What is MDS? How do we predict prognosis?

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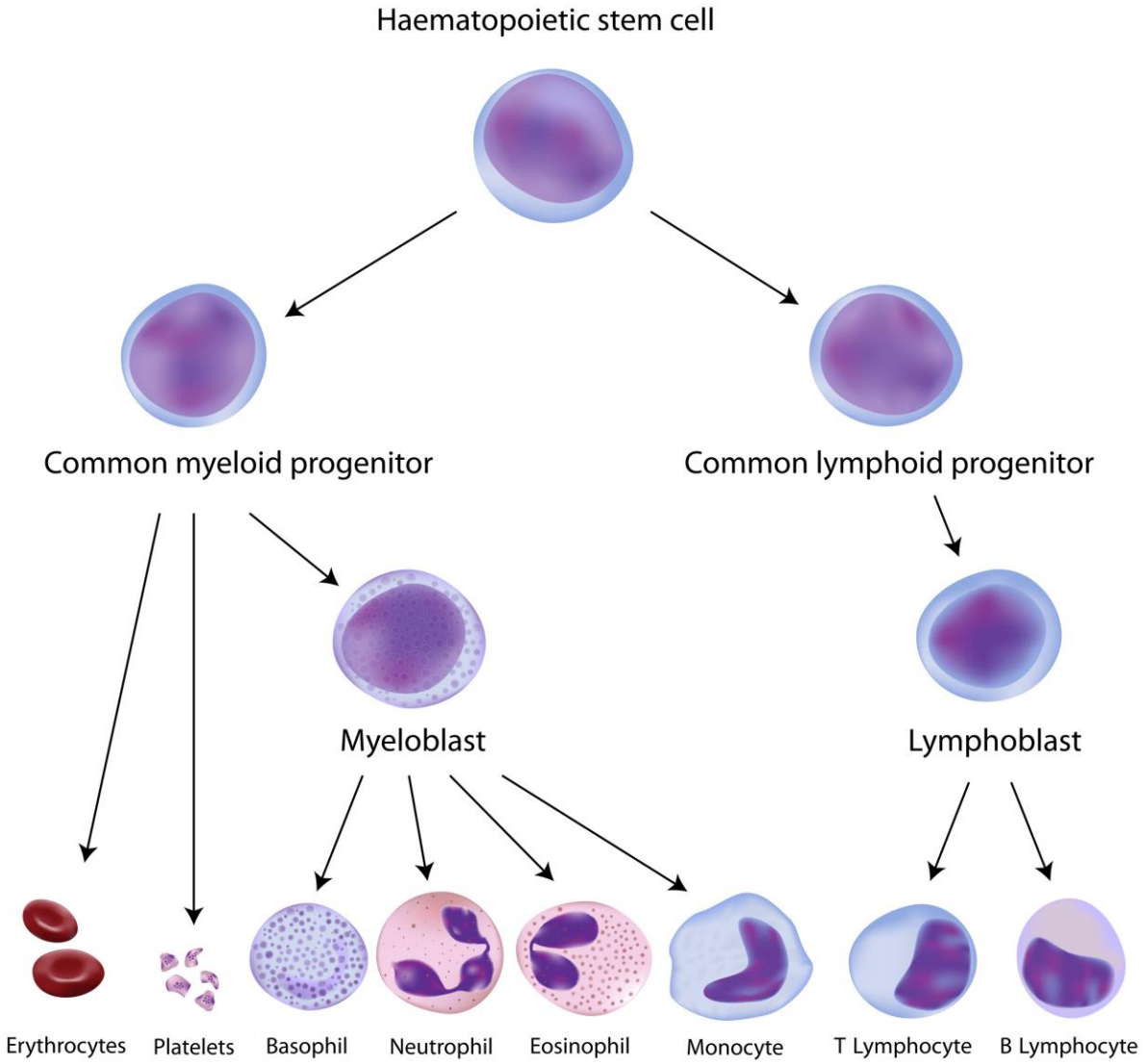
How Does MDS Happen?



- **All blood cells come from HSCs**
- **HSCs are the only long lived cells in the blood system**
- **HSCs develop mistakes in DNA with age or exposure to toxins**
- **MDS happens when mistakes in DNA impair the function of HSCs**

The Myelodysplastic Syndromes
Clinical Features

- Peripheral blood cytopenias
- Risk for progression to acute leukemia (AML)
- But…
  - Not all MDS cases will progress to AML
  - Not cytopenias are from MDS
  - Not all MDS cases are alike- it is "heterogenous"

Fatigue, shortness of breath- Anemia

Infection- Leukopenia

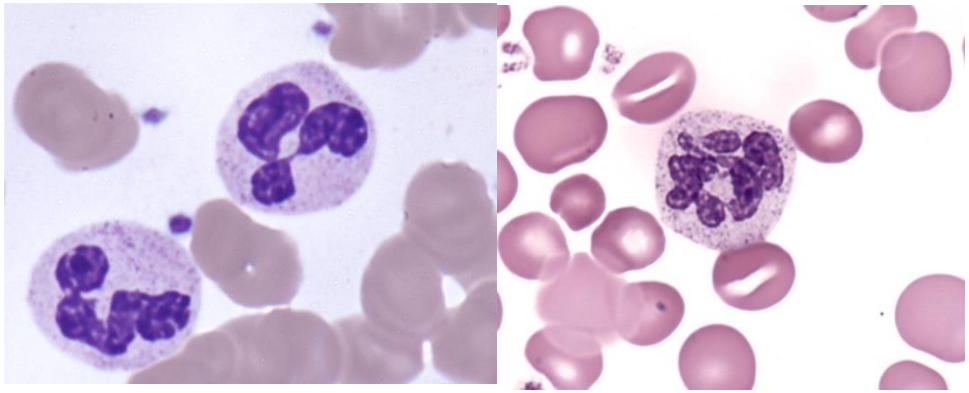
Bleeding- Thrombocytopenia

The Myelodysplastic Syndromes- Key Features

- Clonal disorders
  - All starts with one abnormal cell (a clone)
- Impaired differentiation
  - Immature blood cells don't grow up correctly
- Dysplasia
  - Maturing blood cells look abnormal
- Increased apoptosis
  - More cell death

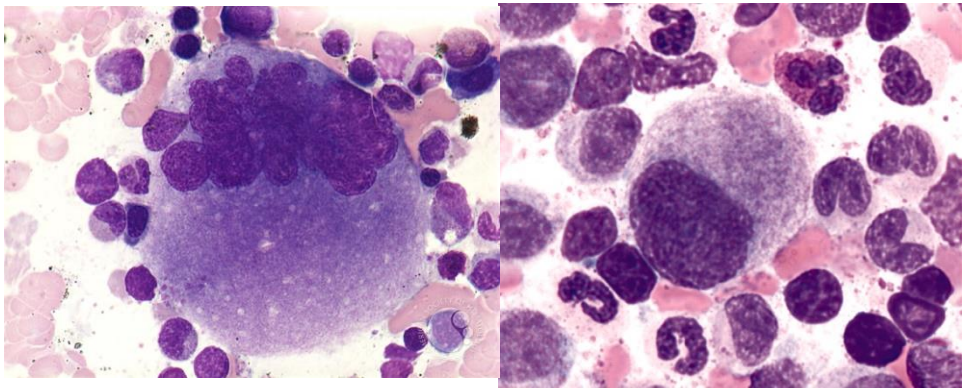
Neutrophils

Normal **Dysplastic**



Megakaryocytes- Platelet Precursors

Normal **Dysplastic**

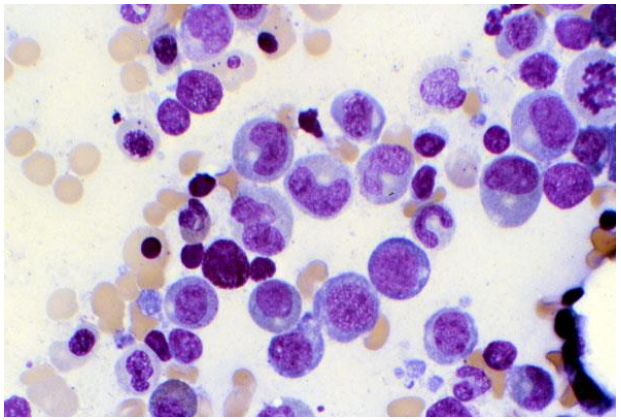


ASH Image Bank, 2004

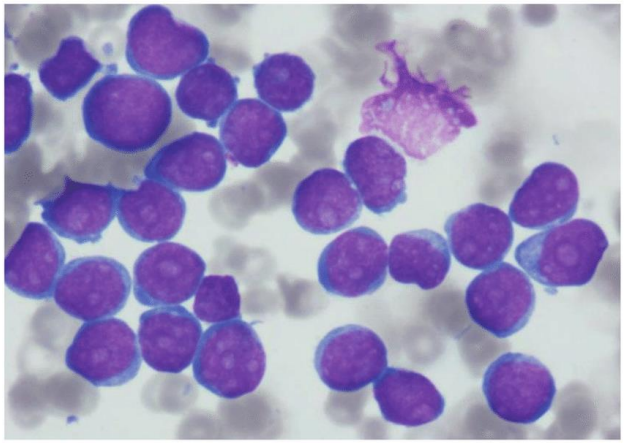
The Myelodysplastic Syndromes- Key Features

- Blasts
  - Immature cells
  - Normal to have up to 3-5%
  - If these immature cells become >20%, we call it acute myeloid leukemia (AML)
  - Only ~1/3rd of MDS progresses to AML

Normal Bone Marrow



Leukemia Bone Marrow



ASH Image Bank, 2004

Diagnosis of the Myelodysplastic Syndromes

- Cytopenias
  - Hemoglobin <10 g/dL
  - Absolute Neutrophil Count <1.8 x 10^9/L
  - Platelets <100 x 10^9/L

  and
- 1. Dysplasia in >10% of cells in at least one lineage

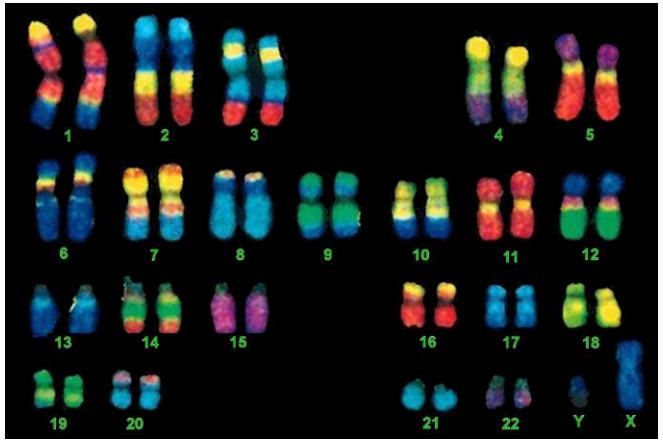
  or
- 2. MDS-defining cytogenetic (chromosome) abnormalities

  or
- 3. >5% blasts

MDS Defining Cytogenetic Abnormalities

Unbalanced abnormalities	Balanced abnormalities
−7 or del(7q)	t(11;16)(q23;p13.3)
−5 or del(5q)	t(3;21)(q26.2;q22.1)
i(17q) or t(17p)	t(1;3)(p36.3;q21.1)
−13 or del(13q)	t(2;11)(p21;q23)
del(11q)	inv(3)(q21q26.2)
del(12p) or t(12p)	t(6;9)(p23;q34)
del(9q)	
idic(X)(q13)	

Complex karyotype (3 or more chromosomal abnormalities) involving one or more of the above abnormalities.

