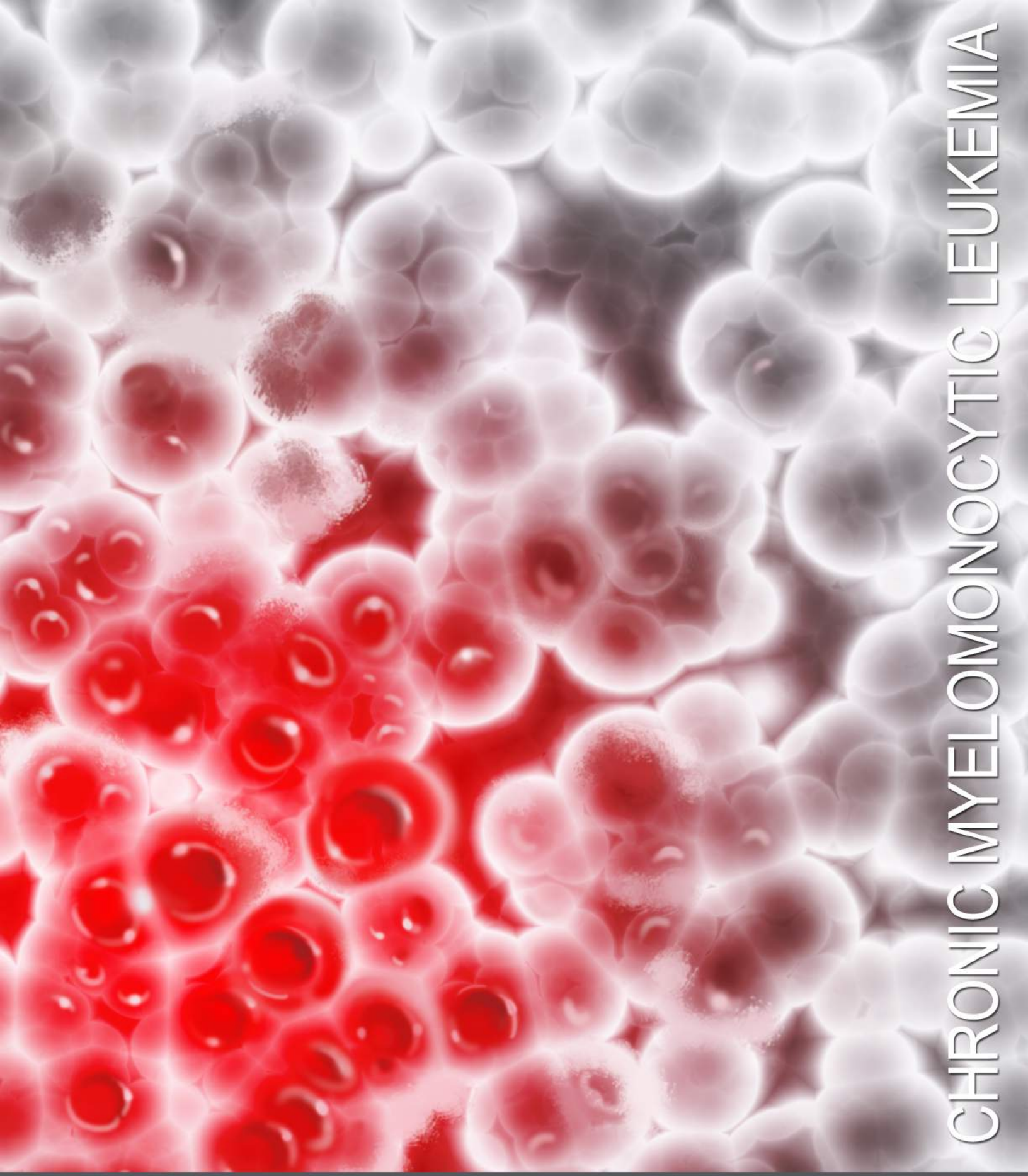

CHRONIC MYELOMONOCYTIC LEUKEMIA

A GIVING SMARTER GUIDE

PHILANTHROPY ADVISORY SERVICE
MILKEN INSTITUTE

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EXECUTIVE SUMMARY

Leukemia is a cancer of the blood-forming cells of the body. Each year in the United States, the disease claims the lives of more than 24,000 people and affects another 330,000. While daunting, sustained public and private investments in leukemia research have refined what was known as a "disease of the blood" into approximately 38 different types of leukemia. With targeted research into specific leukemias, medical breakthroughs have led to an impressive quadrupling of the five-year survival rate for leukemia patients since 1960.

This report will focus on the disease chronic myelomonocytic leukemia, or CMML. Patients suffering from this disease are affected by dramatic overproduction of abnormal white blood cells, which, although numerous, are ineffective against fighting infections. Patients also experience low levels of red blood cells and platelets, leading to constant fatigue and bleeding disorders. As a research field, CMML has been hindered by its incorrect leukemic classification for many years, dearth of funding, and limited diagnostic tools. As a result, the few approved CMML treatments are not optimized, with little understanding of their limited and transient effects on CMML patients.

However, if the historical arc of leukemia research is applied to CMML, then improved diagnosis and dedicated research efforts will greatly benefit CMML patients. Philanthropic support can build the needed foundation for CMML research, which, if coupled with existing efforts and infrastructure, can offer a brighter future for CMML patients and their families. Furthermore, research into CMML will likely benefit the closely related disease juvenile myelomonocytic leukemia, which affects young children and shares many biological and pathological features with CMML.

The Milken Institute Philanthropy Advisory Service has developed this Giving Smarter Guide for CMML with the express purpose of empowering patients, supporters, and stakeholders to make strategic and informed decisions when directing their philanthropic investments and energy into research and development efforts. Readers will be able to use this guide to pinpoint research solutions aligned with their interests. This guide will help answer the following questions:

- *Why should I invest in CMML research?*
- *What is the current standard of care?*
- *What are the barriers preventing development of new therapeutics?*
- *What is the current state of CMML research efforts?*
- *What key things should I know about this disease?*
- *How can philanthropy expand infrastructure to support CMML research and advance new therapies?*

OVERVIEW

Leukemia is cancer of the blood-forming cells of the body. The disease affects around 330,000 people in the United States, with an estimated 54,000 new diagnoses in 2015. Although the incidence and burden of the disease are staggering, focused and sustained leukemia research has led to a quadrupling of the five-year survival rate since 1960.

