APLASTIC ANEMIA & PNH: NEW UNDERSTANDING & NEW THERAPIES

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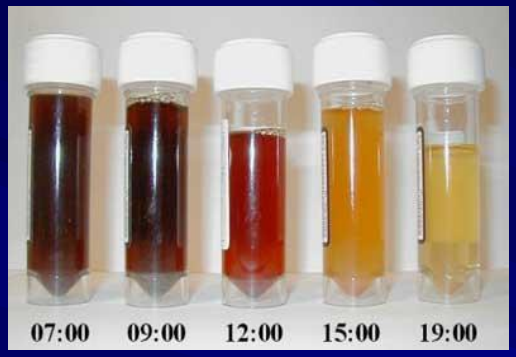
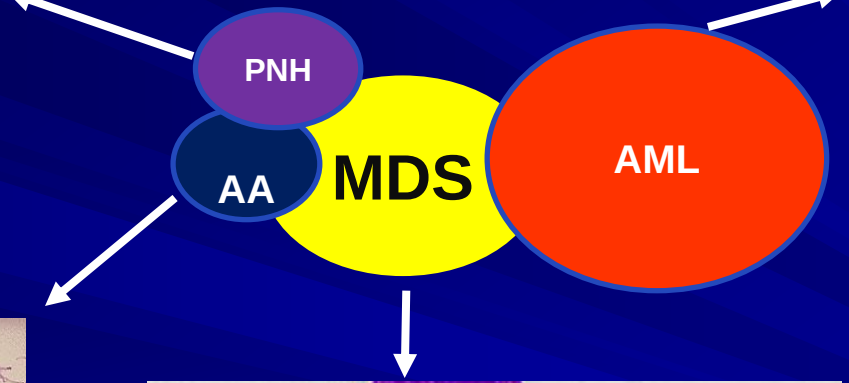
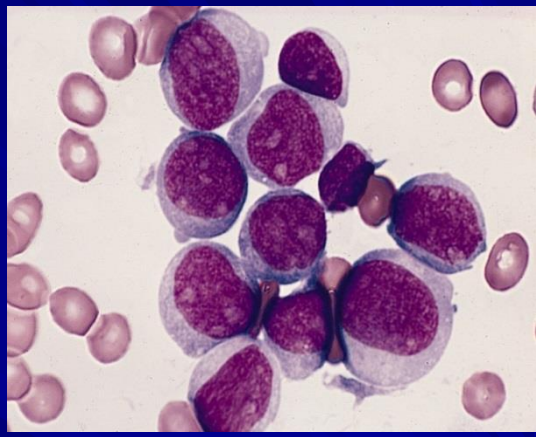
Bone Marrow Failure Syndromes

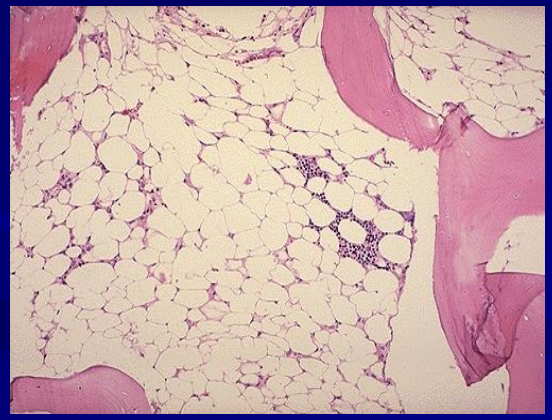
"Rare diseases -- either inherited or acquired -- characterized by inability to make enough red cells, white cells and/or platelets"

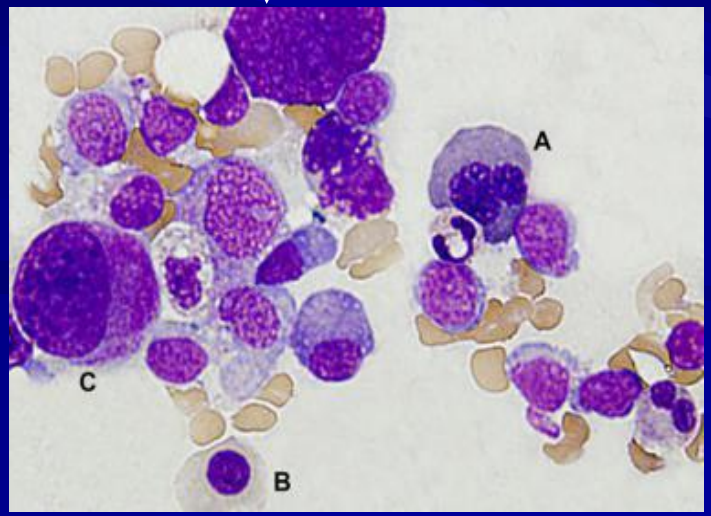
Marrow Failure Overlap: Traditional View



