How to treat non-clonal polyglobulia: to bleed or not to bleed

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Disclosures

Institutional research support: Novartis and Shire Pharmaceuticals

Speaker: Novartis, Sanofi Avensis, Shire, CTI, Prime oncology, Medscape

Consultancy work: Novartis, Sbio, YMBioscience, Cellgene, Sanofi Avensis, Gilead, CTI, NICE

Learning outcomes

- To be able to classify erythrocytosis
- To understand the investigation of a suspected erythrocytosis
- To consider possible management options for a patient with an erythrocytosis…..

“To venesect or not”

Who should be investigated?

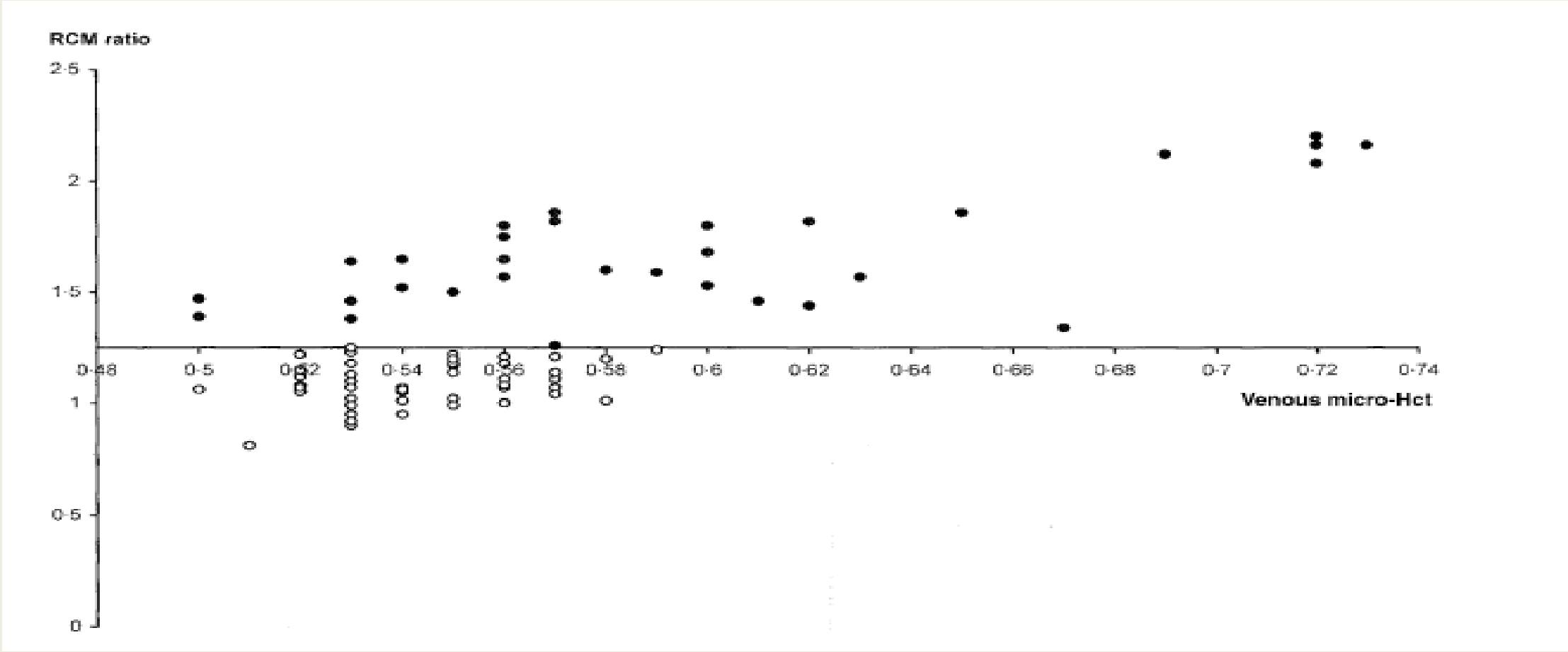
- A persistently raised venous haematocrit (>0.52 males , >0.48 in females for >2 months) should be investigated.
- A Hct above 0.60 in males and 0.56 in females can be assumed to have absolute erythrocytosis.

Caution

- Patients with iron deficient red cell indices

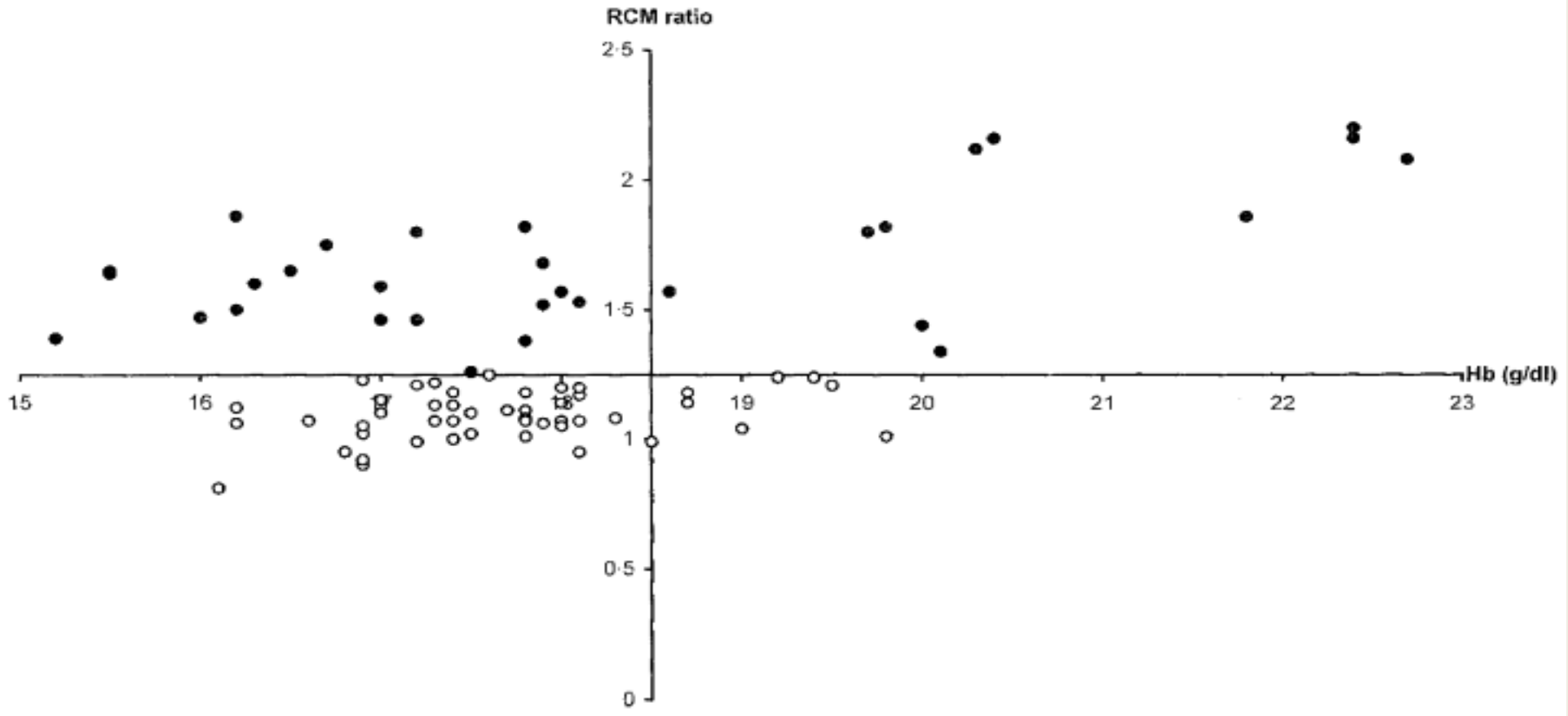
BCSH guidelines 2007 McMullin etal

RCM shows better correlation with HCT



Johansson Pl et al. Br. J. Haem. 2005; 129, 701-5

Haemoglobin and red cell mass (males) shows less good correlation



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Diagnostic criteria for Polycythemia Vera
WHO 2016

- **Major**
- HCT > .49 (men), .48 (women) or other evidence of increased red cell mass
- *JAK2* mutation
- Bone marrow biopsy showing panmyelosis

- **Minor**
- Serum Epo below the normal reference range

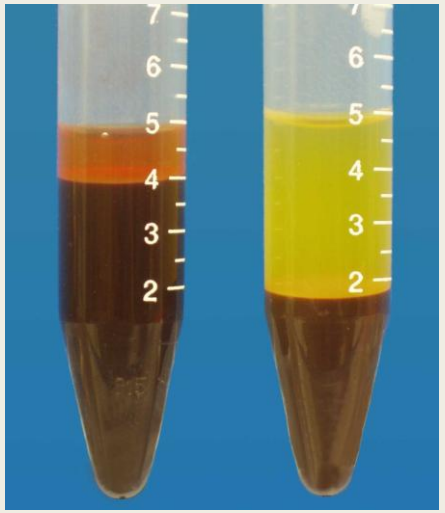
all major or
Two major and one minor establishes PV

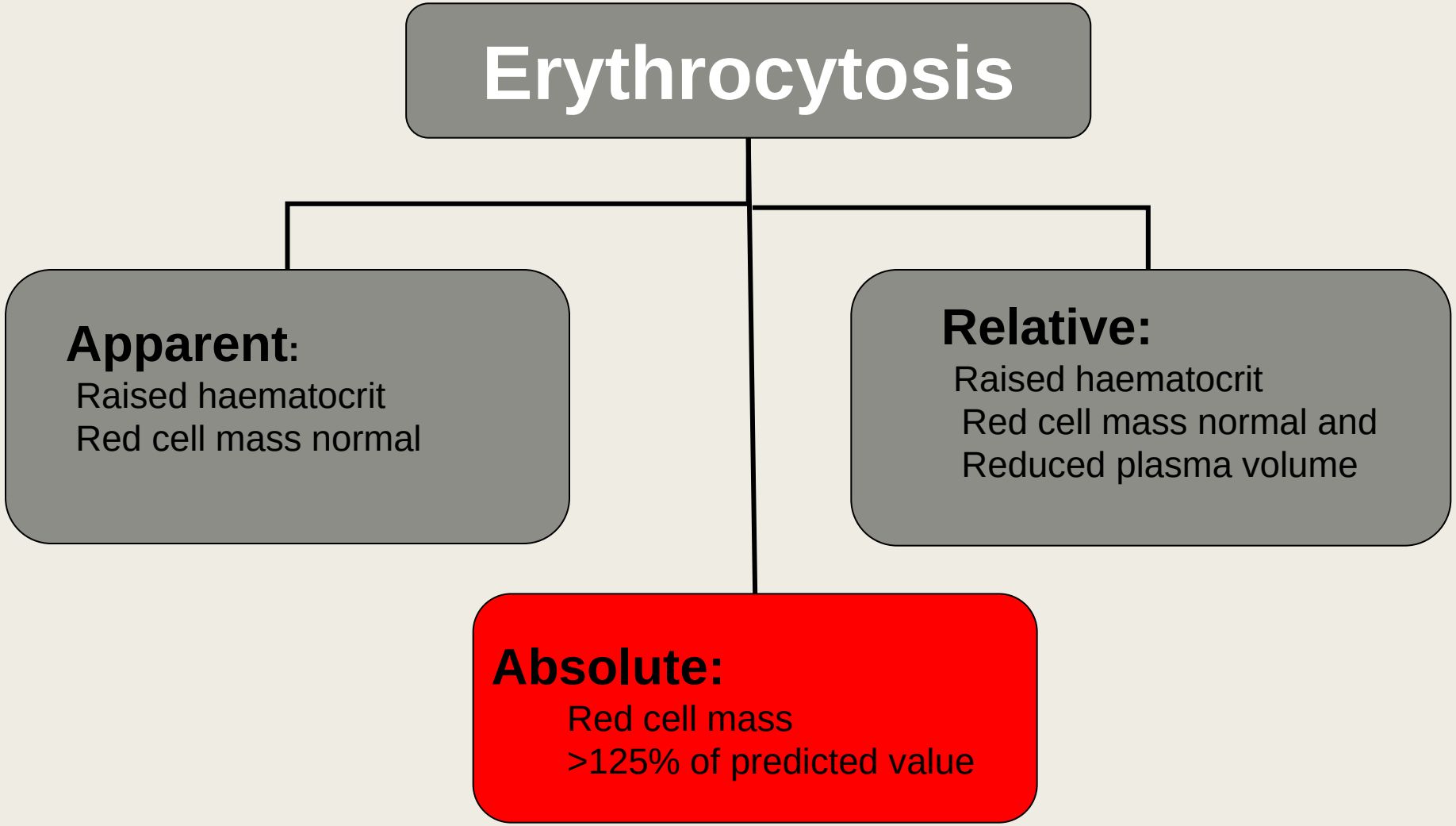
Erythrocytosis

Apparent:
Raised haematocrit
Red cell mass normal

Relative:
Raised haematocrit
Red cell mass normal and
Reduced plasma volume

Absolute:
Red cell mass
>125% of predicted value

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- **Primary erythrocytosis**
  - **Congenital**
    - **Acquired**
    - Polycythemia vera
    - *LNK* mutations (congenital and acquired)
- **Secondary erythrocytosis**
  - **Congenital**
  - **Acquired**
    - **Central hypoxic process**
    - **Local hypoxia**
    - **Pathologic EPO production**
    - **Exogenous EPO**
- **Idiopathic erythrocytosis**

Congenital erythrocytosis:

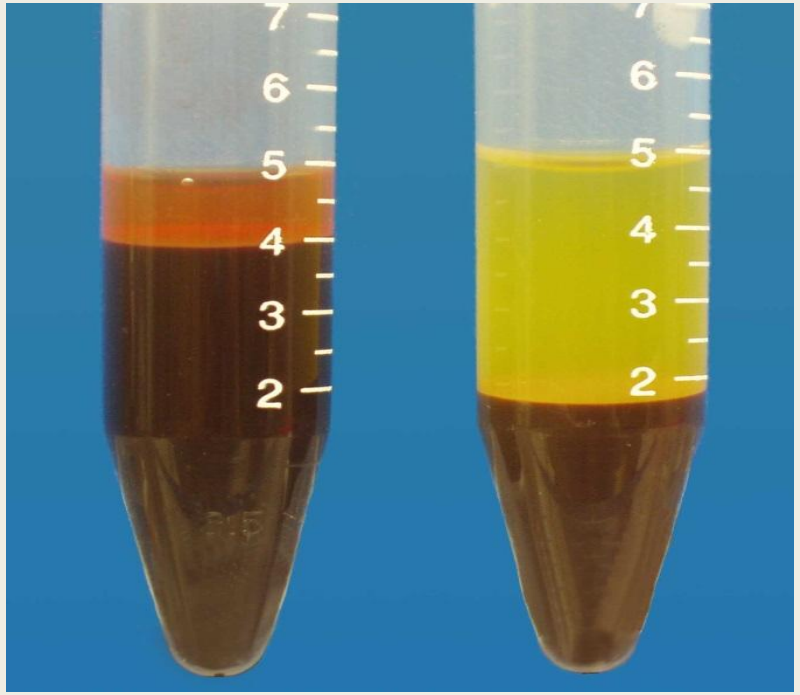
- **Primary**
- ***EPO receptor* mutations**
- **Secondary**
- Oxygen sensing pathway mutations
  - *VHL gene mutations*
  - *PHD2 mutations*
  - *HIF -2a mutations*
- Bisphosphoglycerate mutase deficiency
- High oxygen-affinity haemoglobin
- Methaemoglobinaemia
- Hereditary ATP increase

