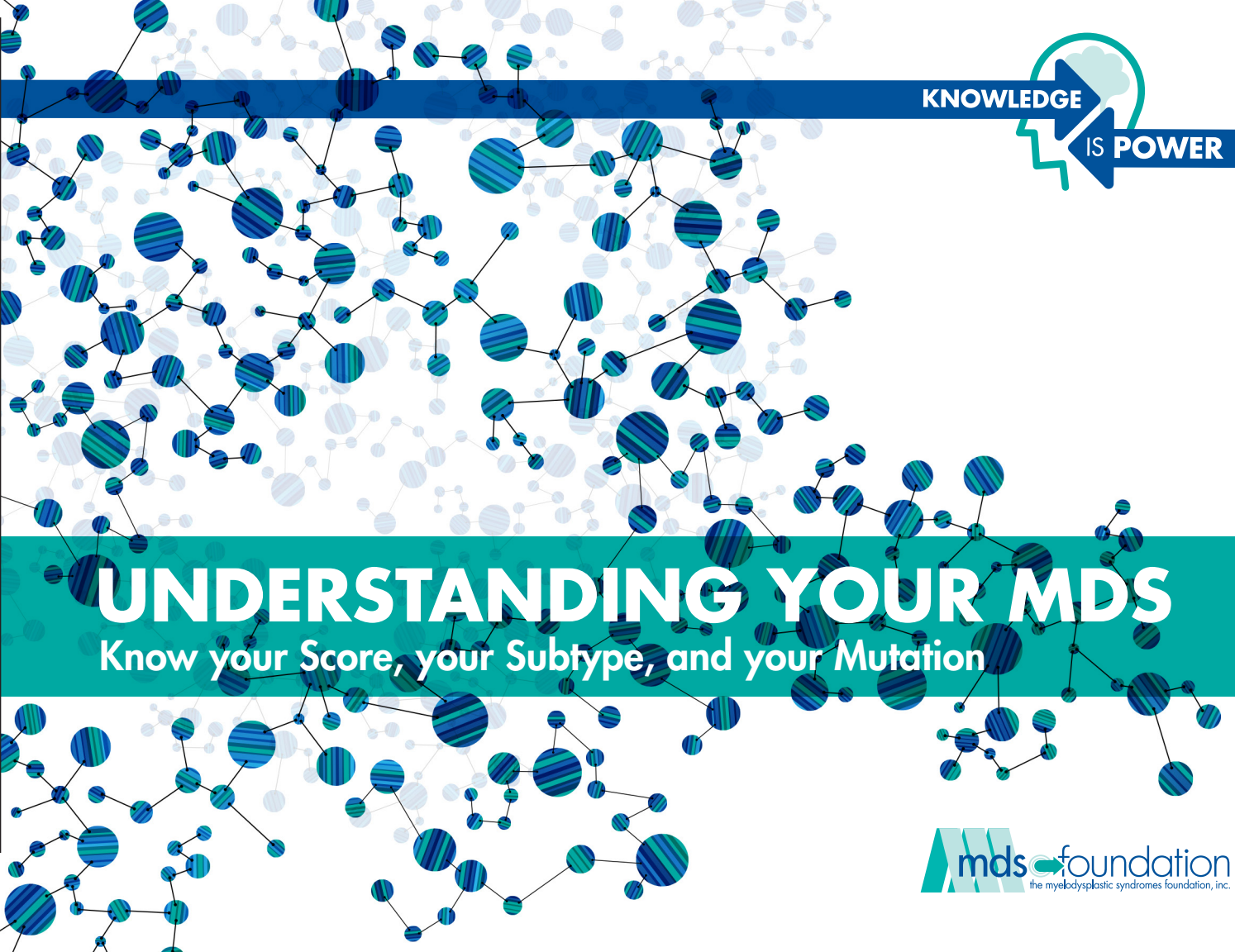
KNOWLEDGE IS POWER

UNDERSTANDING YOUR MDS

Know your Score, your Subtype, and your Mutation



mds foundation
the myelodysplastic syndromes foundation, inc.

This brochure is intended to help you better understand the diagnosis of MDS. Created by the MDS Foundation staff, Board of Directors, and medical and scientific leaders, it will explain the various MDS subtypes; how a prognostic scoring system is designed and where you can place yourself with the help of your physician and other health professionals.

You will learn about normal and abnormal blood cells; leukemic blasts; blood counts; chromosomes and molecular mutations that may assist your provider in further modifying your subtype and, possibly, selecting the type of therapy for you.

John M. Bennett, MD

First Chair and Founding Member of the MDS Foundation

DO YOU KNOW YOUR MDS SUBTYPE, IPSS-R SCORE AND GENE MUTATION PROFILE?

