sagentia

The future of tissue sample preparation for cancer diagnosis

Author: Nicholas Collier

Cancer is the second leading cause of mortality worldwide, accounting for around 1 in 6 deaths globally, yet survival rates are higher than ever in many parts of the developed world thanks to earlier diagnosis and treatment. A key tool in the fight against cancer is tissue sampling, which enables pathologists to diagnose symptomatic patients and provide specific information regarding the stage and form of the tumor, as well as to identify potential treatment options. More and more of these tests are becoming available to clinicians, offering a wide array of techniques that provide results at ever quicker speeds with greater accuracy, but navigating the options on offer and keeping track of developments within this area can be challenging.

Among developments in this field, the proliferation of Companion Diagnostic (CDx) tests – most of which take tissue samples and match a patient with the safe and effective use of a specific drug or other therapy – should be of particular interest to In-Vitro Diagnostic (IVD) manufacturers. Guardant Health and Foundation Medicine are among the companies who have had CDx tests which use liquid biopsy – a technology we cover in more detail below – approved this year. There are currently ~40 CDx tests with FDA approval and the global market is expected to be worth $6.8 billion by 2025, expanding at a compound annual growth rate of 12.9% during that period. Increasing automation of the preparation of tissue samples for analysis by CDx tests is a key area for potential growth within this sector, providing benefits for patients, clinicians and technicians, in addition to new revenue streams for the companies that create them. And that's not to mention the significant patient benefit that would impact millions of people every year worldwide.

What are companion diagnostic tests?

CDx testing devices are a relatively new technology that enable technicians to analyse tissue samples locally, in pathology labs, rather than external molecular labs. These tests often require a range of lab equipment and lots of manual intervention. Reviews by NICE in the UK and others have shown that it is not uncommon for external lab reports, which can take between 5 and 7 days from receipt of a sample to return results, to have a total turnaround time of 17 days, clearly a less than desirable outcome.

Testing could be made more readily available, without the need for highly skilled molecular labs, if more molecular instruments that integrated sample preparation were available. These local tests also provide quicker results and faster therapy decisions, meaning patients spend less time worrying about their results, can access the best therapy for them, and start their treatment more quickly. Only one such device, which fully integrates and automates sample preparation into the testing process, is currently available but many existing CDx testing devices could be adapted to perform this function.

How are tissue samples processed in the lab?

Formalin Fixed Paraffin Embedded (FFPE) samples for use in CDx tests are often provided to the lab as a paraffin block or slides. The minimum sample area/ volume depends on the test and is typically somewhere between >4 mm^2 all the way up to 250 mm^2.

Before doing a CDx test, the pathologist or technician working on the sample will look for tissue sections containing a high tumour cell content, as that gives the test the best chance of performing optimally, so some dissection from slides may be necessary. Tissue samples used in a CDx test must also be unstained, although a stained section may be used to identify the size and content of the unstained section.

How can this process be improved?

Automation of FFPE extraction at lab scale is possible, and instruments to automate FFPE extraction are already available for laboratory use, but many still require a manual deparaffinisation and Proteinase K (PK) step. Additionally, instructions for use for Food and Drug Administration (FDA) approved tests in the US specify that a sample must be manually prepared.

Some of the challenges of FFPE sample preparation include the fact that tissue samples are precious and not easy to obtain. Most of the Nucleic Acid (NA) extracted cannot be amplified, due to damage from the formalin fixation process, so extraction needs to be efficient to make best use of available material and minimise input volumes.

Automation (or semi-automation) for use in CDx is by no means impossible, however, there are many existing testing instruments, primarily aimed at infectious diseases, that already provide multiplex Polymerase Chain Reaction (PCR) for blood, plasma, saliva, urine and other samples which can't currently process FFPE samples. These platforms could be adapted and modified to create a more user-friendly integrated process.

Why integrate sample preparation?

The increasing availability of therapies is rapidly driving a need for testing. More affordable drugs, including the increased availability of biosimilars, also drive the need for affordable diagnostics but testing remains highly skilled and diagnostics are not readily available to meet this demand. Tissue sample preparation could be integrated into a molecular diagnostic instrument for rapid sample-to-answer test results (artist's impression, below).

