

Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML)

No. 17 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- Chronic myelomonocytic leukemia (CMML) occurs in adults, and juvenile myelomonocytic leukemia (JMML) occurs in infants and young children. These uncommon blood cancers are similar because, in both, mutations (changes in the DNA of a cell) lead to increased numbers of a type of white blood cell called “monocytes.”
- Common CMML symptoms include weakness, fatigue, unexplained bruising, infection, and enlarged liver and spleen.
- Over the past decade, scientists have gained a greater understanding of the genetic features associated with CMML. About 20 to 30 percent of CMML patients have chromosomal abnormalities and approximately 90 percent of CMML patients have one or more DNA mutations that occurred after conception (called somatic mutations).
- Most CMML patients are treated with drug therapy. Allogeneic stem cell transplantation is a potential curative option for some patients.
- JMML is typically diagnosed in infants and children younger than 4 years. Common JMML symptoms include pale skin, lack of appetite, shortness of breath, rash, enlarged abdomen and bone pain.
- The only potentially curative treatment for JMML is allogeneic stem cell transplantation. Patients with certain gene mutations can experience spontaneous resolution of the disease but this is difficult to predict.
- New treatments for CMML and JMML, including approaches that target chromosomal and DNA mutations, are being researched in clinical trials.

Introduction

CMML and JMML are uncommon blood cancers that have overlapping features of two other types of blood cancers: myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs). The World Health Organization (WHO) has classified chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML) as “myelodysplastic/myeloproliferative neoplasms.”

Myelodysplastic syndromes (MDS) are a group of diseases in which immature blood cells in the bone marrow do not mature to become healthy blood cells nor do they look or function like healthy cells. Myeloproliferative neoplasms (MPN) are blood cancers that occur when the bone marrow makes too many red blood cells, platelets or certain types of white blood cells. In CMML and JMML, the MPN component most often manifests as an increase in monocyte (a type of white blood cell) counts in the blood.

Major scientific advances in the past decade have allowed scientists to get a better understanding of the cytogenetic and molecular abnormalities that cause these diseases. This is expected to lead to new and improved therapeutic treatments.

This fact sheet provides additional information about the diagnosis, treatment, expected outcomes, clinical trials and support resources for patients who have CMML and JMML.

Chronic Myelomonocytic Leukemia (CMML)

CMML starts when a stem cell in the bone marrow mutates. This results in abnormal blood cell production and an overproduction of blasts and immature monocytes, types of white blood cells that crowd out other blood cells. The blasts never mature completely into normal monocytes so they can't carry out their normal functions. Over time, the abnormal monocytes accumulate in the marrow and in

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other organs and interfere with the normal production of other types of blood cells, including red blood cells (which carry oxygen to all the tissues of the body) and platelets (which form clots to help stop bleeding after an injury).

Monocytes represent about 5 to 10 percent of the cells in normal human blood. These cells and other white cells called “neutrophils” are the two major microbe-eating and microbe-killing cells in the blood. When monocytes leave the blood and enter the tissue, they are converted to macrophages. Macrophages are “monocytes-in-action”: they can combat infections in the tissues, ingest dead cells and assist other cells, such as lymphocytes, in carrying out their immune functions.

Subtypes. In most healthy people, there are no blasts in the blood and fewer than 5 percent in the bone marrow. The WHO categorizes CMML into the following three subtypes based on the percentage of blast cells found in the blood and bone marrow:

- CMML-0: Less than 2 percent blasts circulating in the blood and less than 5 percent blasts present in the bone marrow
- CMML-1: 2 to 4 percent blasts circulating in the blood and 5 to 9 percent blasts present in the bone marrow
- CMML-2: 5 to 19 percent blasts circulating in the bloodstream; 10 to 19 percent blasts present in the bone marrow, and/or the presence of Auer rods. Auer rods are rod-shaped inclusions seen in the blast cells of certain patients with leukemia.

In addition, based on the white blood cell (WBC) count, CMML can be grouped into two subtypes:

- A dysplastic type (MD-CMML) defined by $WBC < 13 \times 10^9/L$ (liters)
- A proliferative type (MP-CMML) defined by $WBC \geq 13 \times 10^9/L$

The dysplastic and proliferative subtypes affect patients differently. Those with the dysplastic type have disease complications similar to those of patients with MDS. Patients with the proliferative type often have organ enlargement. In addition, proliferative subtypes are associated with higher rates of mortality and morbidity, with an increased risk of progression to acute myeloid leukemia (AML). See *Signs and Symptoms of CMML* in the next column for more information.