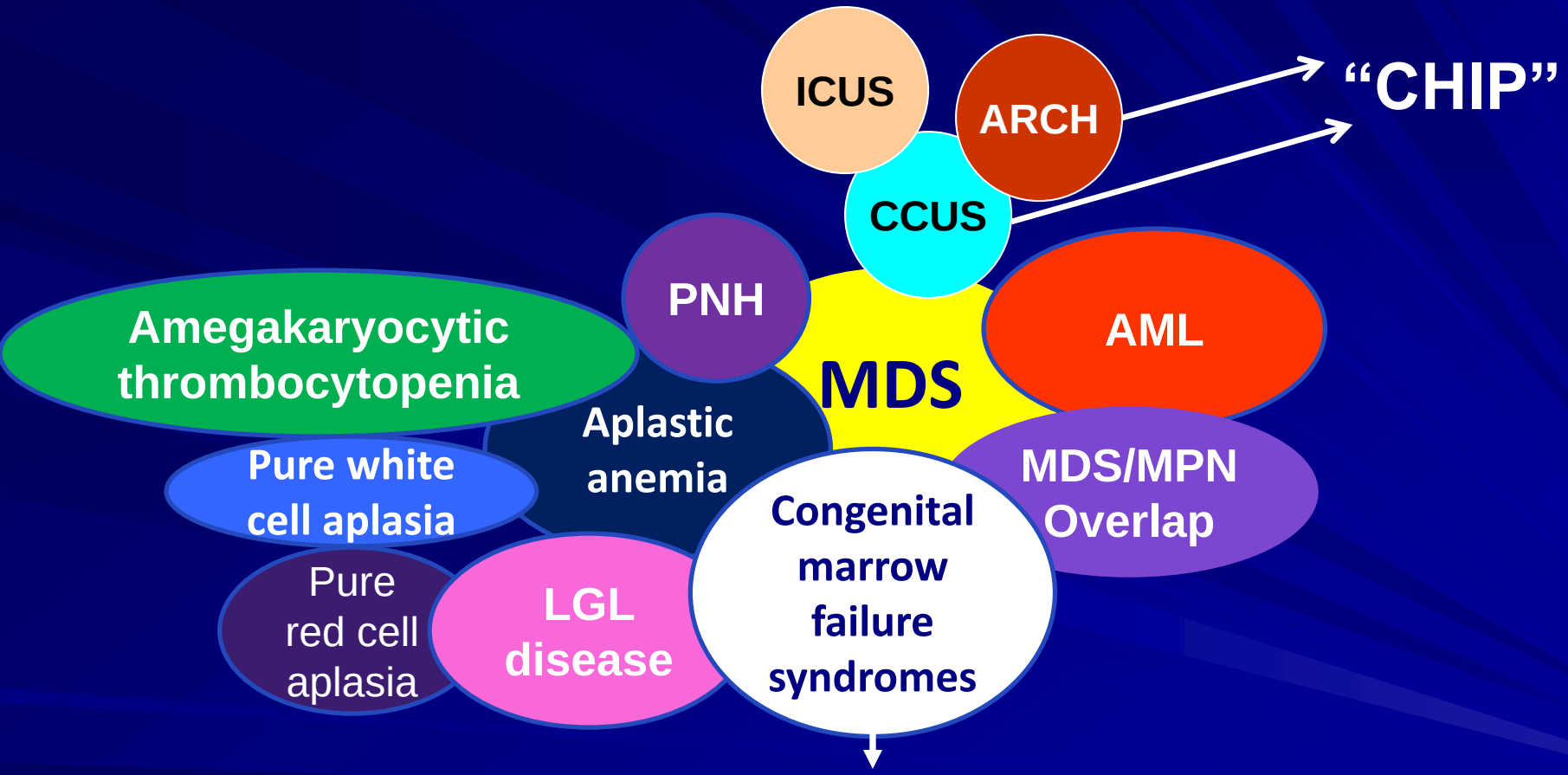






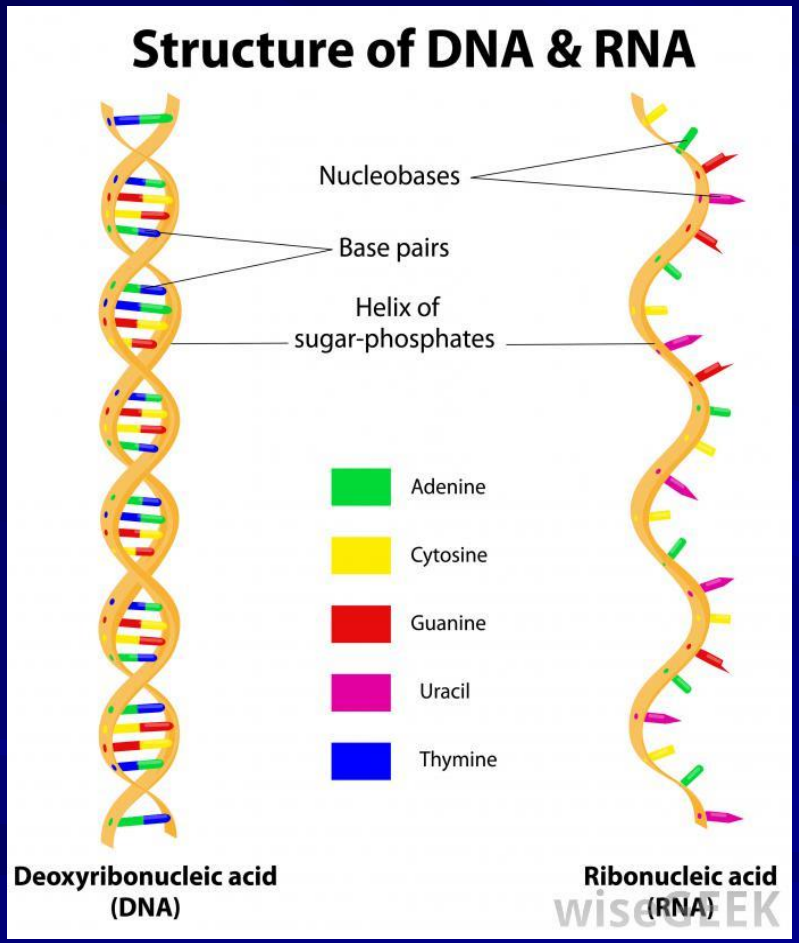


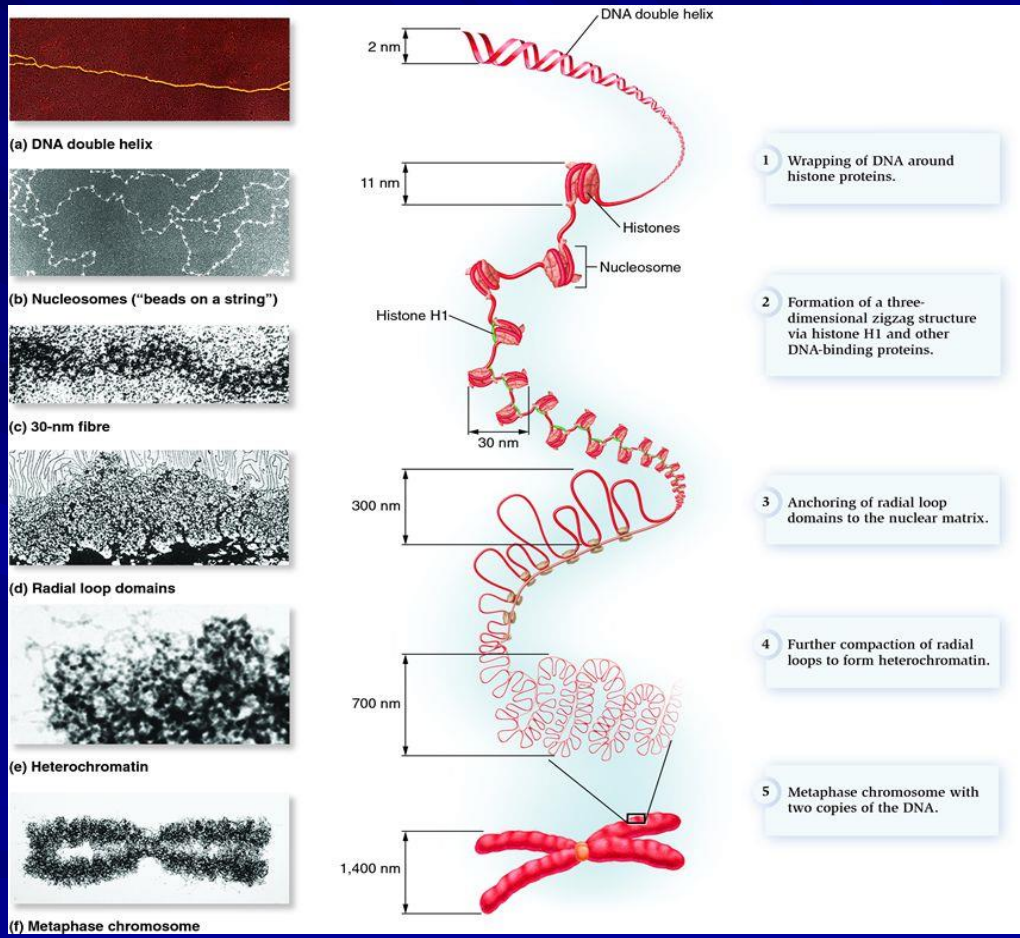
Marrow Failure Syndromes 2017



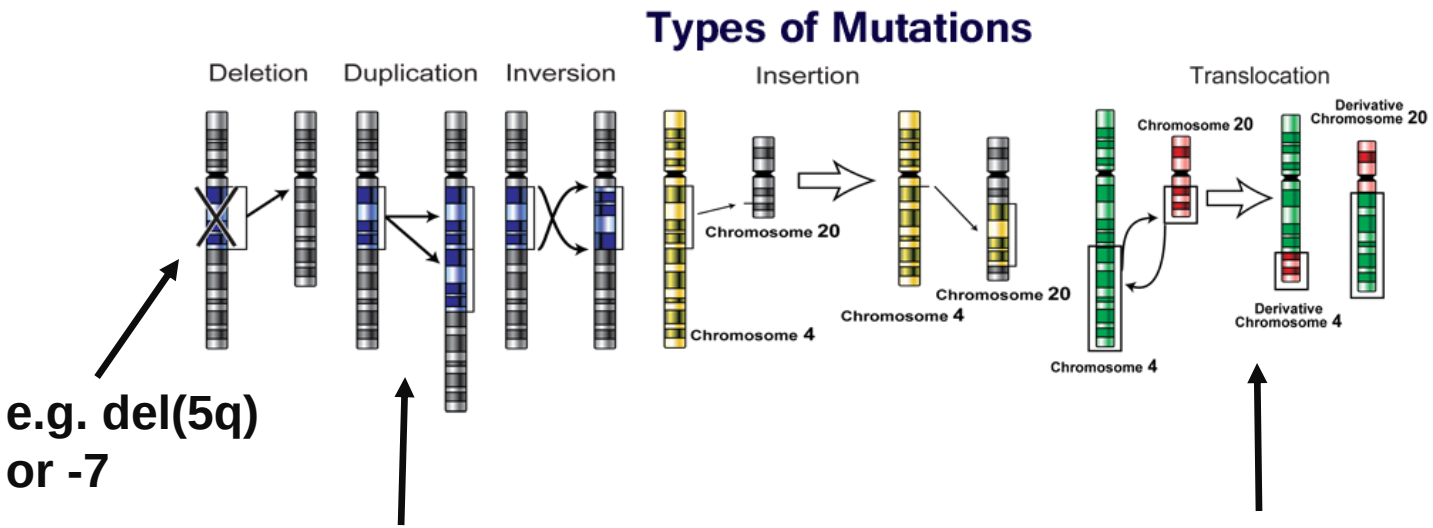
- Fanconi Anemia
- GATA2 mutations
- Telomeropathies
- Ribosomopathies

