

**No. 35** in a series providing the latest information for patients, caregivers and healthcare professionals

## Highlights

- Even if a patient achieves a complete remission based on standard test results, there still may be cancer cells that remain in the body. This is known as measurable (minimal) residual disease (MRD).
- MRD describes the low level of cancer cells that remain in the body after cancer treatment. An MRD positive test result means that disease is still detected after treatment. An MRD negative result means that no disease is detected after treatment.
- For patients who are MRD positive, the number of remaining cancer cells may be so small that they cannot be detected through traditional tests, such as viewing cells under a microscope or through imaging tests.
- A few tests can measure MRD. The more sensitive a test is, the more effective it is at finding a small amount of cancer cells among the many healthy cells. The most widely used tests to measure MRD are multiparameter flow cytometry (MFC), polymerase chain reaction (PCR), and next-generation sequencing (NGS).
- The clonoSEQ assay is an NGS test that is FDA-cleared to assess MRD in patients with acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM).
- Doctors use MRD to measure the effectiveness of treatment and to predict which patients are at risk of relapse. It can also help doctors confirm and monitor remissions, identify an early return of the cancer and guide treatment decisions, such as when to change or discontinue treatment.

## What Is Measurable Residual Disease (MRD)?

Measurable residual disease (MRD) – sometimes referred to as minimal residual disease – refers to the small number of cancer cells remaining in the body during and after cancer treatment. The number of remaining cells may be so low that they do not cause any physical symptoms and often cannot even be detected through traditional methods, such as viewing cells under a microscope or getting imaging scans. However, these remaining cancer cells can start to multiply, causing a relapse of the disease.

## The Importance of MRD Assessment

An MRD test can find remaining cancer cells even in very small numbers. These tests use very sensitive technologies that can detect a single cancer cell in 100,000 or even 1 million healthy cells. MRD may be present after treatment because not all the cancer cells responded to the therapy, or because the cancer cells became resistant to the medications that were used. For cancers considered curable, like ALL, detecting MRD may indicate that the treatment was not completely effective or that the treatment was incomplete. For cancers considered incurable, like MM, detecting MRD can help guide decisions about how long to continue maintenance therapy.

MRD testing can help:

- Determine how well the cancer is responding to a specific treatment.
- Guide future treatment options (e.g., determine if a patient might benefit from a different treatment approach).
- Confirm and monitor remissions.
- Identify patients who may be at a higher risk of relapse.
- Identify disease recurrence sooner than other tests.
- Determine the efficacy of an ongoing clinical study treatment.

**Your MRD Status: Positive or Negative?** A patient can have a positive or negative MRD status. This is determined by the result of their MRD tests. When a patient tests positive for MRD, it means that there are still residual cancer cells in the body after treatment. When MRD is detected, this is known as “MRD positivity.” When a patient tests negative, no residual cancer cells are found. When no MRD is detected, this is known as “MRD negativity.” The type of test being used, and how “sensitive” it is (how many cancer cells it can detect), matters a lot. In some cases, doctors may consider patients “MRD negative” because the levels of residual cancer cells – even if present – are below the cutoffs set in previous studies.

Being “MRD negative” is often an encouraging outcome for a patient with blood cancer because it means that even with sophisticated, sensitive tests, no cancer cells can be found. Studies have shown that MRD negativity is associated with longer remissions and potentially longer rates of survival for people with certain blood cancers. However, being “MRD positive” is not the same as relapse. In certain blood cancers, like MM, patients who are “MRD positive” may live for years with low levels of residual disease. Doctors and scientists are still learning more about how and why this may happen.

**When to Test for MRD.** There are different criteria for when to test for MRD. These are based on factors specific to the patient’s disease. The treatment team may recommend testing at certain times:

- After the final cycle of combination therapy
- Before or after stem cell transplantation
- During treatment to determine the depth of remission
- After one year on maintenance therapy
- At regular intervals after treatment is finished

### Tests Used to Detect MRD

MRD testing uses highly sensitive methods that can look for a small number of cancer cells in a very large sample of cells. The most widely used tests are flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing (NGS). These tests use samples of bone marrow cells (taken by bone marrow “aspiration”) and/or peripheral blood cells (taken from blood, through a vein). Bone marrow aspiration is a procedure in which a small sample of bone marrow is removed, typically from the hip bone.

**Multiparameter Flow Cytometry (MFC).** Multiparameter flow cytometry – sometimes referred to as multicolor flow cytometry – is a technique that evaluates individual

cells by checking for the presence or the absence of certain protein markers on the surface of cells. Based on how the flow cytometry is set up, this approach can find one cancer cell among 100,000 normal bone marrow cells. Results can be available in less than one day and don’t require any previous testing.