CMML Incidence

CMML affects approximately 4 out of 1 million people in the United States each year with about 1,100 new cases annually. The median age at diagnosis is about 72 years. Ninety percent of patients are older than 60 years at the time of diagnosis. There are approximately twice as many male CMML patients as female CMML patients. CMML is rare in children.

Signs and Symptoms of CMML

Signs and symptoms vary from patient to patient and depend on the type of CMML.

Those with a myelodysplastic subtype (MD-CMML) tend to present with low blood cell counts. Signs and symptoms may include:

- Weakness and fatigue due to anemia (a condition in which blood lacks adequate healthy red blood cells to carry sufficient oxygen throughout the body)
- Petechiae (pinhead-sized sites of bleeding in the skin), bruising and bleeding due to thrombocytopenia (low platelet counts)
- Recurrent infections due to leukopenia (a below-normal white blood cell count)

Patients with a myeloproliferative subtype (MP-CMML) tend to have high blood cell counts. Signs and symptoms may include:

- Enlargement of the spleen and liver
- A feeling of fullness below the ribs due to spleen enlargement
- Fatigue
- Drenching night sweats
- Bone pain
- Weight loss

Diagnosis of CMML

Patients who are eventually diagnosed with CMML may first seek medical attention because of physical weakness, infection or unexplained bleeding. A diagnosis of CMML cannot usually be confirmed with a single lab test result that shows abnormal blood counts. The diagnosis can only be confirmed after a patient has been monitored over time and after repeated lab tests in which results are evaluated

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to rule out other forms of MDS and MPNs. Findings from a blood smear and a bone marrow aspiration and biopsy are required to make a diagnosis of CMML. CMML is difficult to diagnose. A number of mutations that are seen in CMML are seen in other diagnoses (MDS, MPN, AML). If there is uncertainty in the diagnosis, it is important to consider getting a second opinion.

The hematologist-oncologist will be looking for the following criteria:

- A persistent elevated monocyte count in the blood (greater than or equal to $1 \times 10^9/L$ of blood, which is equivalent to greater than or equal to 1,000 monocytes per microliter [$1,000/\mu l$] of blood). Monocytes must account for greater than or equal to 10 percent of the total number of white blood cells (WBC) in the blood.
- No evidence of a Philadelphia chromosome, which is seen in a similar disease known as chronic myeloid leukemia (CML). This can be determined based on a blood test looking for a particular abnormality known as a *BCR/ABL* fusion gene.
- Increased numbers of eosinophils (a type of white blood cell) are uncommon in CMML. If the eosinophil count is elevated, there should be no evidence of *PDGFRA*, *PDGFRB* or *FGFR1* rearrangements, or the presence of the *PCM1-JAK2* fusion gene.
- Less than 20 percent blasts in the blood and bone marrow. Blasts include myeloblasts, monoblasts and promonocytes (types of immature white blood cells).
- Abnormalities in one or more types of precursor cells that develop into red blood cells, certain types of white blood cells or platelets. These abnormalities are referred to as “dysplasia,” which means abnormal growth of cells.
 - If dysplasia is absent or minimal, the diagnosis of CMML may still be made if a clonal (mutation involving the following genes: *ASXL1*, *TET2*, *SRSF2* and *SETBP1*) molecular or cytogenetic abnormality is identified or if there is persistent monocytosis (an increased number of monocytes circulating in the blood) for at least 3 months with no evidence of other causes of monocytosis.

Cytogenetic and Molecular Abnormalities.

Cytogenetic abnormalities refer to abnormal changes in chromosomes, which may include broken, missing, rearranged or extra chromosomes. Approximately 20 to 30 percent of CMML patients have chromosomal abnormalities. Some of these abnormalities have prognostic implications, as indicated below. The most common abnormalities are:

- Trisomy 8, the presence of an extra copy of chromosome 8; associated with poor prognosis
- $-Y$, the loss of the Y chromosome
- Monosomy 7, the absence of one member of a pair of chromosomes—in this case, one copy of chromosome 7; associated with poor prognosis
- *Del(7q)*, the loss of the long arm of chromosome 7; associated with poor prognosis
- Trisomy 21, the presence of an extra copy of chromosome 21
- Complex karyotype, the presence of 3 or more chromosomal abnormalities; associated with poor prognosis

Molecular abnormalities refer to abnormal changes in genes. These abnormalities are known as gene mutations. Mutations that are acquired and not inherited are called somatic mutations. In CMML, almost 90 percent of patients exhibit one or more somatic mutation.

Table 1 on page 4 lists the most common gene mutations in CMML and their associated frequency.

SF3B1 and *DNMT3A* mutations are generally found in the myelodysplastic type of CMML (MD-CMML) while mutations affecting the RAS pathway, *RUNX1* and *EZH2* are more common in the myeloproliferative type (MP-CMML). *ASXL1* mutations are associated with an unfavorable prognosis. *NPM1* mutations are associated with an increased tendency to progress to AML and a poorer prognosis, indicating the need for aggressive treatment.

