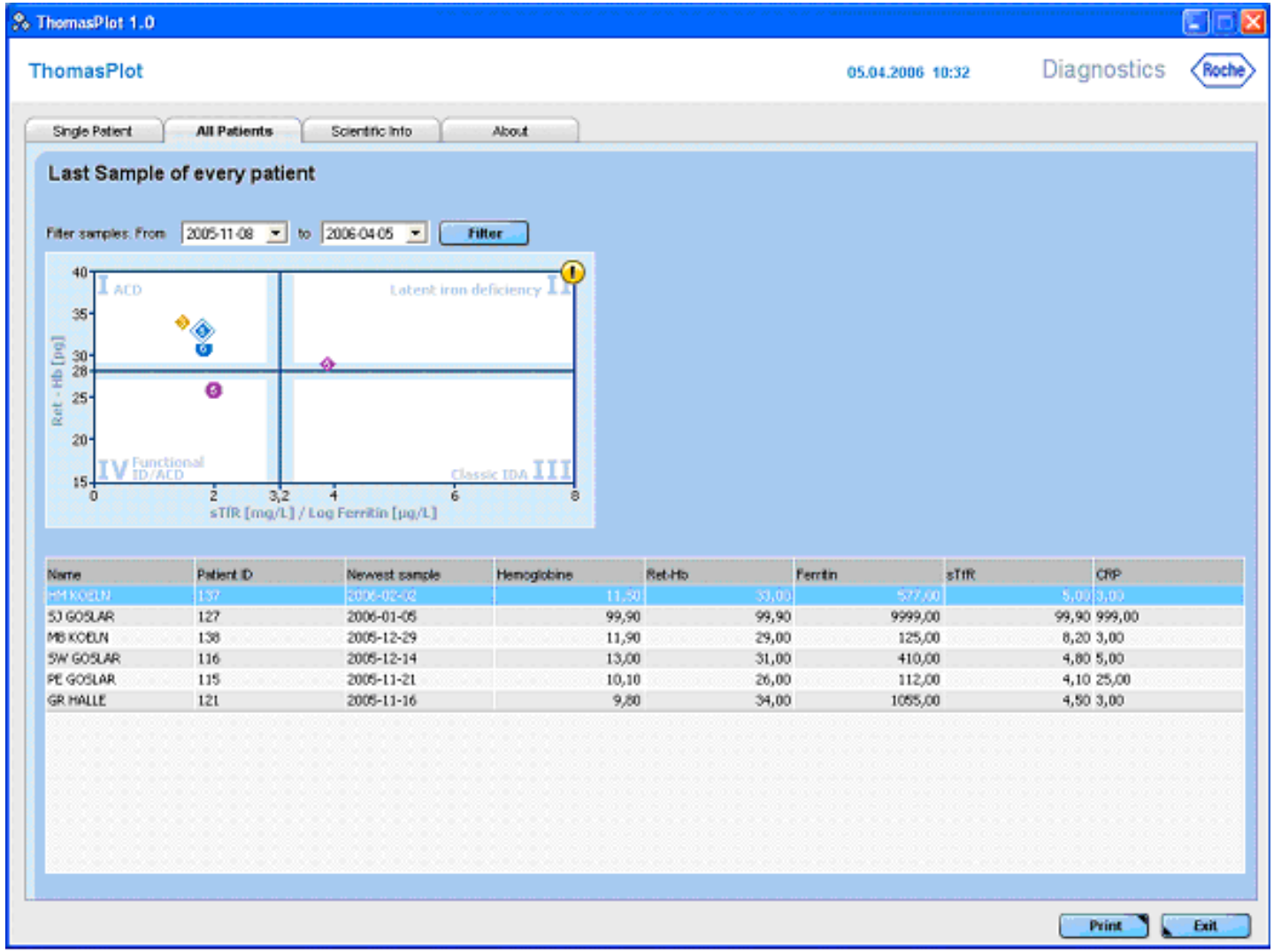

