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The future of brain tumor liquid biopsies in the clinic

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An impressive array of liquid biopsies have been reported in this special supplement, each with the potential to transform how we diagnose, prognosticate or treat patients with brain tumors. Alongside further refinements in each technology to improve test performance, a focus is now needed on how to translate these liquid biopsies into the clinic. There will be challenges, and anticipating these could help accelerate the process.

A first challenge is that the real-world application of a liquid biopsy will be very different to the research laboratory. Assays that work in small-scale, highly optimized test systems will need to be adapted for implementation at scale in diagnostic laboratories across the world. This may require assay refinement or technical innovation, which will contribute to the marketplace cost of the test.

Another challenge is to work out where specifically a particular liquid biopsy will be used in the diagnosis and treatment pathway. An area of particular focus is earlier brain tumor diagnosis. In most healthcare systems, the gold standard investigation for patients with a suspected brain tumor is brain imaging. So, to diagnose patients earlier, a liquid biopsy will need to be applied in a population of symptomatic patients, to support decision making about who to prioritize for brain imaging. The test will need to cost less than imaging, if clinicians are to choose to use it.

Intuitively, an early diagnosis liquid biopsy will not be needed for patients in whom there is a strong suspicion of brain tumor. These patients are already prioritized for rapid brain imaging. Instead, a liquid biopsy will be beneficial for early diagnosis in patients with new-onset nonspecific symptoms, such as headache or cognitive change, where there is a low clinical suspicion of brain tumor.[1] These patients usually see their family doctor several times before diagnostic imaging, because their symptoms are more likely to have a non-tumor cause.[2] Diagnosis is often delayed until patients then present to the Emergency Department following clinical deterioration. In this scenario of testing in a population assessed as "low-risk" by clinicians, the early diagnosis test may be best positioned as a "rule-out test." Such a test would be applied to support clinical assessment that a patient probably does not have a tumor. Clinicians would be testing patients with nonspecific symptoms whom they don't expect to have a tumor. This is the best way to earlier detect more patients who actually have a brain tumor, because the patients we suspect to have a tumor based on standard care clinical assessment are already prioritized for brain imaging.

The incidence of a brain tumor in low-risk patients with nonspecific symptoms is less than 2%.[3] An early diagnosis liquid biopsy test should therefore be low-cost, because it needs to be applied in lots of patients for it to be useful. The marketplace cost of a liquid biopsy is rarely a consideration in the early stages of development, but it could be critical to the success of the test when applied to routine care. The optimal price-point of a liquid biopsy can be assessed in a health economic evaluation. For example, in an evaluation of a spectroscopic liquid biopsy for brain tumor early diagnosis, the price-point for cost-effectiveness in a UK setting was approximately £100.[4] This price-point will vary between countries and health care systems. The spectroscopic liquid biopsy test uses Fourier transform infrared (FTIR) spectroscopy to analyze more than 20 000 macromolecules in the serum, with machine learning to analyze the data and provide rapid (minutes), low-cost tumor detection.[5]The inventors developed a disposable silicon-based internal refractory element (IRE) to replace the more expensive standard diamond IRE used in low throughput spectrometers.[6] This innovation specifically addressed the need for a low-cost, high-throughput technology predicted by the economic evaluation. By comparison, liquid biopsies incorporating more complex technical assays, such as nucleic acid sequencing, may find it difficult to be commercially viable at this early diagnosis price-point.

Early diagnosis is though just one indication for brain tumor liquid biopsy. Other indications include predicting tumor type to guide surgical decision making, assessing treatment response, or differentiating true tumor progression from pseudo-progression. Test performance and cost will influence where each liquid biopsy is best suited to be deployed. Liquid biopsies based on nucleic acid detection may perform best downstream of surgical tumor biopsy, where knowledge of the tumor genome enhances test sensitivity and specificity. Multiple liquid biopsy strategies may even be used in parallel to maximize their utility. For example, the low-cost high-throughput spectroscopy test could be used to target use of more expensive and time-consuming nucleic acid-based liquid biopsy tests in the most "at-risk" patients, making the latter more cost-effective.