MDS treatment is individualized based on a patient's subtype, IPSS-R score and, to some extent, genetic mutation. This knowledge will empower patients and their caregivers to take a more active role in decisions about their treatment and advocate for appropriate treatments that may prolong their life and improve their quality of life. The following information is designed to help you understand how your subtype and IPSS-R score are determined, as well as general information on genetic mutations commonly found in MDS and the importance of genetic testing for these mutations.

Knowing your subtype, IPSS-R score and gene mutation profile will help facilitate discussions with your healthcare provider on what this means for you personally and help select the best treatment options.

IPSS-R SCORE: The IPSS-R is a classification system used by doctors to help predict a person's risk of developing AML and overall survival without treatment.

MDS SUBTYPE: MDS is classified into several different subtypes based on the following features: Blood cell counts, Percentage of blasts in the bone marrow, and Cytogenetics.

MUTATION PROFILE: Genetic mutations occur when a gene is damaged and alters the genetic message. Mutations can potentially identify effective therapies to treat your disease.

IPSS-R SCORING SYSTEM

The prognosis and disease course may vary widely among patients with MDS based on the type of MDS and the risk category (estimate of severity). The system most widely used to estimate the severity of MDS is the International Prognostic Scoring System (IPSS). This system has been revised and is now known as the Revised International Prognostic Scoring System (IPSS-R). The IPSS-R may be used to estimate life expectancy (survival) for a patient newly diagnosed with MDS without treatment and estimate the risk of developing acute myelogenous leukemia (AML).

The bone marrow biopsy and aspirate, the cytogenetics and the peripheral blood (CBC, differential and platelet count) are used to determine the risk category. The impact of molecular features is not yet included in this system. It is important to know that these criteria are used to guide treatment selection and to guide patient and caregiver counseling. They do not represent patients who are receiving treatment where survival may be extended.

There are five overall risk scores in the IPSS-R with estimated survival and median risk of AML:

Score	<1.5 Very Low	>1.5-3 Low	>3-4.5 Inter-mediate	>4.5-6 High	>6 Very High
Overall Survival (mean)	8.8 yrs	5.3 yrs	3.0 yrs	1.6 yrs	0.8 yrs
Risk of AML in 25% of patients (median)	Not reached	10.8 yrs	3.2 yrs	1.4 yrs	0.73 yrs

PROGNOSTIC VALUES FOR DETERMINING IPSS-R SCORE

A bone marrow biopsy and aspirate, cytogenetics and peripheral blood counts are used to determine your risk category (Very Low, Low, Intermediate, High, Very High). On the following pages you will learn more about each.

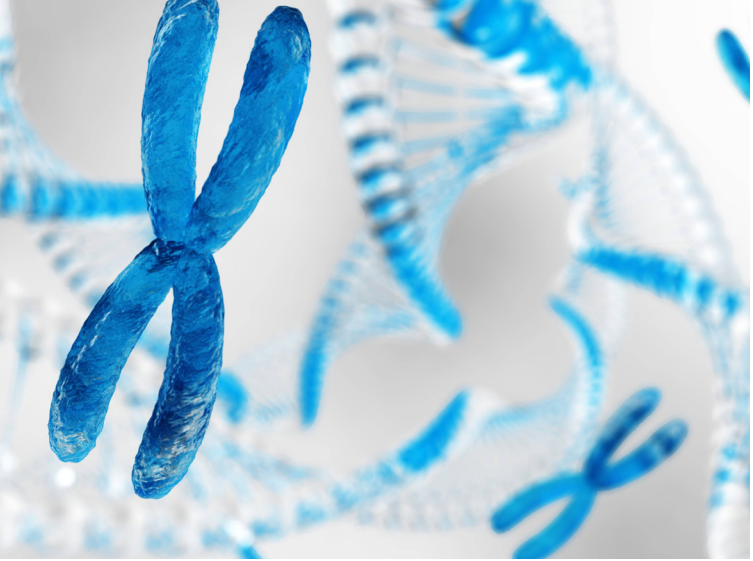
CYTOGENETICS

Cytogenetics is the study of the structure and function of the chromosomes. Long strings of DNA are coiled up with proteins to form the chromosomes. A chromosome abnormality is a missing, extra, or irregular portion of chromosomal DNA.[1] These can occur in the form of numerical abnormalities, where there is an atypical number of chromosomes, or as structural abnormalities, where one or more individual chromosomes are altered.

Certain cytogenetic changes are considered favorable, while others are considered less favorable. Some cytogenetic abnormalities are associated with a more favorable response to certain treatments, such as del(5q). MDS patients with del(5q) have been shown to respond more favorably to Lenalidomide (Revlimid®). The cytogenetic report will describe the number of cell divisions (usually 20), the number of normal chromosomes, and any chromosomes that are abnormal. The number of cell divisions (metaphases) is represented in brackets [ ].

