Blood tests could be faster and cheaper than tissue biopsies, but a Thermo Fisher exec argues they are likely to be more of an add-on technique.

Within a year the first blood test for solid tumours could be approved in the US. Guardant Health’s Guardant360 and Foundation Medicine’s FoundationOne Liquid are the frontrunners to become the first of these so-called liquid biopsies to gain the FDA’s rubber stamp, and approval would lead to an uptick in sales.

But blood tests might never take the place of tissue testing. “We should try to move away from the discussion that liquid biopsies are a replacement for a tissue biopsy,” says Luca Quagliata, global head of medical affairs for clinical next-generation sequencing and oncology at Thermo Fisher Scientific. “They can be complementary approaches and they might give, if used together, important additional information that can guide the oncologist’s decision.”

Several blood tests using next-generation sequencing to analyse the mutational profile of cancers are already on sale in the US, but none is formally approved. Their use is recommended in guidelines published by Esmo and the National Comprehensive Cancer Network, but only in cases where tumours are not suitable for biopsy, or where not enough tissue can be harvested. Around 20-25% of cancer patients fall into this category.

Second choice

It will take time for liquid biopsies to move out of this second-choice niche. This is despite their obvious advantages: they are less traumatic, return results faster, and are cheaper than testing tissue samples. They can also be done repeatedly, allowing a patient’s progress, and the effects of therapy, to be tracked.

But there are certain data that blood testing cannot provide. “With tissue biopsy you actually have a look at the cells,” Mr Quagliata points out. “Say you have a PD-L1-positive patient – this actually per se is very limited information. You want to know whether those PD-L1-positive cells are at the tumour edge, inside the tumour, in a necrotic area. That is information that you can only get when you are looking at the cells.”

Because of this Mr Quagliata believes that the widespread adoption of liquid biopsies will see them used alongside tissue analysis. A blood draw would be taken at the same time as the tumour is biopsied and the results from the blood test – which can arrive in less than a week – used to put the patient on an initial course of targeted therapy. Then the more detailed data from the tumour itself, which will appear a few weeks later, would be used almost as a confirmatory check.
For this widespread adoption to happen, though, several hoops will have to be jumped through. First will be regulatory approval, which Mr Quagliata describes as a “prerequisite” for boosting oncologists’ confidence in the tests. Guardant Health plans to seek FDA approval for Guardant360 early next year; the Roche subsidiary Foundation Medicine and new player, Thrive, have said they will go to the agency, though not when. Grail, the richest of the private blood test developers, has not disclosed regulatory plans.

But the FDA’s blessing – though an important validation that a manufacturer could use as a selling point – is just the start. Oncology associations would have to change guidelines to recommend this belt-and-braces approach of simultaneous tissue and blood biopsies.

Ultimately, liquid biopsies will only become a standard technique when doctors become comfortable with them, which will take time and data.

“Having it in the guidelines is for sure extremely important, but it’s not enough,” says Mr Quagliata. “You need to generate that kind of confidence within the community and this is not simply generated by a single prospective clinical trial.” He concedes that evidence here is mounting, but says it will take multiple studies from many parts of the world to get oncologists on side.

All the mutations

Not to be left behind, Thermo Fisher is developing its own liquid biopsy platform, the Oncomine Lung cfDNA Assay. A recent study looking at matched tissue and liquid biopsies showed that among 94 non-small cell lung cancer patients tested with the Oncomine assay at diagnosis there was 88% concordance between the tissue and plasma samples.

Interestingly the Oncomine test found mutations including EGFR, ALK and Braf that were not present in the initial tissue biopsy in 29 of the plasma samples. These were not false positives, Mr Quagliata says, but a reflection of tumour heterogeneity – the part of the tumour that was excised only contained some of the tumour’s range of mutations.

This ability to capture all of a patient’s mutations is another advantage blood testing has over tumour sampling. It also comes into play in metastatic disease; different metastatic sites could accumulate additional mutations not found in the primary tumour.

“It is unfeasible in a patient that is in advanced stage of disease with multiple metastases to take a biopsy from each of the metastatic sites. Liquid biopsy would allow you to look at all of them at once,” Mr Quagliata says.

So, on current showing, which is the best liquid biopsy? Mr Quagliata says most of the excitement among oncologists is focused on Guardant and Foundation’s products – as well as the offering from Thermo Fisher, of course.

Analysts from Leerink tend to agree, writing that at Asco oncologists were increasingly comfortable with liquid biopsy in the metastatic setting, with the most commonly cited product being Guardant360. The same company’s Lunar test was also the subject of excitement (Asco 2019 – Guardant and Grail square up, May 16, 2019).

There are many other factors to consider when attempting to forecast exactly how liquid biopsies might come to establish themselves. The relative advantages of pan-cancer testing versus single indication tests will have to be considered, for example – Mr Quagliata is cautiously in favour of the disease-by-disease approach owing to the genetic heterogeneity of cancers, pointing out that even in the same patient a tumour’s mutational profile can alter over time.

Then there is their potential utility as screening tests, which could one day see blood testing offered to healthy people. Mr Quagliata says the evidence here is lagging behind that for the theranostic use of liquid biopsies, though not for lack of trying.

These are arguments for the future. The immediate question is how long it could take for these tests to become established as a theranostic add-on to tissue biopsy. Next stop, the FDA.