Jury out on liquid biopsies for cancer

A recent paper showing a poor concordance between two similar tests from different commercial laboratories caught the media's attention, and brought into sharp focus the challenges facing liquid biopsies, as these blood tests are known. The study published in a letter in December in *JAMA Oncology* (doi:10.1001/jamaoncol.2017.4027, 2017) showed that 65% of specimens from prostate cancer patients had only partial or no congruence between the tests done on blood samples. The findings were "disturbing," wrote Daniel Hayes of the University of Michigan Comprehensive Cancer Center in Ann Arbor in an accompanying editorial. Another much more upbeat paper published in *Science* shows that liquid biopsies that combine DNA and protein measurements from blood can identify early-stage disease about 70% of the time. Although such contradictory outcomes put a damper on the growing buzz surrounding liquid biopsies, they highlight the hurdles that still need to be overcome to ready technology for the clinic.

Liquid biopsies analyze cell-free DNA circulating in blood (*Nat. Biotechnol.* **34**, 1090–1094, 2016). In people with cancer, a portion of this plasma DNA comes from cancer cells, as tumors shed DNA fragments into blood when growth outstrips blood supply and some of the cells start to die. This portion of DNA is known as circulating tumor DNA, or ctDNA, and its make-up can provide molecular information on the presence of cancer and how it is evolving, and the presence of acquired mutations that might lead to resistance to treatment.

Physicians at Johns Hopkins University School of Medicine in Baltimore wanted to identify a liquid biopsy test to help guide treatment in metastatic prostate cancer patients. They ran two different plasma DNA measurement tests to determine which test would have the best reliability and clinical utility. The clinicians sent blood samples from 40 patients to Personal Genome Diagnostics, in Baltimore, and Guardant Health, in Redwood City, California, for mutational analysis.

Once the tests results were in, the team found them to be widely discordant. "We would not be able to reach any further conclusion because we cannot determine which test works (if any)," says the paper's first author Gonzalo Torga. "We wrote the papers from the end user perspective of people receiving the report," he adds.

They did not have the DNA to re-test and evaluate the samples and the companies offered little guidance concerning their methods, he says.

"It may not be a perfect study but they tried to open people's eyes to the fact that there are still problems and that liquid biopsy is still in its infancy," says Ben Ho Park, an oncologist at Johns Hopkins, who was not part of the prostate cancer study.

In blood, ctDNA percentages fluctuate based on whether a patient is in treatment, the extent of their tumor burden and the type of cancer they have. To obtain the most accurate measurements with a liquid biopsy test, one should draw blood when the patient is off treatment, as it is then that ctDNA abundance is highest. "If you send a liquid biopsy test two weeks after chemo, the utility of that test will be significantly lower, just like if you do a tumor

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Blood-based cancer tests have the potential to detect tumors early and monitor treatment, but so-called 'liquid biopsies' may not be ready for the clinic.

EPO revokes Broad's CRISPR patent

The European Patent Office (EPO) has revoked one of the Broad Institute's foundational patents for CRISPR–Cas9 gene editing in eukaryotes because papers describing the technology had already been published, that is, they were in the public domain when the patent was filed. The January 17 decision is a setback to Broad and its partners, Harvard University and the Massachusetts Institute of Technology, as several of their other CRISPR–Cas9 patents could now face the same fate in Europe, resulting in a loss of royalties. The patent application was filed in December 2013, but Broad wanted to claim priority from earlier-filed US patent applications and so benefit from an effective filing date of December 2012. But the EPO determined that its strict requirements for claiming priority had been flouted, because an inventor named on the US applications from Rockefeller University was absent from the European application. This loss of priority dealt a fatal blow to the patent, since between December 2012 and December 2013, several key scientific results were published that disclosed the use of CRISPR–Cas9 gene editing in eukaryotes (*Nat. Biotechnol.* **31**, 227–229, 2013; *Science* **339**, 823–826, 2013), meaning that Broad's patent claims were no longer novel. Royalties aside, the overall effect of the decision may be more limited. "CRISPR technology will continue to move on quickly and, as one of the groups at the very cutting edge of the field, the Broad will continue to expand its CRISPR patent portfolio [beyond Cas9]," says Daniel Lim, an intellectual property lawyer at Allen & Overy, London. "And of course, the decision only affects the position in Europe; the Broad's key US patents are unaffected," he adds (*Nat. Biotechnol.* **35**, 184, 2017). Broad said it will appeal the EPO's decision on the grounds of "international inconsistency," but this could be will be a Sisyphean task, as it would require the EPO to change its rules on claiming priority.

Charlotte Harrison

"If I was a healthcare leader, I'd be scared. This is a pivotal moment for healthcare leaders to pause and reflect on the fact that they, frankly, waited too long to consider advancing their customer engagement and customer experience strategies to be competitive with other digital industries." Kate McCarthy, an analyst at Forrester, talking about the recent announcement that Amazon, Berkshire Hathaway and JP Morgan are joining forces to offer healthcare to their 1.2 million employees. (*Health Data Management*, 31 January 2018)

"No ethical company will provide drugs under right to try." Biotech veteran Kenneth Moch tells the Health Subcommittee of the House of Representatives' Energy and Commerce Committee, about the perils of cutting the FDA out of the process under the so-called "right to try" laws, proposed by President Trump in his State of the Union address in January. (*Forbes*, 1 February 2018)