

HSCT in inherited bone marrow failure syndrome

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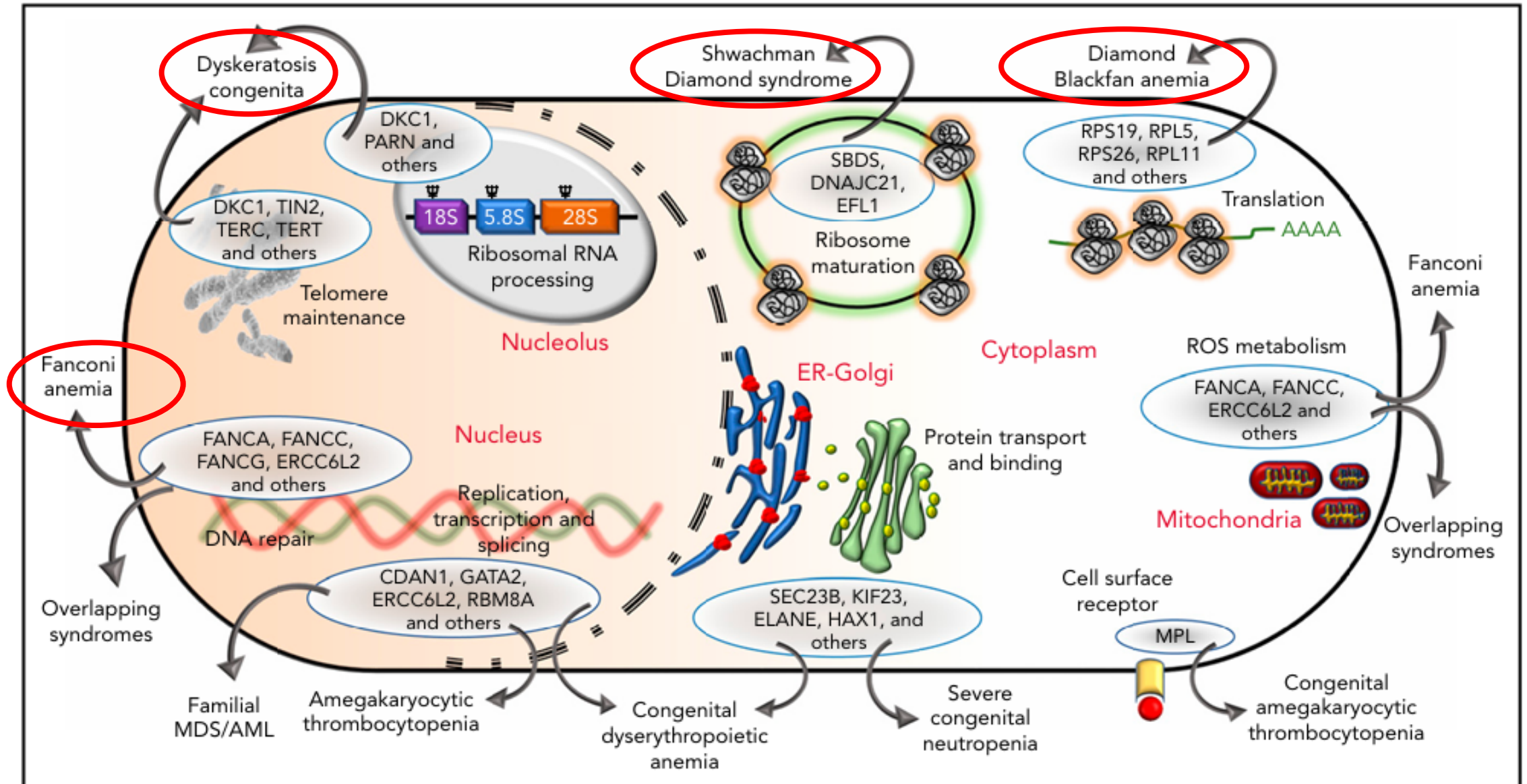
**TSH meeting
17th March 2025**

- Short review of IBMFS
- HSCT in IBMFS
 - Fanconi anemia
 - Dyskeratosis congenita
 - Shwachman-Diamond syndrome
 - Diamond Blackfan anemia
- Special considerations for HSCT in IBMFS

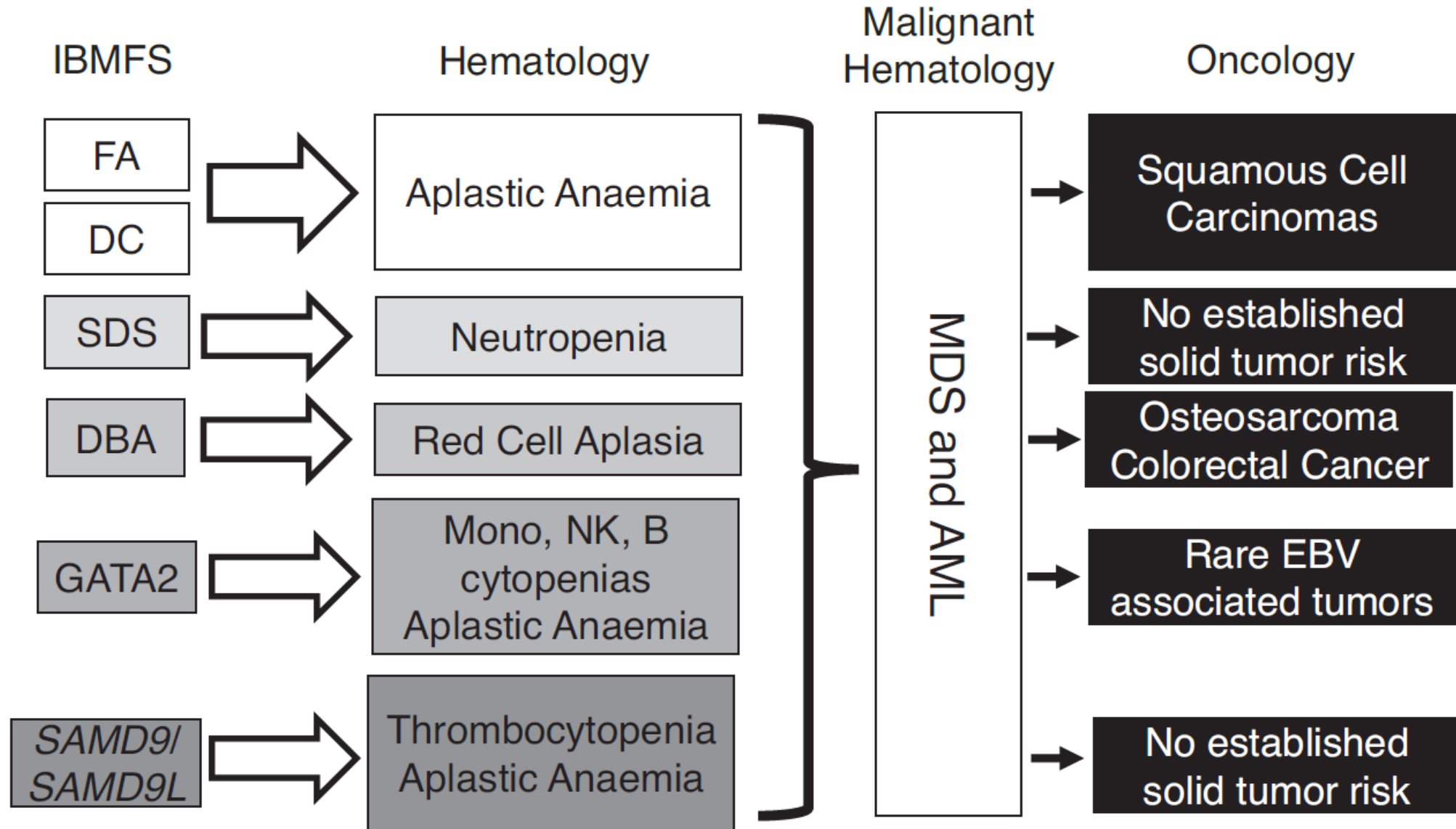
Summary & clinical features of IBMFS

Disease	Affected pathway	No. of known genes	Inheritance	Clinical features
Fanconi anaemia (FA)	DNA damage response	22	AR, XLR(1), AD(1)	•Thumb defects •Short stature •Skin hyperpigmentation •Genitourinary malformations
Dyskeratosis congenita (DC)	Telomere biology	18	XLR, AD, AR, <i>de novo</i> (<i>TINF2</i>)	•Dystrophic nails •Lacey pigmentation •Early grey hair •Leukoplakia •Pulmonary fibrosis
Shwachman Diamond syndrome (SDS)	Ribosome biogenesis	4	AR	•Pancreatic Insufficiency •Skeletal dysplasia •Neutropenia
Diamond Blackfan anaemia (DBA)	Ribosome biogenesis	26	AD, XLR	•Short stature •Thumb defects •Congenital malformations •Red cell aplasia
GATA2 deficiency	Haematopoietic stem and endothelial cell development	1	AD	•Recurrent severe infections- warts, NTM •Pulmonary alveolar proteinosis •Lymphedema •Hearing loss
<i>SAMD9</i> / <i>SAMD9L</i> syndromes	Cell proliferation, endosome fusion	2	AD	•MIRAGE syndrome •Ataxia-pancytopenia syndrome