……And many others now being

Diagnostic pathway

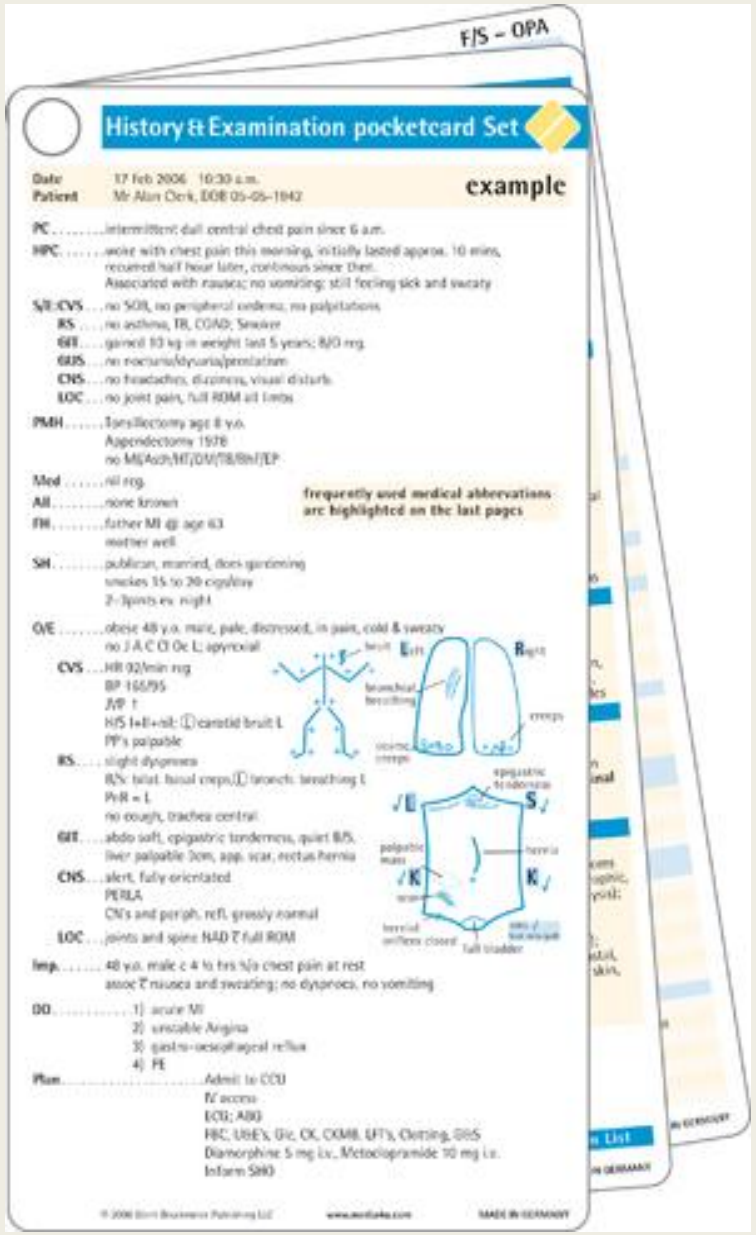
- Persistence
- History and examination

- EPO level +/- JAK2 mutation test
- CarboxyHaemoglobin



Diagnostic pathway

- History and examination
- Symptoms of hyperviscosity
- Predisposing factors
- Drugs including recreational
- Lifestyle
- Family history:
  - Vascular disease &
  - Erythrocytosis



Investigations

- Repeat confirmatory FBC
- Erythropoietin level, Carboxyhaemoglobin, JAK2 mutations

- Bone marrow biopsy
- Imaging
- Overnight oximetry
- Red Cell Mass
- P_{50}- Oxygen dissociation curve
- Haemoglobin electrophoresis
- Sequencing of known gene mutations

- NGS….. Can replace p50, electrophoresis and sequencing

Erythrocytosis

Measurement of EPO levels

Primary if low/normal (10%)

Secondary if normal/high

Defect intrinsic to erythroid cell

Erythropoietin driven

Investigations

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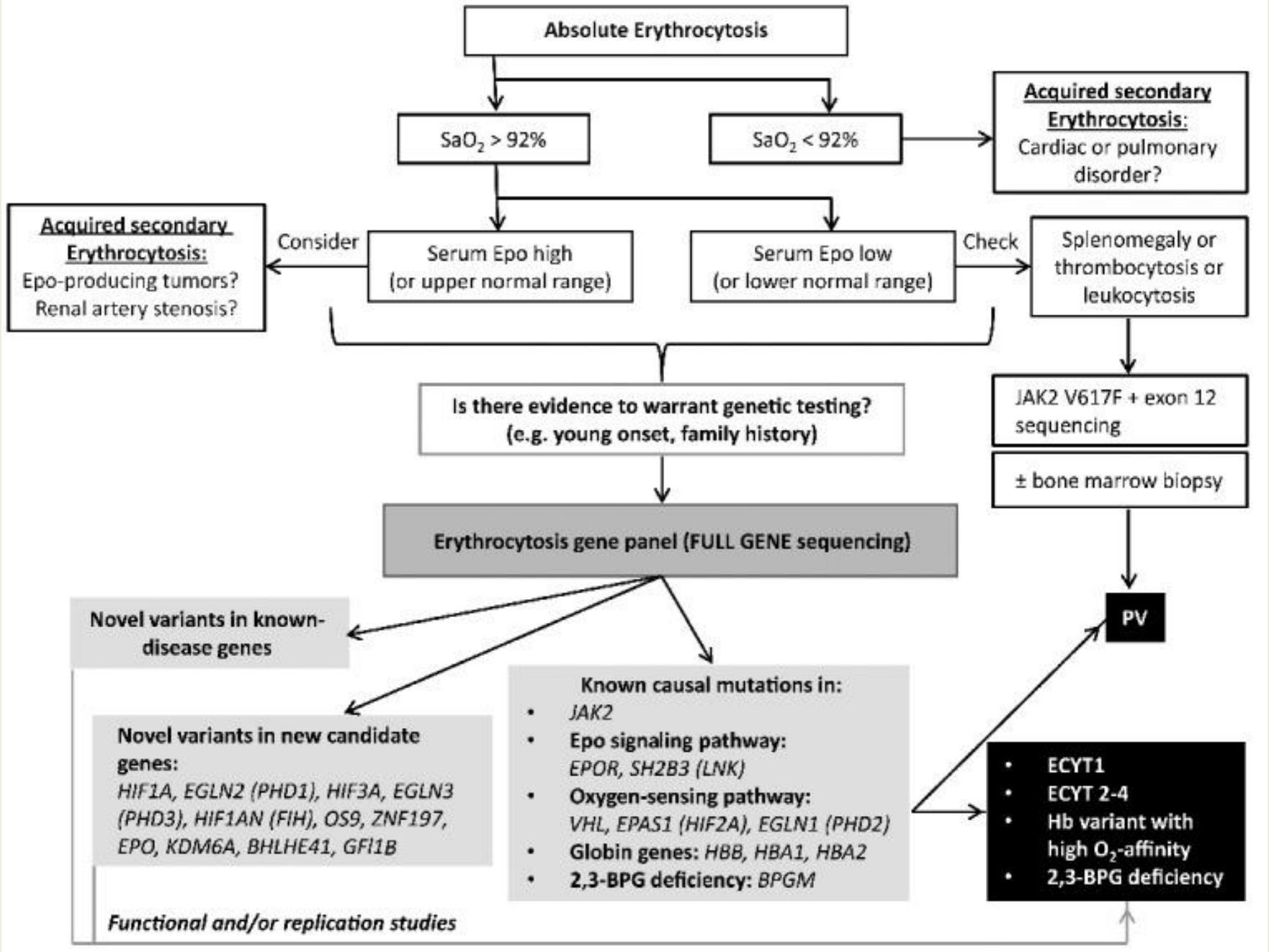
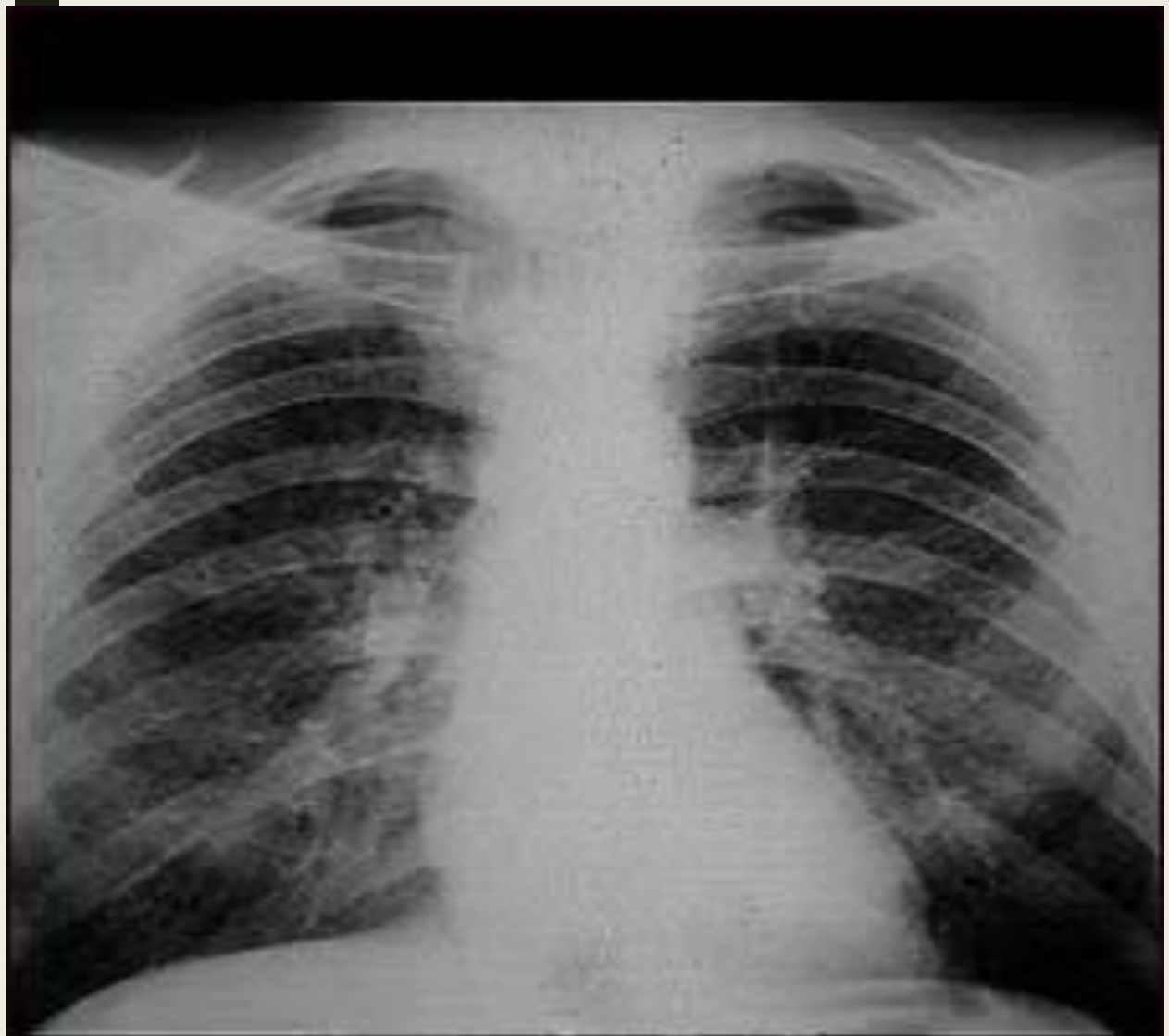
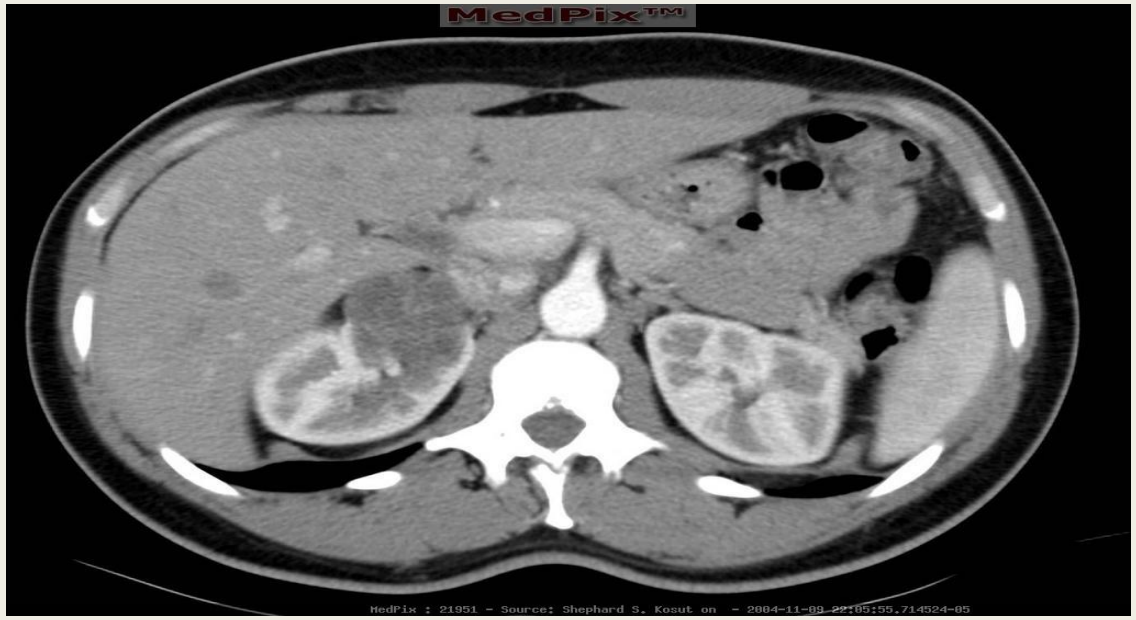
As directed by history, examination and clinical findings

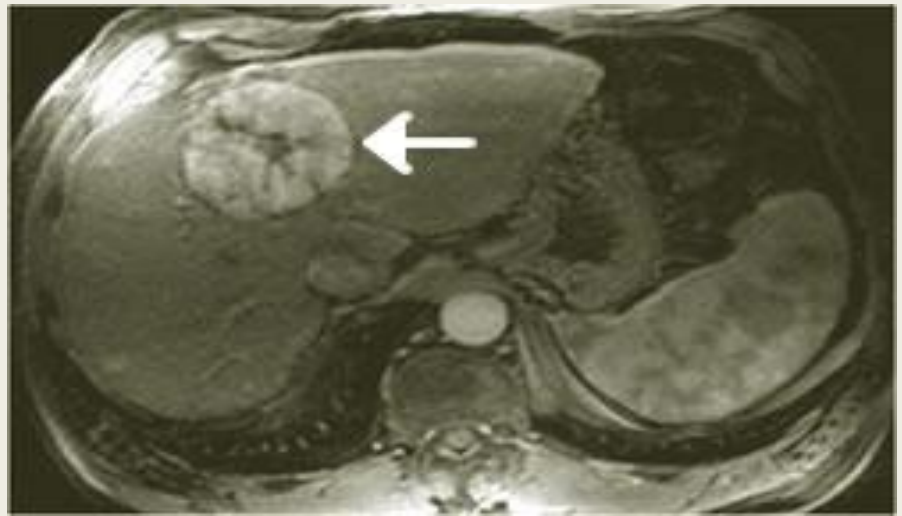
- NGS….. Can replace P_{50}, electrophoresis and gene sequencing