Genomics 101





Genomics 101 – Changes in Chromosomal Structure

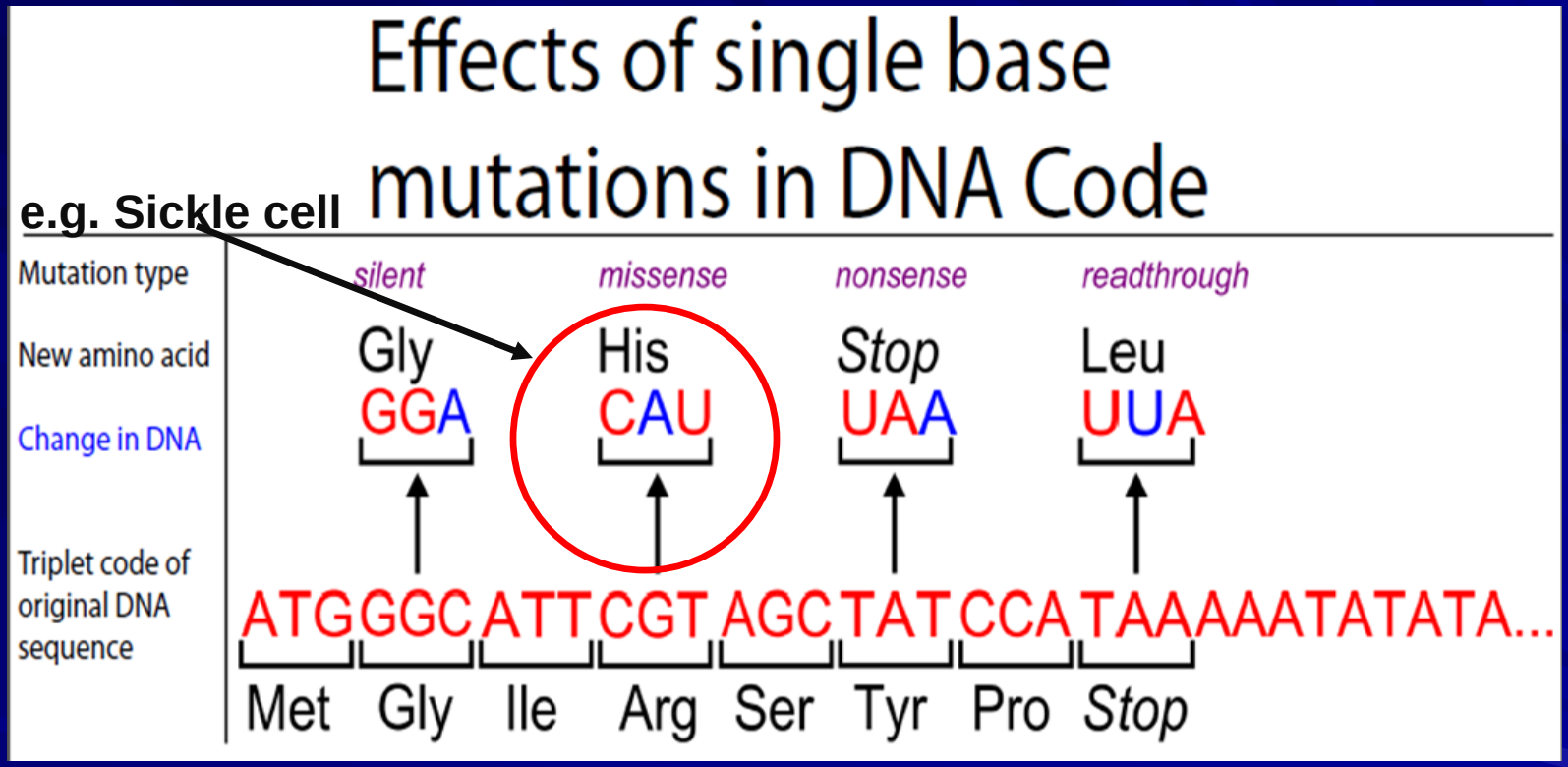


e.g. del(5q) or -7

e.g. +8, +21

e.g. Philadelphia chromosome

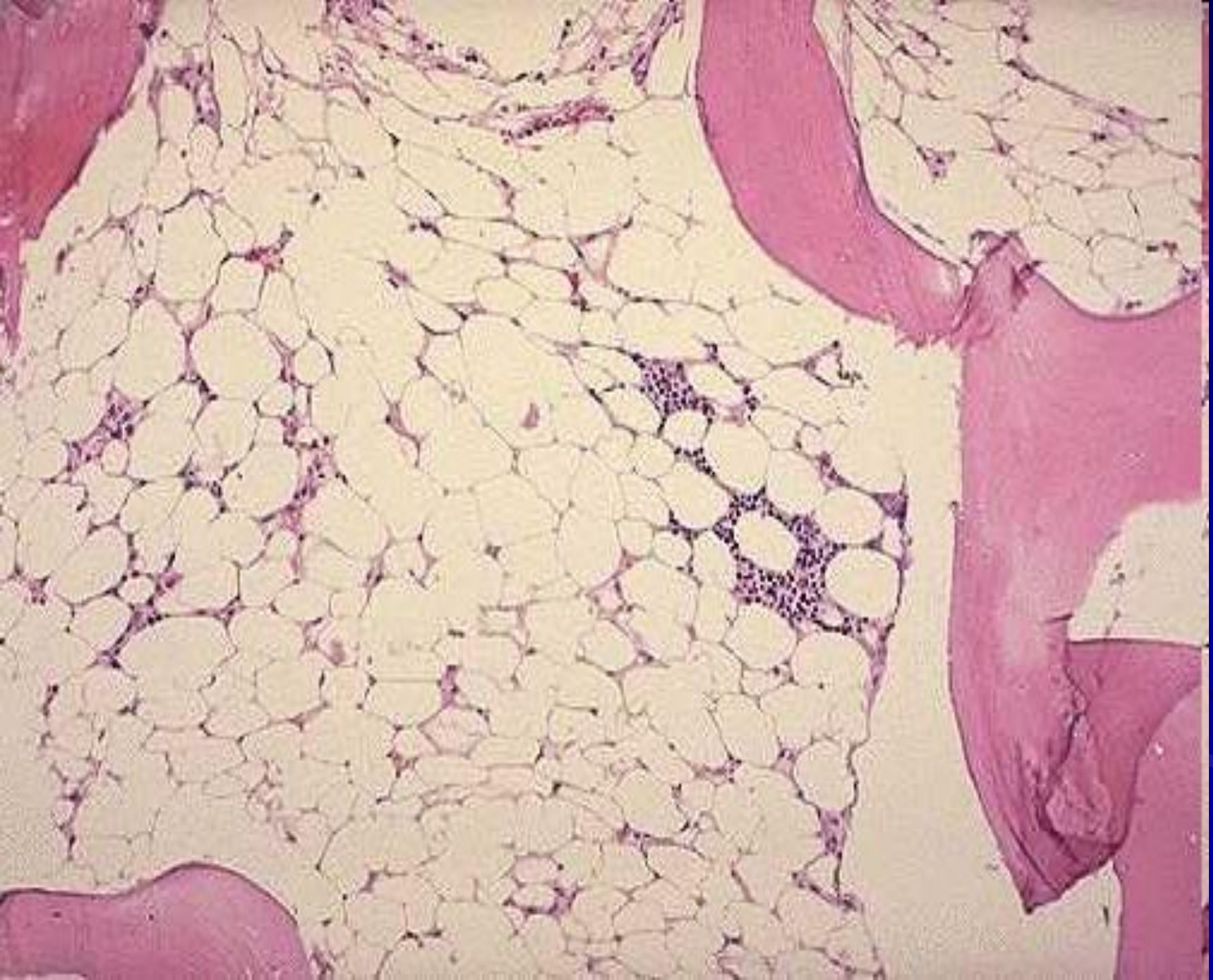
Genomics 101 – Point Mutations



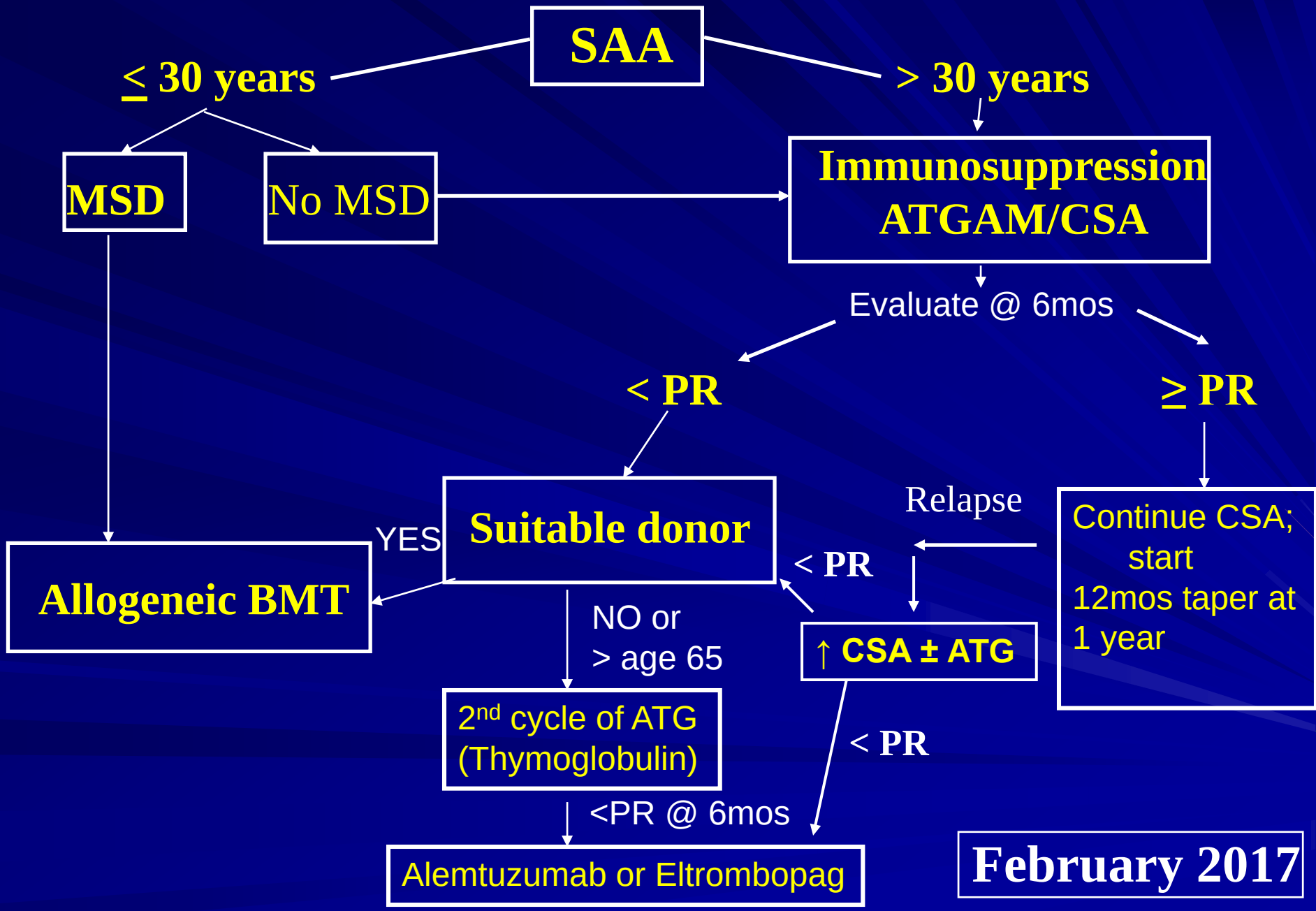
Point mutations by next generation sequencing (NGS) is the most important development in medicine in the past decade – it is providing key diagnostic, prognostic & therapeutic information!!

APLASTIC ANEMIA

- Rare stem cell disorder (2 cases/million/yr)
- M=F
- Biphasic (teens/young adults & > age 60)
- Caused by immune system overactivity
- Drugs, chemical/radiation, virus, pregnant (~5%)
- Presentation is pancytopenia & marrow “empty”
- No abnormal WBCs or platelet precursors
- Chromosome analysis of marrow usually normal



