LEUKEMIA & LYMPHOMA SOCIETY®

# Minimal Residual Disease (MRD)

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

## Highlights

- Minimal residual disease (MRD) is a term used to describe the small number of cancer cells in the body after cancer treatment. An MRD positive test result means that disease was still detected after treatment. An MRD negative result means that no disease was detected after treatment.
- 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, and possibly identify an early return of the cancer.
- To test for MRD, doctors use samples from either a blood draw or a bone marrow aspiration.
- 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.
- There are a few tests that 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 flow cytometry, polymerase chain reaction (PCR) and next-generation sequencing (NGS).

## What Is Minimal Residual Disease (MRD)?

Minimal residual disease (MRD) refers to the small number of cancer cells that remain in the body after treatment. The number of remaining cells may be so small that they do not cause any physical signs or symptoms and often cannot even be detected through traditional methods, such as viewing cells under a microscope and/or by tracking abnormal serum proteins in the blood. An MRD positive test result means that residual (remaining) disease was detected. A negative result means that residual disease was not detected.

## The Role of Minimal Residual Disease (MRD) Assessment in Patient Care

After treating cancer, any remaining cancer cells in the body can become active and start to multiply, causing a relapse of the disease. Detecting MRD may indicate that the treatment was not completely effective or that the treatment was incomplete. Minimal residual disease may be present after treatment because not all of the cancer cells responded to the therapy, or because the cancer cells became resistant to the medications used.

### When Being Negative Means Something Positive.

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 were found. When no MRD is detected, this is known as “MRD negativity.”

Being “MRD negative” is actually an encouraging outcome for a patient with blood cancer, because that 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 certain blood cancers.

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**How MRD Testing Can Affect Your Treatment.** Testing for MRD can help the treatment team distinguish between patients who need additional (or different) treatment from those who do not. This knowledge can also potentially guide treatment decisions and improve patient outcomes.

Minimal residual disease testing can help:

- Show how well the cancer has responded to treatment
- Confirm and monitor remissions
- Find cancer recurrence sooner than other tests
- Identify patients who may be at a higher risk of relapse
- Identify patients who may need to restart treatment
- Identify patients who may benefit from other treatments, such as stem cell transplantation or combination therapy

**When to Test for MRD.** There are different criteria for when to test for MRD, based on factors specific to the patient's disease. Patients may be tested after the final cycle of a planned combination therapy, after bone marrow transplantation, during treatment to confirm the depth of remission, after one year on maintenance therapy, at regular intervals after treatment is completed, or at other specific times.

## Techniques to Detect MRD

Minimal residual disease testing uses highly sensitive methods. 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 aspiration) and/or peripheral blood cells (taken through a vein).

**Flow Cytometry.** Flow cytometry is a technique that evaluates individual cells by checking for the presence or the absence of certain protein markers on the cell surface. A fresh bone marrow aspirate sample is required for reliable results. The bone marrow aspirate sample is treated with special antibodies that stick only to the cells that have a specific protein on them. Based on how the flow cytometry is set up, this approach can find one cancer cell among 100,000 bone marrow cells. Results can be available in less than one day.

**Polymerase Chain Reaction (PCR).** This technique expands trace amounts of DNA so that a specific segment of DNA can be studied. Polymerase chain reaction can identify malignant cells based on their characteristic genetic abnormalities, such as mutations or chromosomal changes. Polymerase chain reaction 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, genetic abnormalities can be detected by PCR even when a very small number of cancer cells remain. With PCR, it is possible to identify one cancer cell within 100,000 to one million normal cells. The test is done with a bone marrow or blood sample. It may take several weeks for results to be available.

**Next-Generation Sequencing (NGS).** This technique refers to a number of different sequencing technologies. Next-generation sequencing tests can rapidly examine stretches of DNA or RNA. Next-generation sequencing 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 one million bone marrow cells checked. Test results are usually available within one week. Both fresh and frozen/stored samples can be used for NGS-based MRD testing. The US Food and Drug Administration (FDA) has approved a test called clonoSEQ,® an NGS test designed to detect MRD in B-cell acute lymphoblastic leukemia (ALL) and myeloma.

**For more information about the techniques mentioned above, please see the free LLS publication *Cancer Molecular Profiling.***

## MRD Testing in Specific Blood Cancers

The type of minimal residual disease (MRD) testing used varies depending on the type of blood cancer.

### Acute Lymphoblastic Leukemia (ALL)

- MRD is detected through flow cytometry, PCR and next-generation sequencing (NGS).
- MRD is part of routine testing in the treatment of pediatric and adult ALL.
- Studies show that MRD can predict the effectiveness of a given treatment after the induction phase of ALL treatment.
- MRD can help identify which patients are at higher risk for relapse, allowing for earlier or additional treatments. MRD may also determine which patients may benefit from a bone marrow transplantation.

### Chronic Lymphocytic Leukemia (CLL)

- MRD is detected by flow cytometry and PCR.
- Patients who remain MRD negative after the end of therapy for CLL may have better treatment outcomes.
- Patients who are MRD positive after the end of treatment may be candidates for treatment intensification, consolidation and maintenance strategies.

### Chronic Myeloid Leukemia (CML)

- MRD is detected through PCR.
- PCR can detect the Philadelphia (Ph) chromosome which is found in 95 percent of all CML patients.
- PCR can detect one Ph+ CML cell among one million normal cells.
- MRD monitoring helps predict treatment resistance and guide the course of treatment.
- PCR is one factor used in deciding whether to discontinue or change tyrosine kinase inhibitor (TKI) therapy.

### Lymphoma

- MRD is detected through flow cytometry and PCR.
- MRD testing is used in follicular, mantle cell and diffuse large B-cell lymphoma (DLBCL).
- MRD testing helps detect patients who are at risk of relapsing. These patients can then receive additional treatment.
- Patients who are treated for mantle cell lymphoma and achieve an MRD-negative status have been shown to have longer remissions before their disease progresses.
- Several studies have shown that DLBCL patients who achieved remission after treatment and were also MRD negative were more likely to remain in remission than MRD positive patients who had achieved remission.

### Myeloma

- MRD testing in myeloma uses flow cytometry, next-generation sequencing and imaging tests.
- Imaging techniques such as PET-CT scans, in addition to other tests, allow doctors to find disease outside the bone marrow.
- Studies have shown that patients who achieve an MRD-negative status after treatment live longer without disease progression.

## Will Insurance Cover MRD Testing?

Minimal residual disease 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 their treatment team the following questions:

- Do I need MRD testing for my specific cancer?
- What type of MRD testing do I need?
- Will my insurance plan cover MRD testing?

- Will I need pre-authorization from my insurance provider before the test is done?
- If the testing is not covered by insurance, is there any financial assistance available to complete the necessary testing?
- Where will the test take place?
- How often will MRD testing be needed during and after treatment?
- How long will it take to get results?
- How will the results of the MRD testing affect my treatment?

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.

## Acknowledgment

The Leukemia & Lymphoma Society appreciates the review of this material by

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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 Web site at www.LLS.org/ChapterFind or contact:

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

Call 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 master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, from 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists
- Visit: www.LLS.org/InformationSpecialists

**Clinical Trials (Research Studies).** New treatments for patients are ongoing. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with our LLS Information Specialists who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available. 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.

**Financial Assistance.** LLS offers financial assistance to individuals with blood cancer. Visit www.LLS.org/finances for more information.

***Co-Pay Assistance Program.*** LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

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

**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 by a registered dietitian with experience in oncology nutrition. Dietitians assist callers 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 consult 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 health care 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), in-person 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.

**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.

**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

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