

The role of NGS in detecting resistance to targeted therapies in CLL

Targeted therapies (BTKis and BCL-2is) have transformed CLL management but often fail after an initial response.¹

Acquired resistance is the leading cause of targeted treatment failure.²

10%

80%

~45%

~10–80% who relapse on a BTKi have *BTK* variants.¹

~45% who progress on a BCL-2i have *BCL-2* variants.^{3,4}

Multiple co-existing resistance mechanisms can exist within the same patient.^{1,3}

Understanding and detecting resistance mechanisms is critical for long-term disease control in CLL.¹



Different resistance mechanisms may require different treatment strategies.*¹



Failure to detect low-frequency resistant subclones can lead to ineffective next-line therapy.¹



Identifying co-existing mechanisms helps guide sequencing and combination decisions.¹



Early detection of emerging resistance can support timely intervention before clinical relapse.¹

* Including changing therapy within a drug class or switching to a different drug class.

NGS enables sensitive detection of resistance mutations in CLL treated with targeted therapy.^{1,5}



Clinical relevance
NGS assesses full coding regions, enabling detection of multiple resistance mutations within a gene.^{1,5}



Sensitivity
NGS can detect low-VAF emerging subclones before clinical relapse.^{1,5}



Subclonal evolution
NGS supports tracking of clonal dynamics over time, revealing patterns associated with emerging resistance.^{1,5}



Turnaround time
NGS workflows typically provide results within clinically actionable decision-making windows.^{1,5}

NGS is increasingly used in routine CLL care; ERIC recommends NGS-based *TP53* testing before treatment decisions due to its ability to detect low-VAF variants, and NGS can also identify recurrent mutations such as *NOTCH1* and *SF3B1* that contribute to disease characterization.^{5,6}

Targeted therapies have transformed CLL management, but resistance can limit durable responses. Broad NGS-based profiling enables early detection of resistance-associated alterations and clonal evolution, and advances in sequencing technology are increasingly supporting the integration of NGS into routine hospital-based care to guide timely, personalized treatment decisions.

BCL-2, B-cell lymphoma 2; BCL-2i, BCL-2 inhibitor; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; CLL, chronic lymphocytic leukemia; ERIC, European Research Initiative on CLL; NGS, next-generation sequencing; PCR, polymerase chain reaction; VAF, variant allele frequency.

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