The IPSS-R score is based, in part, on a revised grouping of cytogenetic abnormalities:

Cytogenetic Risk Group	Cytogenetic Abnormalities
Very Good	del(11q), -Y
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q). double including -7/del(7q) Complex: 3 abnormalities
Very Poor	Complex: >3 abnormalities



Cytogenetic abnormalities are present in approximately 40% of all cases of primary MDS, and in the majority of cases of secondary MDS. Cytogenetics play a very important role in estimating prognosis for a patient with MDS. The changes are described based on the actual structural changes seen when evaluating the chromosomes. Cytogenetics is only one of the five prognostic values for determining your risk score.

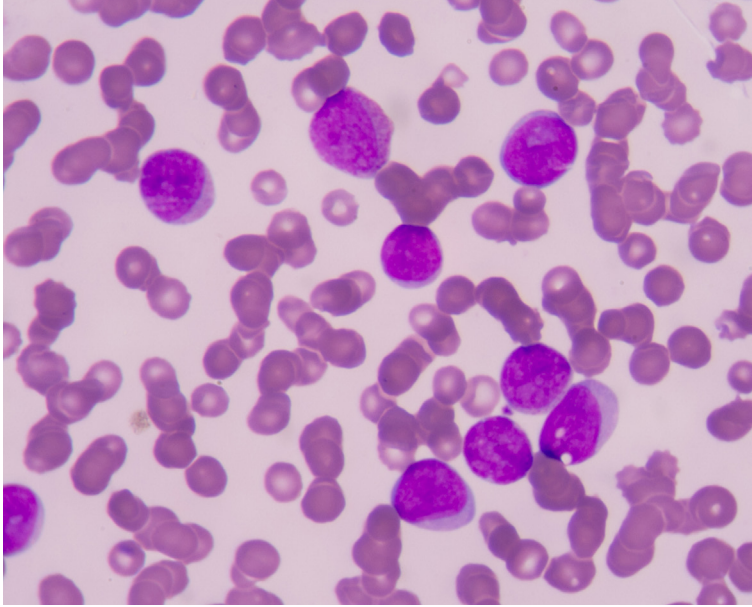
PROGNOSTIC VALUES FOR DETERMINING IPSS-R SCORE

Value/ Score	0	0.5	1	1.5	2	3	4
Cytogenetics Risk Group	Very Good		Good		Intermediate	Poor	Very Poor
Blasts (%)	<2%		>2%-<5%		5-10%	>10%	
Hemoglobin (g/dL)	≥10		8-<10	<8			
Platelets	≥100,000	50,000-<100,000	<50,000				
ANC	≥0.8	<0.8					

BONE MARROW BLASTS

Blasts, also called myeloblasts, are immature blood cells that do not function properly. These young blood cells are produced by stem cells. Too many blast cells interfere with the production of red blood cells, white blood cells and platelets.

The percentage of blasts in the bone marrow impacts prognosis. The higher the percentage of blasts the higher the score on the IPSS-R.



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HEMOGLOBIN

Hemoglobin (Hgb) is a large iron-containing protein found in red blood. This protein is what makes 'red cells' red. Hemoglobin's job is to pick up oxygen in the lungs, carry it in the red blood cells, and then release oxygen into the tissues that need it like the heart, muscles, and brain. Hemoglobin also removes carbon dioxide from the tissues and carries this waste product back to the lungs where it is exhaled.

NORMAL HEMOGLOBIN RANGES

Men: 13.5 to 17.5 grams per deciliter (g/dL)
Women: 12.0 to 15.5 grams per deciliter (g/dL)

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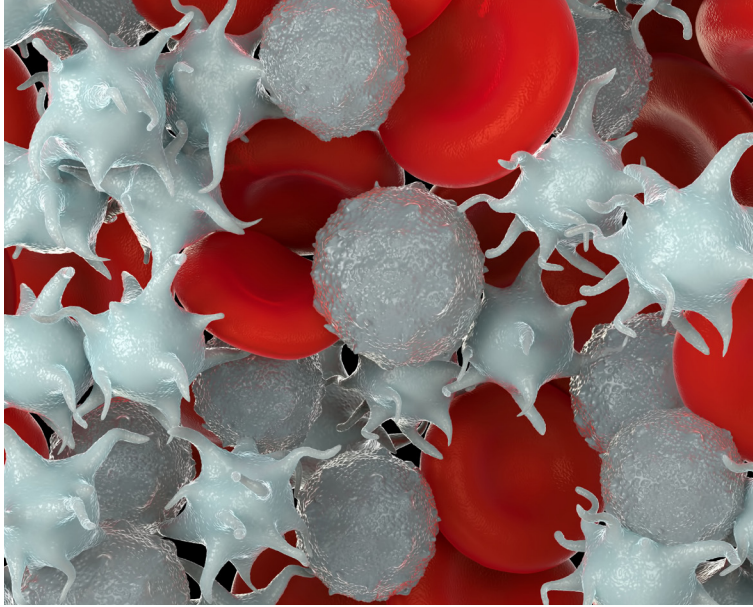
Platelets	≥100,000	50,000-<100,000	<50,000				
ANC	≥0.8	<0.8					

PLATELETS

Platelets, also called thrombocytes, are tiny blood cells that help your body form clots to stop bleeding. Platelets are produced in bone marrow by a process known as thrombopoiesis. Platelets are critical to blood coagulation and the formation of clots to stop bleeding.

