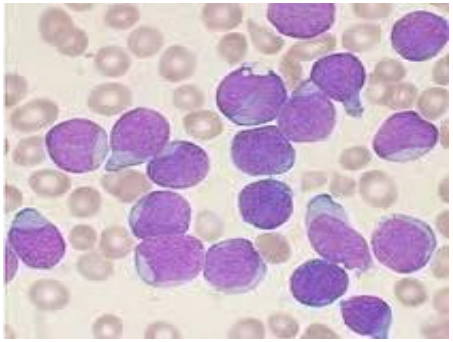
DELIVERING SCIENCE SUPPORTING HEALTHCARE

NHS
North West
London Pathology

GP Educational Webinar

Abnormal haematology blood tests: when to worry and when to refer

Mamta Sohal
Consultant Haematologist
Imperial College Healthcare NHS Trust

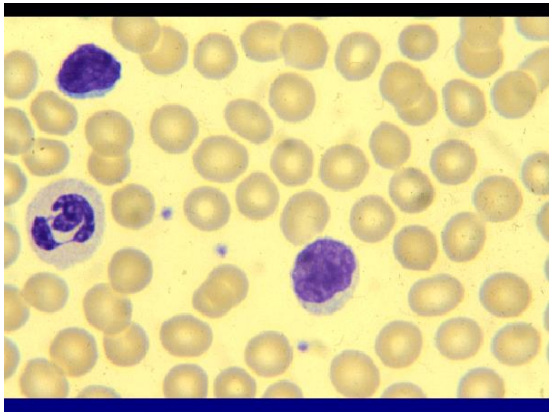


Patient focused Collaborative Expert Caring

Talk outline

NHS
North West
London Pathology

- **Red cells**
  - Anaemia
  - Polycythaemia
- **White cells**
  - Leukaemias – acute & chronic
- **Platelets**
  - Thrombocytosis
  - Thrombocytopenia
- **Paraproteins**



General Considerations 1

NHS
North West
London Pathology

- **Clinical Context**
  eg well / sick patient, pregnant, sepsis etc

- **Historical Data**
  eg duration, trends

- **Co-morbidities**
  incl drugs or recent changes

- **Technical issues**
  eg difficult phlebotomy, aged sample, contamination

General Considerations 2

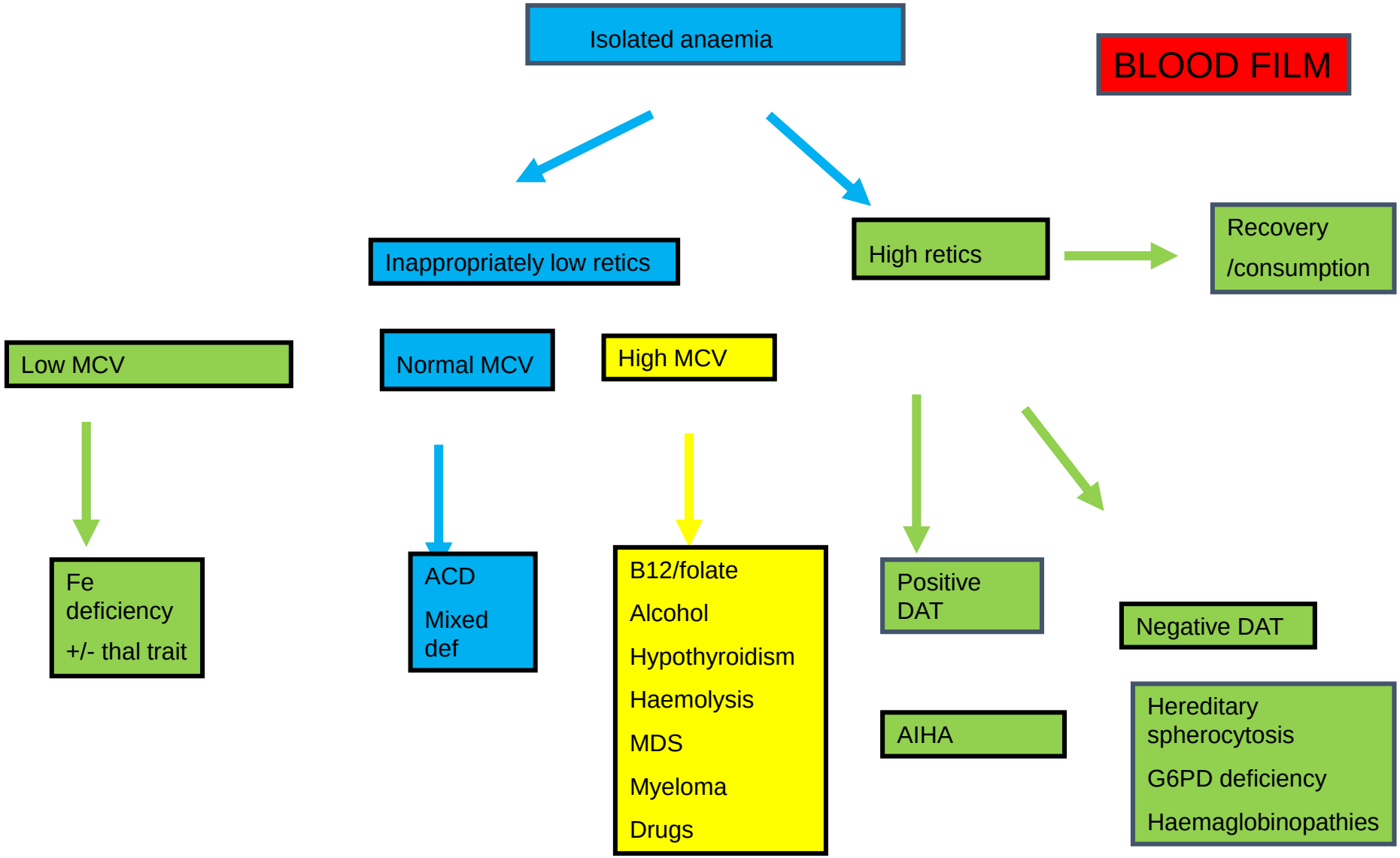
NHS
North West
London Pathology

- Age, Sex, Ethnicity
- Normal ranges
- 1 or more lineage abnormalities

	Hb g/l	Neuts $x10^9$
Birth	140-230	2.7-14
2 / 12	94-130	0.7-4.8
1 yr	101-130	1 - 8
AdultM F	130-168 114-150	2.0 –7.1

Approach to Anaemia

NHS
North West
London Pathology



Beta Thalassaemias

NHS
North West
London Pathology

- Beta thal trait
- Slightly reduced Hb disproportionately low MCV elevated RBC
- Raised Hb A_2

Alpha Thalassaemias

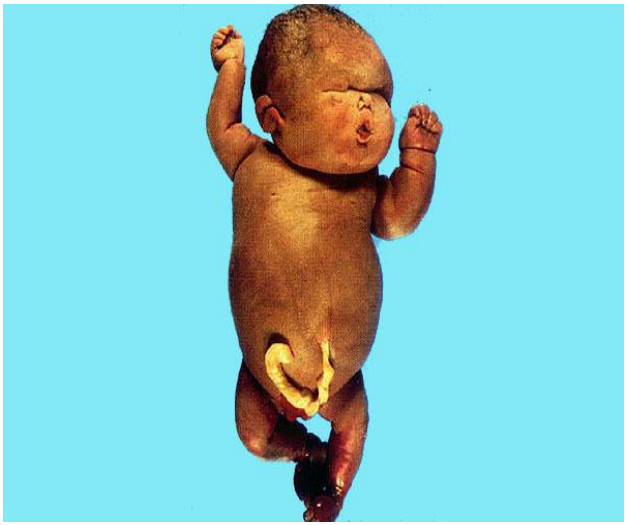
NHS
North West
London Pathology

- Alpha plus trait is the commonest monogenic disorder in the world.
- ¼ of individuals with African ancestry are heterozygous for alpha plus (-a/aa) while 1-2% are homozygotes (-a/-a)
- Clinically silent

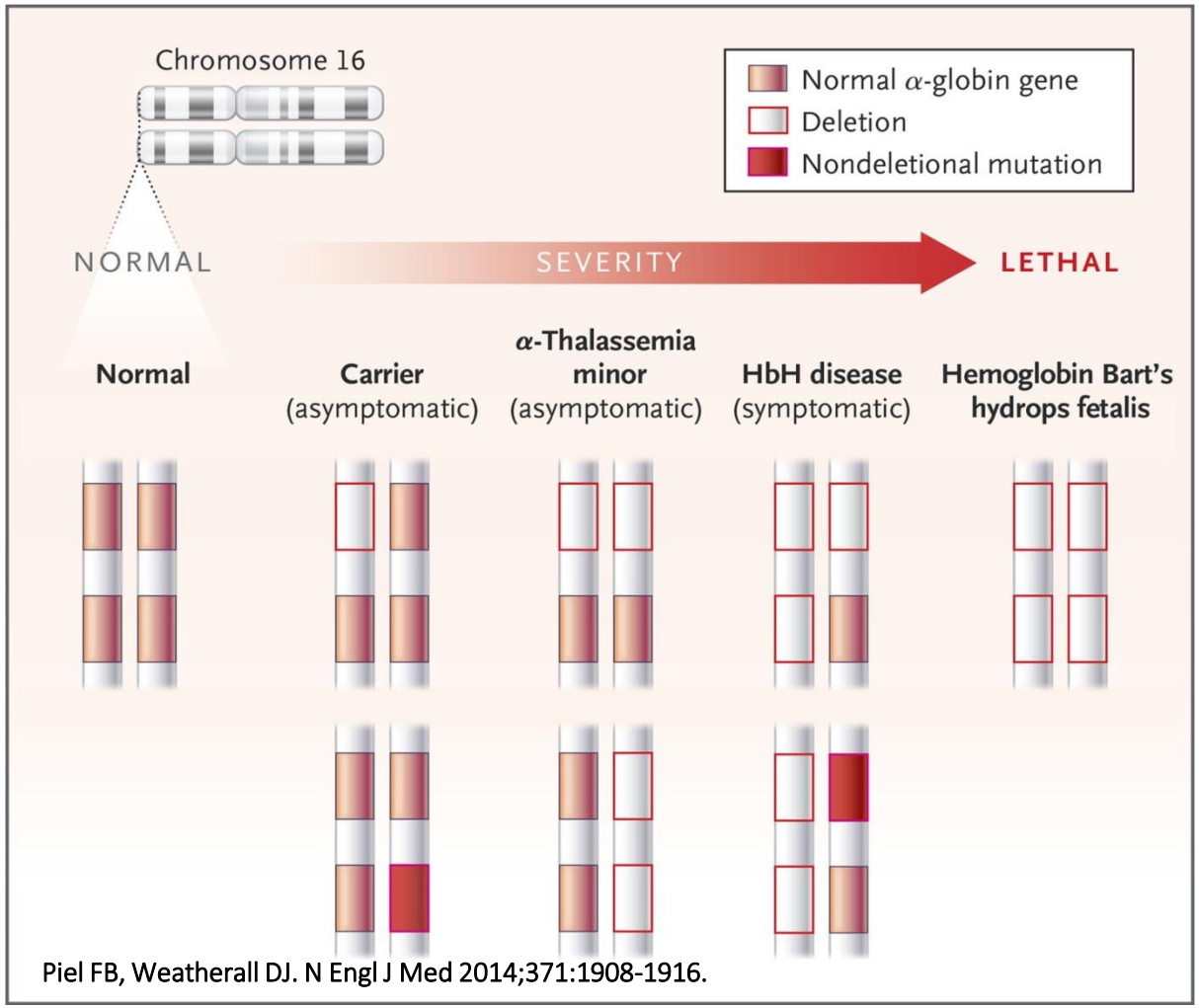
Alpha o trait

NHS
North West
London Pathology

- (--/aa)
- South east asia, Mediterranean
- Mild anaemia MCV and MCH reduced
- Blood film microcytosis and hypochromia
- MCH usually < 25pg



NHS
North West
London Pathology



Piel FB, Weatherall DJ. N Engl J Med 2014;371:1908-1916.

