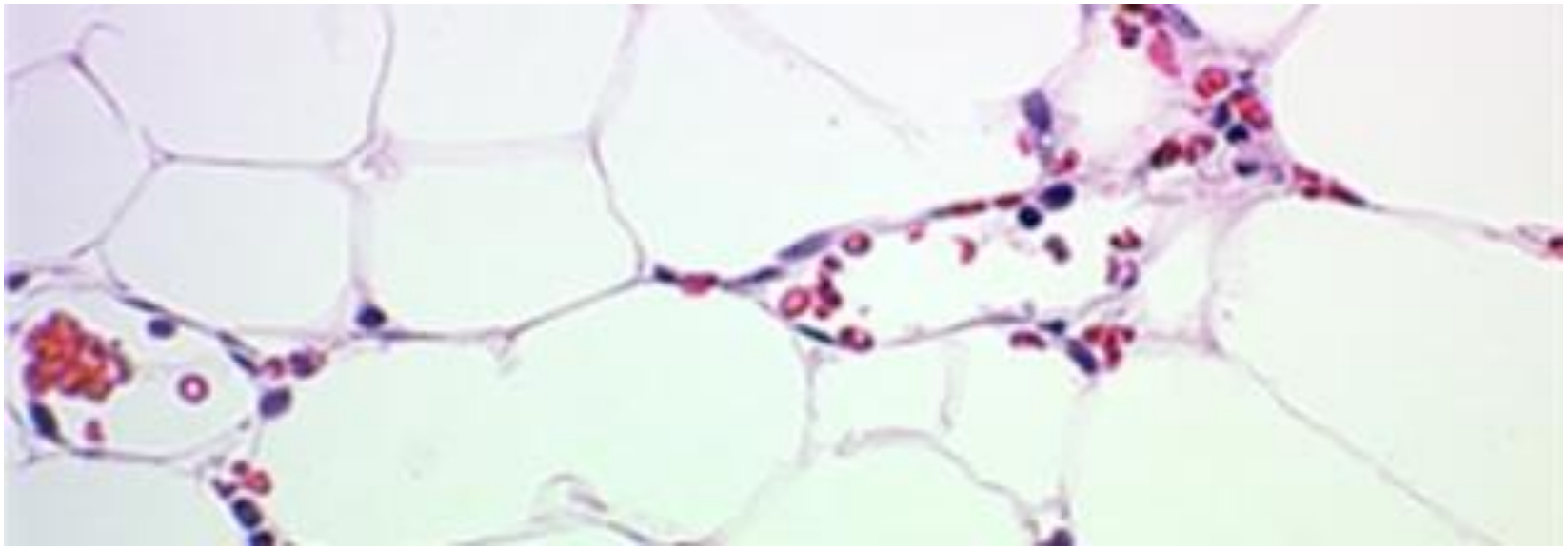
UNIVERSITÄTS KLINIKUM FREIBURG

ZKJ ZENTRUM FÜR KINDER- UND JUGENDMEDIZIN



Severe Aplastic Anemia in Children and Adolescents

Brigitte Strahm

21. April 2018

Acquired Aplastic Anemia in children

What is aquired aplastic anemia ?

Definition

To qualify as severely aplastic, patients had to have at least two of the following three peripheral blood values: (1) granulocytes < 500/cu mm (2) platelets $< 20{,}000$/cu mm and (3) reticulocytes $< 1\%$ (corrected for hematocrit). In addition the marrow had to be either markedly hypoplastic ($< 25\%$ of normal cellularity) or moderately hypoplastic (25%–50% of normal cellularity with $< 30\%$ of remaining cells being hematopoietic) as estimated from biopsies.

Camitta, Blood 1976

How A.L.G. acts is unknown, but our findings accord with the hypothesis that, in a substantial proportion of cases of aplastic anaemia, unspecified autoimmune reactions block the development of residual stem cells.

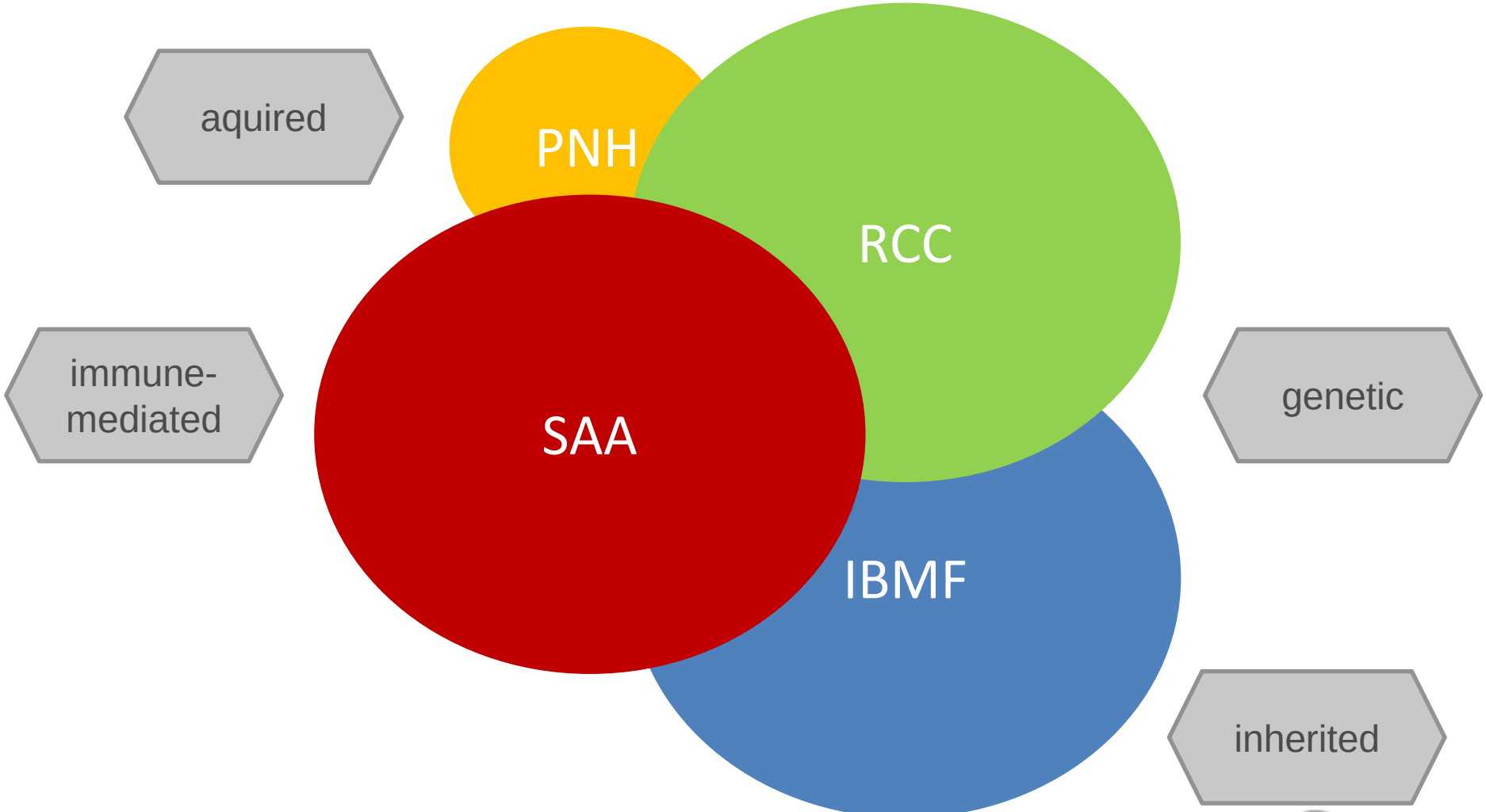
Speck, Lancet 1977

Patients presenting with cytopenia and fitting the above criteria may be affected with different conditions that must be excluded before establishing a diagnosis of idiopathic aplastic anemia. All patients should be studied to rule out hypoplastic myelodysplasia/leukemia, congenital marrow failure, infections, and Paroxysmal Nocturnal Haemoglobinuria (PNH).

Dufour, Int J Hem 2015

(Pan)cytopenia in children

Diagnostic and therapeutic Challenges



Aquired Aplastic anemia in children

Diagnostic tools

- Family history: hematological disease, cancer predisposition
- Clinical assessment: short stature, failure to thrive, dysmorphic features (microcephaly, face, skeletal), organ malformations (heart, GU)
- Bone marrow aspirate and biopsy
- Cytogenetics
- PNH
- Lymphocyte subpopulations, immunoglobulins, autoantibodies
- Functional test to exclude IBMF i.e. FA/DC
- Molecular Genetics

Aquired Aplastic anemia in children

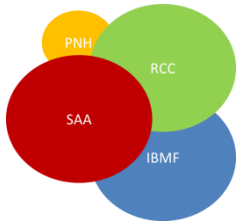
Exclusion of IBMFS: BSH Guidelines

1) Chromosomal breakage test (diepoxybutane stress test) for Fanconi anaemia.
2) Telomere length by flow cytometry-fluorescence *in situ* hybridisation (Flow-FISH) to identify patients with dyskeratosis congenita (DC), although it is noteworthy that not all DC patients will have very short telomeres.

Smarasinghe, BJH 2018

Aplastic Anemia in children

Possibility of undiagnosed inherited bone marrow failure syndrome ?



- Fanconi Anemia

  RCC: 15% patients diagnosed with FA, 8% without typical clinical signs

  Yoshimi, BJH 2012

  30-40% of patients with FA without obvious clinical evidence

  Shimamura, Alter, Blood Reviews 2010

  → Exclusion by chromosomal breakage/growth arrest mandatory

- Dyskeratosis congenita

  RCC: 5% Patienten mit Mutationen mit Dyskeratosis Congenita assoziierten Genen

  Ortmann, Haematologica 2006, Wlodarski/Karow, unpublished

  → Telomere length measurement mandatory ?

Telomere and AA: Recognizing underlying DC ?

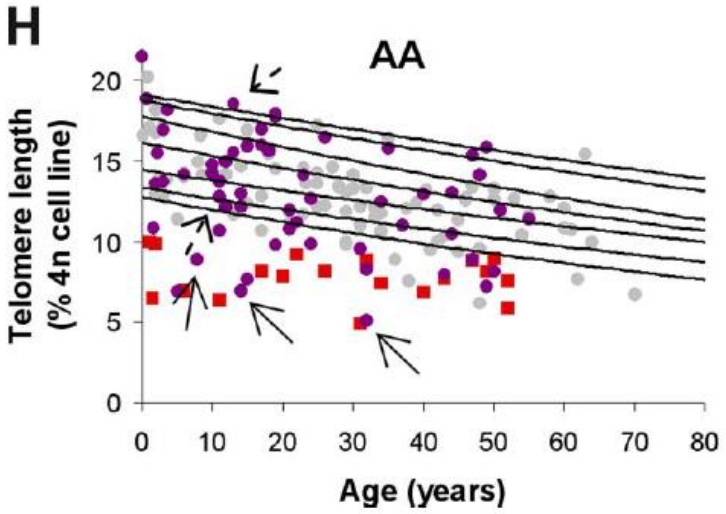
Screening patients with SAA for short telomeres ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 7, 2005 VOL. 352 NO. 14

Mutations in *TERT*, the Gene for Telomerase Reverse Transcriptase, in Aplastic Anemia

Hiroki Yamaguchi, M.D., Rodrigo T. Calado, M.D., Ph.D., Hinh Ly, Ph.D., Sachiko Kajigaya, Ph.D., Gabriela M. Baerlocher, M.D., Stephen J. Chanock, M.D., Peter M. Lansdorp, M.D., Ph.D., and Neal S. Young, M.D.