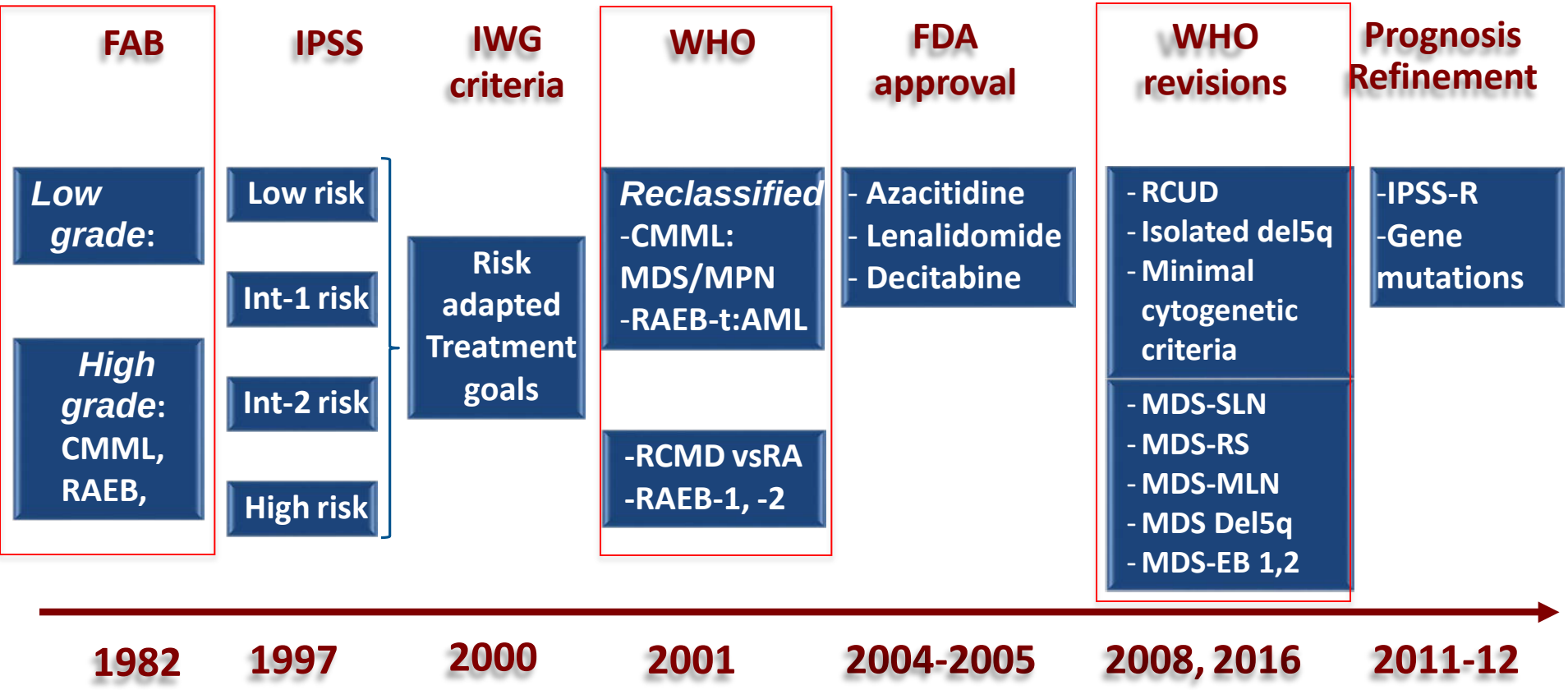


Vardiman et al. Blood, 2009; Arber et al. Blood, 2016

Other Causes of Low Blood Counts or Dysplasia

- Medications
- Viral infections
- Autoimmune disorders
- Other blood disorders
  - (e.g. T-LGL, aplastic anemia)
- Vitamin/Nutritional deficiencies
  - B12, folate, copper
  - Zinc excess
- Toxins
  - Arsenic, chemotherapy, etc.

Milestones in MDS
Classification and Prognostication



French-American-British Classification

- RARS- abnormal accumulation of iron in red cell precursors, favorable subtype
- RAEB- more blasts (5-19%), higher risk
- RAEB-t (RAEB "in transformation")- 20-30% blasts- very high risk

FAB	Blast %
RA (refractory anemia)	<5%
RARS (refractory anemia with ringed sideroblasts)	<5% <5%
RAEB (refractory anemia with excess blasts)	5-9% 10-19%
RAEB-t	20-30%

FAB vs WHO 2000 Classification

FAB	WHO	Dysplasia	Blast %
RA (refractory anemia)	▪**5q- syndrome** ▪**RA** ▪**RCMD** ▪**MDS-U**	erythroid+mega erythroid erythroid+other Non-erythroid	<5% <5% <5% <5%
RARS (refractory anemia with ringed sideroblasts)	▪**RARS** ▪**RCMD-RS**	erythroid only erythroid+other	<5% <5%
RAEB (refractory anemia with excess blasts)	▪**RAEB-1** ▪**RAEB-2**	≥1 lineage ≥1 lineage	5-9% 10-19%
RAEB-t	▪**AML**	myeloid±other	20-30%

- **WHO 2000/2008**
  - 5q- syndrome- a very favorable risk subtype that responds to Revlimid
  - RCMD- multilineage dysplasia associated with somewhat higher risk
  - RAEB-t – very high risk- 20-30% blasts now just called AML

2016 Revisions to WHO MDS Terminology

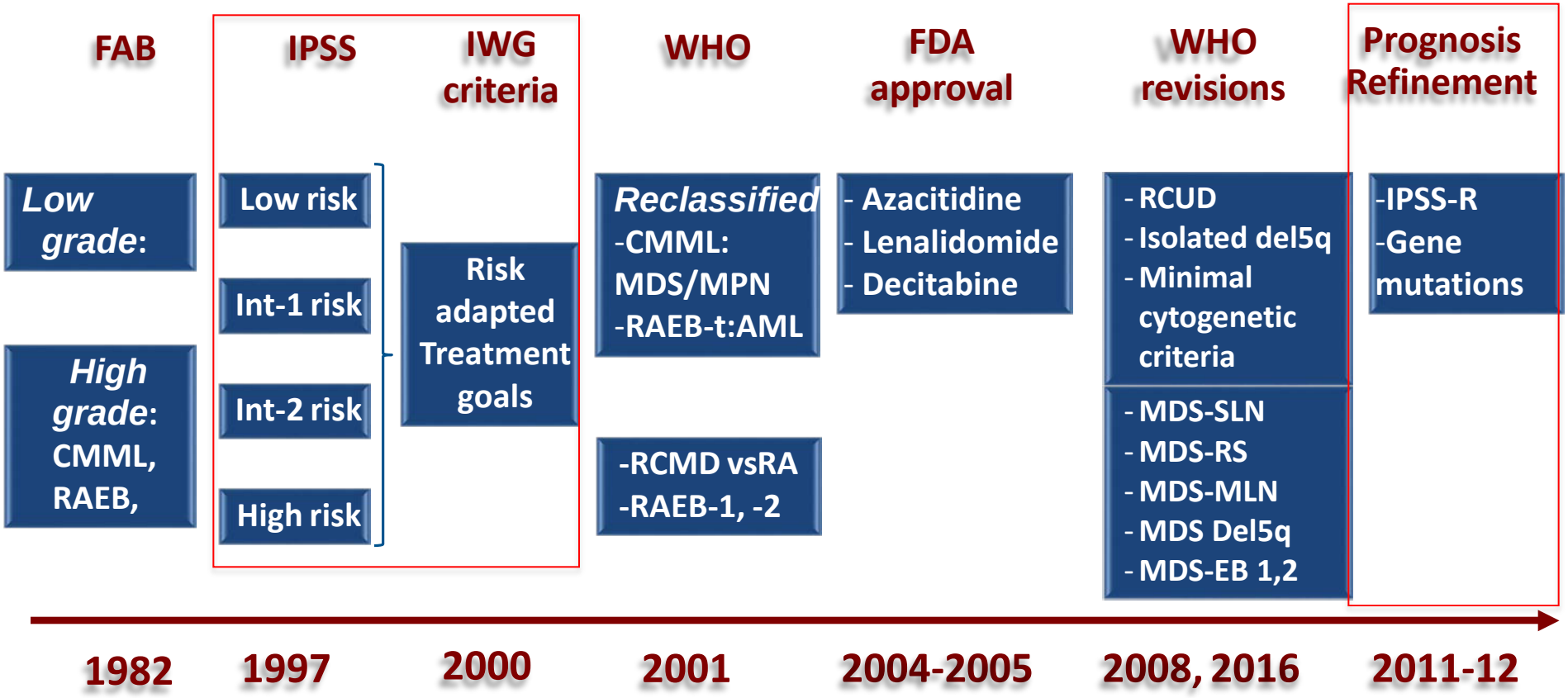
2008 Name	Abbrev.	2016 Name	Abbrev.
Refractory cytopenia with unilineage dysplasia	**RCUD (includes RA, RN and RT)**	MDS with single lineage dysplasia	**MDS-SLD**
Refractory anemia with ring sideroblasts	**RARS**	MDS with ring sideroblasts*	**MDS-RS**
MDS with isolated del(5q)	**Del(5q)**	Unchanged^	**Del(5q) MDS**
Refractory cytopenia with multilineage dysplasia	**RCMD**	MDS with multilineage dysplasia	**MDS-MLD**
		(with ring sideroblasts)	**MDS-RS-MLD**
Refractory anemia with excess blasts, type 1	**RAEB-1**	MDS with excess blasts, type 1	**MDS-EB-1**
Refractory anemia with excess blasts, type 2	**RAEB-2**	MDS with excess blasts, type 2	**MDS-EB-2**
MDS, Unclassifiable	**MDS-U**	unchanged	**MDS-U**

*>15% ring sideroblasts, *or* >5% AND presence of an *SF3B1* mutation.