MANAGEMENT OF SAA



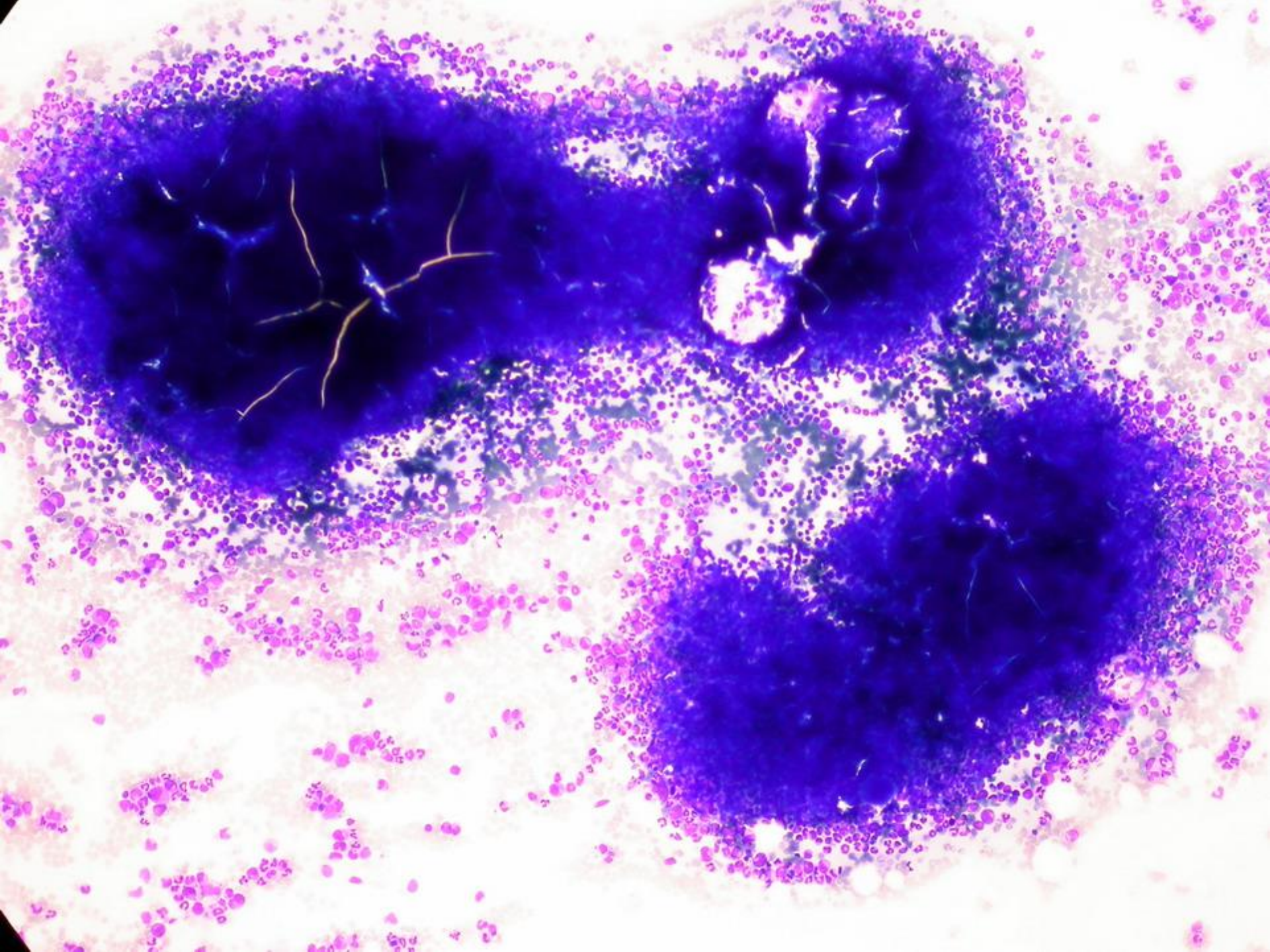
February 2017

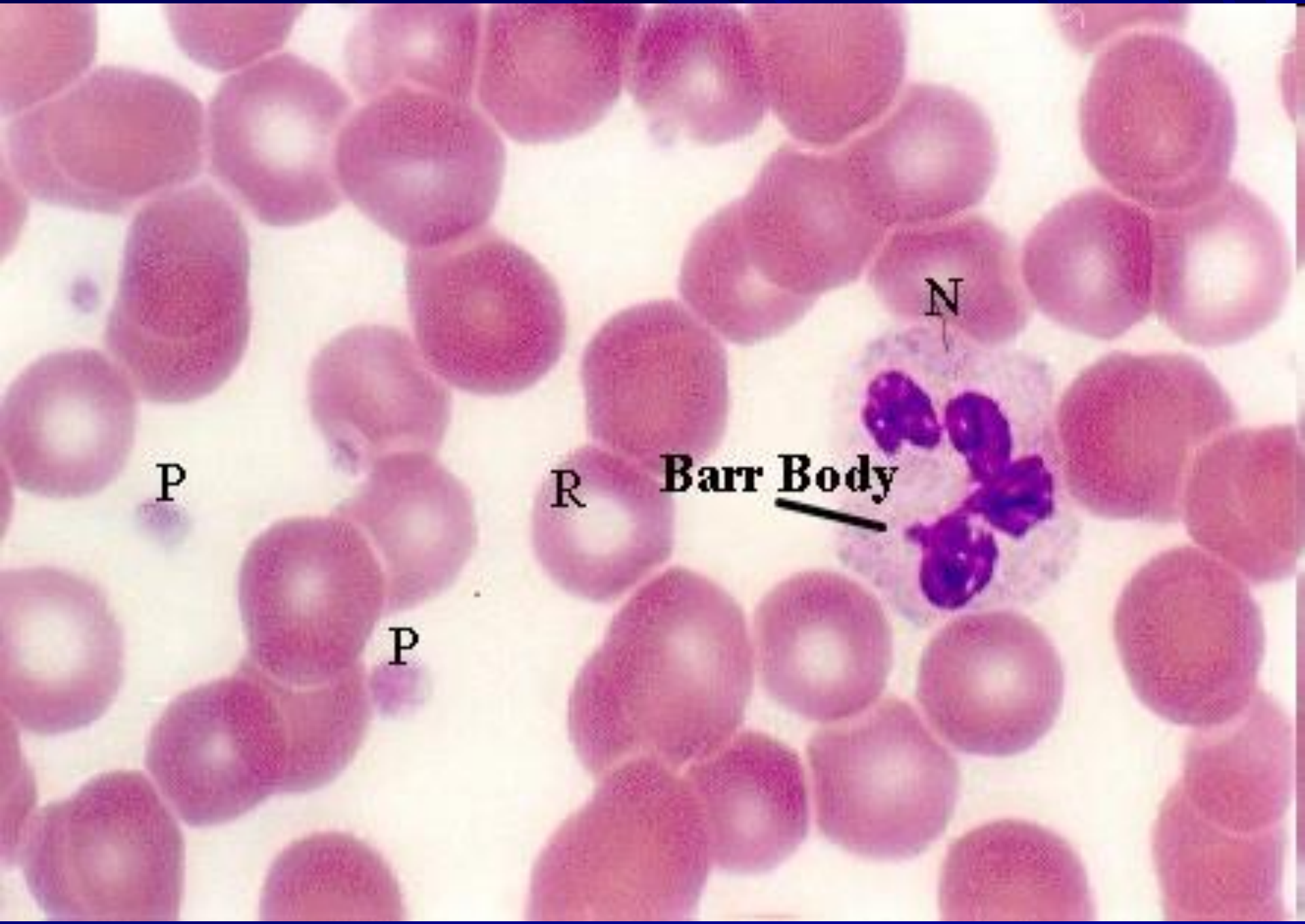
AA: New Trends in Treatment

- Earlier BMT
- TPO agonists
- Alemtuzumab

MYELODYSPLASTIC SYNDROME

- **Clonal** stem cell disorder – it is a malignancy!
- ~50% "transform" to **AML**
- 80% have hyperactive (but ineffective) marrow
- **Abnormal (dysplastic) RBCs, WBCs & platelets**
- 20% have underactive marrow (resemble AA)
- **50% have abnormal chromosomes - >90% have point mutations**