Public and private investments in leukemia research have refined what was known as a "disease of the blood" into approximately 38 different types of leukemia (Figure 1). As the disease has become better understood, better diagnoses and treatments have followed. For example, a diagnosis of chronic myeloid leukemia was accompanied with a dismal prognosis, or outlook. However, research identifying the key genetic mutation responsible for chronic myeloid leukemia (BCR-ABL1 positive) and development of targeted therapy have led to an astonishing 90 percent five-year survival rate.

Figure 1: Leukemia classifications

Acute myeloid leukemia (~12 types)
Acute lymphoblastic leukemia (2 types)
Acute promyelocytic leukemia (2 types)
Acute monocytic leukemia (2 types)
Acute erythroid leukemia (2 types)
Acute megakaryoblastic leukemia
Acute myelomonocytic leukemia (2 types)
Chronic myeloid leukemia
Chronic myeloproliferative disorders (5 types)
Myelodysplastic syndromes (6 types)
Mixed myelodysplastic/myeloproliferative syndromes (MDS/MPN, 3 types)

Similar breakthroughs are needed for other forms of leukemia, particularly the chronic and aggressive disease, chronic myelomonocytic leukemia (CMML). Less than 20 percent of patients diagnosed with CMML live beyond five years after diagnosis. Unfortunately CMML has not garnered the widespread attention that other forms of leukemia have, primarily because only 1,100 people are diagnosed each year. However, breakthrough discoveries in CMML have the potential to inform research in other forms of leukemia, particularly those that share its classification MDS/MPN classification, namely juvenile

Myelodysplastic/Myeloproliferative Syndromes by the Numbers		
CMML	JMML	aCML
• 1,100 diagnoses each year • 90% of diagnoses are in persons aged >60 years • Twice more prevalent in men • 6-12% of cases arise from previous chemotherapeutic regimens • Patients face a 10-20% five-year survival rate, with 30% of patients progressing to acute myeloid leukemia • Bone marrow transplantation has a 30% curative rate • Majority of patients become transfusion-dependent and susceptible to infections	• 25-50 diagnoses each year • Most diagnoses occur at age <5 years, with a median age of 1.8 years • Males are more affected • Related to the childhood diseases neurofibromatosis type 1 and Noonan syndrome • Chemotherapy has a very low success rate • Bone marrow transplantation has a 50% curative rate • Rarely, JMML patients with Noonan syndrome spontaneously resolve the disease	• Very rare, with 1-2 cases for every 100 cases of BCR-ABL1 mutation-positive patients • Majority of diagnoses occur in persons ages 70-80 years • No male or female predominance • Upon diagnosis, patients demonstrate 14-29 months median survival time • 15-40% of patients progress to acute myeloid leukemia • Bone marrow transplantation has a 50-90% curative rate

myelomonocytic leukemia (JMML), which is usually diagnosed in children under the age of five years, and atypical chronic myeloid leukemia (aCML).

ETIOLOGY

Blood is primarily composed of three cell types: white blood cells (WBCs), red blood cells (RBCs), and platelets. These cells originate from the hematopoietic or blood stem cell that resides in the bone marrow, the blood-forming organ of the body (Figure 2).

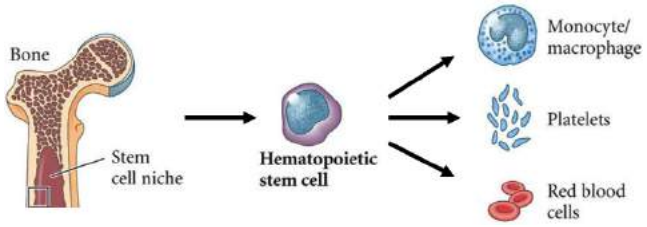


Figure 2: Origin and major cellular components of blood. Hematopoietic/blood stem cells are found in the bone marrow and give rise to blood cells: white blood cells/monocytes, red blood cells, and platelets. (Modified from NCBI)

What causes CMML is poorly understood, but the disease is suspected to originate from an abnormal blood stem cell. Normally, blood stem cells receive signals to differentiate into one of the three cell types, which then enter the circulatory system to perform their various functions—WBCs to help fight infections, RBCs to deliver oxygen to tissues, and platelets to facilitate blood clotting. In CMML patients, however, the process becomes dysregulated, and too many immature WBCs are produced (hence the myeloproliferative designation). Furthermore, the blood stem cell becomes abnormal and fails to produce sufficient platelets and RBCs (hence the myelodysplastic designation).

DIAGNOSIS AND DISEASE STAGING

SIGNS AND SYMPTOMS

CMML patients present a series of symptoms that arise from the abnormal blood stem cell:

- The increased numbers of abnormal WBCs (CMML cells) invade the blood and can cause pain because of enlargement of the spleen (splenomegaly) as it filters the blood
- The lack of normally functioning WBCs (leukopenia) makes the patient prone to infections
- The myelodysplastic aspect of the disease affects the RBCs and platelets and causes
    - insufficient RBCs (anemia), which can lead to fatigue, shortness of breath, and pale skin
    - insufficient platelets (thrombocytopenia), which can lead to easy bruising and bleeding

DIAGNOSIS

Multiple tests are needed to accurately diagnose CMML. Each test builds upon the results of the preceding test and helps to eliminate other potential diseases.