^ May include ≤ 2 cytopenias AND 1 additional chromosome abnormality other than -7/7q; with pancytopenia: MDS-U.

- **WHO 2016**
  - Instead of "refractory anemia," decided to just call it MDS
  - RCMD now called MDS- MLD, RAEB now called MDS-EB
  - MDS-U- MDS-SLD or del(5q) MDS with pancytopenia or 1% circulating blasts- similar prognosis to MDS-MLD

Milestones in MDS
Classification and Prognostication



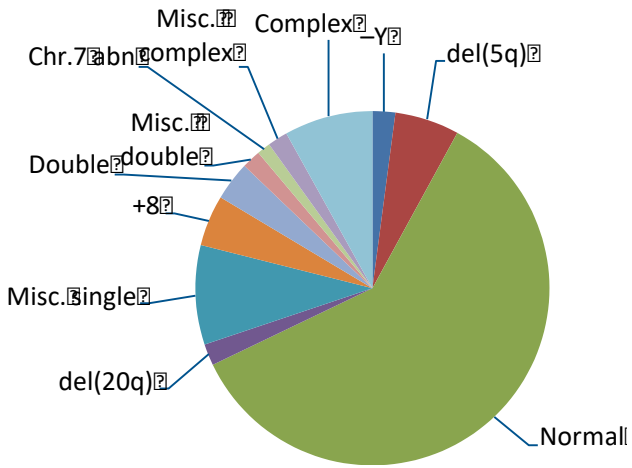
1997 International Prognostic Scoring System

Prognostic Variable	Score				
	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	< 5%	5%-10%	--	11%-20%	21%-30%
Karyotype class*	Good	Intermediate	Poor	--	--
# of cytopenias**	0 or 1	2 or 3	--	--	--

* Karyotype class:
Good = normal, -Y, del(5q) alone, del(20q) alone;
Intermediate = other karyotypes;
Poor = chromosome 7 abnormalities or complex;

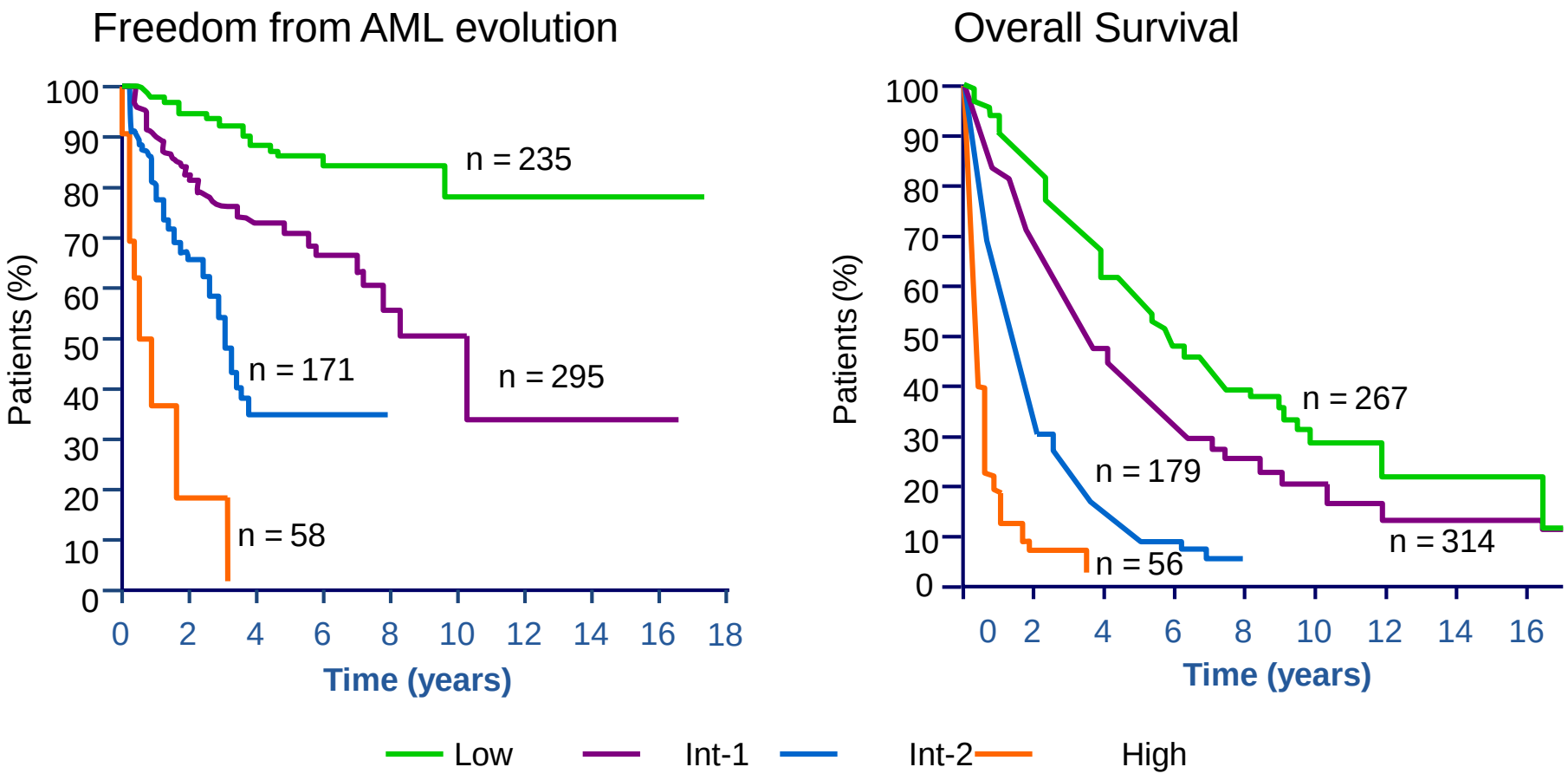
** Cytopenias: Hb < 10 g/dL, ANC < 1800/uL, platelets < 100,000/uL

Risk Groups				
	Low	Int-1	Int-2	High
IPSS	0	0.5-1.0	1.5-2.0	2.5-3.5



Greenberg P et al. *Blood*. 1997;89:2079-2088.

OS and Freedom from AML by IPSS Score



*Estimated survival and risk of AML transformation.

Greenberg P, et al. BLOOD 1997: 89: 2079.

IPSS-R (2012)- More cytogenetic groups and degree of cytopenias

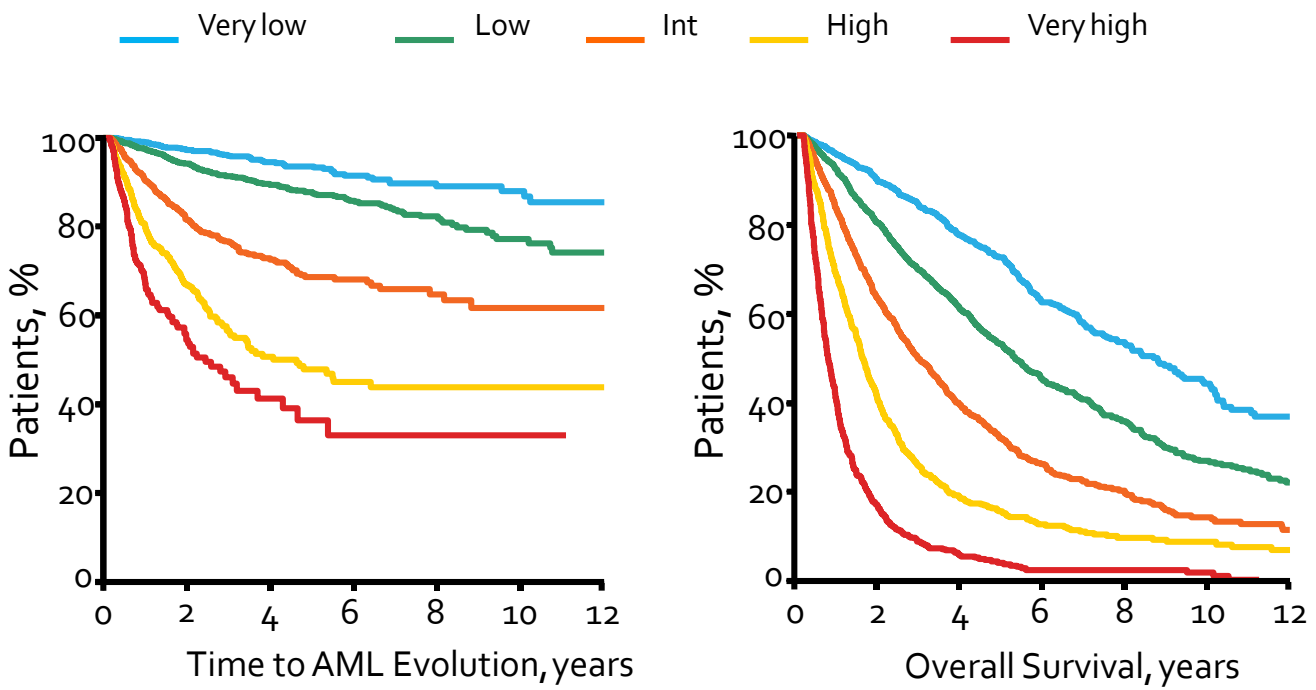
Risk group	Included karyotypes (19 categories)	Median survival (mo)	Proportion of pts (%)
Very good	del(11q), -Y	60.8	2.9
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p), der(1;7)	48.6	65.7
Intermediate	+8, del(7q), abnormal 17q, +19, +21, any other single or double abnormality not listed, 2 or more independent clones	26.1	19.2
Poor	der(3q), -7, double abnormality include -7/del(7q), complex with 3 abnormalities	15.8	5.4
Very poor	Very complex with >3 abnormalities	5.9	6.8

VARIABLE	0 pts	0.5 pts	1 pt	1.5 pts	2 pts	3 pts	4 pts
Cytogenetics	V. Good		Good		Intermediate	Poor	V. Poor
BM Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

Schanz J et al *JCO* 30:820-829, 2012; Greenberg et al. Blood 2012;120:2454-65.

