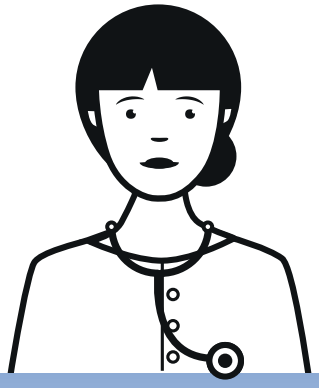
# The importance of minimal residual disease in blood cancer

## Key take-aways

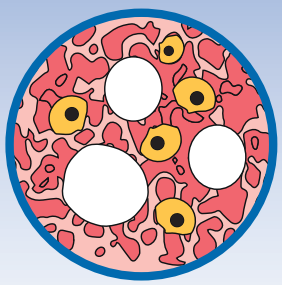
- Blood cancers are the fourth most common cause of cancer death worldwide and lymphoma, leukaemia and myeloma are the main types.[1]
- Minimal residual disease (MRD) is a term used in blood cancer, meaning that small number of cancer cells remain in the patients' blood or bone marrow following treatment. MRD is a major cause of relapse for patients with blood cancer.[2]
- Assessing MRD is important as it allows physicians to assess the extent to which a treatment is working, whether a patient is likely to relapse or if they have achieved a deep remission. MRD is also significant as it is a novel, innovative endpoint which promises to predict longer-term outcomes in people with blood cancers, such as overall survival.[2]



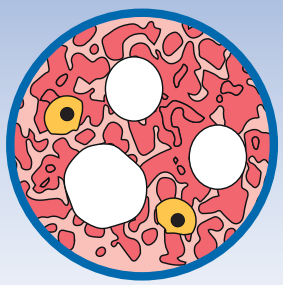
## Blood cancer treatment and MRD

By reducing the number of cancer cells in a patient's blood, bone marrow or lymph nodes to the lowest attainable level, patients can live as normal a life as possible and without symptoms. This is called remission.[3]

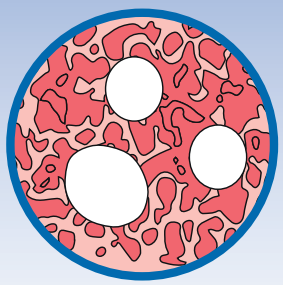
Patients can appear to respond well to treatment, so achieving 'complete remission', meaning there is no evidence of cancer in the body using standard tests and the patient shows no signs or symptoms of disease. However, patients may be left with a tiny number of cancer cells within the blood or bone marrow which can regrow and after a few weeks or months, may cause them to relapse. This tiny population of remaining or residual cancerous cells in the body are termed 'Minimal Residual Disease' (MRD) and are a major cause of relapse in patients with chronic lymphocytic leukaemia (CLL), multiple myeloma (MM) and follicular lymphoma (a subtype of NHL).[2]



**Bone marrow with cancerous B-lymphocytes in an untreated CLL patient**



**Few cancer cells left in the bone marrow (MRD) in a CLL patient**



**No cancer cells left in the bone marrow (negative MRD)**

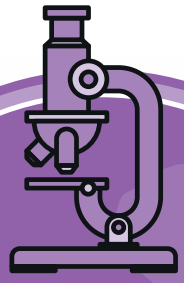
## How do we detect residual cancer cells?

A minute proportion of cancerous cells still present in a patient can cause them to relapse in the future – so measuring MRD is crucial for physicians to assess how well a patient is responding to treatment.

Testing for these cancerous cells previously relied upon microscopes and small numbers of remaining cancer cells after treatment could not always be detected. In these patients, these cells were given the opportunity to regrow and so may have caused the patient to relapse.

Recent advances in scientific knowledge and medical technology have enabled us to detect these residual cells after treatment with greater accuracy. A patient is said to be 'MRD-negative' when even these highly sensitive tests are not able to detect remaining cancer cells.

This means they have achieved a 'deep' remission and are also more likely to sustain a longer-term disease control compared to patients with residual cancer (MRD) after treatment. Importantly, deep remissions are associated with prolonged progression free survival (PFS) and overall survival (OS).[2]

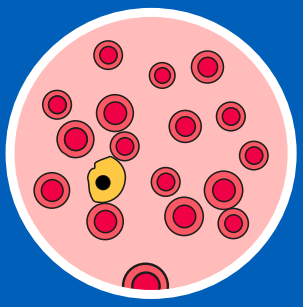


Using a microscope, it can be possible to find roughly **one harmful cell in 100 healthy cells**, which is a very high level of disease.

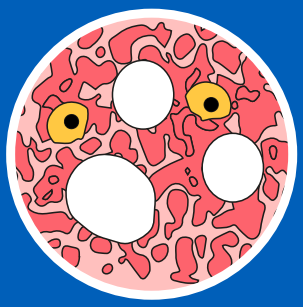
New technology is able to **increase the level of detection to one in 10,000**.[4]

## How are the cancer cells sampled for testing?

Samples of blood or tissue from the bone marrow can be taken and the very low levels of residual cancer cells measured. Although a more invasive sampling method, MRD levels are usually higher in the bone marrow compared to blood, as the bone marrow is harder to clear of the cancer cells.