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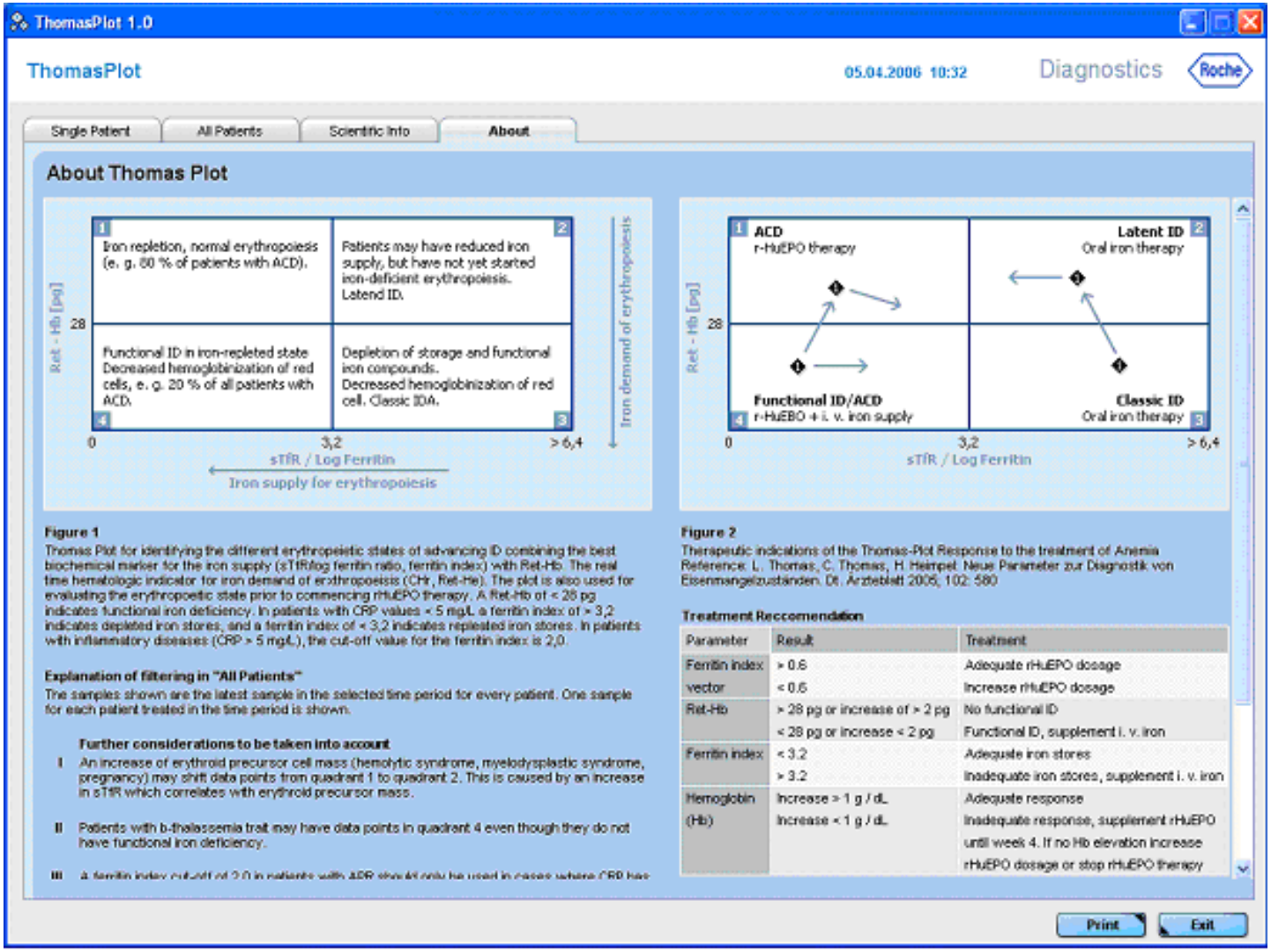