IPSS-R (2012)

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤ 1.5	19 %	8.8	Not reached
Low	> 1.5 – 3	38 %	5.3	10.8
Intermediate	> 3 – 4.5	20 %	3.0	3.2
High	> 4.5 – 6	13 %	1.6	1.4
Very High	> 6	10 %	0.8	0.73



Schanz J et al *JCO* 30:820-829, 2012; Greenberg et al. Blood 2012;120:2454-65.

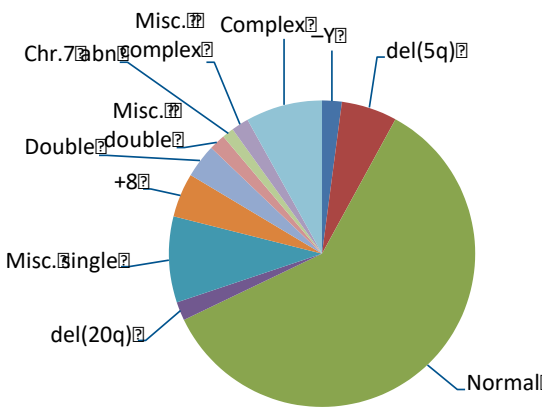
Treatment Approaches Largely Depend on Disease Risk

- Lower Risk- Transfusions, Erythropoeitin, Revlimid
  - MDS-SLD, MDS-MLD
  - MDS-U, MDS del (5q)
  - IPSS Low, Int-1; IPSS-R V. Low, Low

- Higher Risk- Vidaza, Dacogen, Transplant
  - MDS-EB (-1, -2)
  - IPSS Int-2, High; IPSS-R High, V. High

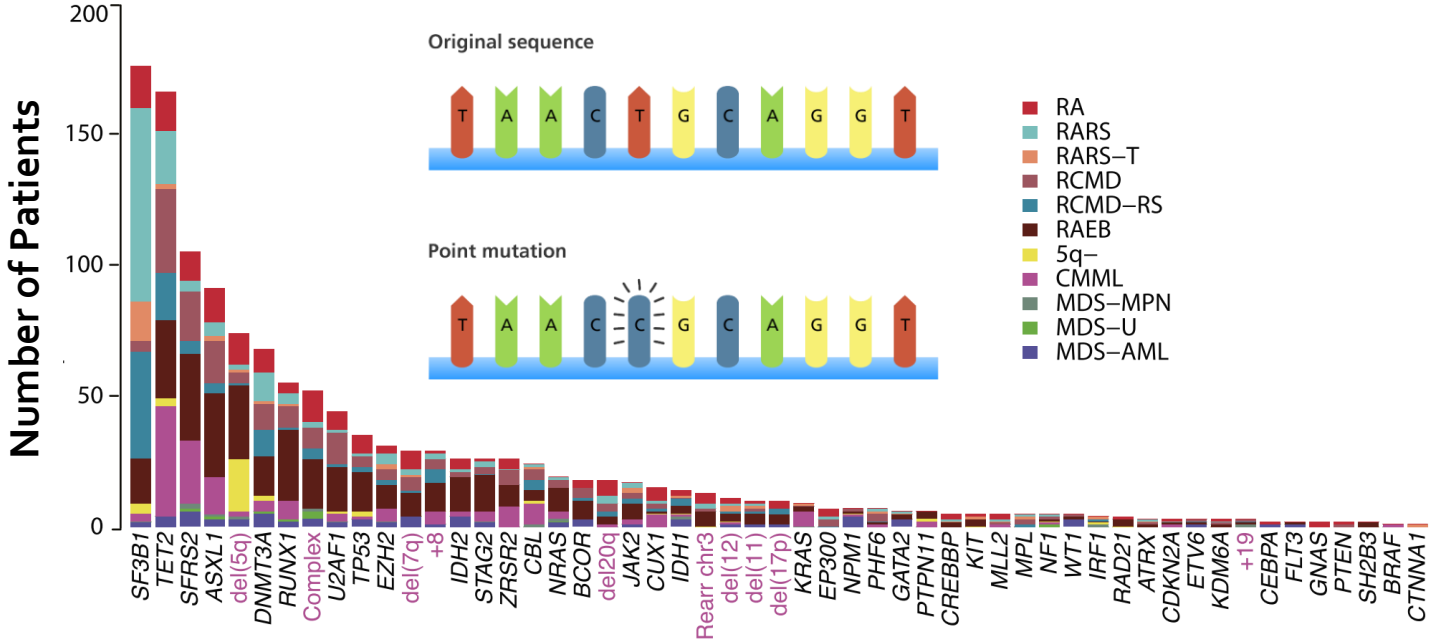
Gene Mutations are found in 80-90% of MDS Cases

Chromosomal Changes in ~50% of MDS



Greenberg P et al. *Blood*. 1997;89:2079-2088

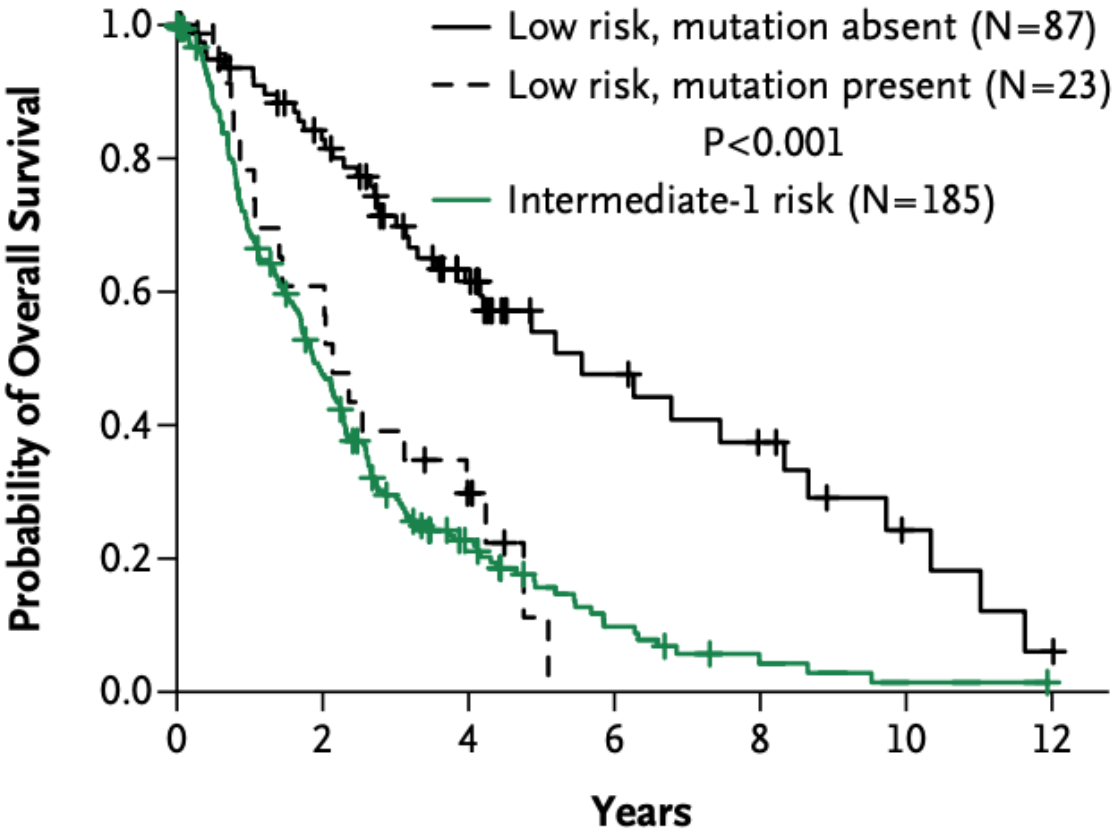
Sequencing of 111 genes in 738 MDS Patients



