

Fresh tissue handling pathway for the 100,000 Genomes Project

In order to optimise and standardise the handling of fresh tissue for The 100,000 Genomes Project, four partner trusts of the West Midlands Genomic Medicine Centre have adopted an innovative vacuum-packing solution.

The West Midlands Genomic Medicine Centre (WMGMC) is one of 13 created by NHS England to transform diagnosis and treatment for patients with cancer and rare diseases, and pave the way for personalised medicine. The WMGMC is a partnership of 16 NHS acute trusts across the West Midlands region working collaboratively to help deliver the nationwide 100,000 Genomes Project. The aim of the project is to create a new genomic medicine service for the NHS – improving the way patients are cared for. To date, four of the partner trusts in the WMGMC – University Hospitals Birmingham NHS Foundation Trust (UHB), The Royal Wolverhampton NHS Trust, University Hospitals Coventry and

Warwickshire NHS Trust, and George Eliot NHS Trust – have adopted vacuum packing for the collection and transportation of surgical specimens from participants who have been recruited into the 100,000 Genomes Project.

Challenges with formalin-fixed samples

The 100,000 Genomes Project has presented pathologists with many challenges, particularly around molecular diagnostics and whole-genome sequencing (WGS) in cancer. The project has highlighted the need to optimise and standardise tissue handling to ensure that high-quality sequencing is achieved, while retaining morphology for routine diagnosis.

During the early phases of the project, extensive experimental work showed that fresh frozen tissue is required for optimal WGS. Formalin-fixed, paraffin wax-embedded (FFPE) samples typically generated by pathology laboratories are available in abundance. However, DNA extracted from FFPE blocks is highly variable due to DNA damage introduced by the fixation process. Formalin fixation causes i) hydrolysis of phosphodiester bonds, leading to varying degrees of DNA fragmentation, and ii) crosslinking resulting in artificial nucleotide mutations. It was also found that DNA extracted from FFPE samples is often limited in quantity and below the yield required for successful WGS.

Collecting fresh tumour samples has presented its own difficulties, and was one of the main drivers for the four partner trusts of the WMGMC to utilise the innovative vacuum-packing solution from Menarini Diagnostics. Around the country, laboratories involved in the 100,000 Genomes Project have had to introduce new processes for collecting



The Queen Elizabeth Hospital Birmingham utilises TissueSAFE in main theatres and day surgery.



Nucleus and Heart/Lung theatres at Wolverhampton's New Cross Hospital are supported by the TissueSAFE system.

Table 1. Number of TissueSAFE installed at each site by the four WMGMC partner trusts.

NHS trust	Hospital site	No. of TissueSAFE	TissueSAFE location
UHB	QE Birmingham	2	Main theatres and Day Surgery
UHB	Birmingham Heartlands	2	Main and Twin theatres
UHB	Solihull	1	Main theatres
UHB	Good Hope	1	Main theatres
Royal Wolverhampton	New Cross	2	Nucleus and Heart/Lung theatres
University Hospitals Coventry and Warwickshire	Coventry	1	Main theatres
George Eliot	George Eliot	1	Main theatres

fresh tumour samples with care and consideration for the impact on the wide variety of diagnostic tests performed on tissues after research sample collection. Once sample collection has taken place, the remaining surgical specimen then enters the routine diagnostic pathway in the laboratory.

Accurate diagnosis is of paramount importance for pathologists to ensure the correct treatment decisions are made for patients in a timely manner. Any new collection and transportation processes considered and employed by the laboratory for fresh tumour samples must not impact on the routine clinical decision. In addition, concerns about the health and safety effects of formalin exposure, together with the reclassification of formaldehyde as a Class 1 carcinogen to humans (IARC) have also acted as additional motivations to drive adoption of fresh frozen pathways and remove formalin from theatres.

Situation before adopting vacuum packing

Prior to the adoption of vacuum-packing technology at the four WMGMC trusts, genomic research nurses worked in conjunction with theatre and pathology laboratory staff to collect fresh tumour samples for the project. Participant surgical resection samples would be collected on demand by the appropriate genomic research nurse and transported immediately to the pathology laboratory where the pathologist would perform the necessary sampling. Recruitment of a participant sample was dependent upon surgery taking place during the working hours of the pathology laboratory (typically, Monday to Friday 9.00 am to 5.00 pm), availability of a pathologist to sample the fresh tumour received, and a genomic research nurse being available to collect and transport the sample in a timely manner.

Typically, during surgery, any specimens generated for the pathology laboratory are placed directly into pre-filled formalin buckets and are transported to the laboratory two or three

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times a day. The collection and transport method utilised for fresh tumour tissue for the 100,000 Genomes Project was a new working procedure and as a result not all nominated samples were viable for use. Some were accidentally placed into pre-filled formalin buckets or it was not clear on the patient documents that they were a participant and their sample needed to be kept fresh. Participant samples were also not able to be used if the specimen was generated over a weekend or outside of the pathology laboratory working hours, as a surgical specimen was unable to be stored fresh for a long period of time without compromising the quality of routine diagnostic tests. Ultimately, the four WMGMC partner trusts needed to overcome these difficulties and ensure maximum patient sample recruitment into the 100,000 Genomes Project.