- DC
- AA
- Other BMFS

TERT mutations

Telomere length < 1.P

- highly sensitive for DC
- not specific for DC

Du, Blood 2009

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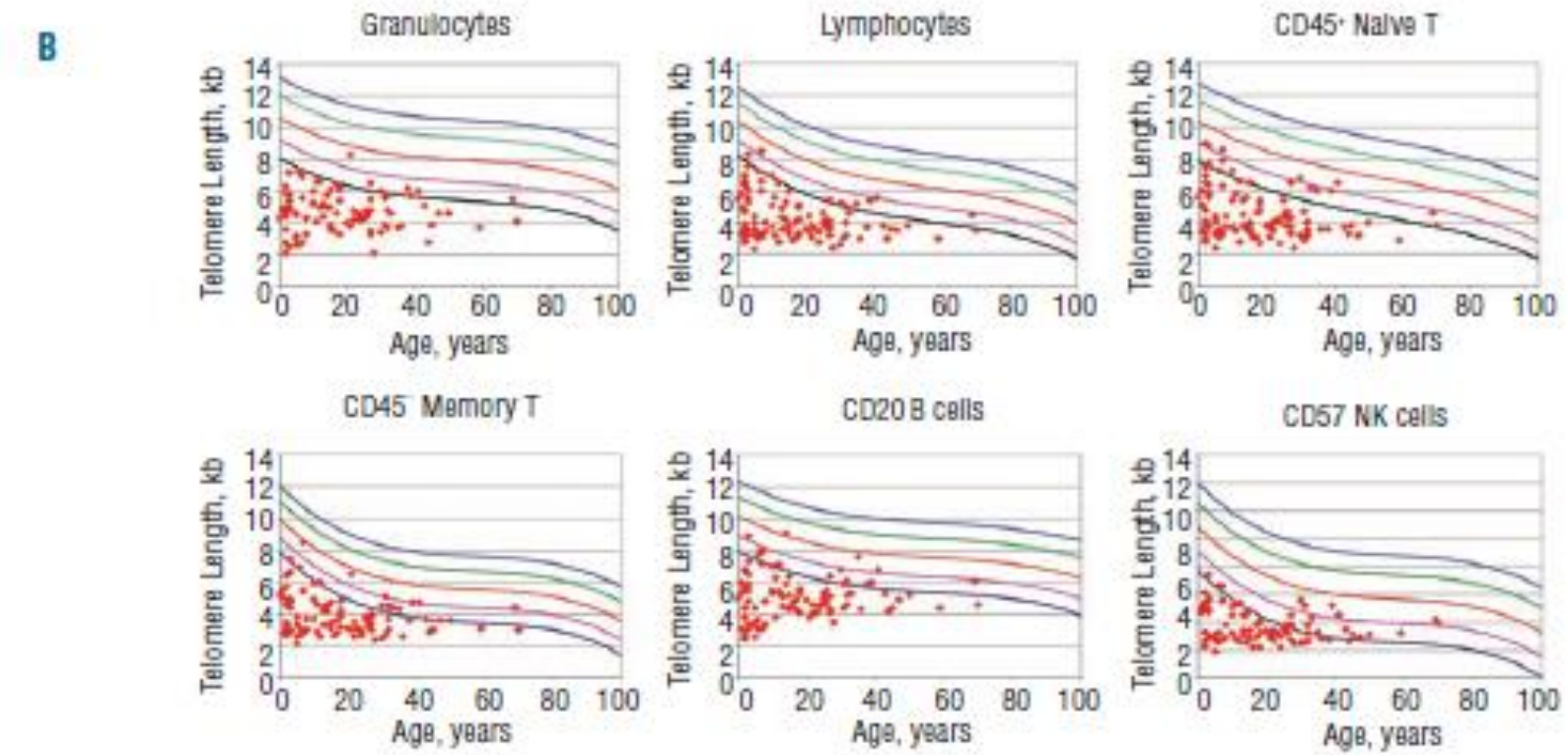
Telomere and AA: Recognizing underlying DC ?

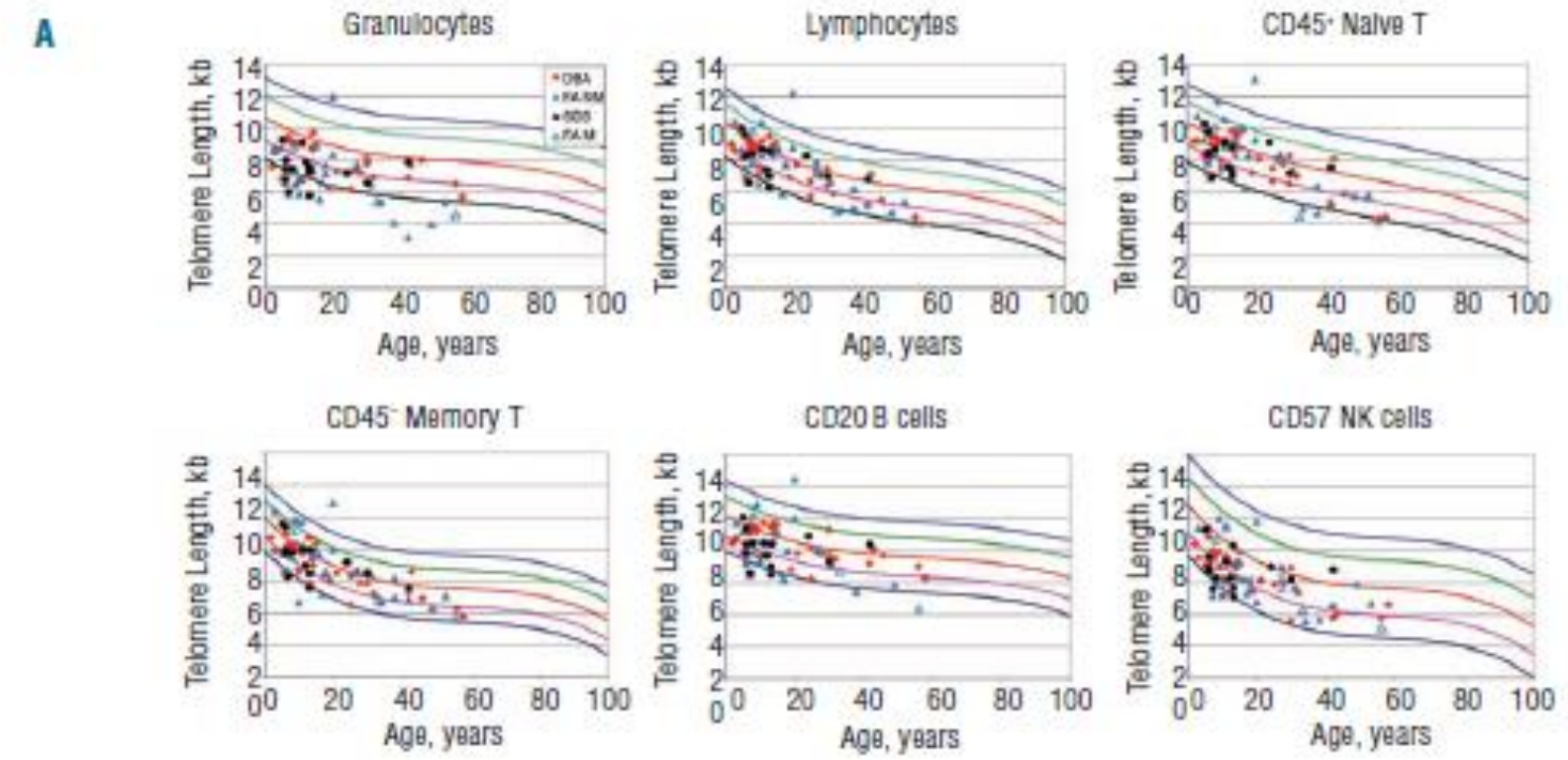
Telomere length in dyskeratosis congenita



Alter, Haematologica 2015

Telomere and AA: Recognizing underlying DC ?

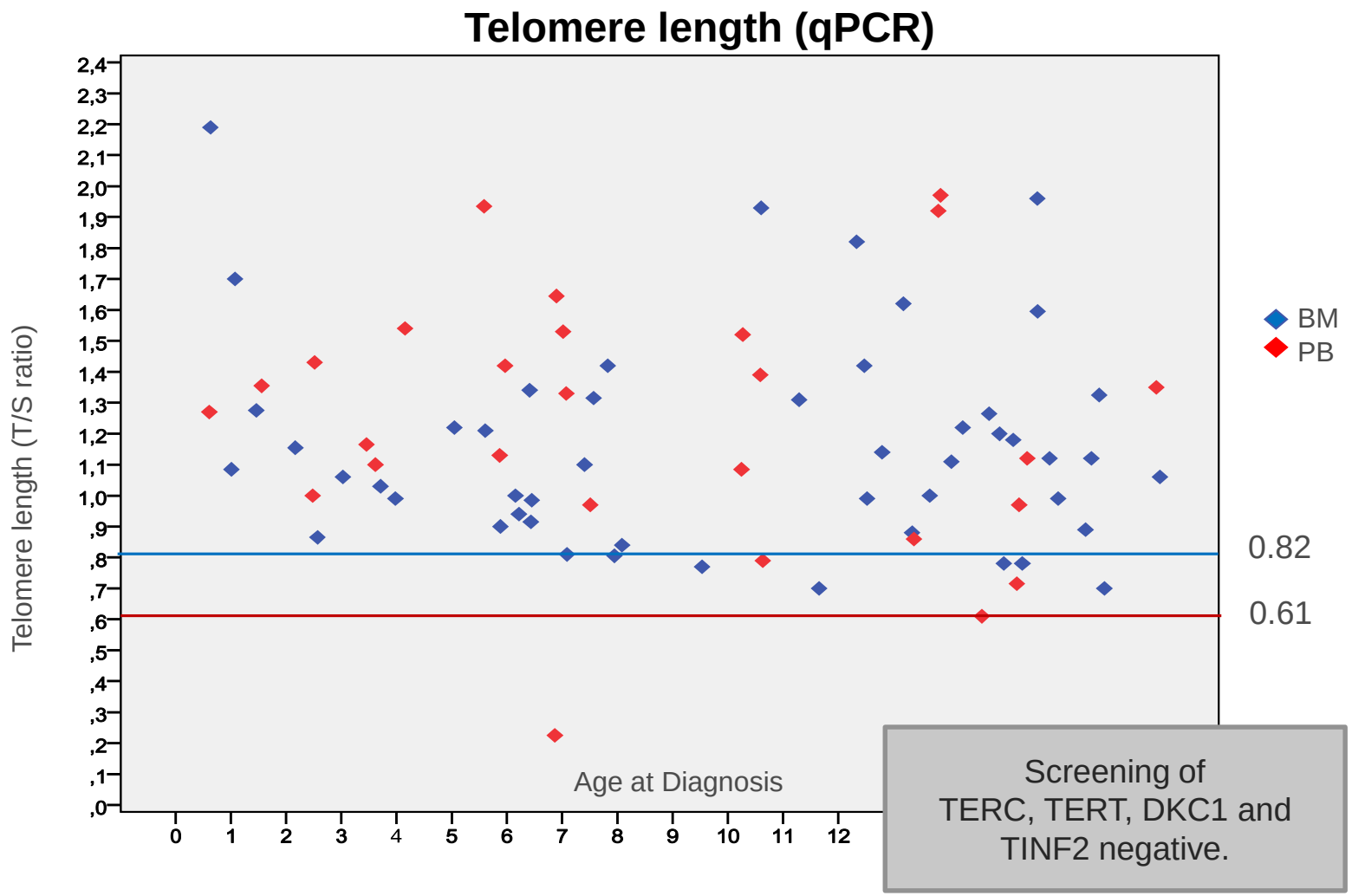
Telomere length in other BMFS



Alter, Haematologica 2015

EWOG-SAA 2010

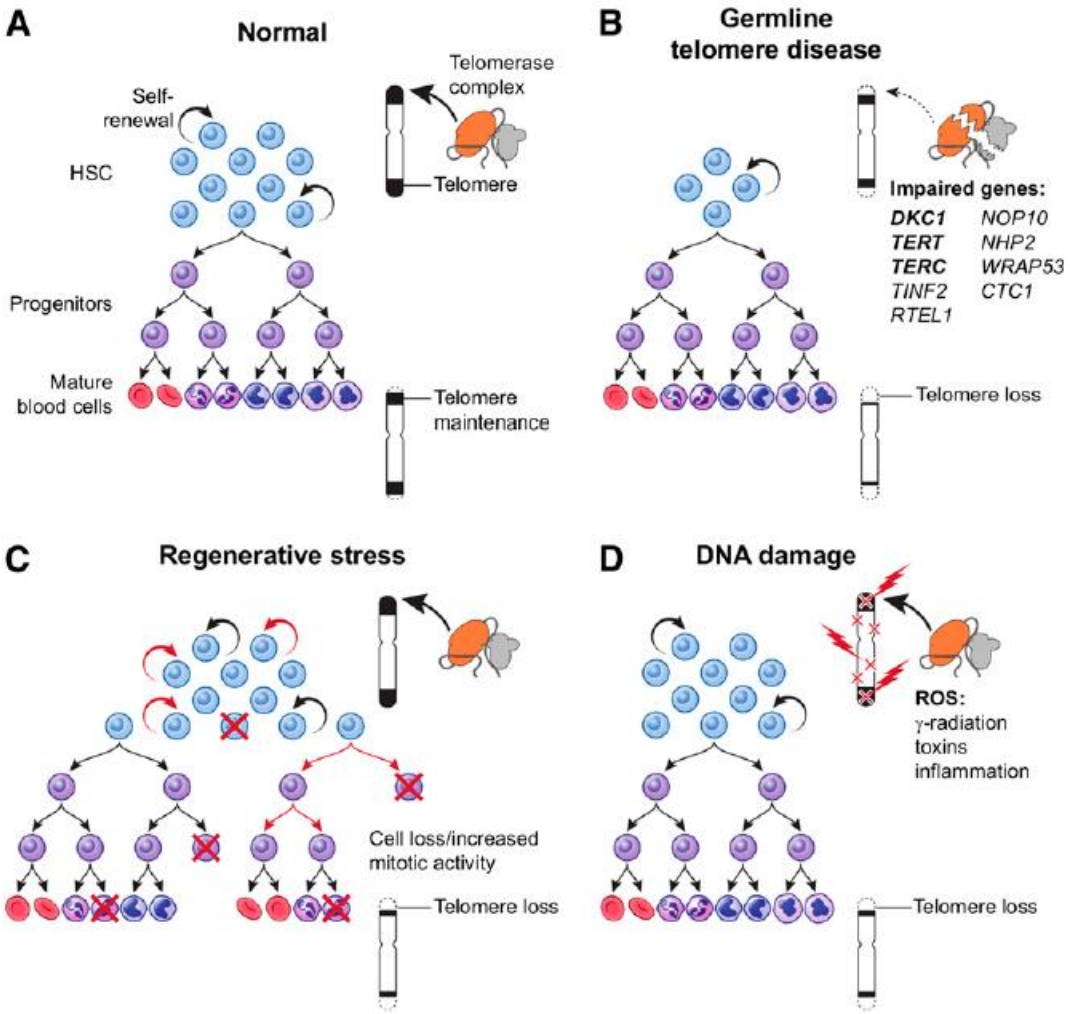
Preliminary result of telomere length measurements in EWOG-SAA 2010 (n=77)



Screening of
TERC, TERT, DKC1 and
TINF2 negative.

