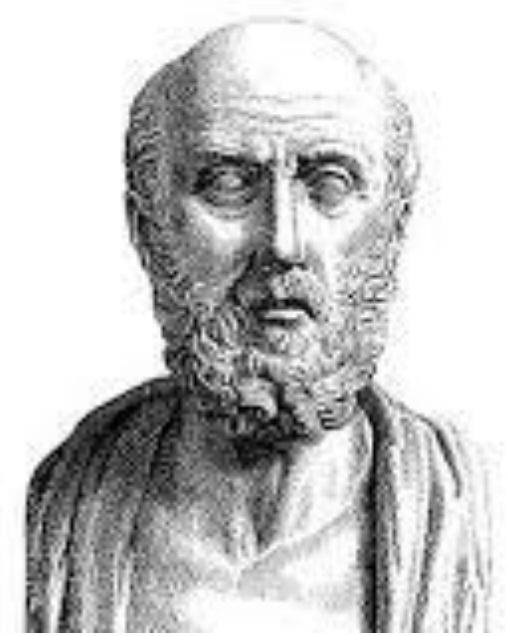
Presidential address

Mary Frances McMullin

Diagnostics

Mary Frances McMullin
m.mcmullin@qub.ac.uk

Hippocrates : The father of modern medicine



Physical Assessment

- Four Basic Skills:
  1. Inspection
  2. Palpation
  3. Percussion
  4. Auscultation

- Sequence for abdominal:

1. inspection, 2. auscultation, 3. percussion, 4. palpation

Diagnostic Aids

- Lydgate not only used his stethoscope (which had not become a matter of course in practice at the time) but sat quietly by his patient and watched him.

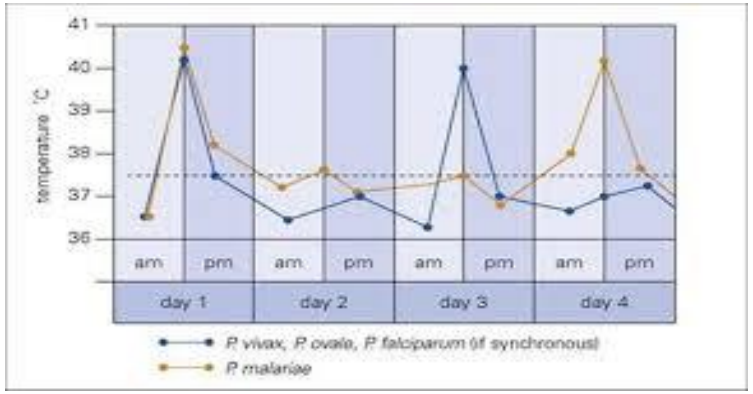
- Middlemarch, George Eliot

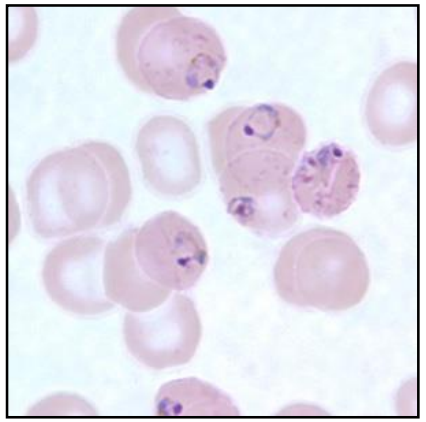
Infectious diseases

Phenotypes

Biological causes

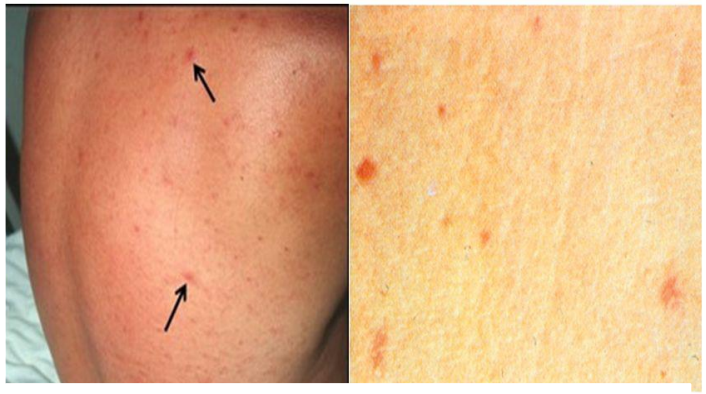
Fever

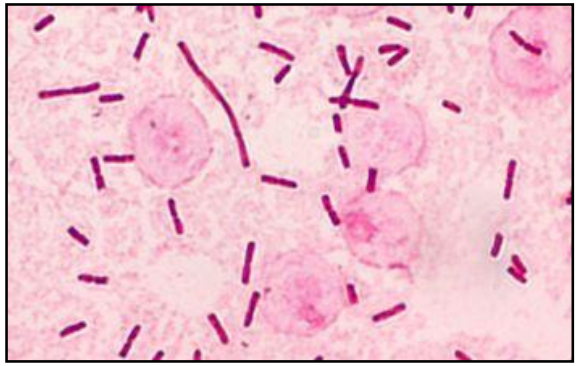




P falciparum

Rash

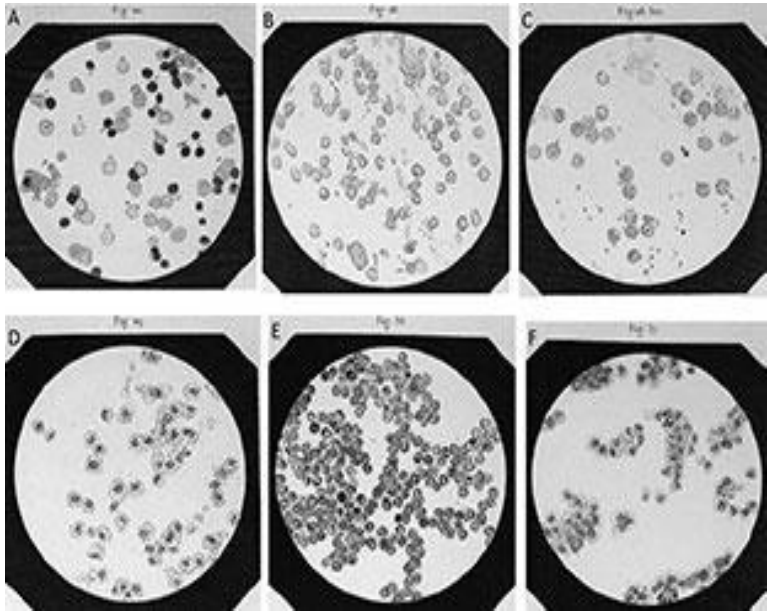




S typhi


Primo Star

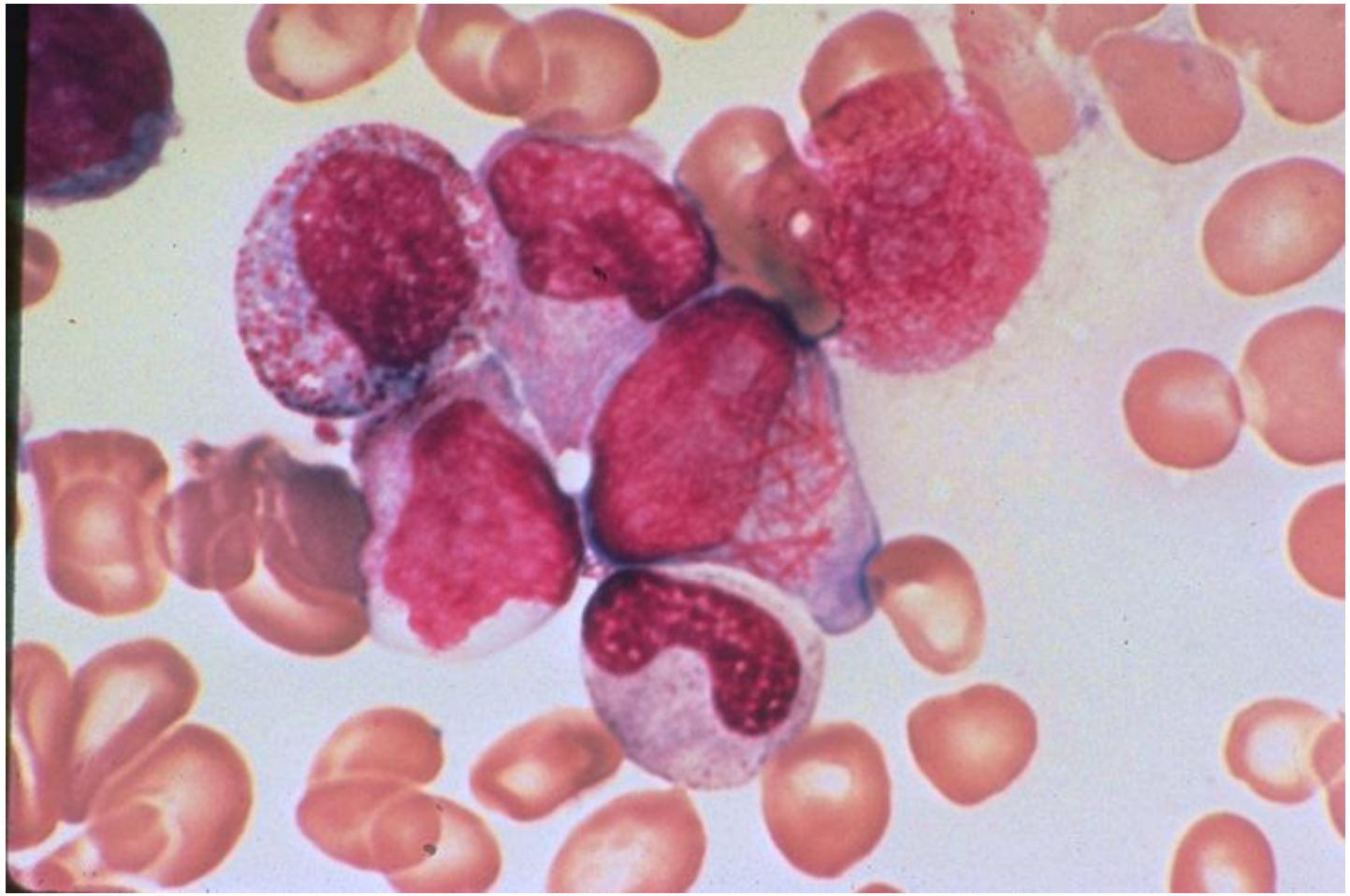
John Hughes Bennet



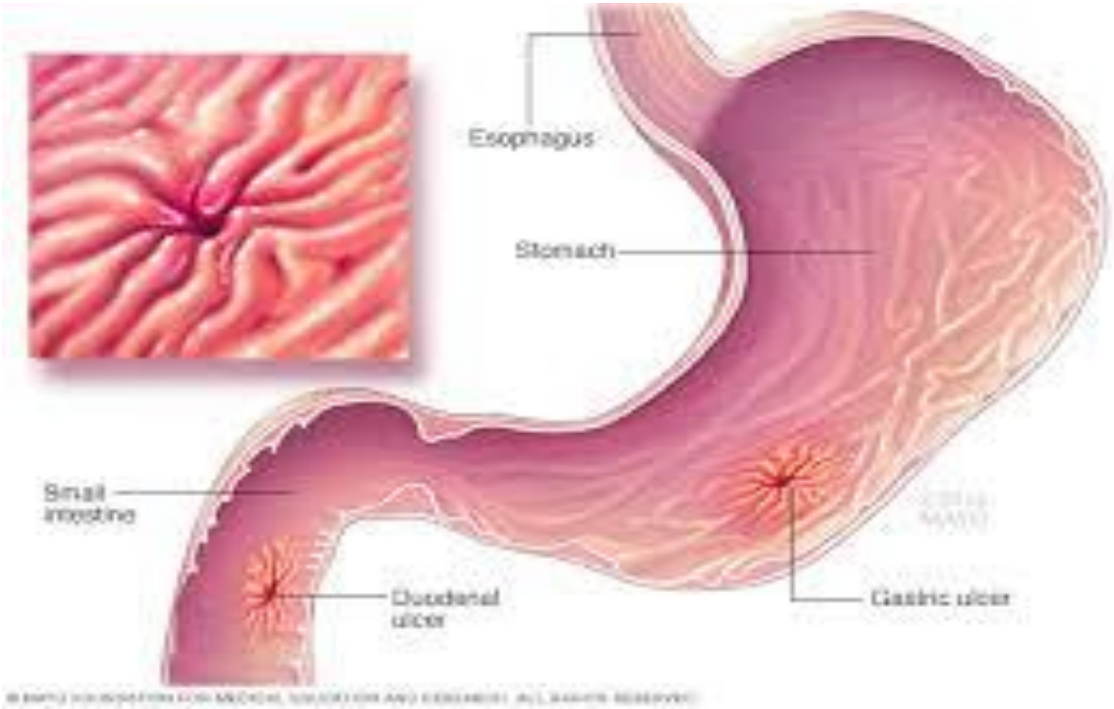
FAB CLASSIFICATION

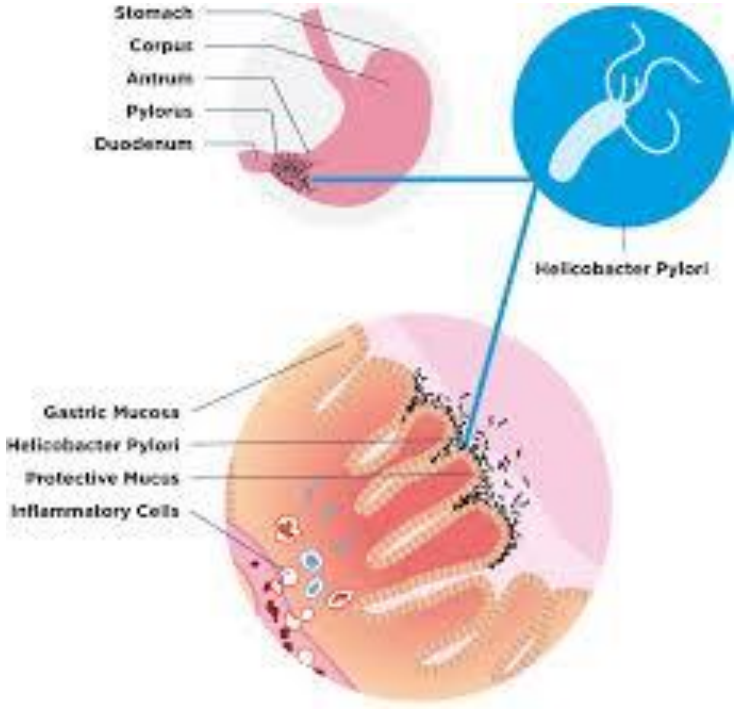
FAB Class		Percent Cases	Morphology	Cytochemistry
M0:	*Minimally differentiated AML*	2	Blasts lack definite cytologic and cytochemical features but have myeloid lineage antigens	Myeloperoxidase –
M1:	*AML without maturation*	20	Myeloblasts predominate; few if any granules or Auer rods	Myeloperoxidase +
M2:	*AML with maturation*	30	Myeloblasts with promyelocytes predominate; Auer rods may be present	Myeloperoxidase +++
M3:	*Acute promyelocytic leukaemia*	5	Hypergranular promyelocytes; often with multiple Auer rods per cell	Myeloperoxidase +++
M4:	*Acute myelomonocytic leukaemia (Naegeli type)*	30	Mature cells of both myeloid and monocytic series in peripheral blood; myeloid cells resemble M2	Myeloperoxidase ++ Non-specific esterase +
M5:	*Acute monocytic leukaemia (Schilling type)*	10	Two subtypes: M5a shows poorly-differentiated monoblasts, M5b shows differentiated promonocytes and monocytes	Non-specific esterase ++
M6:	*Acute erythroleukaemia (Di Guglielmo's syndrome)*	<5	Erythroblasts predominate (>50%); myeloblasts and promyelocytes also increased	Erythroblasts:PAS + Myeloblasts: myeloperoxidase +
M7:	*Acute megakaryocytic leukaemia*	<5	Pleomorphic undifferentiated blasts predominate; react with antiplatelet antibodies	Platelet peroxidase +