Visit www.LLS.org/booklets to order or download a free copy of the booklet *Understanding Genetics*.

Table 1. Frequencies of Gene Mutations in Patients with CMML

Gene	Frequency of mutation
ASXL1^a	40%
EZH2	5%
TET2^b	60%
DNMT3A^a	5%
IDH1	1%
IDH2	5%–10%
JAK2	5%–10%
CBL	15%
NRAS^a	15%
KRAS	10%
PTPN11	5%
FLT3	<5%
SRSF2	50%
SF3B1	5%–10%
U2AF1	5%–10%
ZRSR2	5%
RUNX1^a	15%
SETBP1^a	15%
TP53	1%
PHF6	5%

Table adapted from Patnaik MM, Tefferi A. Chronic myelomonocytic leukemia: 2020 update on diagnosis, risk stratification and management. *American Journal of Hematology*. 2020;95:97-115.

^aDenotes genes that have been shown in various studies to be associated with an unfavorable prognosis.

^bTET2 with an absence of ASXL1 is associated with a favorable prognosis.

Treatment of CMML

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all your treatment options, including clinical trials, you will be taking an active role in this important decision.

For most CMML patients, the disease is treatable, but not curable, using currently available therapies. Patients are advised to:

- Seek treatment from a hematologist/oncologist who is experienced in treating CMML or from a hematologist/oncologist who is in consultation with a cancer center.
- Discuss with their hematologist-oncologist the most appropriate treatment for their situation.

The type of treatment depends on various patient factors, including the:

- Nature and extent of symptoms
- Need for rapid disease control
- Eligibility for stem cell transplantation
- Overall health and quality of life

Prognostic Models. Several prognostic scoring systems have been developed for CMML patients. However, there is significant variation among these models as each one includes different restrictions. This creates a challenge for hematologists-oncologists in treating their patients because treatment recommendations are often based on risk assessment.

The newest prognostic models are incorporating gene mutations to better refine their predictive value. The international working group (IWG) for CMML is currently working on integrating clinical and genetic parameters to develop a more uniform prognostic system.

Drug Therapy for CMML. There is no one standard treatment for CMML. There are three FDA approved treatments for patients, which include:

- **Azacitidine (Vidaza®)**, a hypomethylating agent, given via intravenous (IV) infusion or by subcutaneous injection
- **Decitabine (Dacogen®)**, a hypomethylating agent, administered via IV infusion

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- **Decitabine and cedazuridine (Inqovi®)**, a combination of decitabine, a nucleoside metabolic inhibitor, and cedazuridine, a cytidine deaminase inhibitor, given by mouth

Hypomethylating agents affect the way genes are controlled. They help stop abnormal cells in the bone marrow from dividing into new cells, and they make these abnormal cells more susceptible to death. Studies have shown that these agents are effective in some patients with CMML; however, the response rates are often low or do not last, especially in the proliferative form of the disease (MP-CMML).

New CMML-directed therapies that target the underlying genetic features of the disease are currently under study in clinical trials (See *Treatments Under Investigation* in the next column).

Current treatment approaches also include therapies that target specific symptoms of CMML, such as low blood counts, spleen enlargement and infections. Supportive measures and therapies that can make patients more comfortable include blood transfusions, blood cell growth factors and antibiotics.

You can work one-on-one with an LLS Clinical Trial Nurse Navigator who will personally assist you throughout the entire clinical-trial process. Clinical Trial Nurse Navigators are registered nurses with expertise in blood cancers.

Visit www.LLS.org/CTSC for more information.

Stem Cell Transplantation for CMML. Allogeneic stem cell transplantation uses donor stem cells to replace damaged stem cells in the patient. Allogeneic transplantation allows doctors to give high doses of chemotherapy in order to place new stem cells in the bone marrow. Allogeneic transplant replaces the stem cells destroyed by chemotherapy. The increased use of lower-conditioning regimens and the use of alternative donors, such as cord blood and haploidentical donors, have increased the availability of stem cell transplantation for older CMML patients.

Allogeneic stem cell transplantation is the only curative option for CMML patients. The major cause of failure after transplantation is relapse. In addition, some patients may develop chronic graft-versus-host disease (GVHD), which can decrease quality of life. Currently, there is no consensus about the ideal timing of allogeneic stem cell transplantation in CMML patients and this question is being studied in clinical trials. See *Treatments Under Investigation* below for more information.

For additional information, please visit www.LLS.org/booklets to order or download *Graft-versus-Host Disease and Blood and Marrow Stem Cell Transplantation*.