Telomere biology

Mechanisms of telomere attrition



Townsley, Blood 2014

Telomeres and AA: Recognizing underlying DC ?

Screening patients with SAA for short telomeres ?

Dyskeratosis congenita:

The diagnosis can be made in the clinic examining room, based on a good personal and family history and even a cursory physical examination. Patients may make their own diagnosis using the Internet—better than subspecialists who do not query outside their organ system of interest.

A telomeropathy should be considered in all patients with AA or hypoplastic MDS, and testing should be performed when treatment decisions might be affected.

Townsley, Blood 2014

Aquired Aplastic anemia

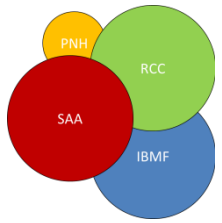
Exclusion of IBMFS: BSH Guidelines

1) Chromosomal breakage test (diepoxybutane stress test) for Fanconi anaemia.
2) Telomere length by flow cytometry-fluorescence *in situ* hybridisation (Flow-FISH) to identify patients with dyskeratosis congenita (DC), although it is noteworthy that not all DC patients will have very short telomeres.
3) Lymphocyte subset testing to identify the presence of B cell lymphopenia; the detection of B cell lymphopenia or monocytopenia, should trigger *GATA2* genetic testing (Ganapathi *et al*, 2015).
4) Next Generation Sequencing (NGS) panels in bone marrow failure to identify cryptic mutations. Screening of children and young people with idiopathic aplastic anaemia in one series identified germline bone marrow failure mutations in in 5·1% of cases (Keel *et al*, 2016). However, NGS bone marrow failure panels are currently unable to provide results in a timely manner (turnaround time typically 2–4 months). Nevertheless, a positive result could subsequently affect genetic counselling and cancer surveillance, and thus samples should be sent where possible at diagnosis.

Smarasinghe, BJH 2018

Aplastic Anemia in children

Detection of germline mutations to identify underlying IBMF



- Identification of germline variants in children with AA (n=98)

Table 1. Clinical and genetic features of AA patients.

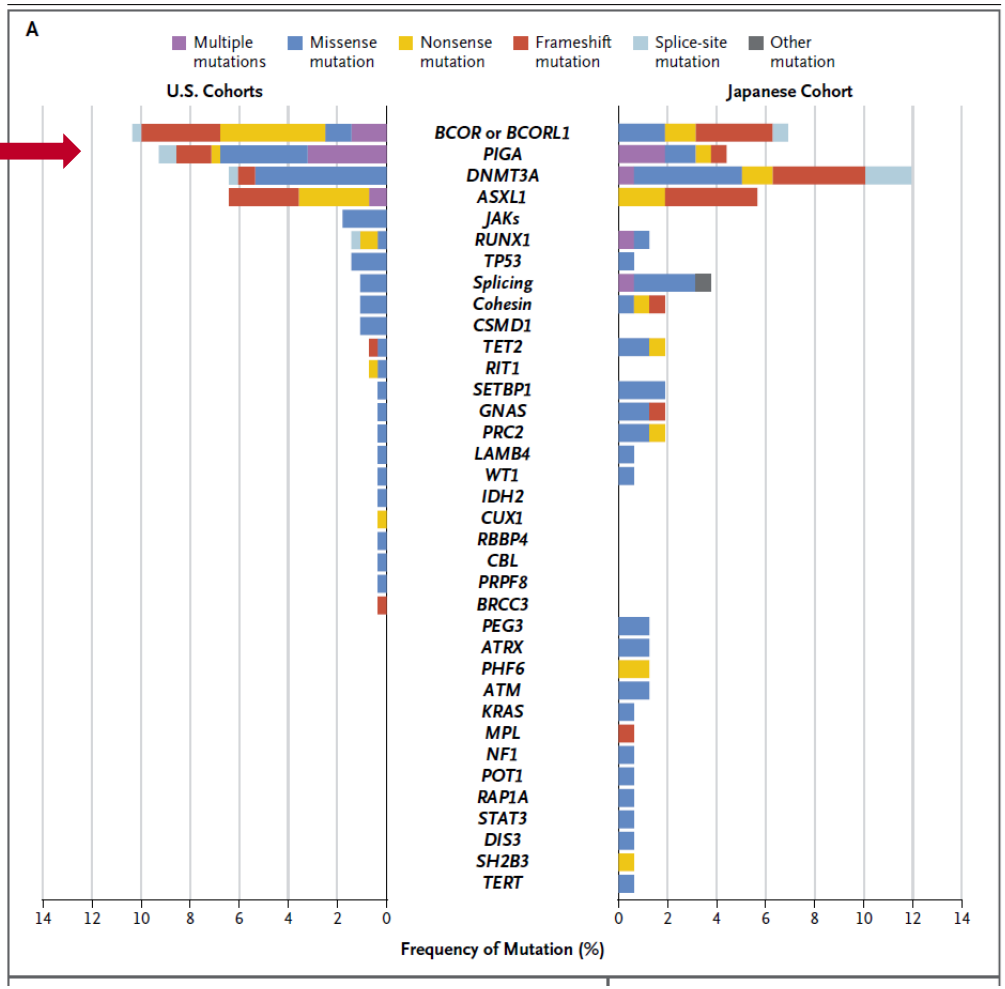
D	Sex	Age (years)	Gene	Mutation	Family history**	Physical anomalies	IST	Sibling donor	Post-transplant complications	Time from transplant until death (months)	Cause of death
AA3	M	33	*DKC1*	T66A	4 brothers with clinical DC; early cancers in family	Nail dystrophy, hyperpigmented macules	-	+	Colon cancer	21	Colon cancer
AA25	F	1	*MPL*	R102P/W515X	-	-	-	-	-	-	-
AA37	F	7	*MPL*	P394S/P394S	-	-	+	-	Failed to engraft initial cord transplant, engrafted 2nd transplant; BOOP	-	-
AA45	M	9	*DKC1*	c.-142 C>G	-	-	-	+	-	-	-
AA79	M	6	*TP53*	R196Q	-	Facial hyperpigmentation	-	+	-	-	-

**Age at transplant; **family history indicates family history of related phenotype or cancer in first- or second-degree relative. AA, idiopathic acquired aplastic anemia; IST: immunosuppressive therapy; DC: dyskeratosis congenita; BOOP: bronchiolitis obliterans organizing pneumonia. Two of the 98 AA patients were included among the pediatric and adult patients with marrow failure or MDS deemed to have idiopathic disease after laboratory and clinically-directed genetic evaluation in the report by Zhang* et al.*" (AA92/FH-50 and AA87/FH-13).*

Keel, Haematologica 2016

Acquired Aplastic Anemia

Somatic mutations and clonal hematopoiesis – link to immune pathology



Yoshizato, NEJM, 2015

Acquired Aplastic Anemia

Clonal hematopoiesis with CNN 6pLOH

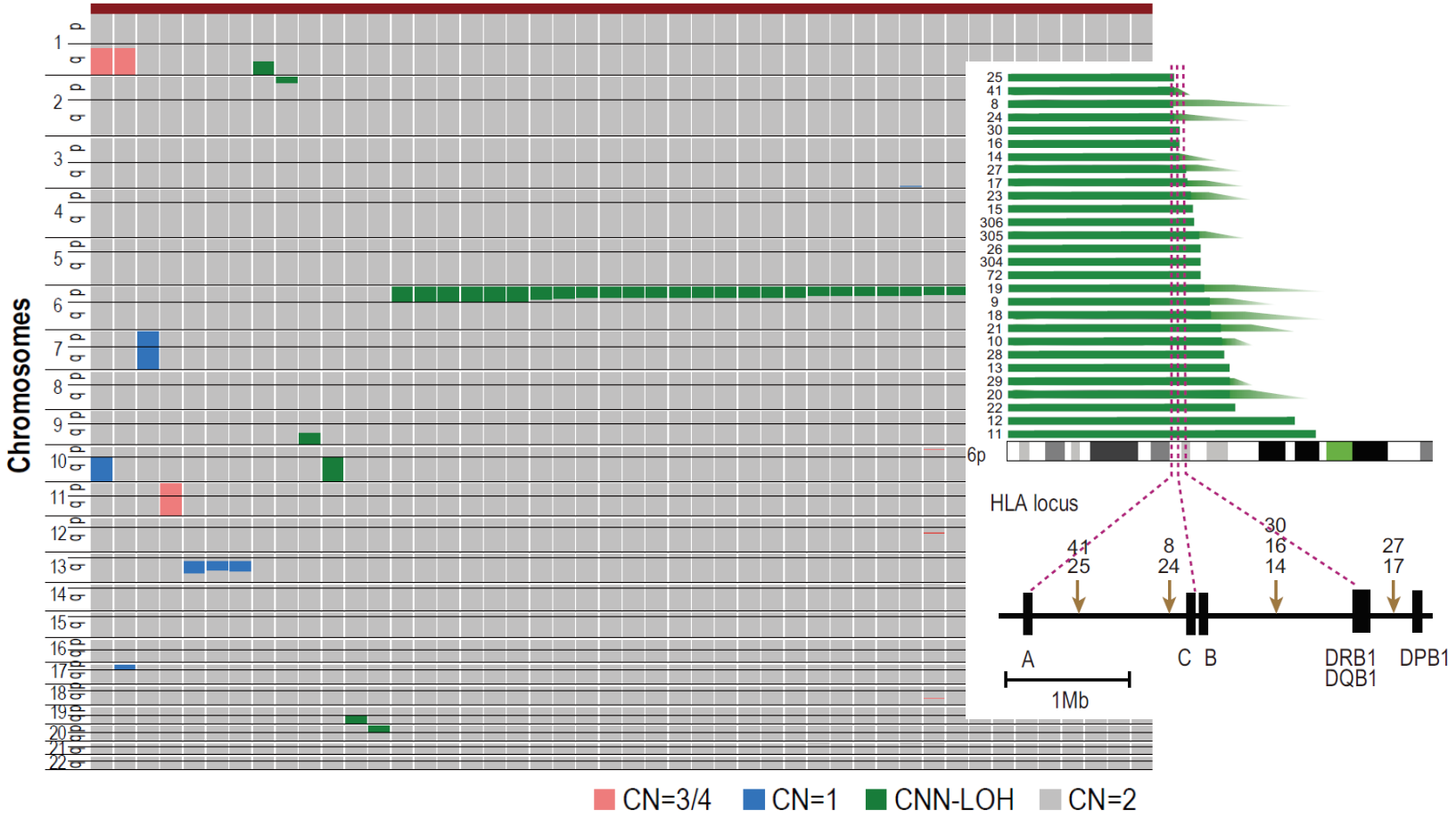


Figure 1. Copy number changes and allelic imbalances in 46 of the 306 AA cases. The copy number changes and allelic imbalances (or CNN-LOHs) in each case are summarized in the chromosomal order vertically for 46 AA cases with copy number abnormalities. Gains and losses, as well as CNN-LOHs, are shown in the indicated colors.

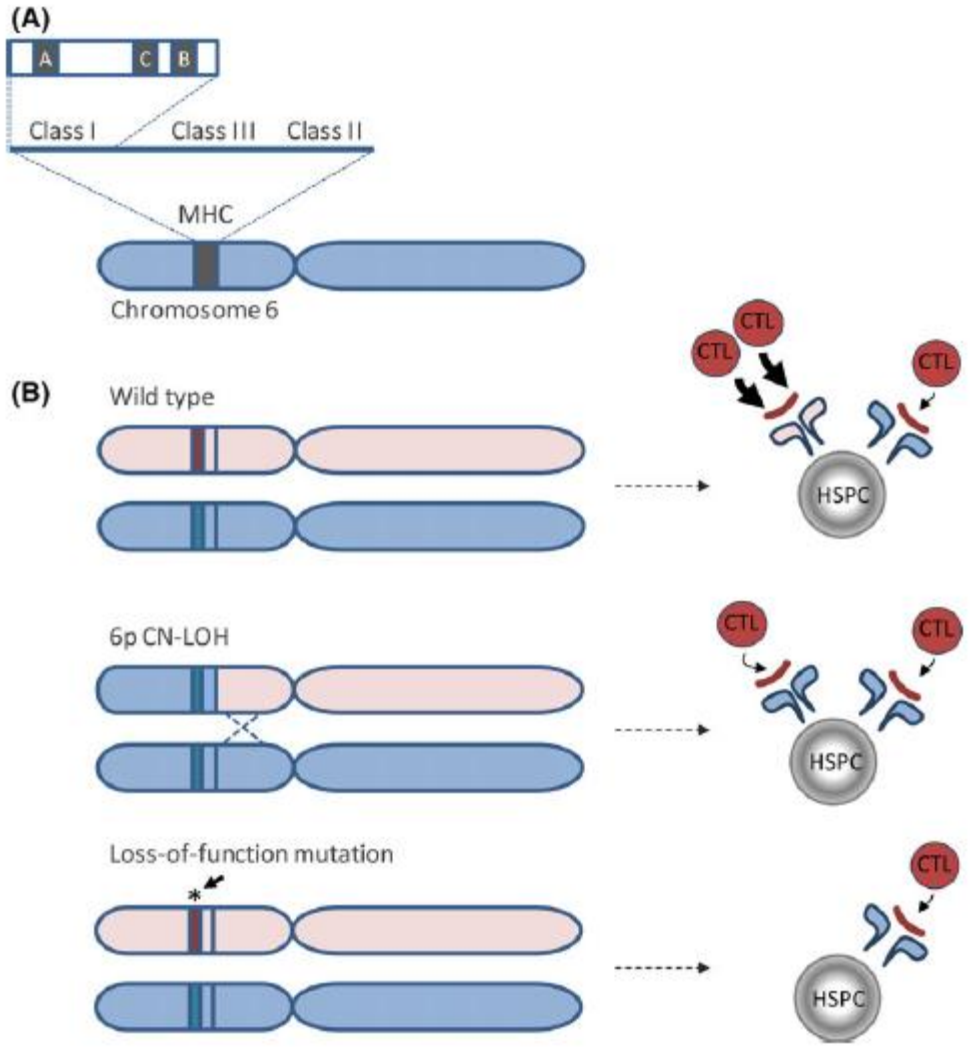
Katagiri, Blood 2011

Acquired Aplastic Anemia

Somatic HLA mutations

Key Points

- Somatic HLA class I gene mutations are frequent in aAA and define HLA class I restricted autoimmunity in aAA.
- HLA alleles targeted by inactivating mutations are overrepresented in aAA and correlate with poor therapy response and clonal evolution.