Genetics & molecular landscape of IBMFS



Hematologic & Oncologic manifestation of IBMFS



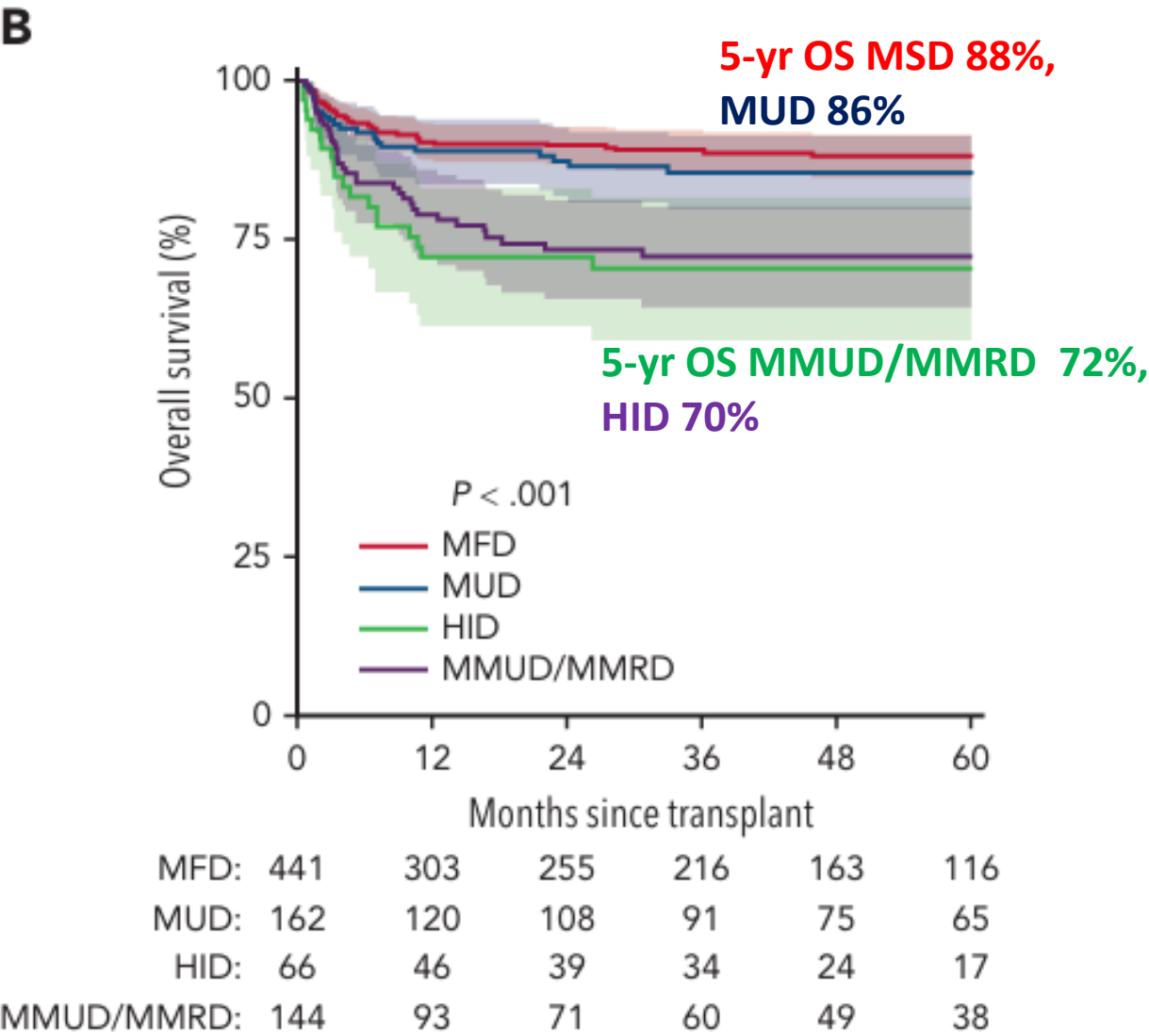
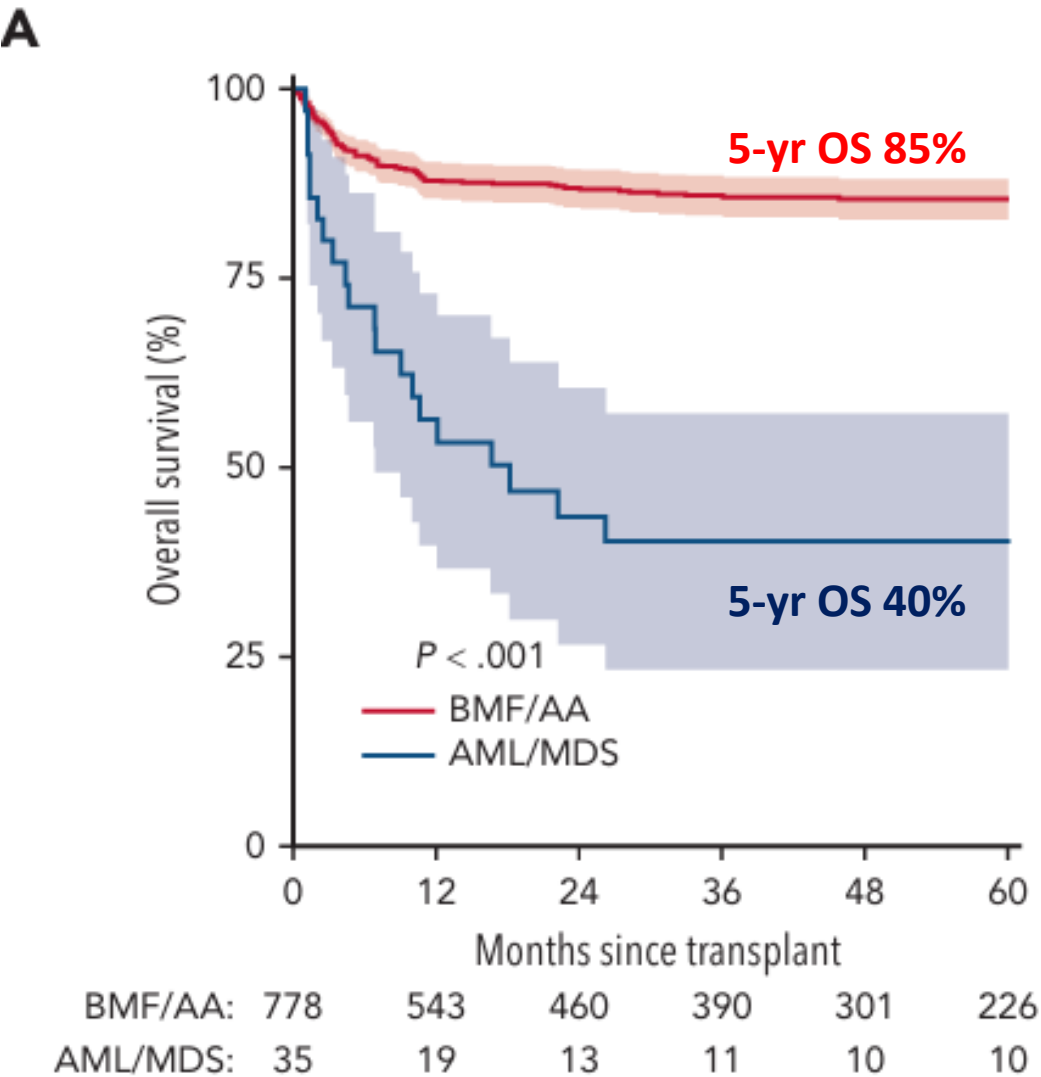
Diagnostic & potential treatment of IBMFS

Disease	Diagnostic tools	Potential treatments	Recent advances
Fanconi anaemia (FA)	Chromosomal breakage	•Androgen therapy •HCT	•Novel pathogenic variants •Germline mosaicism •Fludarabine preparative regimens
Dyskeratosis congenita (DC)	Telomere length	•Androgen therapy •HCT	•Novel genes •Pathomechanisms of specific variants •Tailored HCT preparative regimens
Shwachman Diamond syndrome (SDS)	Trypsinogen, isoamylase, faecal fat	•Pancreatic enzyme replacement •HCT	•New genes •Novel pathogenic variants- large deletions •Understanding clonal haematopoiesis
Diamond Blackfan anaemia (DBA)	Erythrocyte adenosine deaminase	•Corticosteroids •RBC transfusions •HCT	•Novel pathogenic variants identified via whole genome sequencing •Understanding the mechanism of glucocorticoid treatment response
GATA2 deficiency	Germline pathogenic variants in <i>GATA2</i>	•HCT	•HCT demonstrating efficacy •Updated HCT regimens
<i>SAMD9/SAMD9L</i> syndromes	Germline gain-of-function pathogenic variants in <i>SAMD9/SAMD9L</i>	•HCT	•Clonal haematopoiesis leading to somatic genetic rescue •Prevalence in children •Pathogenesis of BMF

