

## storage and cold sorting of clinical research samples in the laboratory for maximum sample integrity

### introduction

This application note describes an automated, high-density sample storage and sorting system that has been implemented at the MRC Epidemiology Unit, University of Cambridge, run by Head of Laboratory Dr. Debora Lucarelli. For the Unit, automation has been central to improving the efficiency of their large-scale sample management and processing, improving sample integrity, the speed at which they work and the scope of their studies.

### background

Biobanks, biorepositories and other bio archives/collections store large numbers of biological samples including DNA and provide a vital resource for groups performing biomedical research such as epidemiological studies, which seek to identify underlying factors in human disease. These facilities curate and supply large collections of individual samples from study participants that have been collected over time.

The key to any successful epidemiological, or other biomedical research study, is that it is powered by sufficient numbers to produce statistically significant findings. The time, manpower, cost to source, and the sample numbers required for analysis are considerable, and beyond the scope of most research groups. Collections of volunteer samples already assembled in dedicated bio repositories offer many benefits to researchers and; more and more, their utility to enable research on statistically significant populations that would otherwise not be possible is being recognised.

Maintaining the integrity of stored samples in any collection is paramount, accounting for factors that can affect long term sample quality in the way they are collected, handled and stored.

Prior to storage, biological variation in samples (such as those that undergo haemolysis during sampling, or natural physiological variability in glucose or fat) can be minimised with careful collection and processing, but never eliminated. With blood samples, haemolysis can be reduced with standardised sampling methods, quick

processing from whole blood to plasma/serum, quick aliquotting and freezing. The method of sampling and time to storage is critical.

Storage of large numbers of samples provides numerous, significant challenges, such as; finding enough space and minimising the footprint, tracking and sorting of samples, and maintaining samples at the correct protective temperatures (typically refrigerated or frozen). Operationally, this is a complicated process. Samples are typically processed by multiple operators requiring training, SOP's and replicate equipment. Samples need to be carefully logged (ideally LIMS) and transported to a final repository.

Individual samples will be used multiple times over an extended period and need to remain uncompromised. Traditionally, tubes have been stored in boxes of samples and undergone manual retrieval and multiple freeze/thawing cycles. With large scale sample management, ensuring all curation and processing needs to be as efficient as possible.

### novel automated sample storage and cold sorting for maximised efficiency and sample integrity

Full or partial integration of high-density, automated tube storage and temperature-controlled handling can overcome many of the issues and improve the capacity of storage facilities of any size. Transferring samples to individual 2D barcoded tubes eliminates cross contamination, sample loss, and unnecessary bulk retrieval and freeze/thawing.



### key benefits

#### arktic:

- high-density storage, small footprint - 140,000 tubes in 1.1 m<sup>2</sup>
- eliminate unnecessary bulk sample freeze/thaw with automated, single tube selection and retrieval
- retrieve individual tubes from -80°C storage in as little as 15 seconds or custom 96-vial rack combinations in less than 10 minutes

#### comPOUND:

- stores 100,000 1.4 mL or 200,000 x 0.5 mL vials (or combination) at -20°C, + 4°C or ambient
- cherry pick any sample in less than 10 seconds
- simple, reliable and proven pneumatic technology
- easy integration of downstream applications

Unique 2D barcodes for every sample permit full LIMS software tracking at every stage of the samples movement, as well as detailed annotation of its analysis and history. Automated storage and retrieval accelerates the preparation of custom sets of samples; significantly reducing manual handling and labour time. Logging of sample information enables cherry picking of sample sets based on many different criteria such as age, sample type, or blood chemistry.

SPT Labtech's arctic is an automated high density -80°C sample storage and retrieval system. arctic securely stores 2D barcoded tubes in a safe, frost-free -80°C environment and employs unique pneumatic technology to transport storage tubes, minimising the use of moving parts for enhanced reliability. Sample integrity is assured with a range of monitoring and back up systems including a 100% refrigeration back up system that can switch on automatically if required. arctic can work with a variety of 2D barcode tube types in the SBS standard 96 sample rack format. It offers rapid cherry picking of samples and only delivers the requested samples, avoiding the unnecessary picking of non-required "innocent" samples. A full rack of 96 samples can be delivered in as little as 10 minutes. Up to 140,000 2D barcoded tubes can be stored in arctic on a footprint of less than 1.1m<sup>2</sup>



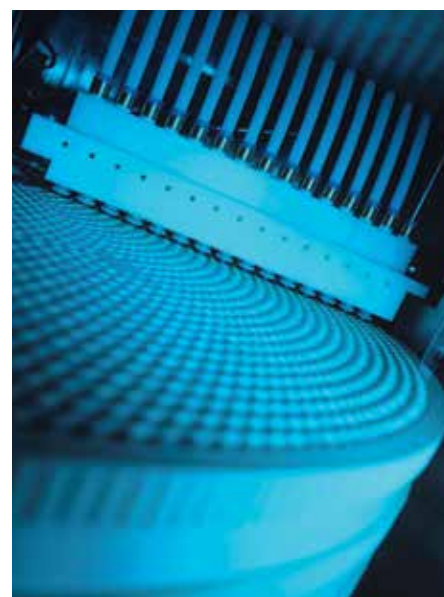
The pneumatic transport system employed in arctic has a proven track record for reliability and assured operation. It was introduced in the first generation of SPT Labtech comPOUND storage systems in 2001.