Treatments Under Investigation

Every new drug or treatment regimen goes through a series of studies called “clinical trials” before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians, researchers and patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time treatment is discussed with the doctor. Patient participation in past clinical trials has resulted in the therapies we have today. Patients interested in participating in a clinical trial for CMML are encouraged to talk with their hematologists-oncologists about whether a clinical trial would be appropriate for them.

When you and your hematologist-oncologist discuss a clinical trial as a potential treatment option for you, it may be helpful to:

- Have a list of questions to ask concerning risks versus benefits of such a trial (visit www.LLS.org/WhatToAsk for lists of suggested questions)
- Ask a family member, friend, or another advocate accompany you—both for support and to take notes

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. **Visit www.LLS.org/CTSC for more information. Also, visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers*.**

Examples of the types of therapies currently under study for CMML treatment are listed here.

- **ABNL-MARRO STUDY.** This study is an initiative from the MDS/MPN International Working Group (IWG) and Vanderbilt University Medical Center. This international collaboration will enroll patients with MDS/MPN overlap syndromes (including CMML) in the

United States and several European countries. The study is designed to allow new drugs and therapy combinations to be introduced into the different clinical sites participating. Researchers also seek to study the biology and pathology of the diseases to identify potential markers of prognosis and response.

- **Monoclonal antibodies.** These immunotherapy agents are proteins made in the laboratory that can bind to substances in the body, including cancer cells. They can work alone or can be coupled with a chemotherapy drug or a toxin, or attached to a toxin to kill malignant cells. Examples include monoclonal antibody targeting GM-CSF (**lenzilumab™**), a cytokine (chemical) to which CMML cells are hypersensitive, and **tagraxofusp (Elzonris®)** (antibody to CD123, conjugated with diphtheria toxin).
- **JAK2 Inhibitors.** The *JAK2* gene makes a receptor (protein) which sends signals into cells that promote cell growth. This protein helps control the number of blood cells made in the bone marrow. Mutated forms of this gene are present in some CMML patients (about 10%); however, the protein is believed to be activated regardless of the presence of the mutation. JAK2 inhibitors target the abnormal protein activation in the cancer cells. **Ruxolitinib (Jakafi®)** and **pacritinib** are two examples of *JAK2* inhibitors in clinical trials for CMML treatment.
- **Hypomethylating agents (HMAs).** These drugs prevent cells from making DNA, thus inhibiting cell division and making cancer cells more susceptible to death. **Decitabine (Dacogen®)** and **azacitidine (Vidaza®)** are two HMAs being studied for use in combination with other agents for CMML treatment. The second-generation HMA **guadecitabine** is under study for patients with MDS and CMML who have not responded to treatment or have relapsed.
- **Reduced-intensity allogeneic stem cell transplantation (also known as nonmyeloablative allogeneic stem cell transplantation).** This treatment may prove effective for CMML patients who do not respond to drug therapy but are also not considered candidates for allogeneic transplant because of older age or other health risks. Patients being conditioned for a reduced-intensity transplant receive lower doses of chemotherapy and/or radiation than the doses usually given to patients before standard stem cell transplantation. Clinical trials are under way to evaluate this type of transplantation and determine its effectiveness in CMML patients.

Outcomes for CMML Patients

All patients are advised to discuss survival information with their hematologist-oncologists. Keep in mind that outcome data can only show how other people with CMML responded to treatment, and cannot predict how any one person will respond.

Unfortunately, lasting remissions are not common. The expected survival time ranges from a few months to a few years after the initiation of treatment, depending on a variety of risk factors including the percentage of blasts in the blood and marrow, the white blood cell count, and the presence of certain gene mutations.

CMML progresses to acute myeloid leukemia (AML) in approximately 15 to 30 percent of patients over 3-5 years. Those with the proliferative form of the disease (MP-CMML) tend to have a higher risk of transformation to AML.

Juvenile Myelomonocytic Leukemia (JMML)

JMML is an uncommon blood cancer that most often occurs in infants and toddlers. It is similar in some ways to adult chronic myelomonocytic leukemia (CMML); in both JMML and CMML, mutations (changes) in the DNA take place in an early progenitor cell, which leads to increased numbers of white blood cells called “monocytes.”

JMML starts in the bone marrow when stem cells acquire mutations that lead to the overproduction of monocytes. These “myeloproliferating” cells accumulate in the marrow and in other organs including the spleen, the liver, and even the lungs and skin. When the spleen becomes enlarged, sometimes dramatically so, there is less room in the abdomen and chest for other organs, causing discomfort. JMML cells can infiltrate the lungs and lead to breathing problems. As too many white blood cells are being produced, there is almost always decreased production of red blood cells and platelets, leading to decreased energy and increased risk of bleeding and bruising.

