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How best to develop a liquid biopsy?

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Natera's cancer blood test is couture, but Guardant's pret-a-porter offering might sell better.

A growing number of companies are developing blood tests for cancer, and many presented data at Asco or will do so at the upcoming AACR meeting. But when assessing how these tests compare, particular attention must be paid to the settings in which they are used.

Broadly, there are three: screening to detect early disease, recurrence monitoring, and tracking response to treatment. Here, *Evaluate Vantage* looks at two liquid biopsy developers, Guardant Health and Natera, which are taking very different strategic approaches.

Natera made its name with a test to detect foetal abnormalities using circulating foetal DNA in the mother's blood. It has adapted this technology to pick up DNA shed by tumours into the patient's blood, and is focusing on detecting cancer recurrence in patients whose tumours have been surgically removed. Its Signatera test is unlike any other in development in that it is custom-made, using the excised cancer tissue as a blueprint.

"We sequence the patient's tumour," says Alexey Aleshin, senior medical director at Natera. "We then use that to design a bespoke assay unique to each patient's tumour that focuses on 16 of the most clonal or truncal mutations." Clonal mutations are those that occur early in the tumour's evolution and are consequently present in all the patient's cancer cells.

Made to measure

This tumour-informed approach, as Natera calls it, is a pretty involved process, but allows high levels of accuracy, Mr Aleshin says. The test avoids picking up mutations that are not related to the tumour, such as those that accrue in the bone marrow with age.

Exquisite accuracy is needed because of the postsurgical setting in which Signatera is used.

"In this space the patient's cancer has been removed, so the levels of circulating tumour DNA we need to detect are 0.01% up to maybe 1% at the higher range," Mr Aleshin says. This is one or two orders of magnitude lower than the levels of ctDNA that tend to be seen in advanced or even early-stage cancer patients who have not been treated surgically. It allows the detection of minimal residual disease – the cancer cells that remain after treatment and can cause relapse.

In a trial published last year, in which Signatera was used to detect post-surgical disease recurrence in breast

cancer, suggested sensitivity and specificity of 89% and 100% respectively. Data presented at Asco suggested that the test identified patients at high risk of recurrence with near 100% specificity.

The intention here is to help doctors to decide whether to administer adjuvant chemotherapy. The ongoing Bespoke trial is assessing whether Signatera can enable exactly this decision in 1,000 colorectal cancer patients. Results will not emerge for some years.

Signatera is also used in Astrazeneca's Columbia-2 study. This is enrolling MRD-positive patients to examine whether the addition of Imfinzi and various other therapies to adjuvant chemo can increase cure rates.

Natera clearly believes that this personally tailored approach has its advantages. But it also has a relatively high up-front cost, Mr Aleshin acknowledges – though he adds that because it is used serially to monitor response to treatment it becomes more economical over time.

It is sold as a lab-developed test in the US, and is also available in Europe and beyond. Natera is working with the FDA for formal approval.

Off the peg

If Natera is focused on tailored tests, Guardant Health is chasing a more one-size-fits-all approach. Or rather three sizes, as its chief executive, Helmy Eltoukhy, explains.

"We're one of the few liquid biopsy companies, maybe the only one, that has active development programmes or products in each of the three buckets of cancer care – early detection, cancer survivors in terms of recurrence monitoring and adjuvant decision-making, and then the late-stage market in terms of treatment selection," he says.

Guardant's Lunar-1 test is in the same setting as Signatera. The single-arm Pegasus trial is looking at the feasibility of using Lunar-1 to guide the post-surgical and post-adjuvant clinical management of colon cancer. The phase II/III Cobra study is more significant, evaluating whether using Lunar-1 in 1,400 subjects with resected stage II colon cancer to help decide whether patients get adjuvant chemotherapy improves recurrence-free survival.

Cobra will yield data in a couple of years, and its results in particular could be extremely meaningful for Guardant – and, by extension, for Natera.

Guardant also has the Lunar-2 programme, looking at screening for colon cancer. Data to be presented at AACR this month show the test to have sensitivity of 90.3% and specificity of 96.6%. These figures are pretty good, but with just 162 patients in that cohort larger trials versus active control will be necessary before the test is ready for prime time.

Gold standard

"You have to compare to the existing standard of care," Mr Eltoukhy says. "It's very difficult to get a physician to forgo use of a guideline-recommended screening method, whether it's a stool test, colonoscopy, mammography, PSA, a low-dose CT scan, without seeing head-to-head data with those specific modalities."

That said, the company's vast registrational Eclipse trial of Lunar-2 does not include a control group; any comparison with current screening would have to be against published data.

Guardant's third liquid biopsy, Guardant360, is a pan-cancer assay to help assign targeted therapy to late-stage patients. Data suggesting that its use in detecting ARID1A mutations, found in around 11% of colorectal tumours, could help oncologists decide whether to administer Erbitux has a late-breaker slot at AACR. Studies in which the blood tests are used to guide treatment are vital, Mr Eltoukhy says.

"Prospective, randomised-control trials are the gold standard. Anything retrospective means there may be some cherry-picking – there may be some bias." Guardant, unlike almost any other developer of cancer blood tests, can afford to run these huge programmes because it is so well funded. It floated in 2018, raising $273m – still one of the 10 largest medtech IPOs in history. Its stock has performed well, though the $315m equity offering it has just closed knocked the shares slightly.

Guardant360 is already sold in the US as a lab-developed test, and is the leading liquid biopsy in the US today, Mr Eltoukhy says, with around 7,000 of the 10,000 oncologists in the US having ordered it.

Ultimately Guardant's "tumour-naive" assays will likely sell better than Natera's tailored test. Guardant sold nearly 50,000 tests for clinical use in 2019, plus more than 20,000 to pharma companies for use in drug trials, with its revenues hitting $214m. Natera, and pretty much all the other liquid biopsy developers, will have some catching up to do.

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