Babushok, Blood Adv 2017, Stanley BJH 2017

Acquired Aplastic Anemia

Somatic HLA mutations

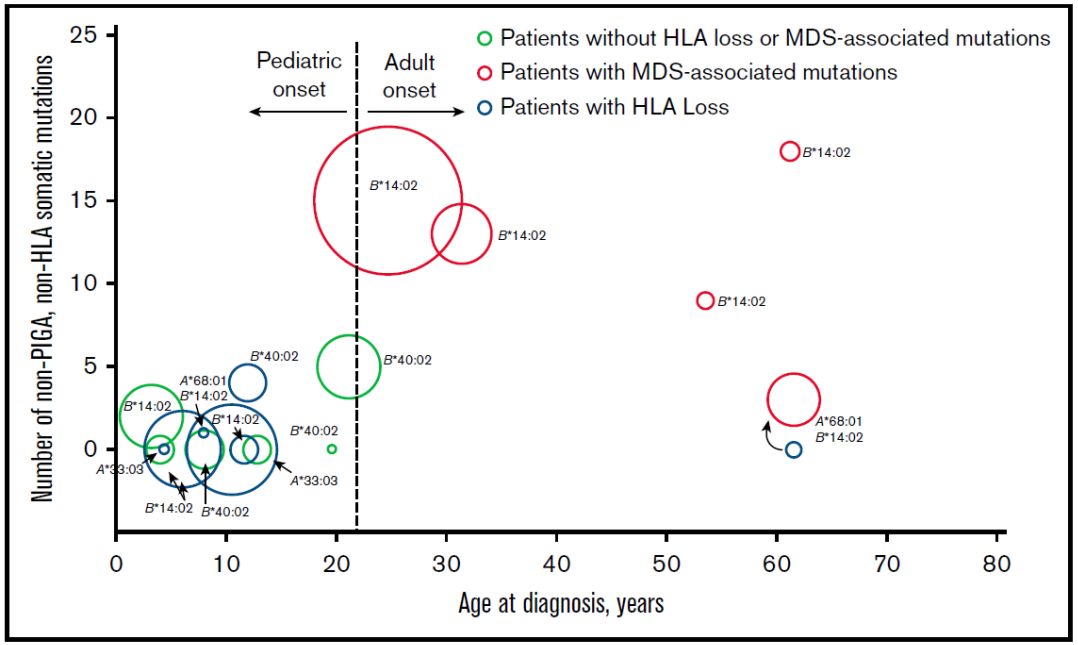


Figure 2. Age-related dichotomy of clonal hematopoiesis in aAA, manifested as frequent HLA loss in younger patients and as MDS-associated somatic mutations in older patients. A bubble scatter plot of somatic mutation analysis of the 17 patients with 1 of the 4 HLA risk alleles (*HLA-A**33:03, *HLA-A**68:01, *HLA-B**14:02, or *HLA-B**40:02); each patient is represented by a circle. The number of somatic nonsynonymous coding and regulatory region mutations identified by comparative WES is plotted on the *y*-axis, with the corresponding patient's age at aAA diagnosis plotted on the *x*-axis; duration of disease at sequencing is depicted as the area of each point. PNH clones are not shown. Patients with HLA loss, as determined by the presence of either 6p CN-LOH or inactivating mutations in HLA alleles, are shown in blue. Patients with MDS-associated somatic mutations are shown in red. One patient had a transient clone of whole chromosome 6 CN-LOH early in disease course (blue circle accompanied by curved black arrow at the bottom right), which disappeared and was replaced by a dominant clone with MDS-associated mutations (red circle, indicated by a curved black arrow at the bottom right). HLA risk alleles are indicated next to each of the points; *A*, *HLA-A*; *B*, *HLA-B*.

Babushok, Blood Adv 2017

Acquired Aplastic Anemia

Clonal Hematopoiesis in AA

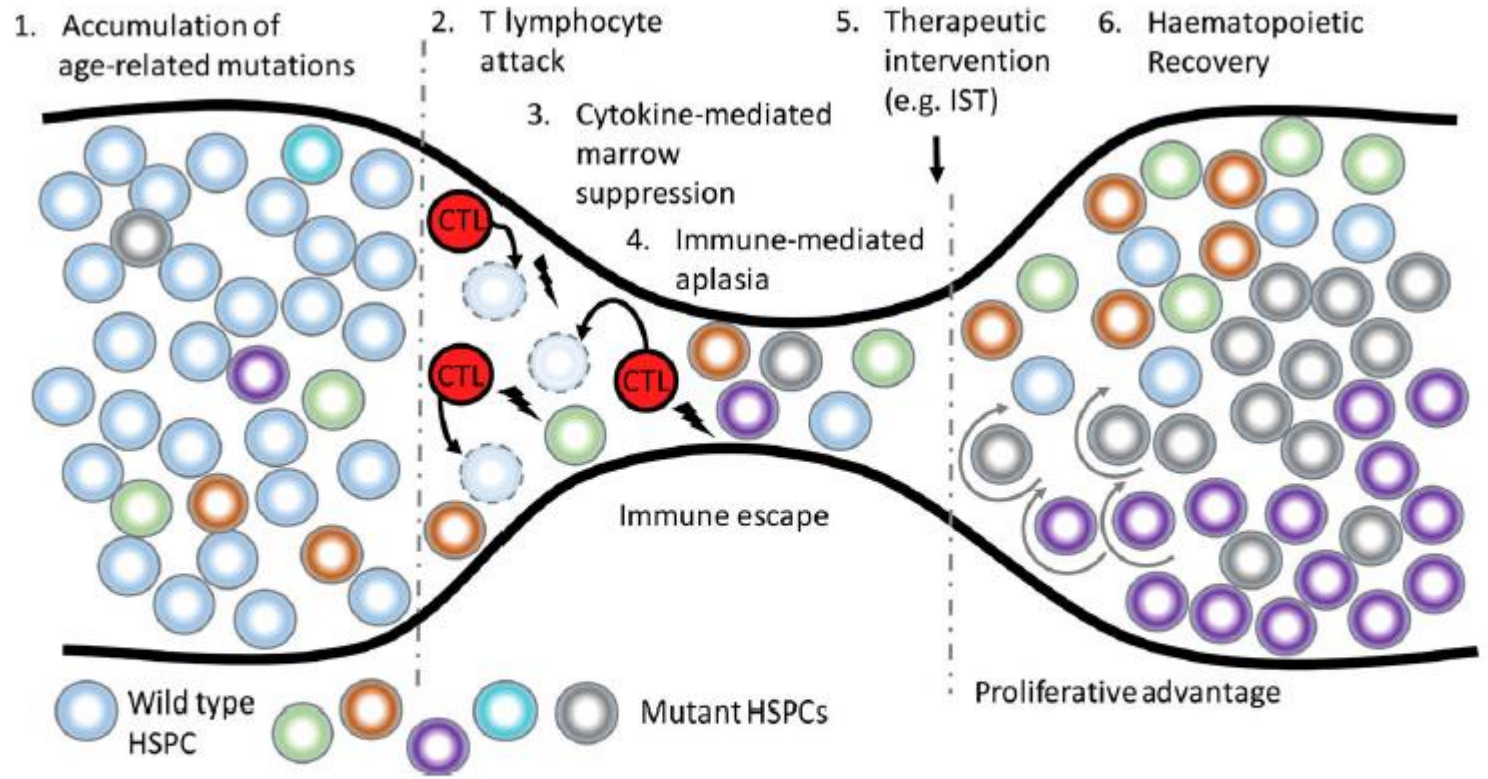


Fig 1. Clonal haematopoiesis in aplastic anaemia. In aplastic anaemia (AA), cytotoxic T lymphocyte (CTL)-mediated attack on the haematopoietic stem and progenitor cells (HSPCs) leads to an evolutionary "bottleneck". Pre-existing age-related genetic mutations (1), depicted as circles of different colors, serve as a substrate for clonal selection. Cells that are either less immunogenic or more resistant to CTL-mediated apoptosis (2) or cytokine-mediated marrow suppression (3) have a relative growth advantage in the setting of autoimmunity, leading to immune escape of mutant HSPCs. During haematopoietic recovery (6), genetic events that increase HSPC replicative potential (depicted by circular arrows) lead to expansion of mutant clones. IST, immunosuppressive therapy.

Stanley, BJH 2017

Acquired Aplastic Anemia in children

What is aquired aplastic anemia ?

How A.L.G. acts is unknown, but our findings accord with the hypothesis that, in a substantial proportion of cases of aplastic anaemia, unspecified autoimmune reactions block the development of residual stem cells.

Speck, Lancet 1977

Aquired aplastic Anemia

An immune mediated disease: Clinical evidence

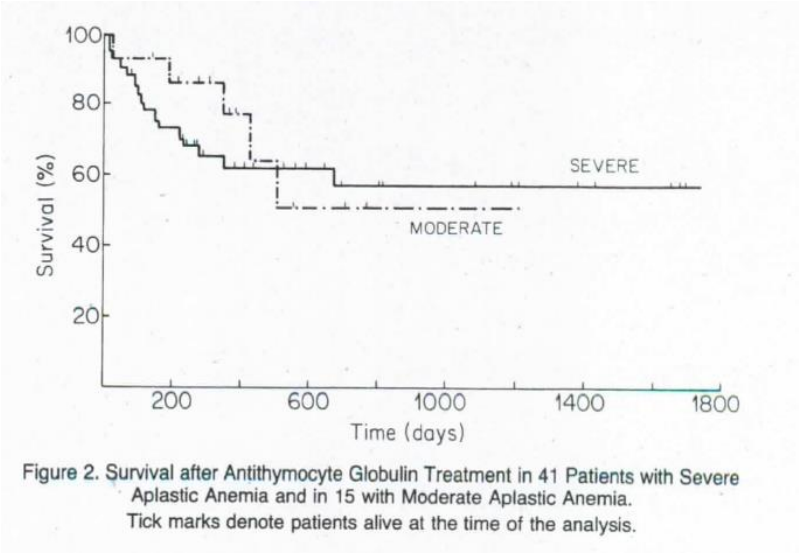


Figure 2. Survival after Antithymocyte Globulin Treatment in 41 Patients with Severe Aplastic Anemia and in 15 with Moderate Aplastic Anemia.
Tick marks denote patients alive at the time of the analysis.

Champlin, NEJM 1983

Table 2. Response to Treatment with Antilymphocyte Globulin, Methylprednisolone, and Cyclosporine in Patients Who Could Be Evaluated 3, 6, and 12 Months after Initial Treatment.*

Time of Evaluation	Control Group		Cyclosporine Group		P Value†
	No. of Patients	% of Total in Remission	No. of Patients	% of Total in Remission	
3 Months	41	39	43	65	<0.03
Complete remission	5		4		
Partial remission	11		24		
No remission	25		15		
Alive	20		11		
Dead	5		4		
6 Months	35	46	39	70	<0.05
Complete remission	6		11		
Partial remission	13		19		
No remission	22		13		
Alive	13		8		
Dead	9		5		

Frickhofen, NEJM 1991

Risk of Relapse	38%
PNH/Clonal evolution/malignancy	25%
CSA dependence (CSA Group)	26%

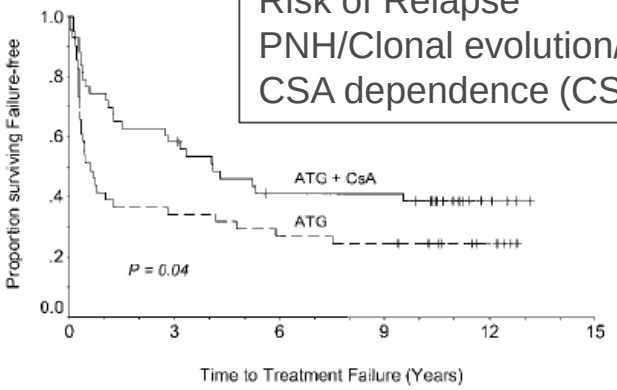


Figure 3. Failure-free survival. Patients treated with CsA (ATG + CsA) had longer failure-free survival times than patients treated without CsA (ATG).