Absolute Erythrocytosis
SaO2 > 92%
SaO2 < 92%
Acquired secondary Erythrocytosis: Cardiac or pulmonary disorder?
Acquired secondary Erythrocytosis: Epo-producing tumors? Renal artery stenosis?
Consider
Serum Epo high (or upper normal range)
Serum Epo low (or lower normal range)
Check
Splenomegaly or thrombocytosis or leukocytosis
Is there evidence to warrant genetic testing? (e.g. young onset, family history)
JAK2 V617F + exon 12 sequencing
± bone marrow biopsy
Erythrocytosis gene panel (FULL GENE sequencing)
PV
Novel variants in known-disease genes
Novel variants in new candidate genes: HIF1A, EGLN2 (PHD1), HIF3A, EGLN3 (PHD3), HIF1AN (FIH), OS9, ZNF197, EPO, KDM6A, BHLHE41, GFI1B
Known causal mutations in:
JAK2
Epo signaling pathway: EPOR, SH2B3 (LNK)
Oxygen-sensing pathway: VHL, EPAS1 (HIF2A), EGLN1 (PHD2)
Globin genes: HBB, HBA1, HBA2
2,3-BPG deficiency: BPGM
ECYT1
ECYT 2-4
Hb variant with high O2-affinity
2,3-BPG deficiency
Functional and/or replication studies

Acquired secondary erythrocytosis







Acquired: EPO mediated: Hypoxia driven

Central hypoxic process

- Chronic lung disease
- Right-to-left cardiopulmonary vascular shunts
- Carbon monoxide poisoning
- Smoker's erythrocytosis
- Hypoventilation syndromes including sleep apnoea
- High-altitude habitat

Local renal hypoxia

- Renal artery stenosis
- End stage renal disease
- Hydronephrosis
- Renal cysts (polycystic kidney disease)
- Post- renal transplant erythrocytosis

Acquired: Excess EPO

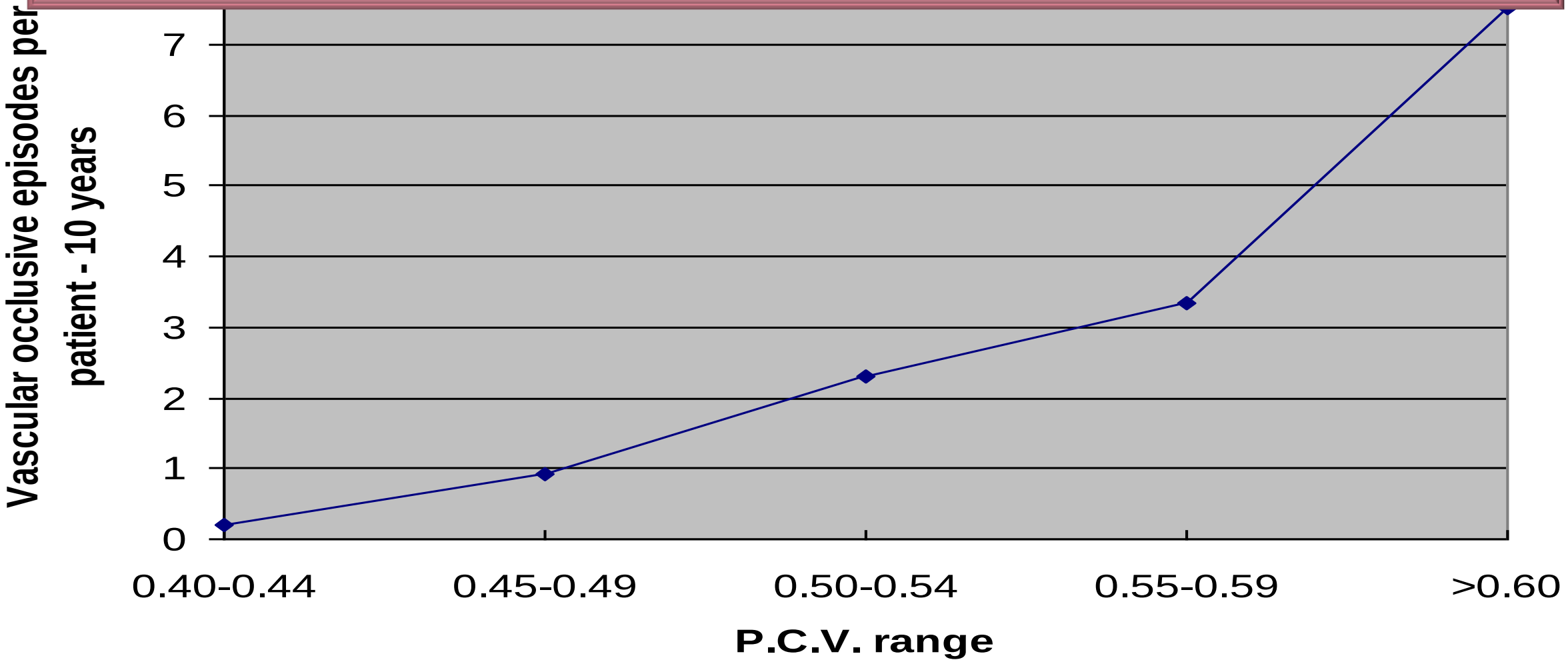
Pathologic EPO production

- Cerebellar haemangioblastoma
- Meningioma
- Parathyroid carcinoma/adenomas
- Hepatocellular carcinoma
- Renal cell cancer
- Pheochromocytoma
- Uterine leiomyomas

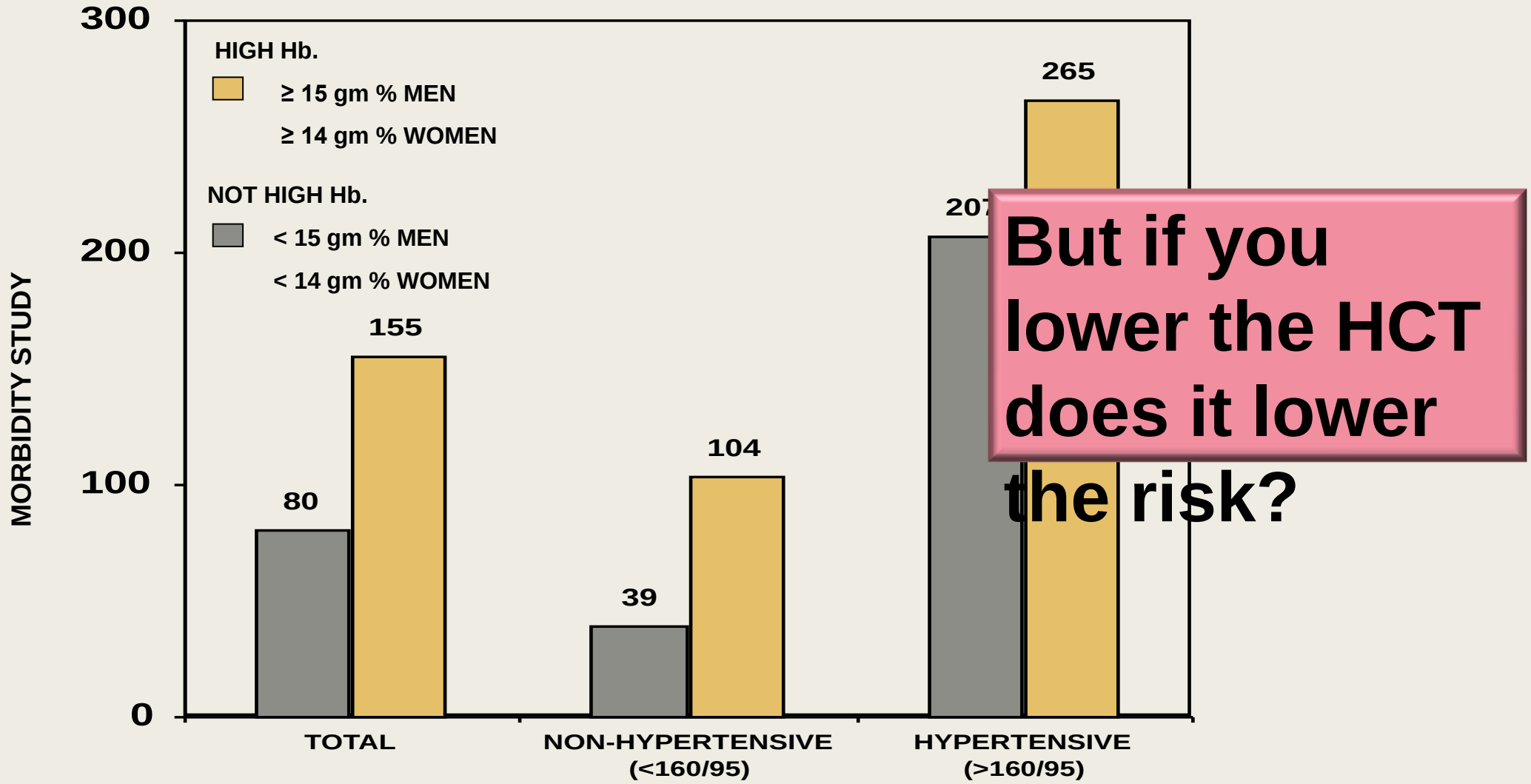
Management of secondary erythrocytosis:

- Venesection is NOT the mainstay

Considering PV there is clear evidence of HCT control being important…….



Relation of PCV range to number of vascular occlusive episodes per 10 patient-years
In patients with primary proliferative polycythaemia.

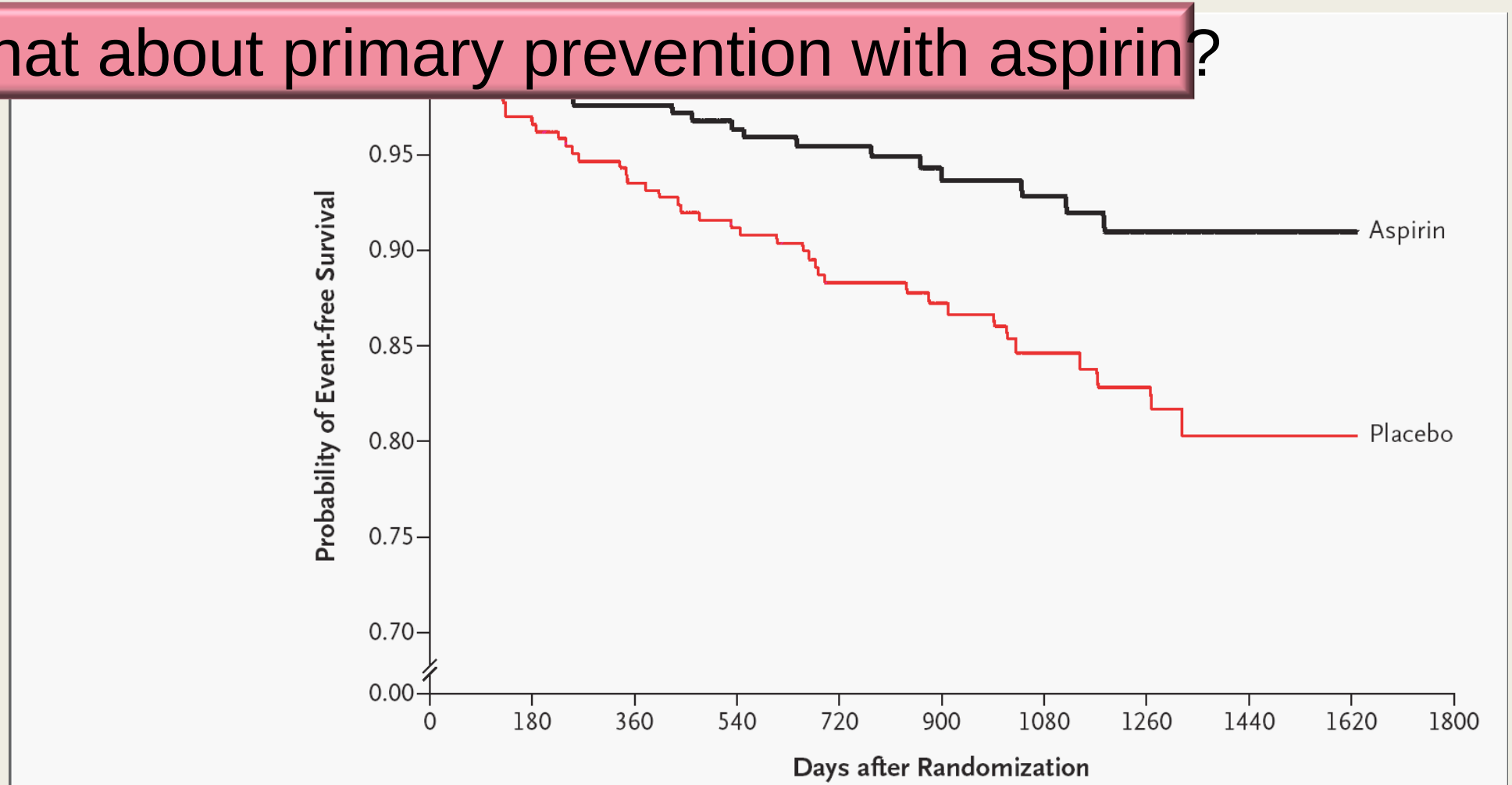


But if you lower the HCT does it lower the risk?

Risk of cerebral infarction (16 year follow up) according to antecedent hemoglobin and blood pressure status. Men and women 30-62 at entry: Framingham Study.

KANNEL, et al, Stroke, 1972, 3, 409-420

What about primary prevention with aspirin?



No. at Risk (No. of Events)											
Aspirin	253 (1)	249 (5)	243 (3)	223 (2)	204 (3)	145 (1)	108 (2)	78 (0)	23 (0)	1 (0)	0
Placebo	265 (10)	254 (8)	242 (6)	226 (7)	214 (2)	157 (4)	112 (2)	70 (2)	22 (0)	1 (0)	0

Figure 2. Probability of Survival Free of a Thrombotic Event.

The analysis was performed according to the intention-to-treat principle. The relative risk of a thrombotic event in the aspirin group, as compared with the placebo group, was 0.42 (95 percent confidence interval, 0.24 to 0.74; P=0.002 by the log-rank test).

Management of acquired secondary erythrocyosis

- Address the underlying cause where possible
- Many require non-haematological input eg sleep apnoea
- Standard lifestyle measures apply

- Only venesect if there is a very clear indication
- Eg very high HCT > 0.54 and symptoms or risk eg pre op
- NB this does NOT apply to cyanotic heart disease
- Aspirin only if otherwise indicated

Recent case from our clinical practice

- 34 year old man presents with episode of black out
- Shortly after arrival had an epileptic seizure, full recovery
- No relevant history, non-smoker, increasing headaches.

FBC

Hb 240g/L

HCT 0.64

Wbc 8 x 10^9

Platelets 341 x 10^9

Advice?