Case 1

NHS
North West
London Pathology

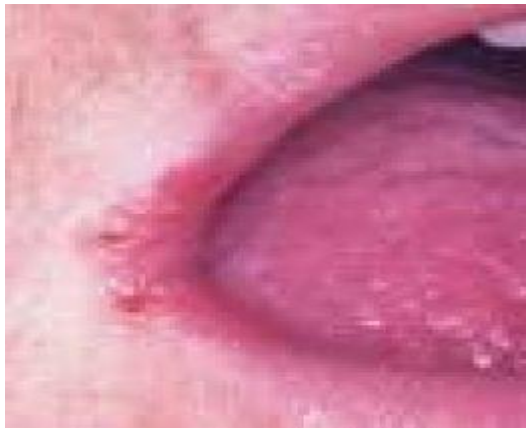
- A 2 year old girl is referred to the paediatric haematology clinic with anaemia and lethargy. She is a picky eater and drinks mainly milk.

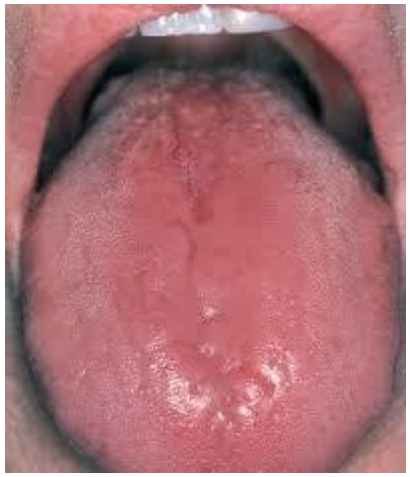
Case 1

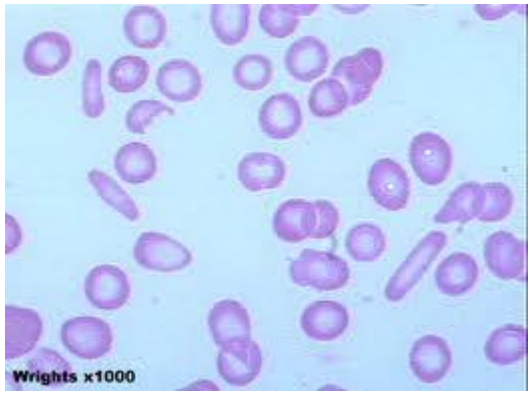
NHS
North West
London Pathology

- Hb 45g/l
- MCV 55 fl
- WBC 6.3 x 10^9/l
- Neuts 4.9 x 10^9/l
- Plts 134 x 10^9/l

NHS
North West
London Pathology

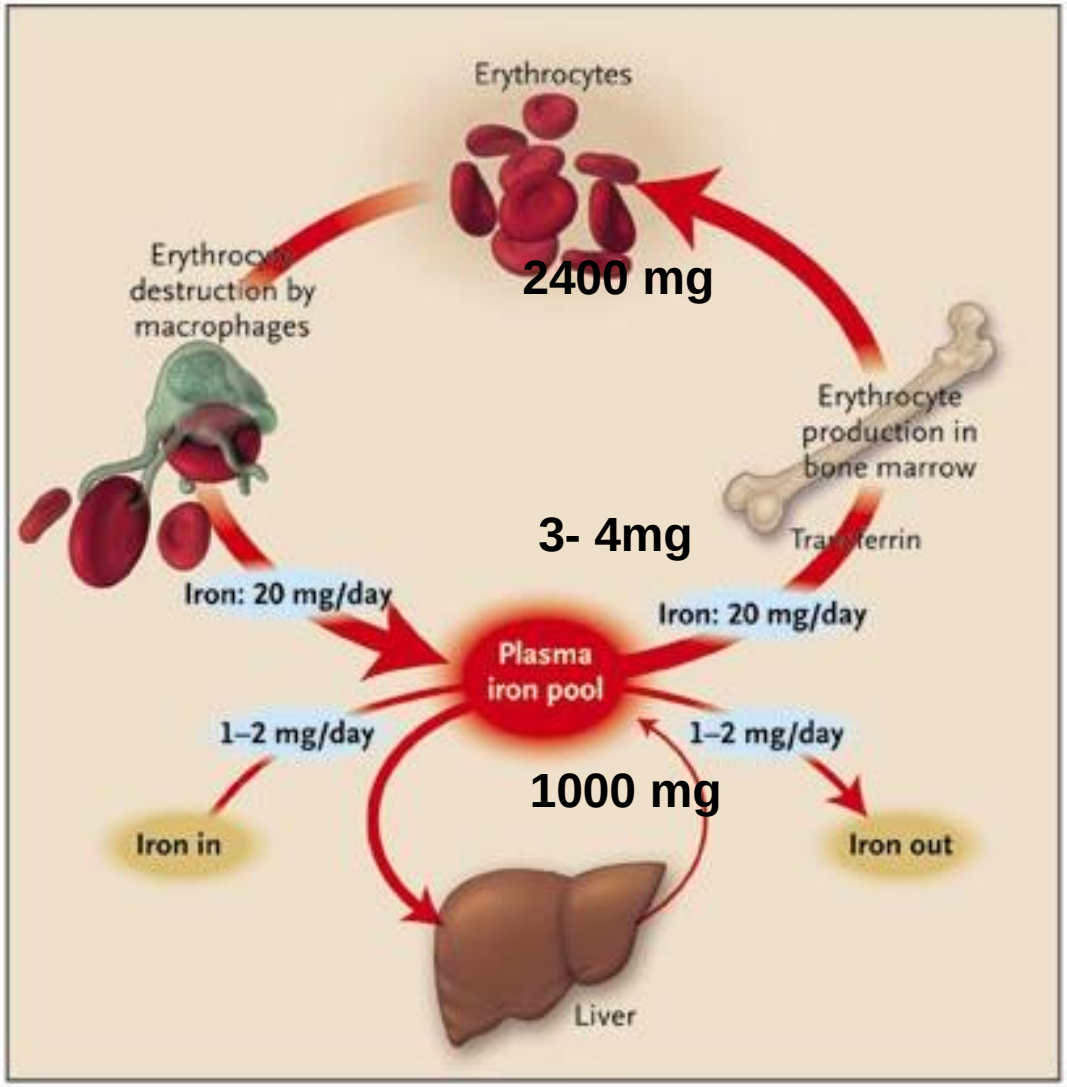






Iron Economy

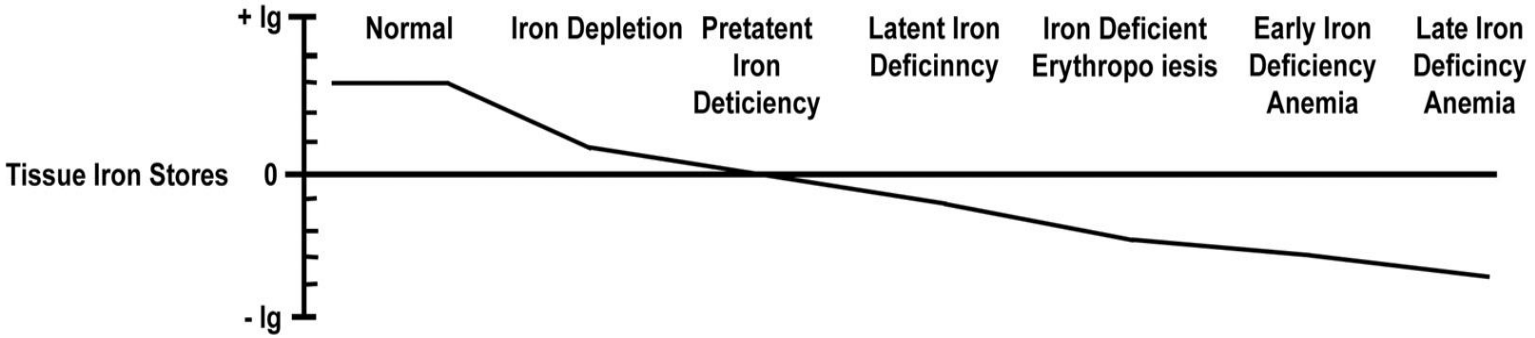
NHS
North West
London Pathology



With permission from Pietrangelo A. *N Engl J Med*. 2004;350:2383-2397.

Investigations

NHS
North West
London Pathology



Serum Ferritin (µg/1)	60	20	<12	<12	<12	<12	<12
Stainable Tissue Iron (0-4+)	2+	1+	0	0	0	0	0
Transferrin Saturation (%)	35	35	35	20	<16	<16	<16
Free Erythrocyle Protoporhyrin (µg/dl)	30	30	30	75	>100	>100	>100
Hemoglobin (g/dl)	14	14	14	14	13	<12	<12
Mean Corpuscular Volume (μ^3)	90	90	90	90	88	86	<82
Mean Corpuscular Hemoglobin Concentration (0/0)	33	33	33	33	33	31	<28

Red cells: Anaemia

NHS
North West
London Pathology

	MCV	Ferritin	TIBC	Serum Fe	Transferrin sats
Iron Deficiency	Usually low, trend important	↓ confirmatory but may be n or ↑	High	Low	Reduced once tissue stores deplete
Anaemia of chronic disease	Normal or low	Usually normal or ↑	Normal or ↓	Normal or ↓	
Thalassaemia	Normal or reduced	Normal or ↑			

Management

NHS
North West
London Pathology

- Fe available in diet, tablet, liquid, IV and IM

Oral Fe preparations

NHS
North West
London Pathology

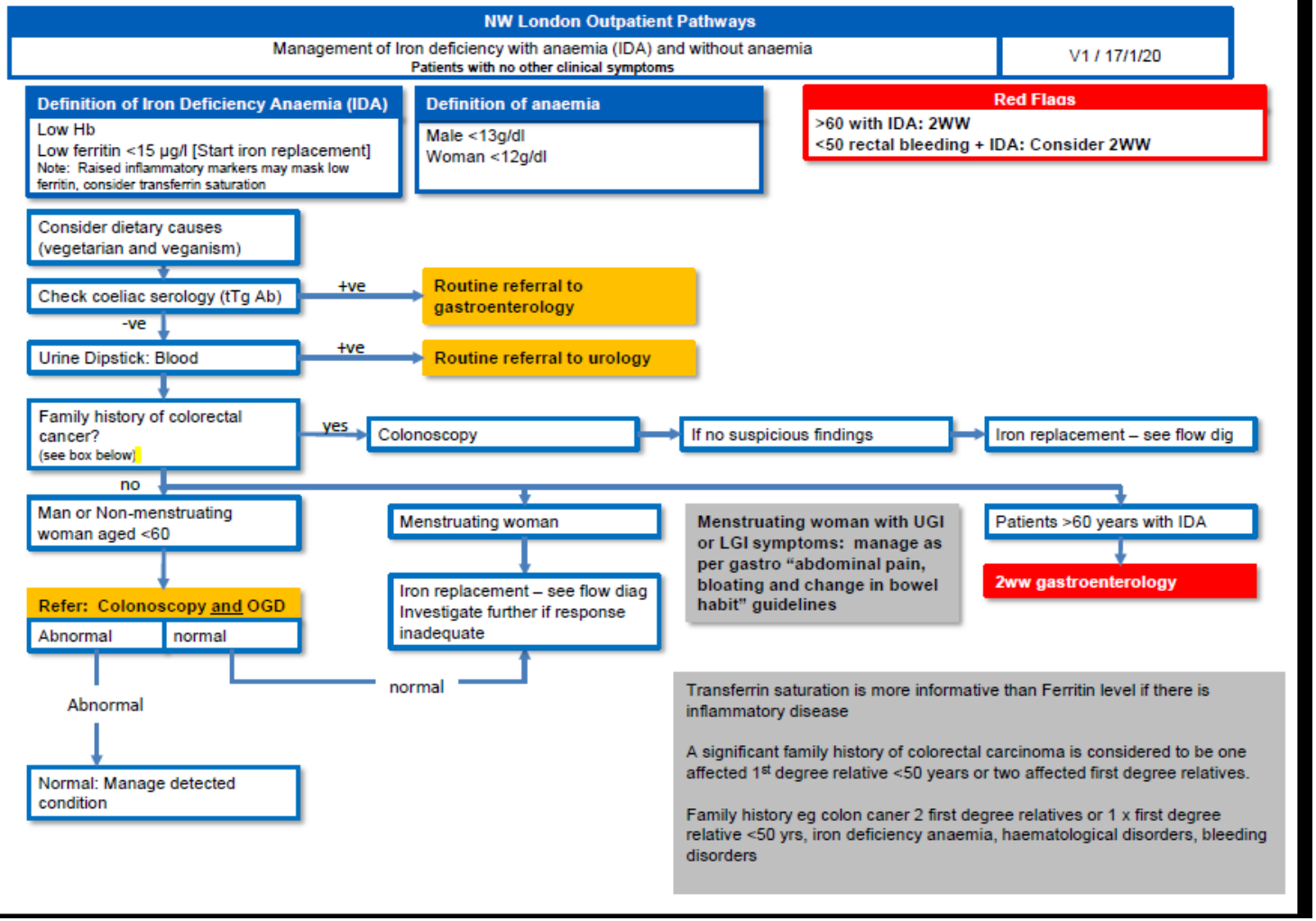
Fe preparation	Fe content
Ferrous fumerate	65mg elemental Fe per 200mg
Ferrous sulphate	65mg elemental Fe per 200mg
Ferrous gluconate	35mg elemental iron per 300mg