Frickhofen, Blood 2003

Immunsupressive Therapy in Children with AA

Excellent OS despite considerable incidence of NR, relapse and clonal evolution

Table V. Paediatric studies of immune suppressive therapy (IST) with horse ATG and ciclosporin.

Study	Number of patients	Treatment (IST)	Study period	Follow up (years)	Overall response	Overall survival	Relapse rate	Clonal evolution
Fuhrer *et al* (2005)	146	ATG, CSA, GCSF	1993–2001	4·1 (median)	CR 69% VSAA, CR 44% SAA	93% VSAA, 81% SAA	13% VSAA, 14% SAA	NR
Kamio *et al* (2011)	441	ATG, CSA, ±Dan ±GCSF	1992–2007	10	59·9%	82% VSAA, 82% SAA, 98% NSAA	11·9%	NR
Saracco *et al* (2008)	42	ATG, CSA± GCSF	1991–1999	10	71%	83%	16%	15%
Scheinberg *et al* (2008)	77	ATG, CSA, ±MMF, ±sirolimus	1989–2006	10	77%	80%	33%	8·5%

ATG, Anti-Thymocyte Globulin; CSA, ciclosporin; Dan, Danazol; GCSF, granulocyte colony-stimulating factor; MMF, mycophenolate mofetil; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia; NSAA, non severe aplastic anaemia; NR, not reported; CR, Complete remission rate.

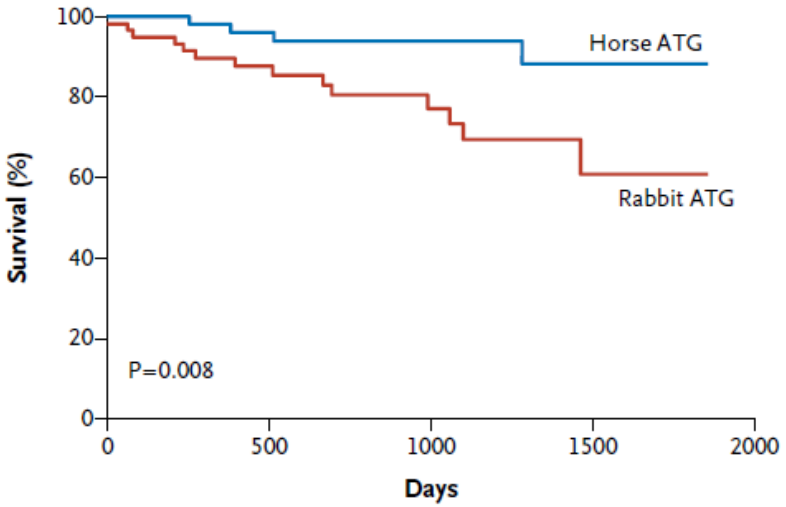
Samarasinghe, BJH 2012

Horse versus Rabbit ATG in SAA

hATG is asociated with a better response to IST and better survival

Table 2. Hematologic Response at 3 and 6 Months to Horse ATG and Rabbit ATG.

Response	Horse ATG (N=60)	95% CI	Rabbit ATG (N=60)	95% CI	P Value
	no. (%)		*no. (%)*		
At 3 mo	37 (62)	49–74	20 (33)	21–46	0.002
At 6 mo	41 (68)	56–80	22 (37)	24–49	<0.001



Scheinberg, NEJM 2011

Horse versus Rabbit ATG in SAA

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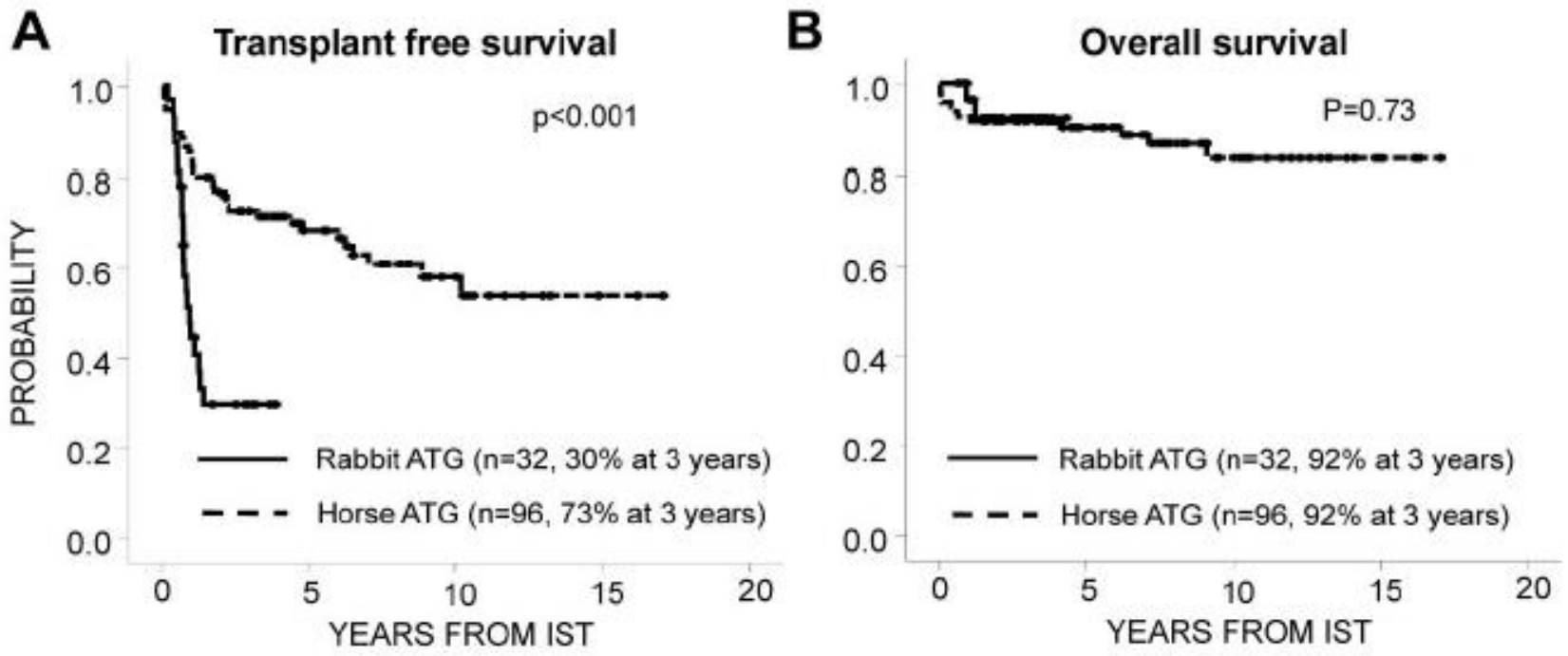
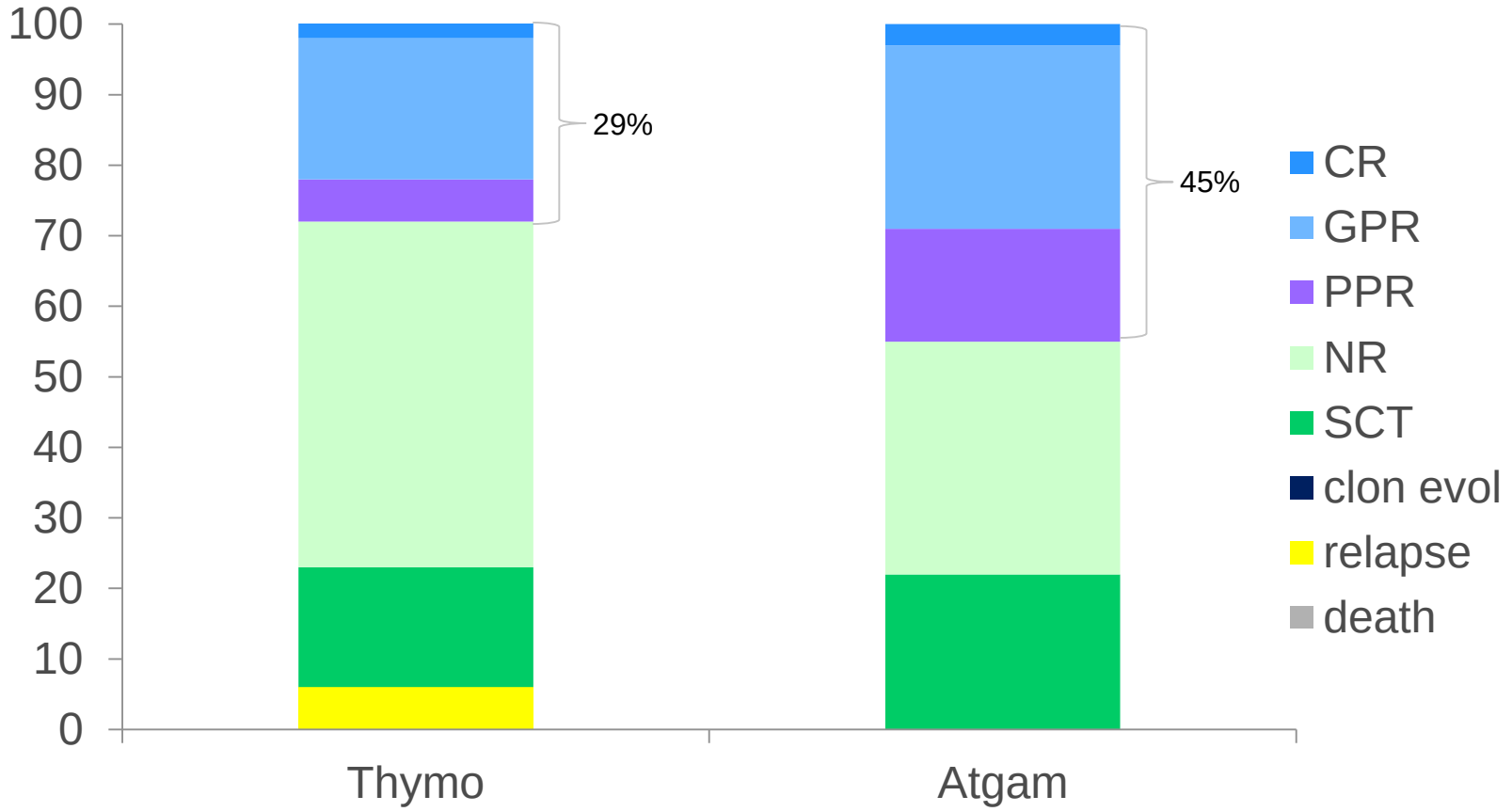


Yoshimi, Blood 2013

EWOG-SAA 2010: IST

Response to IST d180: Thymo (n=35) vs ATGAM (n=69)



Immunosuppressive treatment for aplastic anemia: are we hitting the ceiling?

Jakob R. Passweg[1] and André Tichelli[2]

hATG, CSA and MMF

Table II. Overall response.

Time/response	CR (%)	PR (%)	Total response (%)
3 months	14 (14)	44 (43)	58 (56) **60%**
6 months	16 (16)	48 (46)	64 (62) **61%**

CR, complete response; PR, partial response.

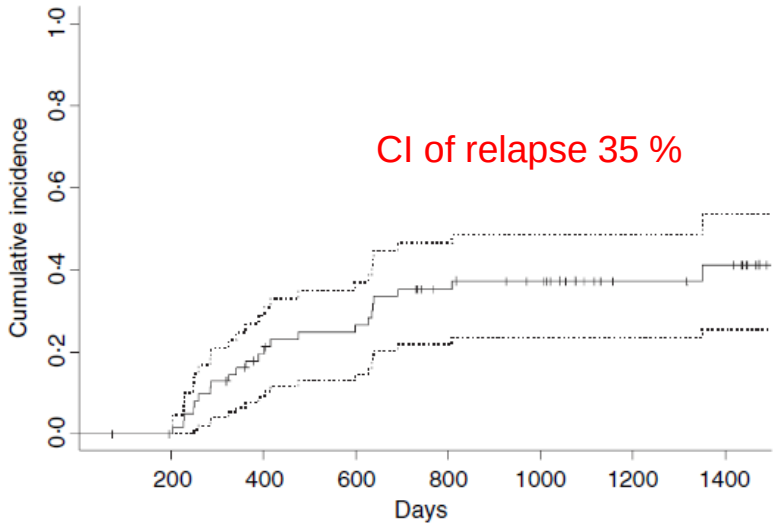


Fig 1. Cumulative incidence of relapses (from day 0 to 1500) among responders (solid line) with 95% confidence intervals (dotted lines).

hATG, CSA ± sirolimus

Table 3. Response to the immunosuppressive regimens.