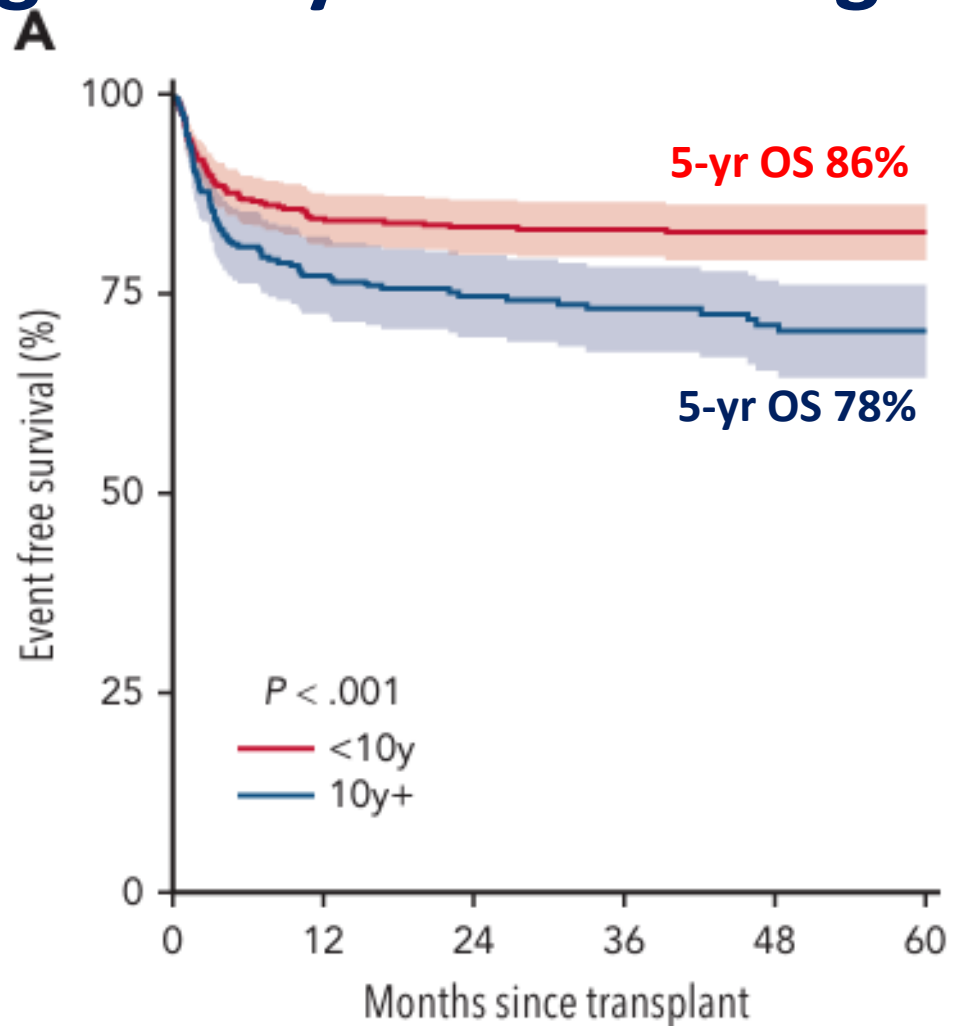
Fanconi anemia (FA)

- Most common IBMFS, incidence 1/200,000
- A disorder of DNA damage repair leads to chromosome instability
- > 22 genes were identified, somatic abnormalities in 70% of patients
- Presentation: BMF, risk of malignancy (MDS, leukemia, head & neck SCC, gynecological cancer)
- Gold standard test: chromosome breakage test with diepoxybutane or mitomycin C, followed by pathogenic variant identification
- Highly susceptible to alkylating agent-based chemotherapy & irradiation-induced damage

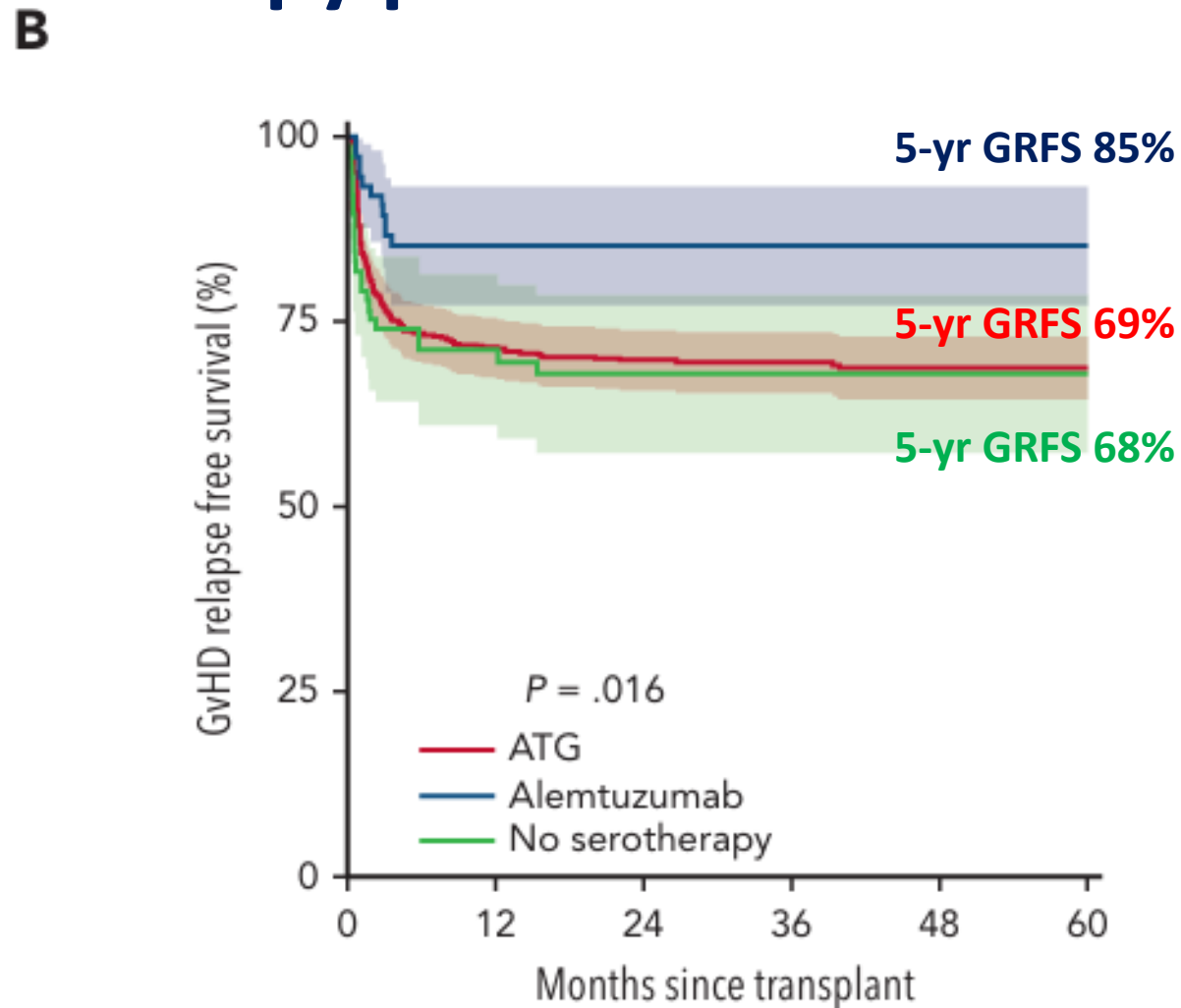
Overall survival of 813 children with FA undergoing HSCT