Monocytes represent about 5 to 10 percent of the cells in normal human blood. These cells, along with other white cells called “neutrophils,” are the two major microbe-eating and microbe-killing cells in the blood. When monocytes leave the blood and enter the tissue, they are converted to macrophages. Macrophages are “monocytes-in-action”:

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they can combat infections in the tissues, ingest dead cells and assist other cells such as lymphocytes in carrying out their immune functions. In patients with JMML, the number of monocytes is often dramatically increased, but many of them are often not functional. Despite the increased number of white blood cells, JMML patients often present with viral or bacterial infections because the white blood cells are not working properly.

Over time, JMML has been known by other names, such as “juvenile chronic myeloid leukemia,” “CMML of childhood,” “chronic and subacute myelomonocytic leukemia” and “infantile monosomy 7 syndrome.”

JMML Incidence

JMML accounts for approximately 1-2 percent of all childhood leukemia cases. It has an incidence of 1.2 cases per million children per year. The median age at diagnosis is 2 years. The disease occurs most commonly in infants and children younger than 4 years but can present in older children, particularly those with neurofibromatosis type 1. JMML is occasionally diagnosed in newborns, but many patients are diagnosed between 3 and 12 months of age. JMML is more prevalent in young males than in females by a ratio of 2 to 1.

Signs and Symptoms of JMML

Signs and symptoms of JMML may develop over a period of weeks or months. They may include:

- Difficulty breathing and/or dry cough
- Enlarged lymph nodes
- Abdominal pain caused by leukemia cells in the kidney, liver, and spleen, enlarging these organs and leading to loss of appetite
- Bone and joint pain
- Fatigue and pale skin due to anemia (low level of red blood cells)
- Easy bruising and bleeding caused by thrombocytopenia (low level of platelets)
- Frequent infection and fever due to decreased

level of healthy white blood cells

Some children may develop a maculopapular rash, which can be characterized by red raised bumps in the skin. JMML patients occasionally develop bluish or greenish discolorations on their skin called chloromas. Some children with JMML are born with café au lait spots, which are smooth coffee-colored skin lesions.

Diagnosis of JMML

Before JMML is diagnosed, other potential diagnoses need to be excluded, especially if a child is older than 6 years. For example, although chronic myeloid leukemia (CML) rarely occurs in children younger than 5 years, it represents about 3 percent of childhood leukemia cases in children aged 15 years and younger.

The tests used to diagnose JMML include:

- Blood tests
- Bone marrow aspiration and biopsy
- Cytogenetic and molecular tests that look for cytogenetic (chromosomal) and molecular abnormalities (gene mutations) in the cancer cells

An older test called a “GM-CSF hypersensitivity assay” was used before genetic mutation testing became routinely available. There were some disadvantages to this test: it required a long turnaround time (several weeks), it was not widely available, and it was difficult to interpret. For these reasons, this test is rarely performed outside of a research setting. Next-generation sequencing is now considered standard of care and all patients suspected of having JMML should have a genetic analysis of their genes comparing their tumor cells to their normal cells. A mutation in the RAS pathway is detected in more than 95% of JMML patients.

Table 2 lists the criteria needed to make a diagnosis of JMML.

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Table 2. Diagnostic Criteria for JMML

<p>Category 1 (all of the following)</p> <ul style="list-style-type: none">• Presence of an enlarged spleen• A persistent elevated monocyte count in the blood (greater than $1 \times 10^9/L$ which is equivalent to 1,000 monocytes per microliter of blood (1,000/μl)• The absence of the Philadelphia chromosome (Ph chromosome) and the <i>BCR-ABL1</i> gene rearrangement. The Ph chromosome is an abnormality of chromosome 22 found in the marrow and blood cells of patients with CML• Less than 20 percent blasts circulating in the blood and present in the bone marrow
<p>Category 2 (at least one of the following)</p> <ul style="list-style-type: none">• Somatic (change in DNA that happens after conception) mutation in <i>PTPN11</i>, <i>KRAS</i> or <i>NRAS</i> genes• Clinical diagnosis of neurofibromatosis type 1 (NF1) or <i>NF1</i> gene mutation^a• Germline <i>CBL</i> gene mutation^b
<p>Category 3 (if criteria from category 2 are not met, two of the following are acceptable)</p> <ul style="list-style-type: none">• Monosomy 7 (only one chromosome from a pair) or any other chromosomal abnormality• Higher levels of hemoglobin F than is normal for the age of the patient^c• Myeloid precursors (predecessor of red blood cells, platelets and some types of white blood cells) in the blood• Granulocyte-macrophage colony-stimulating factor (GM-CSF) hypersensitivity in colony assay• Hyperphosphorylation of <i>STAT5</i>^d

Table is adapted from Locatelli F, Niemeyer C. How I treat juvenile myelomonocytic leukemia. *Blood*. 2015;125(7):1083-1090.