- A **complete blood count** is the first test and measures the absolute number of cell types in the blood including WBCs, RBCs, and platelets. A high and sustained WBC count of >1,000 cells/mm^3 of blood (monocytosis) is the first possible sign of a CMML diagnosis. More than one complete blood count test is required to determine whether the high WBC is due to an infection, because the number will decrease if an infection is cleared but will remain high during the second test in a potential CMML patient. Furthermore, CMML patients present a small number of immature WBCs in the circulating blood, which would not be detected in a healthy person's blood
- **Blood smears** are then performed to view the structure of circulating WBCs, because CMML WBCs display abnormalities in size, shape, and contents
- The next steps are a **bone marrow biopsy and aspiration**. More invasive than the previous two, these tests involve injecting a needle into the bone marrow to obtain a sample of the liquid portion (aspirate) and core (biopsy) of the marrow. These tests allow for a closer examination of the cells present in the bone marrow to determine whether the immature WBCs appear to have CMML-like characteristics (Figure 3). The biopsy will also allow for an absolute count of the cells in the bone marrow. Although normal levels of immature WBCs are no more than 10 percent of all bone marrow cells, CMML immature WBCs represent around 10-20% of all bone marrow cells in a patient. A value higher than 20 percent is considered a diagnosis for acute myeloid leukemia

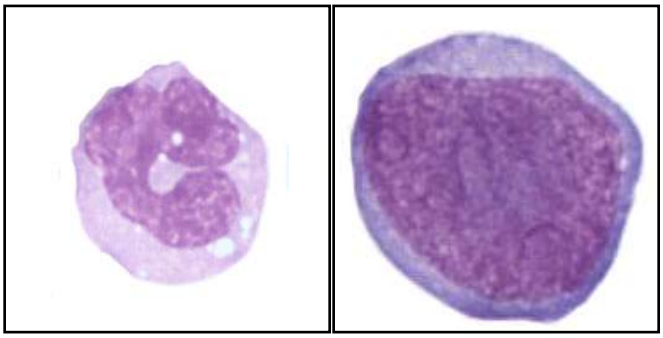


Figure 3: Bone marrow aspirate sample of a normal immature WBC (left) and a CMML immature WBC (right). Note the enlarged nucleus (dark purple) and minimal cytoplasm (light purple) of the CMML immature WBC. (Courtesy of J. Bennet, University of Rochester)

- Using samples from the bone marrow, **cytogenetic studies** are performed to assess the structural integrity of a patient's chromosomes. Abnormal chromosomes are common in CMML patients with multiple gross structural changes arising from deletions, duplications, inversions, or translocations of chromosomes (Figure 4). When CMML patients present more than three gross chromosomal rearrangements, this is referred to as a complex karyotype and is a poor prognostic indicator
- A key cytogenic result that CMML physicians look for is a rearrangement of the *PDGRFB* gene, along with a clinical presentation of a high number of eosinophils (a particular WBC that targets parasites), because this result indicates that the CMML patient may respond to tyrosine kinase inhibitor therapy (see Treatments)

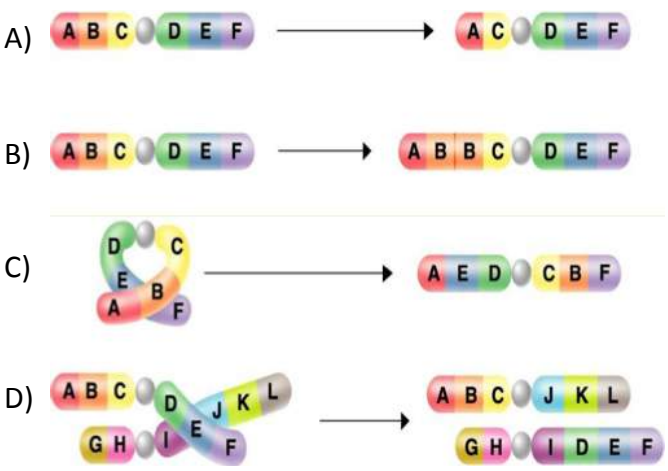


Figure 4: Types of chromosomal rearrangements. A) Deletion, note the loss of the B gene. B) Duplication, note the gain of a second B gene. C) Inversion, note that the chromosomal arms cross and gene order is inverted. D) Translocation, when two different chromosomes rearrange resulting in gene movement. (Courtesy of L. Bridges)

- Advancements in CMML research have led to the use of **molecular testing to identify specific genetic mutations** in CMML patient cells. Using samples from the circulating blood or bone marrow biopses, around 8-40 genes associated with CMML disease are sequenced to determine whether they are mutated. This information helps to determine the disease prognosis of a CMML patient, as well as to identify potential dysregulated pathways that may be targeted by specific therapeutics (see Molecular Biology and Unmet Needs)

DISEASE CLASSIFICATION AND STAGING

As evidenced by the myriad of tests required to identify and diagnose a CMML patient, not enough is known about the disease. One reason for the dearth of information is the previously longstanding misclassification of CMML as solely a myelodysplastic syndrome. As a result, many CMML patients were not properly diagnosed, and even fewer were recruited into clinical trial studies that may have clarified or affected the disease directly. In 2008 the World Health Organization (WHO) redesignated CMML as a standalone disease with proliferative (fast-growing) and dysplastic (abnormal cell) characteristics.

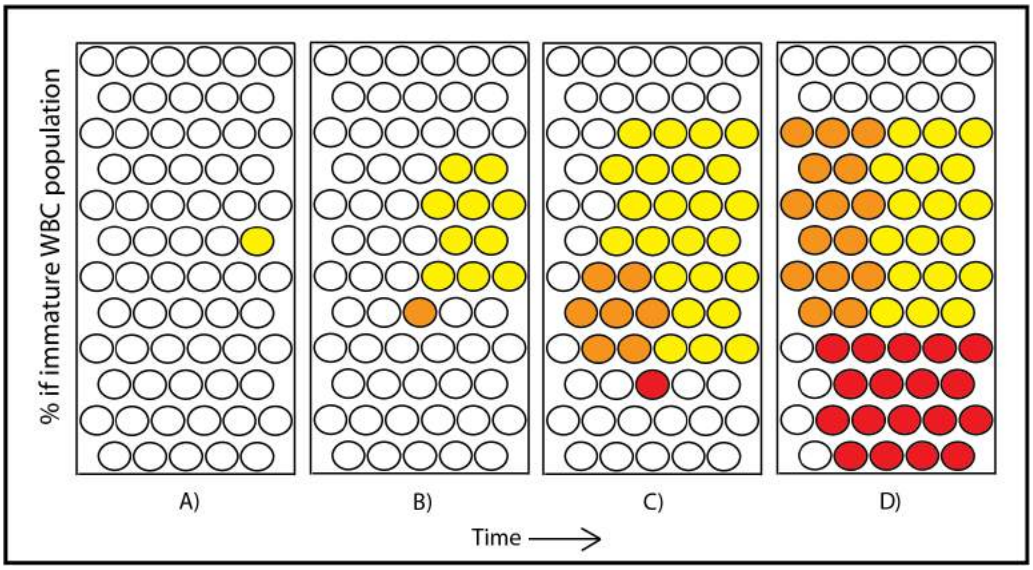
The first step of CMML classification is to determine whether the patient is affected by one of the following:

- CMML-1: Immature WBC in circulating blood <5 percent, immature WBC in bone marrow <10 percent
- CMML-2: Immature WBC in circulating blood 5-19 percent, immature WBC in bone marrow 10-19 percent
- CMML-1 or 2 with eosinophilia: Above criteria with circulating blood eosinophils >1.5 x 10^9 cells/L of blood

The classification/stage of CMML disease, in combination with diagnostic results such as WBC/RBC/platelet counts, percentage of immature WBCs in the bone marrow, complex karyotype, history of transfusion, and presence of the ASXL1 mutation are factored into prognostic scoring systems that determine whether the patient has low-risk or high-risk CMML.