Acute promyelocytic leukaemia



Peptic ulceration



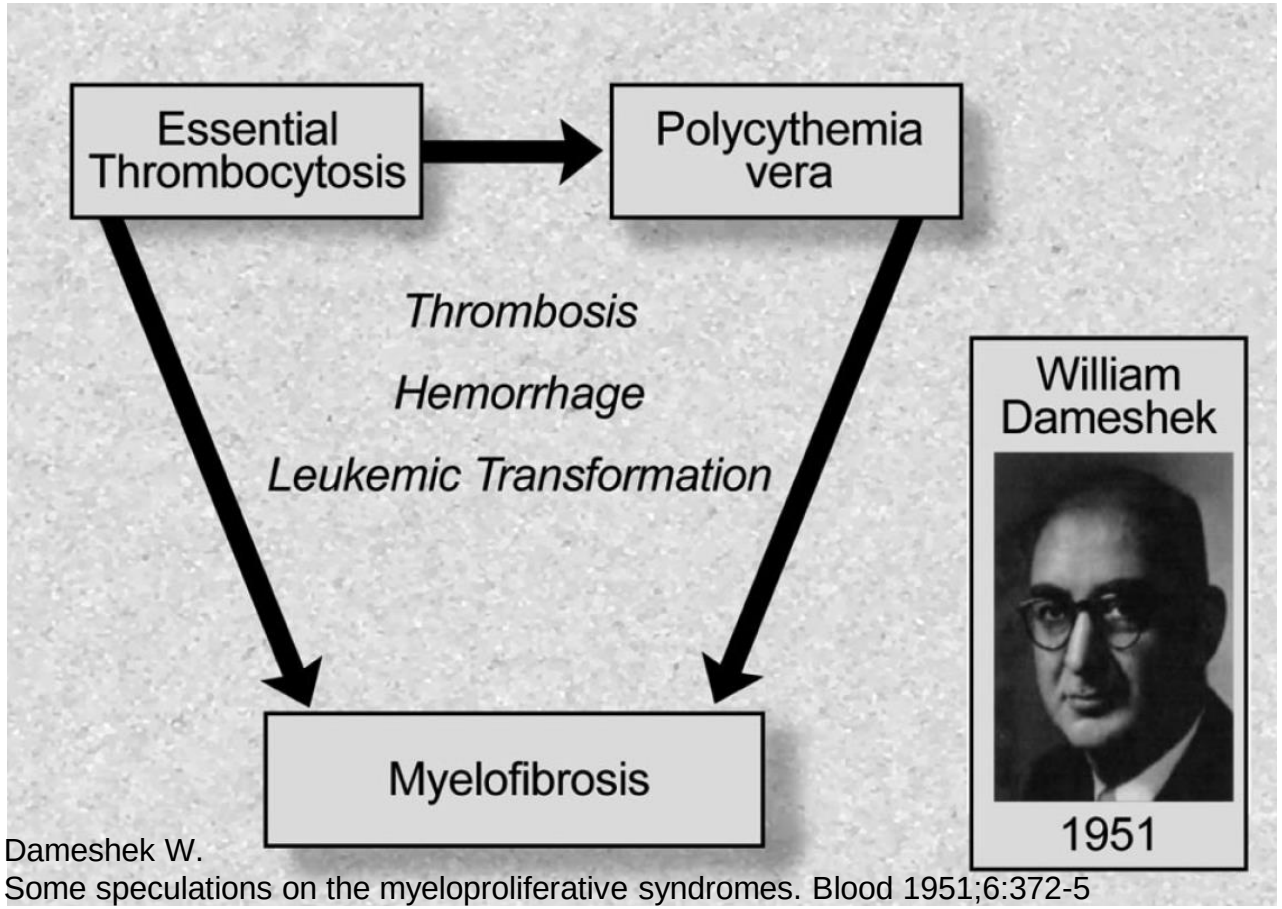


Ph-negative cMPD:

Polycythaemia vera

Essential Thrombocythemia

Primary Myelofibrosis



Dameshek W.
Some speculations on the myeloproliferative syndromes. Blood 1951;6:372-5

Adapted from: Levine RL, Gilliland DG. Blood 2008;112:2190-8

Diagnostic criteria for polycythaemia vera

- A1 Raised red cell mass (>25%above mean normal predicted value or pcv> 0.60 in males and 0.56 in females)
- A2 Absence of a cause of secondary erythrocytosis
- A3 Palpable splenomegaly
- A4 Clonality marker i.e abnormal marrow karyotype

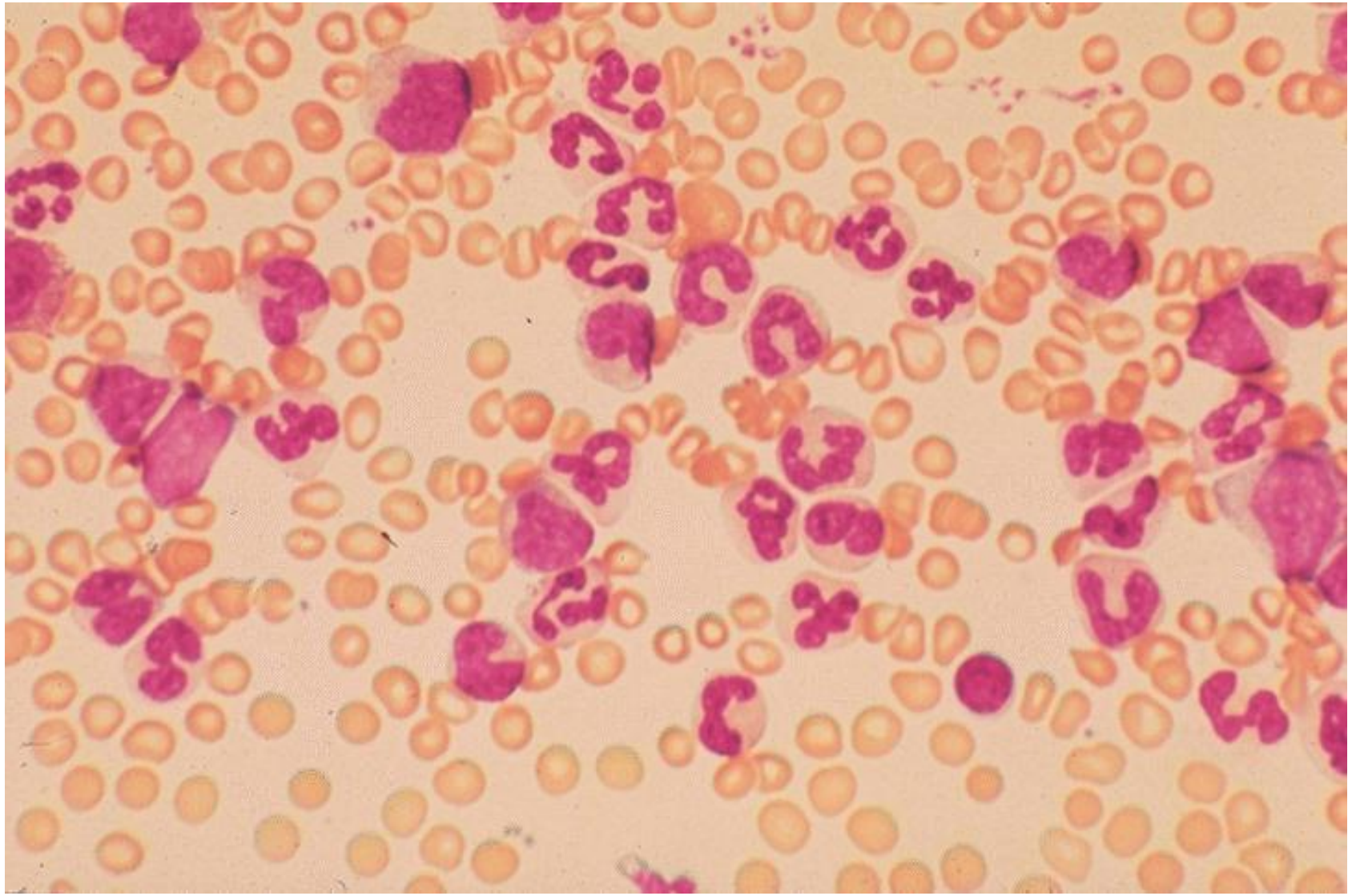
- B1 Raised platelet count (>400 × 10^9/l)
- B2 Neutrophil leucocytosis (> 10 × 10^9/l) (> 12.5 × 10^9/l in smokers)
- B3 Splenomegaly on isotope/ultrasound scanning
- B4 Characteristic BFU-E growth or reduced serum erythropoietin

A1 + A2 + A3 or A4 establishes PV
A1 + A2 + two of B establishes PV

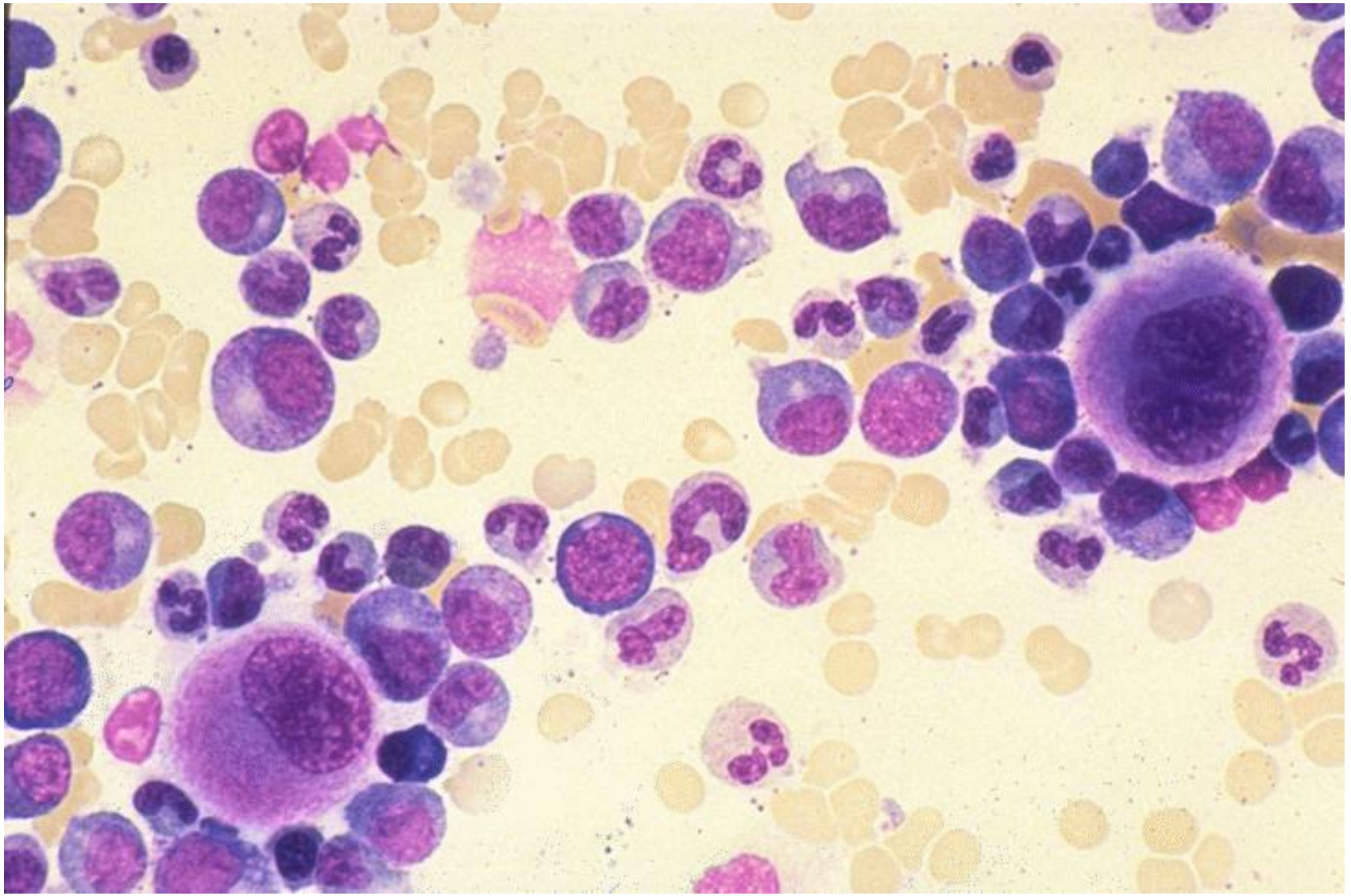
Diagnostic criteria for essential thrombocythaemia

- Platelet count persistently > 600 × 10^9/l
- PCV< 0.51 in males and 0.48 in females or normal red cell mass
- Stainable iron in the marrow of normal serum ferritin
- No philadelphia chromosome or *BCR/ABL* gene rearrangement
- No collagen fibrosis of the bone marrow
- No cytogenetic or morphological evidence of MDS
- No cause for a reactive thrombocytosis