A normal platelet count is between 150,000 to 450,000 platelets per microliter of blood.



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Platelets	≥100,000	50,000-<100,000	<50,000				
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ABSOLUTE NEUTROPHIL COUNT (ANC)

Absolute Neutrophil Count (ANC) is a measure of the number of neutrophil granulocytes present in the blood. Neutrophils are a type of white blood cell that fights against infection. Neutropenia is a low number of neutrophils in the bloodstream which may result in an increased risk of infection. Neutropenia may be either mild, moderate or severe depending on the number of neutrophils present in the blood. A healthy person has an ANC between 2,500 and 6,000 neutrophils/mcL (2.5-6.0).

Mild: 1,000-1,500 neutrophils/mcL (1.0-1.5)
Moderate: 500-1,000 neutrophils/mcL (0.5-1.0)
Severe: <500 neutrophils/mcL (0.5)

PROGNOSTIC VALUES FOR DETERMINING IPSS-R SCORE

Value/ Score	0	0.5	1	1.5	2	3	4
Cytogenetics Risk Group	Very Good		Good		Intermediate	Poor	Very Poor
Blasts (%)	<2%		>2%-<5%		5-10%	>10%	
Hemoglobin (g/dL)	≥10		8-<10	<8			
Platelets	≥100,000	50,000-<100,000	<50,000				
ANC	≥0.8	<0.8					

WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION SUBTYPES*

The WHO classification of MDS was updated in 2018. The WHO classification system has incorporated the key parts of the FAB classification system. The FAB Classification has been replaced by the WHO Classification System and is largely only used for historic reference and comparison. The WHO categories are largely based on morphology (how the cells look under the microscope), the presence of blasts (immature cells), how many cell lines are involved, and specific cytogenetic or molecular findings.

*The subtypes are based on the 2018 WHO Classification System. If you were classified under the 2008 WHO System (RA, RCUD, RARS, RCMD, RCMD-RS, RAEB-1, RAEB-2) your corresponding 2018 classification subtype is:

2008 Classification	2018 Classification
RA	MDS
RCUD	MDS-SLD
RARS	MDS-SLD with ring sideroblasts
RCMD	MDS-MLD
RCMD-RS	MDS-MLD with ring sideroblasts
RAEB-1	MDS-EB1
RAEB-2	MDS-EB2
5q- (5q minus) Syndrome	MDS with isolated del(5q)
Unclassified MDS	MDS-U (MDS, unclassifiable)

