

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

Highlights

- After a patient achieves a complete remission based on standard test results, there still may be cancer cells that remain in the body, known as minimal/measurable 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.
- 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 flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing (NGS).
- 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.

What Is Minimal/Measurable Residual Disease (MRD)?

For some people with blood cancer, their treatment puts their disease into a complete remission. This means there is no evidence of cancer based on standard laboratory tests. It is an indication that the treatment worked. There may, however, still be cancer cells that remain in the body; this is known as minimal/measurable residual disease (MRD). 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 scans. But these remaining cancer cells can start to multiply, causing a relapse of the disease.

The Role of MRD Testing in Patient Care

Detecting MRD may indicate that the treatment was not completely effective or that the treatment was incomplete. MRD 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. A patient can have a positive or negative MRD result.

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.”

Being “MRD negative” is actually 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.

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.

MRD 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, before or 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.

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.

Flow Cytometry. Flow cytometry is a technique that evaluates individual cells by checking for the presence or the absence of certain protein markers on cell surfaces. A fresh bone marrow sample is required for reliable results. The bone marrow 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 10,000 to 100,000 normal bone marrow cells. Results can be available in less than one day.

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 normal cells. It may take approximately 5-14 days 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. 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 one million bone marrow cells checked. Test results are usually available within 10-14 days. 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 MRD testing used varies depending on the type of blood cancer.

Acute Lymphoblastic Leukemia (ALL)

- MRD is detected through flow cytometry, PCR and NGS, such as the clonoSEQ®.
- 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.
- 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 a bone marrow transplantation.

Chronic Myeloid Leukemia (CML)

- MRD is detected through a special PCR test called reverse transcription polymerase chain reaction (RT-PCR).
- RT-PCR can detect the messenger RNA produced by the Philadelphia (Ph) chromosome, which is found in 99 percent of all CML patients.
- RT-PCR can detect one Philadelphia-chromosome cell among 100,000 normal cells.
- MRD monitoring helps predict treatment resistance and guide the course of treatment.
- RT-PCR is one factor used in deciding whether to discontinue or change tyrosine kinase inhibitor (TKI) therapy.

Myeloma

- The most widely used methods to test MRD in myeloma are flow cytometry and NGS, such as the clonoSEQ®.
- Imaging techniques such as PET-CT scans, 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.

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 flow cytometry and PCR.
- Studies in both children and adults with AML have demonstrated a correlation between the presence of MRD and risk of relapse.

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 flow cytometry, PCR and NGS.
- 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 day-to-day clinical practice.
- MRD in lymphoma is detected through flow cytometry, PCR and NGS.
- 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.

Will Insurance Cover 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 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 MRD testing is not covered by insurance, is there any financial assistance available to complete the necessary testing?
- Where will the MRD test take place?
- How often will MRD testing be needed during and after treatment?
- How long will it take to get MRD 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

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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 of the booklet lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

For Help and Information

Consult with an Information Specialist. Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date information about disease, treatment and support. 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

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. 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.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian with 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 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.

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.

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

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

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. Please visit www.LLS.org/HealthManager to download for free.

LLS Coloring for Kids™. This free coloring app allows children (and adults) 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 the time in waiting rooms or during treatment. Visit www.LLS.org/ColoringApp to learn more and download.

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.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

Community Resources and Networking

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.

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

LLS Chapters. 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 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. For more information, please visit www.LLS.org/ResourceDirectory to obtain the directory.

Advocacy. The LLS Office of Public Policy (OPP) enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please

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

Additional Help for Specific Populations

Información en Español (LLS information in Spanish). Please visit 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

World Trade Center Survivors. 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

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 two-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

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