Mutational landscape of CLL and its impact on prognosis and treatment

What is genetic testing?

Genetic testing explores changes in genes, chromosomes and proteins to diagnose diseases, screen for high-risk patients and identify key compounds that could be used to further understand a disease or develop a treatment.[1] In recent decades, genetic testing has seen significant investment and research in various diseases, including cancer and other chronic diseases. Additionally, this technique has been used to explore new preventative treatment pathways.[2]

Importance of genetic testing in CLL

CLL is the most common form of leukaemia in adults with a very variable clinical course.[3, 4]

Historically, prognosis has been based on clinical staging systems developed in the 1970s. Today, we have a clearer understanding of the genetic factors, which complement previous research and provide prognostic and predictive information for improved patient outcomes and treatment response.[5]

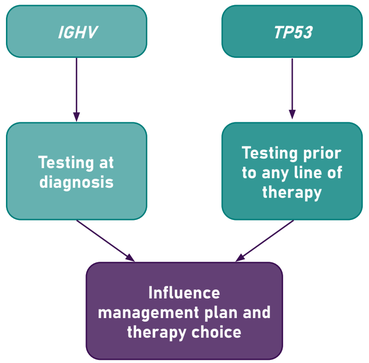
Testing for del(17p), del(11q), del(13q), trisomy 12 and mutations in *TP53* and *IGHV* can indicate a patient's risk of disease development and their potential response to therapy. Thus, understanding the role of genetics is critical in CLL.[6]

Impact of genetic testing in CLL

Clinical trials allow for the identification of underlying mechanisms of therapeutic response. This can help determine patients who benefit most from a given treatment.

Testing for leukaemia cells can be bolstered with genetic testing; patients with *TP53* mutations and/or del(17p) have worse prognosis and carry a resistance to standard chemotherapy.[7] This can help clinicians develop a management plan and therapy choice suitable for their patient.

Most clinical guidelines recommend *IGHV* and *TP53* testing approaches, with these guidelines being followed in normal practice.



What does the future hold?
An ever-increasing number of novel agents (monoclonal antibodies, B-cell receptor inhibitors and BCL2 inhibitors), alone or in combination, form the mainstay of treatment for the majority of CLL patients.[11, 12]

Key genetic information helps to navigate what has now become a complex treatment algorithm.

Key genetic tests used in CLL

A large number of genetic lesions in CLL have shown to have prognostic impact.[4]
Below are two* tests that have been the most important in clinical practice, being used in prognostic scores and treatment algorithms.[8]

IGHV	*IGHV* gene influences speed of progression, response to treatment and overall survival
	Patients with a mutated variant have longer time to first treatment, longer PFS following chemoimmunotherapy, lower transformation risk and better OS[5]
	Assessment at early presentation can help with prospective management of patients, frequency of follow-up and selection of treatment
	In a clinical setting, IGHV testing can be used in younger, fitter patients at diagnosis, guiding forward planning. Asymptomatic, mutated-gene patients may not require therapy, as primary care management can be used and a "watch and wait" strategy may be applied
TP53	*TP53* is activated upon chemotherapy-induced DNA damage, causing CLL cells to undergo apoptosis. When *TP53* is non-functional due to deletion or mutation, apoptosis of CLL cells cannot be triggered. Thus, CLL patients with non-functional *TP53* have shorter PFS and overall poor outcomes[5]
	Looking for *TP53* mutations and/or deletion in 17p is needed to rule out the presence of any aberrations[9]
	TP53 abnormalities result in inherent resistance to chemoimmunotherapy and reduced survival[9]
	In a clinical setting, *TP53* testing is used in patients about to start treatment. Normal gene presence at diagnosis does not mean normal function at the time of treatment, which may be several years later

In order to test for structural changes in the gene, FISH testing can be conducted using a fluorescent dye to observe genetic changes.[10] Observation allows for changes in the sequence, such as del(13q), del(11q), del(17p) and trisomy 12 in peripheral blood lymphocytes.[6, 10]

Mutation	Genetic tests	Prognosis[13]
IGHV	**Genetic sequencing for *IGHV* mutational status**	**Good prognosis**
TP53	**FISH for del(17p)** **Genetic sequencing for *TP53* mutational status**	**Poor prognosis, requires close follow-up**

*Note that neither of these tests are necessary to make a diagnosis of CLL, and they are not mandated at initial presentation

BCL2, B-cell lymphoma 2; CLL, chronic lymphocytic leukaemia; del, deletion; DNA, deoxyribonucleic acid; FISH, fluorescence in situ hybridisation; *IGHV*, immunoglobulin heavy chain gene; OS, overall survival; PFS, progression-free survival; *TP53*, tumour protein 53

1. MedlinePlus. Genetic testing. June 2021. https://medlineplus.gov/genetictesting.html. Accessed 22 March 2023; 2. Oliveri S, et al. Front Genet 2018;9:624; 3. National Cancer Institute. Chronic lymphocytic leukemia treatment (PDQ®) – Patient version. https://www.cancer.gov/types/leukemia/patient/cll-treatment-pdq. Accessed 22 March 2023; 4. Döhner H, et al. NEJM 2000;343:1910–16; 5. Gaidano G, et al. Hematology Am Soc Hematol Educ Program 2017;2017:329–37; 6. Hallek M, et al. Am J Hematol 2021;96:1551–18; 7. Hallek M, et al. Blood 2018;131:2745–60; 8. International CLL-IPI working group. Lancet Oncol 2016;17: 779–90; 9. Rossi D, et al. Blood 2013;121:1403–12; 10. Cancer Research UK. Genetic tests on your chronic lymphocytic leukaemia (CLL) cells. https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/getting-diagnosed/tests/tests-gene-changes. Accessed 22 March 2023; 11. Sethi T, et al. Oncol Hematol Rev 2017;13:34–40; 12. Cramer P, et al. Eur J Haematol 2016;96(1):9–18; 13. Conquer the patient voice. Genetic testing can help to guide the treatment of patients with chronic lymphocytic leukemia. https://conquer-magazine.com/issues/2018/vol-4-no-5-october-2018/792-genetic-testing-can-help-to-guide-the-treatment-of-patients-with-chronic-lymphocytic-leukemia. Accessed 22 March 2023.

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