	3 months		6 months		Total response
	CR (%)	PR (%)	CR (%)	PR (%)	CR + PR (%)
h-ATG/CsA	3 (7)	21 (50)	5 (12)	21 (50)	26 (62%)
h-ATG/CsA/sirolimus	0	13 (37)	0	18 (51)	18 (51%)

Rosenfeld NEJM 2003
Scheinberg, BJH 2006
Scheinberg Haematologica 2009

IST in SAA

Predictive Markers for Repsonse to IST

- Disease Severity
- Age
- Pre-treatment reticulocyte count
- Pre-treatment lymphocyte count
- Interval from diagnosis to treatment
- Skewing of the Vß repertoire
- Presence of PNH clone at diagnosis
- Telomere length

- Score of PNH+/TL not shortened

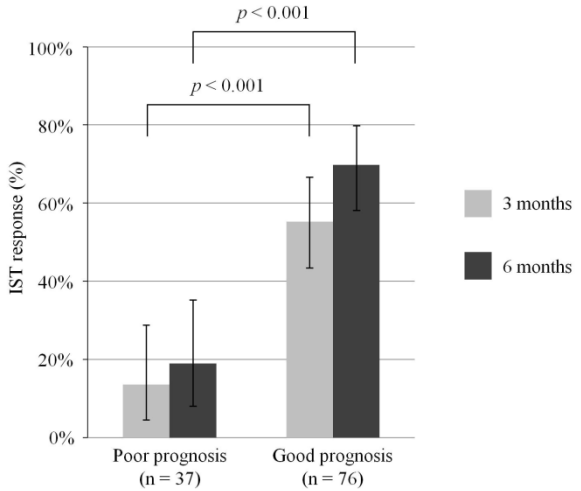


Figure 2. Response rates of immunosuppressive therapy (IST) at 3 and 6 months according to predicting stratification.

No factor with sufficient and reliable prognostic power to allow stratification.

Führer, Blood 2005
Scheinberg, J Pediatrics 2008
Yoshida, Haematologica 2011
Sugimori, Blood 2006
Maciejewski, BJH 2001
Schuster, BJC 2011
Narita, Haematologica 2015

Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

Matthew J. Olnes, M.D., Ph.D., Phillip Scheinberg, M.D., Katherine R. Calvo, M.D., Ronan Desmond, M.D., Yong Tang, M.D., Ph.D., Bogdan Dumitriu, M.D., Ankur R. Parikh, M.D., Susan Soto, B.S.N., Angelique Biancotto, Ph.D., Xingmin Feng, M.D., Ph.D., Jay Lozier, M.D., Ph.D., Colin O. Wu, Ph.D., Neal S. Young, M.D., and Cynthia E. Dunbar, M.D.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Patients (N = 26)
Age — yr	
Median	44
Range	18–77
Race or ethnic group — no. (%)†	
White	12 (46)
Black	7 (27)
Asian	1 (4)
Hispanic	6 (23)
Male sex — no. (%)	14 (54)
Time since diagnosis — mo	
Median	26
Range	13–138
Time since last intensive IST — mo	
Median	14
Range	6–117
Prior courses of intensive IST — no.	
Median	2
Range	1–4
Response to prior intensive IST — no. (%)‡	
Primary refractory	23 (88)
Relapsed refractory	3 (12)

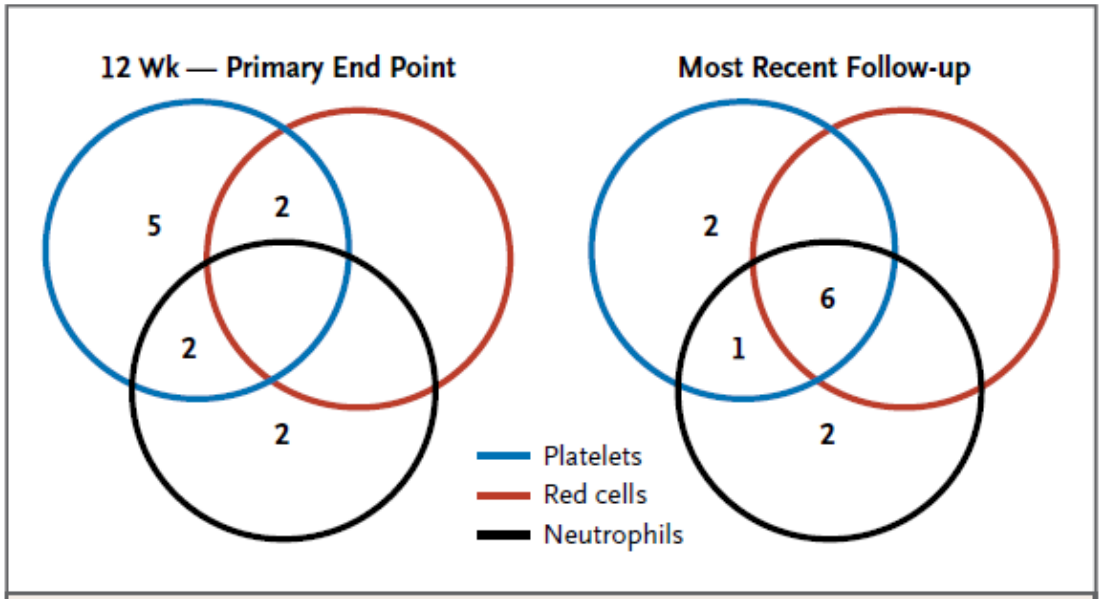


Figure 1. Lineage Characteristics of Responses to Eltrombopag.

The Venn diagrams show the numbers of patients with unilineage, bilineage, and trilineage hematologic responses. The numbers of patients with a response and their response pattern at 12 weeks are shown on the left. The numbers of patients who met the response criteria at the most recent follow-up assessment are shown on the right.

NEJM, 2012

Eltrombopag in SAA

Clinical Trials

Eltrombopag Added to Standard Immunosuppression in Treatment-Naive Severe Aplastic Anemia (NCT01623167)

Sponsor: NIH

Phase 1/2 study to test the safety and effectiveness of adding eltrombopag to standard immunosuppressive therapy for severe aplastic anemia.

Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia

Cohort and Response	Rate at 3 Mo	Rate at 6 Mo	P Value
Cohort 1			
No. of patients	30	30	
Response — no. (% [95% CI])			
Overall response	23 (77 [61–93])	24 (80 [65–95])	
Partial response	18 (60 [41–79])	14 (47 [28–66])	
Complete response	5 (17 [3–31])	10 (33 [15–31])	0.01
Cohort 2			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	24 (77 [62–93])	27 (87 [75–100])	
Partial response	16 (52 [33–70])	19 (61 [43–79])	
Complete response	8 (26 [9–42])	8 (26 [9–42])	0.06
Cohort 3			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	27 (87 [75–100])	29 (94 [84–103])	
Partial response	12 (39 [21–57])	11 (35 [18–53])	
Complete response	15 (48 [30–67])	18 (58 [40–76])	<0.001
All cohorts			
No. of patients	92	92	
Response — no. (% [95% CI])			
Overall response	74 (80 [72–89])	80 (87 [80–94])	<0.001†
Partial response	46 (50 [40–60])	44 (48 [37–58])	
Complete response	28 (30 [21–40])	36 (39 [29–49])	<0.001

Townsley, NEJM 2017

Eltrombopag in SAA

Clinical Trials

Eltrombopag Added to Standard Immunosuppression in Treatment-Naive Severe Aplastic Anemia (NCT01623167)

Sponsor: NIH

Phase 1/2 study to test the safety and effectiveness of adding eltrombopag to standard immunosuppressive therapy for severe aplastic anemia.

RACE: hATG+CsA vs hATG+CsA+Eltrombopag for SAA

Sponsor: EBMT

A Prospective Randomized Multicenter Study Comparing Horse Antithymocyte Globuline (hATG) + Cyclosporine A (CsA) With or Without Eltrombopag as Front-line Therapy for Severe Aplastic Anemia Patients

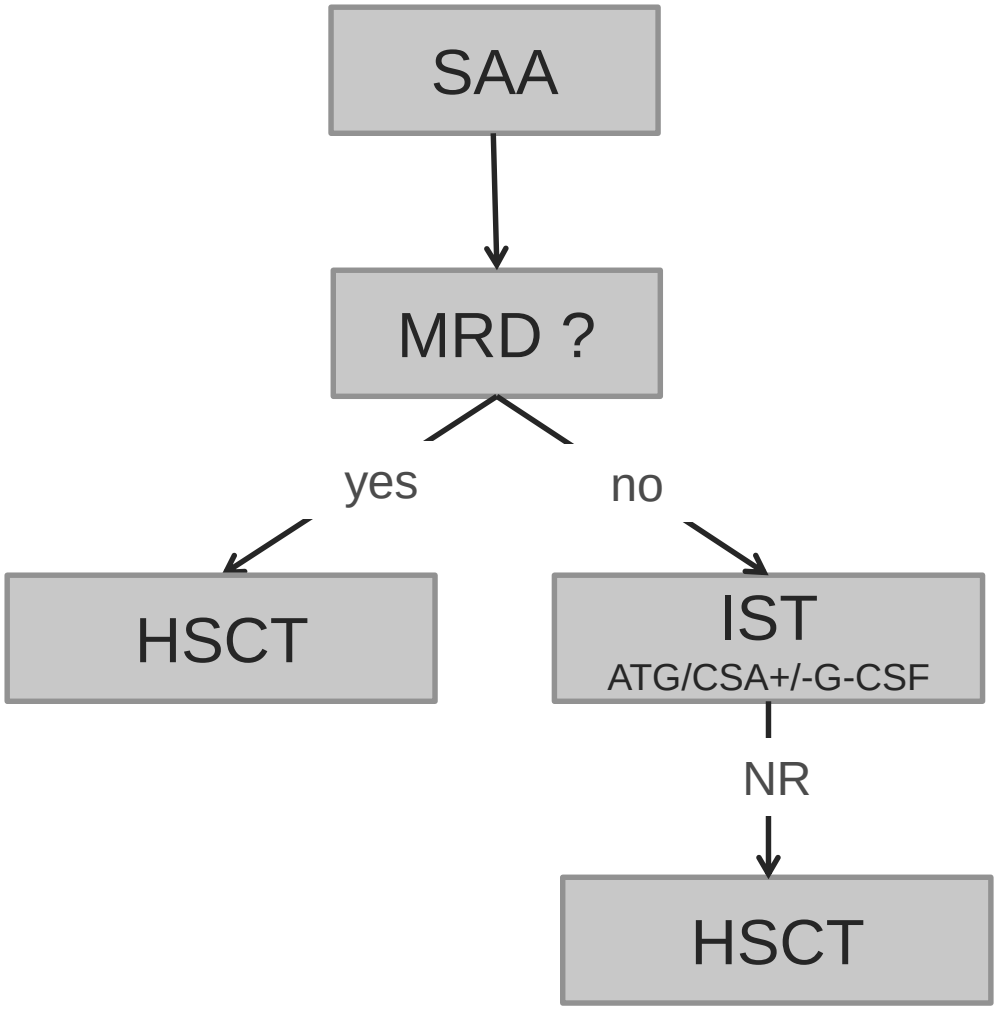
Eltrombopag in addition to standard IST (CETB115E2201)

Sponsor: Novartis

A phase II, open-label, non-controlled, intra-patient dose-escalation study to characterize the pharmacokinetics after oral administration of eltrombopag in refractory, relapsed/recurrent or treatment naïve pediatric patients with severe aplastic anemia

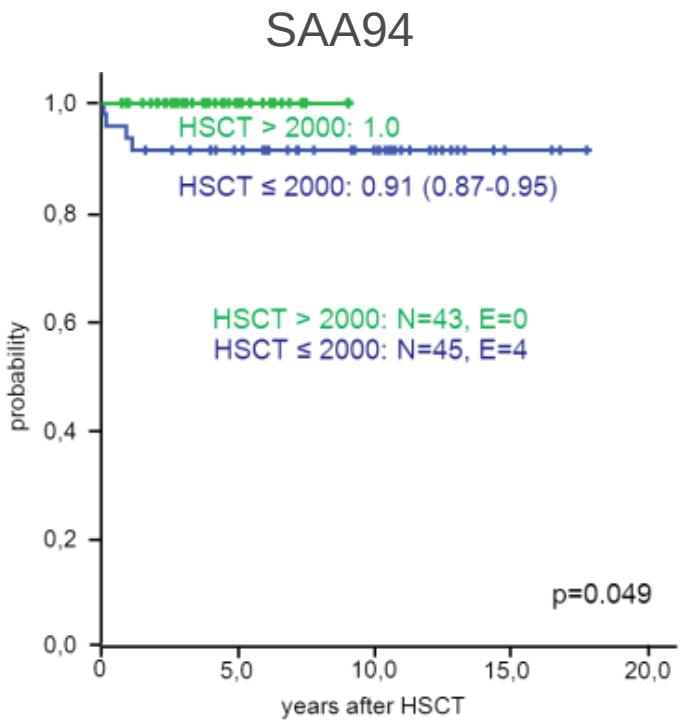
Acquired Aplastic Anemia

Traditional Treatment Algorithm for Children and Adolescents



Acquired Aplastic Anemia in Children

Overall Survival following MSD-HSCT and IST



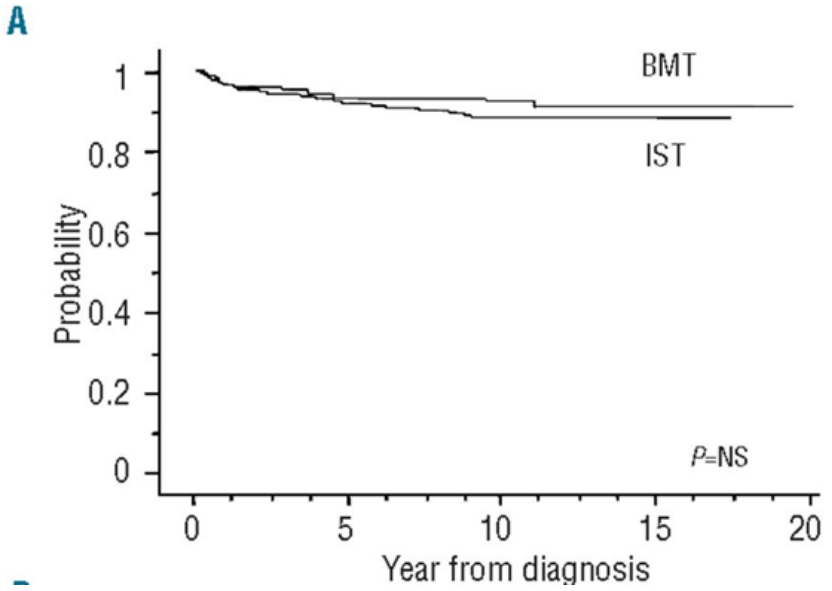


Fig.3: Probability of overall survival according to the year of HSCT.

