



## THE NEW TECHNOLOGICAL CHALLENGES OF LIQUID BIOPSY: THE GENOMIC AND FRAGMENTOMIC LANDSCAPE FROM CFDNA

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Analysis of circulating free DNA (cfDNA), and in particular the tumor-derived fraction known as circulating tumor DNA (ctDNA), represents a major advance in the precision medicine of lymphoma.<sup>1</sup> Quantification of ctDNA at baseline and at the end of induction chemoimmunotherapy and its integration with PET/CT scans provide well-established prognostic biomarkers.<sup>2-5</sup>

Beyond quantification, cfDNA analysis can provide additional insights into lymphoma biology. For example, molecular characterization of diffuse large B-cell lymphoma (DLBCL) using ctDNA recapitulates the molecular subtypes identified in tissue biopsies, offering a non-invasive approach that may guide the design of molecularly driven clinical trials.<sup>6</sup>

In plasma, cfDNA fragments vary in length, display distinct sequence motifs at their fragment ends, and show tumor-specific fragmentation patterns. Collectively referred to fragmentomics, these features provide an additional layer of biological information and may improve outcome prediction in lymphoma.<sup>7,8</sup> For example, cfDNA fragment length has prognostic relevance in DLBCL, with shorter fragments being associated with more aggressive disease.<sup>9</sup> Fragmentomic analyses can also help discriminate the tissue origin of cfDNA, as shorter fragments are more likely to derive from lymphoma cells, whereas longer fragments typically originate from healthy tissues. This distinction may facilitate the identification of clonal hematopoiesis (CH), that in DLBCL has been associated with an increased risk of long-term treatment-related toxicities, and help determine the origin of some mutations (i.e. *TP53* and *TET2*) that are shared between DLBCL and CH pathogenesis.<sup>10,11</sup> Furthermore, cfDNA fragments arising from active promoters exhibit more random fragmentation patterns compared with those from inactive promoters.

This property also enables inference of transcriptomic profiles from cfDNA.<sup>12</sup>

cfDNA analysis therefore represents a powerful biomarker for assessing underlying biology and predicting outcomes in lymphoma patients. The next step will be the standardization of methodologies and their implementation within dedicated clinical trials.

### References

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