Parenteral Fe

NHS North West London Pathology

	Cosmofer **Fe dextran**	**Venofer** **Fe sucrose**	**Ferinject** **Fe carbomaltose**	**Monofer** **Fe isomaltoside**
Dose	50mg/ml	20mg/ml	50mg/ml	100mg/ml
Test dose	Yes each infusion	First dose only	No	No
Route	IV	IV	IV	IV
Able to administer total dose	Yes	No	Yes	Yes
In preg	CI first trimester	CI first trimester	CI first trimester	CI first trimester
Adverse reactions	5% minimal adverse reactions	0-1.5%	3%	1%

NHS
North West
London Pathology



Iron deficiency: when to refer

NHS
North West
London Pathology

- For consideration of IV iron
  - Unable to tolerate oral iron
  - Persistent Fe deficiency despite oral iron
  - Symptomatic / clinically significant anaemia
  - Who you refer to depends on underlying cause

Case 2

NHS
North West
London Pathology

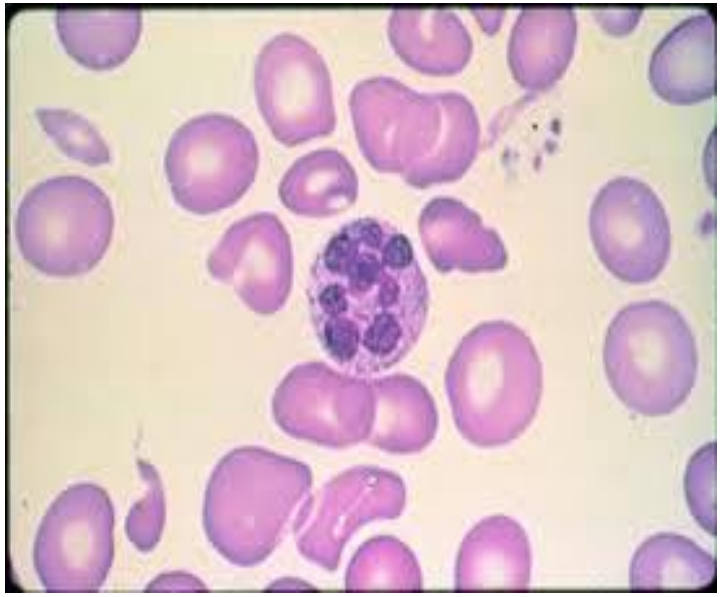
- A 35 year old lady with a history of hypothryoidism presents with increasing lethargy despite normal TFTs. On examination she appears slightly jaundiced.

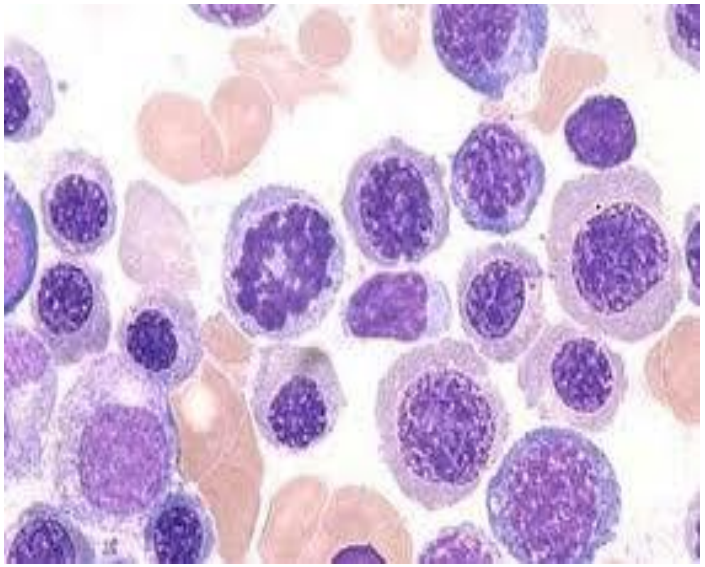
Case 2

NHS
North West
London Pathology

- Hb 72g/l
- MCV 117 fl
- WBC 5.5 x10^9/l
- Neut 3.5 x 10^9/l
- Plt 150 x 10^9/l

NHS
North West
London Pathology





NHS
North West
London Pathology

RED CELL FOLATE

				150 – 850
Red cell folate	*	68	ug/L	

B12 ASSAY

B12 assay	*	93	ng/L	160 - 800

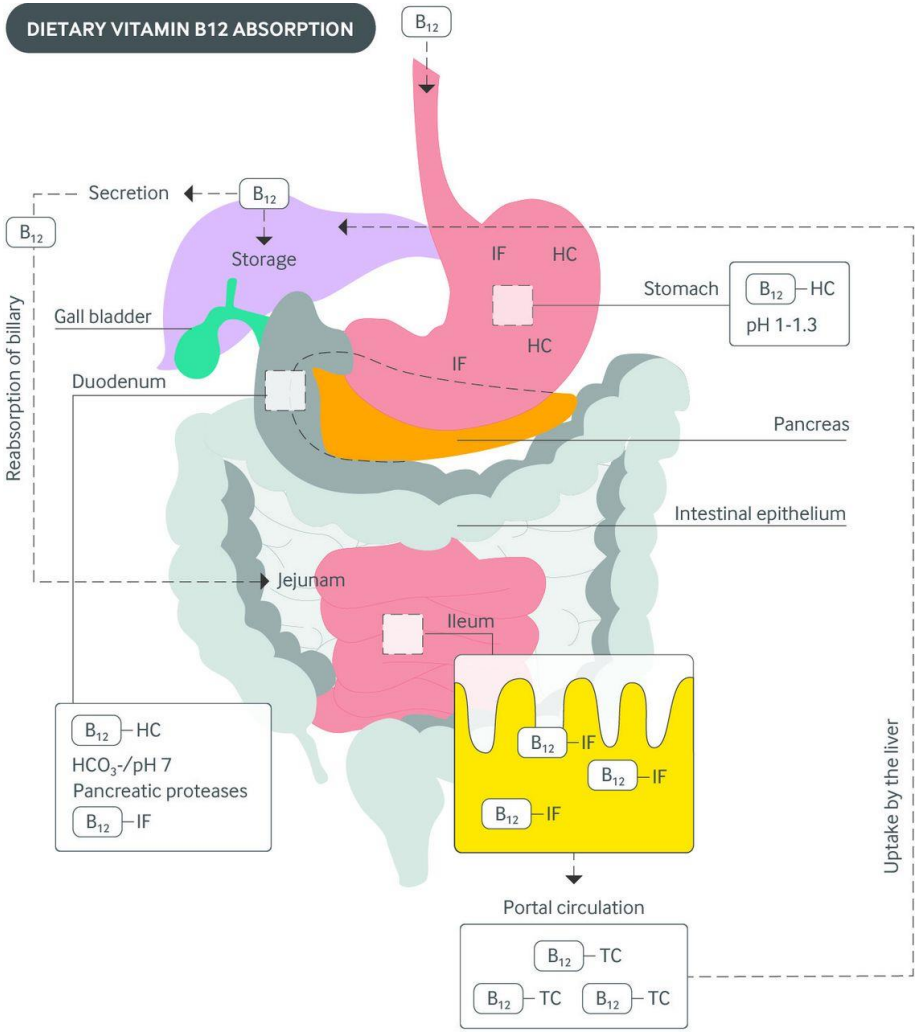
Deficient <160 ng/L
Very low B12. Please load the patient with
Intramuscular Vit B12 and re-check after a month

B12 deficiency

NHS
North West
London Pathology

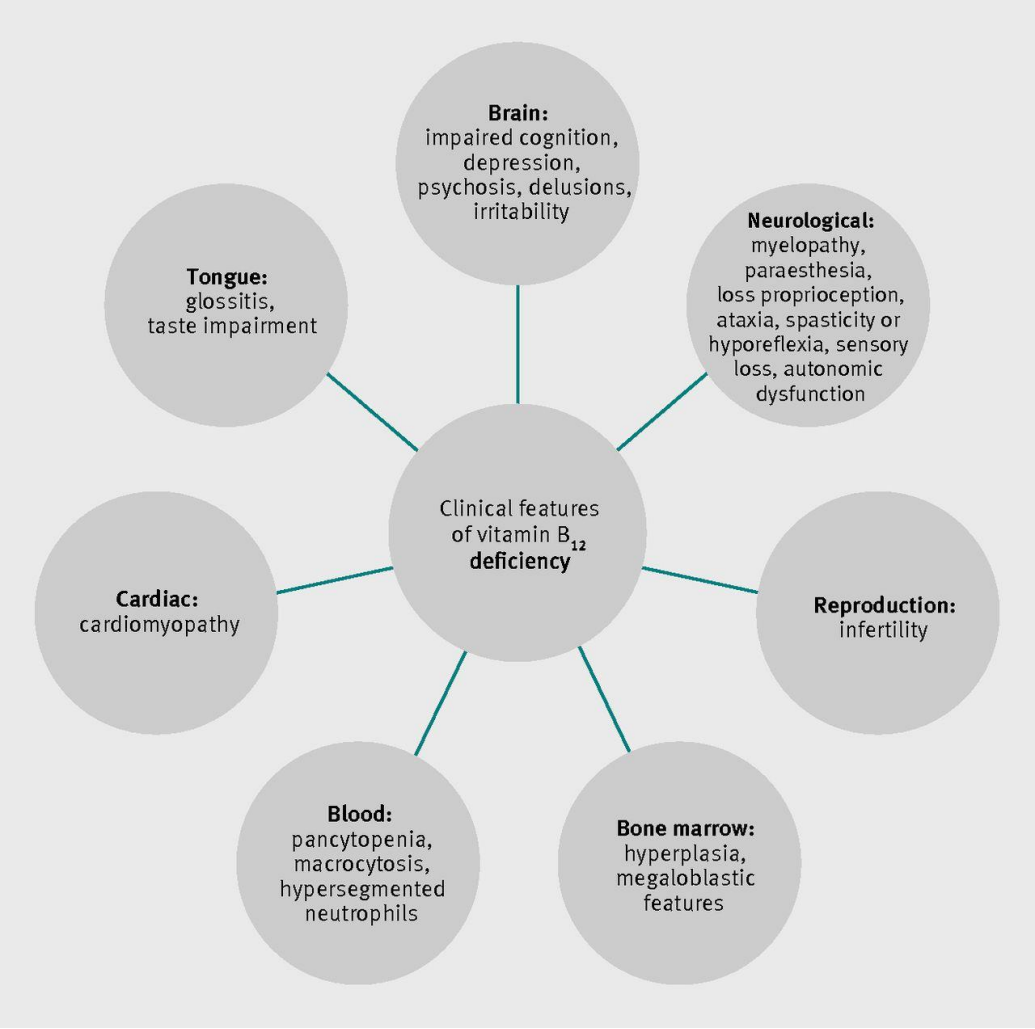
- B12 measures inactive (TC I and TCIII now known as halohaptochorrin and active forms TCII – halotranscobalamin)
- Not always clear cut
- Homocysteine levels and MMA levels

Fig 1 Mechanism of dietary vitamin B12 absorption.