Med. age at Dx:	10.4 (1.9-16.5) years
Severity:	VSAA 53, SAA 29, NSAA 6
Prep. Regimen:	Cy/ATG
GvHD Prophylaxis:	CSA/MTX

Strahm, BMT, EBMT abstract 2013

N=213	
Med. age at Dx:	10 (0-16) years
Prep. Regimen:	Cy+/-ATG+/-TBI, Flu/Cy+/-ATG+/-TBI
GvHD Prophylaxis:	CSA/MTX (174)

Yoshida, Haematologica 2014

Review of major series involving UD Allo-HSCT

Series	N	Allo-HSCT period	OS	Impact of age	Impact of time from diagnosis to Allo-HSCT	Impact of HLA matching
Deeg *et al.*[16]	50	1994-1999	58%	20 years	1 year and 3 years	No
Kojima *et al.*[17]	154	1993-2000	56%	20 years	1 year and 3 years	Yes
Bacigalupo *et al.*[3]	87	1998-2004 2005-2008	68% 83%	13 years	2 years	No
Marsh *et al.*[5]	29	1999-2009	83%	*	*	N/A
Maury *et al.*[4]	37 52	1989-1999 2000-2004	29% 50%	17 years	1 year	Yes
Viollier *et al.*[18]	35 62	1990-1997 1998-2005	32% 57%	*	*	Yes
Devillier *et al.*	46 93	2000-2005 2006-2012	52% 74%	30 years	1 year	Yes

From: Devillier et al. Unrelated alternative donor transplantation for severe acquired aplastic anemia: a study from the French Society of Bone Marrow Transplantation and Cell Therapies and the Severe Aplastic Anemia Working Party of EBMT. Haematologica 2016

Outcome of aplastic anaemia in children. A study by the severe aplastic anaemia and paediatric disease working parties of the European group blood and bone marrow transplant

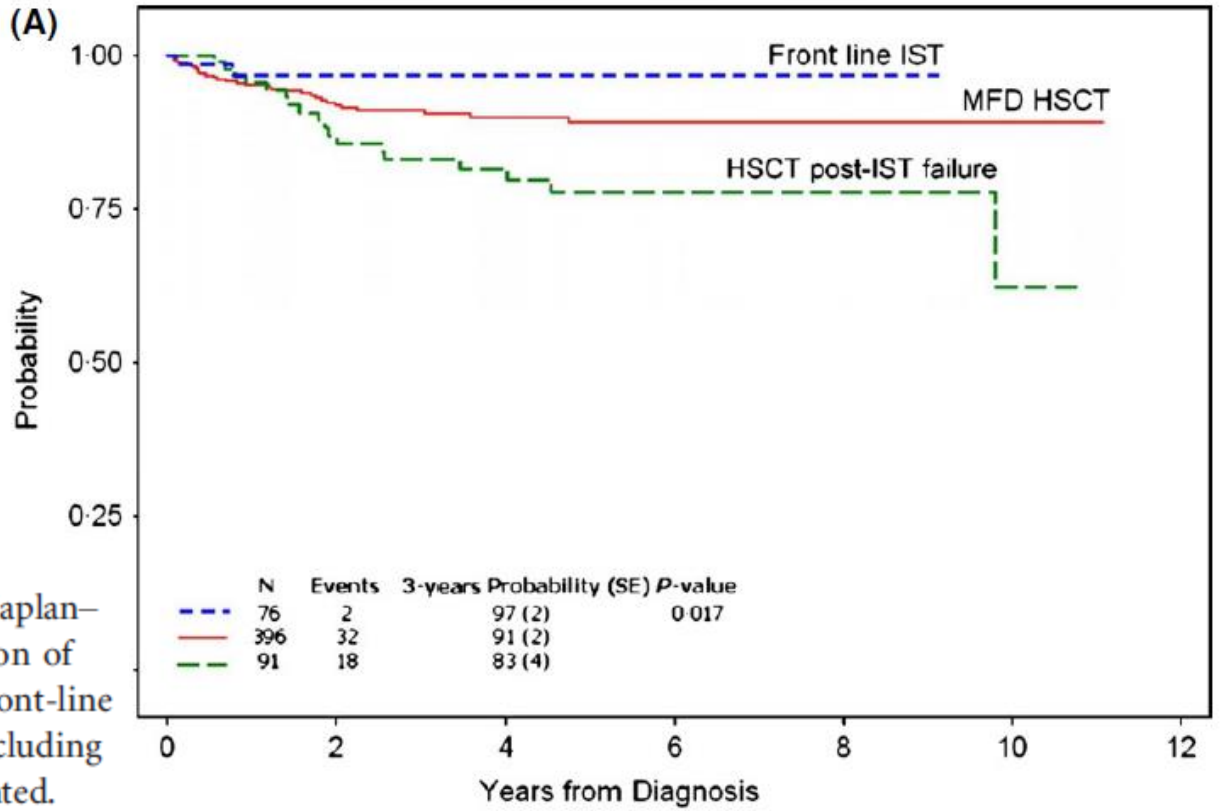
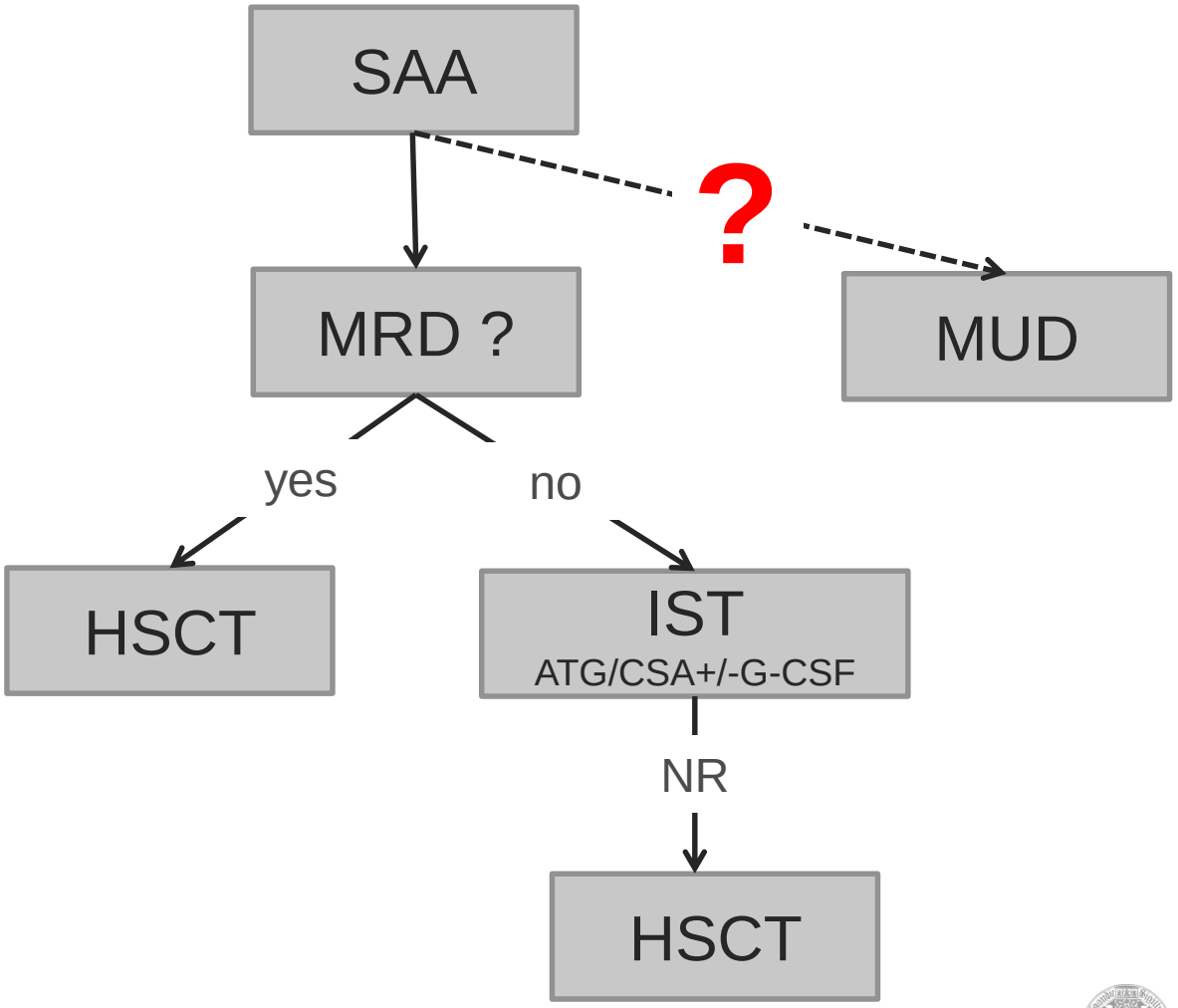


Fig 2. (A) Probability of 3-year OS (Kaplan–Meier method) for the whole population of 537 patients stratified by treatment. Front-line IST: patients receiving IST upfront, excluding those who were subsequently transplanted. Subgroup analysis: First-line MFD HSCT vs. Front-line IST: $P = 0{\cdot}21$. First-line MFD HSCT vs. HSCT post- failed IST: $P = 0{\cdot}02$. Front-line IST vs. HSCT post-IST failure: $P = 0{\cdot}047$. (B)

Dufour C, BJH 2015

EWOG-SAA 2010

Stratification of therapy according to donor availability



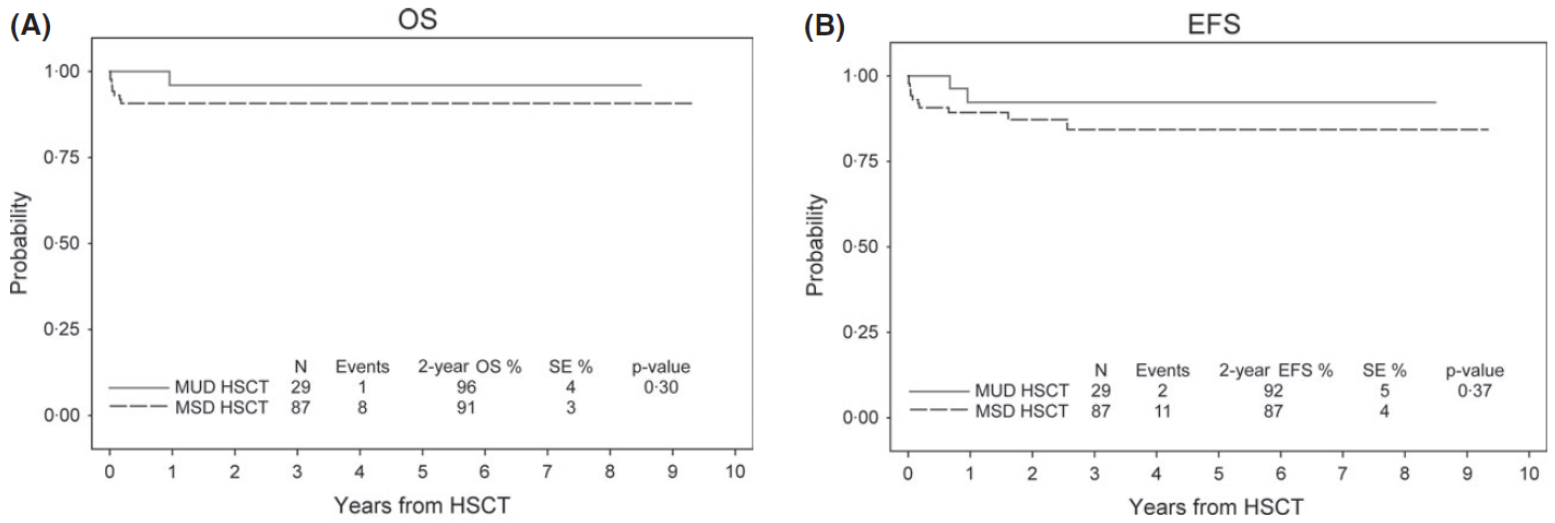
Upfront unrelated HSCT in children with SAA

