Nature Reviews Cancer | Published online 16 Dec 2016; doi:10.1038/nrc.2016.146

LYMPHOMA

Now you see it…

> analysis of ctDNA could reliably distinguish DLBCL that had arisen from FL

Promising a minimally invasive view inside the cancer patient, it is not hard to see why the concept of a 'liquid biopsy' is so popular. But how does reality stack up against the promise? A team led by Ash Alizadeh and Maximilian Diehn set out to find out.

Scherer *et al.* focused on diffuse large B-cell lymphoma (DLBCL), which can range from indolent, slow-growing tumours to those that are aggressive and difficult to treat. Clinicians cannot presently distinguish these tumour types, and they struggle to identify patients most at risk of treatment-refractory disease or relapse because the only robust method to do so usually necessitates invasive biopsy. A simpler way to peer into DLBCL tumour biology is urgently needed.

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High-throughput sequencing can identify and track clonotypic immunoglobulin V(D)J rearrangements in the peripheral blood of patients with DLBCL, but the method fails to capture the full genetic complexity of the tumour. The team upgraded the approach by developing a DLBCL-specific gene panel and using an ultra-sensitive capture-based targeted sequencing approach (Capp-Seq) across a cohort of primary tumours and longitudinal plasma samples. The technique detected somatic mutations in all lymphoma samples, and crucially, it also detected circulating tumour DNA (ctDNA) in all plasma samples tested, with 99.8% specificity. Moreover, applying Capp-Seq to ctDNA in plasma reliably predicted the presence of known driver mutations in 91% of samples tested, providing reassurance that the assay gave an authentic mutational snapshot of the parent tumour.

The group could spot the early emergence of resistance mutations in the Bruton tyrosine kinase (*BTK*) gene in patients treated with the BTK inhibitor ibrutinib. Moreover, Capp-Seq detected ctDNA in the plasma of 8 out of 11 patients before clinical relapse, suggesting that the method could identify early signs of resistance and pick up occult disease.

Capp-Seq of ctDNA also predicted the cell of origin for DLBCL, which is a powerful prognostic indicator. The current gold-standard method to perform this analysis requires fresh-frozen tissue, so these results represent a substantial step forward. DLBCL can also develop as a result of the transformation of indolent follicular lymphoma (FL) — a process that comes with a dismal prognosis. The team showed that analysis of ctDNA could reliably distinguish DLBCL that had arisen from FL from that which had not. In addition, they could forecast transformation up to 66 days before clinical diagnosis.

It is easy to imagine that, by offering this minimally invasive glimpse into DLBCL biology, ctDNA-based approaches could form the backbone of treatment of patients with DLBCL — directing treatment strategies at diagnosis, predicting whether or not a patient will relapse and spotting it when they do. Time will tell whether this turns out to be the case.

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The author declares no competing interests.

ORIGINAL ARTICLE Scherer, F. *et al.* Distinct biological subtypes and patterns of genome evolution in lymphoma revealed by circulating tumor DNA. *Sci. Transl Med.* **8**, 364ra155 (2016)