DISEASE BIOLOGY

Researchers suspect that CMML is the result of an abnormal blood stem cell that begins to divide and crowd out other normal blood stem cells in the marrow. The image below is a graphical representation of the population of immature WBCs in the bone marrow (y-axis) over time (x-axis, years) and *hypothetically* illustrates how a normal bone marrow population is selected into a CMML-like bone marrow.



A) *Outset:* All the blood stem cells are normal and grow into the correct immature WBCs, RBCs, platelets, and blood stem cells. The white circles indicate normal immature WBCs without CMML-related mutations.

B) *The Driver and Passenger Mutations:* If one stem cell acquires a mutation (yellow circle) that begins to drive increased cellular division and growth, then it will begin to outgrow and crowd out normal cells. This process may take many years with few symptoms for the patient, and may contribute to why the majority of CMML diagnoses occur in older patients. The mutated cell growth is visualized by the number of yellow circles in the figure. Random mutations are a natural occurrence during normal cell division. However, because the mutated stem cell now divides at a higher rate, it is prone to developing other cancer-driving mutations, thereby acquiring a second mutation (orange circle) that results in a continually expanding population of mutant stem cells.

C) *The More the Dividier:* Once key genes are mutated (although which genes exactly is not fully known for CMML), the mutated stem cells will expand to become the dominant cells in the population. Normal stem cells will no longer prevail as a dominant proportion of the immature WBCs, but rather one in a population of single mutation- (yellow), double mutation- (orange), and triple mutation-containing (red) cells. Furthermore, mutant cells will continue to expand faster because they have a selective growth advantage over normal cells.

D) *Onset:* Over time, the population of normal cells drop, concomitant with an increase of immature WBCs containing multiple CMML-related mutations. At this stage, the patient will begin to show symptoms of CMML, because the normal stem cells fail to produce sufficient normal WBCs, RBCs, and platelets (diagnosed via blood cell counts), and the mutant stem cells begin to produce a large amount of abnormal immature WBCs. Cytogenetic rearrangements and abnormal cell structures will also become evident blood smears.

CELLULAR BIOLOGY

Although the exact mutations that lead to CMML are not completely understood, multiple cellular pathways have been implicated in the disease:

- *Increased Cell Growth and Decreased Cell Death*—CMML cells demonstrate abnormal activation of cell growth and division pathways, as well as down-regulation of cell death or apoptotic pathways
- *Impaired Immune Surveillance*—Recent work has shown that CMML cells express high levels of the immune checkpoint protein PD-1, indicating that the disease employs mechanisms that hide its dramatic cell growth and division from the immune system, which would normally attack cancerous cells
- *Abnormal Blood Vessel Growth*—In order to facilitate their rapid cell growth and division, CMML cells secrete factors that alter the environment of the bone marrow to promote blood vessel growth, or angiogenesis. The increase in blood vessels then allows greater delivery of nutrients that provide fuel and building blocks to produce the invasive CMML immature WBCs

MOLECULAR BIOLOGY AND THERAPEUTIC TARGET AREAS

Altered signaling, epigenetic regulation, and RNA splicing have been implicated in development of CMML. Advancement of research into these areas will facilitate the identification of potential druggable targets.

- *Signaling Pathways* receive signals from outside the cell and activate downstream proteins that alter DNA transcription and subsequent protein expression
    - The JAK/STAT pathway is involved in cell growth and has been shown to be upregulated in CMML cells. Research has shown that CMML cells are hypersensitive to granulocyte macrophage colony-stimulating factor (GM-CSF), a key activator of the JAK/STAT pathway
    - The RAS pathway is also involved in cell growth. Among blood cancers, CMML presents the highest incidence of RAS pathway mutations, primarily in the NRAS- and KRAS-related genes. Mouse models with mutant NRAS have also been shown to develop CMML-like disease, indicating that proteins in this pathway are potential therapeutic targets

GM-CSF hypersensitivity is a major point of convergence for CMML and JMML, as both diseases upregulate the JAK/STAT pathway. Development and approval of therapeutics targeting this pathway may benefit both CMML and JMML patients.

Several epigenetic and splicing mutations are strongly associated with CMML: TET2, ASXL1, SRSF2, and SETBP1.

- *Epigenetic events* regulate the expression of genes without changing the DNA sequence. Different genes are activated depending on the marks attached to DNA itself and the proteins around which DNA is wound, or histones. Methyl groups can be added to DNA or histones, whereas acetyl groups, phosphates, and small proteins such as ubiquitin only mark histones.
    - TET2 is an enzyme that epigenetically modifies DNA by removing methyl groups. Mutations that reduce TET2 activity have been implicated in multiple blood cancers, indicating its critical role in blood cell development. Furthermore, mutations in TET2 are hypothesized to be a driver mutation for CMML development, because it results in an increase in DNA methylation and a subsequent increase in WBC production. Along with ASXL1, TET2 is the most frequently identified mutation in CMML patients.

- Splicing factors
    - ASXL1 is an RNA splicing factor that modifies the transcripts generated from DNA. When ASXL1 is mutated and loses activity, an epigenetic cascade occurs that ultimately drives the production of CMML immature WBCs. Similar to TET2, ASXL1 is the most frequently identified mutation in CMML patients
    - SRSF2 is a component of the spliceosome, the multi-protein machinery that modifies RNA transcripts generated from DNA. Mutations in SRSF2 are the third most common mutations in CMML patients
- Mutations in SETBP1 are also commonly found in CMML patients. SETBP1 is a protein that interacts with the SET protein, which itself is involved in apoptosis, transcription, and histone assembly. Research has shown that defects in this interaction result in higher rates of cell division

The presence of SETBP1 mutations in JMML patients confers a particularly poor outcome.