Persistently abnormal

Recent case from our clinical practice

- 34 year old man presents with episode of black out
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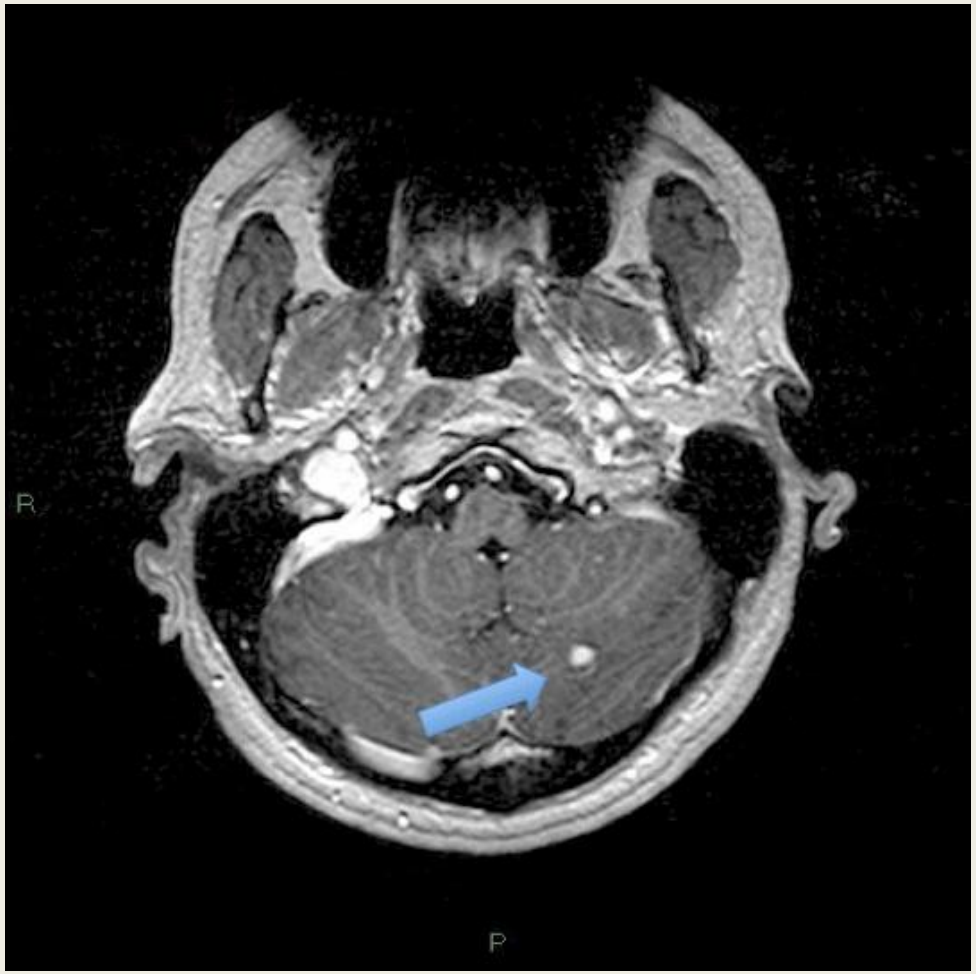
FBC
Hb 240g/L
HCT 0.64
Wbc 8 x 10^9
Platelets 341 x 10^9

- **Check EPO/JAK2 etc**
- **Get urgent imaging**
- **Hydrate and perform isovolaemic venesection**



"POLYCYTHEMIA" ASSOCIATED WITH CEREBELLAR HEMANGIOBLASTOMA

ARTHUR A. WARD, JR., M.D., ELDON L. FOLTZ, M.D., AND LAWRENCE M. KNOPP, M.D.

Division of Neurosurgery, University of Washington, and Neurosurgical Service, Veterans Administration Hospital, Seattle, Washington

(Received for publication December 16, 1955)

In 1943, Carpenter and co-workers[3] reported 2 cases of cerebellar hemangioblastoma with associated "polycythemia vera." They added 3 cases from the literature. Since then, about 22 such cases have been reported in the American literature.[3,4,8,12,21,25] Hemangioblastomas of the posterior fossa constitute only 2 per cent of intracranial tumors[5,6,16] and those associated with "polycythemia" less than 20 per cent of the total number of hemangioblastomas.[4] Thus, the association of "polycythemia" with posterior fossa hemangioblastoma is, to paraphrase Carpenter, an event of the greatest rarity.

Polycythemia rubra vera has been defined as a disease of unknown etiology, characterized by an excessive production of all marrow elements with resultant increase in red blood cell count, total red blood cell volume, white blood cell and platelet counts, and accompanied by increased blood viscosity and decreased velocity of blood flow.[19,23] Since quantitative blood studies have been done in only 1 of the reported cases of cerebellar hemangioblastoma,[3] it is difficult to determine whether polycythemia vera (as defined above) did, in fact, exist in the remainder. Possibly erythrocytosis, in which the red blood cell count is elevated with no increase in white blood cells or platelets, might be a more appropriate term to use.

We have recently studied 2 patients who had posterior fossa hemangioblastomas with associated erythrocytosis. Both patients were treated surgically, one with subtotal and the other with total removal of the tumor. We believe that the hematologic studies made in these 2 cases are more nearly complete than those reported heretofore.

It has not yet been proved that the relationship between the altered blood picture and the tumor is more than fortuitous. Although the basic physiopathology is unknown, the reduction in the degree of erythrocytosis in some cases following removal of the tumor suggests a cause-effect rela-

- **Primary erythrocytosis**
  - **Congenital**
    - **Acquired**
    - Polycythemia vera
    - *LNK* mutations (congenital and acquired)
- **Secondary erythrocytosis**
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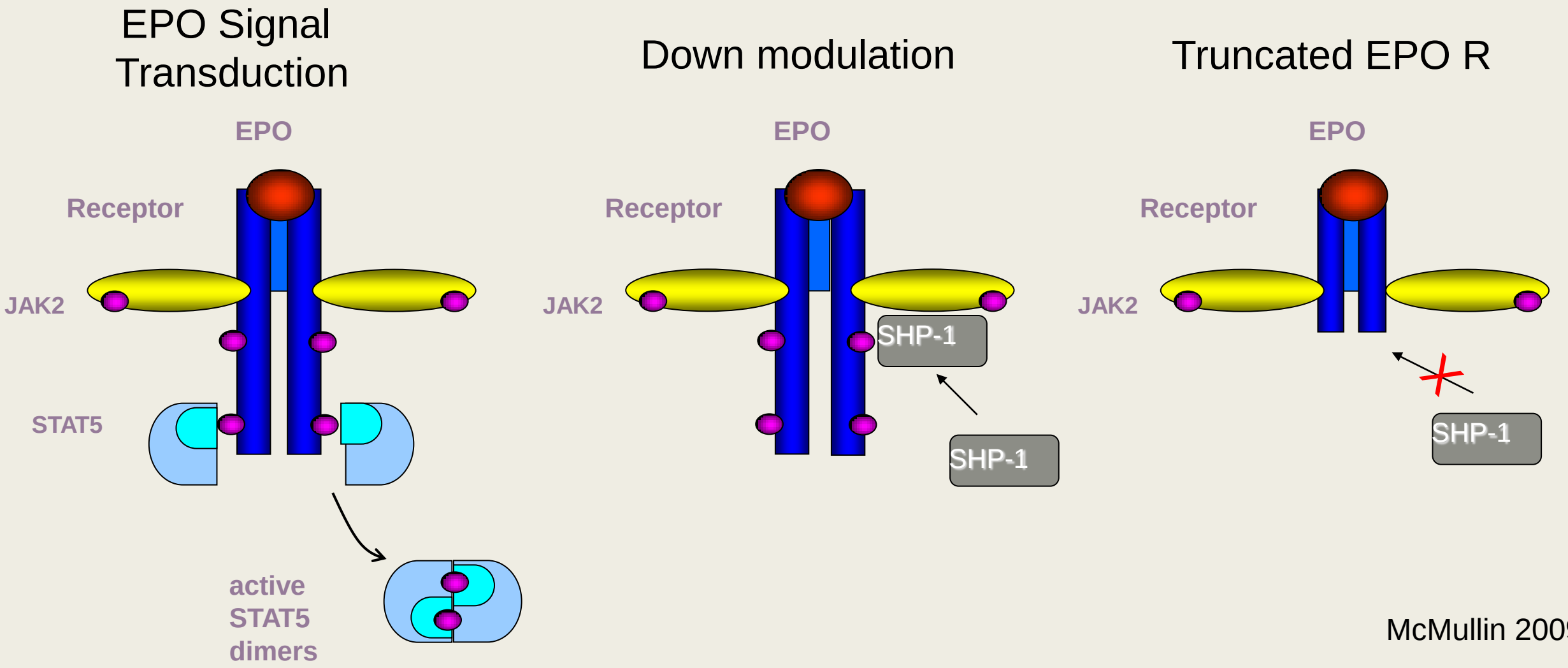
  - ✓ **Acquired**
    - ✓ **Central hypoxic process**
    - ✓ **Local hypoxia**
    - ✓ **Pathologic EPO production**
    - ✓ **Exogenous EPO**
- **Idiopathic erythrocytosis**

Investigation of an erythrocytosis with a low EPO level

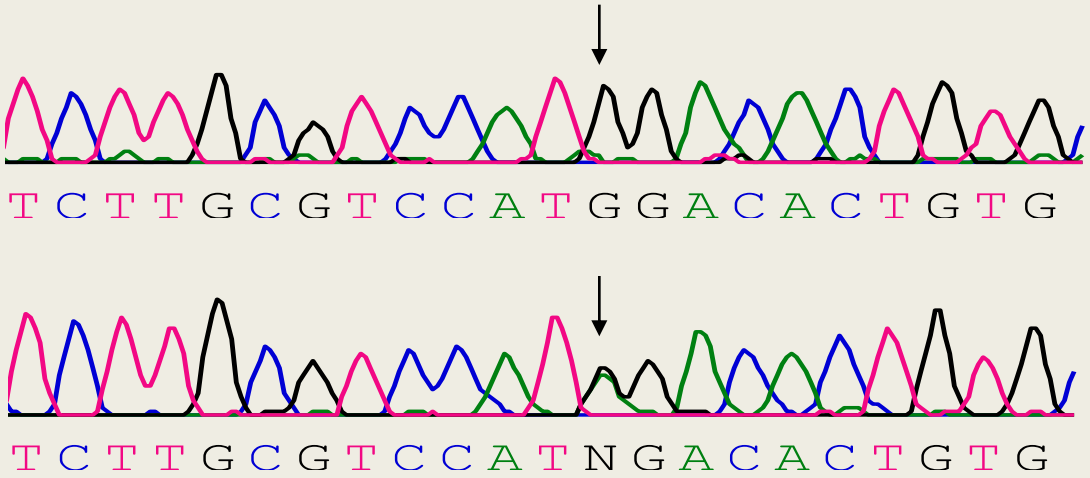
- *EPO* receptor mutations
- *JAK2* mutations
- *LNK* mutations reported some congenital and some acquired

Erythropoietin Receptor



McMullin 2009

EPO receptor truncation mutation



- *De novo* G to A at base 6002
- Stop codon at aa 439

Individual	Hb (g/dL)	PCV	WBC ($x10^9$/L)	Platelets $x10^9$/L)	EPO Level (mIU/ml)
Teenage boy	20.5	0.60	4.1	211	4.4 (NR 9.1-30.8)

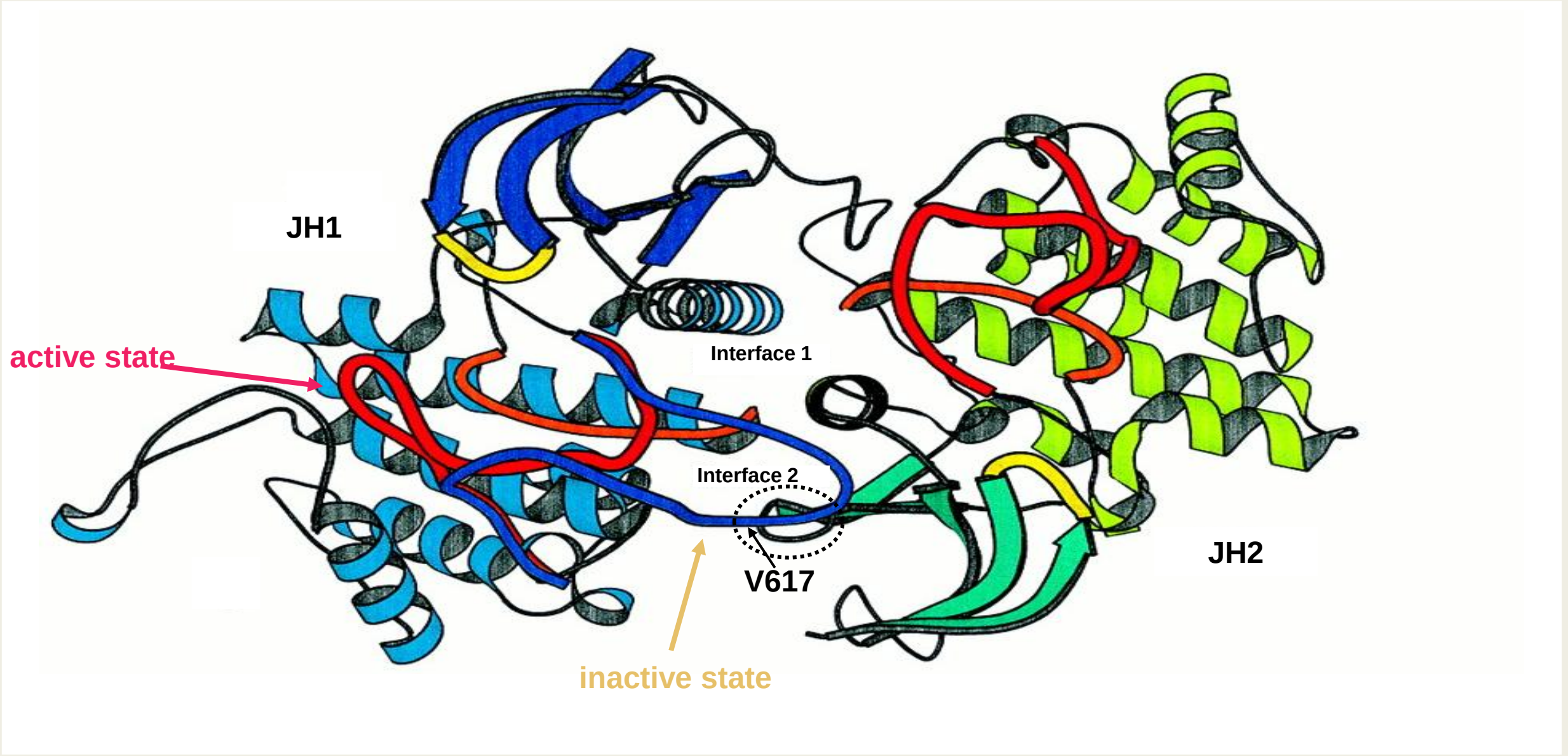
McMullin 2009

Management of patients with EPO R truncation….?