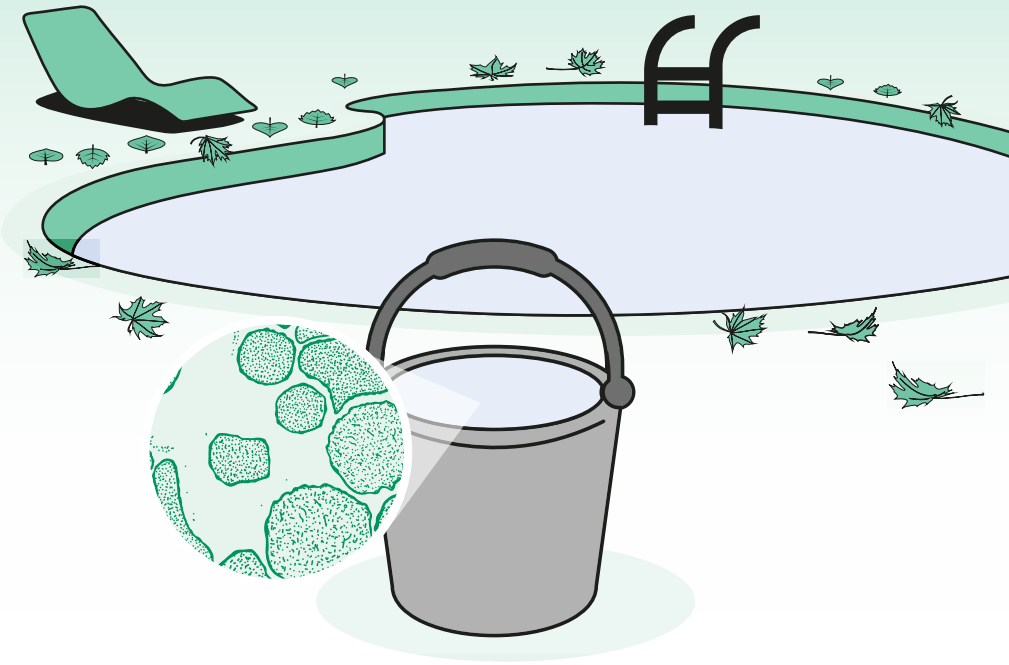
Blood sample



Bone marrow sample

## An analogy of MRD testing: Leaves in a swimming pool[5]

- A standard bone marrow test is like taking a sample from a swimming pool. If leaves are found in the bucket, it suggests there are likely to be leaves floating elsewhere in the pool – or with blood cancer, a notable number of cancer cells remaining in the body.
- MRD testing is like examining the sample of water in the bucket for tiny fragments of substances that exist only in leaves. These tiny fragments represent MRD, or the tiny number of blood cancer cells remaining in the body after treatment, which are only detectable with highly sensitive tests.
- Thus, a negative finding with MRD testing provides much greater confidence that the blood or bone marrow is clear of the abnormal cells.



## Why is testing for MRD in CLL, MM and follicular lymphoma important for patients in both the short- and long-term?

Critically, accurate detection of MRD enables physicians to:[4]

1. Reduce the risk of relapse, as the likelihood of relapse can be assessed and follow-up treatment given, as needed.
2. Identify patients who achieve a deep or MRD-negative remission and require no further treatment, so avoiding unnecessary side effects and time on treatment.
3. Indicate how effectively a treatment is working and predict whether continued treatment is likely to improve a patient's longer term outcomes.

Roche is leading the way in novel clinical trial design, using MRD as both a primary and secondary endpoint to show superiority of one treatment over another. Importantly, the European Medicines Agency has recently published guidelines on the use of MRD in clinical trials as an indicator of the likelihood of a patient achieving longer endpoints such as PFS or OS.[2]

Meanwhile, the US Food and Drug Administration is beginning to recognise MRD as a meaningful endpoint or biomarker in regulatory decisions for blood cancer treatments. This could help decrease lengthy development timelines in the future and reduce delay in patient access to more effective treatment options.

## References


1. GLOBOCAN 2018: World Fact Sheet. [Internet; accessed October 2018]. Available from: http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
2. European Medicines Agency. 2014 Guideline on the use of minimal residue disease as an endpoint in chronic lymphocytic leukaemia studies. [Internet; accessed October 2018]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/12/WC500179047.pdf
3. Cancer.net. Lymphoma - Non-Hodgkin: Risk Factors. [Internet; accessed October 2018]. Available from: http://www.cancer.net/cancer-types/lymphoma-non-hodgkin/risk-factors
4. Boldeanu F et al. Minimal Residual Disease - Generalities and Perspectives. TMJ 2011; 61:3-4
5. Lymphomation.org. Minimum Residual Disease (MRD) with PCR ("molecular photocopying") of blood or marrow samples. [Internet; accessed October 2018]. Available from: http://www.lymphomation.org/MRD.htm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