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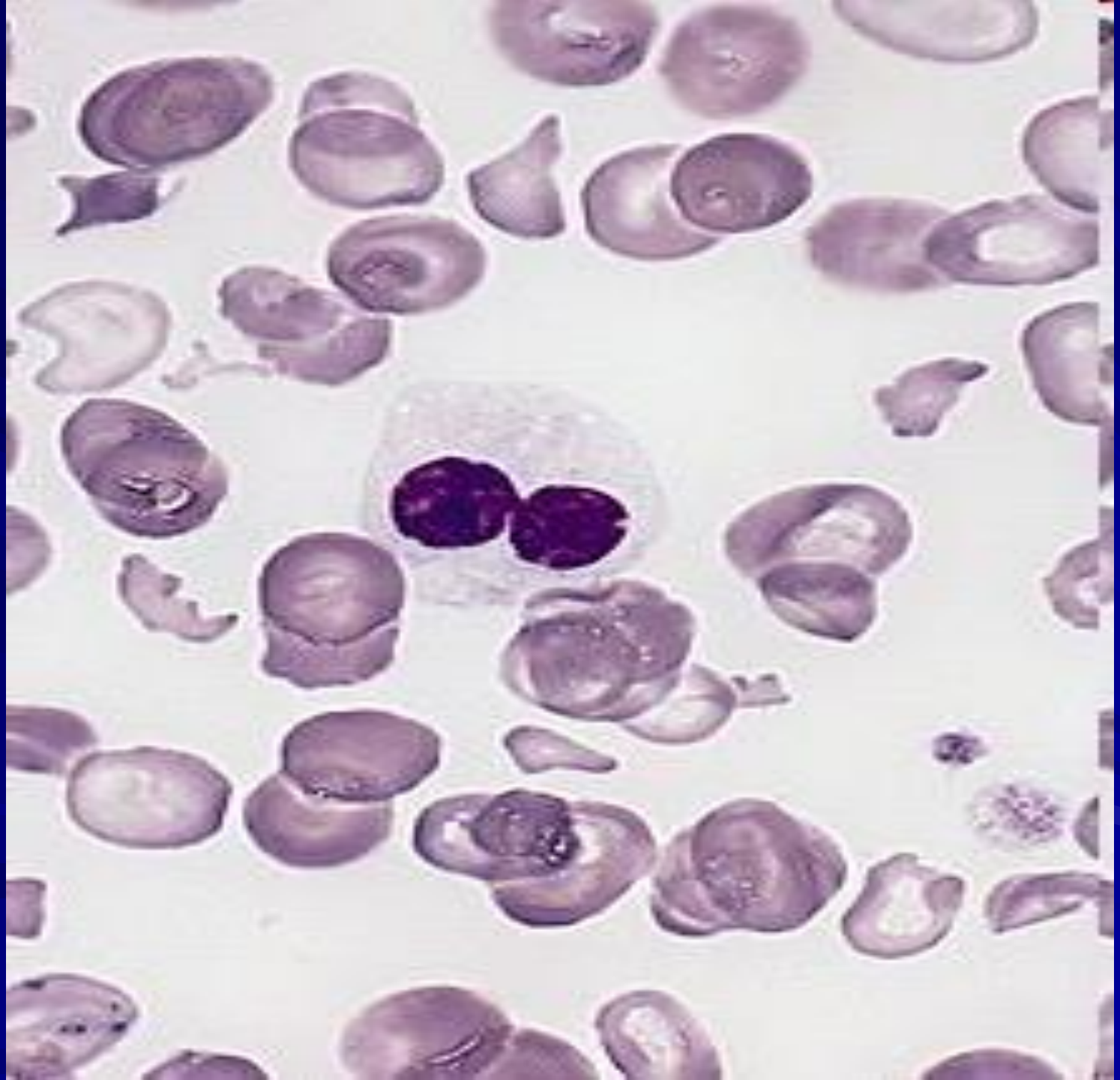

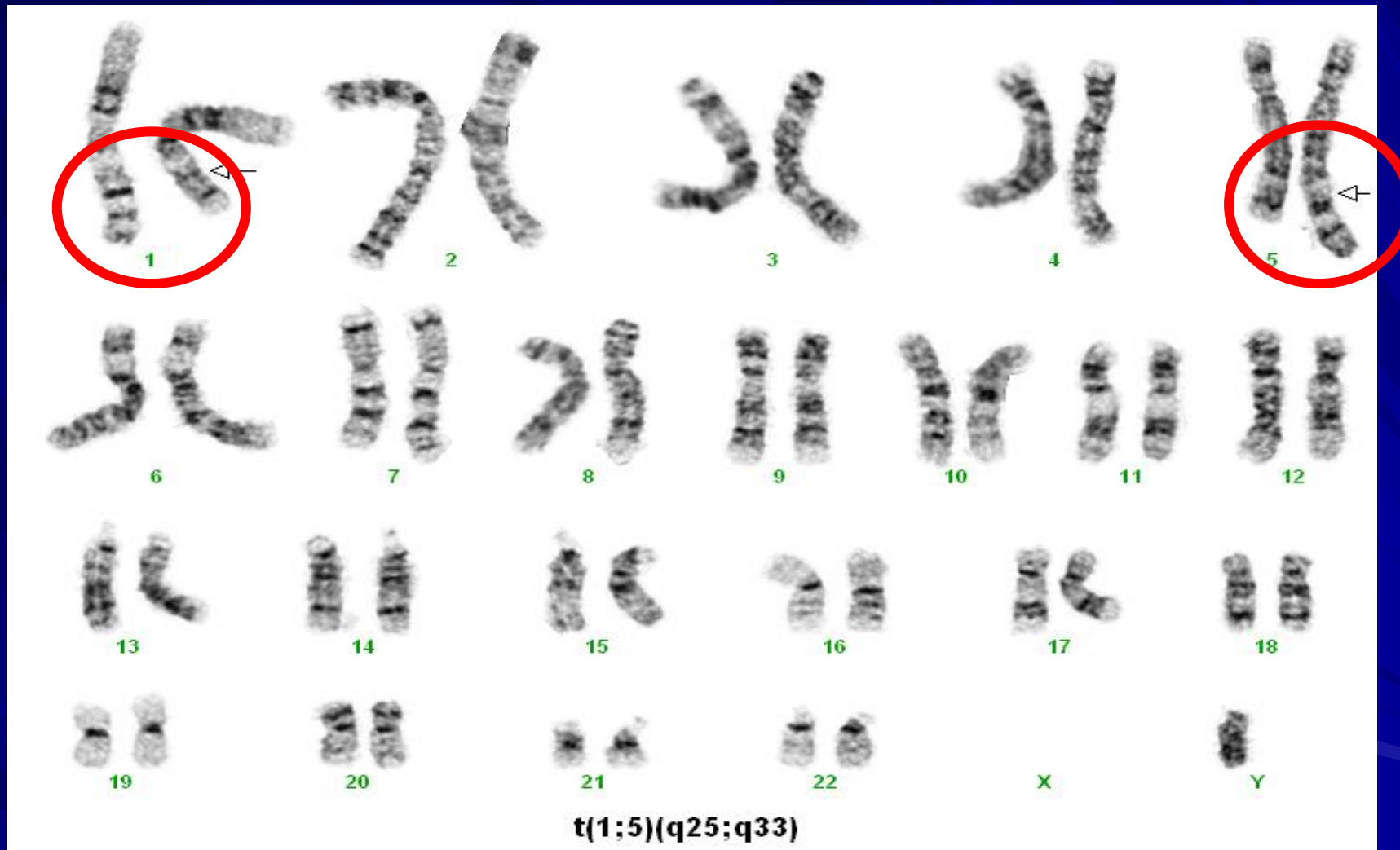
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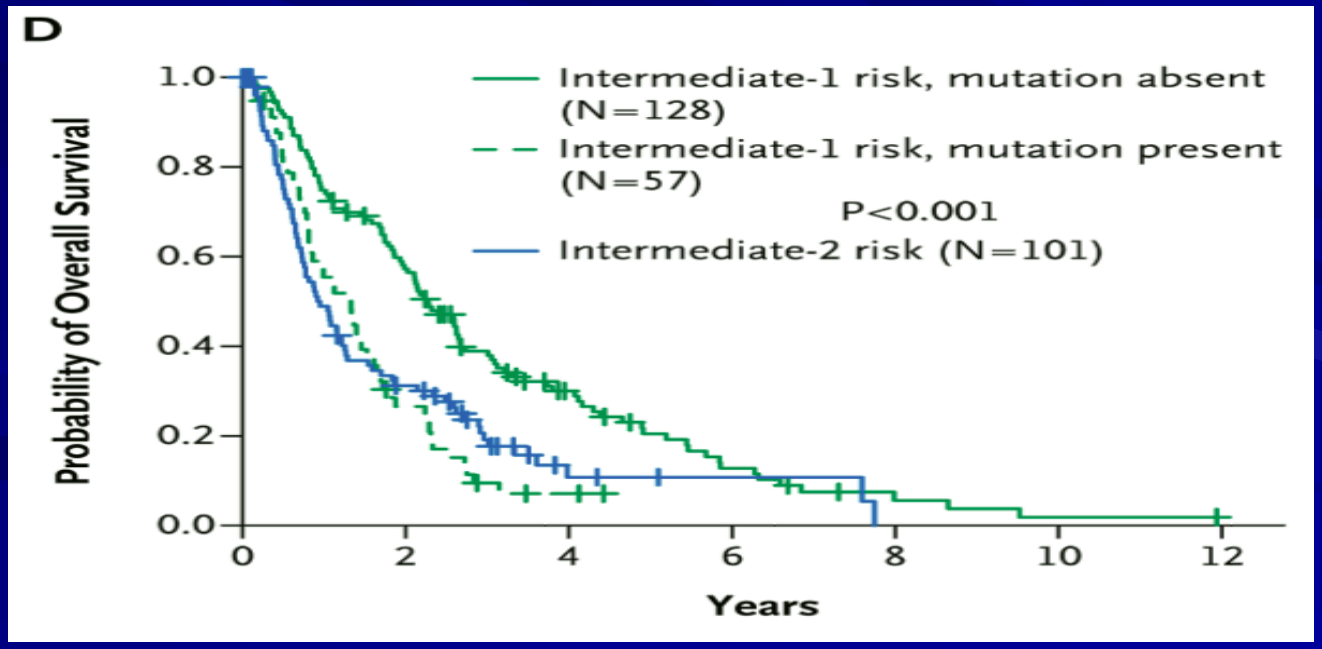
Earlier SCT in MDS: Use of Point Mutations