Hunt A et al. BMJ 2014;349:bmj.g5226

Fig 2 Clinical features of vitamin B12 deficiency.



Hunt A et al. BMJ 2014;349:bmj.g5226

Investigations

NHS
North West
London Pathology

Assessment	Finding	Major limitations/ comments
Physiological		
MCV	Normal or increased (>100fl)	Poor specificity may be normal in co existing Fe def or thal
Hb	Normal or low	Poor Spec and sens
Retic	Low	Poor spec
LDH	Increased	Intramedullary haemolysis
Blood film /BM	See slide	
Static		
cobalamin	Low (<160ng/l) < 70ng/ml if pregnant)	Not highly specific. Normal levels in some deficient patients. Insensitive to inborn errors of metaboolism. Slight to moderate low levels may not reflect deficiency
halotranscobalamin	Low (<5pm/l), replete (>50pmol/l), intermediate (25-50pmol/l)	Not widely available
Functional		
Plasma MMA	Increased (>350nmol/l)	Increased in renal failure and older people
Plasma homocysteine	Raised (>15)	Increased in folate and B_6 deficiencies, renal failure , hypothyroidism

Management

NHS
North West
London Pathology

- A therapeutic trial can confirm the diagnosis
- Hb rises within 10 days and usually returns to normal at 8 weeks
- Hypersegmented neutrophils disappear around 10-14 days
- Watch K+ levels in severely anaemic patients
- Neurological abnormalities slower to improve and can take months
- Parenteral B12 1mg three times a week for two weeks and then every 3 months
- Oral B12 if dietary deficiency
- Remember levels drop in Pregnancy.

NHS
North West
London Pathology

NW London Outpatient Pathways	
5. Raised B12	V1 / 9/7/20

General Advice

The most common medical explanations for a high B12 are liver or renal disease, myeloproliferative disorders and autoimmunity.
Rarely it can be associated with a transcobalamin secreting tumour.
It is worth checking the patient is not receiving supplements for example in a multivitamin or foods that have a high B12 content such as yeast or soya products.
The patient can be reassured that, in itself, a raised Vitamin B12 level is not harmful

↓

Investigations

- Full blood count
- Renal profile
- LFT
- Autoantibody screen

↓

Further Investigations

If initial investigations are returned within normal ranges, and the patient is not taking supplemental Vit B12 (including dietary sources), consider an US Abdomen

↓

Seek routine advice & guidance from haematology if uncertain

Anaemia in the Elderly

NHS
North West
London Pathology

- Incidence in > 65 years 11% and 10% for men and women respectively
- 1/3 nutritional deficiencies
- 1/3 anaemia of inflammation
- 1/3 unexplained

Anaemia of the elderly

NHS
North West
London Pathology

- Increased epo resistance
- Increased proinflammatory cytokine

Anaemia of the elderly

NHS
North West
London Pathology

- Haematinics
- Autoantibodies
- Haemolysis screen
- Myeloma screen
- Consider BM

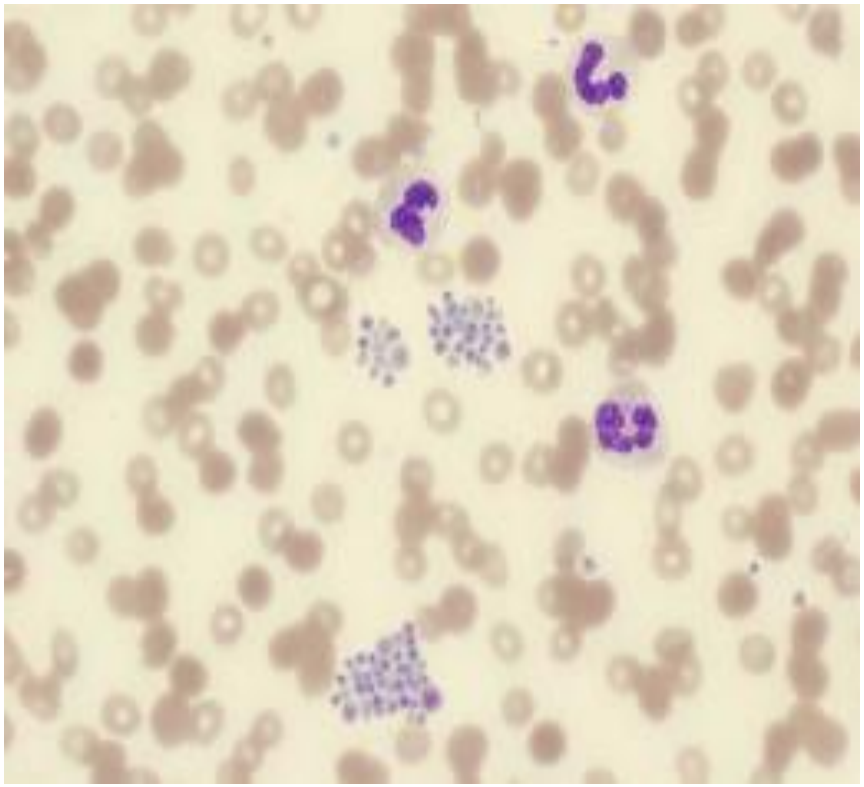
Case 3

NHS
North West
London Pathology

- A GP blood count comes through with no clinical details.
- Hb 135g/l
- WBC 6.3 x 10^9/l
- Neuts 4.9 x 10^9/l
- Plts 10x 10^9/l

Case 3

NHS
North West
London Pathology



Platelets

NHS
North West
London Pathology

• **Low Platelets**	**Technical**	Clot / Clumping
	Temporary	Reactive, post viral
	Persistent	eg drugs, EtOH, liver disease, infections (Hep B, C,HIV), chronic ITP
	Progressive	BM problems

Immune thrombocytopenia (ITP)

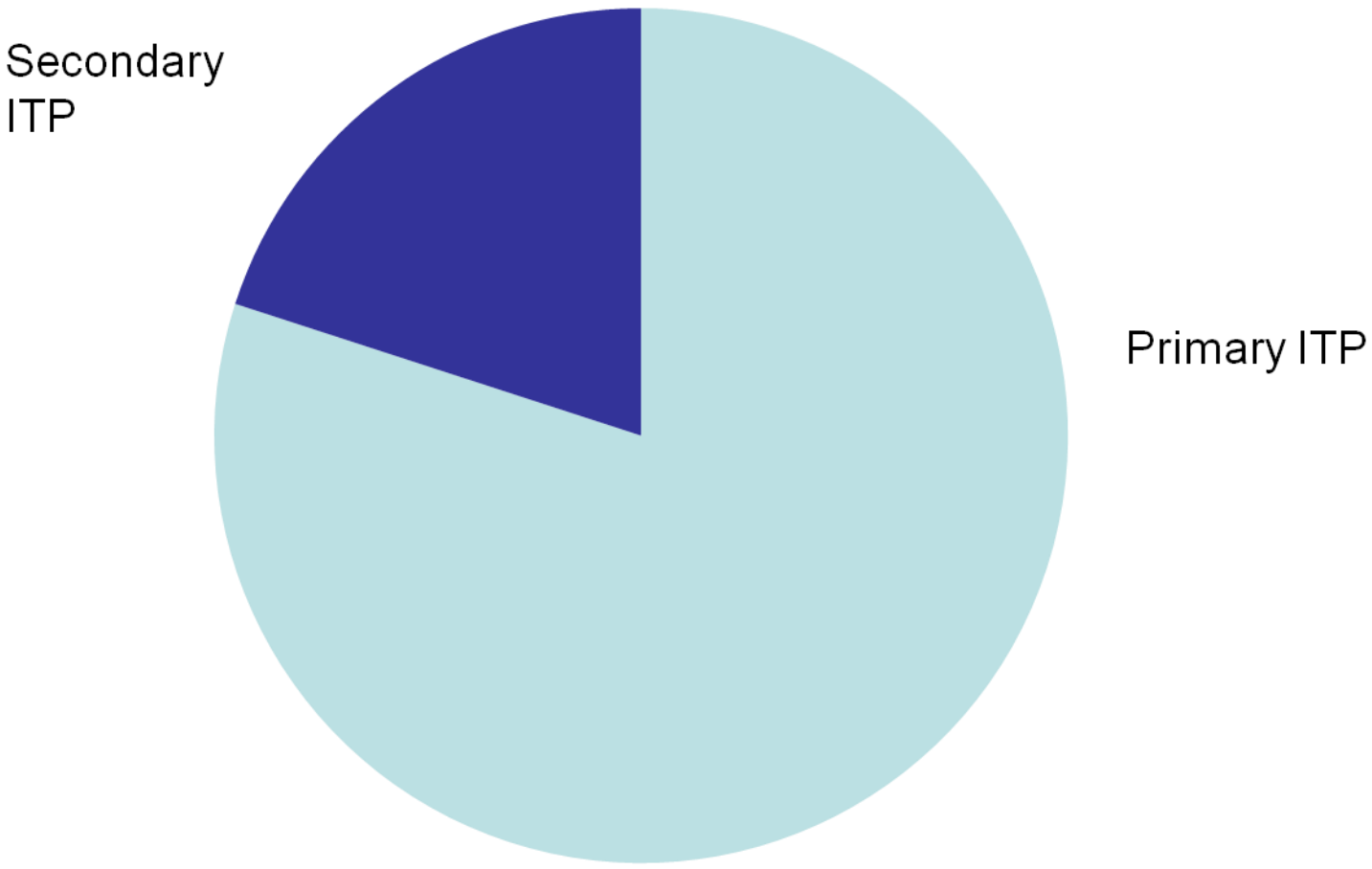
NHS
North West
London Pathology

An autoimmune condition characterized by an isolated low platelet count (<100) in the absence of other underlying causes

- **Newly diagnosed** (< 3 months)
- **Persistent** (3-12 months)
- **Chronic** (≥ 12 months)