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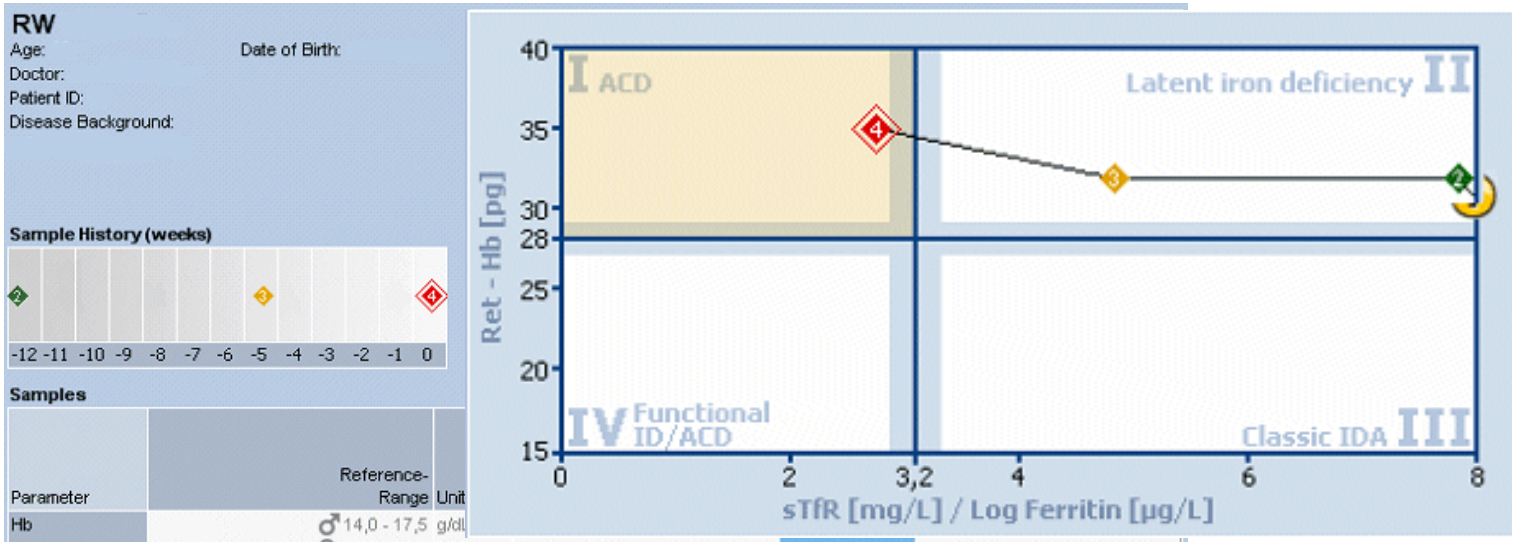

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Anemia

References (1)

1. Thomas C, Thomas L. **Biochemical markers and hematologic indices in the diagnosis of functional iron deficiency**. Clin Chem 2002; 48:1066-76.

2. Brugnara C. **Iron Deficiency and Erythropoiesis: New Diagnostic Approaches**. Clin Chem 2003; 49:10 1573-1578.

3. Brugnara C. **Reticulocyte cellular indices: a new approach in the diagnosis of anemias and monitoring of erythropoietic function**. Crit Rev Clin Lab Sci 2000; 37:93-130.

4. Brugnara C, Zemanovic D, Sorette M, Ballas SK, Platt O. **Reticulocyte hemoglobin. An integrated parameter for evaluation of erythropoietic activity**. Am J Clin Pathol 1997; 108:133-42.

5. Punnonen K, Irjala K, Rajarnäki A. **Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency**. Blood 1997; 89:1052-7.

Anemia

References (2)

6. Suominen P, Punnonen K, Rajarnäki A, Irjala K. **Serum transferrin receptor and transferrin receptor-ferritin index identify healthy subjects with subclinical iron deficits**. Blood 1998; 92:2934-9.

7. Wick M, Pinggera W, Lehmann P. **Iron Metabolism, Anemias Diagnosis and Therapy: Novel concepts in the anaemias of renal and rheumatoid disease**. 4th enlarged edition, Springer Wien New York, 2000.

8. **Der Thomas-Plot – neuer Goldstandard in der Anämie-Diagnostik?** Springer Verlag, Beilage in Der Onkologe, 2005; Band 11:3.

9. Thomas L, Thomas Ch, Heimpel H. **Neue Parameter zur Diagnostik von Eisenmangelzuständen**. Deutsches Ärzteblatt 2005; 102:9, A580-A586.

10. Weiss G, Goodnough LT. **Medical Progress, Anemia of Chronic Disease**. N Engl J Med 2005; 352:10, 1011-1023.

11. Thomas Ch, Thomas L. **Anemia of Chronic Disease: Pathophysiology and Laboratory Diagnosis**. Lab Hematology 2005; 11:14-23.