The Idylla CDx testing device is currently the only example of a PCR-based platform on the market that includes an automated sample preparation step for FFPE tissue. Cepheid has a breast cancer assay on its integrated Xpert cartridge that can use FFPE samples, after a relatively simple manual preparation step, offering one example of what a semi-automated process might look like in practice.

Sales of Idylla are increasing dramatically, with production capacity of more than 1 million kits pet year and Biocartis, who make the testing platform, sold 175k cartridges in 2019, a 30% year-on-year growth in cartridges sales, with 1,300 instruments in the field. The average cost per cartridge is €120 and the average number of tests performed per instrument in 2019 was approximately 134. That's a tiny fraction of the worldwide market for CDx tesing. As we've already considered, the market size was estimated to be $3.5b in 2019, from which we might estimate that more than 20m CDx tests are performed each year.

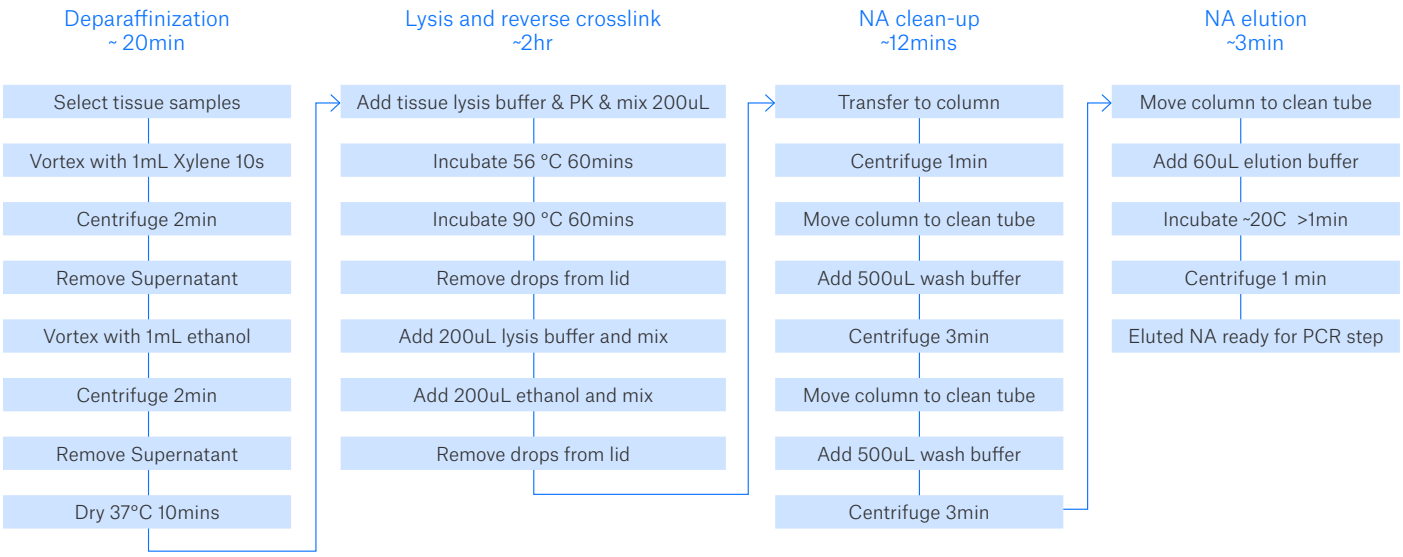
Tissue sample preparation could be integrated into a molecular diagnostic instrument for rapid sample-to-answer test results (artist's impression)

sagentia

How could this be achieved?

Tissue sample preparation in the lab for CDx tests involves more than 30, often time-consuming, steps (see illustration below.) Many existing infectious disease cartridges already include a wide variety of these steps, however, including the lysis and purification steps for NA needed to automate FFPE tissue sample preparation for our integrated CDx test However, they also often include the lysis and purification steps for NA needed to automate FFPE tissue sample preparation. The real stumbling block comes with the first step we would need to undertake to achieve this – the removal of paraffin. This could be achieved in several ways, many of which are already used in the lab but which may not translate well to our proposed cartridge.

