# Automated tissue dissection: its role in personalised medicine

Automating tissue dissection would appear to hold the key to personalised medicine becoming a reality. Here, *Pathology in Practice* has been given an early look at a new Xyall solution for the molecular pathology laboratory.

Worldwide there are likely to be 27.5 million new cases of cancer each year by 2040. According to Cancer Research UK, the incidence of cancer in this country ranks higher than 90% of the world and is two-thirds higher than the rest of Europe.[1]

Molecular diagnostics appears to hold the key to tackling this hidden epidemic. Demand for novel diagnostic tests is escalating with the arrival of high-throughput analysis methods such as next-generation sequencing technology. However, the sensitivity and specificity of the emerging molecular diagnostic tests depend on the quality of the sample, in particular on the number and purity of tumour cells in the sample, especially where the biomarker is expressed only in tumour cells. It also depends on the ability to dissect selected areas from tumour tissue – a process called macro-dissection.

It is here we come to the potential flaw in the race towards personalised medicine. Sample selection for molecular analysis presents numerous challenges for the pathologist and the laboratory. Tissue dissection remains a manual, subjective process – tedious, labour-intensive, with limited precision and carries the risk of contamination and human error. Poor quality control, variability and lack of traceability are other pitfalls.

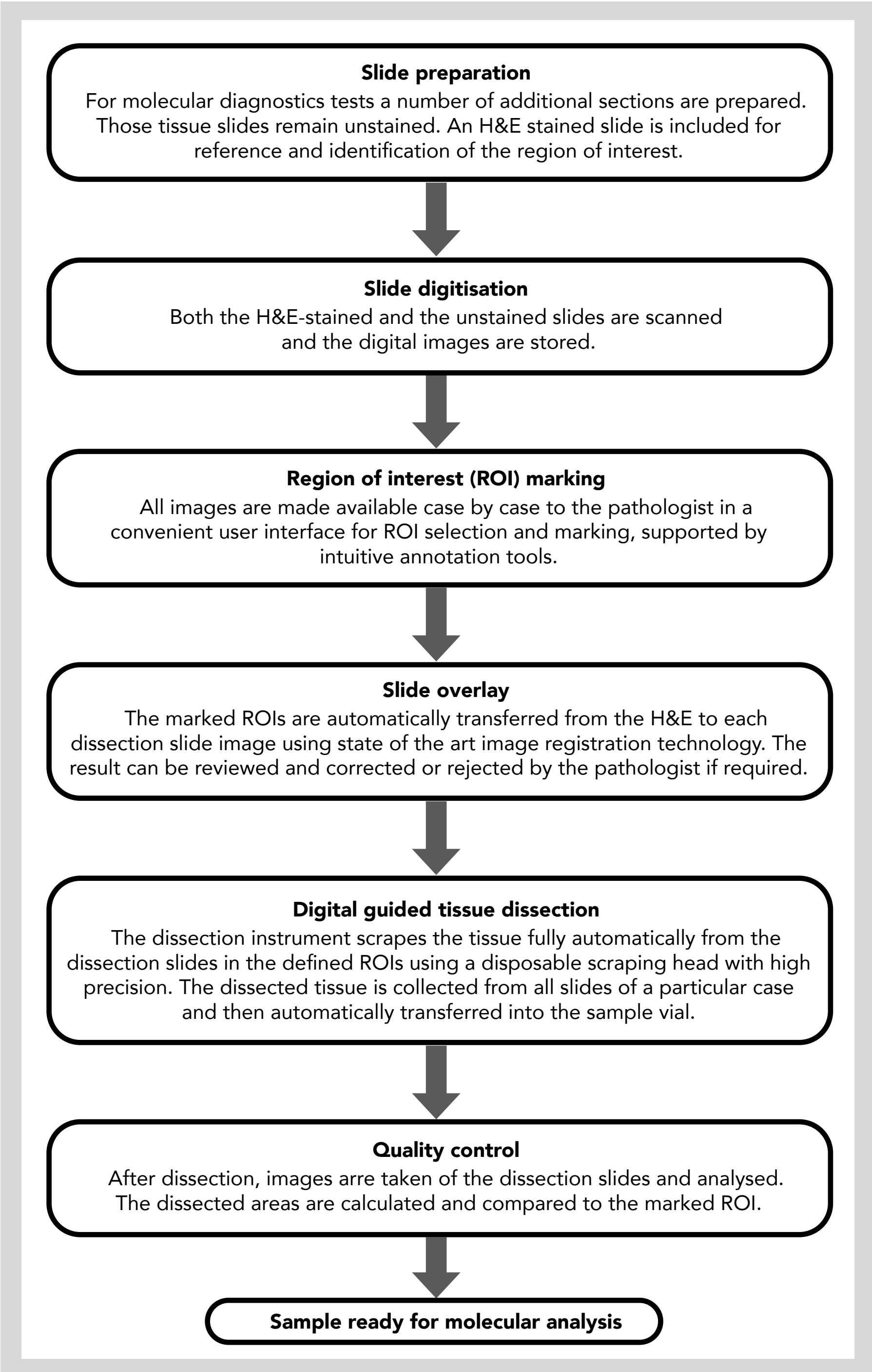
Tissector Table Top TT.