Chronic myeloid leukaemia: Peripheral blood smear

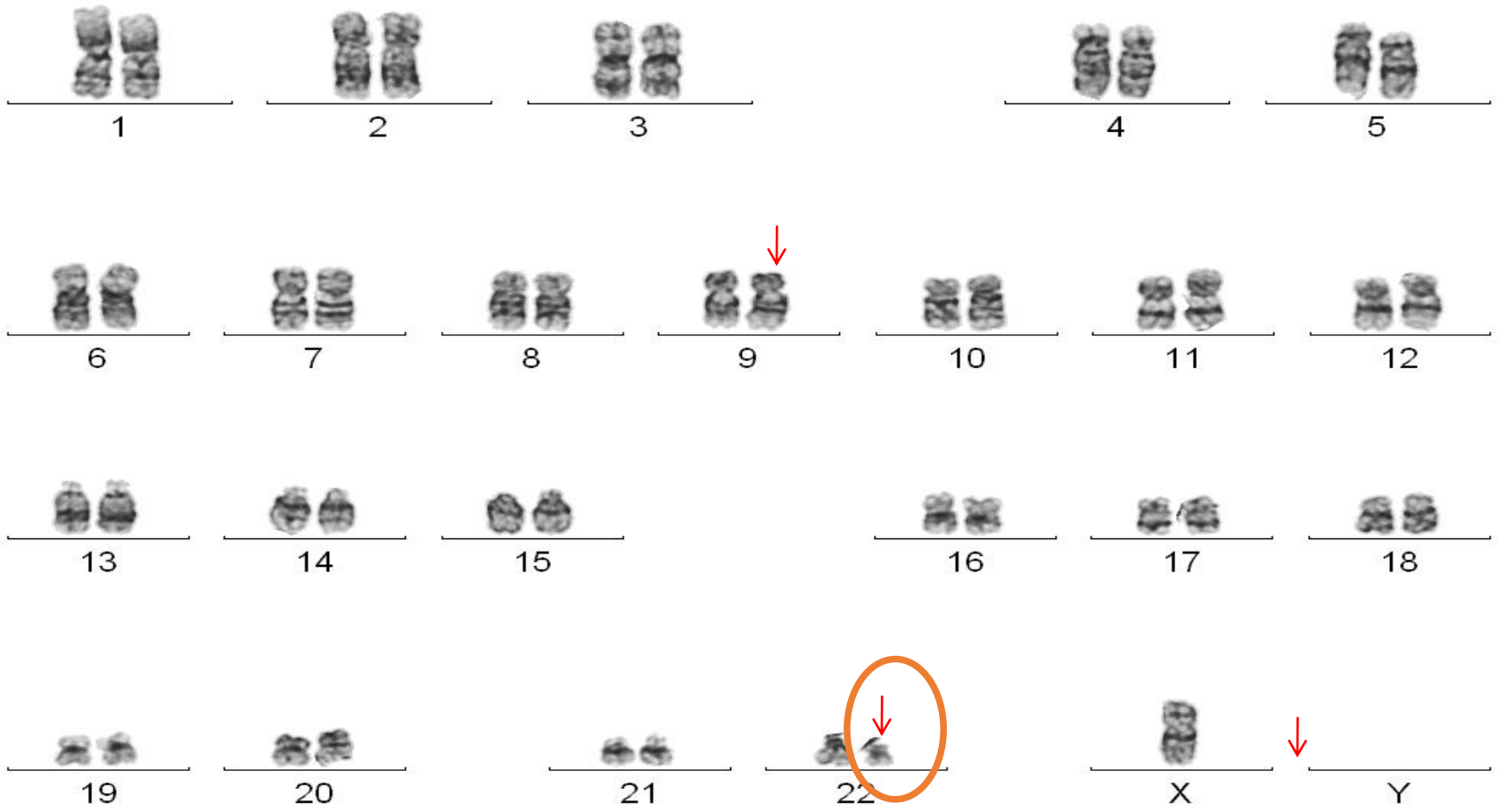


Bone marrow aspirate



Cytogenetics

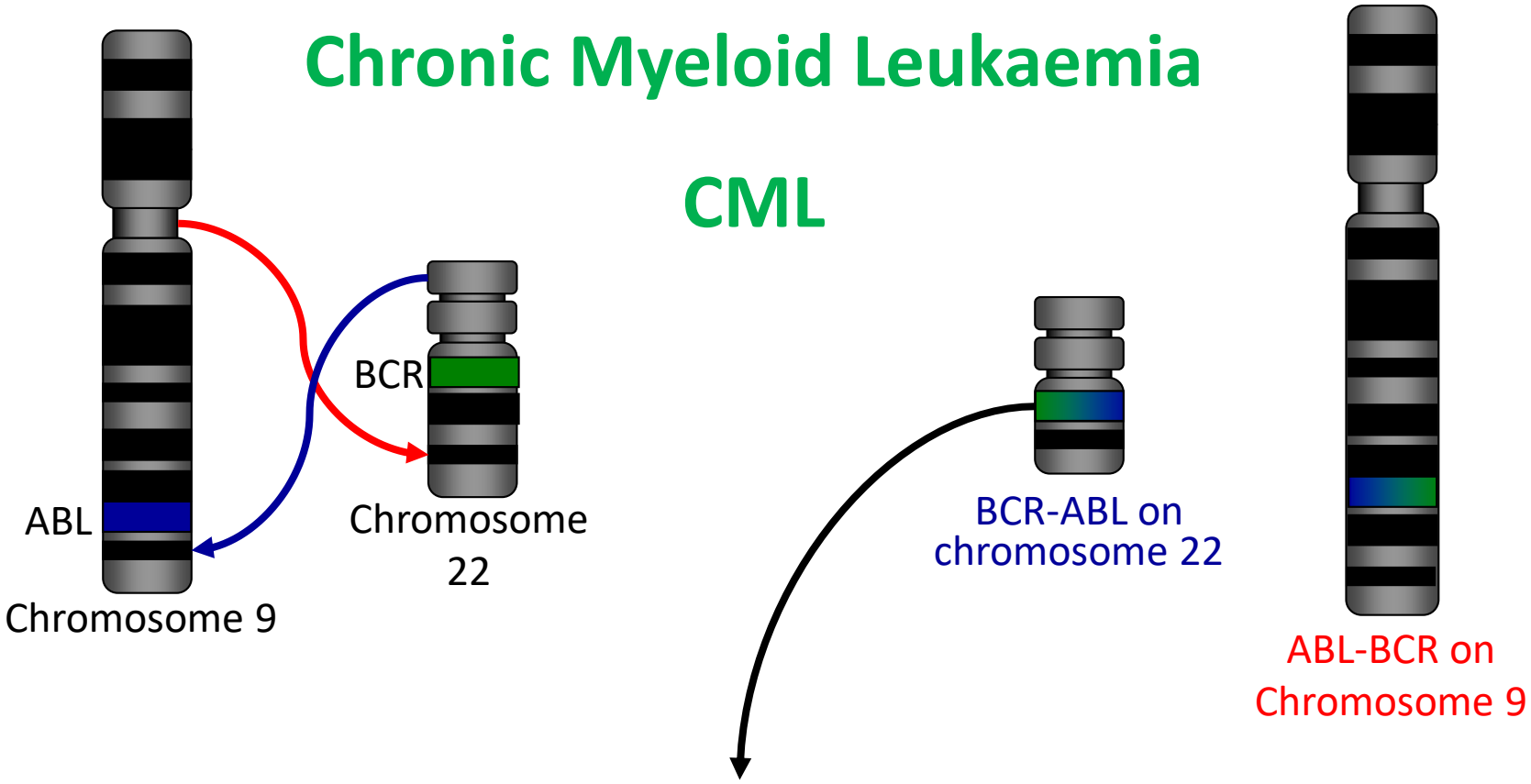
Karyotype: 45,X,-Y,t(9;22)(q34;q11)



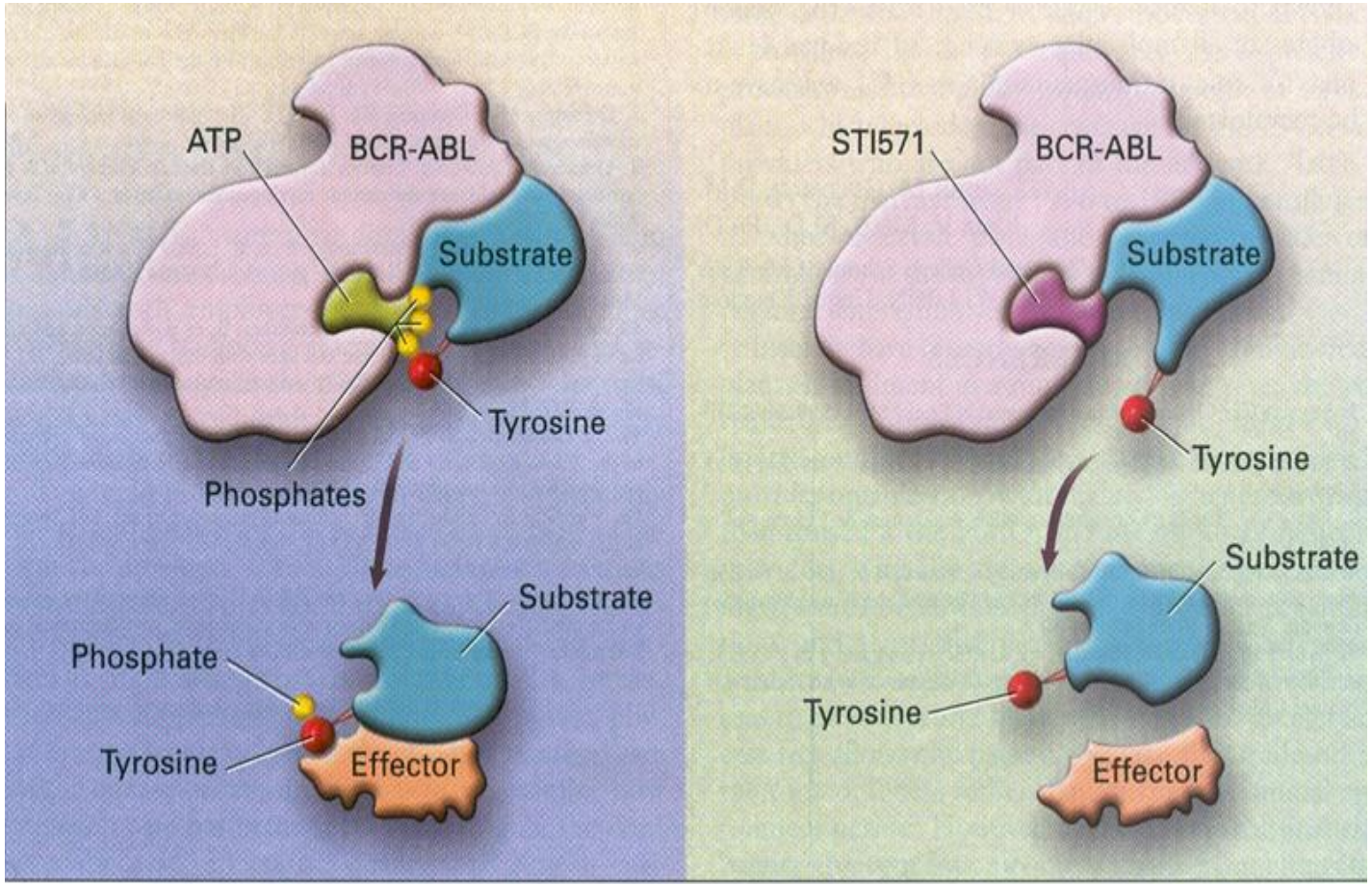
The Philadelphia chromosome

Chronic Myeloid Leukaemia

CML



Mechanism of Action of Imatinib Mesylate

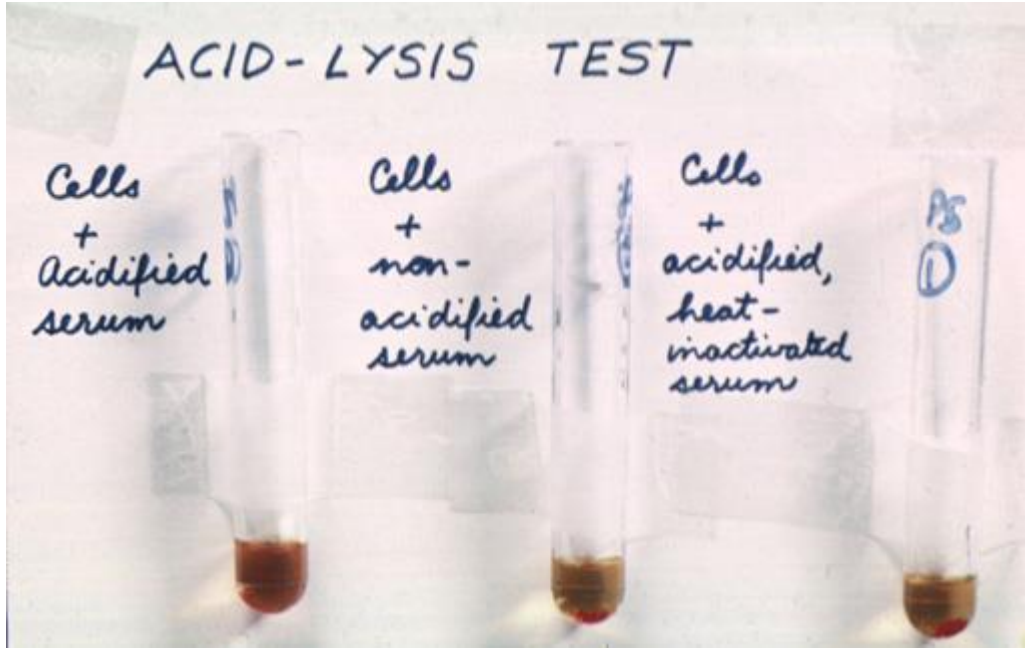


Goldman JM, Melo JV. *N Engl J Med.* 2001;344:1084-1086.