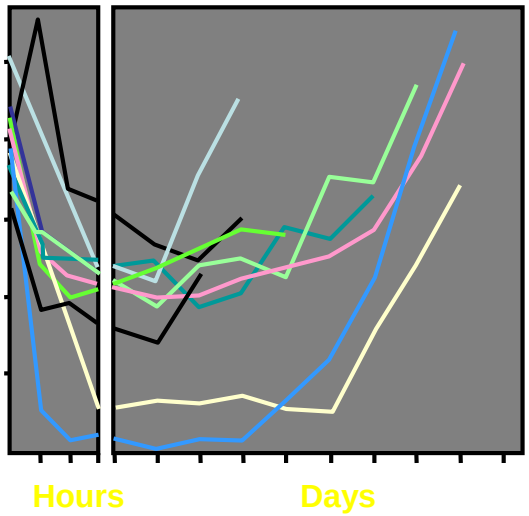
ITP

NHS
North West
London Pathology

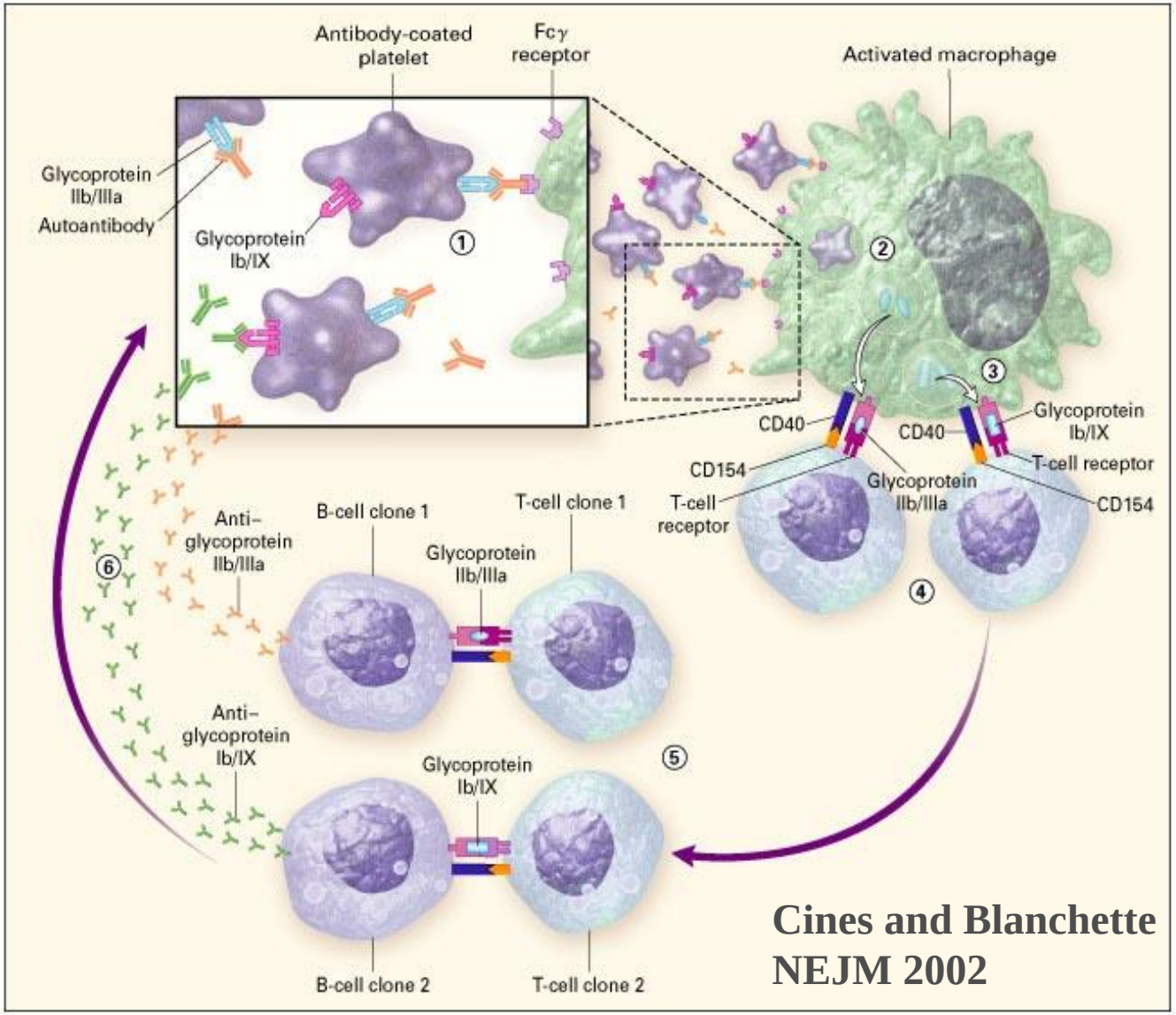


Pathology of ITP

NHS North West



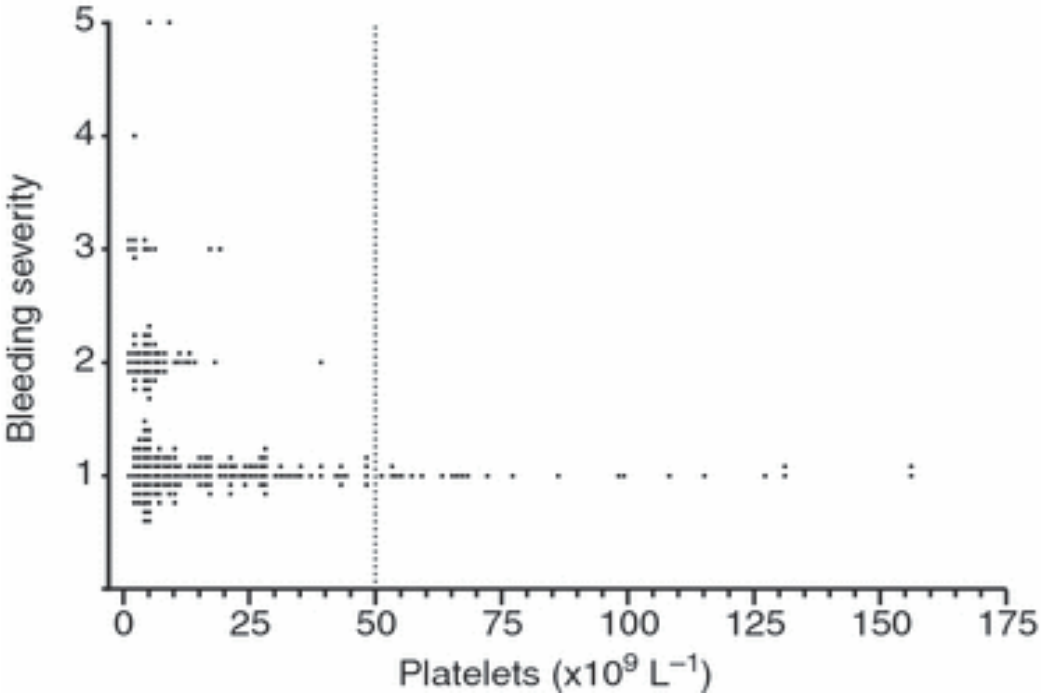
Harrington J Lab Clin Med 38, 1–10 (1951)



Cines and Blanchette NEJM 2002

Is there a platelet count at which serious bleeding occurs?

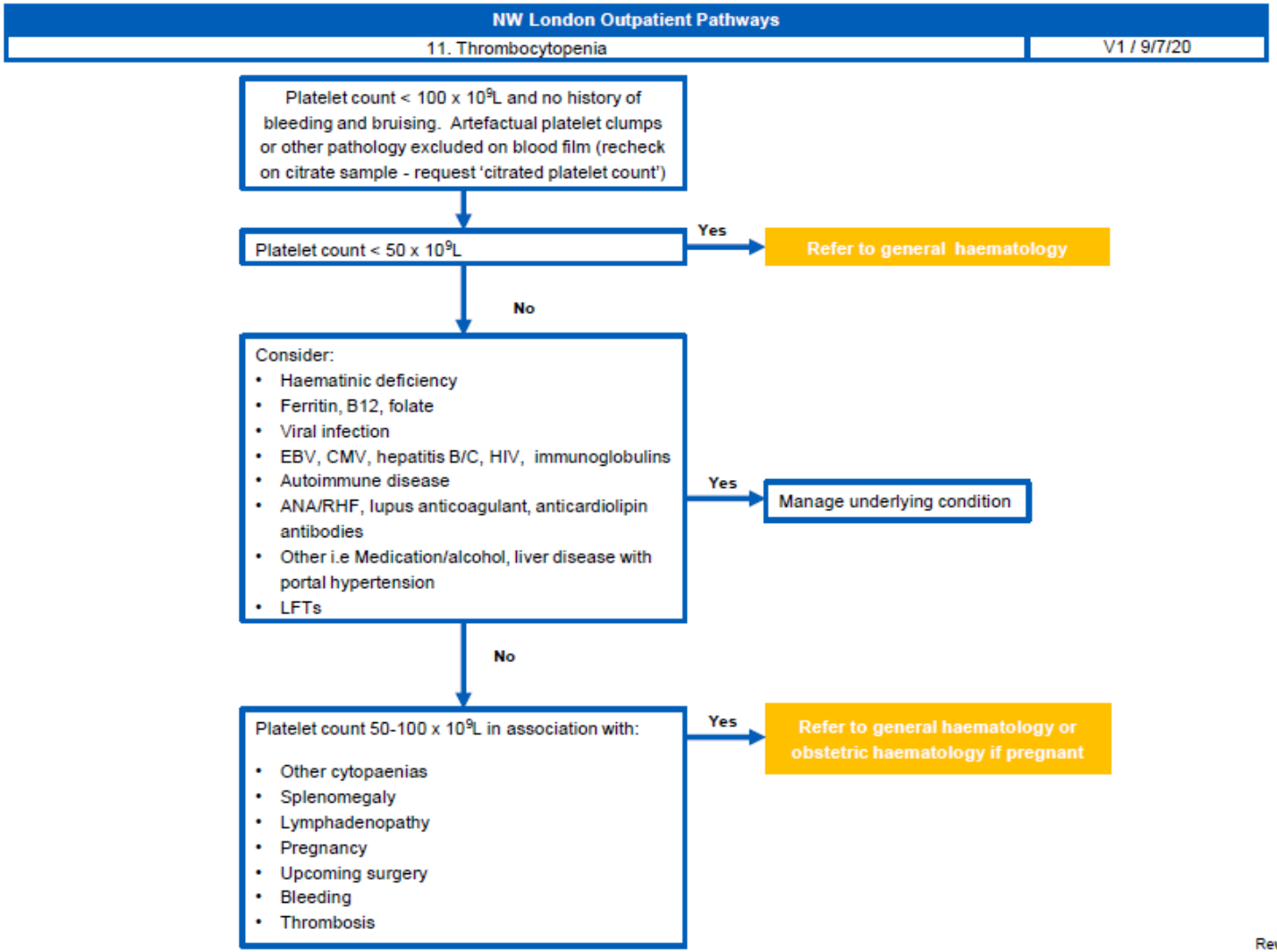
NHS
North West
London Pathology



Distribution of bleeding adverse events by severity and platelet count in both treatment groups in the phase 3 studies. Each point represents one bleeding adverse event. One grade 1 bleeding adverse event that occurred at a platelet count of 505×10^9 L^{-1} is not shown
Gernsheimer, JTH 2010

Management goal: hemostatically active platelet count (usually 30-50K) with minimal side effects