Papaemmanuil et al, Blood 2013

Identification of mutations shifts the IPSS in MDS

Sequencing of 18 genes in 439 MDS Patients

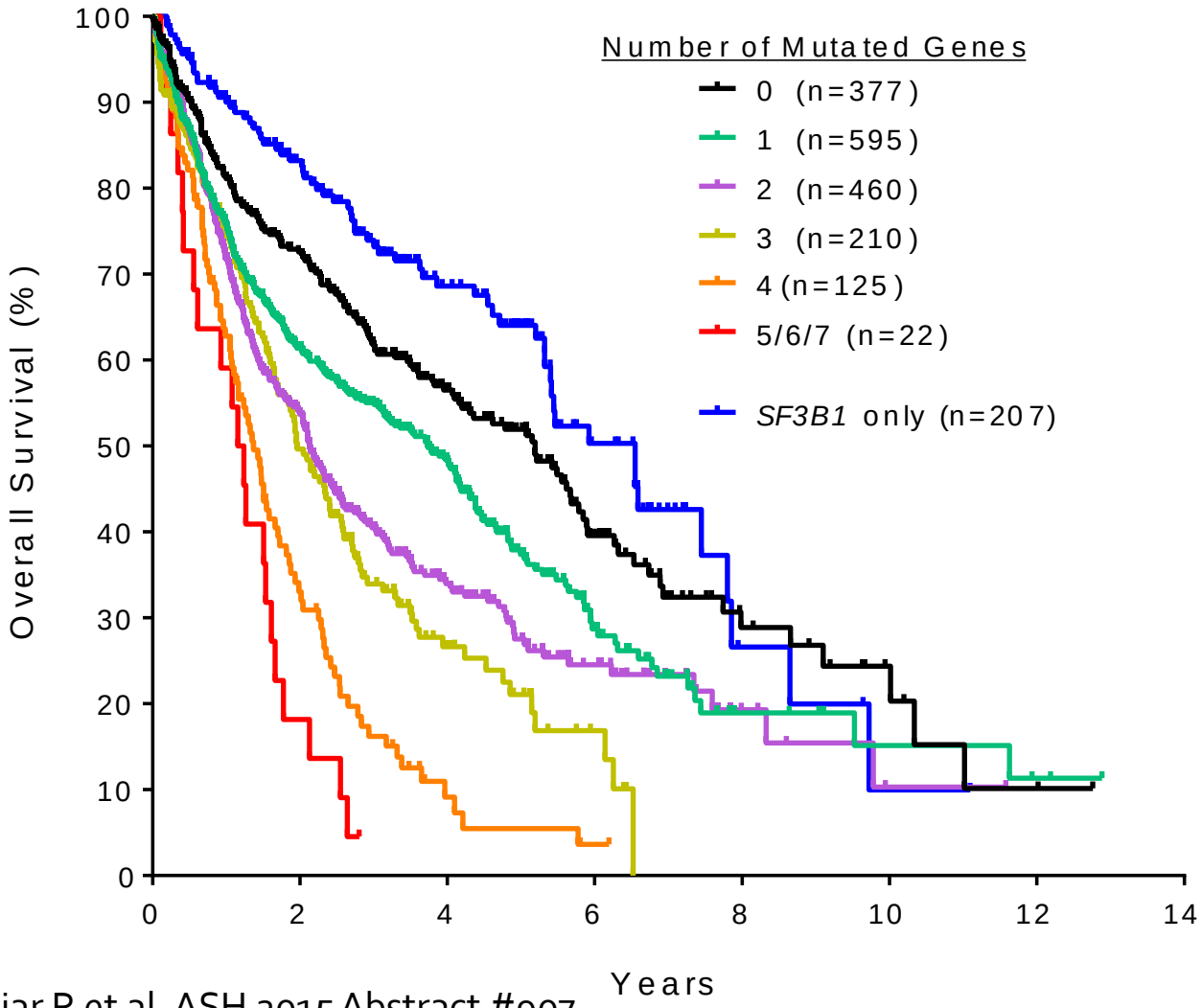


Bejar R, et al. *N Engl J Med.* 2011;364(26):2496-2506.

IWG-PM MDS sample compilation (n=3562): *MDS survival affected by mutation number*

Sequencing of 17 genes in 1996 MDS Patients

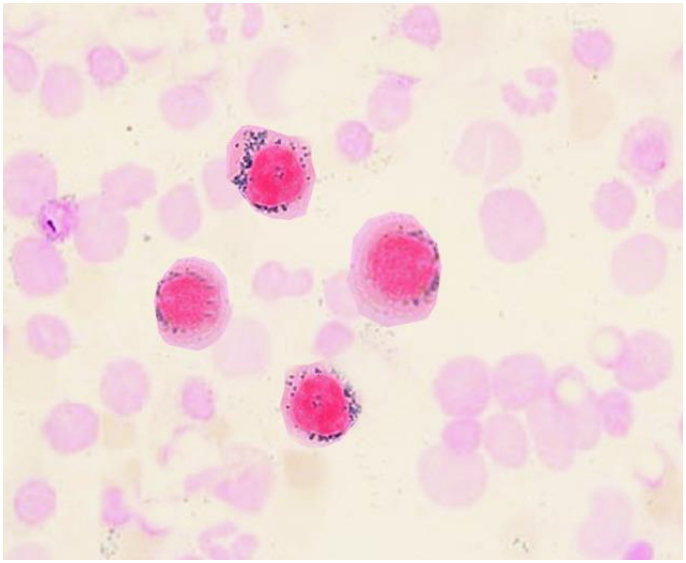
ASXL1
CBL
DNMT3
A ETV6
EZH2
IDH1
IDH2
JAK2
KRAS
NPM1
NRAS
RUNX1
SRSF2
TET2
TP53
U2AF1
SF3B1

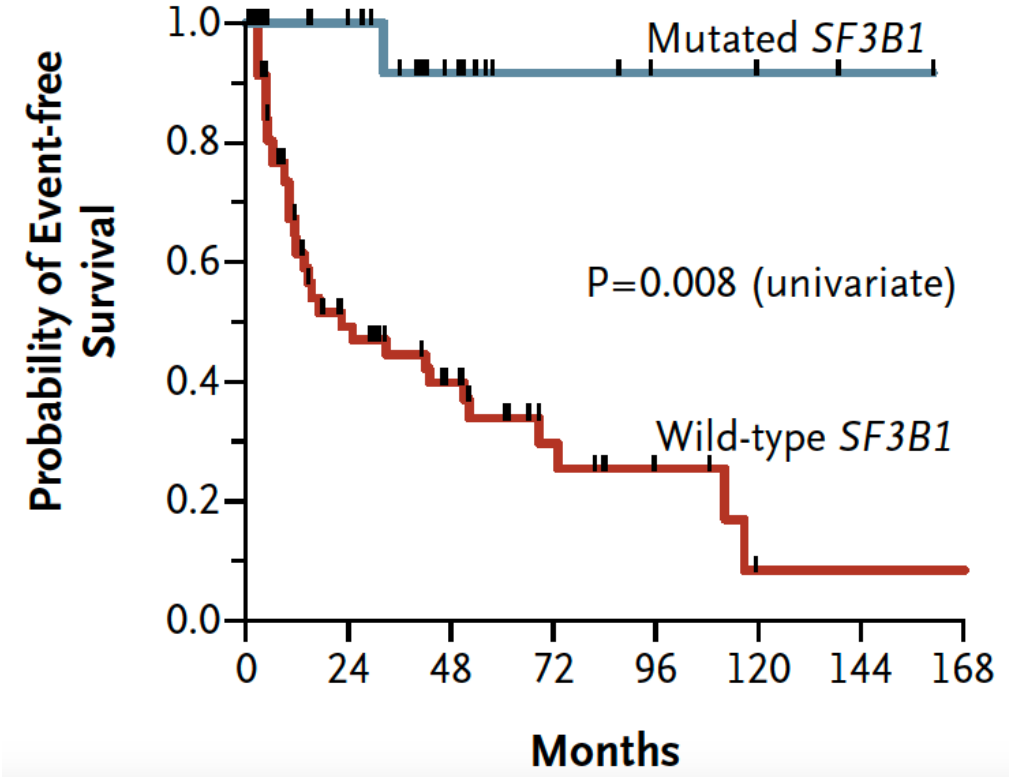


Bejar R et al, ASH 2015 Abstract #907

SF3B1 Mutations in MDS

- Present in 20% of cases
- Associated with:
  - fewer cytopenias
  - longer survival
  - MDS-RS subtype

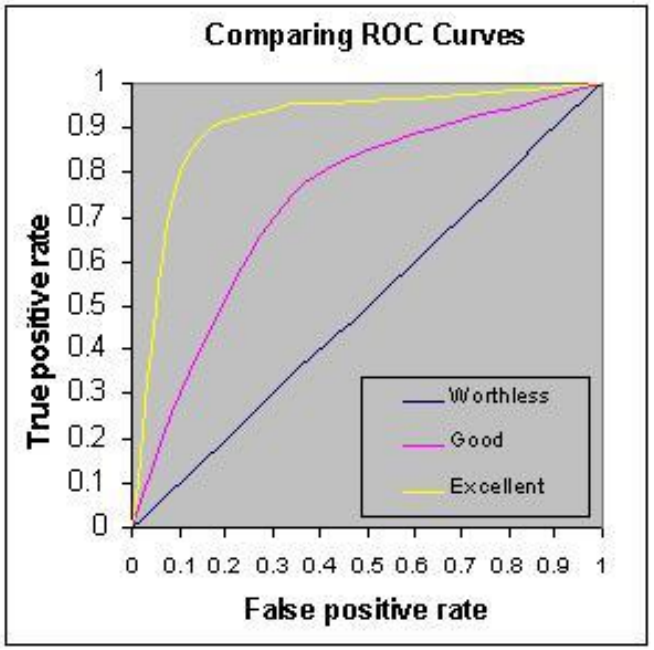




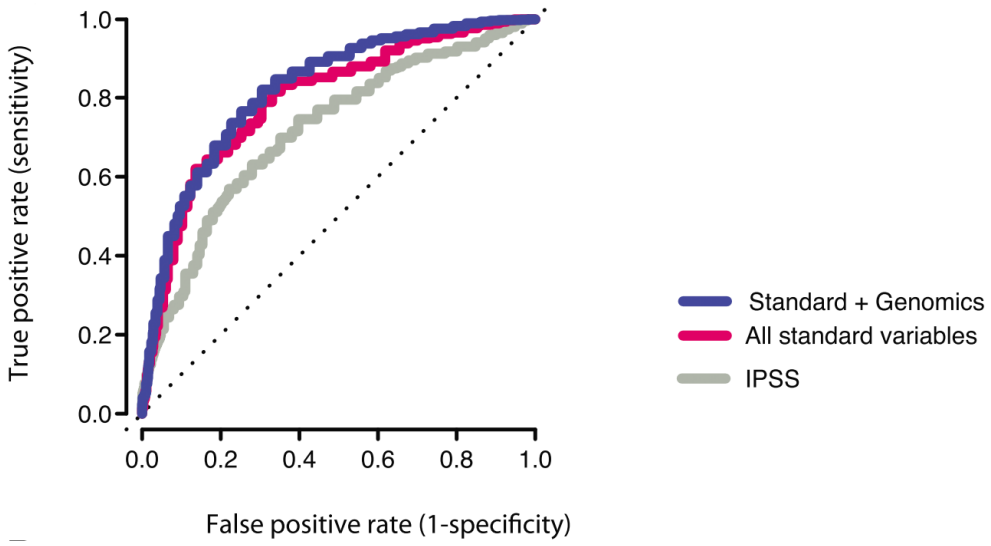
Papaemmanuil et al., NEJM 2011

Do Mutations Really Help With Prognostication?