Links (1)

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Diagnostics

- “Новая концепция диагностики анемий с нарушением метаболизма железа”
  “Дни клинической химии”
  Москава, 7.04.2005 . Кузнецова О.А. (Powerpoint-Präsentation)
  www.roche.ru/diagnostics/ppt/ccdanemia.ppt
- Fachinformationen Medizinische Laboratorien Düsseldorf
  Gemeinschaftspraxis für Laboratoriumsmedizin, Mikrobiologie und Infektionsepidemiologie; Dr. med. Paul Nemes, Dr. med. Stephan Schauseil, Dr. med. Dipl.-Biol. Michael Kux, Dr. med. Andreas Gehrt
  http://www.labor-duesseldorf.de/?p=6&b=T&i=407
- Laborreport 29, Labor Gärtner, Ravensburg
  (Prof. Thomas und der sTfR/log Ferritin-Index kurz erwähnt)
  http://labor-gaertner.com/report.php?report29=show

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Links (2)

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Diagnostics

- Laborfachinformation – Update 2005 (Labor Fenner, Hamburg)
  Eisenmangel – Effiziente Diagnostik und Optimierte Therapiekontrolle
  http://www.fennerlabor.de/uploads/media/EISENSTOFFW_UPDATE_2005_01.pdf
- Jugoslovenska medicinska biohemija
  Year (Volume): 2004(23) / Issue: 3 / Pages: 235-239 / Title: Biochemical markers and haematologic indices in the diagnosis of iron-restricted erythropoiesis and monitoring of r-HuEPO therapy / Author(s): Thomas Lothar, Thomas Christian
  http://www.doiserbia.nbs.bg.ac.yu/Article.aspx?ID=0354-34470403235T
- Vorgehensweise zur differenzierten Diagnostik von Eisenmangelzuständen
  Laborinformation, Labor Enders, Stuttgart
  http://www.labor-enders.de/125.0.html
- Anemia.org
  Research Briefs "Conventional Labs for Iron Deficiency may be Inadequate“
  http://www.anemia.org/professionals/research/briefs/conventional_labs.jsp

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Links (3)

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Diagnostics

- Thomas, Lothar; Thomas, Christian; Heimpel, Hermann
  Neue Parameter zur Diagnostik von Eisenmangelzuständen: Retikulozytenhämoglobin und löslicher Transferrinrezeptor.
  Deutsches Ärzteblatt 102, Ausgabe 9 vom 04.03.2005, Seite A-580 / B-488 / C-455; MEDIZIN
  http://www.aerzteblatt.de/v4/archiv/artikel.asp?id=45682
- Eisenstoffwechsel-Diagnostik
  http://www.laborlexikon.de/Lexikon/Infoframe/e/Eisenstoffwechsel-Diagnostik.htm
- Sysmex Symposium 2003: Clinical Utility of the RET-Y in Functional Iron Deficiency (L.Thomas, S. Franck, M.Messinger. Clinical Laboratory, Krankenhaus Nordwest, Frankfurt/Main, Germany
  http://www.sysmex-europe.com/Science/XE%202100%20New%20technologies%20in%20Hematology/Sysmex%20Symposium/2003/Thomas.asp

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Improved differential diagnosis of iron deficiency – The Thomas Plot

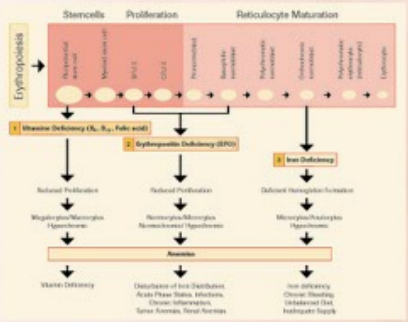
Going straight for the answer

The intended use

The Thomas Plot is a tool to determine and classify the exact iron status of anemic patients also under complex metabolic conditions such as chronic diseases to treat their anemia with recombinant human erythropoietin like (r-HuEPO, NeoRecormon® Roche) and/or iron (oral or i.v.) adequately. The plot was developed in close co-operation with Prof. Lothar Thomas from University Hospital Frankfurt / Germany. It consolidates diagnostic information from hematology (RET-He, hemoglobin content of reticulocytes) and biochemistry (CRP, ferritin, and soluble transferrin receptor/sTfR)*.