Age < 10 yrs and adding serotherapy predict better results



<10y:	507	334	287	244	189	147
10y+:	306	193	154	129	98	68



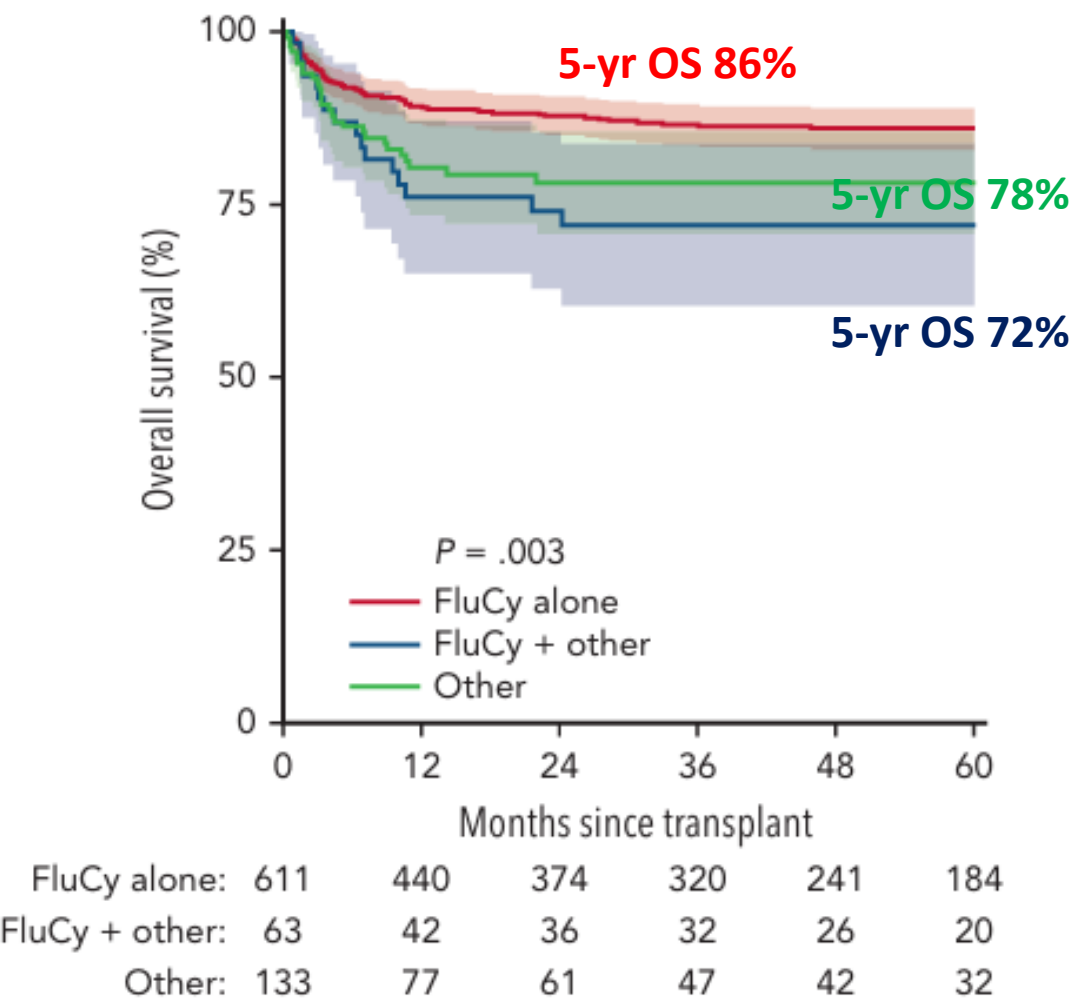
ATG:	502	305	254	219	166	125
Alemtuzumab:	75	63	61	49	43	40
No serotherapy:	77	45	39	35	27	15

Flu-Cy without TBI in MSD/MUD HSCT of pediatric FA

C

Flu 150 mg/m2 + reduced Cy 50 mg/kg

Serotherapy significantly reduced incidence of aGVHD & cGVHD



Serotherapy	Day 100 aGVHD gr 2-4	Day 100 aGVHD gr 3-4	5-yr cGVHD
ATG (n =620)	23%	13%	12%
Alemtuzumab (n=86)	7%	0%	4%
None (n=103)	35%	17%	24%
P-value	< 0.001	< 0.001	< 0.001

HSCT in Fanconi anemia

- **Prognostic indicator**

- Indication: severe AA is better than AML/MDS
- Age > 10 years associated with worse EFS & GVHD-free-relapse-free survival (GRFS)

- **Conditioning regimen: Flu 150 mg/m² + reduced dose Cy 50 mg/kg**

- Flu-Cy without TBI is the best conditioning regimen for MSD/MUD
- Role of low dose TBI in Haploidentical HSCT/still need more data

- **Serotherapy significantly reduced the risk of aGvHD & cGVHD but associated with increase risk of viral infection**

- Alemtuzumab associated with better GRFS (85%) vs ATG (69%)

Dyskeratosis congenita (DC)

- Incidence 1/1,000,000 (Inheritance: XLR, AD, AR, de novo)
- A telomere biology disorder caused by impaired telomere maintenance
- Typical triad: dysplastic nails, lacy reticular pigmentation, oral leukoplakia
- 80% developed BMF before the age of 30
- Increased risk of BMF, MDS, AML and SCC
- Diagnosis: flow cytometry with FISH (flow-FISH) to detect shortened leukocyte telomere length +/- identify pathogenic gene variant
- Abnormal genes encoding the telomerase-shelterin complex including *DKC1, TERC, TERT, NHP2, NOP10, TCAB1, TPP1, TINF2, ACD, POT1, NAF1, STN1, CTC1, RTEL1 and PARN*

Diagnostic criteria of Dyskeratosis congenita (DC)

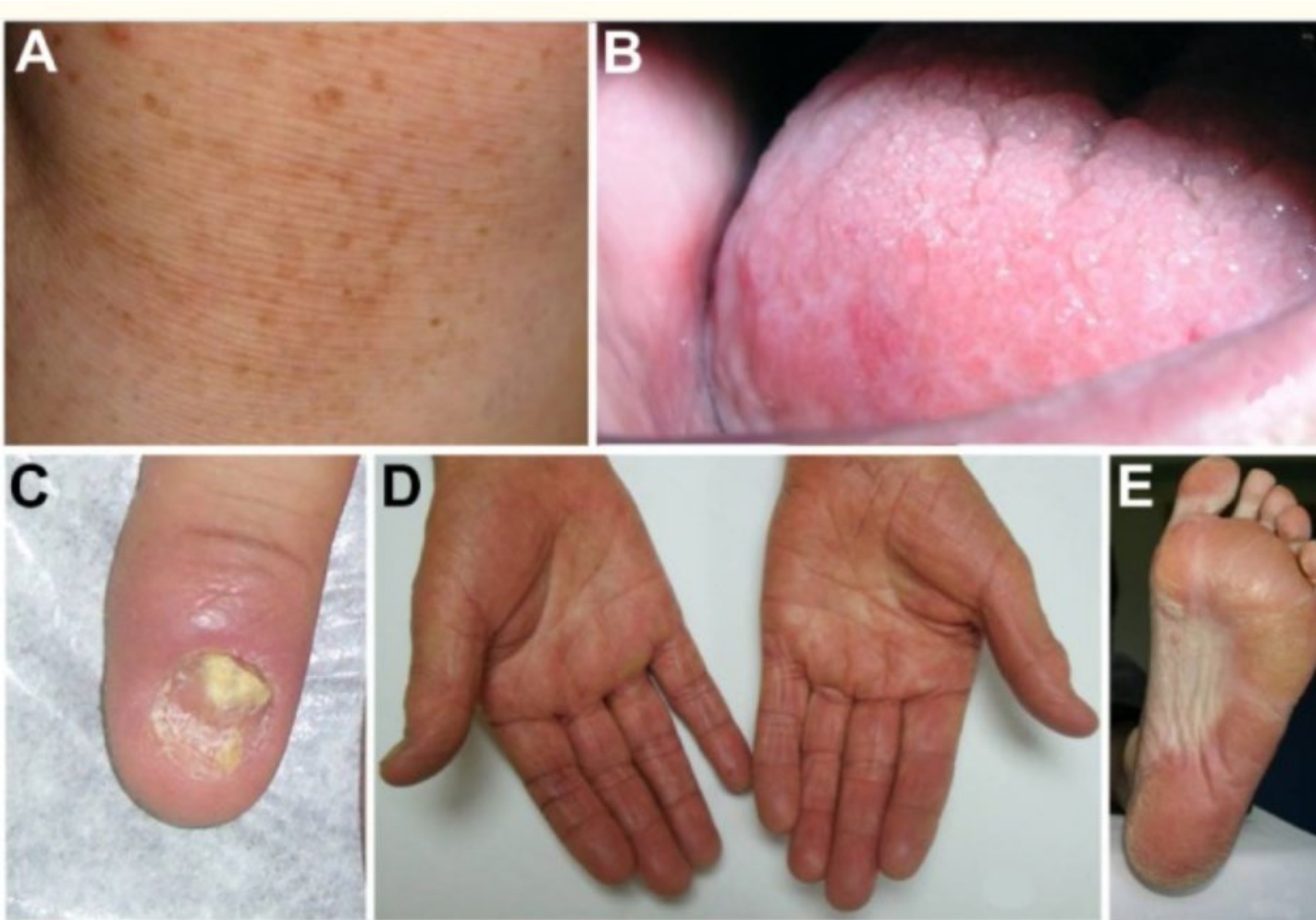
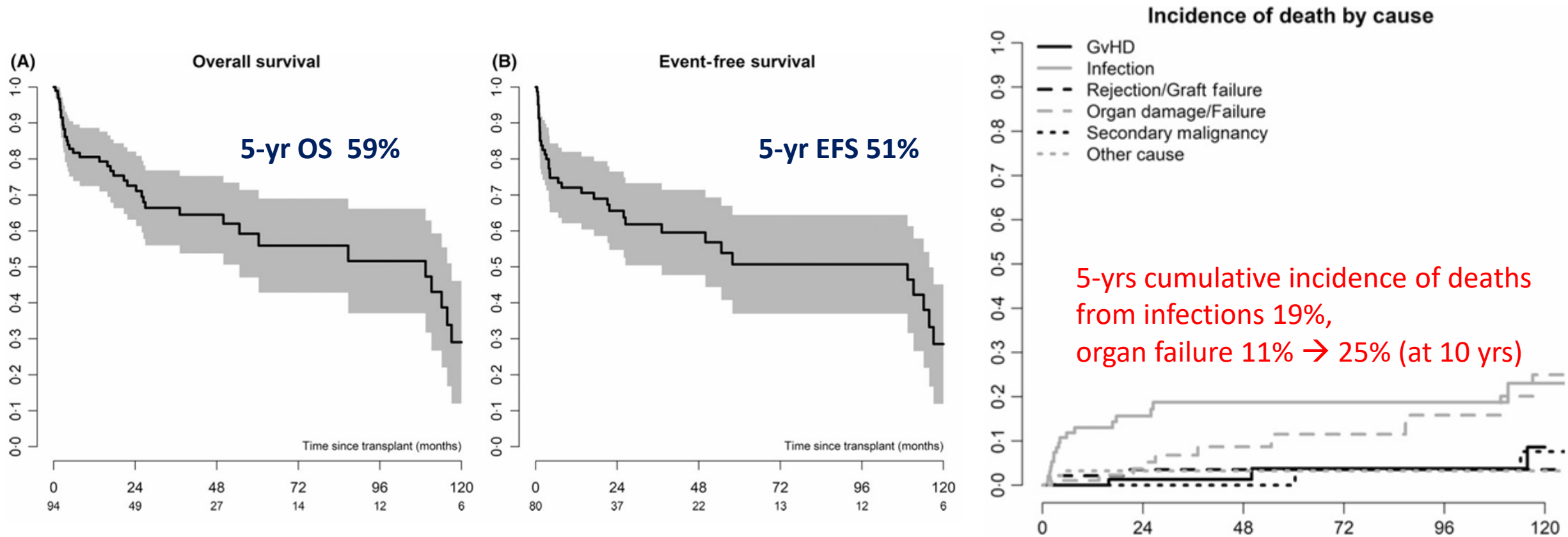