Solvents like Xylene, for example, would present obvious issues around user safety, chemical compatibly and disposal, among others. We could simply melt the wax instead, or perhaps melt it into a mineral oil, or even emulsify the paraffin using surfactants or ultrasound. We could also melt the wax and use its natural hydrophobicity to separate it from the lysis step. We could even combine this melting process with lysis, if not using solvents. The Lysis / NA extraction steps and the final purification steps are already well-established in CDx cartridges and needn't present challenges.



How could automation be implemented?

There are three avenues we might pursue in implementing these steps, each with their own benefits and challenges.

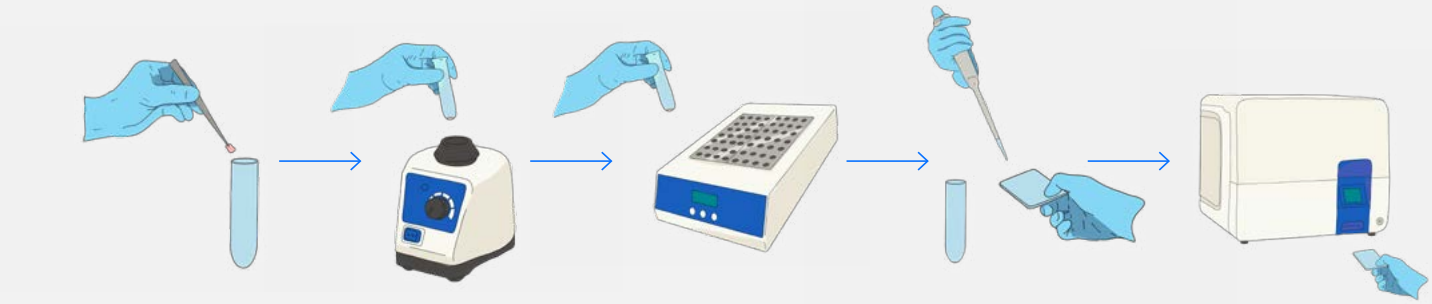
A completely manual process for sample preparation would employ simple steps, using existing equipment. This would involve placing your sample into a test tube with lysis, mixing it, melting it, and then transferring the contents to an adapted cartridge for FFPE sample analysis.

One way to semi-automate this process would be through the addition of a sample pre-processing module. You could place the sample into a cartridge, automate the extraction, and then manually transfer the prepared sample to a second cartridge, for use in the CDx device.

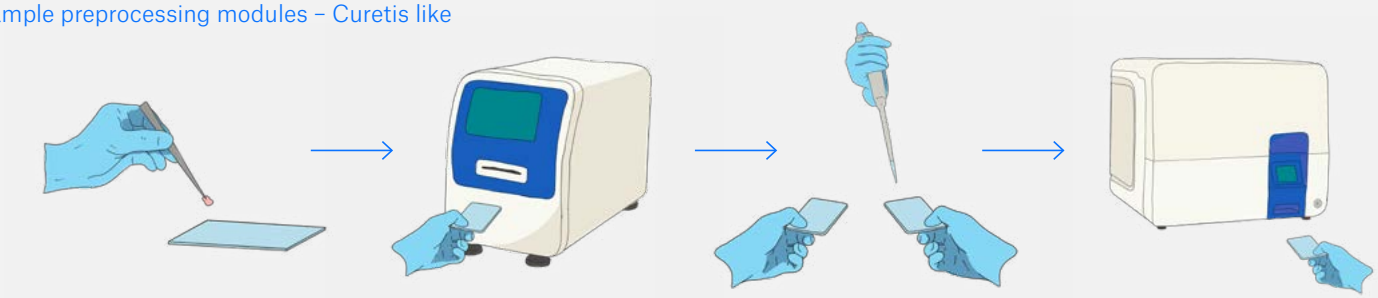
In a fully automated process, you would simply place your sample for processing onto a cartridge. This processing would then take place inside the same device where it is to be tested. This clearly seems to be the most attractive option from a user's perspective but would require a lot of instrument development.