A third challenge is to optimize a liquid biopsy's test performance, its sensitivity and specificity for tumor detection, so that it is accepted by clinicians. A further challenge is to optimize liquid biopsy sensitivity and specificity. The acceptable test performance will vary according to the indication for which the liquid biopsy is deployed. Test sensitivity is the percentage chance that the liquid biopsy will pick up a tumor if there is a tumor present. If the objective is early cancer detection, sensitivity will need to be prioritized over specificity, but this comes at a cost to specificity. Test specificity is the likelihood that a patient with a positive test actually has a tumor. Lowering the threshold at which a test is reported as positive, to increase sensitivity, will lower specificity. More patients will therefore be incorrectly told that they might have a tumor, a false-positive result. In the early diagnosis setting, most patients will not have a tumor, so these false-positive results are particularly important. The putative tumor diagnosis will make patients anxious. This may be acceptable to patients, provided the brain imaging triggered by the positive liquid biopsy result is rapid. The false-positive results also create an economic cost. The increased cost of investigations for false-positive tests may eventually outweigh any cost savings of earlier diagnosis. This could also inadvertently cause delay for people who actually have cancer, because of an increased wait for diagnostic investigations.

To date, liquid biopsies have been almost exclusively validated in patients with more advanced disease. There is concern that the tests may perform less well in patients with early stage disease. This is important, because a false-negative test (when the liquid biopsy incorrectly reports that a patient does not have a tumor), could delay diagnosis and access to treatment. For liquid biopsies that detect tumor nucleic acid, there is less cancer DNA in the blood in early stage disease. For example, the sensitivity of liquid biopsy to detect any cancer DNA in blood is 92% in stage IV disease (when cancer has metastasized and is unlikely to be cured), but only 18% in early stage 1 disease.[7] Genomic information is in minute concentrations in early stage cancers, often beyond current assay capabilities, where instead non-tumor-derived information dominates.[8] Significantly, the spectroscopy liquid biopsy assays both non-tumor- and tumor-derived information, and so test performance is not significantly reduced in early stage disease. In a cohort of 177 patients with high or low-grade gliomas, the test correctly identified tumors as small as 0.2 cm,[3] irrespective of tumor grade.[9] In a prospective, blinded study of 385 patients referred from primary care with suspected brain cancer, or with a confirmed new diagnosis, the same liquid biopsy was performed with 91% sensitivity for the most common and aggressive brain tumor, glioblastoma, and 81% specificity.[5]

We have considered just three of the key challenges for scientists developing liquid biopsies. In whatever was these challenges are overcome, the objective should be to make decision making more agile and patient-centered, and for the liquid biopsy results to positively impact patients. For some patients, early diagnosis may translate into enhanced long-term survival. For others, it will improve quality of life, because treatment when tumors are smaller is likely to be safer, with less risk of harm. An effective early diagnosis strategy will also be valuable as new therapies become available, particularly neoadjuvant therapies where tumor type needs to be confirmed before tissue biopsy. Monitoring of disease response to therapy with a liquid biopsy may be more effective than is possible with brain imaging, which could permit a potentially harmful and ineffective therapy to be halted earlier. Perhaps, one day, liquid biopsies will make early cancer detection possible, months or even years before a patient would develop symptoms. The performance of such a test would have to be very high, because the tumor incidence in asymptomatic patients will be much lower than even the symptomatic population.

The different liquid biopsies under development all show promise for being successfully deployed in the clinic. Attention to how and where in the diagnosis and treatment pathway they are deployed will speed up the clinical translation. Multicenter prospective trials and collaboration between liquid biopsy researchers are now needed to develop further the best liquid biopsy strategies that will facilitate the best outcomes for patients with brain tumors.

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