TREATMENTS

Several treatment options are available for CMML patients—with the regimen dependent on the patient's disease prognosis and clinical symptoms. Specific examples of the approved treatments are listed in Table 1.

> "These patients need better drugs. The ones we have don't work, and if they have *some* effect, we have no idea *why*."

- ***Allogeneic stem cell transplant*** is a possible course of action for high-risk CMML patients
    - This process will replace the patient's abnormal bone marrow with a donor's genetically different (allogeneic) bone marrow. Although a curative treatment option, a stem cell transplant is a very risky procedure with a 70 percent mortality rate. Factors that increase the chances of success are young age as well as few chromosomal abnormalities
- ***Hypomethylating agents (HMA)*** are a likely course of treatment if the patient suffers primarily from a lack of RBCs, platelets, and normal WBCs (cytopenia)
    - CMML cells present an increase in methyl marks on their DNA, resulting in altered epigenetics versus normal cells. Agents that globally reduce the amount of DNA methylation have shown limited success in slowing disease progression. The primary shortcomings of HMAs are as follows:
        - *Selective effectiveness*—Not all CMML patients respond the same way to HMA, with some demonstrating a noticeable drop in WBCs and normalization of RBCs and platelets, while others show no change whatsoever. More research is needed to understand who may or may not respond to HMA treatment
        - *Short-term effectiveness*—For the CMML patients that do demonstrate a good response rate to HMA, these tend to be short-lived, with the disease returning in a matter of months. Treatment failure occurs when the cancer develops resistance to the HMA
- ***Chemotherapy*** is a likely course of treatment if the patient suffers from a high amount of circulating abnormal WBCs
    - Chemotherapy globally reduces cell growth and division, and it has shown some effectiveness in controlling low-risk CMML. However, the treatment involves a wide range of side effects because it affects both normal and cancerous cells. A key question surrounding chemotherapy is whether it affects the source of CMML disease—namely the abnormal stem cell—or only treats symptoms of the cancer

Table 1: FDA-approved therapeutics for CMML

Brand Name	Generic Name	Mechanism of Action
Vidaza	azacytidine	HMA
Dacogen	decitabine	Chemotherapy and HMA
Cytosar-U	cytarabine	Chemotherapy
Hydrea	hydroxyurea	Chemotherapy

CLINICAL TRIALS AND INVESTIGATIONAL THERAPIES

Clinical research is a branch of biomedical research involving human subjects. The goal of clinical research is to evaluate the safety and efficacy of drugs, medical devices, or diagnostics intended for use in human patients.

Clinical trials are an important component of clinical research as they are used to evaluate the safety and efficacy of an experimental drug or therapy in human subjects. They can also be used to collect specimens from human subjects for further research. Importantly, information on potential side effects are gathered during the clinical trial and weighed against the potential therapeutic benefit of the treatment under investigation. Clinical research is divided into three key phases and is described in Figure 5:

A key challenge that has hindered CMML investigational therapies was the misclassification of CMML as a myelodysplastic disease. As a result, few studies have focused on CMML alone (Figure 6). Although agents that affect the fast-growing (MPN) or abnormal cellular aspects (MDS) of CMML hold some promise, targeted therapies that focus on the unique aspects of CMML are needed to make a transformative impact on the disease.

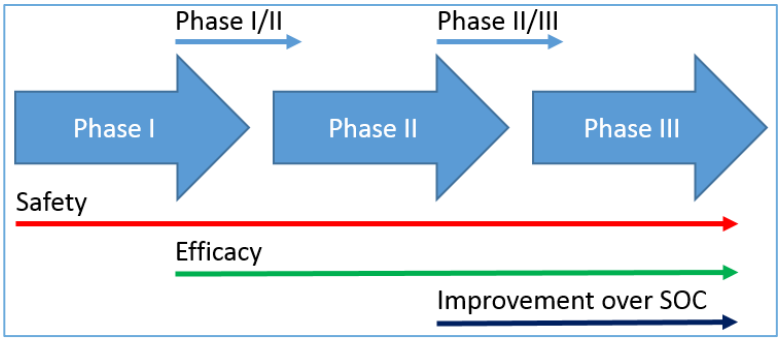


Figure 5: Phases of Clinical Trials. During Phase 1 studies, researchers test a new drug or treatment for the first time in a small group of people to evaluate its safety, determine a safe dose range, and identify potential side effects. During Phase II, proof-of-concept studies are performed as the drug or treatment is given to a larger group of people to determine its efficacy and optimal dose. During Phase III, the drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, and assess its impact compared to the current standard of care (SOC). Some clinical studies involve multiple phases to facilitate seamless transition from one to another and are written as Phase I/II or Phase II/III. These designations are also used in adaptive trials, wherein study parameters for the Phase II study are modified with respect to ongoing Phase I trial results, *etc*.

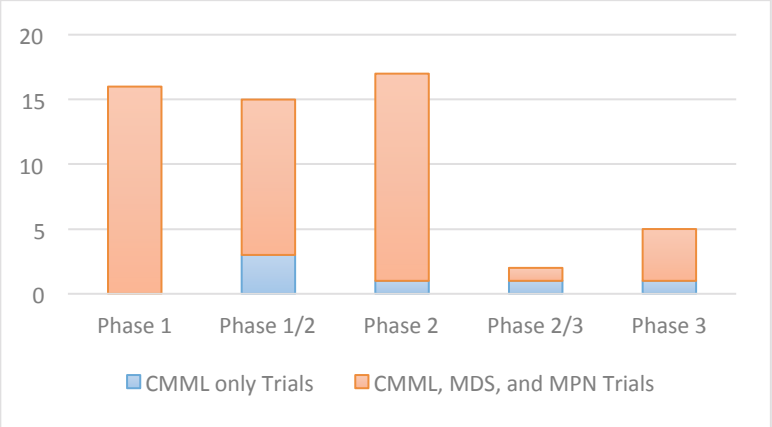


Figure 6: CMML-related clinical trials as of 2015. Trials specific to CMML are in blue, while trials that include CMML as a subtype of MDS or MPN are in orange.