Bejar, 2011 NEJM

- 439 MDS pts sequenced for 18 key genes
- 5 mutations had IPSS-independent prognostic significance
- **TP53, ETV6, EZH2, RUNX1 & ASXL1**



Earlier BMT in AA

- German AA Group & NIH pioneered ATG+CSA
- Response rate (PR+CR) is 60-70% **(1/3 no response)**
- Of the PR/CR patients, **1/3 relapse**
- In relapses, 90% never require transfusions
- **Long-term CSA often needed**
- **Overall only 1 in 3 pts remain in PR/CR without need for indefinite CSA**
- 15% of patients develop MDS, AML or PNH

Point Mutations in AA

- NGS done on 439 AA pts from US & Japan
- 249 mutations found in 156 pts (36%)
- Mutations predict outcome with IST!

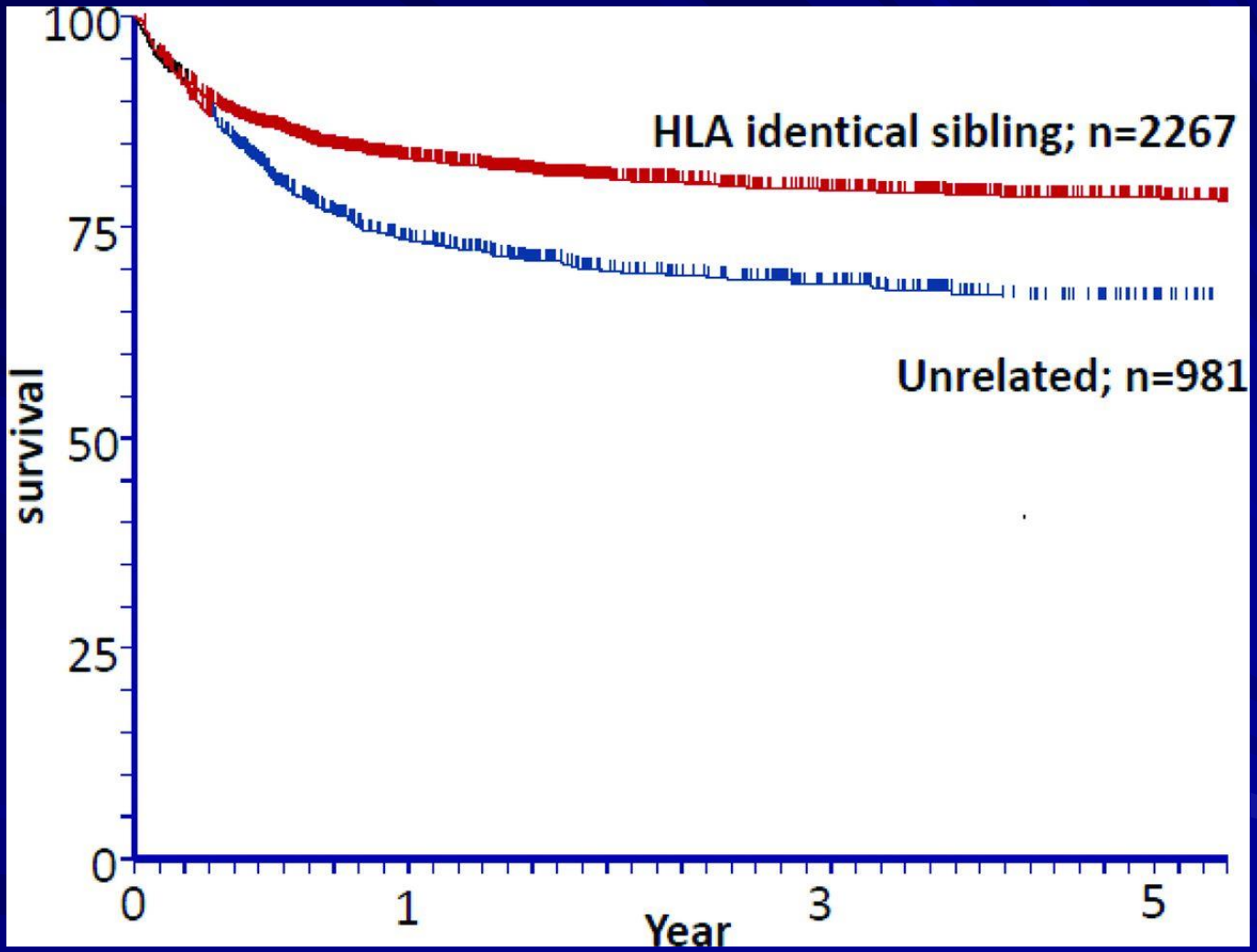
Favourable

- BCOR/BCORL1
- PIG-A

Unfavourable

- ASXL1
- DNMT3A
- RUNX1
- TP53
- JAK2/3
- CSMD1

Acquired SAA Transplantations 1999-2009: Sib donors versus UDs
Unpublished data from the EBMT (courtesy Prof A. Bacigalupo)



80-85%

70-75%

Socié G Hematology 2013;2013:82-86

TPO Agonists in AA

- Thrombopoietin (TPO) – hormone that stimulates marrow platelet production
- Eltrombopag & Romiplostim manufactured as agents that resemble TPO
- Licensed for use in ITP (disorder of excessive platelet destruction)
- Incidentally found to raise **ALL 3 BLOOD COUNTS** in some patients

TPO Agonists in AA

- Use in refractory AA led to a **25% RR** in each cell line; 15% had PR in **ALL** 3 LINES
- Has led to its introduction into upfront CSA + ATGAM immunosuppression
- More rapid response (60% CR) @ 6 mths
- Higher Overall RR – 95% PR/CR @ 6 mths
- In refractory AA, dose-escalating fashion
- Eltrombopag 12 wk trial= $25,000
- Subsequent cost= $100,000/yr