ROC Curves Measure How Accurate a Test is



Mutation Data Actually Adds Little to "All Standard Variables"



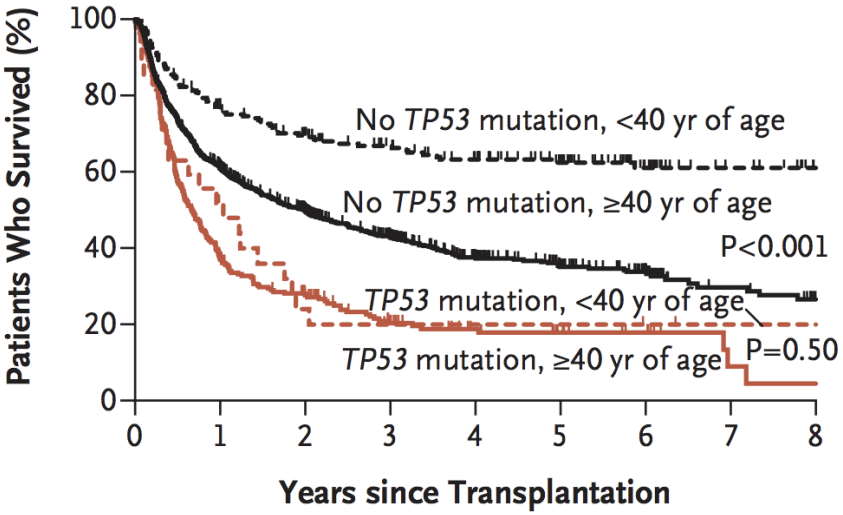
- IPSS- % blasts, number of cytopenias, and chromosomes
- "All Standard Variables"- IPSS + degree of cytopenias, more extensive list of chromosomes, multilineage dysplasia, and demographics
- Why? Many poor-risk mutations are associated with poor-risk disease features, e.g. thrombocytopenia

Papaemmanuil et al, Blood 2013

Why Check Mutations at All?

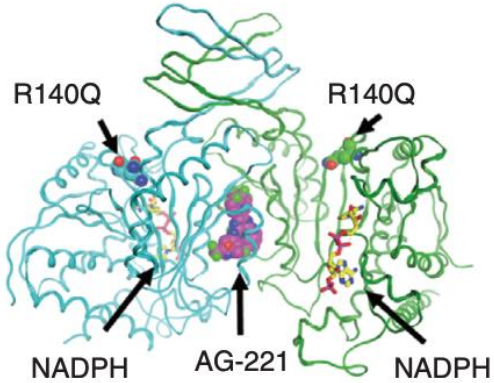
- It can assist with diagnosis
- Some IPSS low risk cases with high risk mutations may require closer observation
- Some IPSS high risk cases may be so high risk that even transplant may not help
- Certain mutations may be targeted using novel therapies on clinical trials
    - IDH mutations
        - AG-221, AG-120
    - SRSF2/SF3B1/U2AF1/ZRSR2
        - H3B-8800
    - TP53 mutations
        - APR-246

TP53 Mutations Predict for Worse Survival After Transplant



Lindsley et al., NEJM 2018

Inhibition of IDH2 with AG-221



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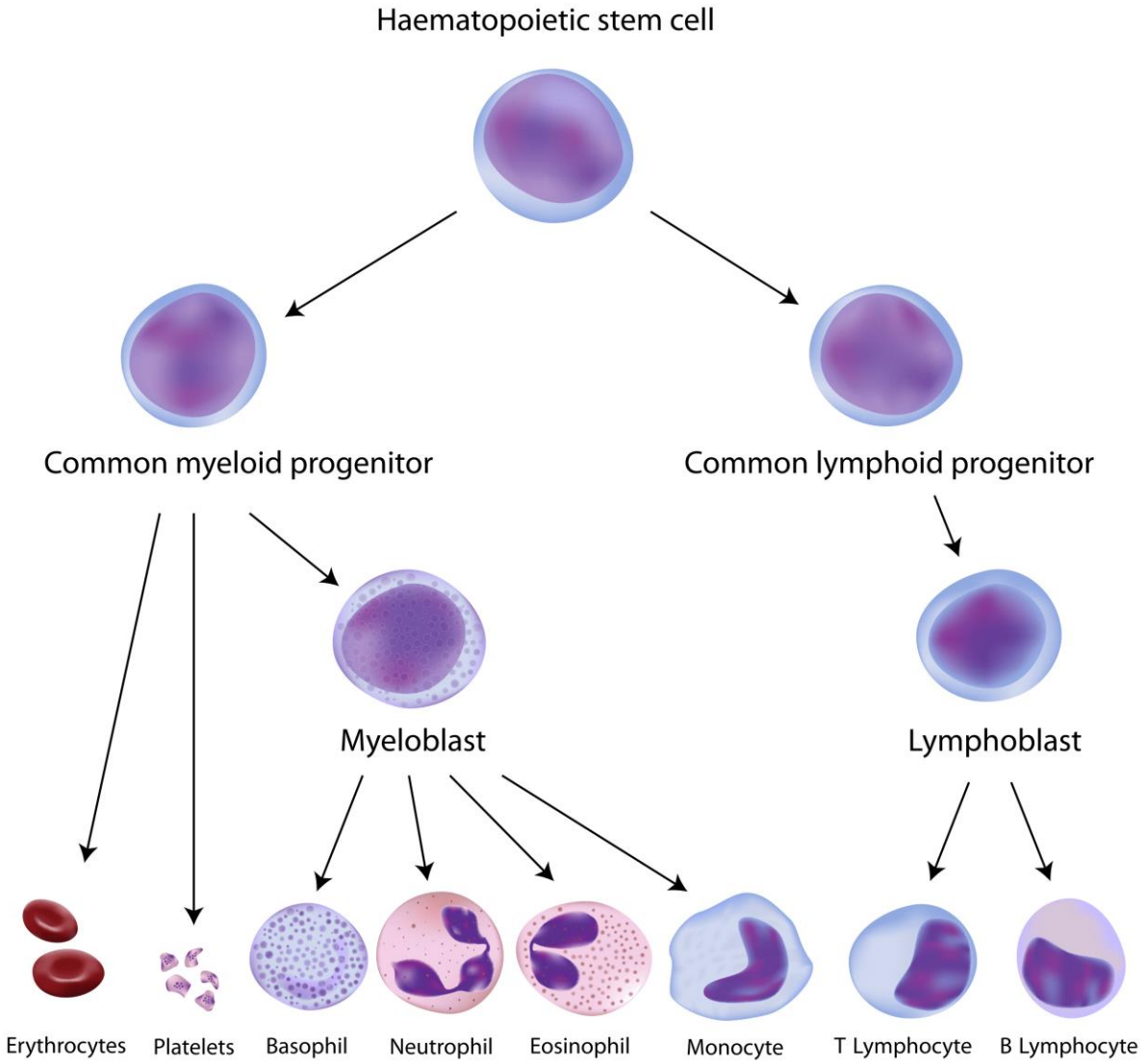
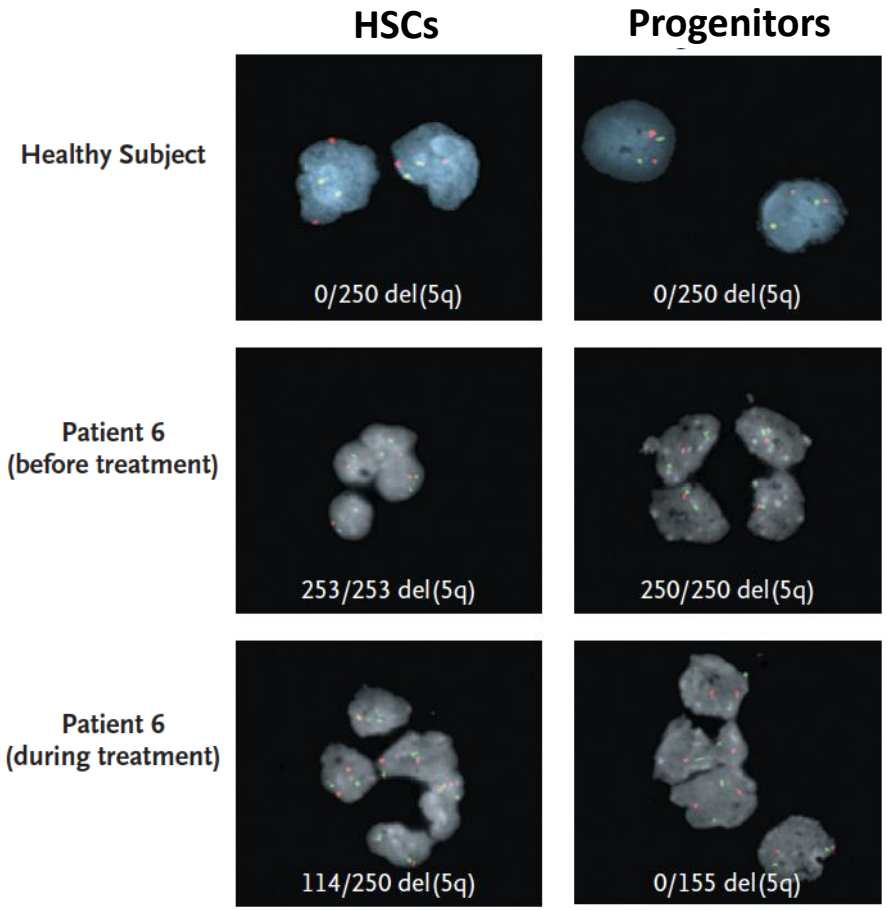


- **All blood cells come from HSCs**
- **HSCs are the only long lived cells in the blood system**
- **HSCs develop mistakes in DNA with age or exposure to toxins**
- **MDS happens when mistakes in DNA impair the function of HSCs**