**Polymerase Chain Reaction (PCR).** This technique can identify cancer cells based on their characteristic genetic abnormalities, such as mutations or chromosomal changes. PCR essentially increases or “amplifies” small amounts of specific pieces of either DNA or RNA to make them easier to detect and count. As a result, PCR can detect genetic abnormalities even when a very small number of cancer cells remain. The test is done with bone marrow or blood cells. With PCR, it is possible to identify one cancer cell within 100,000 to 1 million healthy cells. It may take approximately 1 week for test results to be available.

**Next-Generation Sequencing (NGS).** This technique refers to a number of different sequencing technologies. NGS tests can rapidly examine stretches of DNA or RNA specific to a particular patient’s cancer cells. NGS can detect mutations and other genetic abnormalities in DNA extracted from a bone marrow aspirate sample. This approach offers the potential for increased sensitivity. It can detect one cancer cell in 1 million bone marrow cells checked. Test results are usually available within two weeks. Both fresh and frozen/stored samples can be used for NGS-based MRD testing. However, in most cases, NGS requires a previous sample of cancer cells to “fingerprint” DNA or RNA sequences unique to that patient’s cancer.

The US Food and Drug Administration (FDA) has authorized a test called clonoSEQ®, an NGS test designed to detect MRD in B-cell acute lymphoblastic leukemia (ALL), myeloma and chronic lymphocytic leukemia.

Among these three methods, MFC is the only one that requires a fresh sample for analysis, whereas fresh or stored samples can be used for PCR or NGS.

**For more information about the techniques mentioned above, please see the free LLS publication *Biomarker Testing for Cancer Treatment*.**

### MRD Testing in Specific Blood Cancers

The type of MRD testing used varies depending on the type of blood cancer.

## Measurable Residual Disease (MRD)

### Acute Lymphoblastic Leukemia (ALL)

- MRD is detected through MFC, PCR and NGS (such as the clonoSEQ® assay).
- Testing is done on bone marrow or blood.
- Testing for MRD is routine in the treatment of children and adults with ALL.
- Studies show that the presence of MRD can predict the effectiveness of a given treatment after the induction phase of ALL treatment. If a patient is MRD-positive after induction, the health care team may suggest consolidation treatment.
- The results of MRD testing can help identify which patients are at higher risk for relapse, allowing for earlier or additional treatments. MRD test results may also determine which patients may benefit from allogeneic stem cell transplantation versus doing other treatments first (or instead of transplantation).

### Chronic Myeloid Leukemia (CML)

- MRD is detected through a special PCR test called reverse transcription polymerase chain reaction (RT-PCR).
- Testing is done on bone marrow or blood.
- RT-PCR can detect the *BCR::ABL1* fusion oncogene, which is a product of the t(9:22) chromosomal translocation found in 99 percent of all CML patients. This method can detect one leukemic cell among 100,000 to 1 million normal cells.
- MRD monitoring helps predict treatment resistance and guide the course of treatment.
- It is one factor used in deciding whether to change tyrosine kinase inhibitor (TKI) therapy or discontinue it altogether, an approach known as treatment-free remission.
- MRD assessment is used to monitor remissions and to determine if a patient needs to restart treatment.
- Digital droplet PCR (ddPCR) is a novel PCR method that uses a water-oil emulsion droplet system where the patient sample is partitioned into thousands of droplets and each droplet is assessed to determine MRD. This method is being used in clinical trials to detect residual disease at the time of stopping TKI therapy in patients who attempt treatment-free remission.

### Multiple Myeloma (MM)

- The most widely used methods to test MRD in myeloma are MFC and NGS (such as the clonoSEQ® assay).
- Testing is done on the bone marrow. Ongoing research is studying new types of MRD assessments from the blood. For example, tests that can detect very small quantities of the “M-spike” abnormal protein produced by MM cells are being developed. However, these methods are still being studied.
- Imaging techniques such as PET-CT scans or MRI scans of the bone marrow, in addition to other tests, allow doctors to find myeloma outside the bone marrow.
- At present, researchers are trying to determine exactly when MRD testing should be done.
- Studies have shown that patients who achieve an MRD-negative status after myeloma treatment live longer without disease progression.
- However, some patients may have MRD-positive disease for years (or their whole lives) after treatment without ever having a myeloma relapse. Doctors and scientists are working to understand this principle. Some patients may have “MGUS-like” disease left behind, which means that the actual cancerous cells are gone, but pre-cancerous cells (that aren’t at risk of causing myeloma symptoms) are still being detected.
- MRD status is guiding new treatment strategies in ongoing myeloma clinical trials. The FDA is considering how to use the results of MRD measurements for new drug approval in clinical trials.