- Lack of evidence base
- Consider venesection if patients are symptomatic and HCT > 0.55
- Careful management of anaesthesia etc

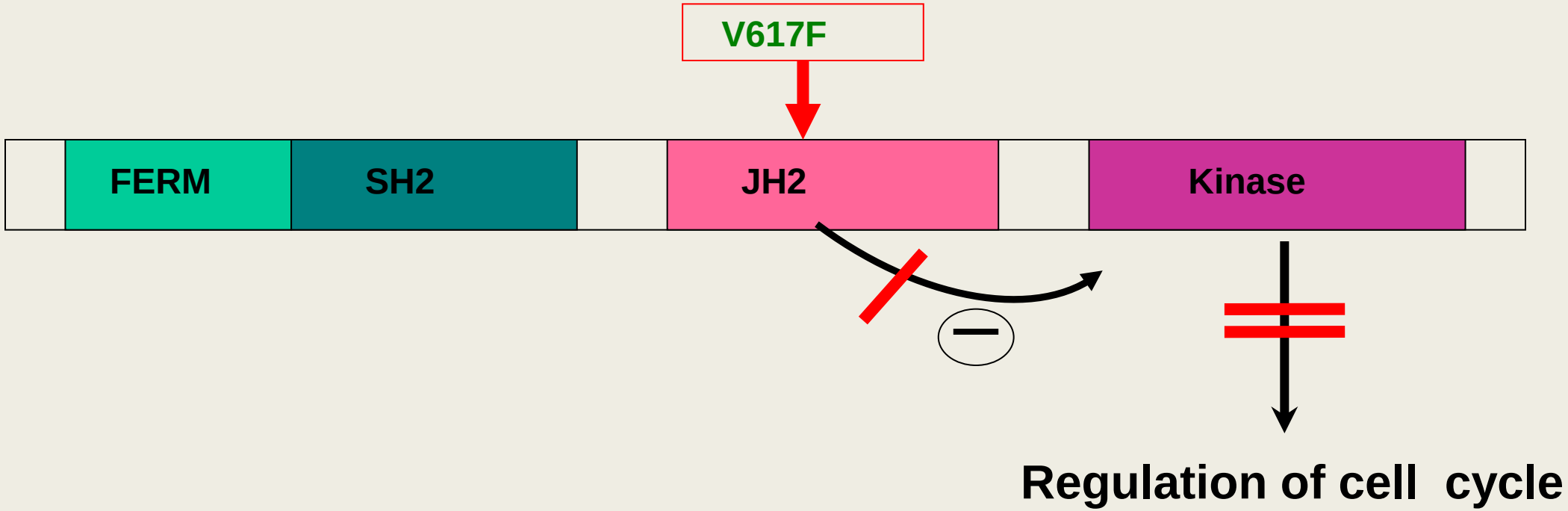
- The teenage boy is now 38 years old has 2 x / year venesections

JAK2 Kinase -JH1 and JH2 Domains

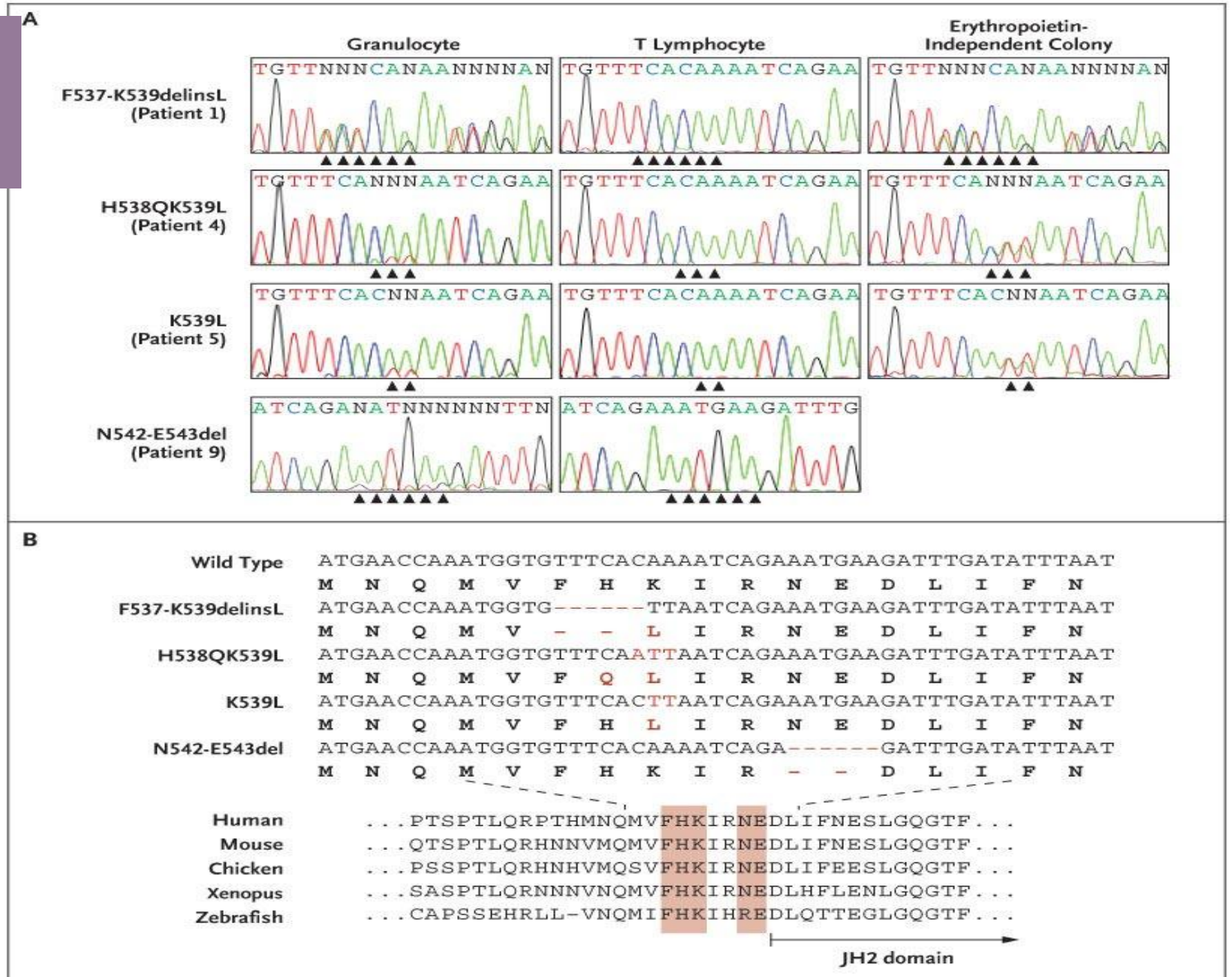


JAK2 mutation in Polycythaemia Vera

- Chromosome 9 exon 12
- G→ T transversion at nucleotide 1849
- Resulting V617F mutation



JAK2 Exon 12 mutations



Scott et al 2007

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WHO 2016

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Very rare JAK2 mutation negative PV cases do exist a bone marrow biopsy if useful to detect them. Very low level JAK2 mutations may also be considered

all major or
Two major and one minor establishes PV

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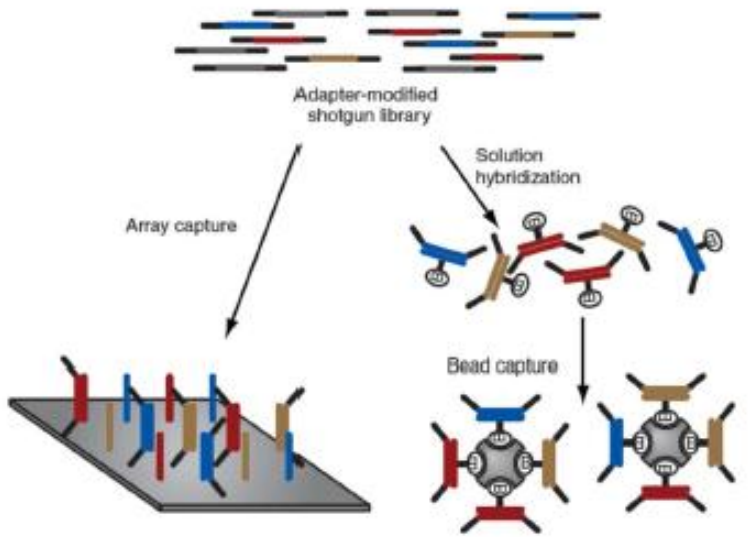
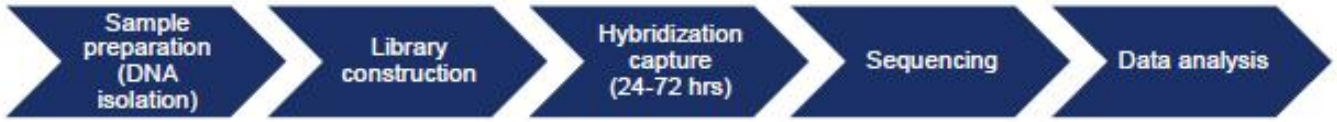
NGS based technologies can be very helpfu

Roche (NimbleGen SeqCap)- SEQCAP

- **Hybridization capture**
  - Large DNA input (1 ug)
  - Long processing time (2-3 days)
  - Large throughput (MB region to whole exome)





Examples of genes on the erythrocytosis NGS

Candidate Gene	Position	No of exons
VHL	Chr3:10183319-10195354	3
EPAS1	Chr2:46524541-46613842	16
EGLN1	Chr1:231499497-231560790	4
EPOR	Chr19:11487881-11495018	8
BPGM	Chr7:134331531-134364568	3
HBB	Chr11: 5225464-5227071	3
SH2B3	Chr12:111405948-111451623	8
JAK2	Chr9:4985245-5128183	25
EGLN2	Ch19:41305048-41314346	5
HBA1	Ch16:22958-22749	3
HBA2	Ch16:22277-22375	3

Management of idiopathic erythrocytosis (ie everything is negative)

- Venesection to HCT target of 0.54
- If previous thrombosis or increased risk of thrombosis then consider a target of 0.45
- Cytoreductive therapy is contraindicated

High Affinity Hemoglobins….. examples

UPN	116	162	214	224	228
Hb	Olympia	Olympia	Pierre Benite	Heathrow	Santa Clara
Age at presentation (yrs)	42	33	56	44	23
Hemoglobin (g/dl)	19.2	18.2	18.1	15.4	19.1
Hct	0.59	0.53	0.54	0.48	0.58
WBC (x 10^9/l)	5.8	5.8	N/A	6.4	6.8
Pts (x10^9/l)	233	186	N/A	334	171
EPO (mIU/ml)	9.1	4.9	23	29.1	5.8

Recommendations: management of high (oxygen) affinity haemoglobins

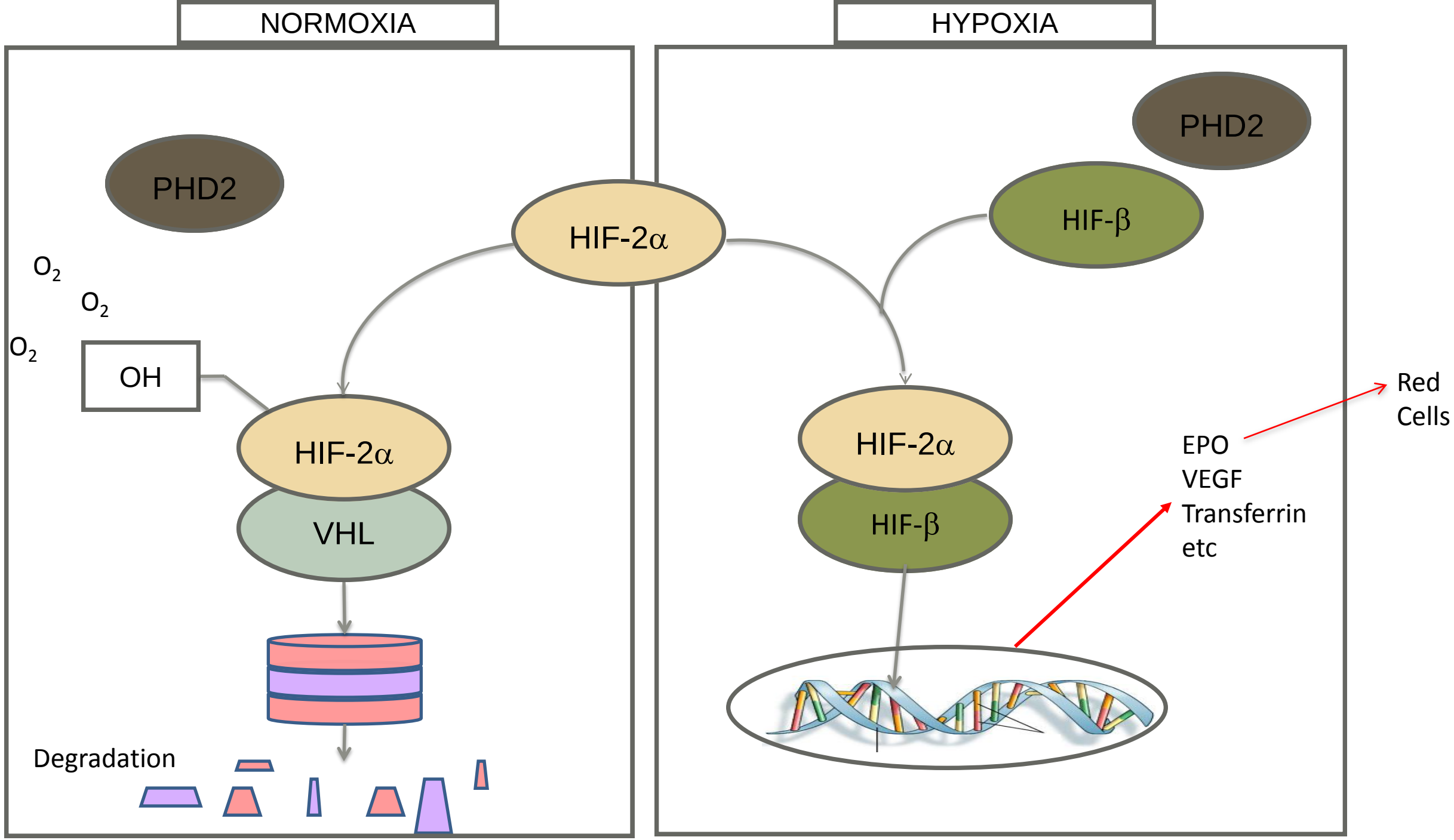
- Possible indications for Venesection include:
- Presence of symptoms such as dizziness, dyspnoea or angina, for which a raised Hct is considered to be a contributory factor.
- One or more previous thrombotic episodes.
- Asymptomatic individuals in whom a family member with a high oxygen affinity haemoglobin, similar haemoglobin concentration, and comparable risk factors for thrombosis has developed a thrombotic problem.