The diagnosis of JMML is made if a patient meets all of the category 1 criteria and one of the category 2 criteria without needing to meet the category 3 criteria. If there are no category 2 criteria met, then at least two of category 3 must be met.

Notes:

^aNeurofibromatosis type 1 (NF1) is a condition that causes tumors to form on nerve tissue.

^bGermline mutation is a gene change in a reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. This cell can be passed from parent to offspring and is hereditary. Germline mutations are present throughout a person's life and are found in virtually every cell in the body. Somatic mutations are acquired (not inherited) and occur at some time during a person's life. They are present only in certain cells.

^cHemoglobin F is fetal hemoglobin found in the blood of fetuses and newborn infants. After birth, it decreases rapidly until only traces are found in children and adults. It is often elevated in individuals with certain blood disorders and in some blood cancers

^d*STAT5* is a signal transducer and activator of transcription 5. The *STAT5* gene produces proteins that regulate vital cellular functions such as proliferation, maturation and survival. Hyperphosphorylation is a biochemical process that can lead to the altered function of a protein.

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Cytogenetic and Molecular Abnormalities. Nearly all JMML patients have an abnormality in a specific gene or chromosome. Some of these include:

Molecular (gene mutation)

- Approximately 95 percent of patients with JMML present with a somatic (a change to DNA that happens after conception) and/or germline mutations (see **Table 2** Notes on page 8) in the genes of the RAS pathway, including *PTPN11*, *NRAS*, *KRAS*, *RRAS*, *RRAS2*, *SH2B3*, *NF1* and *CBL*.
- Mutations of the RAS family of genes including *NRAS*, *KRAS*, *RRAS* and *RRAS2* occur in about 25 to 30 percent of patients.
- Mutation of the *NF1* gene. About 15 percent of JMML patients have the *NF1* gene mutation and about 10 to 15 percent of JMML patients are also diagnosed with neurofibromatosis 1. Neurofibromatosis 1 (NF1) is a rare genetic condition associated with coffee-colored spots and pea-sized tumors on the skin, freckling in skin areas not exposed to the sun, optic glioma (a tumor on the optic nerve that affects eyesight), and developmental abnormalities in the nervous system, muscles and bones. A child with NF1 has about a 300-fold increased risk of developing JMML. Patients with NF1-related JMML can present at an older age compared to other types of JMML.
- Mutation of the *PTPN11* gene occurs in about 35 percent of patients. Older patients with *PTPN11* mutations can have more aggressive JMML. Patients who are born with a mutation in *PTPN11* in every cell of their body leads to a disorder called Noonan syndrome. Patients with Noonan syndrome are at risk of developing a disorder very similar to, but not the same as, JMML.
- Mutation of the *CBL* gene occurs in about 15 percent of patients. Patients are typically born with a mutation in *CBL* that is present in one of two copies of the gene in every cell in their body, which causes a condition called CBL syndrome. If both copies of the *CBL* gene become altered in the blood or bone marrow, it can lead to the development of JMML. In some patients with CBL-related JMML, the leukemia goes away on its own. Some CBL-JMML cases are not germline but are acquired after birth.
- Approximately 25-35 percent of JMML patients have a second mutation besides the RAS pathway mutation that caused the JMML to arise. These

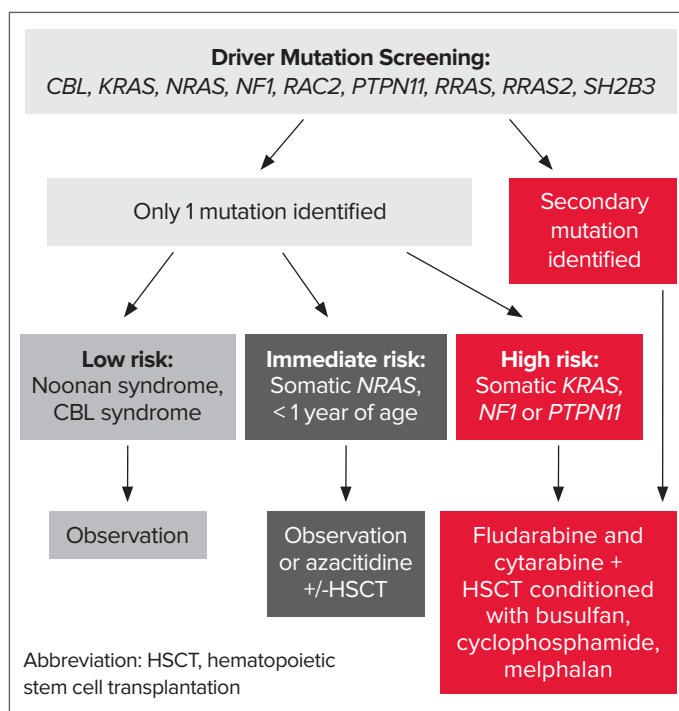
“secondary” mutations can be inside or outside of the RAS pathway but are usually associated with a more aggressive disease course. Secondary genes that are frequently mutated in JMML include *SETBP1*, *SH2B3*, *DNMT3A*, *ASXL1*, *EZH2*, *GATA2* and *RUNX1*.