NHS
North West
London Pathology



Case 4

NHS
North West
London Pathology

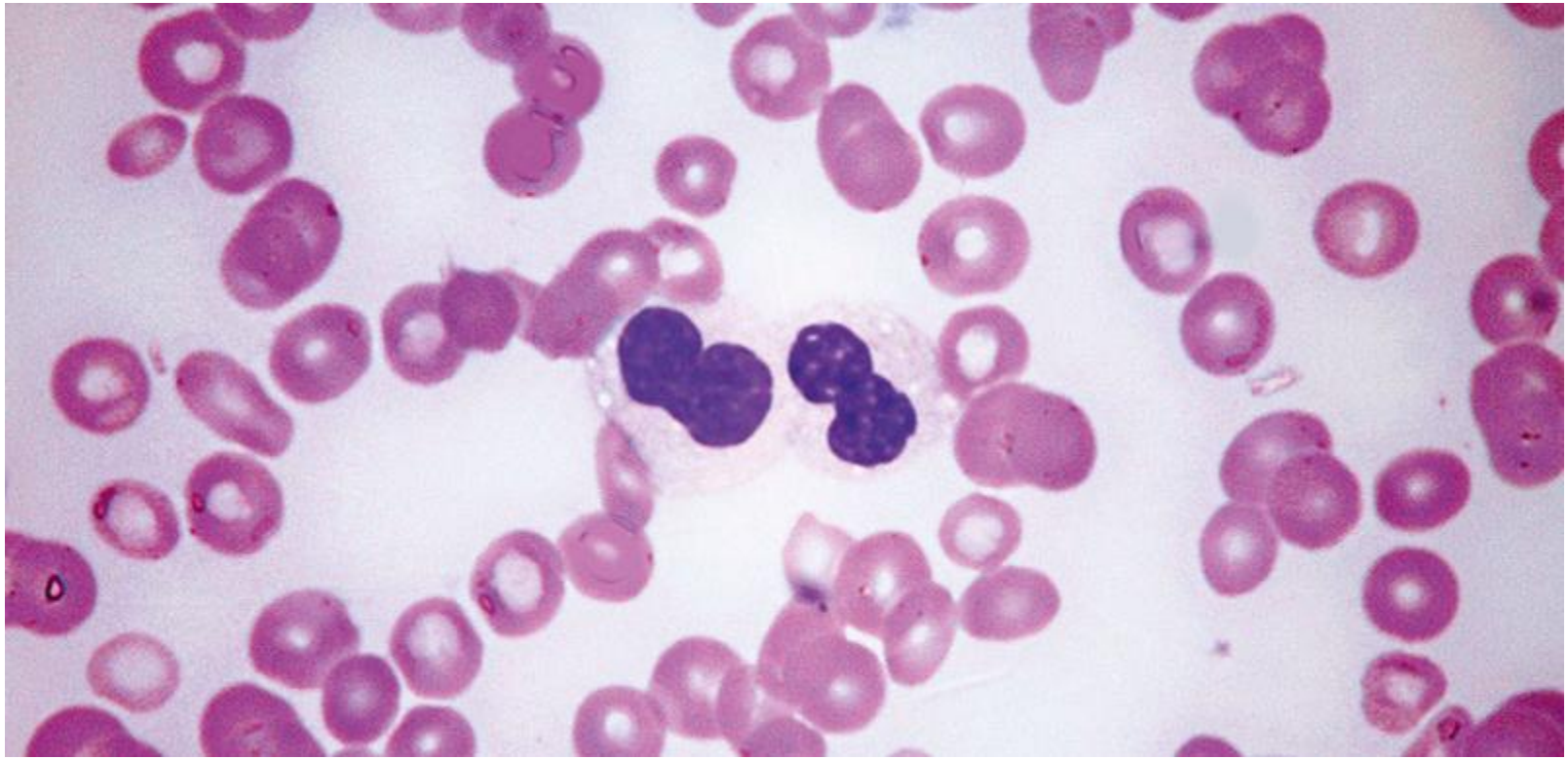
- 78 year old lady presented feeling TATT . Her results were
- Hb 105g/l
- MCV 110fl
- WBC 6.3 x 10^9/l
- Neuts 4.9 x 10^9/l
- Plts 160 x 10^9/l

- Two months later

- Hb 75g/l
- MCV 110fl
- WBC 4.3 x 10^9/l
- Neuts 0.9 x 10^9/l
- Plts 50 x 10^9/l

Blood film

NHS
North West
London Pathology



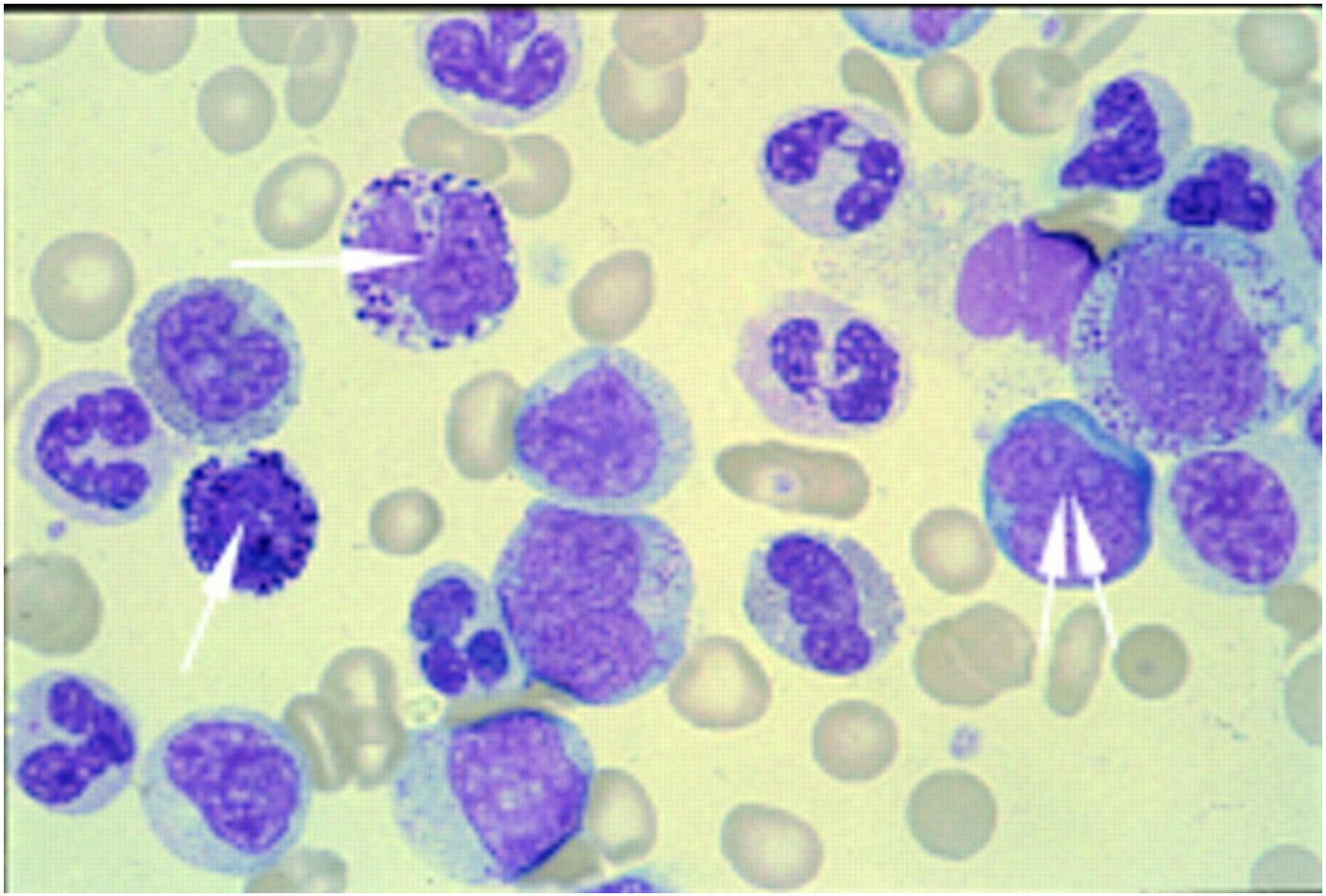
Case 5

NHS
North West
London Pathology

- 35 year old woman presents with feeling tired and a bit dizzy
- Hb 95g/l
- MCV 84fl
- WBC 283x 10^9/l
- Neuts 200x 10^9/l
- Plts 175 x 10^9/l

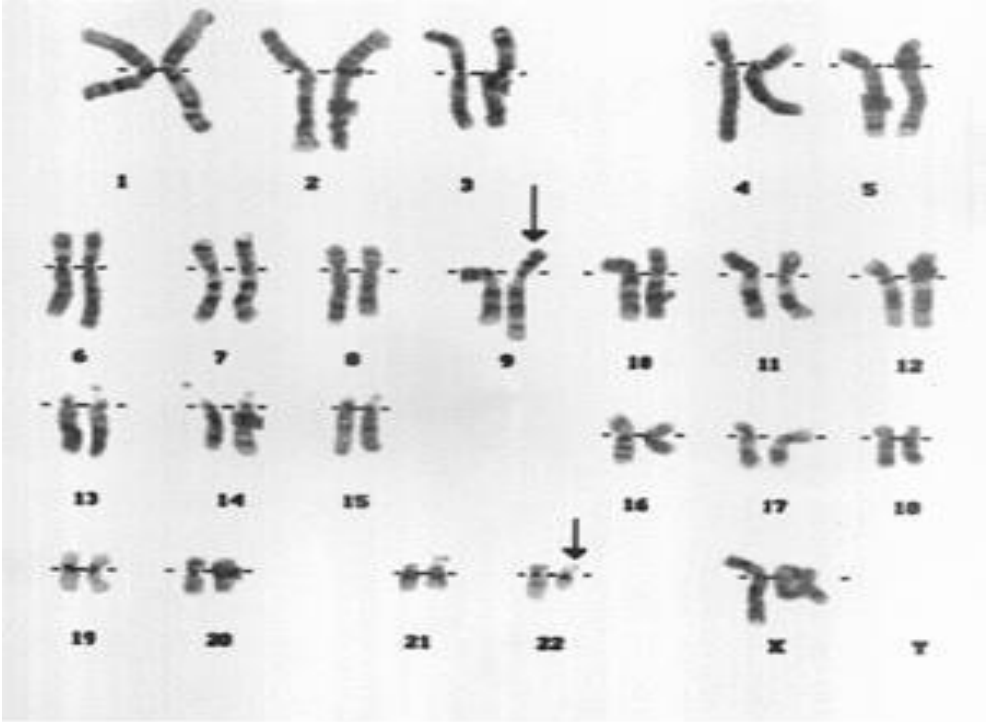
What is the diagnosis?

NHS
North West
London Pathology



CML- Cytogenetics

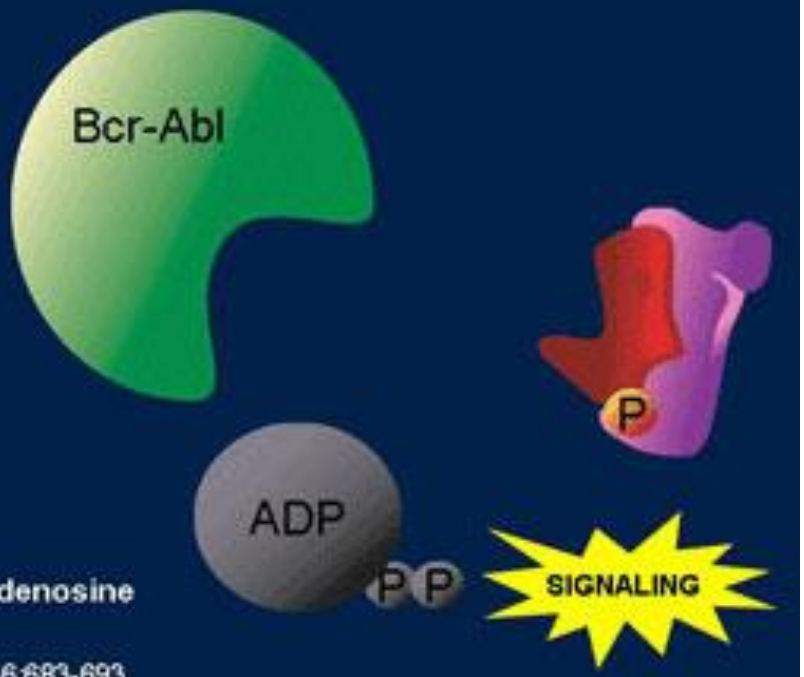
NHS
North West
London Pathology



The abnormality seen by Nowell & Hungerford on chromosome 22, Now known as the Philadelphia Chromosome.