For clinical trial use only
Keep out of reach of children
120 Capsules to be taken orally
STI571 50mg
X026 0100
Take as directed with a large glass of water
Do not store above 25°C
Date of dispensing:
Retest date: 01/2003
Novartis Pharma UK Ltd., Frimley, Surrey GU16


MAY 28, 2001
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLIVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?
AOL Keyword: TIME

Sir John Dacie

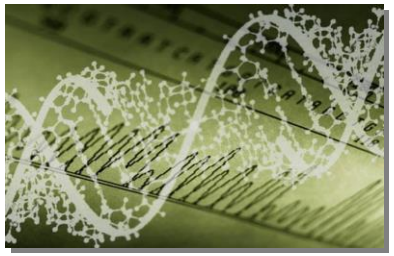


Paroxysmal nocturnal haemoglobinuria

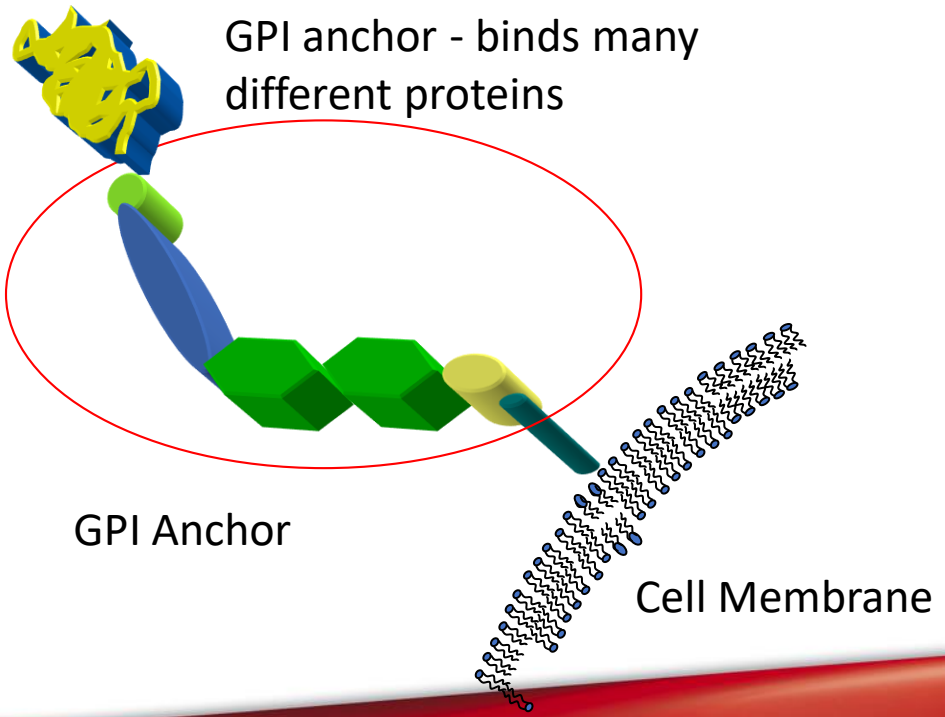
- Gene *PIG-A* (phosphatidylinisitol glycan class A) located on X chromosome (Xp22.1)
- Approximately 100 somatic mutations described

Normal Blood Cells

Normal blood cells have GPI anchors

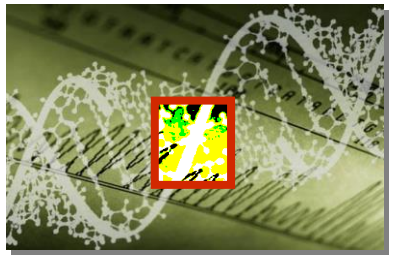


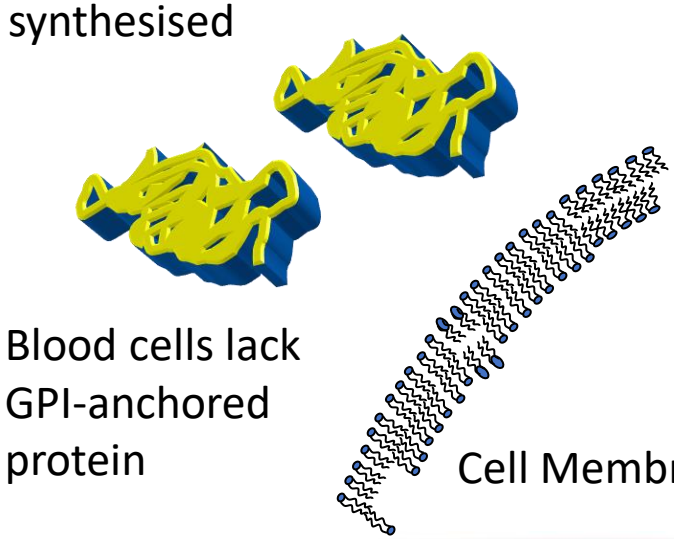
PIG-A gene codes for GPI anchor



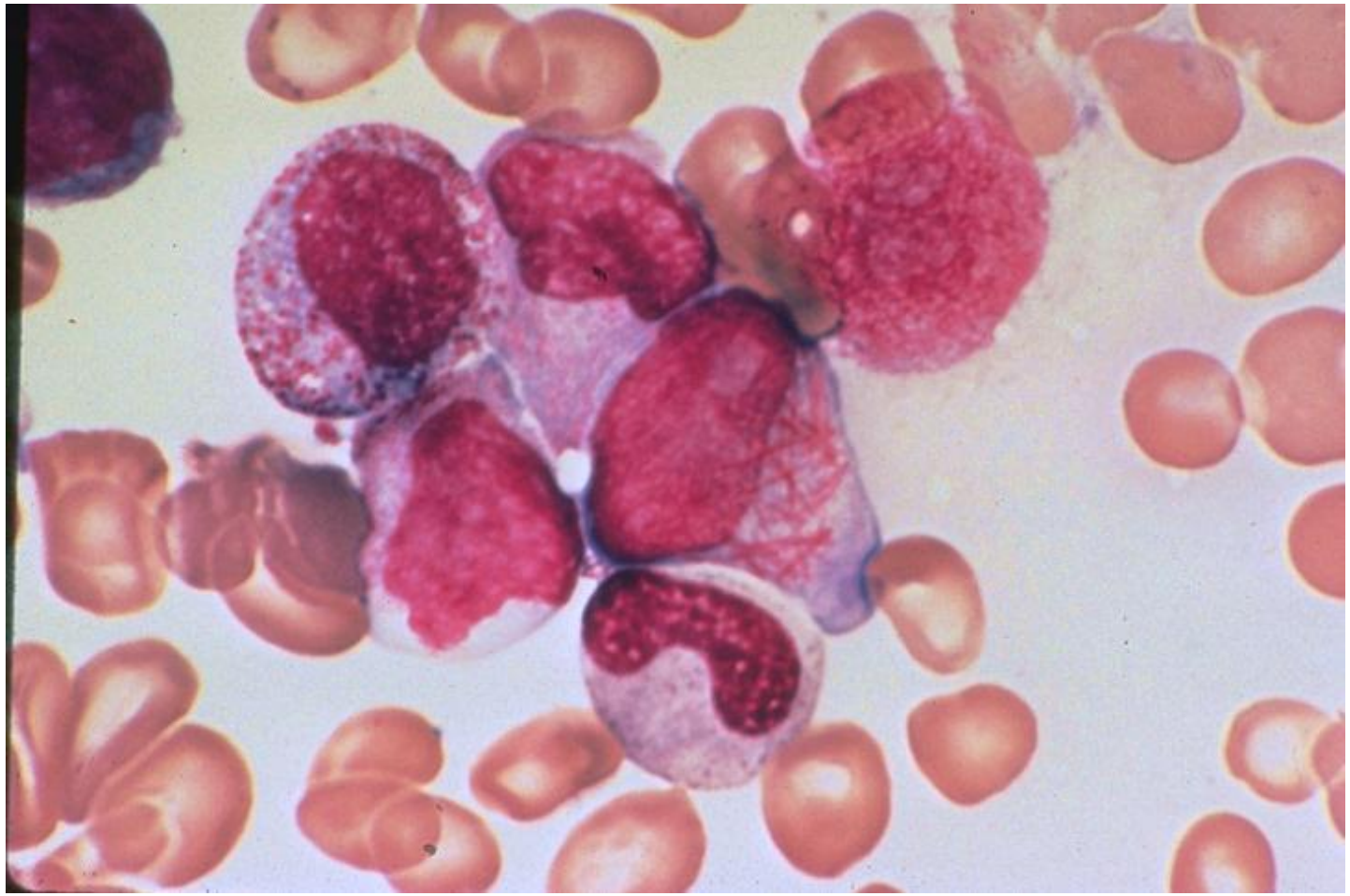
PNH Blood Cells

PIG-A gene mutation



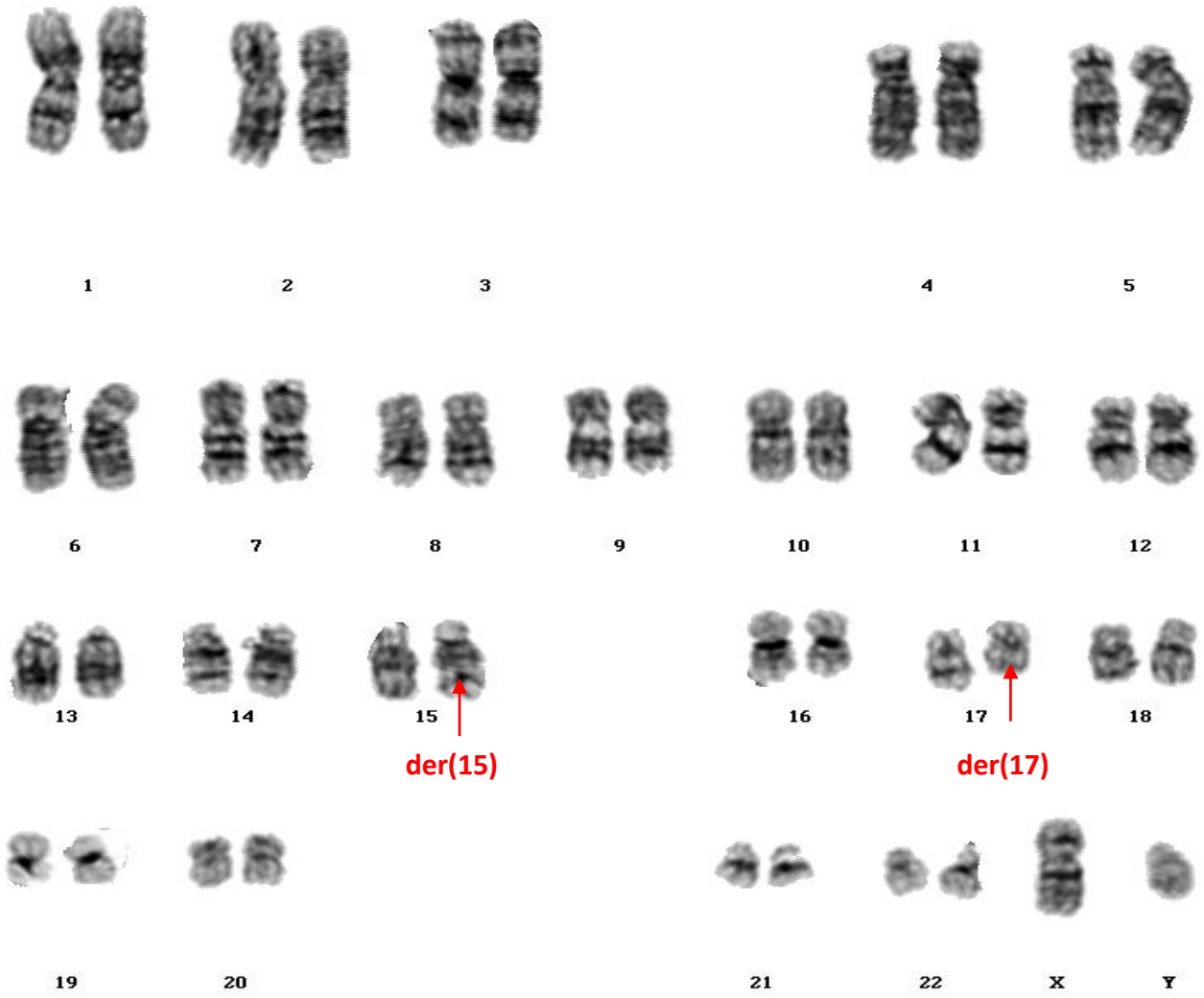


APML: Bone marrow aspirate

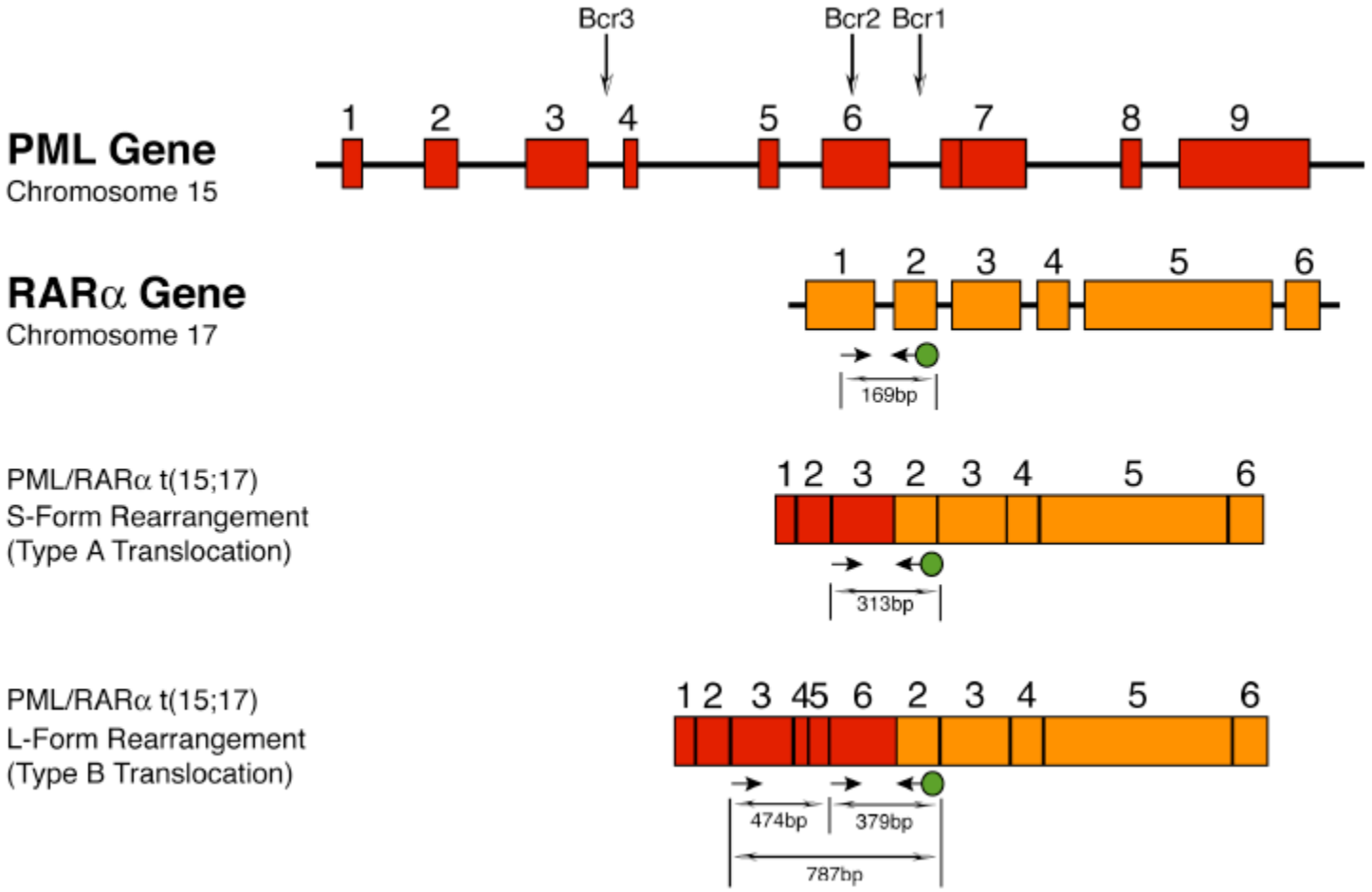


Cytogenetics

46,XY,t(15;17)(q22;q21)