Table 2. Summary of dyskeratosis congenita diagnostic criteria.

Diagnosis	Criteria ^{15,16,43}
DC ^a	1. All three mucocutaneous features: • Abnormal skin pigmentation • Nail dystrophy • Leukoplakia 2. At least 1 out of 3 mucocutaneous feature, combined with bone marrow failure and 2 other somatic features of DC 3. Aplastic anaemia, myelodysplastic syndrome or pulmonary fibrosis associated with a pathogenic telomerase variant 4. 2 or more features seen in DC associated with very short telomeres that are below 1st centile.
Hoyeraal–Hreidarsson Syndrome	Four or more features of: 1. Growth retardation 2. Developmental delay 3. Microcephaly 4. Bone marrow failure 5. Immunodeficiency 6. Cerebellar hypoplasia

Outcome of HSCT in Dyskeratosis congenita

- Age < 20 yrs showed better 3-yr OS (72% vs. 43%, $P = 0.016$).
- MSD/MUD had better 3-yr EFS (69% vs 40%, $P = 0.04$) than MMSD/MMUD.



HSCT in Dyskeratosis congenita

- Recommended in cases of progressive marrow failure without significant organ dysfunction (23% of death vs 61% death with organ damage)
- Organ involvement (pulmonary fibrosis, liver, neurological, GI abnormal) negatively affects HSCT outcome
- A thorough evaluation of lung and other organ damage before HSCT.
- RIC regimen: Flu-Cy regimen
- Sibling donors need to be studied for telomere disease for possible incomplete penetrance may attenuate the phenotype.
- Consider alternative treatment options: androgen, IST, eltrombopag
- IPF → antifibrotics: pirfenidone, nintedanib
- MDS → Azacytidine

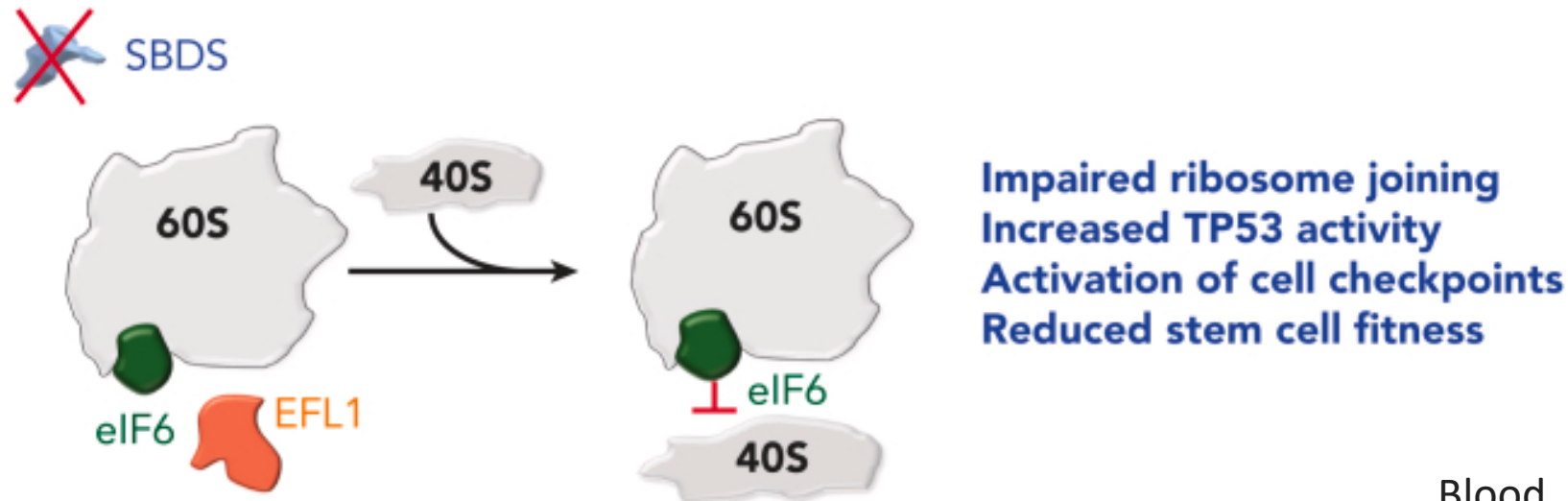
Shwachman-Diamond syndrome (SDS)

- Incidence 1/76,000 (Inheritance: AR)
- caused by ribosomal biogenesis disorder
- > 90% have biallelic *SBDS* gene mutation on chromosome 7q11
- Presentations: exocrine pancreatic dysfunction (fatty stool), skeletal dysplasia, BMF
- Predisposition to MDS & AML
- Diagnosis: A 72-h stool fat quantification test /pancreatic enzyme testing
Inherited BMF gene panel including *SBDS*, *EFL1*, *DNAJC21*, *SRP54*
- Treatment: pancreatic enzymatic replacement, G-CSF for severe persistent neutropenia with recurrent infections