Normal Bcr-Abl Signaling

- The kinase domain activates a substrate protein (eg, PI3 kinase) by phosphorylation
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival

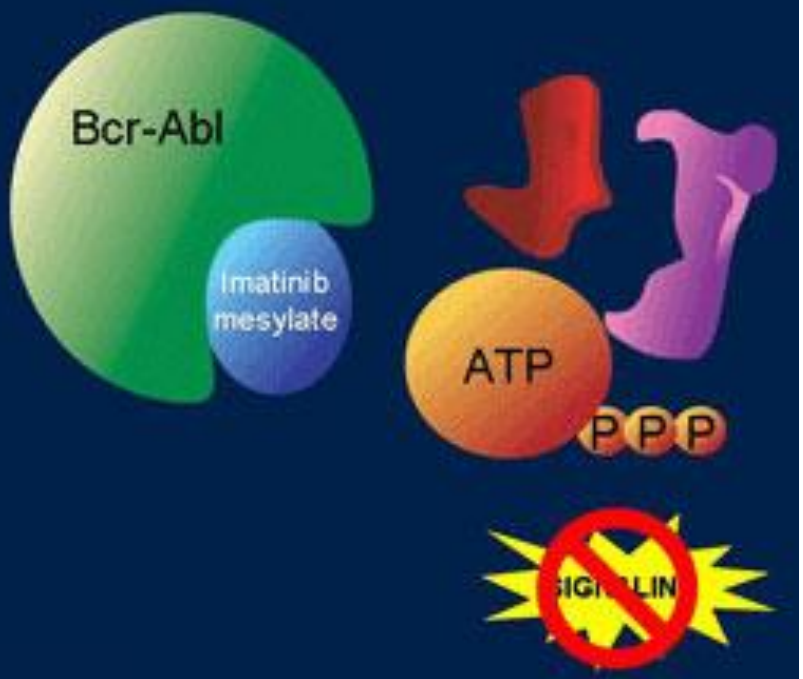


ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Savage DG, Antman KH. *N Engl J Med.* 2002;346:683-693.
Scheijen B, Griffin JD. *Oncogene.* 2002;21:3314-3333.

Imatinib Mesylate: Mechanism of Action

- Imatinib mesylate occupies the ATP binding pocket of the Abl kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



Savage DG, Antman KH. *N Engl J Med.* 2002;346:683-693.

NHS
North West
London Pathology

NW London Outpatient Pathways

14. Leucocytosis

V1 / 9/7/20

Leucocytosis is defined as an elevation of white cell count to >10.6 x 10^9/L. It has a wide differential diagnosis ranging from a normal response to infection through to haematological malignancies including acute leukaemias. Detection of a leucocytosis should prompt scrutiny of the differential white cell count, other FBC parameters and blood film examination.

New suspected Acute leukaemia
New suspected Chronic myeloid leukaemia with either:
- White cell count >100 x 10^9/L
- Hyperviscosity symptoms (Headache, visual loss, acute thrombosis)

→ **Immediate emergency telephone referral**

In an otherwise well patient:-
- Leucoerythroblastic blood picture (from blood film report)
- New chronic myeloid leukaemia not meeting the above criteria
- Unexplained leucocytosis with white cell count >50 x 10^9/L

→ **2WW Haematology**

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:
- Careful history and assessment for 'reactive' causes: smoking, infection, inflammation or neoplasia. A minor non-specific leucocytosis or neutrophilia is often seen in smokers.
- Examination for lymphadenopathy, splenomegaly
- Blood film examination with differential white cell count
- Correlate with inflammatory markers: CRP, ESR
- CXR

Persistent (on two tests a month apart) unexplained:
- White cell count >20 x 10^9/L
- Neutrophilia >15 x 10^9/L
- Eosinophilia >1.5 x 10^9/L, if secondary causes have been excluded (atopy, parasites, drugs, connective tissue disorders, cardiac and respiratory disorder)
- Monocytosis > 1.0 x 10^9/L
- Lymphocytosis > 10 x10^9/L (see lymphocytosis page)

→ **Routine referral to haematology**

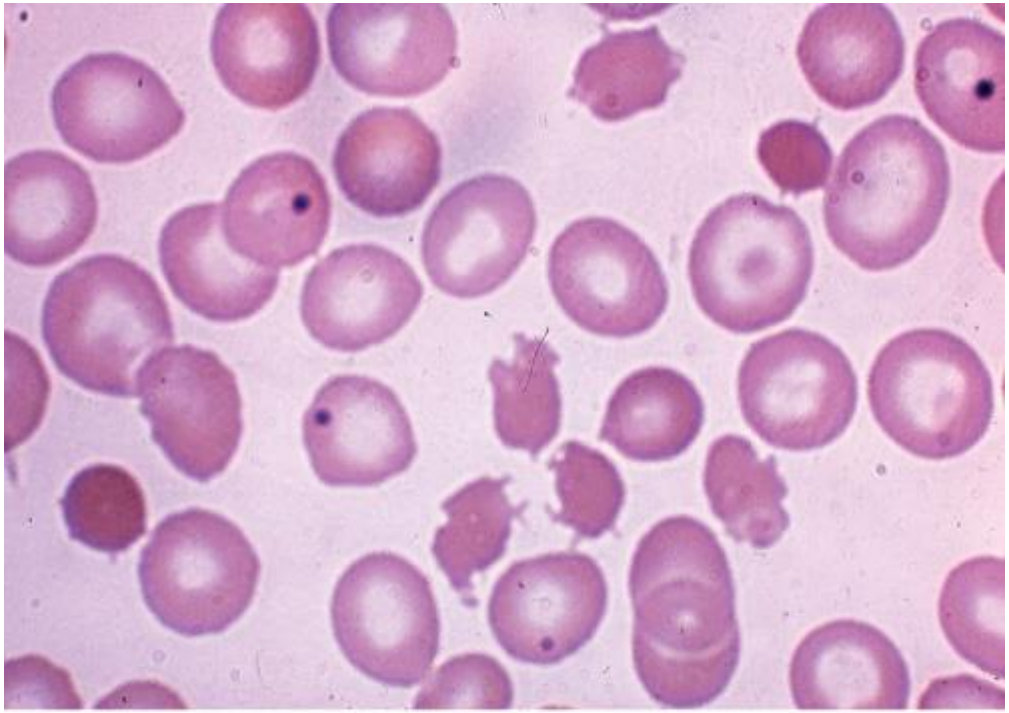
Case 6

NHS
North West
London Pathology

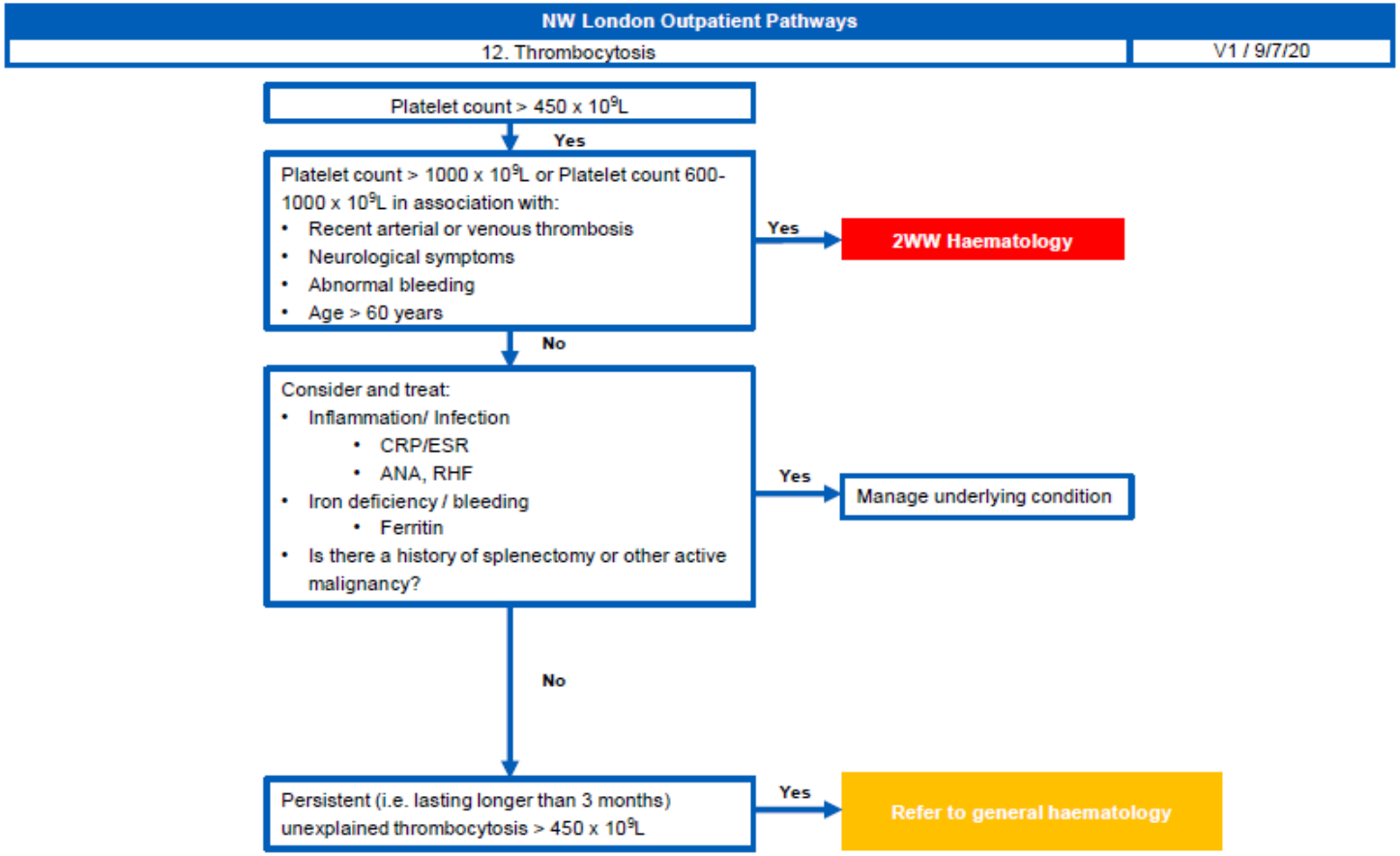
- A 20 year old rugby player prone to injury presented with a dislocated shoulder
- Hb 135g/l
- MCV 84fl
- WBC 15x 10^9/l
- Neuts 9 x 10^9/l
- Plts 700 x 10^9/l

What is the diagnosis ?

NHS
North West
London Pathology



Source: Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology, 8th Edition:* http://www.accessmedicine.com


NW London Outpatient Pathways
12. Thrombocytosis
V1 / 9/7/20
Platelet count > 450 x 10⁹L
Yes
Platelet count > 1000 x 10⁹L or Platelet count 600-1000 x 10⁹L in association with:
• Recent arterial or venous thrombosis
• Neurological symptoms
• Abnormal bleeding
• Age > 60 years
Yes
2WW Haematology
No
Consider and treat:
• Inflammation/ Infection
• CRP/ESR
• ANA, RHF
• Iron deficiency / bleeding
• Ferritin
• Is there a history of splenectomy or other active malignancy?
Yes
Manage underlying condition
No
Persistent (i.e. lasting longer than 3 months) unexplained thrombocytosis > 450 x 10⁹L
Yes
Refer to general haematology