As shown in Table 2, based what is known about the cellular and molecular biology of CMML, investigational therapies can be classified into the following categories.

Table 2: Experimental therapies for CMML

Drug Name(s)	Mechanism of Action	Pathway Targeted
topotecan sapacitabine birinapant clofarabine	Chemotherapy	Cell division and growth
thalidomide lenalidomide pomalidomide	Immunomodulators	Immune system and angiogenesis
entinostat panobinostat vorinostat	Histone deacetylase inhibitors	Epigenetics
lonafarnib tipifarnib	Farnesyltransferase inhibitors	RAS pathway
glasdegib erismodegib	Hedgehog pathway inhibitors	Stem cell differentiation and angiogenesis
rigosertib	Kinase inhibitor	Cell division and growth
midostaurin	Kinase inhibitor	Cell division and growth and angiogenesis
ruxolitinib	Kinase inhibitor	JAK/STAT pathway
imatinib dasatinib	Kinase inhibitors	CMML diagnosis of *PDGFRB* rearrangement and increased eosinophils
E6201	Kinase inhibitor	RAS pathway

RESEARCH CHALLENGES AND PHILANTHROPIC OPPORTUNITIES

CMML has long been an orphaned disease because of the difficulty in accurately diagnosing the disease in patients, coupled with its misclassification for many years as a subset of MDS. As a result, CMML is beset by a number of unmet needs including the following:

- Limited therapeutic options
- Absence of a patient registry and clinical trial infrastructure
- Overall lack of understanding of the basic and translational biology

To address these needs and ultimately benefit CMML patients, the Philanthropy Advisory Service held a retreat with academic, clinical, industry, patient advocate, and foundation partners to chart a scientific roadmap to change the trajectory of this disease.

CMML PATIENT REGISTRY

THE PROBLEM

A central issue in CMML research is the lack of CMML-specific information. Many of the approved, and generally ineffective, treatments for the disease are based on the inclusion of CMML patients as a subset of trial participants for MDS studies. Thus the challenge of diagnosing a patient with CMML, coupled with poor therapeutic options, results in little incentive for physicians to accurately diagnose CMML, because the eventual treatment is similar to an MDS regimen.

POTENTIAL SOLUTION

The CMML research community needs a formalized patient registry. Currently researchers have banded together to informally share de-identified CMML patient information from across multiple clinical trials and research studies. The goal of this effort is to:

- Better define CMML-specific characteristics
- Clarify patient response to approved and investigational therapies
- Assess prognostic scoring systems that include genetic drivers of CMML

With additional support to expand and formalize this effort, the initiative can serve as the touch point for a federated system of tissue banking. The registry can provide a prospective cohort of CMML patients to evaluate over time and can support clinical trial enrollment.

PHILANTHROPIC OPPORTUNITIES

Formalize the CMML patient registry effort to facilitate patient recruitment and biobanking of patient samples. This will primarily require infrastructure support to develop the following:

- Web-based data entry portal with analytic capacity to increase the pool of CMML patient cases
- Resources for data management to facilitate genetic data curation and screening of patients

- Federated tissue sample banking to facilitate collaboration across the CMML field

DIAGNOSTIC AND PROGNOSTIC BIOMARKERS OF CMML

THE PROBLEM

CMML diagnosis is primarily dependent on cell morphology–based (pathological) assessment of immature WBCs as a percentage of circulating blood and bone marrow samples. Although WHO diagnostic criteria are continuously improved and refined, the process is dependent on skilled pathologists accurately determining a CMML versus MDS patient. This poses an issue in accurately diagnosing a patient at the initial point of care. Furthermore, the current classification scheme indicates where the disease is going, rather than where it came from.

POTENTIAL SOLUTIONS

CMML diagnosis and prognosis may be enhanced with the addition of genetic markers of the disease. Genetic sequencing of patient samples have identified 8-40 genes that are highly represented in CMML versus MDS patients. Despite the prevalence of these genes in CMML patients, there is no single gene unique to the disease. However, many of these biomarkers are highly associated with one another, and, if validated and incorporated into the current CMML diagnostic scheme, would improve the identification of CMML patients at earlier disease stages. Research in associated CMML genes would also assess their ability to predict patient response to treatment.

PHILANTHROPIC OPPORTUNITIES

CMML Diagnosis

- Support research to expand the WHO CMML diagnostic criteria to include genetic biomarkers
    - This effort could validate novel assays such as WBC sorting based on expressed surface markers
    - This effort would also aid in the development of a standard JMML diagnostic panel
- Support a national effort to identify individuals who present high levels of WBCs, then subsequently test them for CMML genetic biomarkers to identify early-stage patients
    - Similar to the Leukemia & Lymphoma Society Pre-malignancy program, this effort would aid in the development of a prospective cohort of CMML patients and possibly identify patients suffering from closely related diseases
    - Potential CMML patients would be directed to a website to facilitate referral to a tertiary care center

CMML Prognosis

- Support research efforts such as the International Working Group on Prognostic Markers for MDS (IWG-PM), whose goal is to validate MDS biomarkers via careful assessment of patient samples
    - A CMML-focused effort would carefully assess patient samples to better understand patient disease progression and response to treatment
- Support a Cancer Genome Atlas discovery effort focused on CMML

- A prospective study with long-term collection and testing of samples could identify new biomarkers and potential drug targets

CMML CLINICAL TRIAL NETWORK

THE PROBLEM

Stymied by the lack of a blockbuster drug, broad geographic distribution of the comparatively small number of CMML patients, and lack of awareness surrounding CMML, very few clinical trials dedicated to the disease have been completed. Furthermore, currently approved drugs have not been fully optimized for CMML patients, with limited research to assess their true benefit in patients.

POTENTIAL SOLUTIONS

Development of a CMML-focused clinical trial network is a critical step in impacting the trajectory of this disease. Multiple Centers of Excellence across the U.S. are active in CMML clinical studies, and providing infrastructure support to pool resources would enhance the well-being of and treatment options for CMML patients.