Promyelocytic leukemia and *Retinoic Acid Receptor* a Genes



WHO Classification of AML
2016 Revision: AML and Related Neoplasms

AML with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
- APL with *PML-RARA*
- AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
- AML with t(6;9)(p23;q34.1);*DEK-NUP214*
- AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
- Provisional entity: *AML with BCR-ABL1*
- AML with mutated *NPM1*
- AML with biallelic mutations of *CEBPA*
- Provisional entity: *AML with mutated RUNX1*

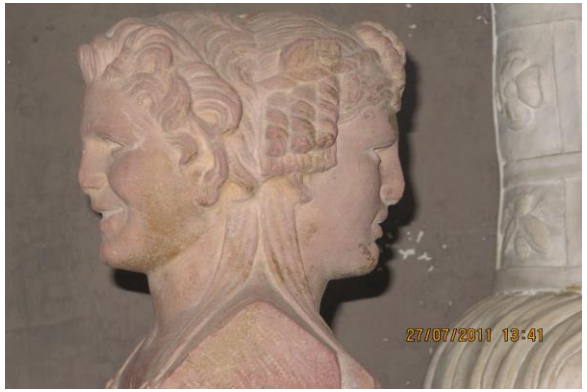
AMLS with myelodysplasia-related changes

Therapy-related myeloid neoplasms

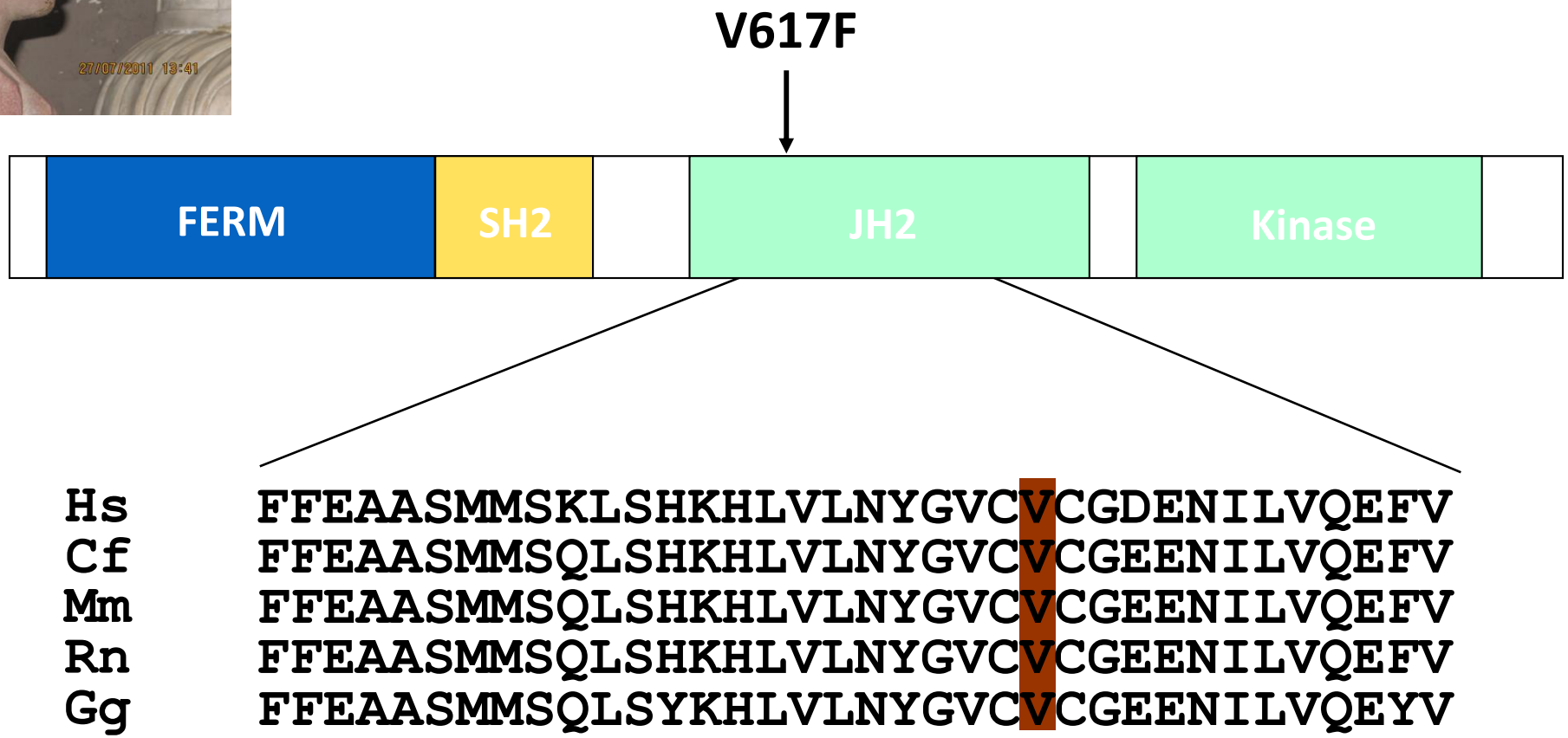
AML NOS

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

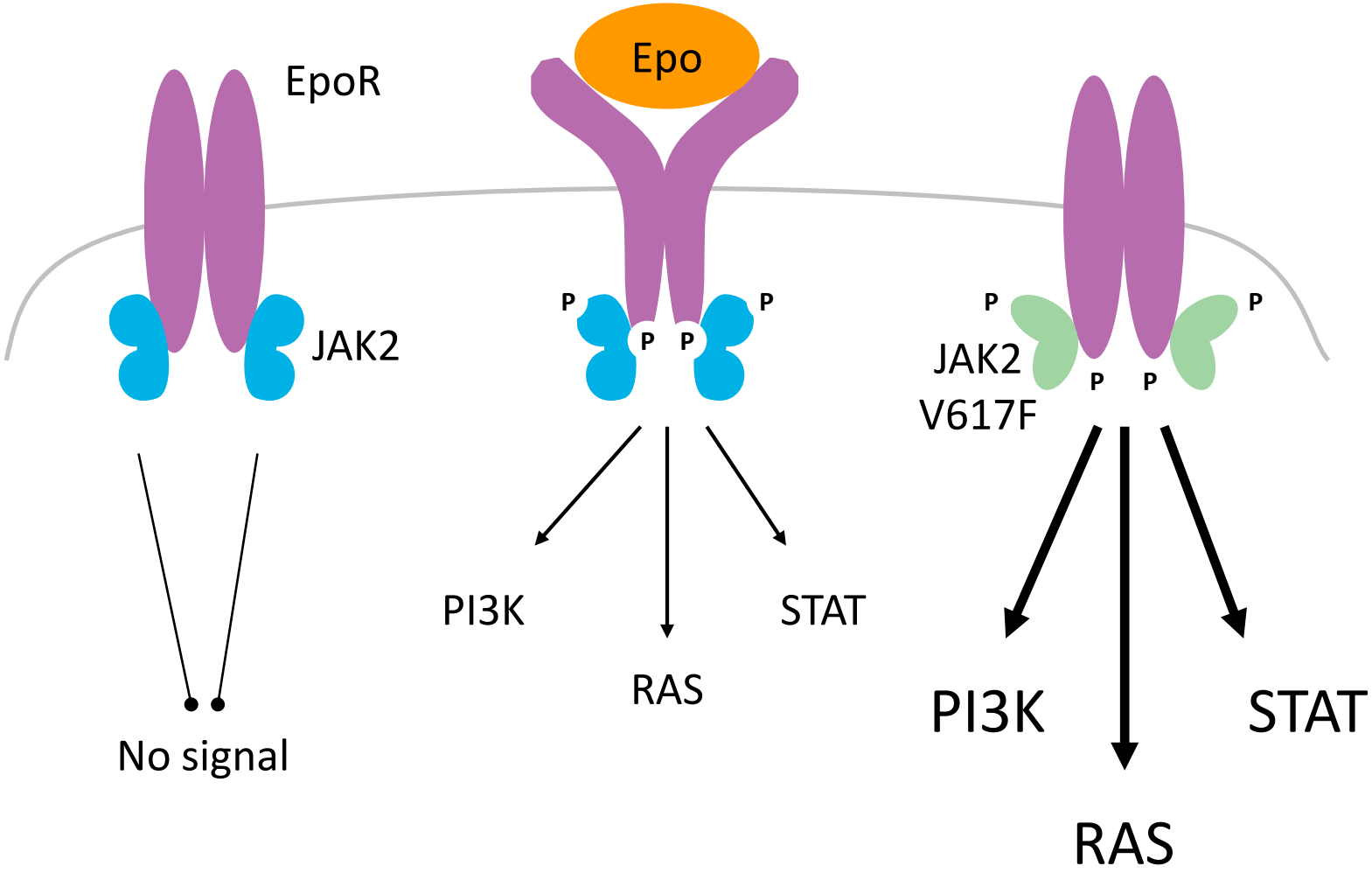
Arber DA, et al. *Blood*. 2016;127:2391-2405.



V617F mutation in *JAK2*

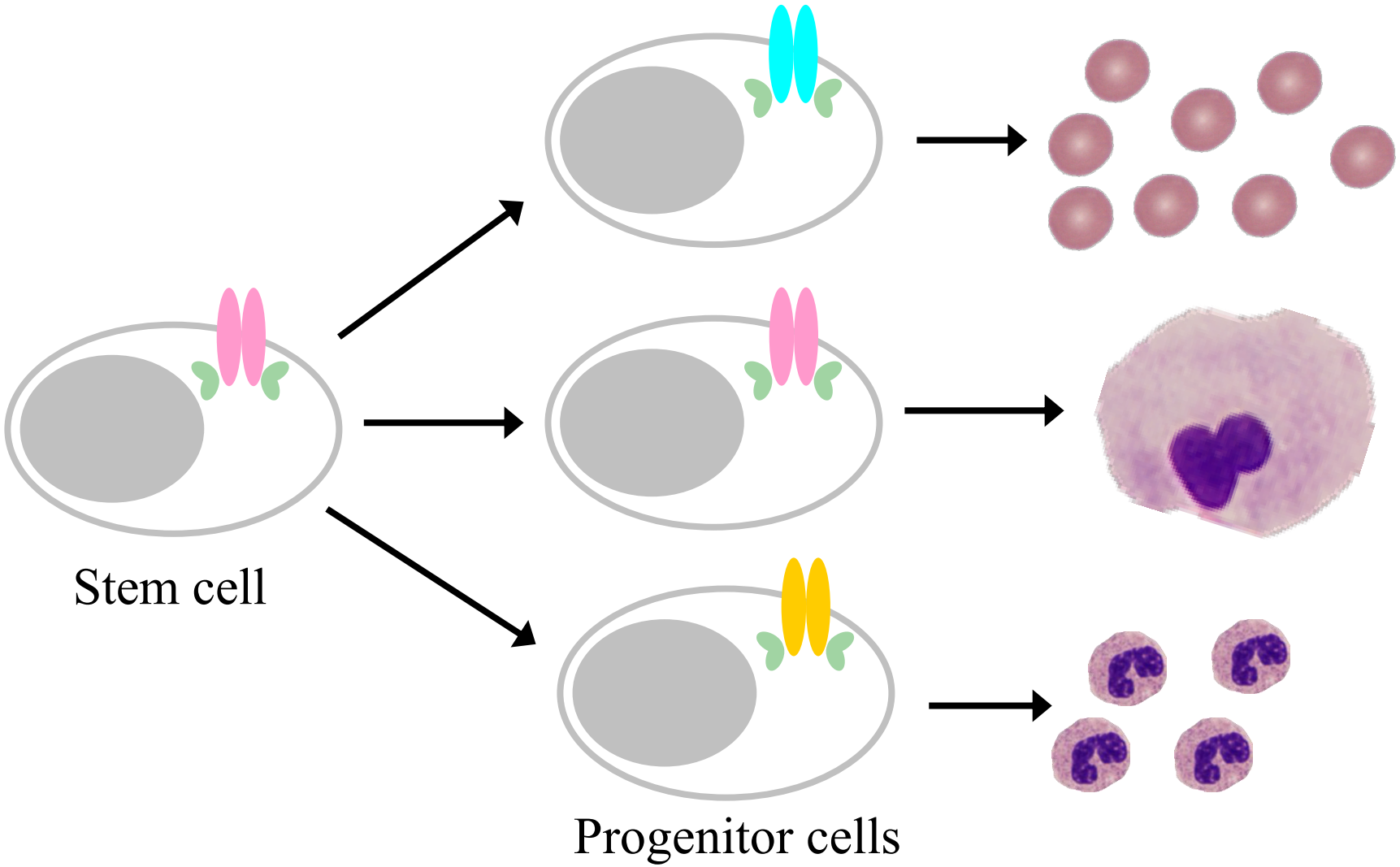


JAK2 signalling



poietin

JAK2 binds to multiple receptors



JAK2 positive disease

- **Polycythaemia vera**
- **A1 High haematocrit >0.52 (men),**
- **>0.48 (women)**
- **OR**
- **Raised red cell mass**
- **(>25% above predicted)**

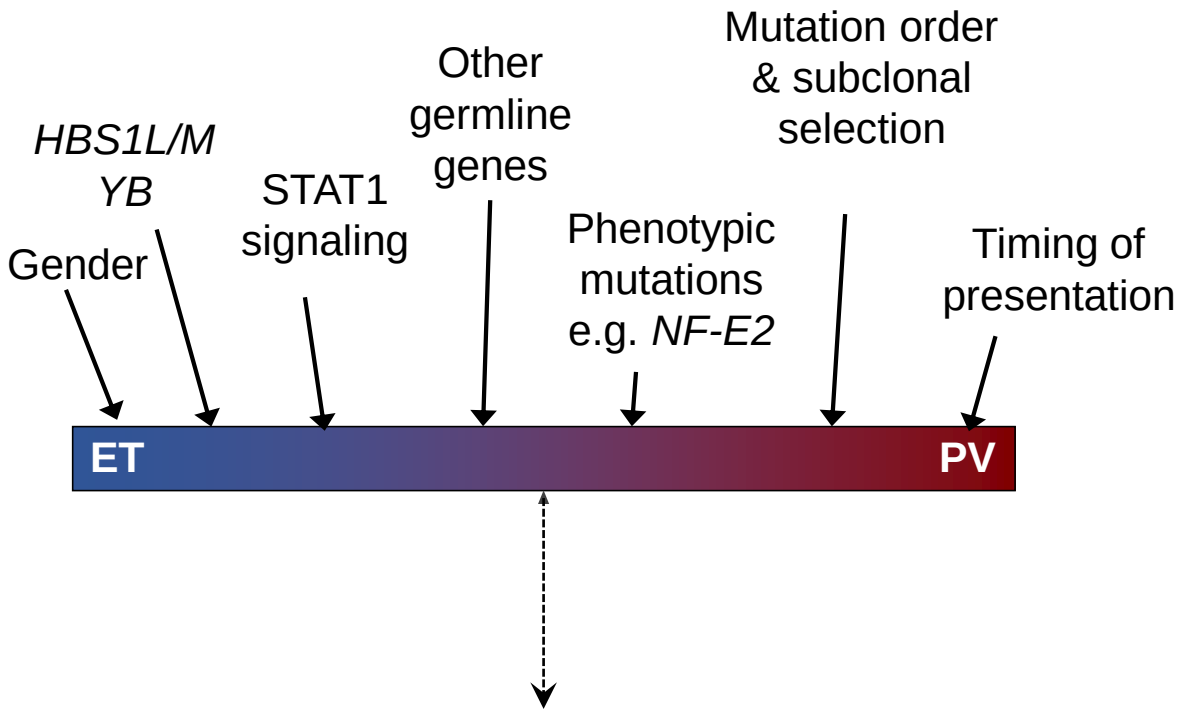
- **A2 Mutation in *JAK2***

- **Diagnosis requires both criteria to be present**

- **Essential Thrombocythaemia**
- **A1: Sustained platelet count ≥ 450 $\times 10^9$/l**
- **A2: presence of an acquired pathogenetic mutation(e.g. *JAK2*, *CALR* or MPL genes)**
- **A3: No other myeloid malignancy especially PV, PMF, CML or MDS**
- **A4: No reactive cause for thrombocytosis and normal iron stores**
- **A5: Typical megakaryocyte appearances in BM aspirate and trephine**