BLOOD CELLS

NORMAL
Red Blood Cells

ABNORMAL
Red Blood Cells

NORMAL
White Blood Cells

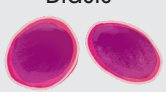
ABNORMAL
White Blood Cells

NORMAL
Platelets

ABNORMAL
Platelets

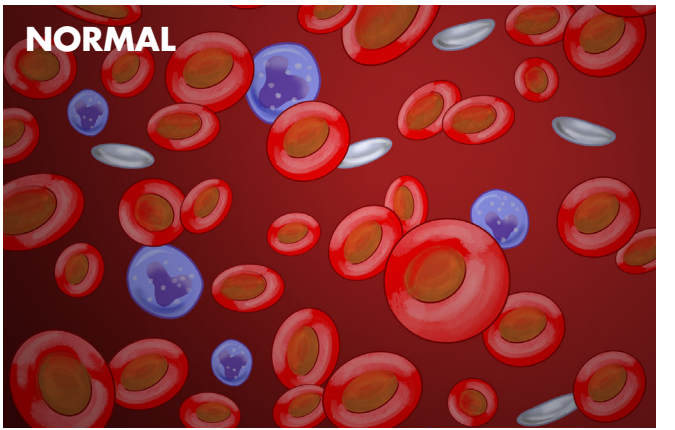
Red Blood Cells
with Sideroblasts

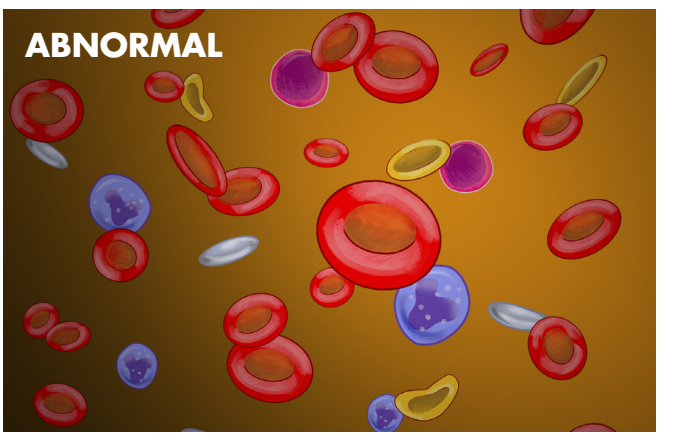
Blasts



MDS WITH SINGLE LINEAGE DYSPLASIA (MDS-SLD)

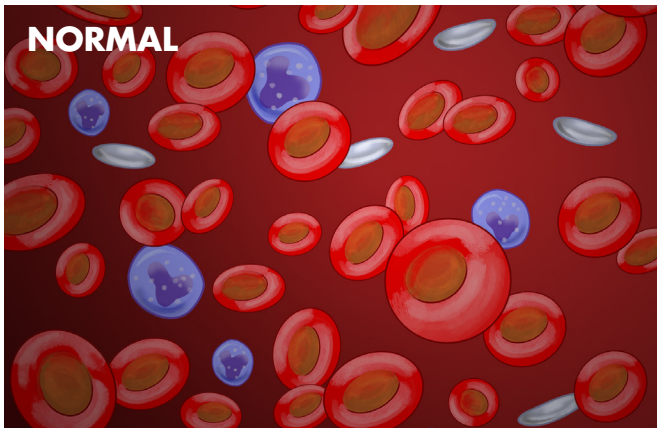
MDS-SLD exhibits a low number of **one to two types of blood cells** in the bloodstream and **one type of blood cell looks abnormal (dysplasia)** in the bone marrow. For the affected cell type, at least 10% of the cells look abnormal (dysplasia). Less than 5% of cells in the bone marrow are blast (immature) cells with no blasts in the bloodstream.

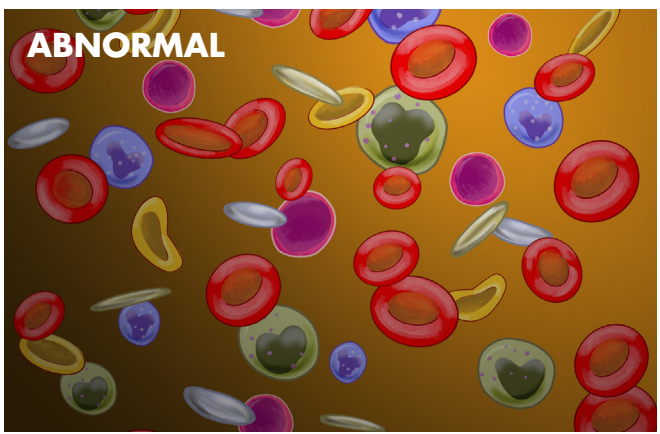




MDS WITH MULTILINEAGE DYSPLASIA (MDS-MLD)

MDS-MDL exhibits a low number of **one or more types of blood cells** in the bloodstream and **two or more types of blood cells look abnormal** in the bone marrow. Of the affected cell types, at least 10% of the cells look abnormal. Less than 5% of cells in the bone marrow are blast cells with no blasts in the bloodstream.





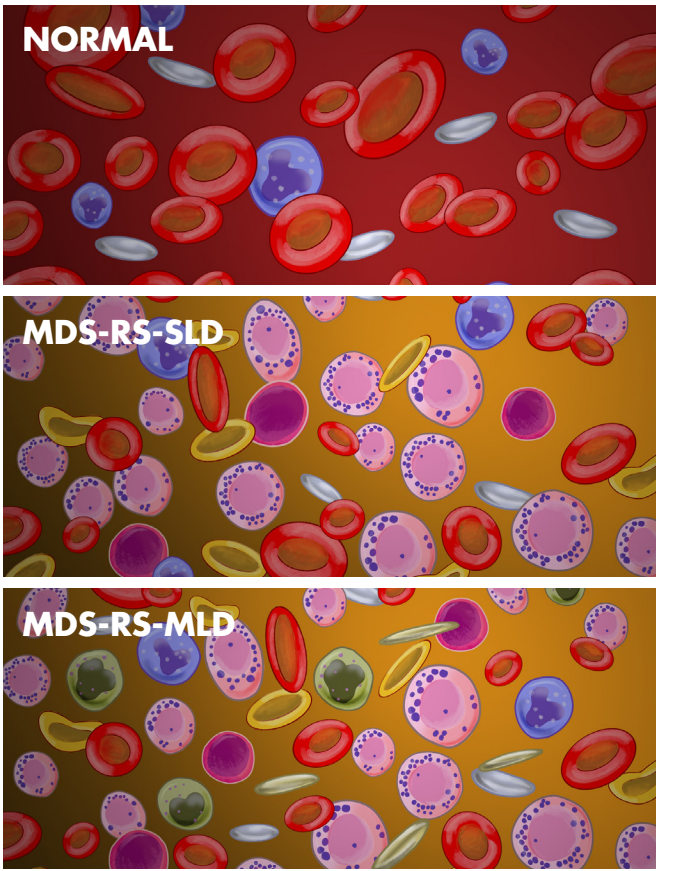
MDS WITH RING SIDEROBLASTS (MDS-RS)

