WHAT IS MEASURABLE RESIDUAL DISEASE TESTING USED FOR?
MRD testing has been used in the management of various blood cancers. It can be used to help assess the effectiveness of a cancer treatment, it can detect cancer recurrence, and research is now looking at how it can be used to guide treatment decisions. Although ongoing research is being conducted on the use of MRD testing for the management of CLL and SLL, it is not yet a standard of care and is not performed in all laboratory settings. While some healthcare providers are beginning to use MRD testing, it has historically only been used in clinical trial settings and at academic centers.

HOW IS MEASURABLE RESIDUAL DISEASE TESTING PERFORMED?
The most frequently used methods to test for MRD include flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing (NGS). These tests can be performed using a blood or bone marrow sample.
• Flow cytometry testing looks for abnormal protein markers on the cell surface.
  » Flow cytometry can detect 1 cancerous cell among 10,000 normal cells (1 x 10^-4).
• PCR testing looks for genetic mutations and chromosomal changes.
  » PCR testing can detect 1 cancerous cell among 100,000 normal cells (1 x 10^-5).
  » MRD testing using PCR is not regularly used in the U.S.
• NGS testing also looks for genetic mutations and chromosomal changes.
  » NGS can detect 1 cancerous cell among 1,000,000 normal cells (1 x 10^-6).
  » ClonoSEQ® is an NGS test that has been cleared by the FDA for MRD analysis in CLL.

WHO BENEFITS FROM MEASURABLE RESIDUAL DISEASE TESTING?
Not everyone with CLL and SLL benefits from MRD testing. The decision of whether to use it and which technique to use depends on various factors. The most significant factor being which treatment is being used to treat the disease.
MRD testing may be beneficial for those who are on fixed-duration therapies (a medication that is only given for a limited amount of time) to see how someone has responded after the treatment cycle is complete. The goal of fixed-duration therapy is to eliminate all traces of the disease that results in a deep remission that allows individuals to go off their treatment, hopefully for a prolonged period of time. MRD testing may be useful in this situation to see just how deep the response has been to treatment.

For those on a continuous treatment regimen, the goal is to control the disease and not necessarily to eliminate all traces of the cancer. Continuous therapies are meant to be taken until the CLL or SLL becomes refractory (resistant) to the medication being taken. In this scenario, MRD testing generally does not provide useful information.

WHAT RESEARCH IS BEING PERFORMED ON MEASURABLE RESIDUAL DISEASE TESTING IN CLL AND SLL?
Since MRD testing is not yet a standard practice, there is ongoing research to determine how it might be the most useful. The possible role of MRD testing in those with CLL and SLL is constantly evolving. Researchers need more information about:
• The ideal timing of MRD testing.
• How to use the MRD test results to help inform treatment decisions.
• Which individuals will benefit the most from MRD testing.
• The use of MRD testing to guide when exactly to stop fixed-duration therapies.
• When treatment may need to be continued or even intensified.

**WHEN EXACTLY SHOULD MEASURABLE RESIDUAL DISEASE TESTING BE PERFORMED?**

There are no formal recommendations yet.

**WHAT DO THE RESULTS OF MEASURABLE RESIDUAL DISEASE TESTING MEAN?**

MRD testing results can have different meanings for different people. When the test detects any CLL or SLL cells that are “measurable,” the test results are reported as detectable MRD. If the test is unable to measure any CLL or SLL cells, the results are classified as undetectable MRD (uMRD). The significance of the MRD test result depends on the sensitivity of the testing technique that was used and whether the sample was taken from blood or bone marrow. NGS testing is much more sensitive than the MRD test technique using flow cytometry.

**Detectable MRD:** This result indicates cancerous cells were measurable in the sample that was tested. However, it does not necessarily mean that you need a new treatment. You only need treatment for CLL and SLL if symptoms are present or for certain lab abnormalities (i.e., anemia). It is important to understand that MRD testing may detect cancerous cells long before the onset of any symptoms, even years before the cancer becomes active and treatment is needed.

**Undetectable MRD:** A finding of uMRD means that no cancerous cells were measurable in the sample that was tested.

**DOES UNDETECTABLE MEASURABLE RESIDUAL DISEASE EQUATE TO A CURE?**

No. Unfortunately uMRD does not imply a cure. Since CLL and SLL are chronic, slow-growing cancers, relapse still occurs. However, uMRD is associated with a deeper remission and a longer progression-free survival time, compared to those who have detectable MRD. It is still necessary to monitor the disease and watch for symptoms to help detect when the cancer is returning.

**SHOULD MEASURABLE RESIDUAL DISEASE TESTING BE REPEATED?**

There are no formal recommendations yet for how often MRD testing should be repeated. However, we do know that repeat testing can help an individual watch the trending numbers over time, and generally, treatment decisions are not made on just one test result. Repeat MRD testing might show that cancer cells are present, but they are stable and not changing hardly at all. If someone is still on a limited-duration therapy, it can commonly be found that the number of cancer cells present decreases with continued treatment. An upward trend in the number of cancer cells can signify that the cancer is starting to become more active and signal your healthcare provider to keep a more watchful eye.

**WHAT DOES THE FUTURE HOLD FOR USE OF MRD TESTING IN THOSE WITH CLL AND SLL?**

MRD testing is now widely used in clinical trials. Once enough data are available, MRD testing may help those with CLL and SLL to make better-informed decisions about when it is time to begin treatment, when to stop treatment, or when to possibly consider a different treatment option.

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**CLL SOCIETY MISSION**

CLL Society is an inclusive, patient-centric, physician-curated nonprofit organization that addresses the unmet needs of the chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) community through patient education, advocacy, support, and research.