- **Diagnosis requires A1-A3 or A1 +A3-A5**

JAK2+ ET *vs* PV

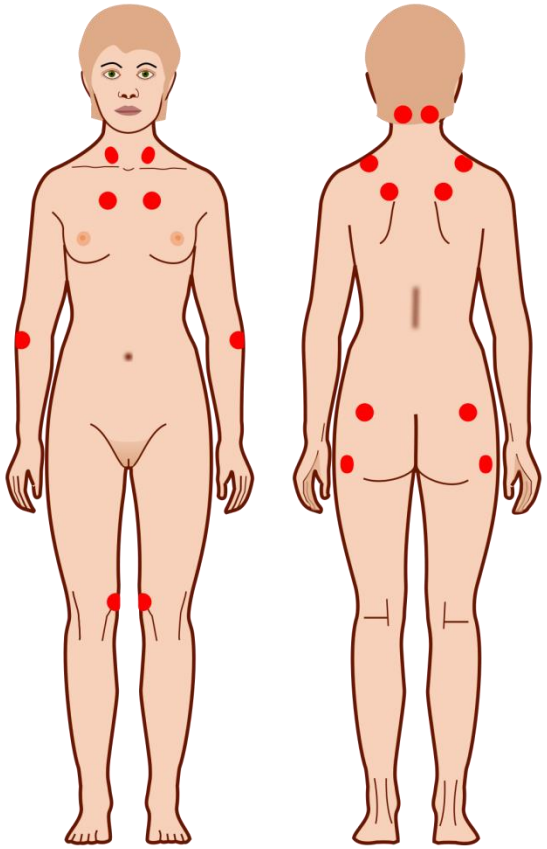


But what diagnosis do I give my patient?

Campbell et al, Lancet 2005

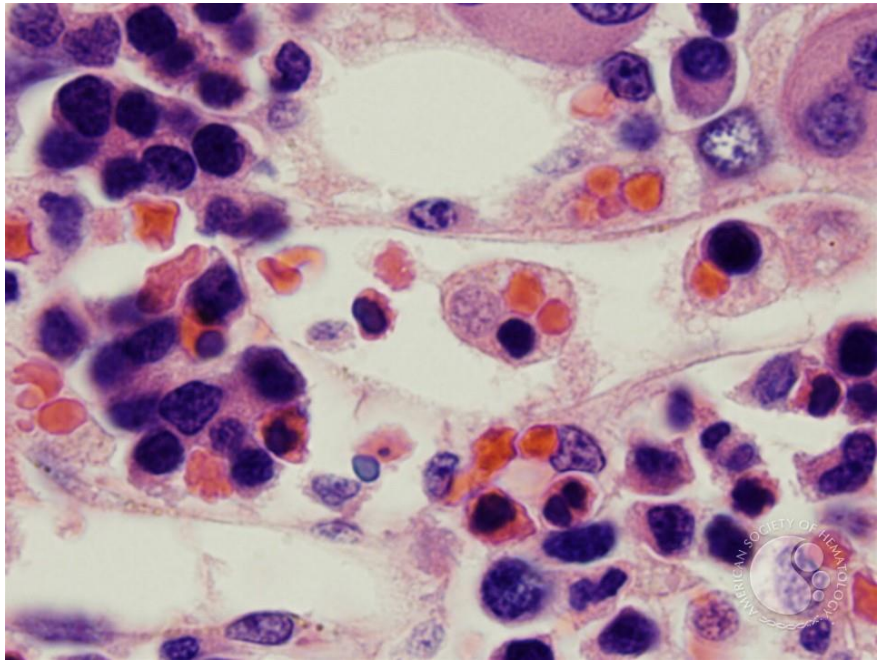
Grinfeld & Godfrey, Blood Rev 2017

Fibromyalgia



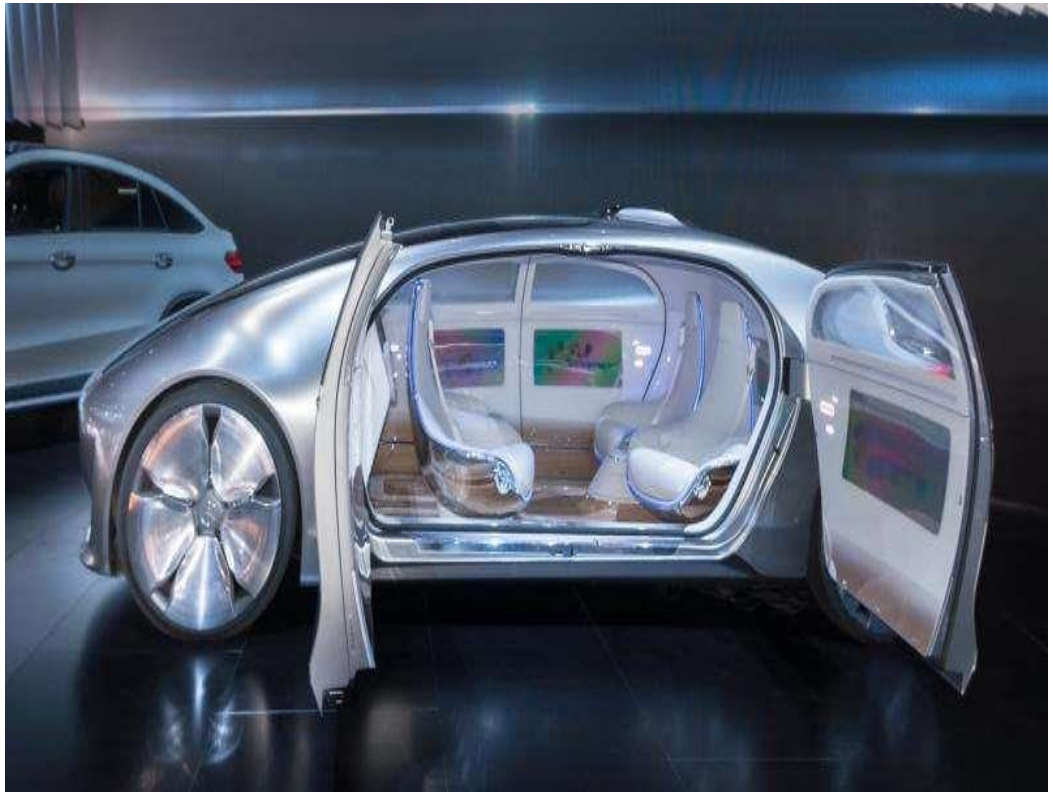
- Severe pain in 3 to 6 different areas of the body of milder pain in 7 of more different areas
- Symptoms at a similar level for at least 3 months
- No other reason for symptoms found

Haemophagocytic lymphohistiocytosis



- Fever > 38.5^{o}C
- Splenomegaly
- Peripheral blood cytopenias
- Hypertriglyceridemia
- Haemophagocytosis in bone marrow, spleen, lymph nodes or liver
- Low or absent NK cell activity
- Ferritin> 500ng/ml(3000ng/ml)
- Elevated soluble CD25 two standard deviations above age-adjusted lab specific norms