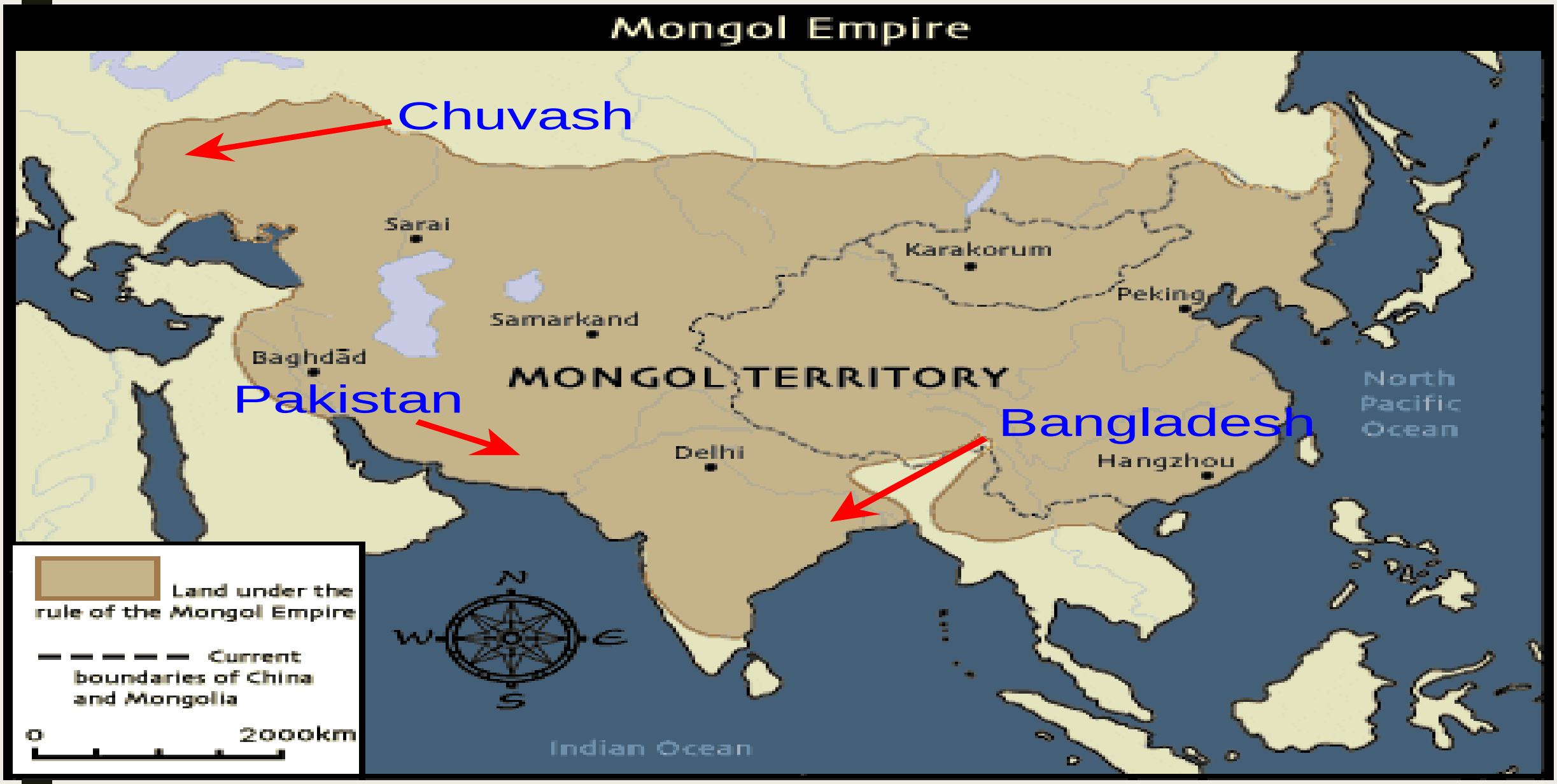
McMullin 2007 BCSH recommendations

High oxygen affinity haemoglobins

- Consideration venesection should be given for individuals with a Hct >0.60 requiring major surgery
- Do not attempt to reduce the Hct to within the normal range. Venesection to maintain the Hct <0.60 has been recommended.
- When thrombosis or symptoms compatible with hyperviscosity develop at a lower Hct, a target Hct of 0.52 has been suggested.

McMullin 2007 BCSH recommendations

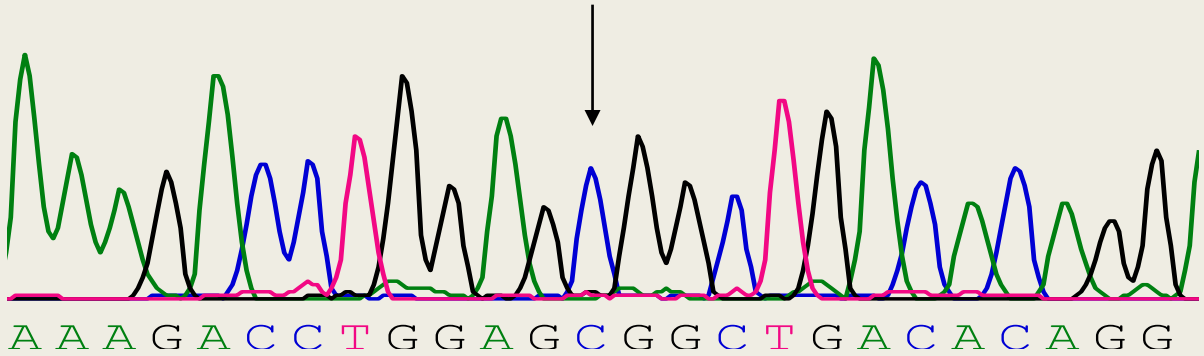

NORMOXIA
HYPOXIA
PHD2
HIF-2α
HIF-β
O_2
O_2
O_2
OH
HIF-2α
VHL
Degradation
PHD2
HIF-β
HIF-2α
HIF-β
EPO
VEGF
Transferrin
etc
Red
Cells



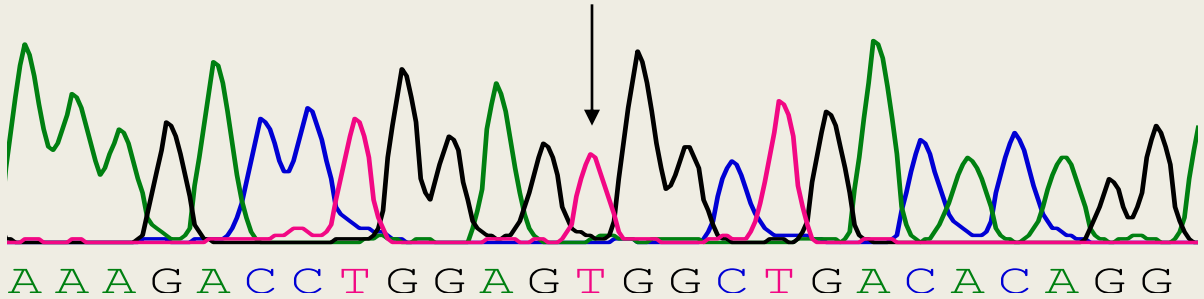
McMullin 2009

VHL Mutational screen

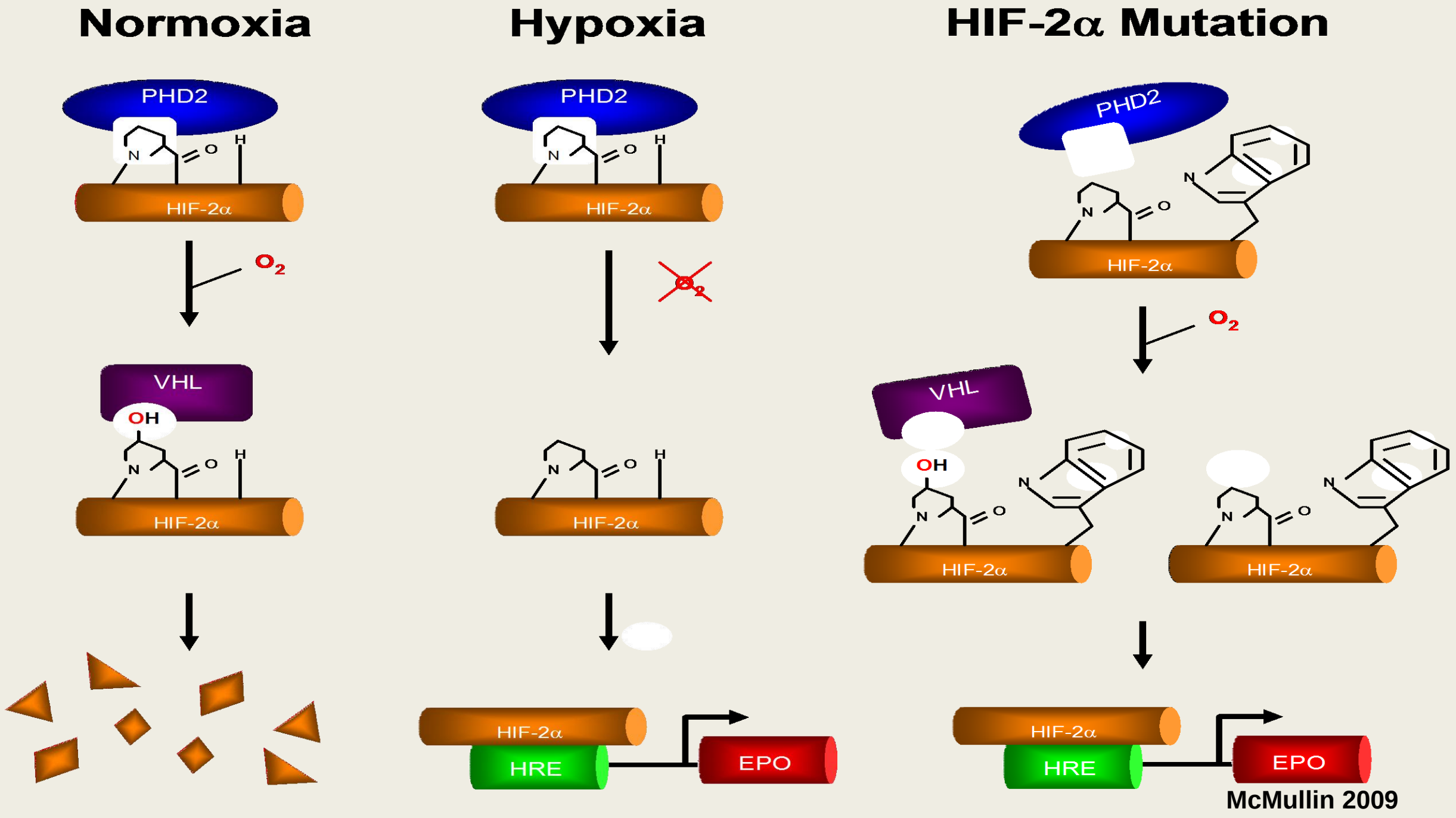
Normal
>100 patients



Homozygous
C598T/Arg200Trp
9 Asian families



Data suggests single founder individual McMullin 2009


Normoxia
Hypoxia
HIF-2α Mutation
PHD2
HIF-2α
O2
VHL
OH
HRE
EPO
McMullin 2009

Patient case:

- 23 year old originally from Bangladesh referred to clinic
- Had hypoplastic left heart, and transposition of great vessels corrected as baby, multiple operations.
- Good function, no exercise limitation, no hypoxia
- 15 months earlier suffered thrombotic CVA at that time (Hb 24 HCT 0.62)

Patient case

- 23 year old originally from Bangladesh referred to clinic
- Had hypoplastic left heart, and transposition of great vessels corrected as baby, multiple operations.
- Good function, no exercise limitation, no hypoxia
- 15 months earlier suffered 2 x thrombotic CVA at that time (Hb 24 HCT 0.62)
- EPO 15 IU/L

Father attends with him and mentions that he was seen at St Thomas' Hospital 18 years before and had lots of tests for "*Too much blood*"
Used to have venesections, well in himself. Hb 18.8 mcv 56 HCT 0.54, EPO 20

Diagnosis?

- Father and son had a known mutation affected HIF 2A (EPAS 1 gene)

Management?

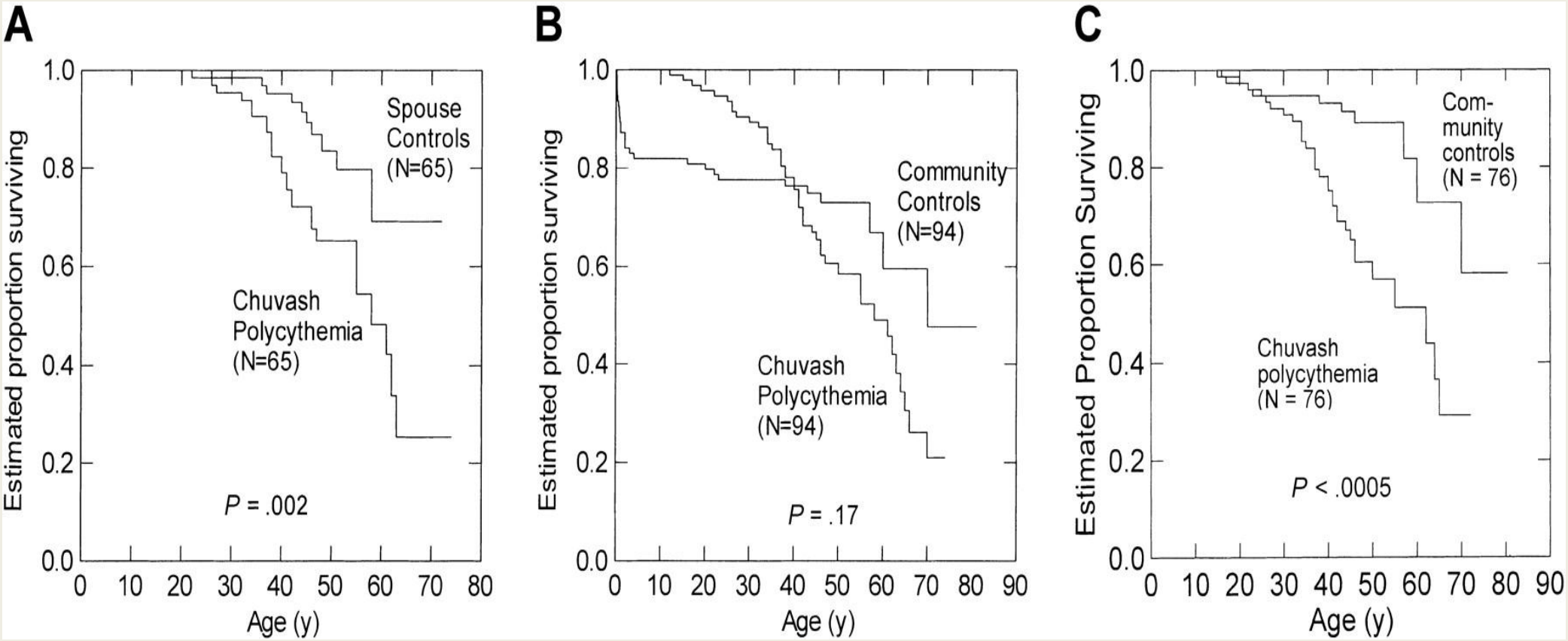
- Father needs venesection target < 0.5
- Son < 0.45 and aspirin
- Screen family members

Clinical events in erythrocytoses

- Homozygotes with Chuvash polycythaemia: increased mortality from cerebrovascular events and mesenteric thrombosis

- *PHD2* and *HIF2A* mutations associated with thromboembolic events

Kaplan-Meier survival curves for Chuvash polycythemia patients and spouses or community members matched for age, sex and place of birth



Gordeuk, V. R. et al. Blood 2004;103:3924-3932

Baseline characteristics of adult Chuvash polycythemia (CP) patients and controls at time of enrollment in the case-control study.