Cytogenetic (chromosomal abnormality)

- Monosomy 7 and other chromosome 7 abnormalities occur in approximately 25 to 30 percent of patients.

For additional information, please see the free LLS booklets *Understanding Lab and Imaging Tests* and *Understanding Genetics*.

Figure 1. Risk-Stratified Treatment Algorithm



Source: Koegel A, Stieglitz E. A risk stratified treatment algorithm for patients with juvenile myelomonocytic leukemia. *Hematologist: ASH News and Reports*. American Society of Hematology. 2017;14(2). Published March 1, 2017.

Treatment of JMML

Before the child begins treatment, the parents, the child (if appropriate) and the doctor will discuss treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all treatment options, including clinical trials, parents will be taking an active role in a very important decision.

Parents are advised to seek treatment from a hematologist/oncologist who is experienced in treating JMML or from a hematologist/oncologist who is in consultation with a cancer center.

Drug Therapy for JMML. Without treatment, JMML progresses rapidly. Using chemotherapy alone will almost always lead to the disease coming back after the treatment is over. **Azacitidine (Vidaza®)** is approved for the treatment of pediatric patients aged 1 month and older with newly diagnosed JMML. Since JMML is difficult to treat with currently available drug therapy, participating in a clinical trial investigating new drugs may be an option for some children, even right after diagnosis.

Work one-on-one with an LLS Clinical Trial Nurse Navigator who will personally assist you throughout the entire clinical-trial process. Clinical Trial Nurse Navigators are registered nurses with expertise in blood cancers.

Visit www.LLS.org/CTSC to learn more about clinical trials and to contact a Clinical Trial Nurse Navigator.

Stem Cell Transplantation for JMML. Currently, the only potentially curative treatment option for JMML is allogeneic stem cell transplantation. During this procedure, the patient is given intense chemotherapy to kill JMML cells and wipe out the bone marrow. Then, stem cells donated from a family member or a matched unrelated donor are transferred into the patient to start rebuilding the bone marrow and immune system with healthy cells.

Stem cell transplantation has been noted to achieve long-term remissions in up to 50 percent of patients; however, relapses occur in about 35 to 40 percent of JMML patients after transplantation, often within the first year. While the rates of relapse are high, patients may achieve a cure with a second stem cell transplant.

The use of standard chemotherapy before a stem cell transplant is often undertaken to control the disease during the 1 to 2-month period that is required to arrange a stem cell transplant. Occasionally, pre-transplant chemotherapy can also result in a temporary remission going into the transplant, which may be associated with improved long-term outcomes.

Transplantation is recommended for all children with *NF1*, somatic *PTPN11* and *KRAS* mutations. For some patients with an *NRAS* mutation, treatment with azacitidine instead of a stem cell transplant may be considered. A “watch and wait” approach can be adopted in children with germline *CBL* mutations and *PTPN11*-mutated Noonan syndrome.

For additional information on stem cell transplantation, please visit www.LLS.org/booklets to order or download the free booklet *Blood and Marrow Stem Cell Transplantation*.

Treatments Under Investigation

Every new drug or treatment regimen goes through a series of studies called “clinical trials” before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians, researchers and patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time treatment is discussed with the doctor. Patient participation in past clinical trials has resulted in the therapies we have today. Patients’ parents interested in participating in a clinical trial for JMML are encouraged to talk to their hematologists-oncologists about whether a clinical trial would be appropriate for their child.