Normal ribosome subunit joining



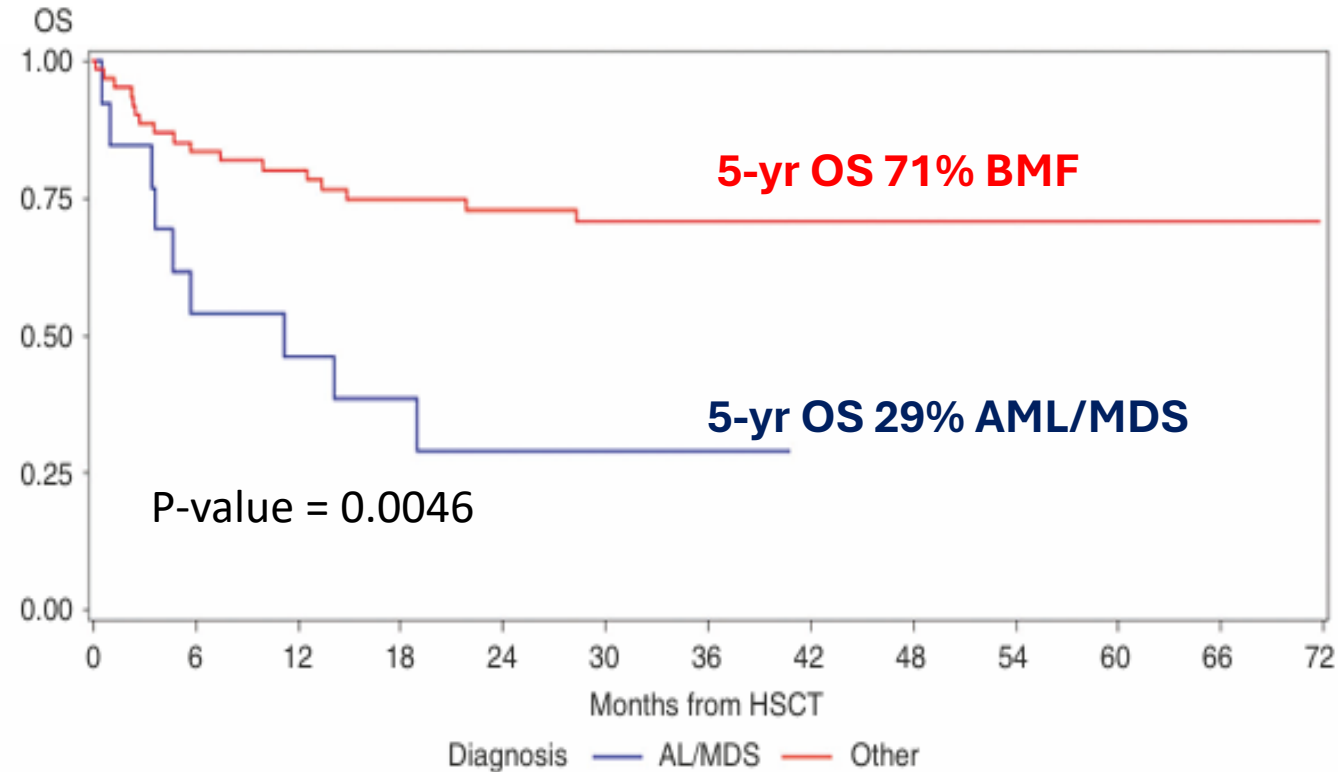
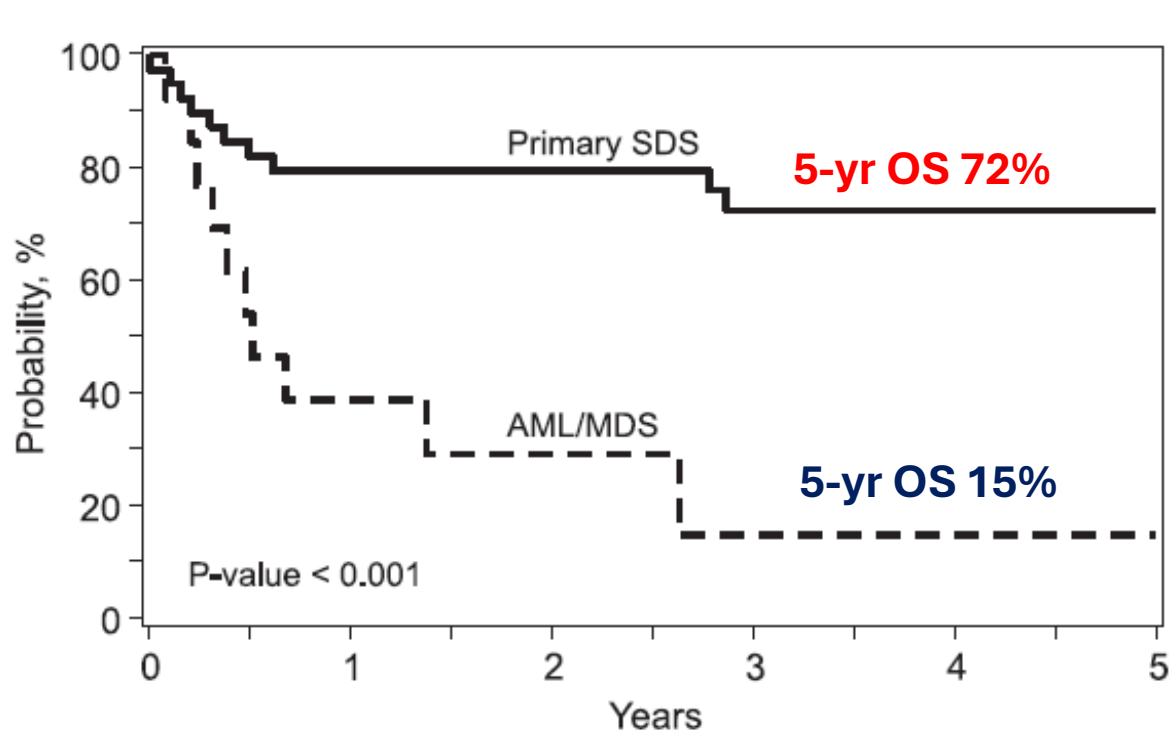
Shwachman-Diamond Syndrome



5-yr OS of children with SDS undergoing HSCT

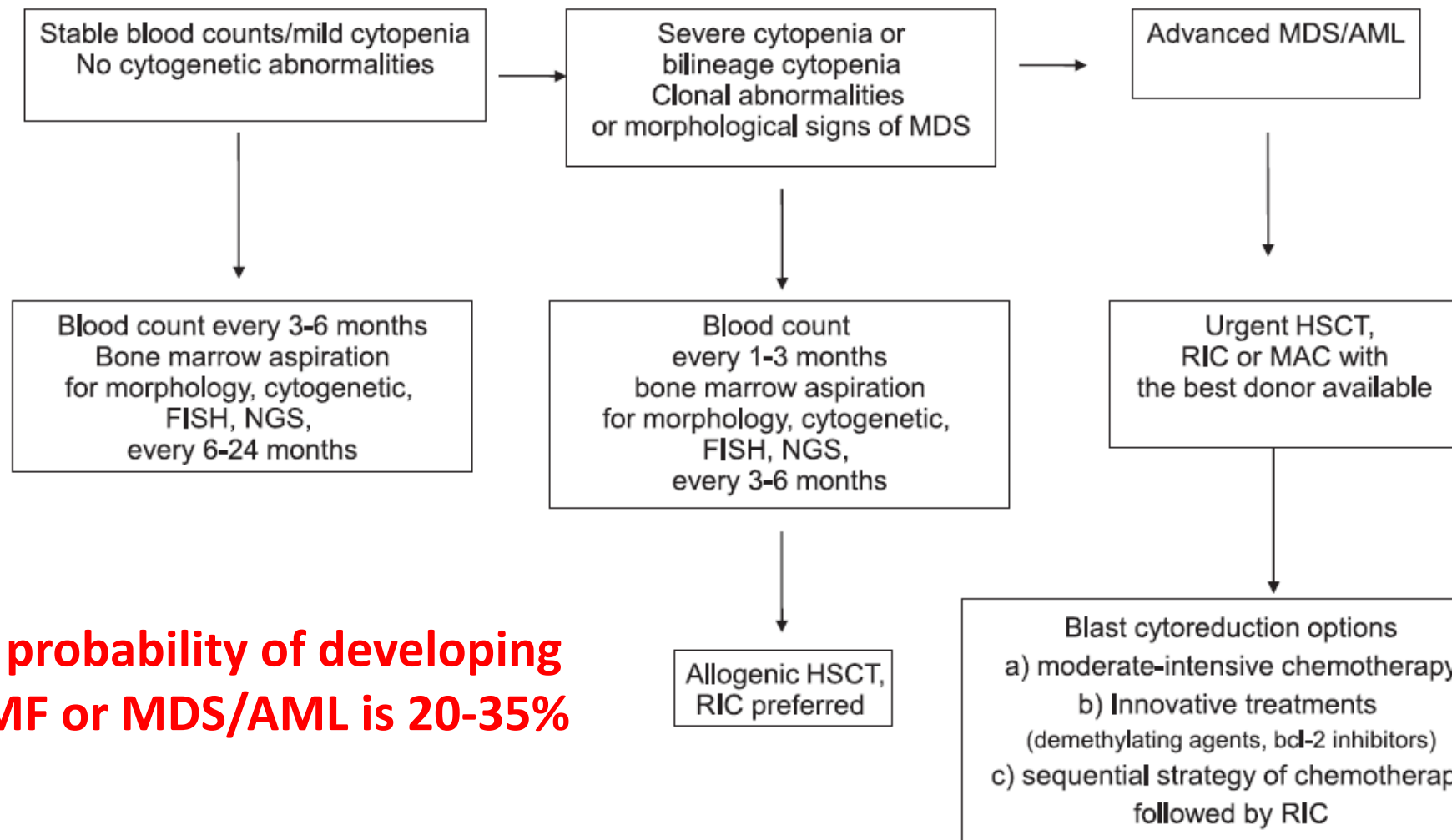
Indication for HSCT: worsening cytopenia with transfusion dependence, MDS or leukemia transformation

HSCT was needed for 12% of SDS patients.