## Novel technology addresses missing link

Novel technology to automate tissue dissection – with the ability to integrate into routine laboratory workflow – offers a compelling way forward. This will become a reality with the forthcoming launch from Xyall of the benchtop Tissector Table Top (TT) designed for hospital-based molecular pathology laboratories. It combines a high degree of precision and reproducibility in a fully integrated solution, with the capacity to run up to 30 dissection slides an hour and a design that eliminates the risk of cross contamination.

The company already has its pioneering, high-throughput (80 slides an hour) industrial system fully operational in the USA at one of the world's largest commercial molecular diagnostic laboratories.

"If we are to get smarter about beating cancer, we need to change the way we handle test samples," said Guido du Pree, CEO of Netherlands-based Xyall. The molecular pathology company was established in 2018 to spearhead the development of new technologies specifically to address the 'missing link'. Mr du Pree and co-founder Hans van Wijngaarden were part of the original emerging business team at Philips, responsible for developing the company's global digital pathology offering.




Amended from Xyall BV

**Fig 1.** Workflow for automated histopathology.

## Digitising dissection slides

For hospital-based histopathology, the digitisation of whole-slide imaging is already transforming workflow with artificial intelligence (AI)-based algorithms becoming available for assessing tissue morphologies, classifying cancer subtypes and segmenting the tumour area.

"Xyall technology takes this one step further, by digitising the sample selection process and designing it to integrate into routine clinical practice," said Mr du Pree.

"Our unique technology addresses existing limitations, delivering a fully automated tissue dissection process, while matching the resolution needs of routine clinical practice," as shown in Figure 1.

While the overall digital pathology solution of the laboratory is responsible for scanning the stained haematoxylin and eosin (H&E) slides, the new Xyall instrument makes it possible to digitise the unstained dissection slides. Further, using Xyall's dedicated software package (VAR), pathologists can also view the H&E images at the right magnification for convenient and accurate ROI selection.

The Tissector TT exploits the recent availability of image registration algorithms to automatically map the marked ROI images to the dissection images. They can then be dissected with a high degree of precision using a robotic arm and dissection knife. The coordinates of the transferred annotations are used to guide the robotic dissection device so that it removes the material from the region of interest with high precision. The same device can subsequently collect and transfer the material to the sample tube. The system automatically disposes of the scraping head further minimising the risk of cross-contamination. No liquids are used in the entire process to make it fully compatible with all molecular sample preparation protocols.

Full traceability and quality control are provided, including the ability to take and analyse images after dissection.

Pathologists will be given an early look at the new platform in November at the Annual Molecular Pathology meeting with the global launch across all territories starting in March 2023.

Mr du Pree pointed out that other automated tissue dissection solutions, like laser capture micro-dissection (LCM), do provide high precision for research purposes, but were not feasible for routine diagnostic workflows. The LCM systems require highly skilled operators, are time consuming and cannot be fully integrated.