	CP		Controls		
	N	Result	N	Result	P
Age (years)	128	38 (26-50)	128	40 (26-50)	0.4
Female sex	128	70 (54.7%)	128	68 (53.1%)	0.8
History of phlebotomy therapy	128	100 (78.1%)	128	0 (0%)	<0.001
History of smoking	128	41 (32.0%)	128	23 (18.0%)	0.009
History of thrombosis*	128	27 (21.1%)	128	3 (2.3%)	<0.001
History of bleeding	128	14 (10.9%)	128	2 (1.6%)	0.002
History of hypertension	128	8 (6.3%)	128	27 (21.1%)	0.001
History of diabetes mellitus	128	3 (2.3%)	128	1 (0.8%)	0.3
History of malignancy**	128	2 (1.6%)	128	1 (0.8%)	0.6
BMI (kg/m^2)	128	21.5 (19.8-23.7)	128	23.3 (21.1-26.3)	<0.001
Mean arterial pressure (mm Hg)	128	91 (85-97)	128	94 (88-102)	0.009
Erythrocytes (x10^9/uL)	127	6.45 (6.00-7.19)	127	4.69 (4.22-4.99)	<0.001
Hemoglobin (g/dL)	127	17.9 (15.9-19.8)	128	13.8 (12.6-15.0)	<0.001
Hematocrit (%)	115	53.4 (47.7-58.5)	127	40.3 (37.2-43.4)	<0.001
MCV (fL)	110	80.7 (74.0-87.0)	127	87.7 (84.3-90.8)	<0.001
MCH (g/dL)	119	27.3 (23.7-30.9)	128	29.9 (28.4-31.2)	<0.001
MCHC (g/dL)	111	33.2 (31.3-35.0)	127	34.2 (33.0-35.3)	0.001
White blood cells (per uL)	127	5.70 (4.60-7.12)	128	6.40 (5.34-7.46)	0.001
Neutrophils (per uL)	92	3.03 (2.07-3.79)	122	3.52 (2.95-4.47)	<0.001
Lymphocytes (per uL)	98	1.90 (1.55-2.32)	126	2.19 (1.83-2.54)	0.003
Platelets (per uL)	127	219 (165-268)	128	247 (209-300)	<0.001
Erythropoietin (U/L)	89	48.6 (24.4-88.3)	44	8.9 (7.3-13.8)	<0.001
Serum ferritin (ug/L)	86	11 (6-23)	43	53 (23-105)	<0.001

*Twenty-seven CP patients had a history of 40 thromboses- 18 with 1 thrombosis, 5 with two thromboses, 4 with three thromboses: stroke (n=10), myocardial infarction (n=10), splanchnic thrombosis (n=9), deep vein thrombosis (n=8), pulmonary embolism (n=3). Three controls had a history of a single thrombosis: stroke, pulmonary embolism, myocardial infarction. **History of breast carcinoma and Hodgkin lymphoma in CP patients; history of breast carcinoma in a control. BMI: body mass index; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration.

Adelina Sergueeva et al. Haematologica 2017;102:e166-e169

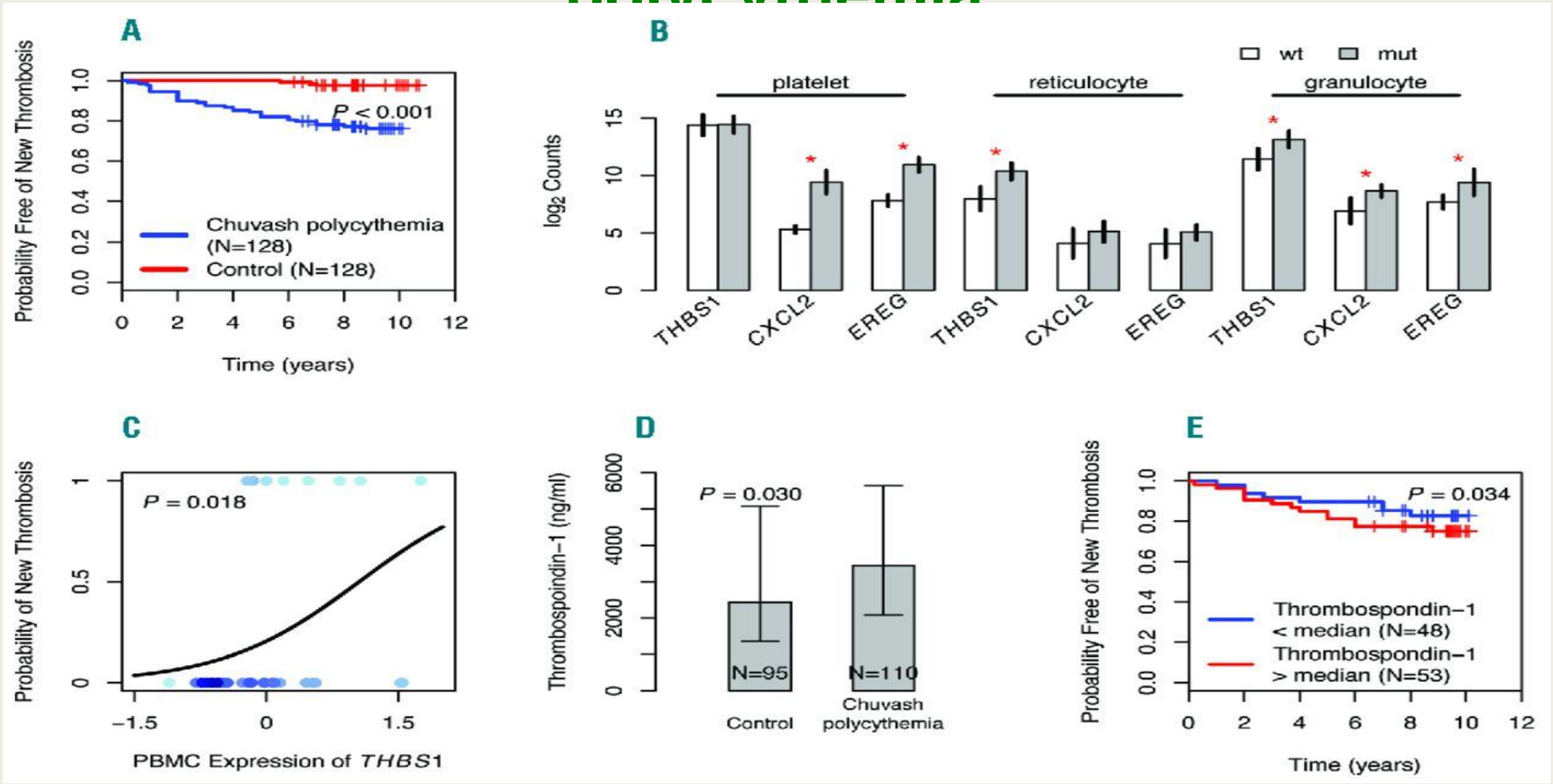
Multivariate Cox Proportional Hazards Model of predictors of new thrombosis during follow up in 128 CP patients.

Variable	Hazards Ratio	95% Confidence Interval	P
Number of past thromboses (range from 0 to 3)	1.9	1.3-2.8	0.001
Treatment with pentoxifylline	3.3	1.5-7.2	0.003
Average number of cigarettes smoked per day in the past year (increments of 10)	1.9	1.1-3.3	0.018
Remote and recent phlebotomy categories	2.0	1.01-3.8	0.045
Age (increments of 10 years)	1.3	0.99-1.9	0.060

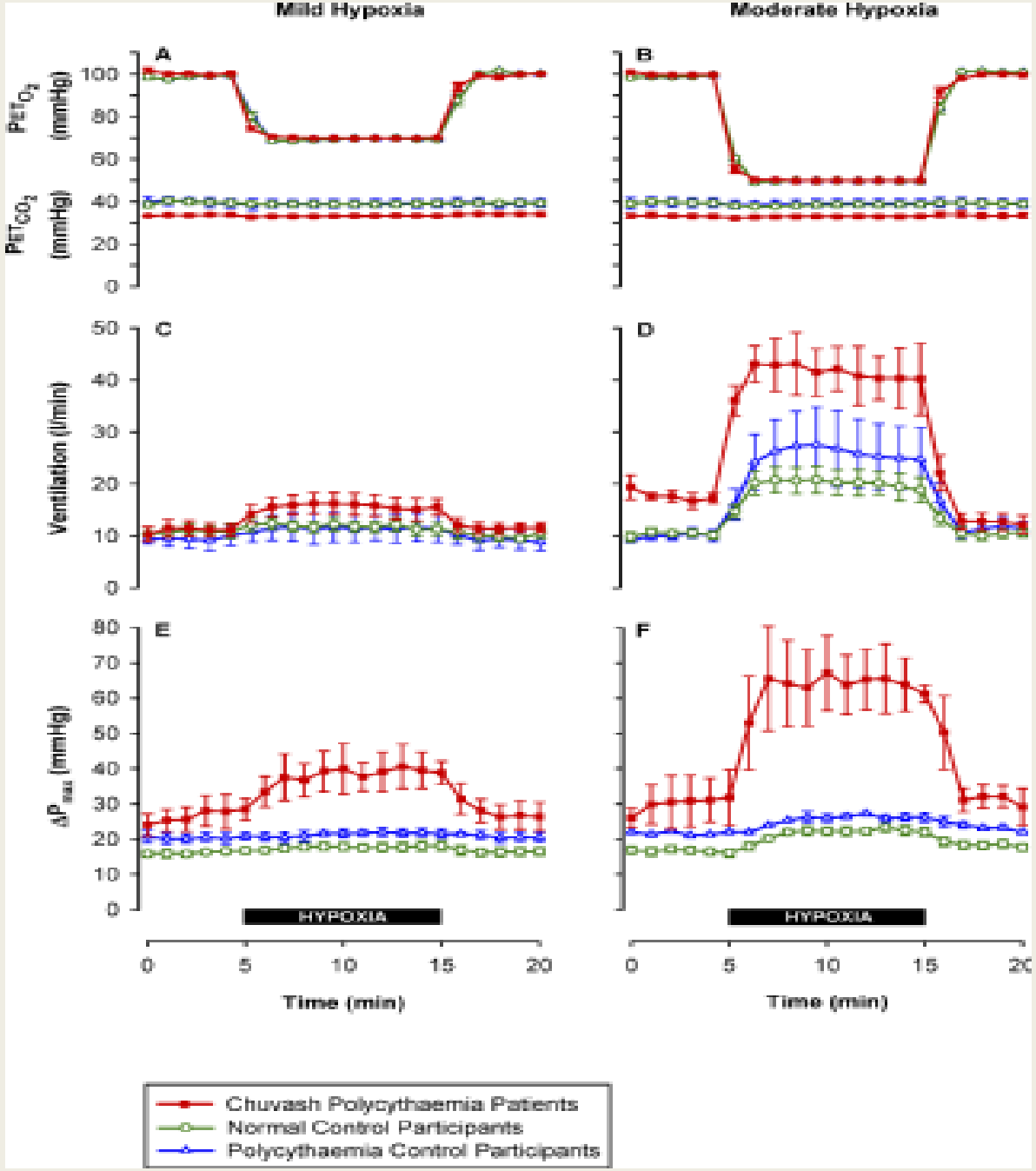
- Prospective evaluation of 128 CP subjects & controls (matched by age, sex, residence) over median of 8.8 years.
- The rate of new thrombosis was higher in CP subjects (HR 12.7).

Adelina Sergueeva et al. Haematologica 2017;102:e166-e169

Thrombosis and THBS1 expression in Chuvash polycythemia



Adelina Sergueeva et al. Haematologica 2017;102:e166-e169

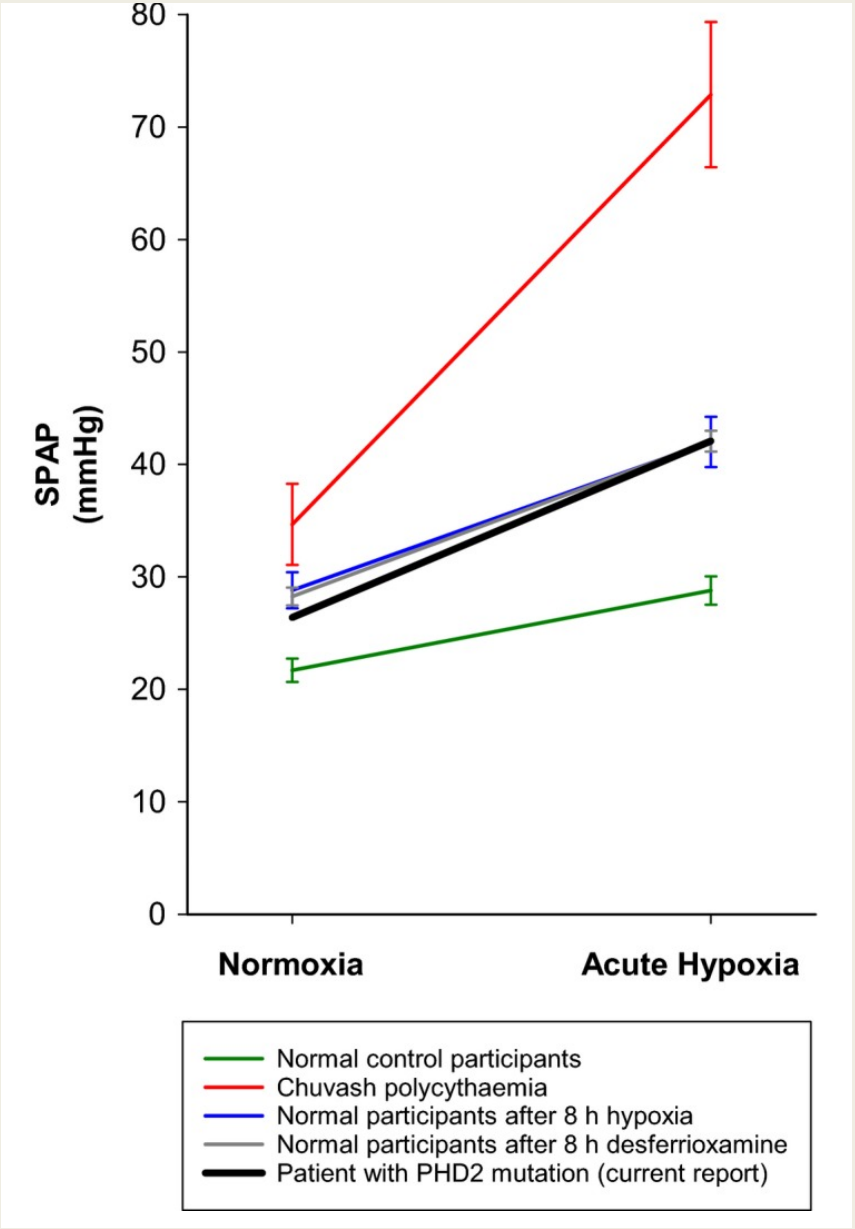


Chuvash polycythemia patients have different cardiovascular responses to hypoxia…….

Smyth,PLOS, 2005,3,e290

Chuvash polycythemia patients have different cardiovascular responses to hypoxia…….