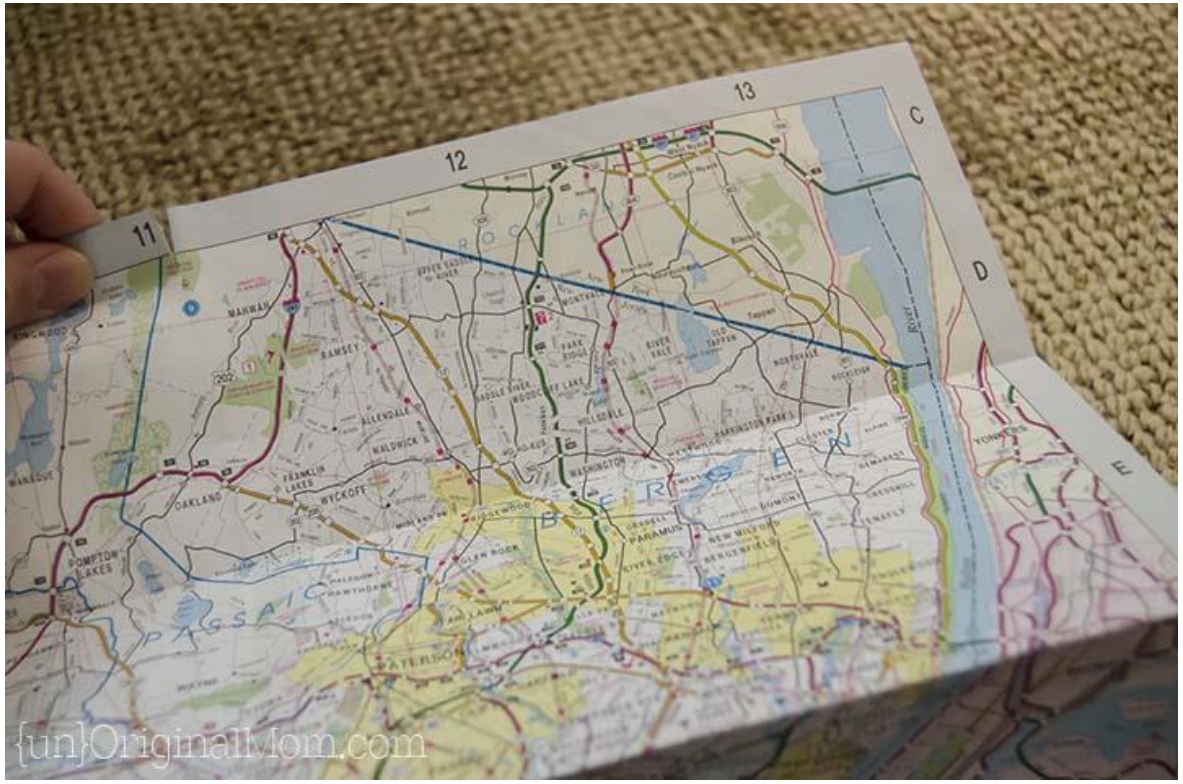
Cars of the future



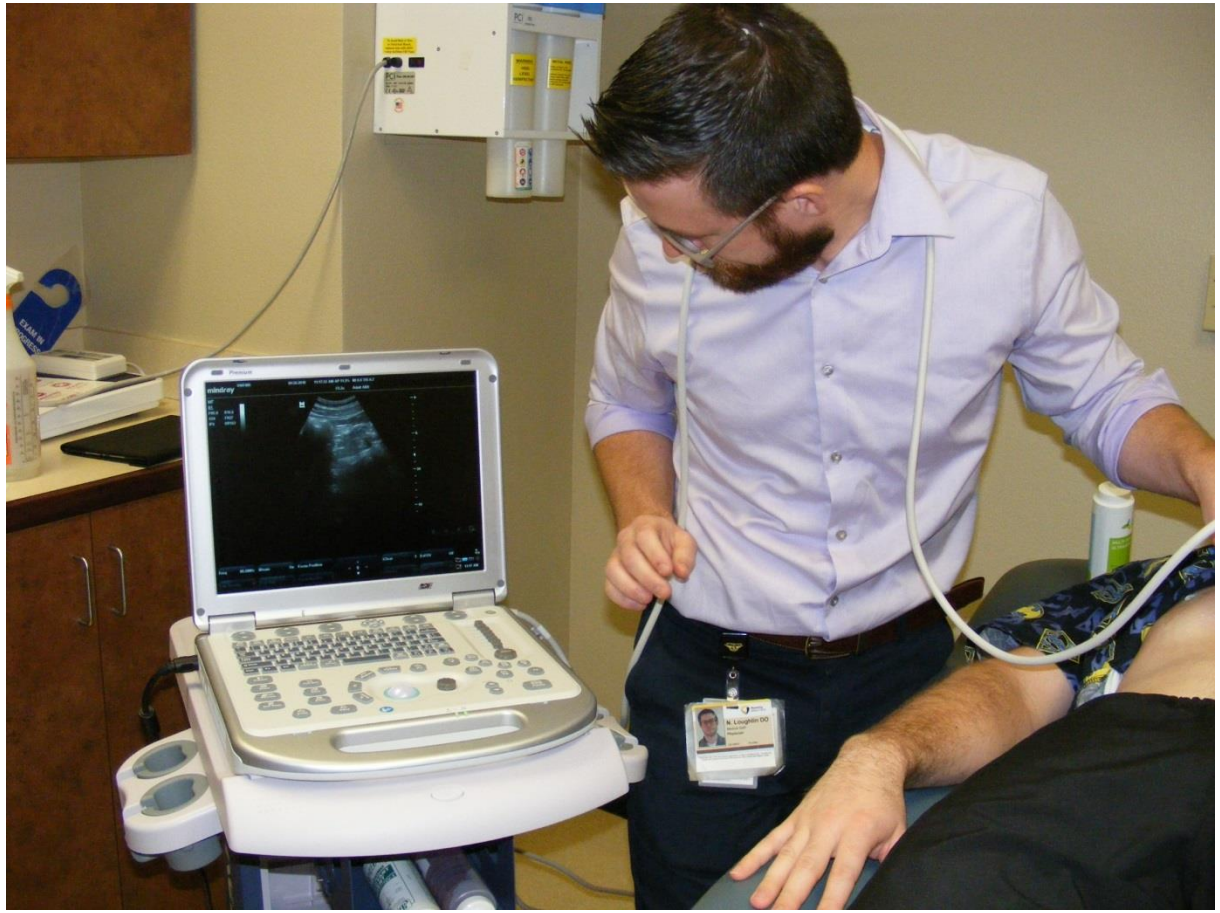
Phones


IN CASE OF EMERGENCY
DIAL "999"
FOR OTHER INFORMATION SEE TELEPHONE DIRECTORY

Maps



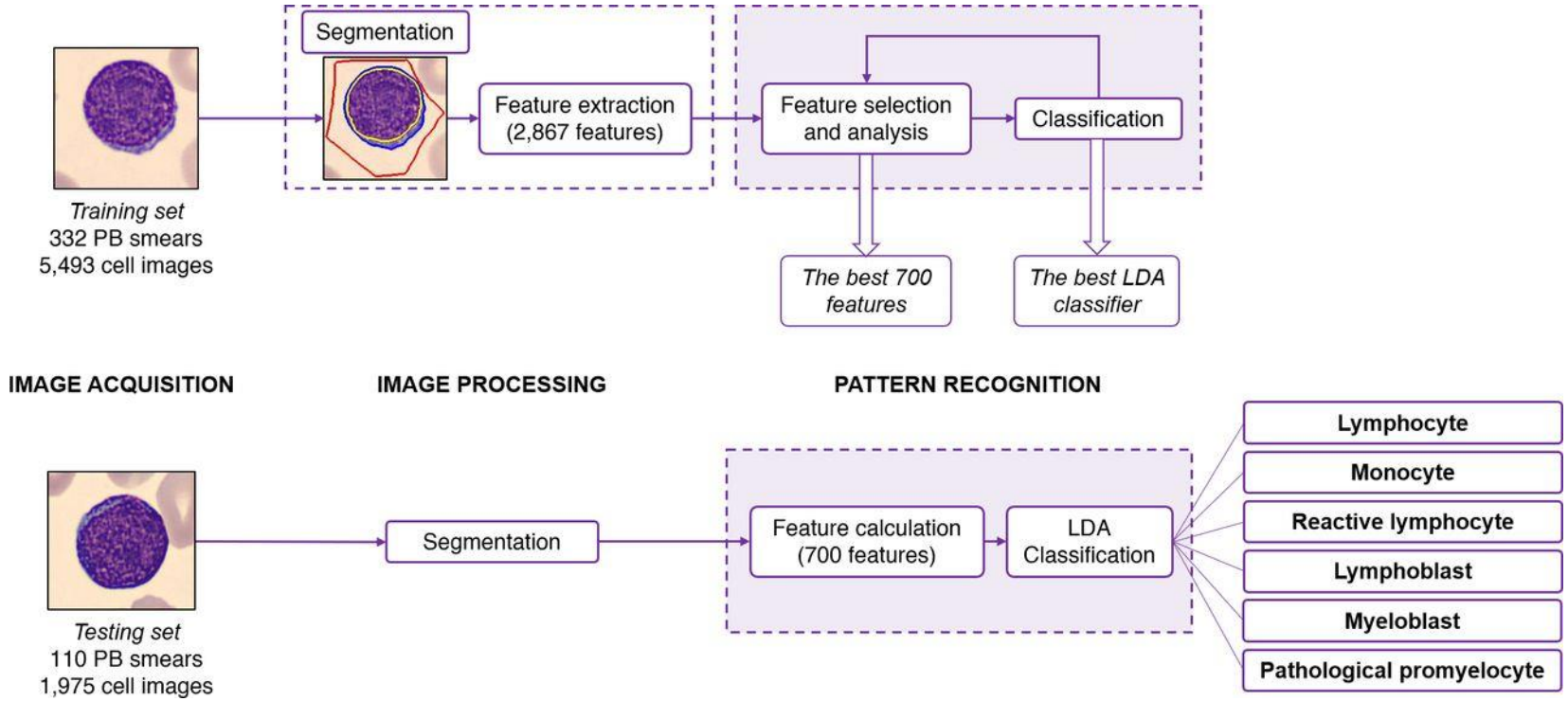
The stethoscope of the future?



POCUS

Point-of-Care Ultrasound Certification Academy™

Automatic image analysisis



Laura Boldú et al. J Clin Pathol doi:10.1136/jclinpath-2019-205949

JCP

Future diagnostics

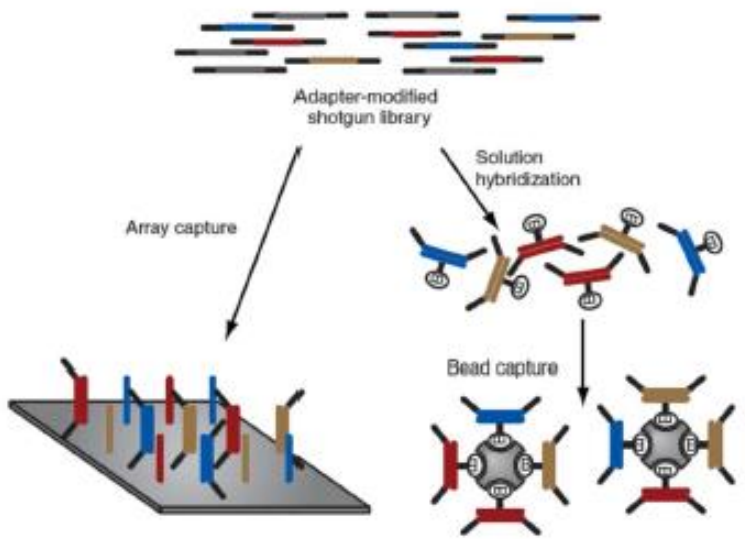
- Phenotypic classification

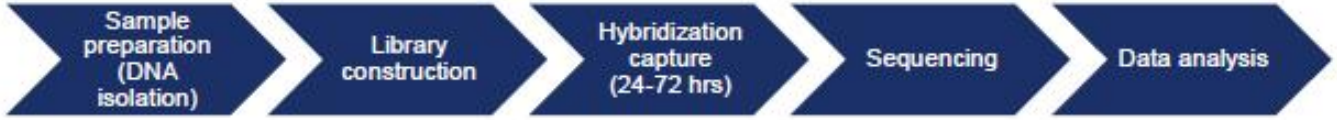
- Classification based on biological causes

Next general sequencing based technologies

Roche (NimbleGen SeqCap)- SEQCAP

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

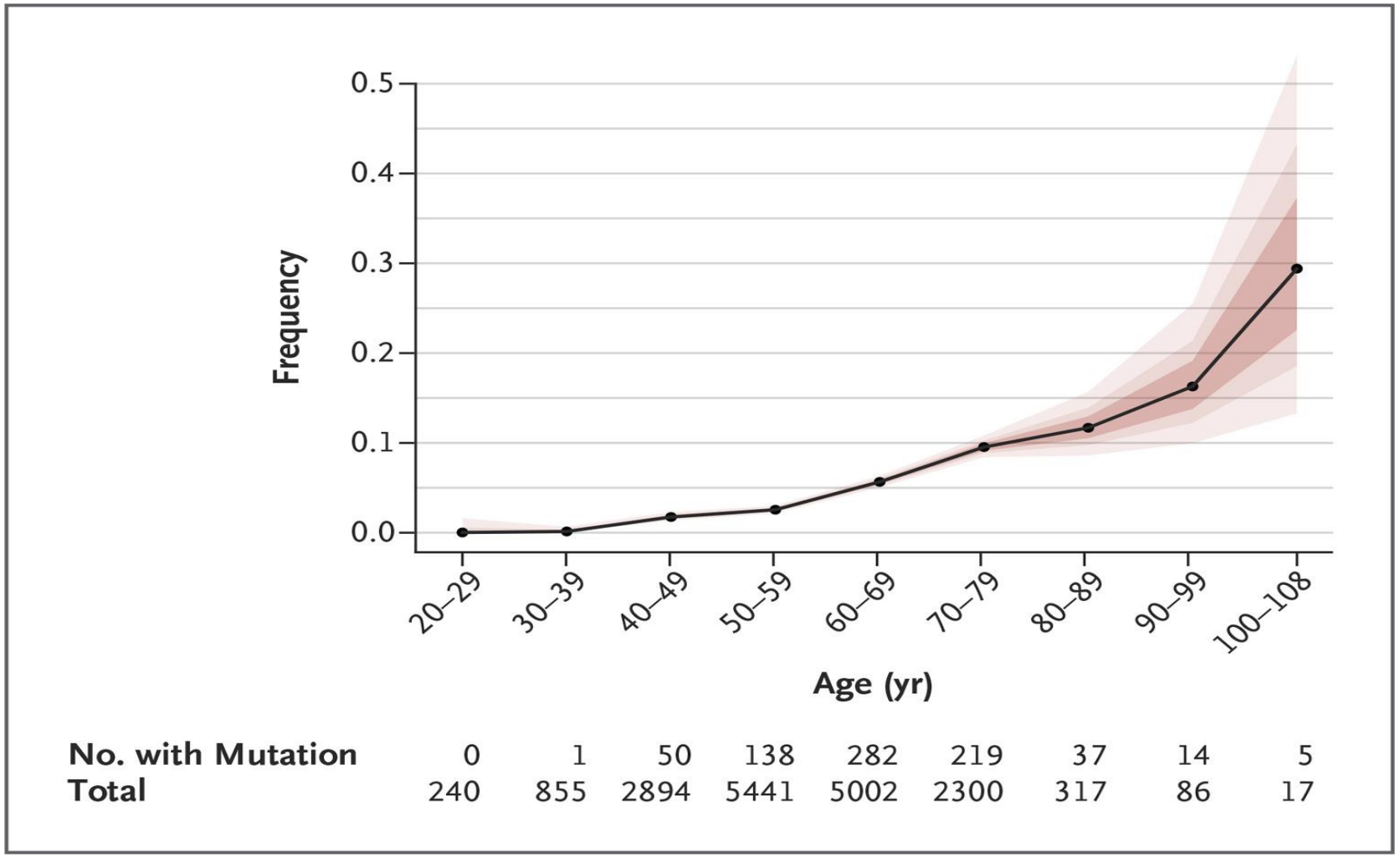




Next generation sequencing panel for erythrocytosis

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

Age related clonal haematopoesis (ARCH)