MDS-RS exhibits a low number of **one or more types of blood cells** in the bloodstream and bone marrow. At least 15% of immature red blood cell precursors (contain a nucleus) in the bone marrow show rings of iron called ring sideroblasts (or at least 5% of the cells also have a mutation in the SF3B1 gene). Less than 5% of cells in the bone marrow are blast cells.

There are 2 types of MDS-RS:

MDS-RS and Single Lineage Dysplasia (MDS-RS-SLD): has the same characteristics as MDS-SLD; where only one type of blood cell has at least 10% of the cells that look abnormal (dysplasia) but this subtype also has ring sideroblasts on the red blood cell precursors.

MDS-RS and Multilineage Dysplasia (MDS-RS-MLD): has the same characteristics as MDS-MLD; where two or more types of blood cell has at least 10% of the cells that look abnormal (dysplasia) but this subtype also has ring sideroblasts.



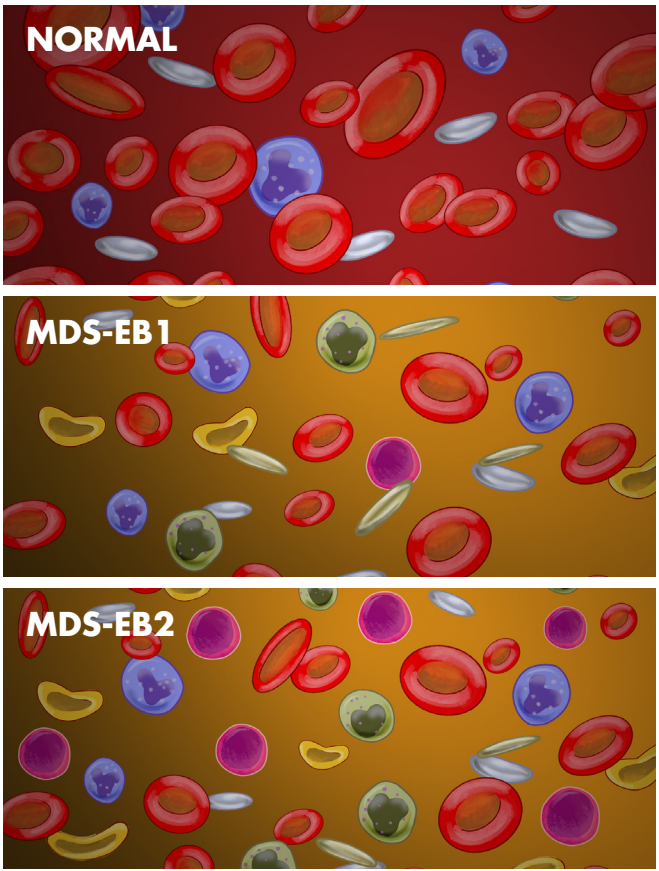
MDS WITH EXCESS BLASTS (MDS-EB)

MDS-EB exhibits a low number of **one or more types of blood cells** in the bloodstream that also look abnormal in the bone marrow with an increased number of blast (immature) cells.

There are 2 types of MDS-EB:

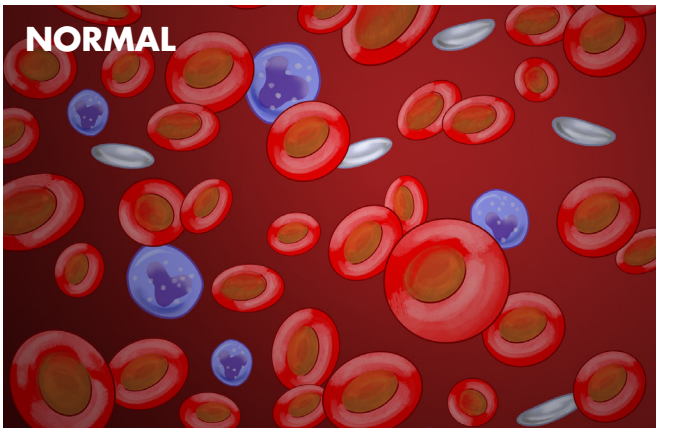
MDS-EB1: less than 5% of cells in the bloodstream are blasts. In the bone marrow, 5-9% of cells are blast cells.