	Upfront MUD/MMUD HSCT (n=27)
Median age at HSCT (range), years	7.6 (0.6-19.7)
Ethnicity (Caucasian:Other) (n=26)	22 (84.6%):4 (15.4%)
Median year of HSCT (range)	2012 (2005-2013)
Median interval between diagnosis and HSCT (range), months	4 (1-16)
Stem cell source: Bone marrow/PBSC	18 (66.7%):9 (33.3%)
Median CD34 cell dose ($x10^6$/kg) (n=23)	7.00 (2.4-50)
Median In-patient hospital stay (range), days	39 (17-105)
Median time to neutrophil recovery (>0.5$x10^9$/l), days (range)	17.5 (9-29)
Median time to platelet recovery (>50$x10^9$/l), days (range)	18 (10-40)

Outcome :		
	Median FUP	22 months
	pOS at 2.5 yrs	95 %
	pEFS at 2.5 yrs	92 %
	Donor chimerism, median(range)	100 (88-100) %
	aGvHD °III-IV	7.4 %
	cGvHD	22.2 % (limited to skin)

Bathnagar, BMT – EBMT abstract 2014

Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia. A study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT

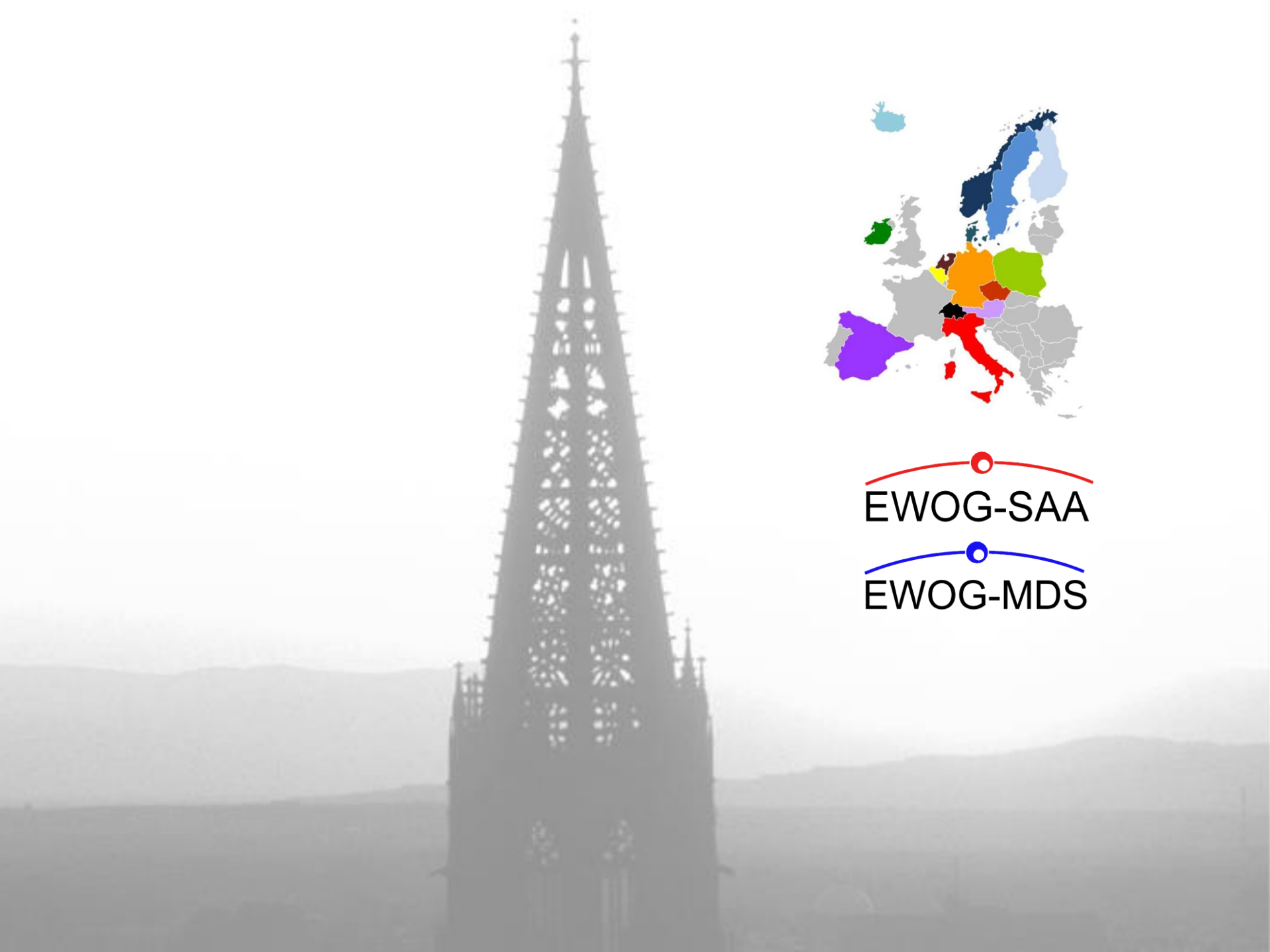


Dufour C, BJH 2015

Acquired Aplastic Anemia in children

Summary and future challenges

- AA is an acquired immune-mediated disease
- Exclusion of IBMF and other differential diagnosis is essential
- Diagnostic tools must be clinically meaningful and should not delay treatment
  - Teleomere length
  - Screening for germline and/or somatic mutations
- Immunosuppressive therapy remains a valuable treatment option
  - no improvement by intensified IS
  - no valuable biomarker for stratification available → TL/PNH?
  - addition of eltrombopag should be studied within clinical trials
- HSCT offers excellent outcome
  - MSD-HSCT is considered standard of care
  - MUD-HSCT is considered standard of care after IST failure
  - role of upfront MUD HSCT should be studied in clinical trials



EWOG-SAA

EWOG-MDS

EWOG-SAA

EWOG-MDS

The EWOG-Community

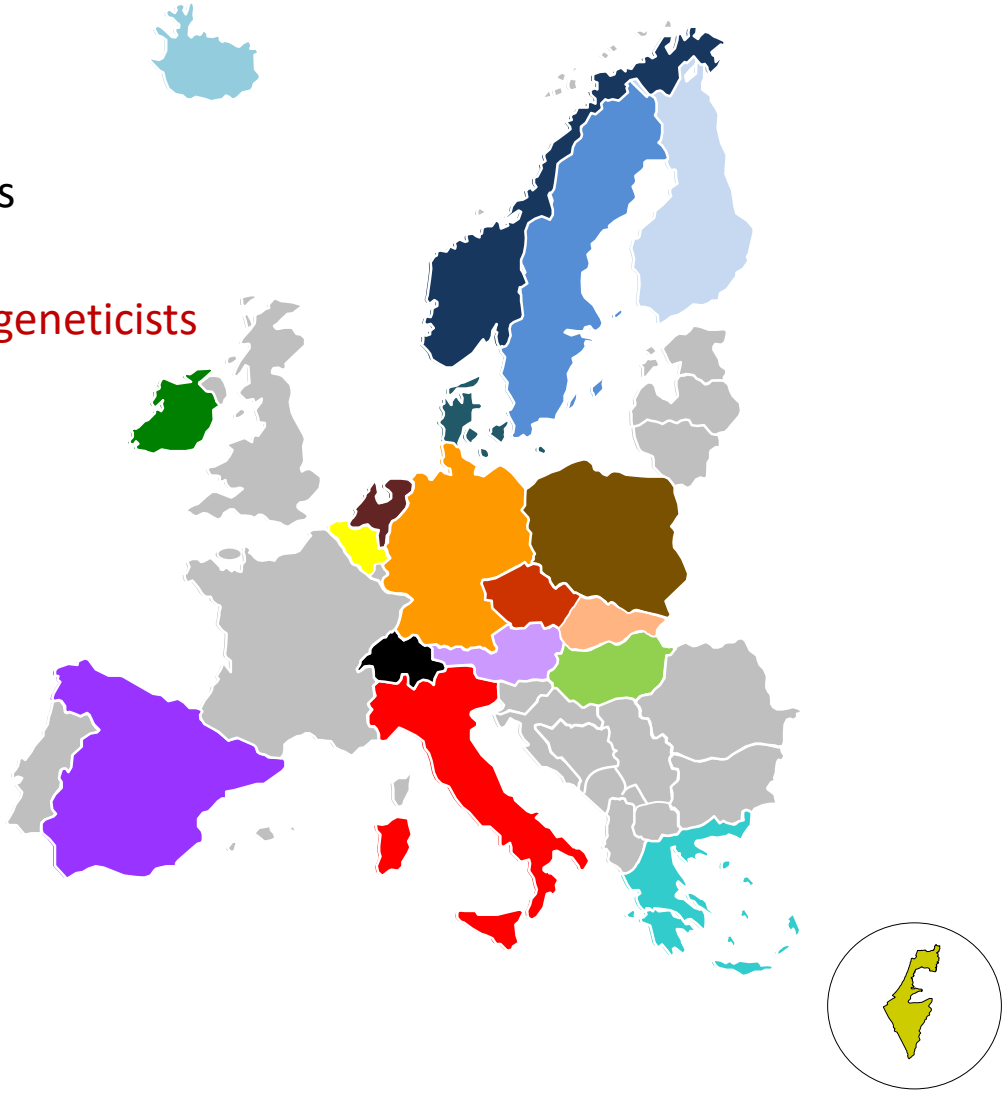
Members

Pediatric Hem/Onc Societies of 18 Nations

Organized by

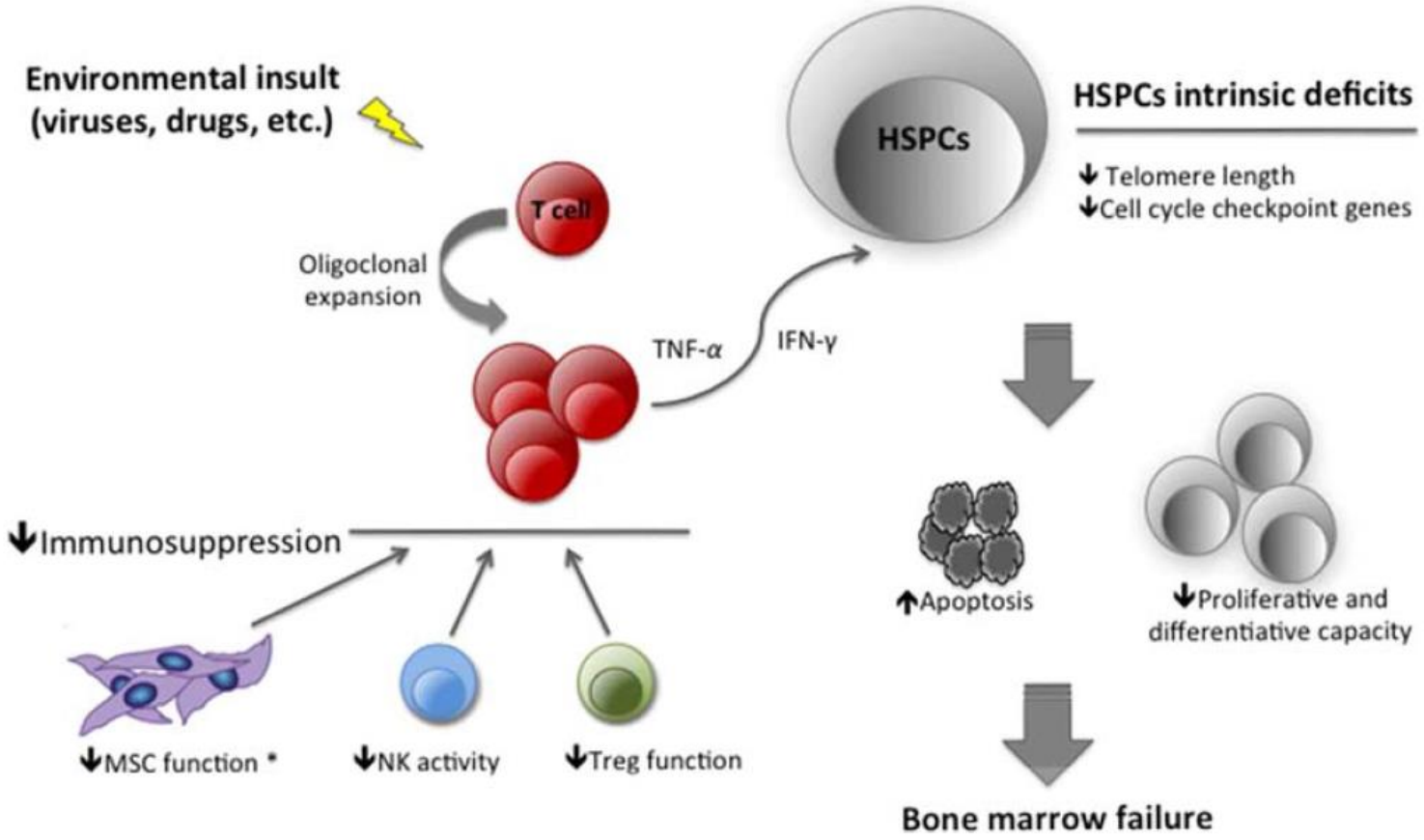
Regional Coordinators, Pathologists, Cytogeneticists

Austria	Belgium
Czech Republic	Denmark
Germany	Greece
Hungary	Island
Israel	Italy
Ireland	Norway
Poland	Slovakia
Spain	Sweden
Switzerland	The Netherlands



Acquired Aplastic Anemia

- An immune-mediated disease: destruction of HSPC



Zeng, Clin & Exp Immunology 2015