MDS HSCs are Resistant to Standard Therapies

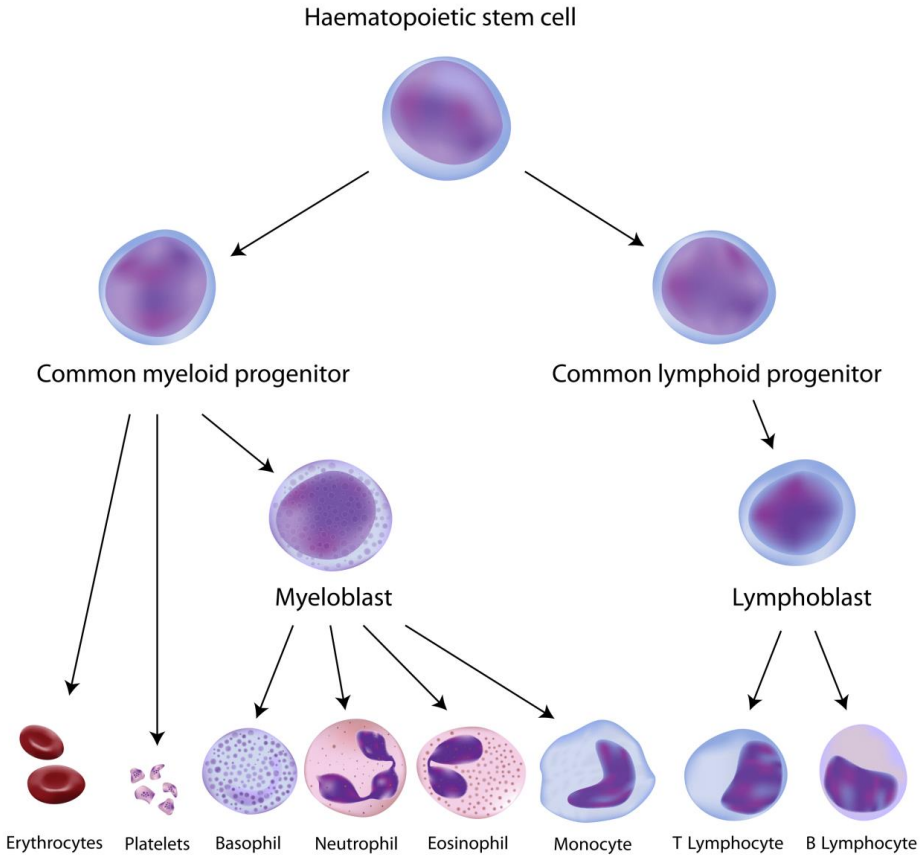
del 5q Persists in HSCs Despite a Clinical Complete Cytogenetic Remission on Revlimid



Tehranchi et al, NEJM 2010;363:1025

Role for Bone Marrow Transplantation

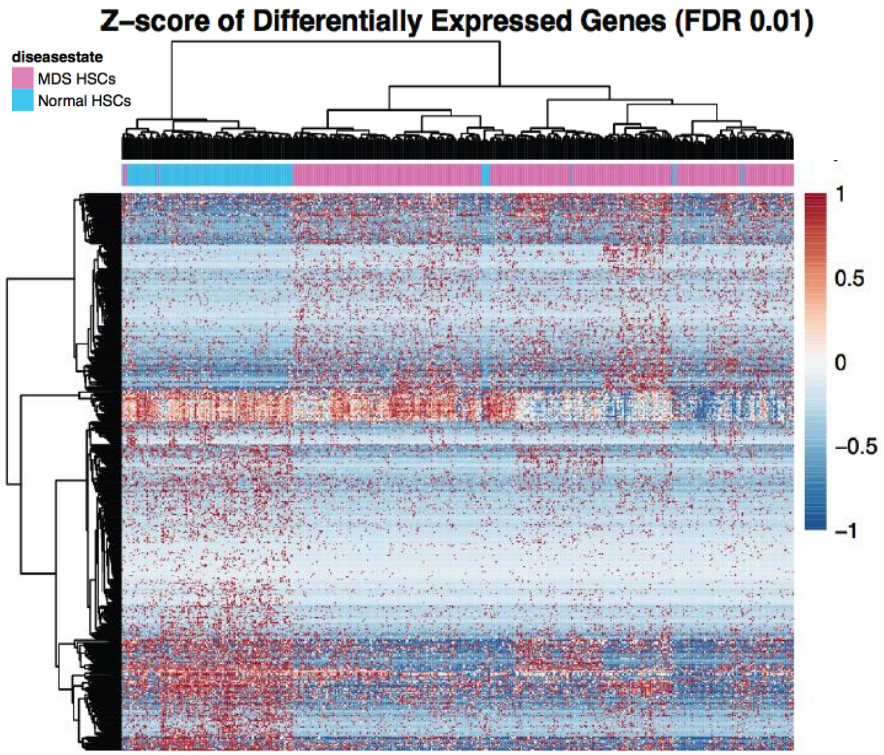
- Remains the only curative therapy for MDS
- Risk may outweigh the benefit if:
  - disease is low risk
  - patient is frail/very elderly
  - disease is very high risk- transplant may not be effective



MDS and Normal HSCs Exhibit Unique Gene Expression Signatures

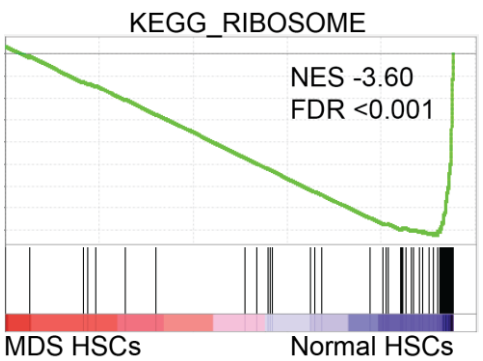
HSCs from Seven MDS Patients (pre-treatment or untreated) and Two Age-Matched Controls

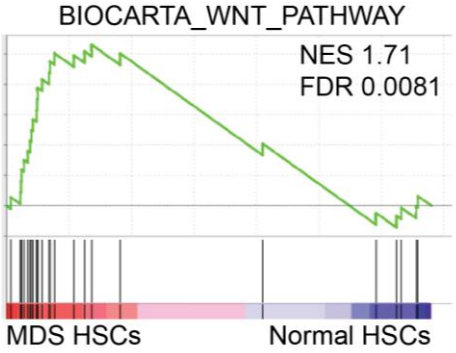
MDS Compared with Aged Matched Normal HSCs



2,606 DEGs with FDR <0.01, FPKM>1

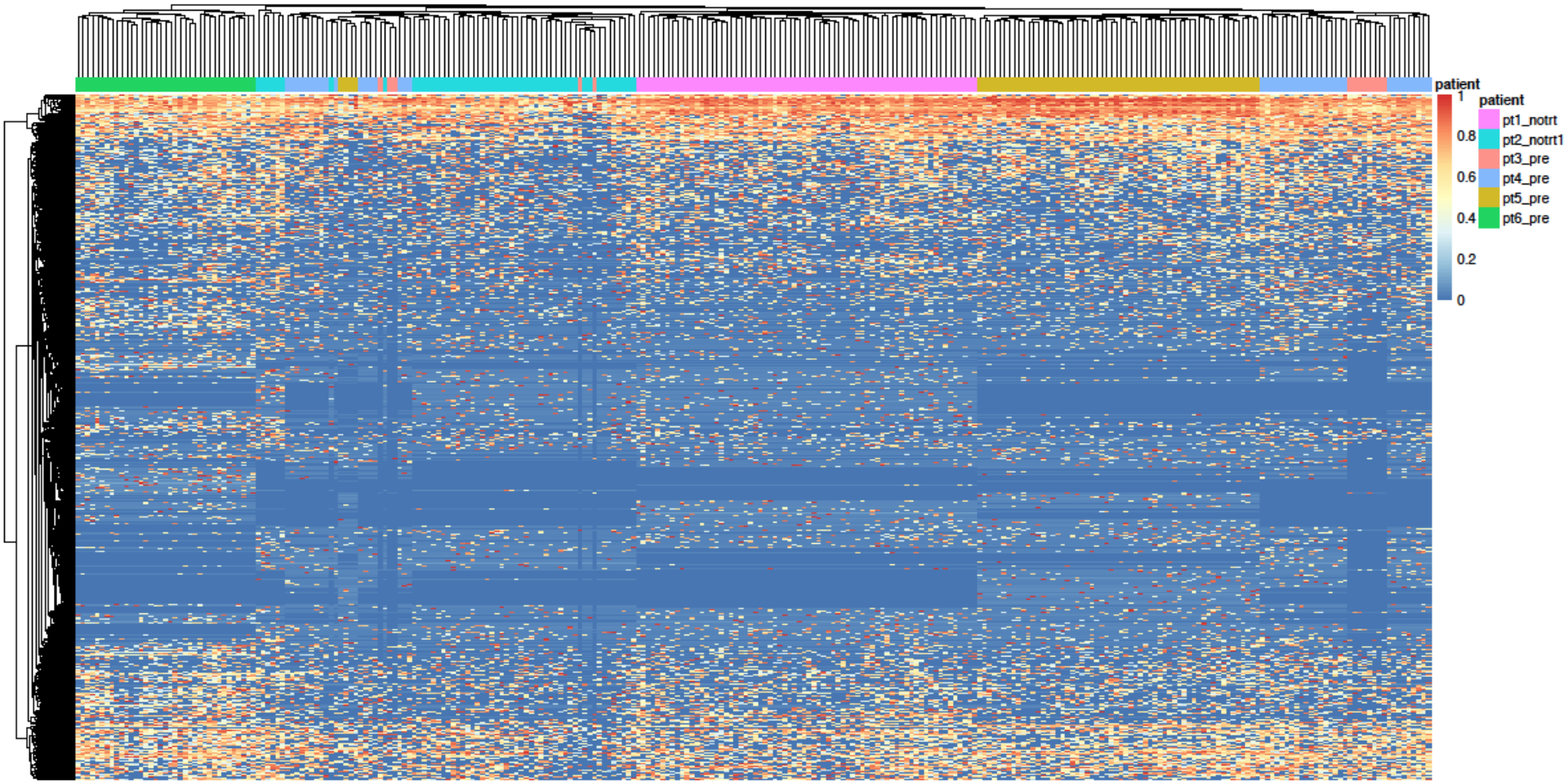
Gene Expression Signatures Associated with MDS HSCs