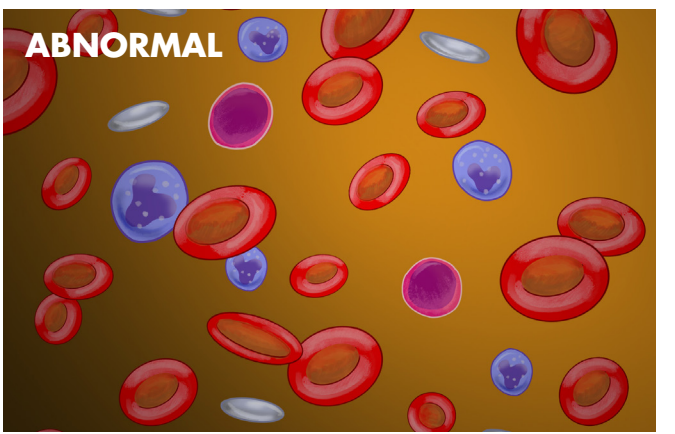
MDS-EB2: 5-19% of cells in the bloodstream are blast cells and 10-19% of cells in the bone marrow are blast cells.



PROVISIONAL ENTITY: REFRACTORY CYTOPENIA OF CHILDHOOD (RCC)

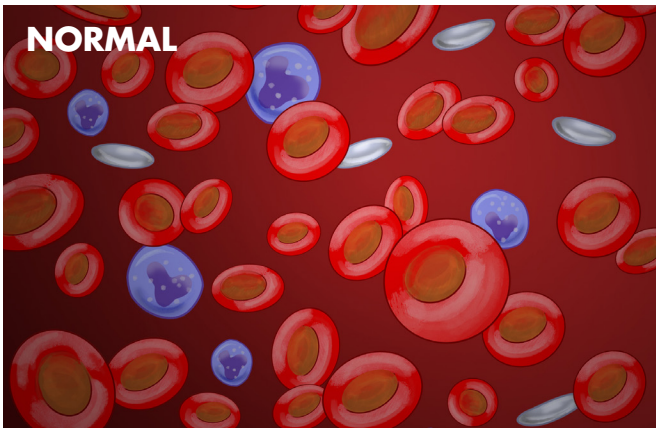
Refractory Cytopenia of Childhood (RCC) is characterized by persistent cytopenia with less than 5% blasts in bone marrow and less than 2% blasts in the bloodstream. This is the most common subtype of childhood MDS.

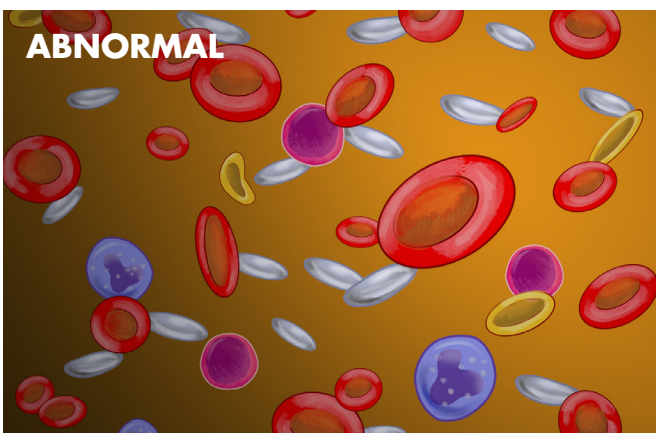




MDS WITH ISOLATED DEL(5Q)

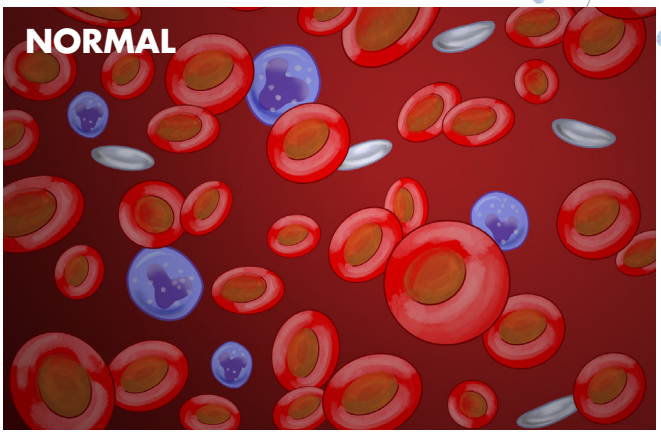
MDS with isolated del(5q) is identified when part of chromosome 5 is missing (deleted), this change is called del(5q). One additional chromosome abnormality is also permitted as long as it does not involve chromosome 7. There is a low number of red blood cells in the bloodstream and the number of platelets is normal or high. There is dysplasia in at least one cell type in the bone marrow and less than 5% of the cells are blast (immature) cells.