Clinical background

- Iron Deficiency (ID) and Iron Deficiency Anemia (IDA) are a widespread medical problem affecting a great portion of the world's population.
- IDA patients with anemia caused by e.g. infections, inflammation, and cancer are quite often featuring normal or even increased iron stores. However, in about 20% of these patients iron cannot be mobilized from the stores to provide the erythropoiesis (red cell synthesis) with sufficient amounts of iron. These patients are in a state of Functional Iron Deficiency (FID), an imbalance of iron needs and iron supply.
- FID leads to a reduction of hemoglobinization of red blood cells causing hypochromic microcytic erythrocytes finally resulting in anemia.



The challenge

- Iron deficiency and Iron Deficiency Anemia are not difficult to diagnose. There are several diagnostic parameters used in clinical routine for the estimation of available iron stores such as ferritin, transferrin saturation, etc. for laboratories and physicians. However, correct diagnosis becomes a challenge in patients with chronic inflammatory processes.
- Ferritin and transferrin are acute phase reactants and do not present correct information about the iron status under these conditions. Also the transferrin saturation may lead to wrong results.

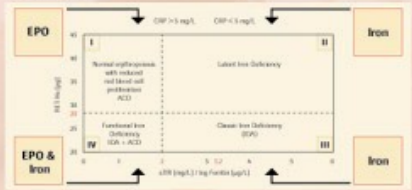
*Ref.: Thomas C, Thomas L, Biochemical markers and hematological indices in the diagnosis of functional iron deficiency. Clin Chem 2002; 48:1066-1076

The solution – The Thomas Plot

- It combines Ferritin, sTfR (both expressed as ferritin index), CRP, and RET-He in a diagnostic plot using a software algorithm.

The analytical tools

- Dependent on the measured concentrations patients are allocated in one of four different sections of the plot each representing a specific area of IDA and requiring specific treatment with either recombinant human erythropoietin (r-HuEPO, NeoRecormon® Roche) and/or iron (oral or i.v.).



- In addition to that it provides early information about treatment response which is important for dosage adjustment and health economical reasons.

The ferritin index cut-offs are dependent on the patient's CRP value: CRP >5 mg/L → ferritin index = 2; CRP <5 mg/L → ferritin index = 3.2

The treatment can be monitored and controlled by multiple plotting over time:

This chart demonstrates the typical course during correction of the iron deficiency under the appropriate medication.

Summary

The Thomas Plot is a prominent example of actionable health information combining information from various analytical sources to better manage patients with iron deficient anemia of different genesis.

Roche Diagnostics

Roche Diagnostics GmbH
Roche Centralized Diagnostics
68298 Mannheim
Germany
www.roche.com

Anaemia Testing

Going straight for the answer

The indication

Anaemia is the inability of the blood to supply tissue with adequate oxygen for proper metabolic function.
Anaemia is usually associated with decreased levels of haemoglobin or a decreased packed red cell volume, also known as the hematocrit.
About 30% of the world's population suffers from anaemia.
Approximately 50% of all anaemias are caused by iron-deficiency.
A wide variation in the prevalence of anaemia has been reported with the highest rates occurring in the less developed regions of the world.

The diagnostic challenge

- Anaemia is a sign of an underlying pathology whose recognition requires the identification of the mechanism and causes of red blood cell deficit.
- Determining the specific cause of anaemia is important to the physician in order to apply the appropriate therapy.
- The primary diagnosis of anaemia is made by referring to patient history, signs and symptoms, and haematological laboratory findings.