Guideline

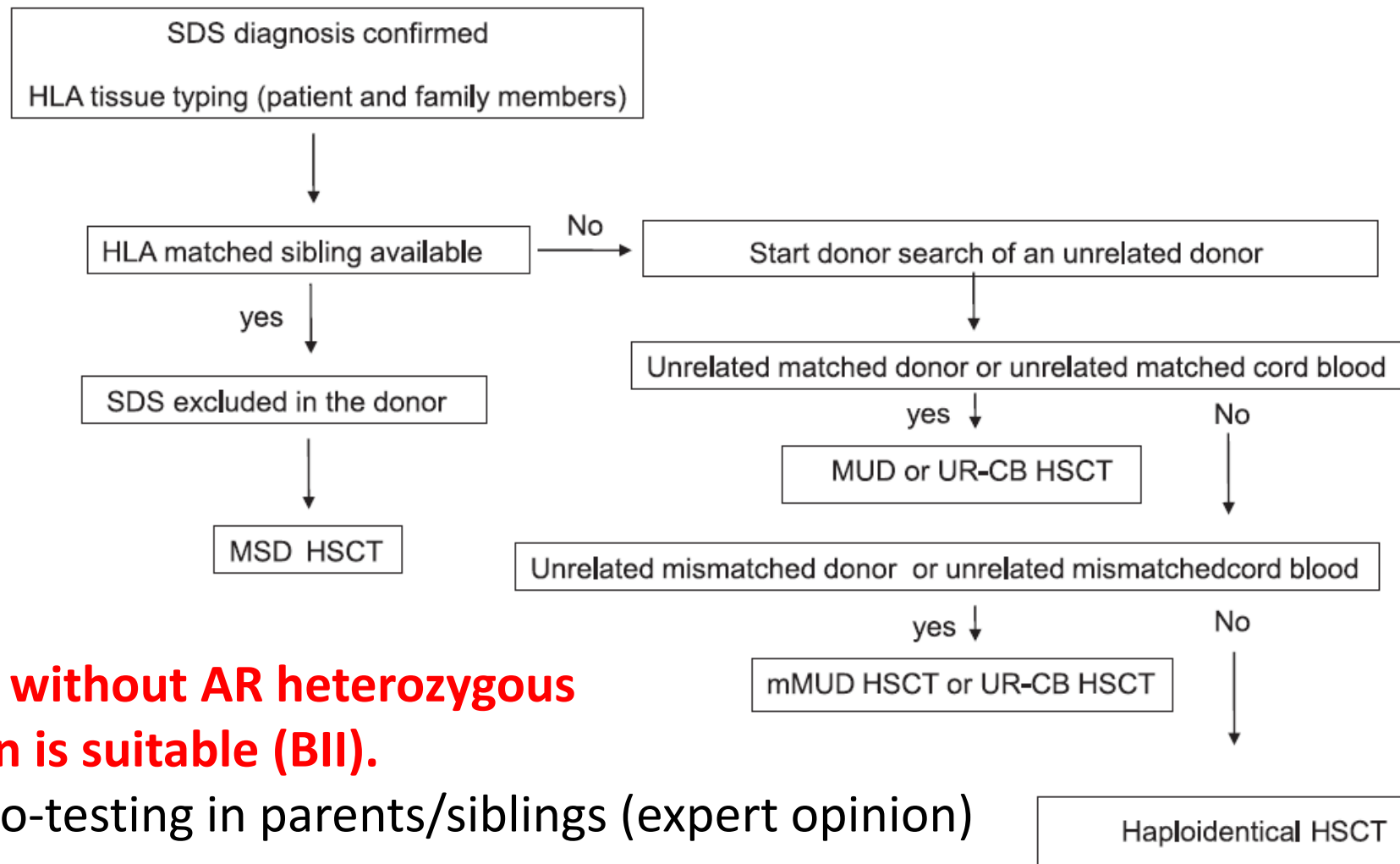
Stem Cell Transplantation in Patients Affected by Shwachman-Diamond Syndrome: Expert Consensus and Recommendations From the EBMT Severe Aplastic Anaemia Working Party



**20-yr probability of developing
SC/BMF or MDS/AML is 20-35%**

Guideline

Stem Cell Transplantation in Patients Affected by Shwachman-Diamond Syndrome: Expert Consensus and Recommendations From the EBMT Severe Aplastic Anaemia Working Party



**MSD with or without AR heterozygous
SDS mutation is suitable (BII).**

Advice for trio-testing in parents/siblings (expert opinion)

HSCT in Shwachman-Diamond syndrome

- Conditioning regimen: No significant difference in OS b/w MAC vs RIC
- EBMT: MAC used in 54% (indication of BMF 82%)
International registry: RIC used in 66%
- Transplant-related mortality 23-28%
- RIC regimen: treosulfan, fludarabine or melphalan (avoid Cy)
- Recommendation: RIC regimen in SDS pt with SC/BMF, In MDS/AML MAC could be used with careful evaluation case by case (no TBI)
- GVHD prophylaxis: CSA or tacrolimus +/- short course MTX or MMF

Diamond-Blackfan anemia (DBA)

- Incidence 5-7 cases /1,000,000 (Inheritance: AD)
- Ribosomal dysgenesis: common pathogenic variant in *RPS19* gene
- Presentation: severe macrocytic anemia with reticulocytopenia
congenital PRCA presents in the 1st year of life, abnormalities (craniofacial, skeletal, short stature, cardiac, genitourinary)
- Increased risk for AML, MDS, osteosarcoma, colorectal cancer
- Diagnosis: clinical & confirm molecular testing, increase eADA (85%)
- Treatment: corticosteroid in children aged ≥ 1 year (80% respond), red cell transfusion, iron chelation

Indication & decision guide for HSCT in DBA

- **Steroid unresponsive**

Reticulocyte not increased
at prednisolone ≥ 1 MKD

- **Steroid responsive**

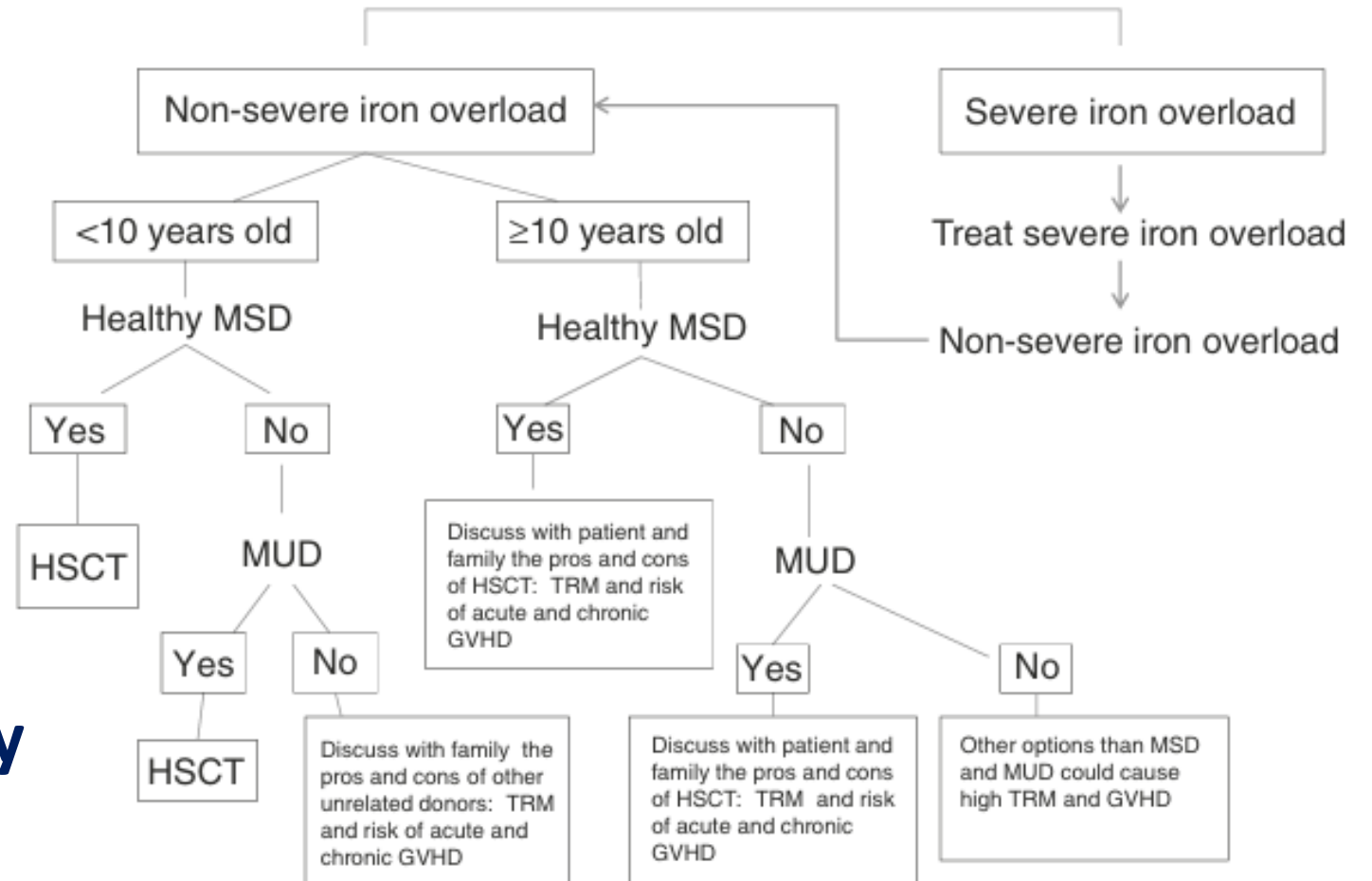
Need prednisolone > 0.3 MKD
to maintain Hb levels