When you and the hematologist-oncologist discuss a clinical trial as a potential treatment option for your child, it may be helpful to:

- Have a list of questions to ask concerning risks versus benefits of such a trial (visit www.LLS.org/WhatToAsk for lists of suggested questions).
- Ask a family member, friend, or another advocate to accompany you—both for support and to take notes.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how parents can work with their child’s doctors to determine if a specific clinical trial is an appropriate treatment option. LLS offers help for parents, patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, parents and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. **Visit www.LLS.org/CTSC for more information. Also, visit www.LLS.org/booklets to order or download the free booklet *Understanding Clinical Trials for Blood Cancers*.**

Examples of therapies currently under study to achieve longer-lasting remissions for JMML patients are:

- **Hypomethylating agents (HMAs).** These drugs stop cells from making DNA, which inhibits cell division and makes cancer cells more likely to die.
- **Azacitidine (Vidaza®)** is a medication approved for treating chronic myelomonocytic leukemia (CMML). It is currently being studied as a single agent and in combination with other drugs to treat JMML patients.

- **MEK inhibitor.** The majority of JMML patients harbor a mutation in the RAS pathway. Inhibition of this pathway is one therapeutic strategy currently under investigation. The efficacy of the MEK inhibitor **trametinib** is being tested in a clinical trial sponsored by the Children's Oncology Group (COG), for treating relapsed and refractory JMML patients.
- **Second stem cell transplantation.** The effectiveness of second allogeneic stem cell transplantation in JMML patients who have relapsed after a first transplant is being studied in clinical trials. For more information on this therapy, see *Stem Cell Transplantation for JMML* on page 10.

Outcomes for JMML Patients

Parents of JMML patients are advised to discuss survival information with their child's hematologist-oncologist. Keep in mind that outcome data can show how other children with JMML responded to treatment, but it cannot predict how any one child will respond.

Outcomes for JMML patients are variable. Some patients have rapidly progressing disease while others have a relatively slow-growing course. To date, the only potentially curative therapy is allogeneic stem cell transplantation. The median survival time for patients who have aggressive JMML and who do not receive a transplant can be as short as 10 to 12 months and, on average, is less than 2 years.

There are individual factors that influence patient outcome. Factors that may indicate a less favorable outcome include:

- Age greater than 2 years
- A low platelet count at diagnosis
- Elevated hemoglobin F levels
- More than one gene mutation detected in JMML cells at diagnosis

In contrast, in a small percent of patients the disease resolves spontaneously, without the need for treatment. Spontaneous improvement of some JMML patients with somatic *NRAS* mutations and germline *CBL* mutations has been noted.

Feedback. Visit www.LLS.org/PublicationFeedback to access the LLS Survey and give suggestions about this booklet.

Acknowledgment

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our website at www.LLS.org/chapterfind or contact:

The Leukemia & Lymphoma Society
3 International Drive, Suite 200
Rye Brook, NY 10573

Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org

LLS offers free information and services for patients and families touched by blood cancers. The following entries list various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

Consult with an Information Specialist. Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date disease, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information.

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm ET)

Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML)

- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists
- Visit: www.LLS.org/InformationSpecialists

Clinical Trials Support Center (CTSC). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Free Information Booklets. LLS offers free education and support booklets that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

LLS Health Manager™ App. This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format and share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Visit www.LLS.org/HealthManager to download for free.

LLS Coloring for Kids™. This free coloring app allows children to express their creativity and offers activities to help them learn about blood cancer and its treatment. The app includes blank canvases, general coloring pages, and pages from LLS coloring books. This app can be used anywhere and may help pass time in waiting rooms or during treatment. Visit www.LLS.org/ColoringApp to learn more and download.

Financial Assistance. LLS offers financial support including insurance premium and medication co-pay assistance, as well as travel and other needs, to eligible individuals with blood cancer. For more information, please

- Call: (877) 557-2672
- Visit: www.LLS.org/finances

Información en Español. (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit www.LLS.org/community to join.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian who has experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or for more information.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients to reach out and share information. Please visit www.LLS.org/chat for more information.

Podcast. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe.

LLS Chapters. LLS offers support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), local support groups, and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. Please visit www.LLS.org/ResourceDirectory for more information.

Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML)

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/agentorange

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a 2-week period. For more information, please

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter “depression” in the search box

Other Resources

Children’s Tumor Foundation (800) 323-7938

www.ctf.org

Organization dedicated to finding effective treatments for people living with neurofibromatosis. This foundation supports research endeavors and provides information and resources to patients.

National Cancer Institute (NCI) (800) 422-6237

www.cancer.gov

The National Cancer Institute (NCI), part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including CMML and JMML. The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trial Registry, at www.cancer.gov/clinicaltrials, where CMML/JMML patients can look for clinical trials.

National Organization for Rare Disorders (NORD) (800) 999-6673

www.rarediseases.org

Patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD provides programs of education, advocacy, research and patient services. The website provides concise information about uncommon diseases such as JMML.

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Information Specialist: **800.955.4572**

The mission of The Leukemia & Lymphoma Society (LLS) is to cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families. Find out more at www.LLS.org.