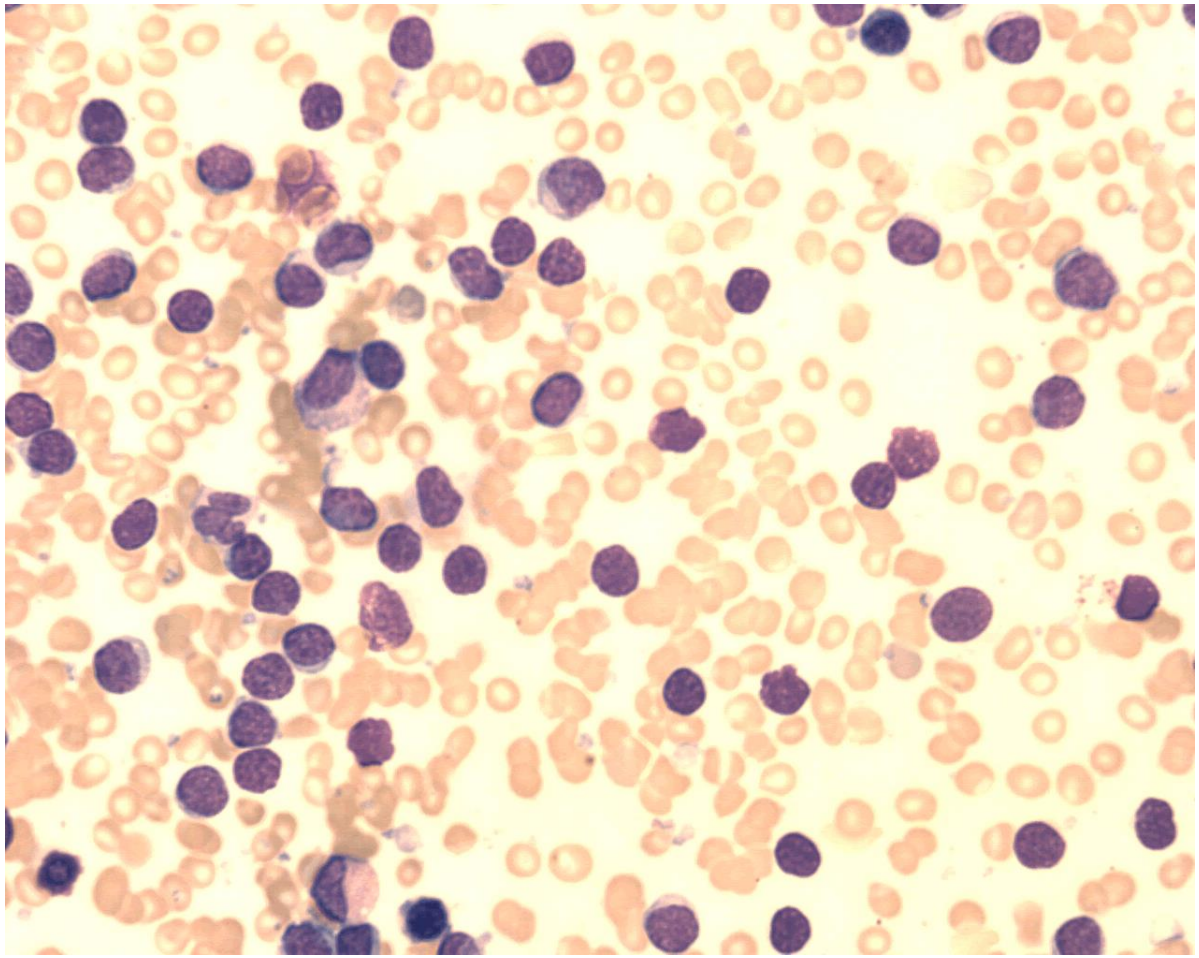
Case 7

NHS
North West
London Pathology

- A 75 year old gentleman comes for a routine check . Other than hypertension he is fit and well.
- Hb 135g/l
- MCV 84fl
- WBC 30x 10^9/l
- Neuts 5 x 10^9/l Lymp 20 x 10^9/l
- Plts 400 x 10^9/l

What is the diagnosis?

NHS
North West
London Pathology



CLL

NHS
North West
London Pathology

- Most common type of chronic leukaemia
- Mostly occurs in those >60
- No cure but a very slowly progressing disease
- 50% diagnosed incidentally on a routine blood test
- Most patients die with it rather than of it
- Active monitoring for a large proportion

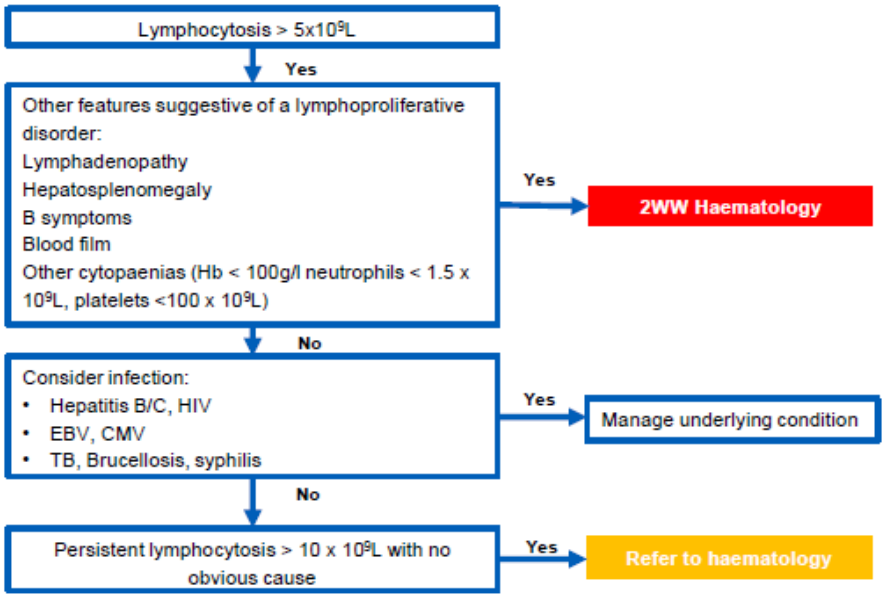
CLL- when to treat

NHS
North West
London Pathology

- Rapidly rising WBC
- B symptoms- weight loss, drenching sweats
- Bulky lymphadenopathy
- Bone marrow failure

NHS
North West
London Pathology

NW London Outpatient Pathways	
10. Lymphocytosis	V1 / 9/7/20



MGUS – monitoring

NHS
North West
London Pathology

- Purpose is to identify transformation to a malignant disorder (eg myeloma, WM) at an early stage

NHS
North West
London Pathology

NW London Outpatient Pathways	
15. Paraproteinaemia (1 of 2)	V1 / 9/7/20

Disorders characterised by the production of a paraprotein include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma and Waldenströms macroglobulinaemia. Paraproteins may also be a feature of CLL, NHL or amyloidosis.

MGUS is a diagnosis of exclusion: 3% of over-50s, 5% of over 70s and 7.5% of over 85s have paraproteins which are frequently found incidentally and not associated with symptoms or physical findings. The overall risk of MGUS progression to myeloma is around 1% per year - this remains constant over time.

***Referrals to haematology should not be made for patients with raised immunoglobulin levels in the absence of a monoclonal paraprotein band on serum electrophoresis. Polyclonal gammopathy implies a non-specific immune reaction ***

Risk Group	20 year risk of progression to myeloma (%)
Low Risk Serum Paraprotein <15g/l IgG isotype Appropriate FLC ratio	5%
Low-Intermediate Risk Presence of an IgA or IgM isotype (NB: Paraprotein must be less than 10g/l) OR Inappropriate FLC ratio	21%
High-intermediate Risk Presence of an IgA or IgM istotype (NB: Paraprotein must be less than 10g/l) AND Inappropriate FLC ratio	37%
High Risk If IgG, Paraprotein >15g/l If IgA or IgM, Paraprotein >10g/l Inappropriate FLC ration	58%

Serum Free Light Chains

Light chains can be elevated in a variety of conditions

- Both kappa and lambda light chains will be raised in renal failure
- Please repeat one off borderline abnormalities
- Please refer if the kappa or lambda light chains are > 200mg/ml
- If the light chain ratio is clearly abnormal, i.e. >4 or < 0.25 the patient should be referred to a myeloma clinic (2 week wait).
- Renal impairment may lead to an increased serum FLC ratio. The proposed sFLC ratio reference range for these patients is 0.37-3.10
- Please note that the free light chain assay is not a substitute for other laboratory evaluations such as protein electrophoresis.

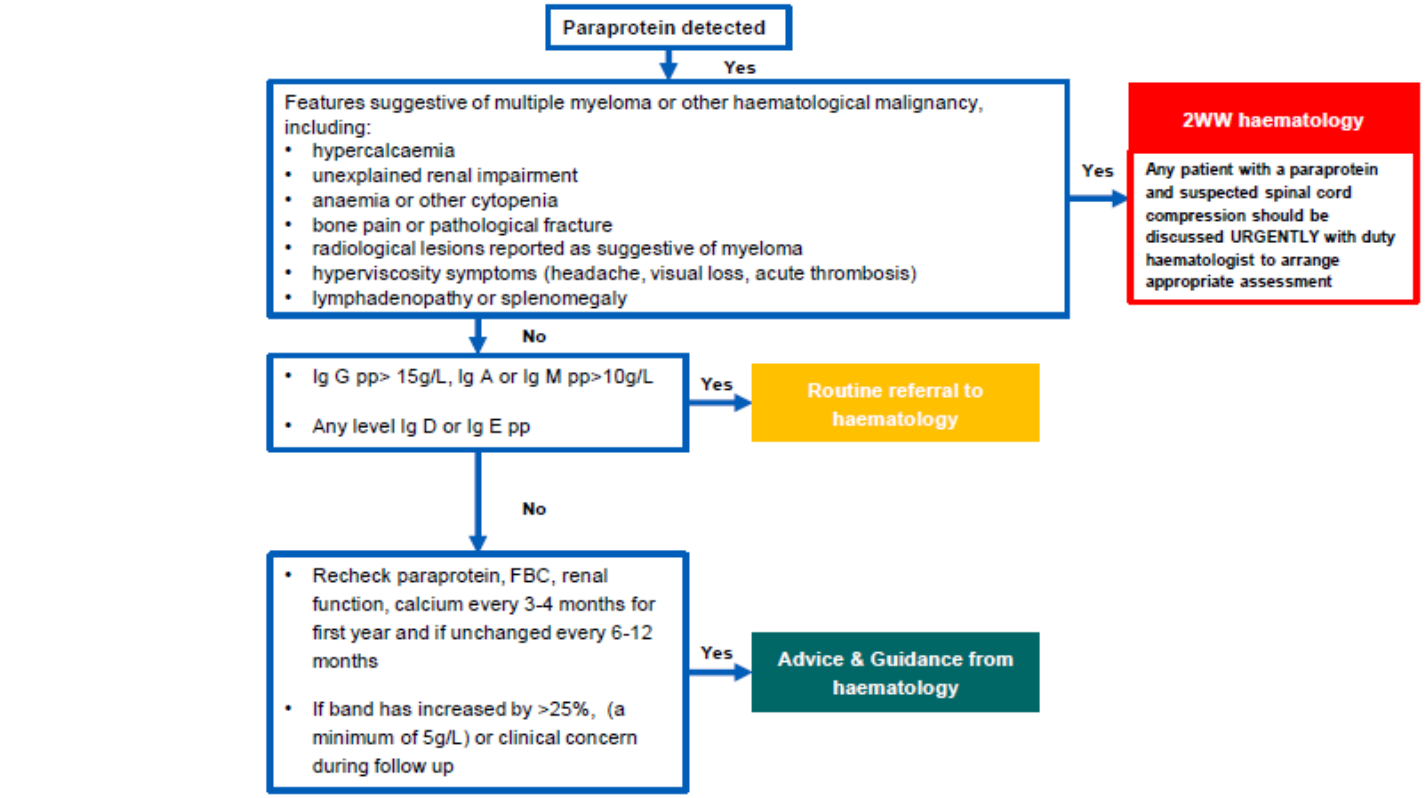
Monitoring in primary care

NHS North West London Pathology

- M protein at levels below in whom there are no symptoms, signs or results of initial investigations suggestive of myeloma, LPD, or AL amyloidosis
- IgG M protein <15g/l
- IgA or IgM < 10g/l
- **This forms the vast majority of M proteins detected in routine practise**

NHS
North West
London Pathology

NW London Outpatient Pathways	
15. Paraproteinaemia (2 of 2)	V1 / 9/7/20



Review 2021

Useful links

NHS
North West
London Pathology

- NWL CCG GP Haematology guidelines: https://www.nwlondonccgs.nhs.uk/professionals/referral-guidelines-and-clinical-documents/haematology

- Imperial GP Haematology email advice line: haematologyadvice.imperial@nhs.net