No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

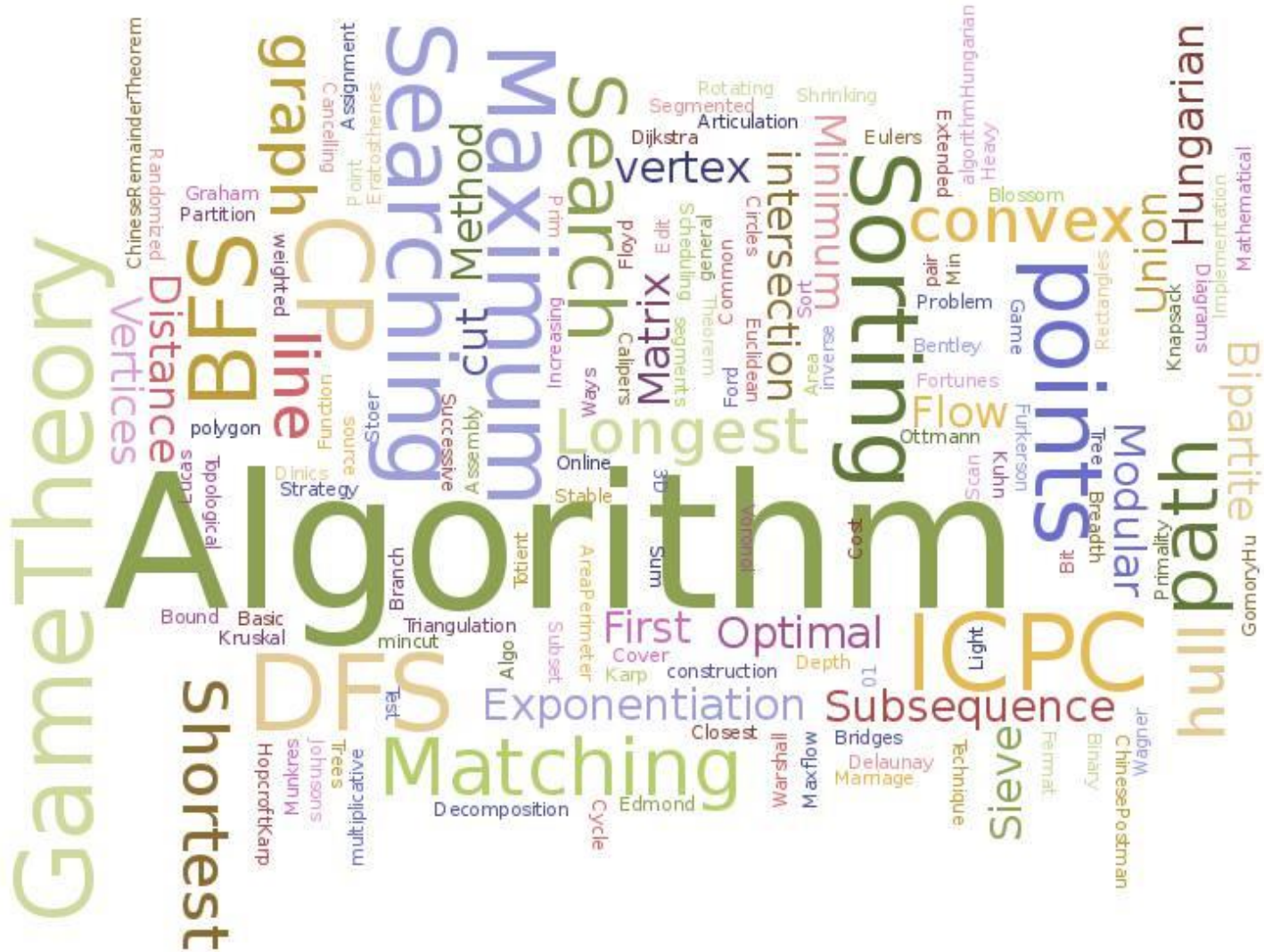
Big Data

Data lakes

Centre data in a bucket-shared data lake

Temporary cloud based analysis

‘Fish’ out data from the lake


Algorithm
GameTheory
DFS
BFS
CPline
graph
Searching
Maximum
Search
Sorting
points
convex
Hungarian
Union
Bipartite
path
hull
ICPC
Shortest
Matching
Exponentiation
Subsequence
Optimal
First
Longest
Flow
Modular
Sieve
Minimum
Matrix
intersection
vertex
Method
cut
Distance
Vertices
polygon
Strategy
Online
Stable
Triangulation
Branch
Bound
Basic
Kruskal
mincut
Dijkstra
Articulation
Segmented
Rotating
Shrinking
Extended
Eulers
Blossom
Graham
Partition
Assignment
Problem
Bentley
Fortunes
Ottmann
Knapsack
Mathematical
Implementation
Primality
GomoryHu
ChineseRemainderTheorem
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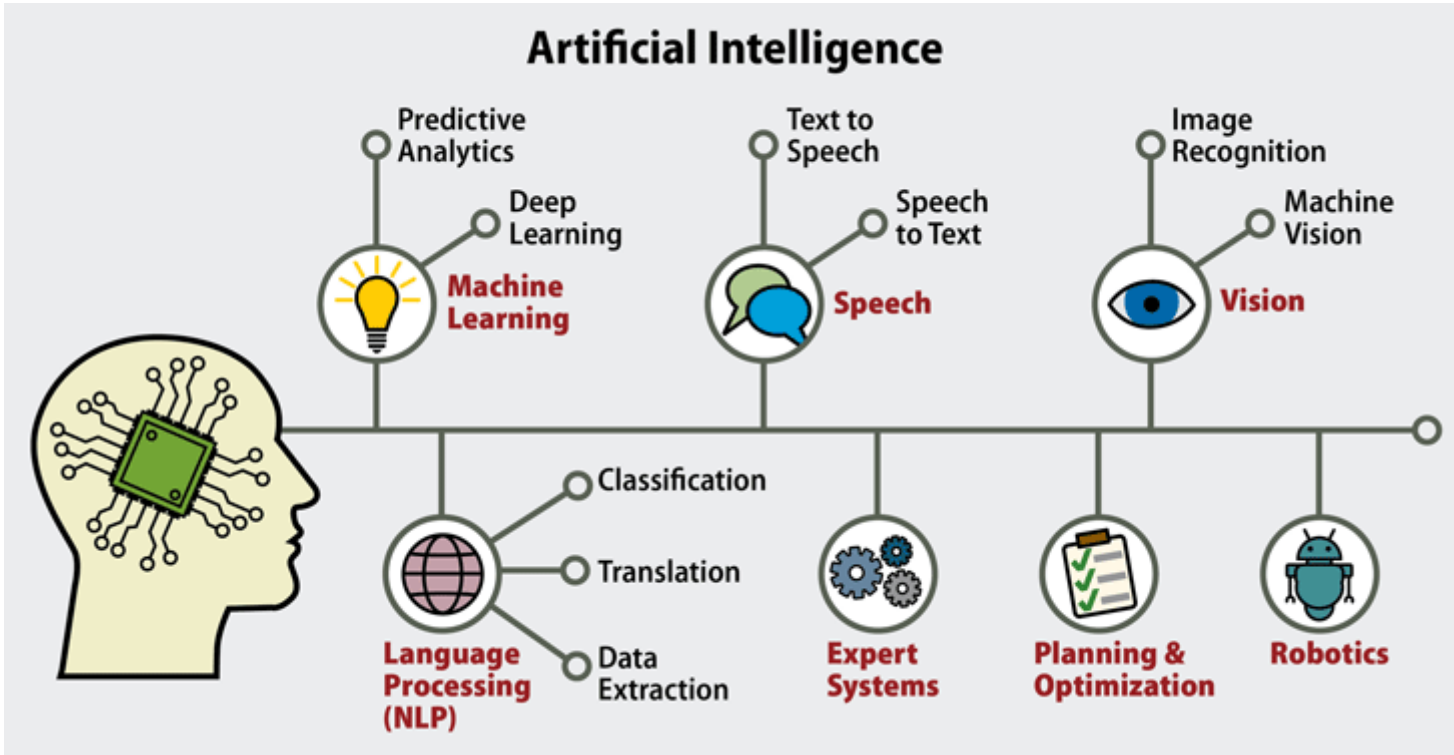
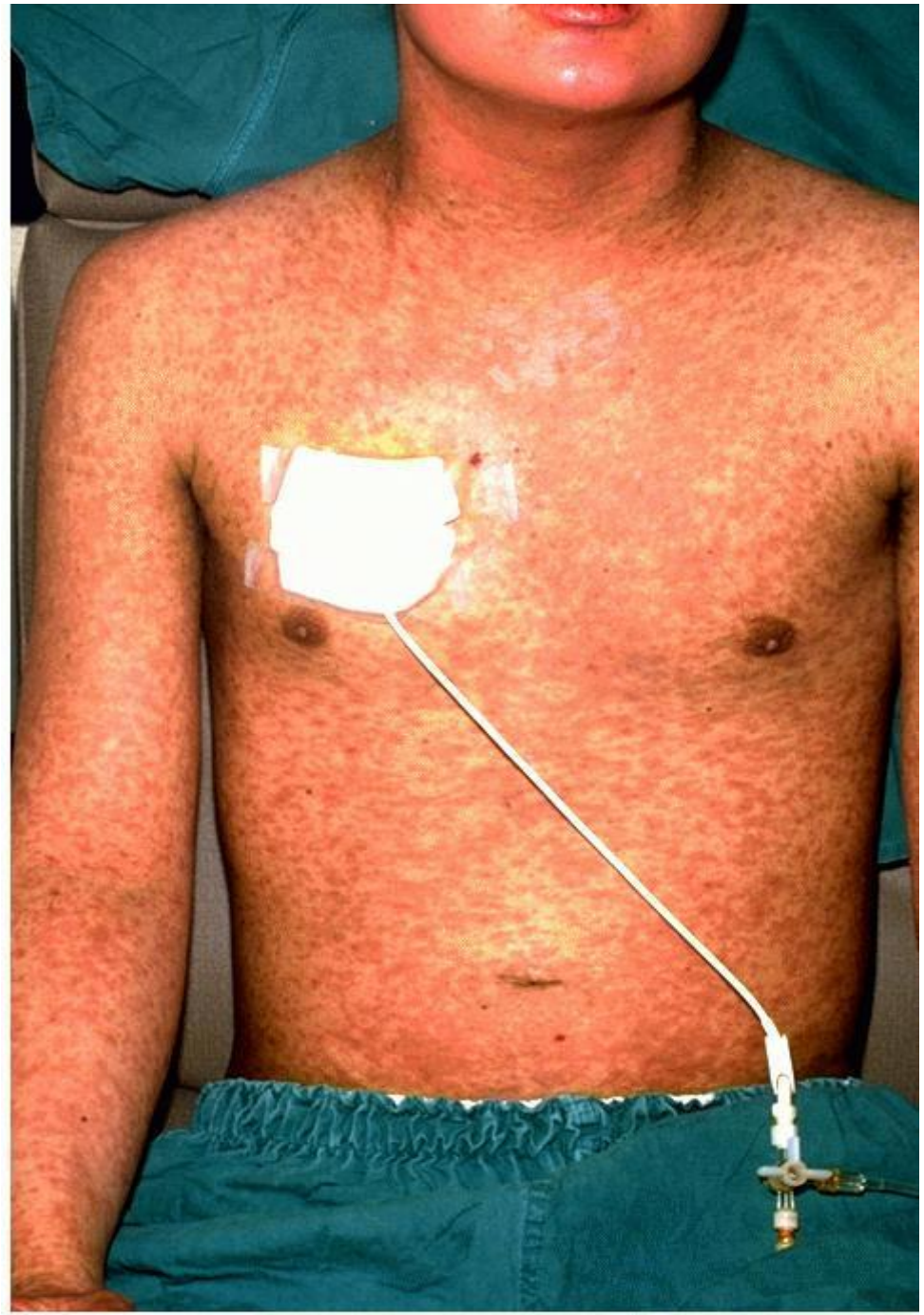

Artificial Intelligence
Predictive Analytics
Deep Learning
Machine Learning
Text to Speech
Speech to Text
Speech
Image Recognition
Machine Vision
Vision
Classification
Translation
Data Extraction
Language Processing (NLP)
Expert Systems
Planning & Optimization
Robotics

“Bloodletting” 18th Century Persian manuscript illustration



AUTUMN SEMESTER

Day and Date	Lecture	Subject	Venue	Time
Thursday 3rd October, 2019	Presidential address	**Prof Mary F McMullin** *'Diagnostics in the Future'*	BCH Postgrad Centre	20.00 hrs
Thursday 17th October, 2019	UMS/QUB/NIMDTA Trainee research day	**Prof Fionnuala Ní Áinle, Dublin** *'The patient voice in collaborative academic research'*	BCH Postgrad Centre	09.00-16.00hrs
Thursday 7th November, 2019	UMS The Robert Campbell Oration	**Prof Cecilia O'Kane, QUB** *Advanced therapeutics for the 'acute respiratory distress syndrome (ARDS)'*	BCH Postgrad Centre	20.00 hrs
Thursday 14th November, 2019	Joint meeting with Belfast City Hospital Medical Staff	**Prof Dr Jörg Goldhahn, Institute of Translational Medicine, Zurich** *'Artificial intelligence will make doctors obsolete?'*	BCH Postgrad Centre	20.00 hrs
Thursday 28th November, 2019	The Desmond Whyte Lecture	**Prof Manuel Salto-Tellez, QUB** *'The promise and reality of precision medicine in N. Ireland'*	Altnagelvin Centre for Medical and Dental Education	Buffet 17.00hrs
Thursday 12th December, 2019	UMS	**Prof Eileen Murphy, Professor of Archaeology, QUB** *'Life and Death in Medieval Ireland: Insights from Palaeopathology'*	BCH Postgrad Centre	20.00 hrs

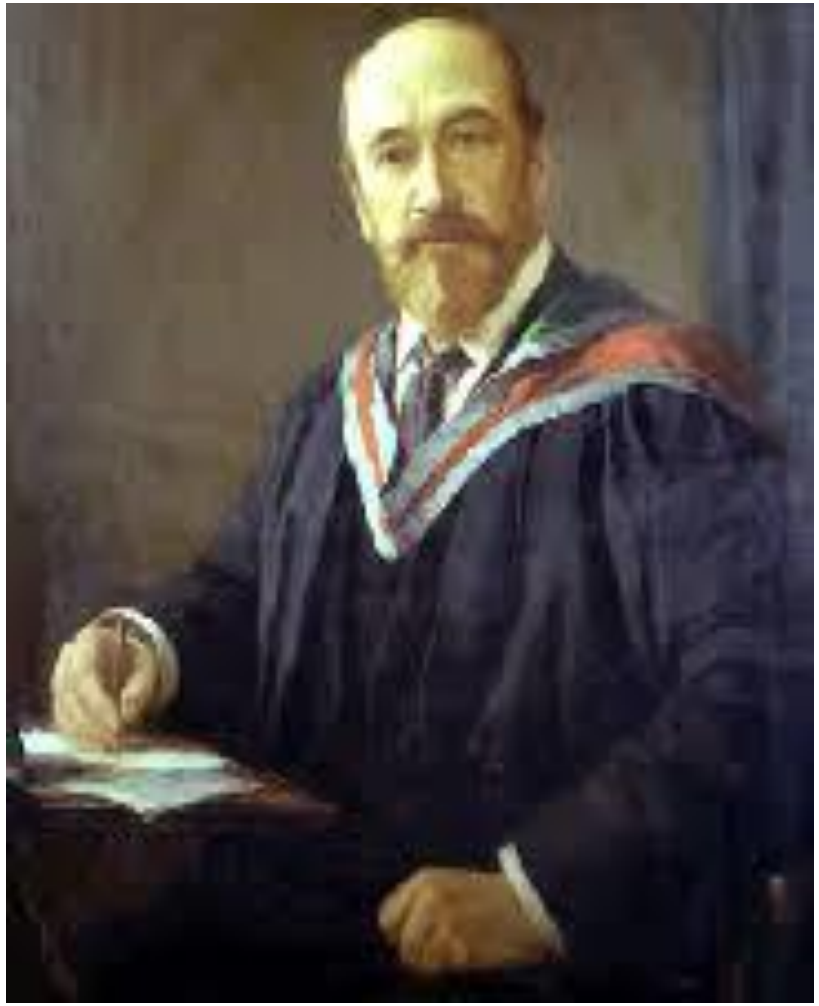
SPRING SEMESTER

Day and Date	Lecture	Subject	Venue	Time
Thursday 9th January, 2020	Joint meeting with Ulster Obs and Gynae Society	**Prof Basky Thilaganathan, Professor of Fetal Medicine, London** *'Preeclampsia is a placental disorder: lies, damn lies and medical science'*	BCH Postgrad Centre	20.00 hrs
Thursday 23rd January, 2020	The Gary Love Lecture Joint meeting with Ulster Society for History Medicine	**Dr Harriet Wheelock, Keeper of Collections, Royal College of Physicians of Ireland** *'Managing the heritage of Irish medicine-tales from the archives'*	BCH Postgrad Centre	20.00 hrs
Thursday 6th February, 2020	UMS	**Dr Jyoti Nangalia, Sanger Centre, Cambridge** *'Towards personalised medicine in blood cancers'*	BCH Postgrad Centre	20.00 hrs
Thursday 27th February, 2020	UMS	**Dr Brenda Moore-McCann, Dublin** *'Medical Semiotics and its influence on art, psychoanalysis and Sherlock Holmes'* and **Prof Shaun McCann, Dublin** *'Microscopes and corkscrews: a future perspective'*	BCH Postgrad Centre	20.00 hrs
Thursday 5th March, 2020	Joint meeting with Belfast City Hospital Medical Staff	**Prof Ann Mullally, Harvard, USA** *'The Physician-Scientist: Rewards and Challenges. A Personal Perspective'*	BCH Postgrad Centre	20.00 hrs
Thursday 19th March, 2020	UMS, Sir Thomas and Lady Edith Dixon Lecture	**Prof Irene Roberts, University of Oxford** *'GATA1, trisomy 21 and leukaemia- unravelling the link'*	BCH Postgrad Centre	20.00 hrs
Friday 3rd April, 2020	UMS	**Annual Dinner**	Canada Room QUB	19.30
Thursday 7th May 2020	UMS	**Annual General Meeting**	UMS Rooms, Whitla Medical Building	17:00hrs


THE·QUEEN'S·UNIVERSITY·OF·BELFAST


THE WHITLA MEDAL
AWARDED TO
MARY E.McMULLIN
1978

Sir William Whitla and Ulster Medical Society



Ulster Medical Society

The Ulster Medical Society was founded in 1862 by the amalgamation of the Belfast Medical Society, the Belfast Clinical and Pathological Society, and the Ulster Medical Protective Association.

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We are a general medical society and ordinary membership is open to everyone eligible for registration under the Medical Acts.

*

Medical students may join as student members for free and certain non-medical health professionals may join as associate members.

*

The Society holds a series of lectures from October to March on topics of general interest. The lectures are open to all members of the Society and interested healthcare workers.

*

The Ulster Medical Journal is published three times a year. It is sent free to all non-student members of the Society. The Editor always welcomes offers of papers.

*

Please visit our website for more details and application forms.

www.ums.ac.uk

JOINT MEETING WITH NIMDTA AND QUB

Trainee Research Day

Guest Speaker

Professor Fionnuala Ní Áinle

The Mater Hospital, Dublin

The patient voice in collaborative academic research

Thursday 17 October 2019
9am to 4pm

Postgraduate Lecture Theatre
Belfast City Hospital
Lisburn Road, Belfast

This lecture is open to all registered medical practitioners, medical students and other interested health professionals.