The pathology laboratory at

Birmingham Heartlands Hospital also received surgical resection specimens in pre-filled formalin buckets from on-site theatres and from Solihull and Good Hope hospitals. Owing to the distance between the pathology laboratory and the operating theatres at the two outlying hospitals, 100,000 Genomes Project participant samples were not able to be recruited from these sites. This was primarily due to a costly process, limited genomic research nurse availability for sample collection, and urgent transport demands to ensure the fresh specimens could be processed by the pathology laboratory without compromise in the quality of routine diagnostic results.

Vacuum packing – an innovative solution to ensure maximum patient recruitment

To ensure maximum patient sample recruitment into the 100,000 Genomes Project without compromising on sample quality, the TissueSAFE by Menarini Diagnostics was installed in the operating theatres of the four WMGMC partner trusts (Table 1). TissueSAFE instruments typically were installed into the formalin storage/specimen collection rooms in the theatres indicated at each site. Final theatre locations were decided based on those surgical areas that were generating the highest number of 100,000 Genomes Project samples. Pathology laboratory location was site-dependent, with not every theatre being situated in close proximity to specimen reception (Table 2).

Table 2. Pathology laboratory location in relation to TissueSAFE installed in theatres.

Site	Pathology laboratory location
QE Birmingham	On-site
Birmingham Heartlands	On-site
Solihull	Birmingham Heartlands
Good Hope	Birmingham Heartlands
New Cross	On-site
Coventry	On-site
George Eliot	Coventry



Using the TissueSAFE, fresh specimens nominated for the 100,000 Genomes Project are sealed in a dedicated vacuum bag and refrigerated prior to transport to the laboratory.

Vacuum-packing technology

Using the TissueSAFE, fresh specimens (without formalin) nominated for the 100,000 Genomes Project are sealed in a dedicated vacuum bag and placed into a refrigerator at 4°C until transport takes place. Specimen transport typically utilises a cool box and is tracked using a temperature monitoring system supplied with the TissueSAFE solution. Upon receipt into the laboratory, specimens are either placed into a refrigerator until a pathologist is available, or are sampled immediately. During sampling, the vacuum bag is opened, the specimen removed, examined and a sample collected.

Depending upon availability of the SealSAFE instrument, the specimen is either placed into a bucket and formalin solution added (10:1 ratio), as per the routine diagnostic pathway, or the SealSAFE instrument is used to dispense automatically a fixed volume of formalin into the bag (depending upon weight of the specimen) and the bag is resealed.

Samples are then classified as part of the routine diagnostic pathway and examination and grossing are performed after fixation. Typically, laboratories using the SealSAFE instrument validate the volume of formalin being dispensed into the bag (2:1 ratio). After examination and grossing, the specimen is returned to the same bag and vacuum packed (without formalin) for storage.

Benefits of TissueSAFE and SealSAFE

The benefits achieved by the sites employing the vacuum-bagging technology for collection of 100,000 Genomes Project samples are as follows:

- Fresh vacuum-packed specimens (without formalin) can be stored at 4°C for 24–72 hours (depending on

specimen type), allowing for maximum sample recruitment outside pathology laboratory working hours and based on pathologist availability.

- Fresh vacuum-packed specimens entering the laboratory have been shown not to be compromised in quality with respect to downstream routine diagnostic testing, ensuring pathologists are able to perform accurate diagnosis.
- New collection pathways from outlying hospitals have been recognised as fresh vacuum-packed specimens can now be transported utilising trust-established specimen transport networks as oppose to relying on genomic nurses and urgent transport carriers.
- Genomic nurses have been redeployed to perform other valuable activities associated with the project as they do



Following genomic sampling, the SealSAFE instrument adds a fixed volume of formalin to the specimen in a bag, which is then resealed and stored.

not need to collect samples on a demand basis. Owing to the ability to perform transport at set times, hospital portering staff can be utilised as per normal trust practice.

- Improved operator safety when handling hazardous fixative solutions for theatres, portering staff and laboratory personnel.
- The solution has allowed the laboratories involved to recognise that they are able to achieve complete control over specimen fixation to achieve improvements in the quality of diagnostic tests performed.
- For those sites with the SealSAFE instrument, the storage of fixed specimens in vacuum-sealed bags without fixative means that less storage space is required than currently needed for buckets. Much more rapid specimen disposal is also achieved, freeing personnel time to be employed in other areas of the laboratory.
- Specimens are tracked and temperature-monitored between theatres and laboratories to ensure they are received in a timely and appropriate manner. This has improved the chain of custody for each specimen and has provided the laboratory with a complete pre-analytical audit trail of the specimen from the patient, which previously had not been possible.

Vacuum packing – the future

As well as employing the vacuum-packing technology offered by TissueSAFE and SealSAFE for 100,000 Genomes Project samples, several trusts in the UK have gone entirely ‘formalin free’ in their theatres. The individual trusts at the WMGMC, which have already adopted this technology, are looking to extend their scope of use especially as genomic testing is now transitioning into routine NHS care, via a national Genomic Medicine Service, which is due to be available in 2019. Vacuum packing will be required to be used for collection of all patient surgical samples in the future, with Dominic Hassett (clinical educator for theatres at Heartlands) saying: “We are very pleased to have introduced vacuum packing for our 100,000 Genomes Project specimens and look forward to the possibility of reducing the use of formalin in theatres even further in the future. Starting training on processing the first specimens took only one week, which is a really fast turnaround.”



Further information is available online from Menarini Diagnostics (www.totaltissuediagnostics.com).