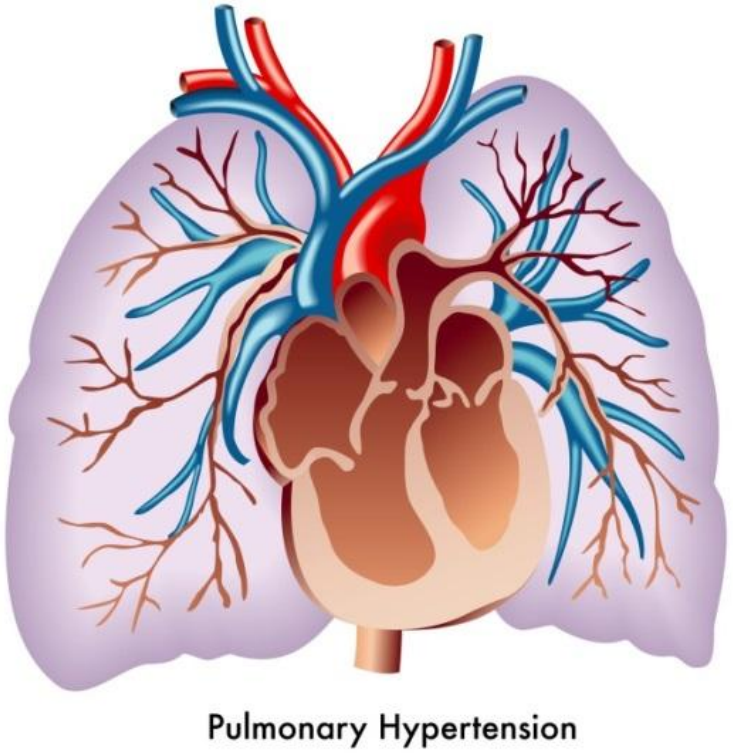
This was also seen in PHD2 mutation proband and mimics by iron deficiency and chronic hypoxia



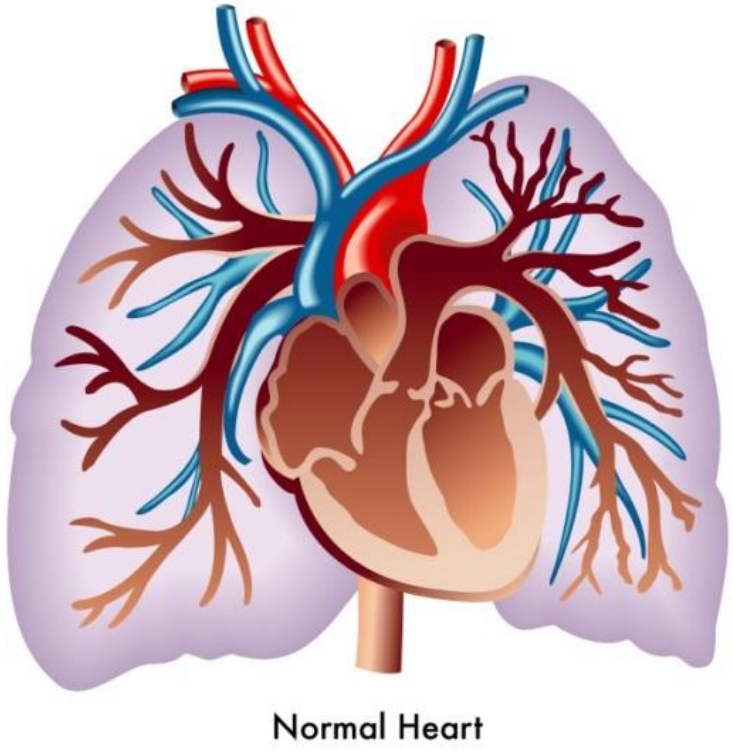
Smyth,PLOS, 2005,3,e290

Chuvash polycythemia patients have different cardiovascular responses to hypoxia

Implications for therapy and monitoring for complications



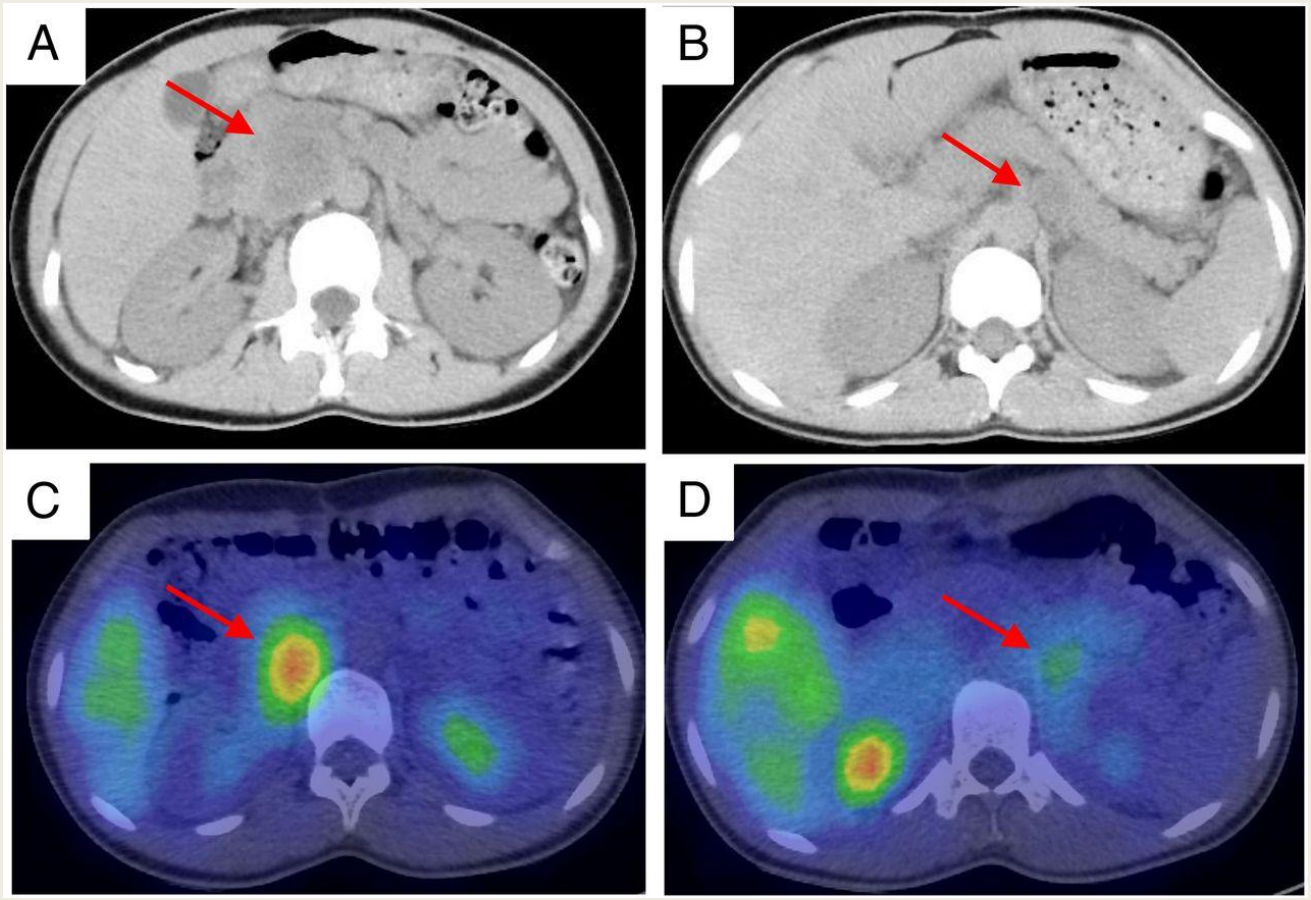
Pulmonary Hypertension



Normal Heart

Smyth,PLOS, 2005,3,e290

Paraganglioma have been reported in patients with HIF 2 α mutations



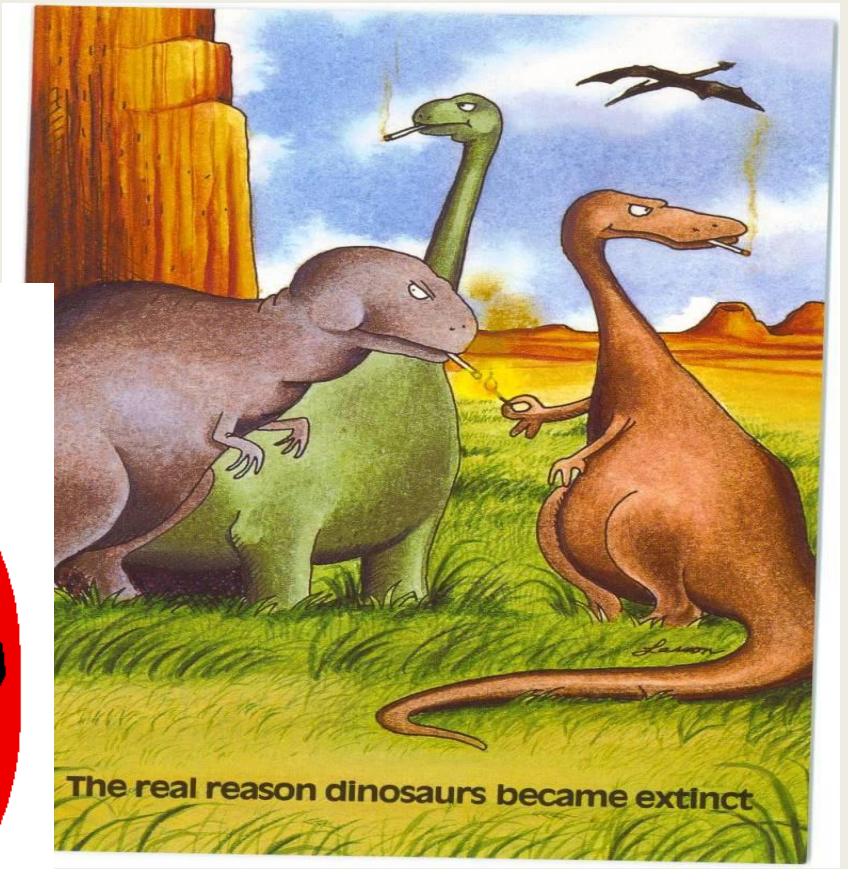
Hidemi Toyoda et al. Pediatrics 2014;133:e1787-e1791

Management options: Congenital erythrocytosis

- Rare individuals may have a congenital erythrocytosis which often present at a young age and have a family history
- An investigation for known molecular defects should be carried out
- Venesection and low dose aspirin are possible management options
- Ruxolitinib may have efficacy in managing Chuvash polycythaemia
- Screening for complications such as pulmonary hypertension

Lifestyle modification:

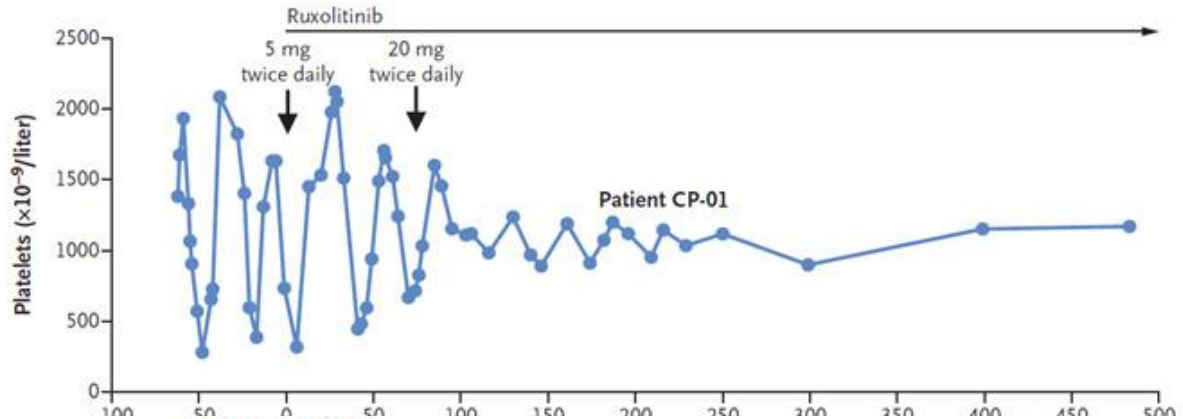
Just as important for congenital erythrocytosis

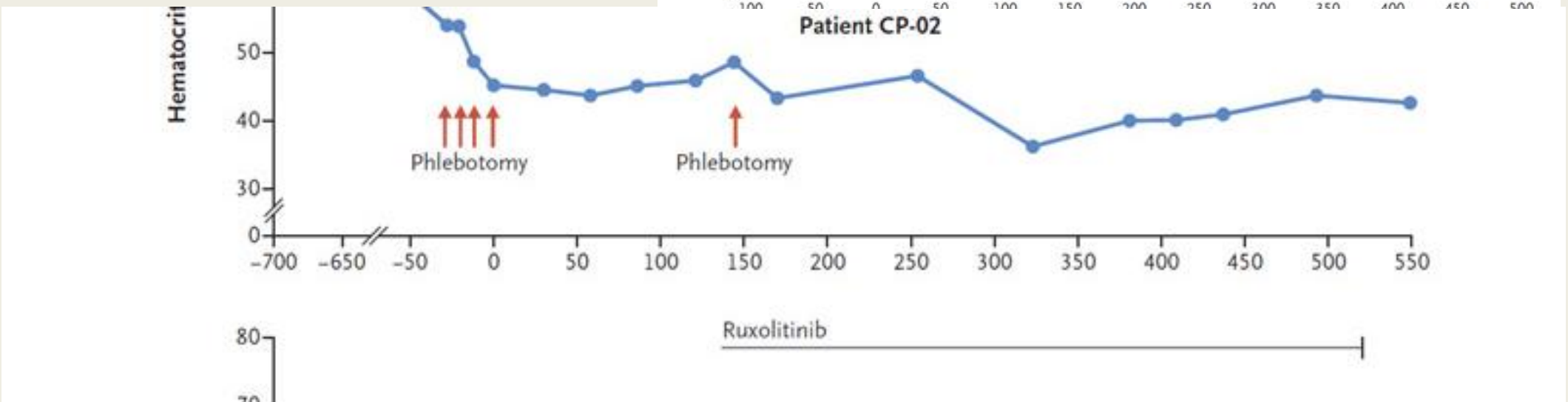


Erythrocytosis & symptoms response: Ruxolitinib in Chuvash Polycythaemia

Zhou et al NEJM 2016

	Patient CP-01		Patient CP-02		Patient CP-03	
	33 yr of age		23 yr of age		28 yr of age	
	Before treatment	During treatment (69 wk)	Before treatment	During treatment (78 wk)	Before treatment	During tre (21 w
(×10⁻⁹/liter)	8.5	4.8	10.8	15.4	8.1	8.5
n (g/dl)	13.8	16.5	12.6	11.8	13.7	15.(
(%)	46.0	55.9	45.2	42.6	43.7	47.(
10⁻⁹/liter)	1500	1037	380	736	228	302
tin (IU/liter)	1707	1081 (36 wk)	133	968 (54 wk)	32	ND
frequency	Weekly	Less than 1×/mo	4× in 4 wk before ruxolitinib	1× in 78 wk with ruxolitinib	3× in 7 wk before ruxolitinib	1× in 2 with ruxo
	Headaches, back pain	Markedly improved	Episodic, severe abdominal pain	Markedly improved	Fatigue, aquagenic pruritus	Marke impro





Management of a congenital erythrocytosis

- Assess individual patient
- Consider reduction of HCT to achievable target level ? <0.5
- Consider aspirin if no specific contraindication
- Need for long-term follow-up of treatments and outcomes

? Need for global registry

Summary:

- Erythrocytosis is classified by cause measurement of EPO levels are useful way to subclassify
- Red cell mass is a useful test and HCT is more predictive than Hb
- Most cases of secondary acquired erythrocytosis are best managed by addressing the underlying cause and venesection is NOT a mainstay of therapy
- Congenital erythrocytosis is rare but important venesection needs to be carefully considered and long term monitoring for other late complications is important
- A registry for these conditions would inform future management