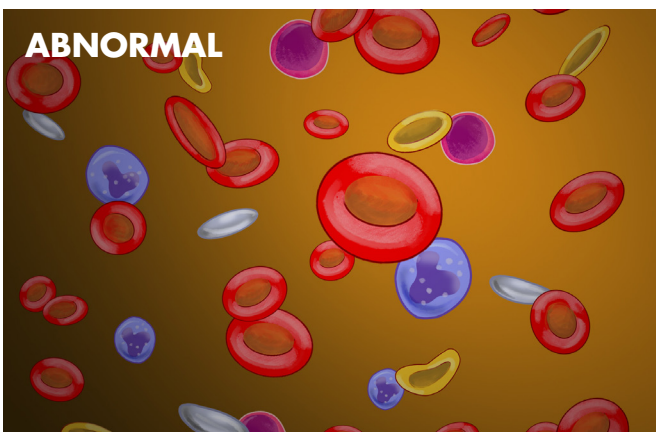




MDS UNCLASSIFIABLE (MDS-U)

MDS-U exhibits features of the blood and bone marrow that don't fit any of the other subtypes. One or more types of blood cells are low in the bloodstream, but less than 10% of that cell type may look abnormal in the bone marrow. Very few or no blast (immature) cells are found in the bloodstream on at least 2 occasions and less than 5% of the cells in the bone marrow are blasts. Sometimes the diagnosis is made solely based on the presence of a typical chromosome abnormality that is linked with MDS.





A GUIDE TO MUTATIONS

Mutation testing is gaining importance in MDS. It is estimated that 90% of patients with MDS harbor one or more genetic mutations. Chromosomes contain several thousand genes. Genes are shorter sections of DNA. Each gene acts as a code or set of instructions for making a specific protein. These proteins control the cell's activity, telling the cell what to do. Genes can become mutated (altered, faulty). In most cases, the cause of these mutations is not fully understood but we know that mutations accumulate as we age. Knowing which genes are mutated can help your doctor understand how you are likely to be affected by your MDS. In some cases, a mutated gene can be targeted to interrupt the abnormal production of blood cells common in MDS.

Mutations are currently identified by sequencing the DNA, commonly using a technique called "next generation sequencing" (NGS) using the material from a bone marrow or blood sample. Today, the mutation profile is used primarily for estimating prognosis. Several clinical trials are exploring the potential therapeutic benefit of targeting genes known to promote MDS. Importantly, the mutation profile may change over time. This is why it is important to re-characterize MDS at points of progression.

The International Working Group for Prognosis in MDS (IWG-PM) is working to better define individual molecular (genetic) abnormalities and their significance in MDS. There are many clinical trials focused on exploring the potential benefits of targeting genes known to cause and promote MDS. In some cases, the production of abnormal cells can be interrupted and lead to improved blood counts.

Your doctor may have ordered a DNA sequencing study to identify mutated genes in your MDS cells. This test can help confirm your diagnosis and provide information about which subtype of MDS you have. Some mutated genes are associated with lower risk disease while others may indicate greater risk. Mutations can potentially identify effective therapies to treat your disease. Knowing which genetic mutations are present in your MDS cells will open discussions with your healthcare provider about individualized risk assessment and treatment. Your genetic profile may change over time therefore it is important to re-characterize MDS at points of progression.

SOME COMMONLY MUTATED GENES IN MDS

SF3B1	DNMT3A	IDH2	ASXL1	SRSF2
IDH1	TET2	TP53	RUNX1	U2AF1

CHROMOSOMES

Chromosomes are structures within cells that contain a person's genes. Every person has 46 chromosomes. Each chromosome contains thousands of genes.

GENES

Genes, contained in chromosomes, are segments of deoxyribonucleic acid (DNA) that contain the code for making a specific protein that functions in one or more types of cells in the body.

MUTATIONS

Mutations occur when a gene is damaged and alters the genetic message.

Myelodysplastic syndromes (MDS) are an often unrecognized, under-diagnosed rare group of bone marrow failure disorders, where the body no longer makes enough healthy, normal blood cells in the bone marrow. The disease is also known as a form of blood cancer.

MDS Foundation supports and educates patients, their communities, and healthcare providers, and contributes to innovative research in the fields of MDS and its related continuum of diseases to better diagnose, control and ultimately cure these diseases.

The MDS Foundation, Inc.
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Thank you to Acceleron Pharma, Novartis Pharmaceuticals, and Takeda Oncology for supporting this resource.

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