The solution

- *Haematological status* - Anaemia is defined as hemoglobin concentrations lower than reference value. Therefore, the assessment of the haematological status is the initial test for the primary diagnosis of anaemia (Hemoglobin, haematocrit, RBC count, reticulocyte count, NRBC, differential count).
- *Iron Status* – The regulation of the iron balance is critical because both iron deficiency and iron overload may be deleterious. Therefore the assessment of iron status is extremely important for differential diagnosis and definitive evaluation of iron in patients who have iron-deficiency anaemia (Iron, Transferrin, UIBC/TIBC, Ferritin, Soluble Transferrin Receptor, Ceruloplasmin, Haptoglobin).
- *Vitamin Status and antioxidative potential* – The initial diagnosis of megaloblastic anaemia is usually suspected if the mean corpuscular volume is elevated. In more than 90% of these cases, the cause is either vitamin B12 or Folate deficiency (Vitamine B12, Folate, Homocysteine).
- *Classification according to the red blood cell indices* – the RBC indices are the mean corpuscular volume (MCV), mean cell hemoglobin (MCH) and mean cell hemoglobin Concentration (MCHC). These RBC indices are calculated by automated blood profiling systems.

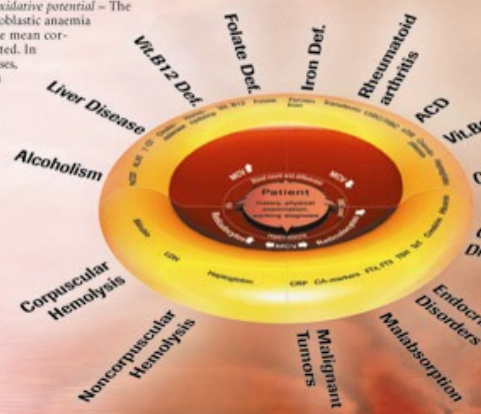
Roche Diagnostics offers one of the most comprehensive menus for the differential diagnosis and management of Anaemia patients.

The analytical tools for anaemia testing

Reagent portfolio and instruments for consolidated anaemia testing

	Roche/Hitachi Systems 902, 912, 917	COBAS INTEGRA	Elecsys	MODULAR ANALYTICS
Iron	●	●		D/P
Transferrin	●	●		P
UIBC/TIBC	●	●		D/P
Ferritin	●	●	●	P/E
sTfR	●	●		P
Ceruloplasmin	●	●		P
Haptoglobin	●	●		P
Vitamin B12			●	E
(RBC) Folate			●	E
Homocysteine	(●)	(●)		(P)
LDH	●	●		D/P
%CDT	●			P
Serum work area				
●() in development; D = D 2400 module; P = P 800 module; E = E 170 module				
Haematology analyser				
Haemoglobin Haematocrit	Complete blood count: - Red blood cell (RBC) count (MCV, MCH, MCHC)		- Reticulocyte count - White blood cells (WBC) count (lymphocytes, monocytes, granulocytes) - Platelets	
Blood work area				

Not all products are available in all countries.



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Thank you for your attention

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Anemia

Cell size, Cell staining

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Diagnostics

Normochromic and normocytic anemia

Reduced proliferation of erythrocytes with normal Hb content and normal cell size (seen in Erythropoietin deficiency).

Hypochromic and microcytic anemia

Erythrocytes with decreased Hb content and low cell size (seen in iron deficiency).

Hyperchromic and macrocytic anemia

Erythrocytes with increased Hb content and high cell size (seen in vitamin deficiency)

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Anemia

Anemia is a Sign of an underlying Pathology

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Diagnostics

ACD (Anemia of chronic disease)

ACD is characterized by inadequate production of erythropoietin, inhibition of the proliferation of erythroid progenitor cells in the bone marrow, and disturbances in iron distribution. ACD results from activation of the immune and inflammatory systems. In ACD the supply depends on its role of mobilization.

IDA (Iron – deficient anemia)

The diagnosis of IDA is based on the presence of anemia and erythrocyte morphology in conjunction with low serum ferritin, decreased TfS or increased sTfR. In IDA, the iron supply depends on the amount of iron stores.

Functional iron deficiency

Functional iron deficiency is defined as discrepancy between marrow iron availability and requirements. This leads to reduced reticuloyte and erythrocyte cellular hemoglobin (Hb) content.

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Iron Distribution

- 35 – 45 mg/kg iron in adult male body
- Total aproxx 4 g
  - Red cell mass as haemoglbon – 50 %
  - Muscles as myoglobin – 7 %
  - Storage as ferritin – 30 %
    - Bone marrow (7 %)
    - Reticulo-endothelial cells (7 %)
    - Liver (25 %)
  - Other Haem proteins – 5 %
    - Cytochromes, myoglobin, others
  - In Serum – 0.1 %