- **Growth impaired**

- **Unacceptable steroid toxicity**

- **Transfusion dependence**

- **Clonal evolution /MDS**



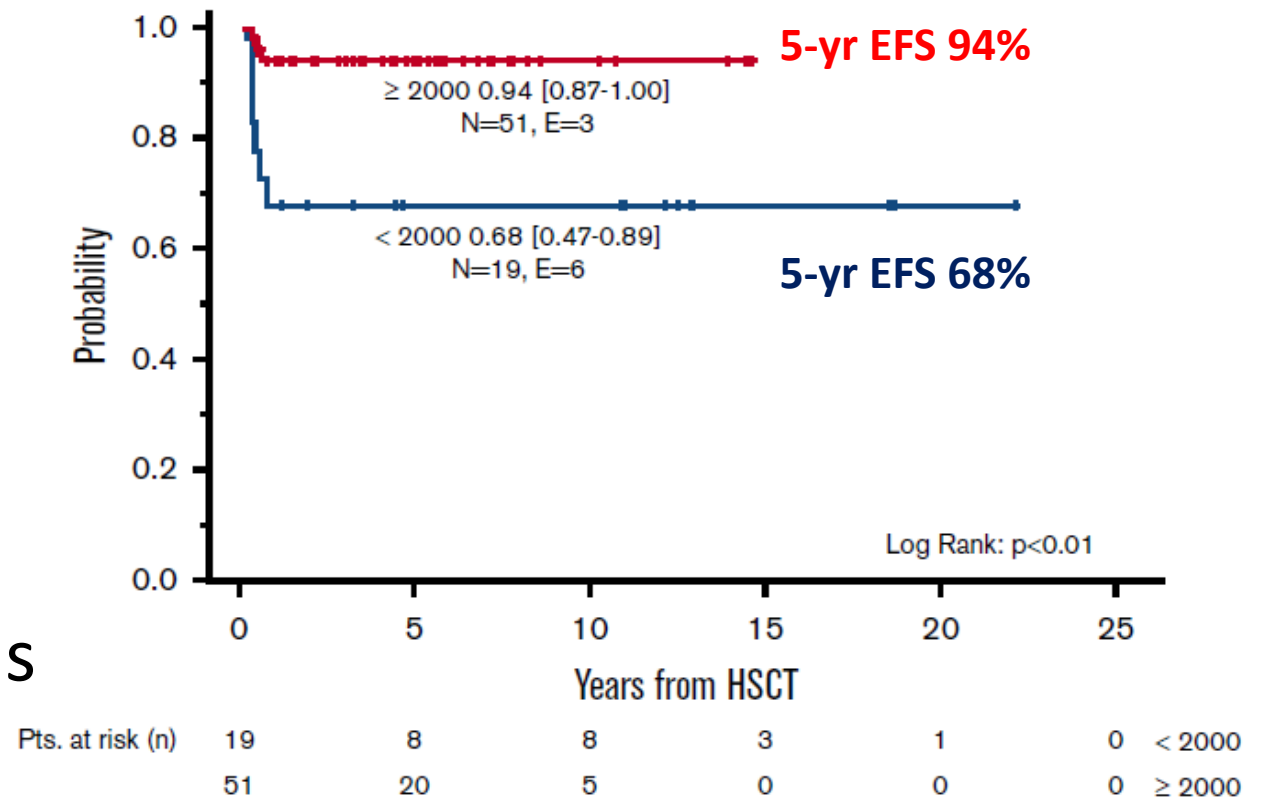
Abbreviations: MSD, matched sibling donor; HSCT, hematopoietic stem cell transplantation; MUD, matched unrelated donor; TRM, transplant related mortality; GVHD, graft versus host disease

Recommendation for condition regimen & GVHD prophylaxis

- MAC regimen (BU+Flu+Thiotepa or Treosulfan+Flu+Thiotepa)
- Adding ATG in MSD with multiple transfusions or MUD
- RIC regimen: Treosulfan + Flu +ATG (investigational)
- GVHD prophylaxis: CSA or tacrolimus +/- short course MTX or MMF

Outcome improved over time

A



Special pre- and posttransplant considerations in inherited bone marrow failure and hematopoietic malignancy predisposition syndromes

BEYOND THE MARROW



- Complete family and patient's history with careful evaluation of physical findings according to disease type.
- Multidisciplinary team: Visual, hearing, endocrine, nutritional, and neuropsychologic evaluation in all patients. Oral examination performed by a dentist. Detailed skin examination in FA and TBD. Other evaluations as needed (such as gastrointestinal endoscopy or nasolaryngoscopy screening)
- Hematologic evaluation: disease phase (single or multilineage cytopenias, MDS, AML). CBC, fetal hemoglobin, eADA (Diamond-Blackfan anemia), α -fetoprotein, bone marrow aspirate, biopsy, cytogenetics and flow cytometry. FISH for chromosomes 3 and 7 in FA.
- Previous transfusions (iron overload): Check number of transfusions, chelation history and ferritin levels. Consider T2* MRI to determine liver/heart iron overload. Check for alloimmunization and presence of DSA.
- Prior use of androgens: describe type, duration and dose. Check for signs of virilization, growth problems, and liver dysfunction. Check abdominal ultrasound, liver function, lipid metabolism, and bone age.
- Prior use of steroids: describe type, duration, and dose. Check for signs of Cushing's syndrome; hyperglycemia, hypertension, metabolic syndrome, avascular necrosis, and adrenal insufficiency.
- For adults: special attention to genitourinary and gynecologic issues. Address fertility and options available for cryopreservation before HCT. Aggressive cancer screening is very important in this population.
- Lifestyle evaluation: Recommend complete abstinence from smoking and alcohol especially for FA and TBD, good oral hygiene, sunscreen use, healthy diet, and exercise.

Special pre- and posttransplant considerations in inherited bone marrow failure and hematopoietic malignancy predisposition syndromes

BEYOND THE MARROW



Disease-specific pretransplant evaluation

FA	DC	DBA
Address congenital abnormalities (head, heart, skeletal, genitourinary, and gastrointestinal).	Address congenital abnormalities. Brain MRI is indicated in HH and Revesz and/or development delay	Address congenital abnormalities
Brain MRI is indicated for children with multiple birth defects (pituitary gland evaluation)	Immune abnormalities are common in early-onset cases.	Prolonged use of steroids may cause pathologic fractures, avascular necrosis, cataracts, growth retardation, hypertension, and diabetes
	Avascular necrosis of the hips	
Attention to endocrine problems such as short stature, thyroid function, glucose, gonadal function, and lipid metabolism	Attention to PFTs and SpO ₂ before HCT. Chest CT scan when indicated.	Iron overload is the major complication leading to heart and liver hemosiderosis, insulin-dependent diabetes mellitus, hypothyroidism, and delayed puberty
Postpuberty: Fertility evaluation	Check for signs of pulmonary and liver fibrosis and arteriovenous malformations in the lung, liver, and gastrointestinal tract, especially in adult patients	

Take Home message

- **Fanconi anemia**
 - Perform HSCT before developing AML/MDS & age < 10 years
 - Adding serotherapy (ATG/Alemtuzumab) reducing aGVHD & cGVHD
- **Dyskeratosis congenita** pulmonary function test +/- CT chest
- **Conditioning for FA+DC recommended RIC (Flu-Cy)**
- **Shwachman-Diamond syndrome** prefer RIC regimen to reduced toxicity
- **Diamond Blackfan anemia** try steroid as first line therapy, evaluate iron overload toxicity before HSCT, prefer MAC > RIC
- **Patients:** complete PE & looks for associated anomalies
- **Donor:** MSD (exclude mutation) > MUD > MMUD > HFD
- **Avoid TBI in IBMFS that increases the risk of second malignancy**



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ผสานผสมเป็นหนึ่งเดียว

Thank you for your kind attention