comPOUND is available in RT, +4°C and -20°C configurations and works with a variety of 2D barcoded tubes from a range of manufacturers. comPOUND is able to access any sample in as little as 6 seconds and can cherry pick a whole rack of 96 storage tubes in less than 10 minutes. comPOUND can store up to 200,000 half height storage tubes (e.g. 0.5 ml 2D barcoded tubes) or 100,000 full height storage tubes (e.g. 1.4 ml 2D barcoded tubes)

comPOUND and arctic are designed as scalable modular units so that customers can address their immediate storage needs with compact solutions, adding further units as their collections grow. A range of complimentary automation solutions offer the ability to store and retrieve sample tubes from several stores to a single point using SPT Labtech's lab2lab technology. This pneumatic delivery system allows a great deal of flexibility in the location of storage units, with the possibility of placing numerous arctic and comPOUND systems across a site with delivery and collection to a single location (or even numerous locations).

comPOUND and arctic are easily integrated with both commercial and in-house LIMS systems.

arctic (top left), input/ output tray (top right), arctic high density storage pipes (middle left), comPOUND (middle right), comPOUND storage carousel with mixed tubes (bottom left), comPOUND pneumatic transport pipes & carousel (bottom right)



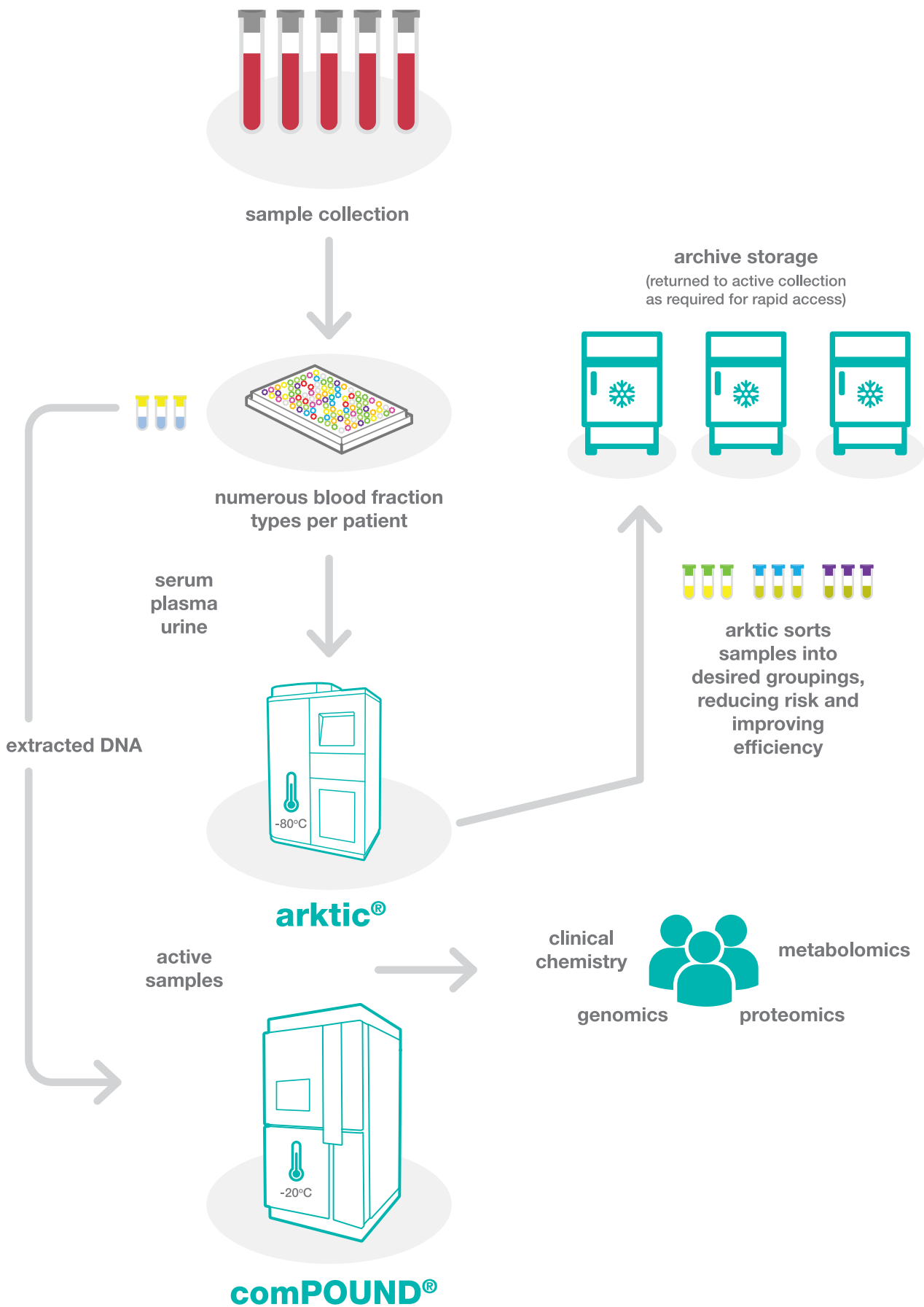


Figure 1. Workflow illustrating how a combination of arctic and compound storage modules can be combined with existing large-scale manual storage in biorepositories and biobanks to facilitate sample management / organisation and arrangement / allocation / distribution / short term holding.

