Perspective: The future of liquid biopsy

The approach is starting to transform cancer diagnosis. Now the challenge is to make it a standard clinical tool, says Catherine Alix-Panabières.

During the past decade, liquid biopsy — the analysis of tumours using biomarkers circulating in fluids such as the blood — has received tremendous attention. The ability to detect and characterize tumours in such a minimally invasive and repeatable way could have considerable clinical implications, and huge progress has been made in the development of devices that can do just that. But the technique is not yet a standard tool in the clinical oncologist's arsenal.

The abundance of work, involving a wide variety of assays based on different principles, has confused the cancer-research community. In addition, the two most well-developed biomarkers detected by liquid biopsy — circulating tumour cells (CTCs) and circulating cell-free tumour DNA (ctDNA) — are subject to technical variability in the pre-analytical and analytical steps. To address these issues and put liquid biopsy in the hands of more clinicians, the research community must now focus on proving the utility of these biomarkers. Efforts are under way, including the European Liquid Biopsy Society and the US-based BloodPAC project. These consortia, which combine academic and industry expertise, offer hope for the development of robust and reproducible liquid-biopsy assays.

The intention is not to select and refine a single approach to liquid biopsy. In fact, the synergy of multiple circulating biomarkers can reveal the specifics of a cancer. What is important is to identify the specific combinations of markers that signal a cancer's status, origin and progression, and to make that information available to clinicians. Moreover, it is not only circulating tumour biomarkers that must be considered: as immunotherapy grows in importance as a treatment option, so too does the need to monitor the immune cells of the circulating microenvironment.

I therefore urge the development of an algorithm that can combine all these data to obtain a precise tumour profile. Such a development could guide treatment choices. For example, in people with non-metastatic pancreatic cancer, it has been shown that CTCs and extracellular vesicles called exosomes, released by tumours, could be used to diagnose surgically removable tumours[1]. And a blood test can already detect and localize eight surgically resectable cancers through assessment of levels of circulating proteins and mutations in ctDNA[2].

ANDRÉ HAMPARTZOUMIAN

"To push liquid biopsy into widespread use, more intervention studies are needed."

Catherine Alix-Panabières is a cancer cell biologist at the University Medical Centre of Montpellier in France. e-mail: c-panabieres@chu-montpellier.fr

A lack of preclinical and clinical standardization has so far prevented the development of such an algorithm, but progress is being made. For example, the European project PROLIPSY is studying how liquid biopsies can aid the early detection of prostate cancer. The researchers will combine analysis of CTCs, circulating cell-free DNA (cfDNA) and exosomes in people with high serum levels of the protein prostate-specific antigen. The aim is to first identify people with prostate cancer, and then to distinguish those with aggressive cancer from those with non-aggressive disease.

Observational clinical trials have already shown that CTCs and ctDNA are clinically relevant for different cancer types[3]. To further prove their utility and cement liquid biopsies in clinical guidelines, interventional clinical trials are needed. These will take the information gleaned from research programmes such as PROLIPSY, and test whether detection of CTCs or ctDNA can be used to help patients. For example, a blood sample could be taken before therapy and used to match people to the best drugs for them. During treatment, regular liquid biopsies could reveal the persistence or increase of CTCs or ctDNA — which would indicate resistance to the chosen therapy. People could then be offered a more effective treatment before the tumour burden becomes excessive and incurable. Regular liquid biopsies could also be used to monitor people at risk of relapse.

Lack of standardization has allowed only a few interventional clinical trials, which are ongoing. The STIC CTC METABREAST study has demonstrated the clinical utility of CTCs in assigning people with metastatic breast cancer to either chemotherapy or hormonal therapy. In most people, a CTC count confirmed that an appropriate clinical choice had been made; when this was not the case, a CTC count could be used as a basis to modify the therapeutic approach[4]. And the TACTIK clinical trial is using CTC numbers to define when resistance to chemotherapy appears in people with metastatic, castration-resistant prostate cancer, and as an indication of when to change the therapy being used.

The extent to which liquid biopsy might ultimately replace standard tissue biopsies is still unclear. For diagnosing primary tumours or determining the stage of metastatic lesions in tissues where it is difficult to extract a sample, liquid biopsy might provide a reliable alternative. Liquid biopsy could also help to avoid complications that occur after invasive tissue biopsy, such as bleeding, infections and pain.

Researchers have known about the clinical potential of liquid biopsies for many years. To push them into widespread use, more interventional clinical trials are now needed, as well as the development of an algorithm to combine the appropriate circulating biomarkers. This is where policymakers and industry must step in. Only then will these elegant and powerful techniques fulfil their promise of becoming rapid, reliable and non-invasive decision-making tools.

1. Buscail, E. *et al. Cancers* **11**, 1656 (2019).
2. Cohen, J. D. *et al. Science* **359**, 926–930 (2018).
3. Alix-Panabières, C. & Pantel, K. *Cancer Discov.* **6**, 479–491 (2016).
4. Bidard, F-C *et al. Cancer Res.* **79**, GS3-07 (2019).