MDS is Heterogeneous

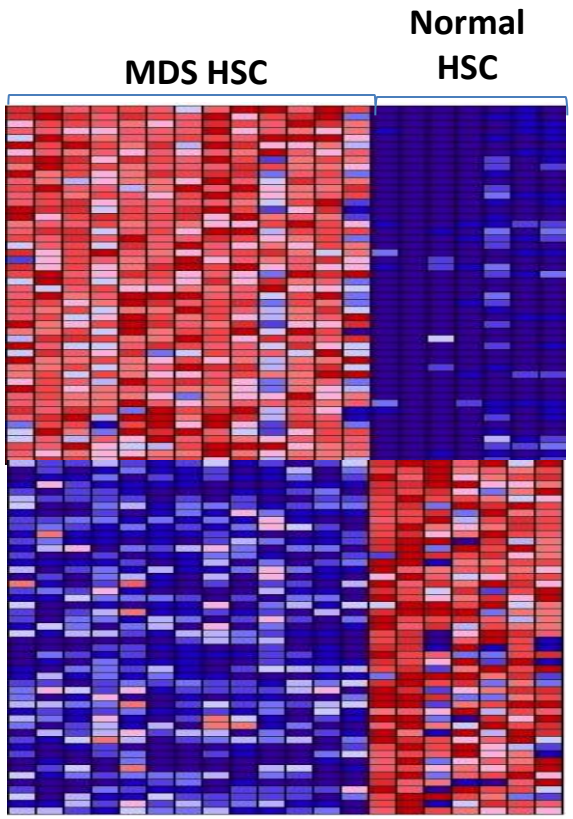
HSCs from Six MDS Patients (pre-treatment or untreated)



union of genes in top 10% of loadings on PC2, PC3, PC4

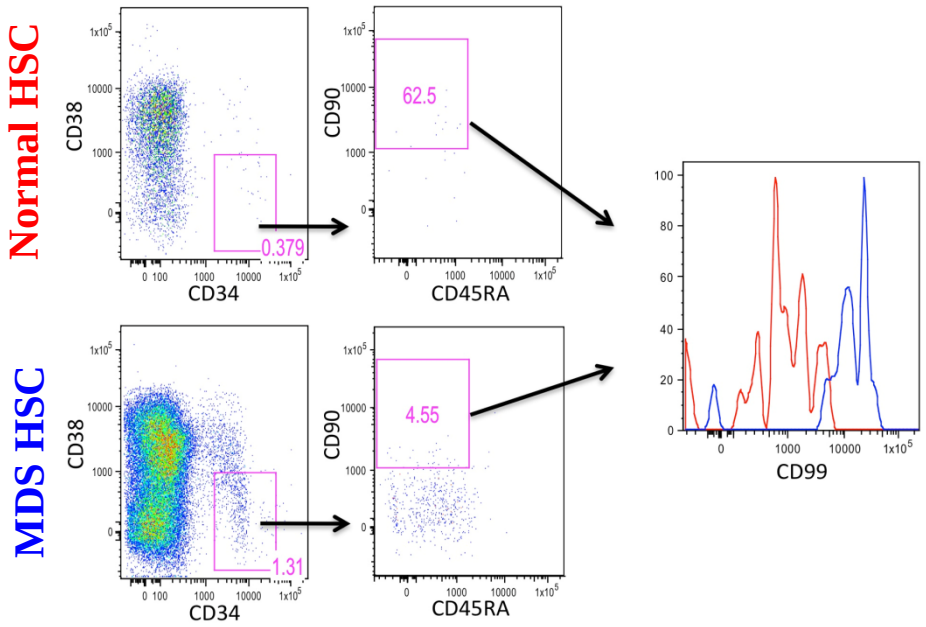
Discovery of Methods to Eradicate MDS HSCs

Genes Abnormally Expressed in MDS HSCs

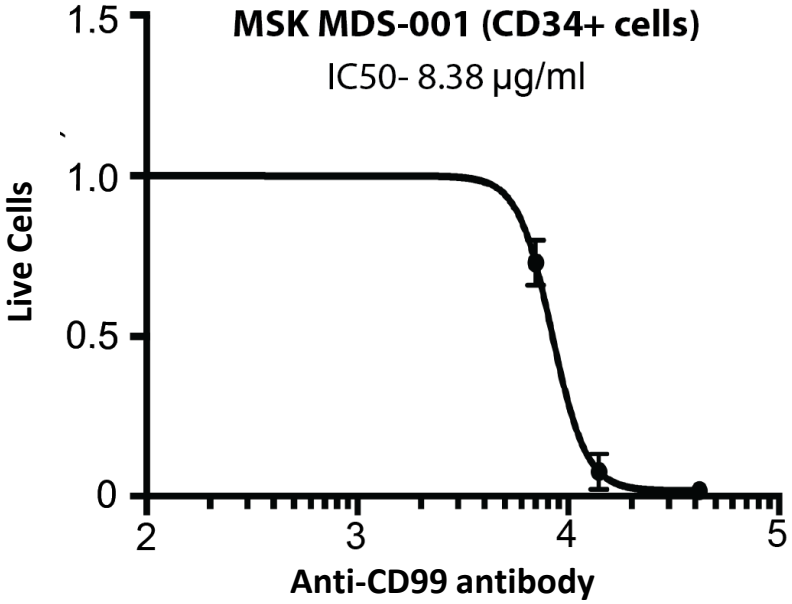


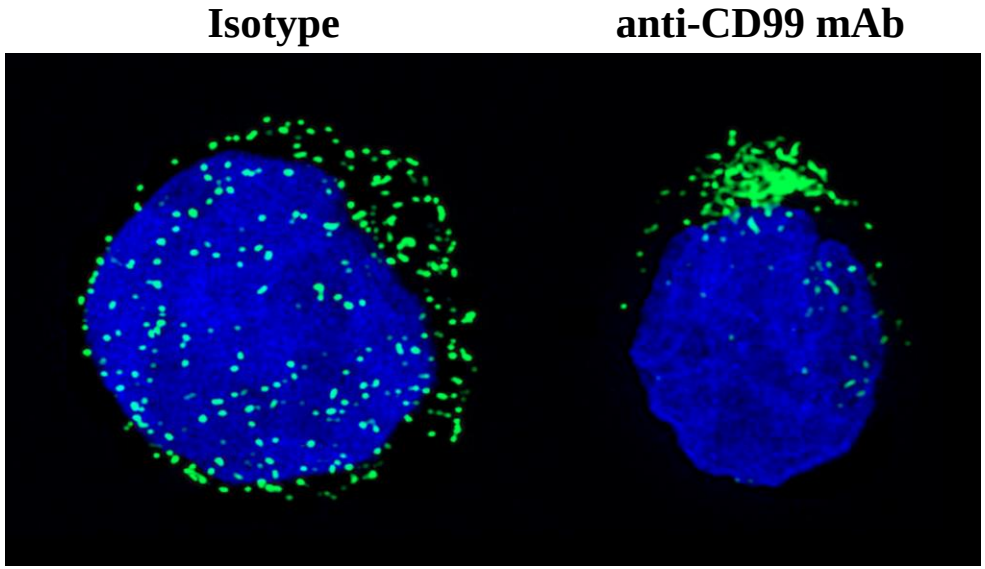
25 predicted to encode cell surface proteins

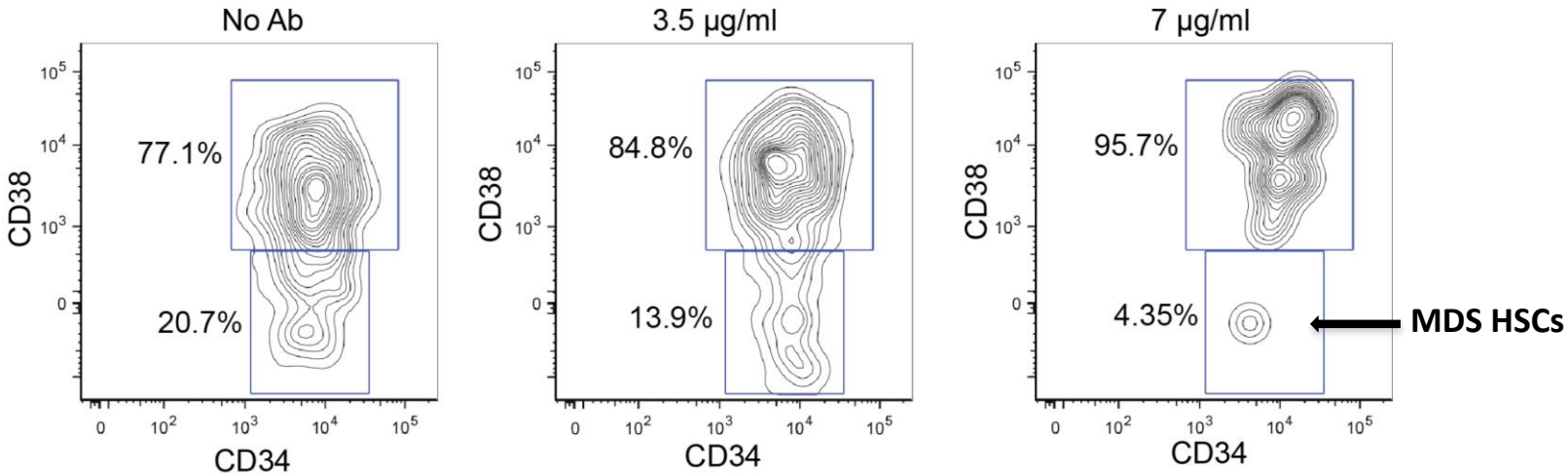
CD99 is Highly Expressed in MDS HSCs



Discovery of Methods to Eradicate MDS HSCs







Summary and Key Points

- MDS is diagnosed by:
  - Low blood counts
  - Dysplasia in the bone marrow
  - +/- Characteristic chromosome abnormalities
- Prognosis in MDS is determined by:
  - % blast cells in the bone marrow
  - How many cytopenias you have and how severe they are
  - Chromosomal abnormalities and gene mutations
- Therapies for MDS are largely recommended based on disease risk
- Mutations may allow for participation in certain clinical trials
- Cure of MDS requires eradication of HSCs

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