## case study: Innovative clinical research sample management at MRC Cambridge Addenbrookes.

The MRC Epidemiology Unit conducts epidemiological studies into type II diabetes, obesity and other metabolic disorders. Samples from multiple studies have been collected since 1990 and the unit now stores over 1.5 million samples at 4°C, -80°C, -20°C and -196°C.

The MRC Epidemiology Unit collects whole blood, plasma, serum, urine and PBMC samples from study participants. DNA is extracted from whole blood and stored in the SPT Labtech comPOUND at +4°C. The remaining samples are fractionated and stored in 2D barcoded tubes. Racks containing the tubes are then placed in the SPT Labtech arctic for storage and re-arranging. The lab houses and organises samples for medium to large scale studies (up to 40,000 samples in a study), usually case control-based studies or prospective cohort studies. The samples are finite and usually irreplaceable so maintaining sample integrity is their biggest priority for the Unit.

Analysis performed on samples includes traditional clinical biochemistry, genetic analysis such as GWAS, methylation-based analysis, nutritional biomarkers and various protein markers. Underpinning all the measurement activities at the Unit is the sample management. The aim is to get consistent, reliable and reproducible data from all the samples.

The MRC Epidemiology Unit has set up an automated system using two arctic modules (60,000 tubes in one system and eventually 100,000 in the other) and a comPOUND that manages the storage and retrieval of over 100,000 DNA samples. Particularly interesting is the novel application of the arctic for cold-sorting of samples.

## methods/workflow

Samples need to be prepared within a standard time-frame in the clinics/ laboratories, ideally staying within 2 hours from sampling a participant, to reaching cold storage.

Samples are transferred from field collection tubes to 2D-barcoded 1 mL tubes. The arctic is then used to organise and reshuffle samples within the store, keeping one aliquot of each type of sample and releasing the remaining ones to be stored in the archive manual freezers. Once stored, arctic is also used to prepare orders overnight - loading and dispensing a rack in a predefined arrangement. In the morning, samples are then immediately stamped out for specific assays using further automated platforms. The arctic offers agility to the measurement pipelines, as samples can be retrieved and organised within a few hours thus avoiding trips to a storage facility for sample retrieval, the time required to array samples on plates, or racks, whilst allowing sample tracking at all times.

## EPIC-Norfolk study – automated storage and processing of extracted DNA

The EPIC-Norfolk study provides a good example of how the automated processing has made a significant difference to sample quality. The EPIC-Norfolk study is a large study using 25,000 DNA samples from participants aged between 40-79 years, collected since 1993.

Previously, individual samples were condensed into 96-well microtitre plates and sealed. For such a large collection, accessing individual samples was very labour intensive and there were significant issues with cross contamination, sample loss and the many hours it took to access and process the DNA samples manually.

Following the introduction of the SPT Labtech's comPOUND, samples could be transferred and stored in individual 2D-barcoded tubes. This enabled automated quantification, normalisation and storage, as well as the ability to keep both a high concentration archive stock at -80°C, and a standard dilution working stock at + 4°C within the automated system.

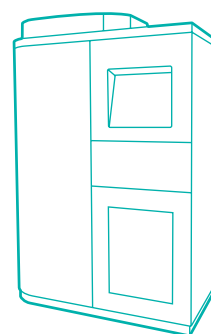
The Unit is now able to select individual samples and prepare genetic analysis studies quickly; a process that would previously have taken months, now takes just days. This has also released scientists to focus on analysis of data, rather than wasting valuable time on the laborious and error-prone task of sample picking.

Barcode scanning and LIMS software permit data capture at different points during lab processing and analysis; such as sample volume, concentration and location. This provides a comprehensive audit trail on each sample and greater confidence in the quality of analysis.

## conclusion

SPT Labtech's arctic and comPOUND can be easily installed in biorepositories of any size to maximise the capacity, efficiency and quality of sample management.

Our high-density, automated storage solutions safeguard sample integrity and provide rapid sample retrieval and organisation of many samples in the smallest footprint possible.



Sample integrity is the highest priority from sample collection from the patient and storage through to sample analysis and generation of data.

Matt Sims, Head of Research Operations & Head of NIHR BRC-MRC BioRepository. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine



The arctic has revolutionised our sample collections. We are now able to track and reorganise samples automatically thus reducing a lot of the manual procedures previously involved in the process.

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for discovery



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