3 avenues for implementing automation steps

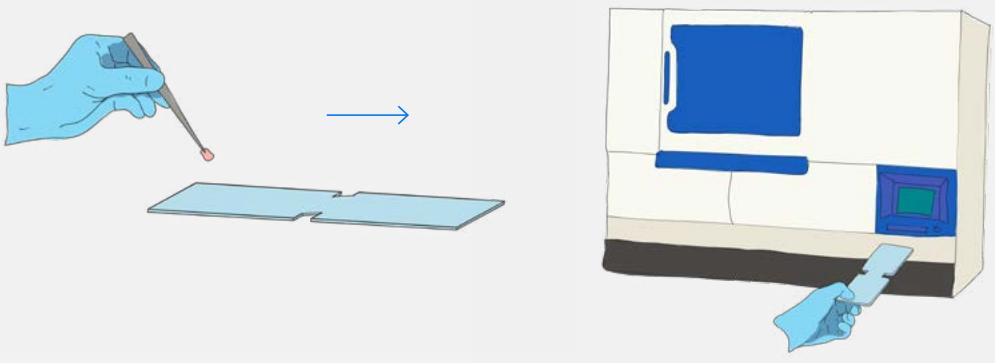
Simple manual steps - Cepheid



Sample preprocessing modules – Curetis like



Integrated sample processing cartridge – Idylla like



Wouldn't liquid biopsy be preferable?

Liquid biopsy is a very exciting technology, which Sagentia will be covering in a separate white paper. It's particularly attractive because it's a non-invasive technique that potentially works across the whole treatment journey for the patient, from screening and diagnosis to making a treatment decision and monitoring response to therapy. For those with symptoms, however, tissue sampling is currently the gold standard of care and to move away from that will take a long time. One reason for this is that not all tumours shed DNA at the same rate. Liquid biopsy is therefore unlikely to replace FFPE samples altogether, with various sample types likely to be more suited to different tasks. We might also see FFPE samples being analysed by spatial genomics in the future, to identify the spatial distribution of mutations within the tissue.

Conclusions

There is an increasing demand for affordable CDx tests to guide therapeutic decisions. Making instruments available at the pathology lab decreases the time it takes to obtain results, as well as reducing the amount of time technicians spend working on each test. As we have already considered, this leads to better outcomes for patients, who spend less time worrying about their results, can access the best therapy for them, and start their treatment more quickly.

Many molecular point-of-care cartridges already demonstrate significant steps in the process needed to make this happen and would form a good basis for an FFPE cartridge. This could take the form of a simple preparation module or could be fully integrated into the cartridge. Both options have their benefits.

Companies that have already invested significant R&D time and costs into developing an existing molecular cartridge may be able to add a sample preparation step or module that extends the market for its existing technology and leverages their existing manufacturing capabilities. Others developing new tests and instruments may prefer to create a fully automated system, with all the benefits that brings to the user. It might also include the ability to work with multiple sample types, including liquid biopsy samples such as plasma and urine.

Ready to go?

Whatever decision is right for your business, Sagentia is uniquely placed to assist you in the journey. We can offer advice on what the market for these integrated tests looks like. We are also able to establish the potential value to clinicians and pathologists, including what they care about, whether this process would add value for them, and what they would need from an integrated test. On the product development side, we will work with you to take your assay from the development lab through to market-ready, easy-to-use devices. We can design integrated microfluidic consumables and the associated instruments and transfer them to manufacture in your own facilities or at a Contract Manufacturing Organization.

About Sagentia

Sagentia is a global science, product and technology development company. Our mission is to help companies maximize the value of their investments in R&D. We partner with clients in the medical, consumer, industrial and food & beverage sectors to help them understand the technology and market landscape, decide their future strategy, solve the complex science and technology challenges and deliver commercially successful products. Sagentia employs over 150 scientists, engineers and market experts and is a Science Group company. Science Group provides independent advisory and leading-edge product development services focused on science and technology initiatives. It has ten offices globally, two UK-based dedicated R&D innovation centres and more than 400 employees. Other Science Group companies include OTM Consulting, Oakland Innovation, Leatherhead Food Research, TSG Consulting and Frontier Smart Technologies.

For further information visit us at: www.sagentia.com or email info@sagentia.com

sagentia

Sagentia Ltd
Harston Mill
Harston
Cambridge
CB22 7GG
UK

Sagentia Ltd
First Floor
17 Waterloo Place
London
SW1Y 4AR
UK

Sagentia Inc
One Beacon Street
15th floor, Suite 1500
Boston
MA 02108
USA