### Acute Myeloid Leukemia (AML)

- MRD testing for AML is still under investigation and is being evaluated in clinical trials.
- MRD testing for AML is most often detected by MFC and PCR.
- Testing is done on bone marrow or blood.
- Studies in both children and adults with AML have demonstrated a correlation between the presence of MRD and risk of relapse.
- In 2022 the Foundation for the National Institutes of Health (FNIH) announced the launch of the AML MRD Biomarkers Consortium, which involves the National Institutes of Health, the FDA and over 20 research and pharmaceutical industry partners. The goals of this consortium are to generate reference standards for AML MRD assessment and to compare methods for MRD detection with the aim of advancing AML research and improving treatment outcomes.

## Measurable Residual Disease (MRD)

### Chronic Lymphocytic Leukemia (CLL)

- MRD testing has become widespread in CLL clinical trials, but it is not currently part of routine patient management for CLL.
- MRD testing for CLL is detected by MFC, PCR and NGS (such as the clonoSEQ® assay).
- Testing is done on bone marrow or blood.
- In research studies, patients who remained MRD-negative after the end of CLL therapy had better treatment outcomes.

### Lymphoma

- MRD testing is being studied in clinical trials for patients with follicular, mantle cell and diffuse large B-cell lymphoma (DLBCL), but it is not currently part of the day-to-day clinical practice.
- MRD in lymphoma is detected through MFC, PCR and NGS.
- Testing is done on bone marrow or blood.
- Several studies have shown that lymphoma patients who achieved remission after treatment and were also MRD negative were more likely to remain in remission than patients who had achieved remission but who were MRD positive.
- MRD assessment using peripheral blood and liquid biopsy specimens instead of bone marrow tissue is an emerging technique that is currently being studied in ongoing trials for DLBCL, follicular and mantle cell lymphoma. With a liquid biopsy, cell-free cancer DNA from the blood and other bodily fluids can be collected and analyzed to detect and quantify MRD.

## Clinical Trials for Blood Cancers

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called clinical trials and they are used to find better ways to care for and treat people with cancer.

In the United States, the FDA (U.S. Food and Drug Administration) requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer

clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to:

- Treat cancer using
  - A new drug
  - An approved drug to treat a different kind of cancer
  - A new combination of drugs
  - A new way of giving a drug—by mouth (pill), intravenously (IV)
- Manage cancer symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit [www.LLS.org/WhatToAsk](http://www.LLS.org/WhatToAsk) for lists of suggested questions).
- Ask a family member or friend to go with you to your doctor visit—both for support and to take notes.

Clinical trials can be difficult to navigate and figure out, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find potential clinical trials, overcome barriers to enrollment and provide support throughout the entire clinical trial process. Our **Clinical Trial Nurse Navigators** are registered nurses who are experts in pediatric and adult blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals.
- Help you understand the clinical-trial process, including your rights as a patient.
- Ask you for details about your diagnosis (like past treatments, treatment responses, and your cancer genetic profile), your current health, and your medical history. These details might impact whether you can take part in certain clinical trials.

## Measurable Residual Disease (MRD)

- Help you understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials.
- Guide you and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites.
- Help deal with any problems you might have as you enroll in a trial.
- Support you throughout the clinical trial process.

**Call an LLS Information Specialist at (800) 955-4572 or visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information about clinical trials and the Clinical Trial Support Center (CTSC) at LLS. Also, visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to view the free LLS booklet *Understanding Clinical Trials for Blood Cancers*.**

### Questions for the Treatment Team

It is likely that you will have questions about MRD testing and/or the significance of MRD test results. It is important to share all your questions and concerns with your treatment team.

Patients may want to ask the following questions:

- Do I need MRD testing for my specific cancer?
- What type of MRD testing do I need?
- When and how often should I have an MRD test?
- Where will the MRD test take place?
- What does an MRD-positive or an MRD-negative test result mean in my case?
- How long will it take to get MRD results?
- How will the results of MRD testing affect my treatment plan?

### The Cost of MRD Testing

MRD tests are considered specialized tests and can be expensive. Patients need to be aware that MRD testing may require prior authorization from an insurance provider. When MRD testing is ordered by the doctor, the sample may be sent to an out-of-network laboratory because not all laboratories have the capability to perform MRD testing. This can result in out-of-network fees for patients. Ask your treatment team to inform you if an MRD sample is being sent out to a laboratory. Speak to your insurance provider to find out the cost of MRD testing.