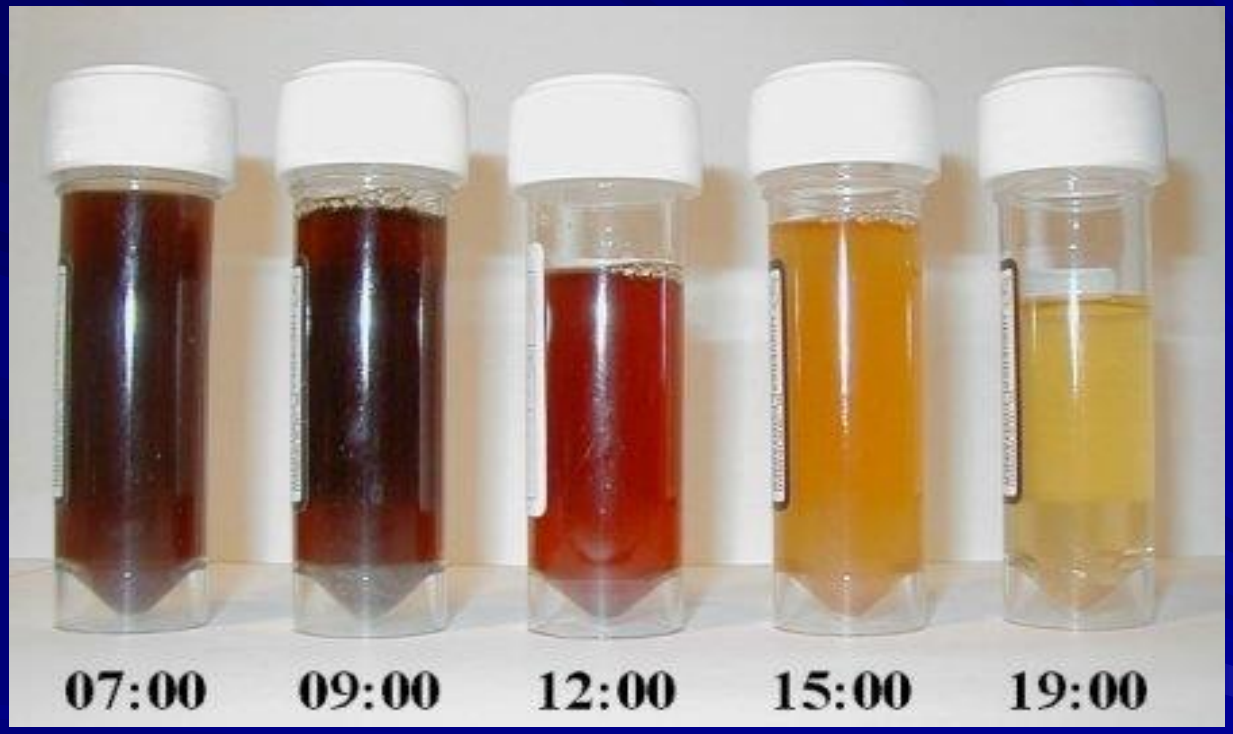
Alemtuzumab in AA

- For patients refractory to CSA + ATG, response rate 37%
- For patients relapsed after IST response, response rate 56%
- Given as 10-day IV infusion
- Concerns: Infectious complications, infusional reactions

Paroxysmal Nocturnal Hemoglobinuria (PNH)

- Acquired deficiency of blood cell membrane protein (“GPI”)
- Susceptiblity to destruction (esp. in low pH)
- **“Hemolytic PNH”:** characterized by episodes of bloody/tea-coloured urine in AM or during infections – 25% of pts
- Protean manifestations but **thrombosis** and **marrow failure** are key parts of the spectrum

“Coca cola” urine



Only 25% of patients with PNH!

Still the most common cause of Coca cola urine:

Paroxysmal Nocturnal Hemoglobinuria (PNH)

- Patients usually anemic but may have low WBCs and platelets
- Marrow may be normal, underactive or overactive
- Percent of abnormal (GPI-deficient) cells in blood variable – 0.01%-99%

Treatment of PNH: Eculizumab

- Anti-C5 antibody
- Effective at reducing:
  - Hemolysis
  - Blood transfusions
  - Thrombosis
- Improves QOL and SURVIVAL
- Minor infusional reactions can occur
- BUT ↑ risk ***Meningococcal*** infections!!

New Trends in PNH

- None! – yet
- New longer half-life products – “ALXN1210”
- **Being given once monthly** -- studies in humans underway
- May be able to give it every 2-3 months – also has been studied in humans
- Mutation studies may alter therapy – earler BMT

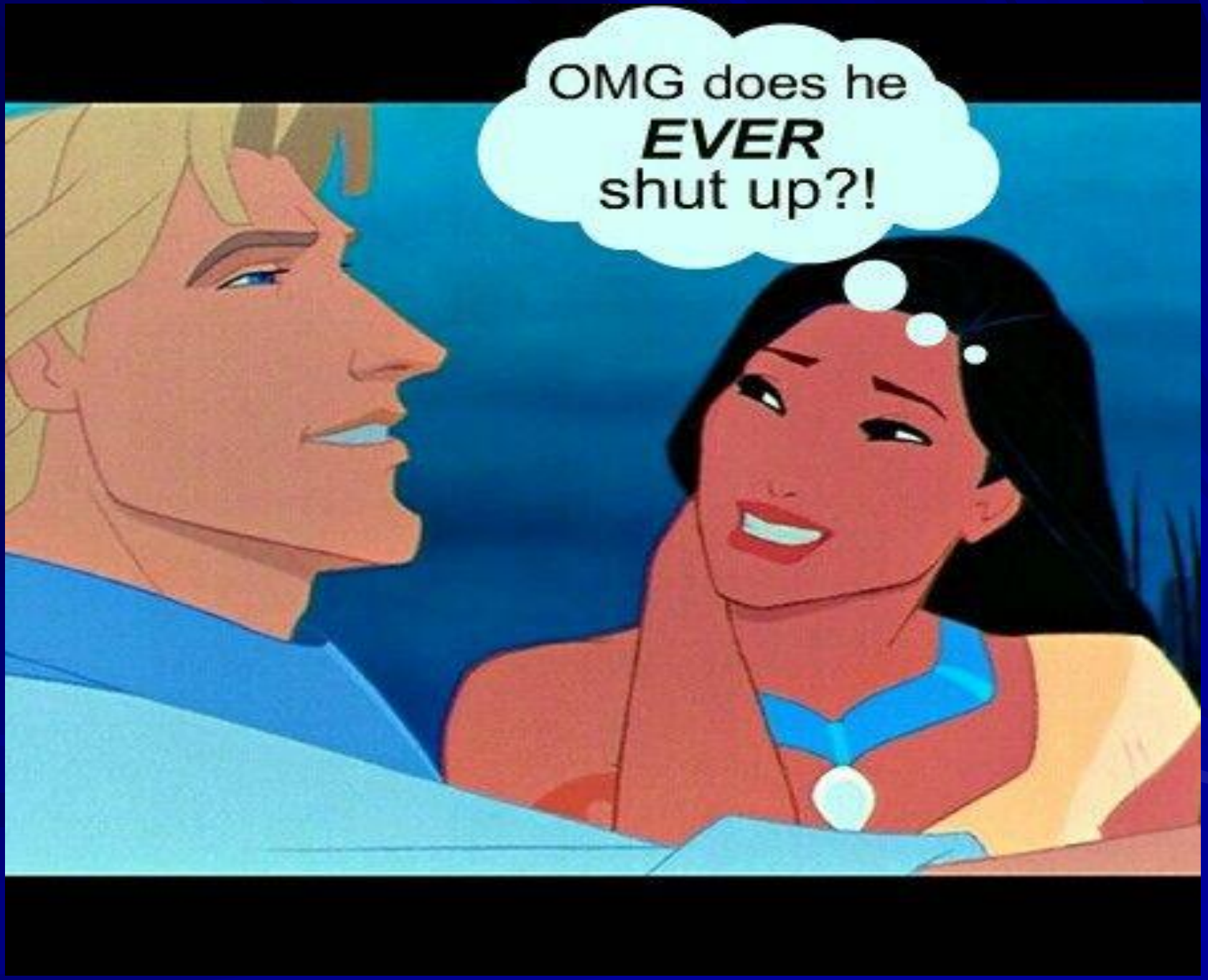
Paroxysmal Nocturnal Hemoglobinuria (PNH)

- In “Classic” or “Hemolytic” PNH, GPI-deficient cells always >50%
- 50% of AA pts (& 20% of low-risk MDS) will have demonstrable PNH cells (usually <1%)
- Patients with 5-50% PNH cells and “empty” marrows are often termed AA/PNH Overlap
- PNH pts may go on to develop MDS or SAA or vice versa

NGS in PNH Patients

(Wenyi Shen - J Clin Invest 2014)

- 60 PNH pts
- 83% had a gene mutation identified
- Genes mutated were similar to MDS and AA pts
- Presence of a mutation correlated with larger percentage of PNH cells


OMG does he
EVER
shut up?!