Proposed clinical trials would:

- Optimize current treatment options to determine the initial regimen for CMML patients
- Build a trial network foundation to test combinations with experimental therapeutics
- Standardize clinical trial measurements of drug efficacy and trial endpoints

PHILANTHROPIC OPPORTUNITIES

- Support expansion of the MDS-focused clinical trial network
    - This effort will leverage the existing infrastructure to test new CMML treatments and improve existing clinical care standards
    - This effort will facilitate CMML patient engagement, education, and clinical trial enrollment, while benefitting MDS clinical research efforts
    - Development of this network will drive the collection of patient samples to support basic and translational studies to advance CMML science
- Support development of a CMML Clinical Trial Master Protocol, which involves determination of the ideal starting regimen and a structured approach to assessing new experimental therapeutics
- Support efforts to address patient engagement, education, and patient-specific roadblocks to trial participation such as transportation and compensation options

CMML BASIC AND TRANSLATIONAL SCIENCE

THE PROBLEM(S)

A key unanswered research question is how multiple genetic mutations manifest into the clinical presentation of CMML. Current research has successfully identified many of the genetic drivers of CMML, which range from splicing defects, altered epigenetics, and dysregulated signaling pathways. However, how these pathways interact are poorly understood and yet present a potential trove of drug targets. For known CMML-related genes, single gene knockout (KO) mouse models have been developed for preclinical testing of experimental treatments, but the KO combinations and models that best mimic human disease are currently unknown. Lastly, currently approved drugs that target epigenetic regulation have shown some measure of efficacy in CMML patients, but how they work and their mechanisms of action are not well-defined.

PROPOSED SOLUTIONS

CMML GENOTYPE → PHENOTYPE

Identification of the genes most commonly associated with CMML (genotype) presents an excellent opportunity to understand how the blood stem cell abnormally differentiates and results in CMML disease (phenotype).

Proposed scientific efforts include the following:

- Identification of the key mutation(s) that results in the initial abnormal differentiation, and the secondary mutations that then drive development of the disease.
- Targeted drug development performed with CMML patient samples

The ultimate goal of these efforts is to use the basic understanding of CMML genetics and cell growth to identify the key pathways that drive the disease. Advancements in this research will contribute to the development of the next generation of CMML drugs.

CMML MOUSE MODELS

The next key step in CMML mouse models is to understand which model best mimics human disease. Understanding whether KO or xenograft models (wherein patient cells are grafted onto mice) are the ideal vehicles to test experimental therapies and will greatly facilitate the preclinical process.

EPIGENETICS OF CMML

In order to capitalize on the limited efficacy of hypomethylators for CMML patients, research is needed to understand how these drugs work in patients who respond to treatment. Epigenetics research will determine the mechanism of action of hypomethylators, as well as whether younger versus older patients respond differently. Identification of which cells respond to hypomethylators may also determine the potential use of immunotherapy in CMML.

PHILANTHROPIC OPPORTUNITIES

CMML GENOTYPE → PHENOTYPE

Support research effort to:

- Initiate a functional genomics study to develop targeted therapeutics
    - Utilize patient registry/database to identify genetic mutations present in CMML patients
    - Utilize patient samples to identify potential therapeutic targets
- Utilize patient samples to identify the initial genetic mutations that develop CMML versus the secondary mutations that drive the disease
- Address the potential of the RAS pathway and GM-CSF hypersensitivity as a point of convergence for CMML and JMML

CMML MOUSE MODELS

- Support research efforts to determine the ideal mouse for preclinical therapeutic studies
- Support a biobank of transplantable patient samples for use in mouse xenograft studies
    - Samples would be collected from clinical trials and the patient registry
- Support research efforts to extensively test novel therapies and combinations of therapies in mouse models

EPIGENETICS OF CMML

- Support research efforts to identify common epigenetic changes across treated CMML patients, which would also expand the understanding of the role of epigenetics in JMML
    - Compare patient samples before and during treatment to assess a patient's epigenetic response based on their own CMML-related mutations
    - Identify the correct target cell affected by hypomethylating agents

JMML UNMET NEEDS

The greatest unmet need of JMML patients is access to drugs. Pediatric studies often pose recruitment and logistical challenges for drug developers, and are thus not always performed alongside adult studies. Furthermore, most clinical trials have an age restriction of 18- to 65-years-old, thereby depriving children suffering from leukemia the opportunity to participate in trials that may affect their disease. Advances in CMML research will aid not only patients who suffer from the disease, but also JMML patients. Although there are differences between the two diseases, several CMML initiatives would support and advance JMML research.

- Support research efforts to develop a standard CMML diagnostic panel with genetic biomarkers
    - The majority of JMML diagnoses are accomplished via genetic sequencing. Efforts to develop a combined pathology and genetic biomarkers diagnostic panel would benefit both CMML and JMML diagnosis
    - CMML epigenetic studies would also contribute to the epigenetic profile of JMML cells affected by hypomethylating agents
- Support development of CMML mouse models with genetic lesions similar to JMML to facilitate shared preclinical screening of approved and experimental drugs
- Support research to understand the central role of GM-CSF hypersensitivity in CMML and JMML
    - Understanding downstream pathways of JAK/STAT activation may identify common drug targets between the two diseases
- Support clinical trials that plan to use a MEK kinase inhibitor to assess its impact on JMML patients

RESEARCH GRANTMAKING ORGANIZATIONS IN THE LEUKEMIA AND CMML COMMUNITY

This section provides a brief overview of the nonprofit organizations involved in CMML research. Their involvement can be through direct funding of research or support of research efforts.

APLASTIC ANEMIA AND MDS INTERNATIONAL FOUNDATION CLINICAL RESEARCH CONSORTIUM

Established in 1983, the AA&MDS International Foundation is a leading nonprofit that focuses on supporting patients and families living with aplastic anemia, myelodysplastic syndromes, and paroxysmal nocturnal hemoglobinuria. The foundation's patient-centered efforts focus on diagnosis, treatment, and life-long implications of living with a chronic disease. Supported by the Edward P. Evans Foundation, AA&MDS developed and funds the MDS Clinical Research Consortium, a six-institution effort designed to facilitate MDS clinical trials. The Consortium fills a major gap in MDS-related clinical research by providing a critical mass of patients and patient data to evaluate new therapies for MDS. Consortium activities are directed by a steering committee composed of MDS researchers who will assess and approve proposed studies.