Patients may want to ask the following questions about insurance coverage:

- Will my insurance plan cover MRD testing?
- Will I need pre-authorization from my insurance provider before the test is done?
- If the MRD testing is not covered by insurance, is there any financial assistance available to complete the necessary testing?

Some treatment centers have resources to help patients access programs that help cover the costs of testing and treatment. Some clinical trials may cover the costs of MRD testing and/or treatment drugs for all participants.

**For more information and resources on coping with the financial aspects of cancer care, please see the LLS booklet *Cancer and Your Finances*. You can also contact LLS Information Specialists at (800) 955-4572 for information about financial assistance programs.**

**Feedback.** To make suggestions about the content of this booklet, visit [www.LLS.org/PublicationFeedback](http://www.LLS.org/PublicationFeedback).

### Acknowledgment

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### We're Here to Help

LLS offers free information and services for patients and families affected by blood cancers. This section lists various resources you may find helpful.

#### **For Help and Information**

**Consult with an Information Specialist.** Information Specialists can assist you through cancer treatment, financial and social challenges and give accurate, up-to-date disease, treatment and support information. Our Information Specialists are highly trained oncology social workers and nurses. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. ET)
- Email and Live chat: [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)



## Measurable Residual Disease (MRD)

**Clinical Trials (Research Studies).** Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Pediatric and adult patients and caregivers can work with our Clinical Trial Nurse Navigators who will help find clinical trials and provide personalized support throughout the entire clinical trial process. Visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information.

**Nutrition Consultations.** Schedule a free one-on-one nutrition consultation with one of our registered dietitians who have expertise in oncology nutrition. Consultations are available to patients of all cancer types and their caregivers. Dietitians can assist with information about healthy eating strategies, side effect management and more. Please visit [www.LLS.org/nutrition](http://www.LLS.org/nutrition) for more information.

**Free Information Booklets.** LLS offers free education and support booklets for patients, caregivers and healthcare professionals that can either be read online or ordered. Please visit [www.LLS.org/booklets](http://www.LLS.org/booklets) 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](http://www.LLS.org/programs) for more information.

**Financial Assistance.** LLS offers financial support to eligible individuals with blood cancer for insurance premiums, co-pays, and non-medical expenses like travel, food, utilities, housing, etc. For more information, please:

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

**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](http://www.LLS.org/TheBloodline) for more information and to subscribe to access exclusive content, submit ideas and topics, and connect with other listeners.

**3D Models.** LLS offers interactive 3D images to help visualize and better understand blood cell development, intrathecal therapy, leukemia, lymphoma, myeloma, MDS, MPNs and lab and imaging tests. Visit [www.LLS.org/3D](http://www.LLS.org/3D) for more.

### Free Mobile Apps.

- LLS Coloring For Kids™ — Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit [www.LLS.org/ColoringApp](http://www.LLS.org/ColoringApp) to download for free.
- LLS Health Manager™ — Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit [www.LLS.org/HealthManager](http://www.LLS.org/HealthManager) to download for free.

**Suggested Reading.** LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit [www.LLS.org/SuggestedReading](http://www.LLS.org/SuggestedReading) to find out more.

### Connecting with Patients, Caregivers and Community Resources

**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](http://www.LLS.org/community) to join.

**Weekly Online Chats.** Moderated online chats can provide support and help cancer patients and caregivers reach out and share information. Please visit [www.LLS.org/chat](http://www.LLS.org/chat) for more information.

**Local Programs.** LLS offers community 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 region, please:

- Call: (800) 955-4572
- Visit: [www.LLS.org/LocalPrograms](http://www.LLS.org/LocalPrograms)

**Advocacy and Public Policy.** Working closely with dedicated volunteer advocates, LLS's Office of Public Policy elevates the voices of patients to state and federal elected officials, the White House, governors and even courts. Together, we advocate for safe and effective treatments. We pursue policies that would make care more accessible to all patients. And, most of all, we advocate for the hope for a cure. Want to join our work? Visit [www.LLS.org/advocacy](http://www.LLS.org/advocacy) for more information.

**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. For more

information, please visit [www.LLS.org/ResourceDirectory](http://www.LLS.org/ResourceDirectory) to view the directory.

### Additional Help for Specific Populations

#### Información en Español (LLS information in Spanish).

Please visit [www.LLS.org/espanol](http://www.LLS.org/espanol) for more information.

**Language Services.** Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

**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](http://www.publichealth.va.gov/exposures/AgentOrange)

**Information for Firefighters.** Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit [www.LLS.org/FireFighters](http://www.LLS.org/FireFighters) for resources and information.

**World Trade Center Health Program.** People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get 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 and those who lived, worked or were in school in that 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](http://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](http://www.nimh.nih.gov) and enter “depression” in the search box

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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](http://www.LLS.org).