## Accuracy and reproducibility

"A platform designed for routine clinical practice does not need the high spatial resolution of LCM (1 µm). Xyall's solution, the Tissector TT, offers an accuracy of <100 µm and far greater reproducibility than manual dissection, particularly for very small specimens and samples with minute, subpopulations of tumour cells," Mr du Pree explained. "Additionally, our automated device will be able to run continuously, delivering a more consistent and higher throughput than manual tissue dissection."

Mr du Pree referred to recent global research commissioned by Xyall that pinpointed how accuracy and cross-contamination were two of the biggest concerns of molecular diagnostic laboratories worldwide.

"Clinicians and laboratory scientists recognise the vulnerabilities of manual detection and need faster and more accurate tissue dissection so that precision medicine could become a reality."

The Xyall findings also warned that workloads for handling breast, lung and colon cancers were set to increase exponentially over the next three years. Current practices of manual dissection of tissue were seen as a hindrance to


Convenient case loading into an instrument supports efficient laboratory workflow.

Representation of AI-based automatic transfer of ROI marking to dissection slides.

efficiency and turnaround time, with around a third of respondents specifically wanting this process to be automated. "Lack of automation in the area of tissue dissection was seen as a glaring gap in the otherwise automated laboratory workflow process," he added. Finding qualified people and quality control were also identified as areas of concern.

Further evidence of the diagnostic benefits can be seen in a 2016 study by University of Utah's Department of Pathology,[2] which performed digitally guided dissection and the traditional dissection method on a series of pancreatic adenocarcinoma specimens to compare their effectiveness. It found that the *KRAS* mutant allele fraction and the estimated neoplastic cell fraction were significantly higher in samples obtained from digitally guided micro-dissection. In 22% of the samples, a detectable mutation was found only with this digital method.

This is in direct contrast to current practice, where histopathologists review the tumour tissue under a microscope to identify regions of interest. Using their experience, they then make an educated guess on the tumour cell percentage, marking the outline of these likely ROIs on an H&E-stained slide with a pen.

The laboratory scientist then manually transfers the annotated area from the reference slide to a number of unstained dissection slides, matching these by visual judgement. The dissection operation itself is often done with a scalpel, with the laboratory scientist aiming to follow the annotation as accurately as possible. These steps determine the cellular composition of the sample and therefore the reliability of the test results, and it falls short for several reasons.

As Mr du Pree explained: "Manual macro-dissection relies solely on the judgement and skills of individuals who often don't have the tools to meet the requirements. Tests need a minimum amount and percentage of tumour cells in the sample, but at the moment this is not really measured. Pathologists make an estimate based on their experience.

"With the fraction of biopsies increasing, tumour samples are getting increasingly smaller. Lung cancer biopsies, for instance, are invasive and painful. It's difficult to get these samples, so they are typically very small. The smaller the sample, the more challenging it is to draw with a pen on a glass slide with sufficient precision, let alone to scrape such a small area of tissue. A poor selection increases the risk of a false-negative result, meaning the patient will not be eligible for the most effective treatments."

## Improving diagnostic accuracy

In other areas of the clinical laboratory, automated workflows are part of modern NHS laboratory practice, making best use of scarce and valuable staff resources. This delivers increased efficiency, faster turnaround time, high-throughput sample processing, and increased reproducibility.

Histopathology has benefitted hugely from the digitisation of whole-slide imaging, allowing remote discussions (telepathology), image archiving, improved storage and retrieval, comparison of areas on different slides, and direct slide annotation. However, until recently, the selection of tissue from the slide for further downstream molecular analysis has remained a time-consuming, manual process. Xyall's automated tissue dissection solution offers a compelling way forward, able to integrate into a laboratory's automated workflow and deliver robust, standardised, molecular diagnostic testing for laboratories of all sizes.

## References


1 Cancer Research UK. *Worldwide cancer incidence statistics*. London: CRUK, 2022 (www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer/incidence).

2 Geiersbach K, Adey N, Welker N *et al*. Digitally guided microdissection aids somatic mutation detection in difficult to dissect tumors. *Cancer Genet* 2016; **209** (1–2): 42–9. doi: 10.1016/j.cancergen.2015.12.004.


This is a complementary article to 'Tissue dissection: the missing link in modern molecular pathology' by Dr Reinhold Wimberger-Friedl published in *Clinical Laboratory International* 2021; September: 20–2.