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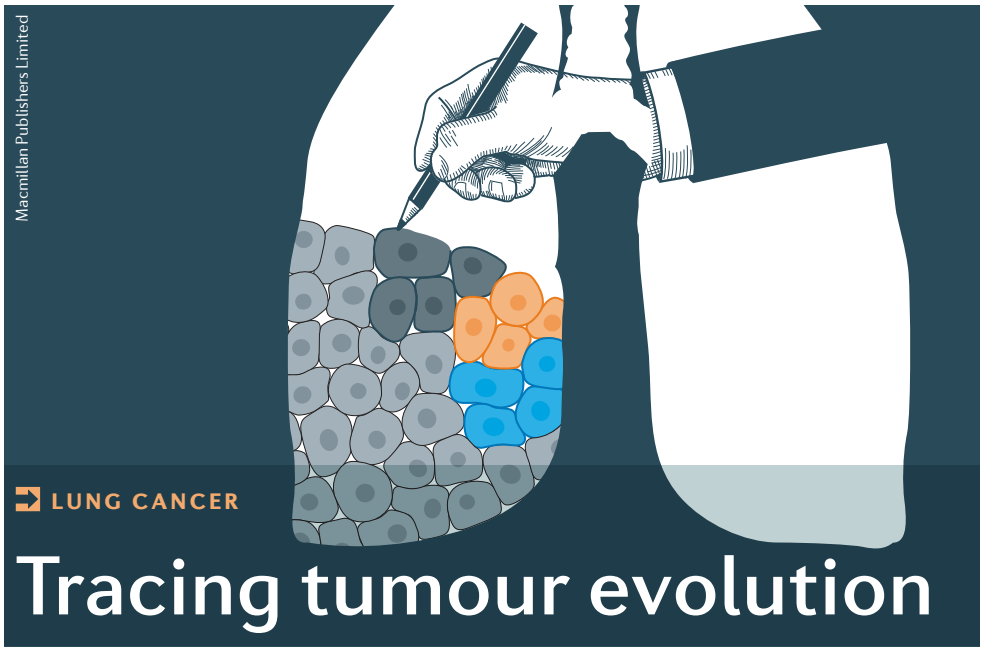

Tracing tumour evolution

One key hypothesis proposed to explain the resistance of tumours to otherwise effective therapies is the existence of an evolution process whereby cancer cells harbouring or acquiring resistance mechanisms escape selective pressure. Results of several studies have confirmed this hypothesis, which is reinforced by the publication of the first results from the Lung TRACERx (TRAcking CancER evolution through therapy) study, led by Charles Swanton.

In order for TRACERx to meet its primary end point — determination of how intratumour heterogeneity affects clinical outcome following surgery for early-stage disease — 842 patients with non-small-cell lung cancer (NSCLC) will be recruited. The current results are from a 100-patient cohort, larger than those analysed in previous studies of tumour heterogeneity.

In the study presented in the *New England Journal of Medicine*, deep, whole-exome, multiregion sequencing of primary tumours was performed. "The phylogenetic trees generated enabled us to select representative mutations from both the clonal and various subclonal populations. This approach opened up the possibility of tracking exactly which subclones were involved in disease progression", investigator Gareth Wilson explains. For Nicholas McGranahan, also involved in the study, the main finding is "the demonstration that genomes from lung cancers are frequently highly aneuploid, with evidence that the majority of tumours double their genomes early in development. Crucially, however, a large proportion of copy-number alterations (CNAs) were found to be heterogeneous, strongly suggesting that NSCLCs are characterized by dynamic chromosomal instability". Investigator Tom Watkins points out that "within a single tumour, distinct subclonal populations of cancer cells were evolving similar CNAs independently from different parental chromosomes. This parallel evolution might indicate ongoing selective pressures that could be exploited therapeutically." Importantly, a high degree of intratumour heterogeneity was found to be associated with poor outcome.

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As Nicolai Birkbak states, "finding the proportion of subclonal CNAs to be prognostic was thrilling, as it might have implications on how we view lung cancer from a therapeutic perspective in the future".

A companion manuscript focusing on tracking tumour phylogenies longitudinally by profiling circulating tumour DNA (ctDNA) was published in *Nature*. Using phylogenetic data from the primary tumour to design patient-specific ctDNA panels, the investigators identified the tumour subclones involved in relapse from therapy. Rafael Rosell, an independent commentator not involved in TRACERx, considers "bespoke ctDNA profiling a breakthrough advance in the further understanding of the tumour's evolutionary tree. TRACERx paves the way for the use of bespoke ctDNA for gauging branched evolution of NSCLC, not only in early resected NSCLC, but also in the vast majority of NSCLCs diagnosed at advanced stages".

Importantly, ctDNA analysis enabled the detection of residual cancer in some patients, suggesting that ctDNA can be used to monitor benefit from therapy. Investigator Christopher Abbosh comments: "we could improve pretreatment risk-stratification in patients with NSCLC and thus minimize the morbidities and costs associated with treating those who will not derive benefit from adjuvant chemotherapy."

Finally, investigator Mariam Jamal-Hanjani reminds us that "TRACERx exists because of the generosity of the patients. We are hugely grateful to everyone involved in the study and hope to move research forward so that ultimately patients with lung cancer can benefit."

Diana Romero

ORIGINAL ARTICLES Jamal-Hanjani, M. *et al.* Tracking the evolution of non–small-cell lung cancer. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1616288 (2017) | Abbosh, C. *et al.* Phylogenetic ctDNA analysis depicts early stage lung cancer evolution. *Nature* http://dx.doi.org/10.1038/nature22364 (2017).