THE LEUKEMIA AND LYMPHOMA SOCIETY

The mission of The Leukemia and Lymphoma Society (LLS) is to cure leukemia, lymphoma, Hodgkin's disease, and myeloma and to improve the quality of life of patents and their families. Given the difficulty of prevention or early screening for blood cancers, the LLS research agenda is focused on finding cures. LLS actively funds all stages of blood cancer research, from discovery science to clinical trials, and provides career support to early and established investigators. LLS drives research in areas of unmet clinical need, and via innovative programs such as the Therapy Accelerator Program (TAP), helps to bridge the gap between academic drug discovery and drug development. The TAP program has two primary facets:

- The *Biotechnology Accelerator Division* identifies companies developing novel anti-cancer therapies, supportive care or diagnostics and co-funds specific projects that will enable a company to partner or raise additional funding to complete the testing, registration and marketing of new therapies or diagnostics for blood cancer indications.
- The *Academic Concierge Division* capitalizes on LLS's academic grant-supported portfolio of development-stage projects. This division supports the further development of selected academic projects (with or without prior LLS grant support) to gain clinical proof of concept. Successful projects will potentially be advanced for further clinical development by creating additional partnerships with pharmaceutical or biotechnology companies.

THE MYELODYSPLASTIC SYNDROME INTERNATIONAL FOUNDATION

The MDS Foundation was established by an international group of physicians and researchers to provide an ongoing exchange of information relating to MDS. Since its inception, it has conducted 13 international symposia across 12 countries. The foundation serves as a nexus for MDS research and information that provides:

- Patients with referrals to Centers of Excellence and active clinical trials
- Dissemination of treatment options and educational support for health providers

Supported by the MDS Foundation, the IWG-PM analyzed clinical features and outcome data from more than 7,000 patients and revised the international prognostic scoring system for MDS. By comprehensively integrating

known clinical features of MDS, the revised scoring system has improved the prediction of clinical outcomes in untreated MDS patients, while aiding the design and analysis of clinical trials.

GLOSSARY OF TERMS

Acute myeloid leukemia	An aggressive cancer of the blood and bone marrow that results in increased immature blood cell growth
Allogeneic bone marrow transplant	A surgical procedure that replaces a patient's abnormal bone marrow with a donor's genetically different (allogeneic) bone marrow
Anemia	A condition describing insufficient red blood cells, which can lead to fatigue, shortness of breath, and pale skin
Atypical chronic myeloid leukemia	A rare subtype of myelodysplastic/myeloproliferative neoplasm (MDS/MPN) largely defined morphologically. It is currently unclear whether aCML-associated features are distinctive enough to allow its separation from unclassifiable MDS/MPN
Biomarker	A distinct biochemical, genetic, or molecular characteristic that is objectively measured and evaluated as an indicator of a particular biological condition or process
Blood smears	A diagnostic test used to look for abnormalities within the blood, wherein cell types are examined under a microscope for unusual shapes or sizes
Bone marrow	A soft fatty substance in the cavities of bones from which blood cells are produced
Bone marrow aspiration	A procedure that involves injecting a needle into the bone marrow to obtain a sample of the liquid portion of the marrow
Bone marrow biopsy	A procedure that involves injecting a needle into the bone marrow to obtain a sample of the core of the marrow
Chronic myeloid leukemia	A type of leukemia, designated by the BCR-ABL transgene, that drives expansion of certain blood-forming cells of the bone marrow
Complete blood count	A diagnostic test that measures the absolute number of cell types in the blood including WBCs, RBCs, and platelets
Complex karyotype	A situation where a patient presents $\geq$3 chromosomal rearrangements
Cytogenetic studies	Tests that assess the structural integrity of a patient's chromosomes using bone marrow samples
Cytopenia	A condition that describes a lack of RBCs, platelets, and/or normal WBCs
Cytoplasm	The material within a living cell excluding the nucleus and other membrane-bound compartments
DNA	A molecule that carries most of the genetic information used in the development, function, and reproduction of living organisms and viruses
Eosinophils/Eosinophilia	A type of white blood cell that targets parasites; eosinophilia refers to an abnormally high amount of these cells
Epigenetics	Changes in the genome relating to or arising from nongenetic influences

	on gene expression
Genotype	Identification of the genes most commonly associated with a disease
Hematopoietic stem cell	Located in the bone marrow, these cells that give rise to all the blood cells
Histones	The proteins around which DNA is wound
Immature WBC	The cell differentiation stage in between the hematopoeitic stem cell and the fully differentiated white blood cell
Juvenile myelomonocytic leukemia	A serious chronic leukemia that affects children mostly aged 4 and younger
Karyotype	The number and visual appearance of the chromosomes in the cell nuclei of an organism
Leukopenia	A condition wherein a patient presents a reduction in the number of WBCs in the blood
Monocytosis	A high and persistent WBC count of >1,000 cells/mm^3 of blood
Myelodysplastic syndrome	A group of diseases in which immature blood cells in the bone marrow do not mature or become healthy blood cells
Myeloproliferative neoplasms	A group of diseases in which the bone marrow makes too many RBCs, platelets, or certain WBCs
Myeloproliferative/myelodysplastic syndromes	A group of diseases that have features of both myelodysplastic syndromes and myeloproliferative neoplasms
Nucleus	A dense organelle, typically a single rounded structure bounded by a double membrane, containing genetic material of the cell
Pathological assessment	The science of the causes and effects of diseases, especially the branch of medicine that deals with the laboratory examination of samples of body tissue for diagnostic purposes
Phenotype	The composite of an organism's observable characteristics or traits, such as its morphology, development, biochemical, or physiological properties
Platelet	A blood cell whose primary function is to facilitate blood clotting
Red blood cell	A blood cell whose primary function is to carry oxygen to tissues
RNA	A molecule similar to DNA, it plays a role in coding, decoding, regulation and expression of genes
Signaling pathways	A process by which cells receive signals from outside the cell and activate downstream proteins that alter DNA transcription and subsequent protein expression
Splenomegaly	A condition that describes enlargement of the spleen
Thrombocytopenia	A condition that describes insufficient platelets, which can lead to easy bruising and bleeding
White blood cell	A blood cell whose primary function is to help fight infections

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