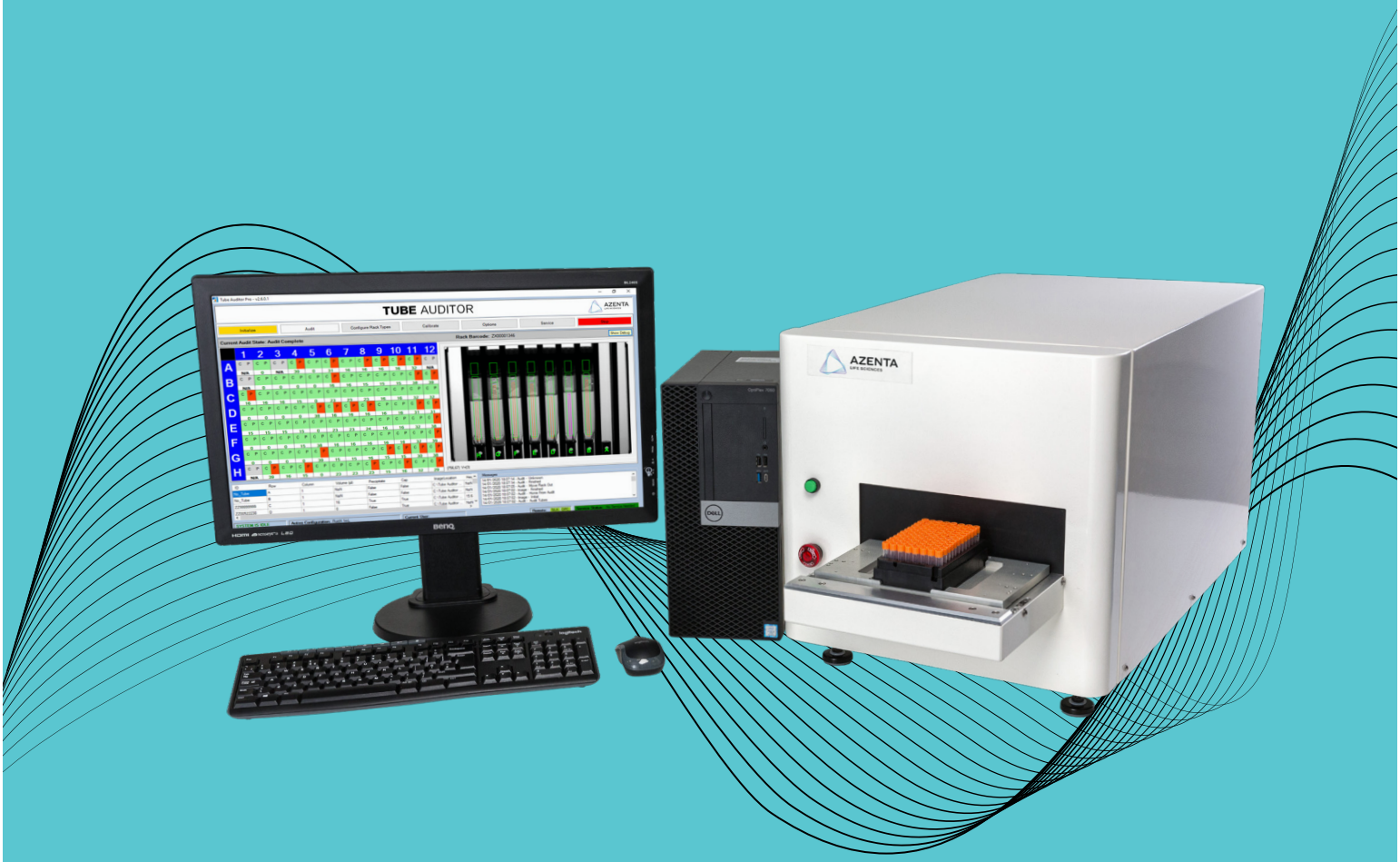
Consumables & Instruments

APPLICATION NOTE

UK Biobank Health Study & the Critical Role of Sample Auditing



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Abstract

UK Biobank is a centralized repository for use by approved researchers around the world. This paper provides an overview of the UK Biobank operation and information regarding workflows and automation. Particular focus is applied to high throughput sample volume tracking and the need for accurate volume measurement to ensure the Biobank is able to fulfill the requirements of proposed projects.

Background

In 2010 UK Biobank completed the collection of samples for a major health initiative aimed at improving the prevention, diagnosis and treatment of a wide range of illnesses. Over a 5 year period, data and samples from more than 500,000 volunteers aged between 40 and 69 years were collected. Each participant donated a range of biological samples – typically blood, urine and saliva; underwent a series of physical measures; and each provided a range of health and lifestyle information. Importantly, each participant also agreed to UK Biobank having access to their health records.

Using the Resource

The physical samples collected by UK Biobank are stored in a centralized repository for use by approved researchers from around the world. Scientists wishing to use data or samples from UK Biobank must register with the resource (via the UK Biobank Access System) and provide information about their study. Following approval of an application, samples and/or data are released to the researcher for the purpose of executing the project detailed in their application; the only conditions placed on the research team are that the research is in the public interest, that any publications

generated reference UK Biobank and that (specific, agreed) methods / data generated by the project are returned to UK Biobank to augment the data set for the benefit of future projects / research. Applications to use the UK Biobank resource have been steadily increasing since the Access System "go live" in March 2012 and current projects vary greatly in scope, from hearing and visual impairment to cardiovascular disease and cancer.

"Three key strengths of UK Biobank are the size of the cohort, the range of health-related information we collected on participants at baseline recruitment and since then, and the ability to link to medical records," explained Dr Simon Sheard, UK Biobank's Director of Operations. "Together these make UK Biobank one of the largest and most powerful studies of its kind ever undertaken. Whilst the data collected at baseline represents an important data source in its own right, the additional data generated by enhancement projects plus the data returned from external research projects ensure that the resource continues to grow in both breadth and depth. We expect the resource to be able to contribute significantly to health research over the coming years as subsets of the cohort begin to develop age-related diseases."

From the outset, UK Biobank invested heavily in automation and "industrial" workflows. This was necessary in order to safely process the samples at the rate required and to achieve the consistency of approach and timing dictated by the sample chemistry. Blood fractionation and sample aliquotting were automated, as was sample storage. A custom laboratory

information management system (LIMS) was developed to keep track of everything. This philosophy is still evident in the current enhancement projects underway at UK Biobank – projects designed to add further value to the resource. Two of these – Biochemistry and Genotyping projects – will generate additional data from samples already stored at UK Biobank and, as with the baseline recruitment, will make extensive use of automation to achieve the throughput and quality required.

The dual goals of high throughput and excellent sample quality are key at UK Biobank and a requirement on both these projects was fast, accurate and robust sample volume tracking. The Azenta Tube Auditor was assessed as a potential method of achieving the needs of these projects and shown to give the required accuracy for the range of liquids. Five Tube Auditors were purchased by UK Biobank – two are in use on Biochemistry and three on Genotyping.

Measuring Biomarkers

The Biochemistry project involves the measurement of 36 biomarkers and involves the retrieval and analysis of over 2,000,000 samples – half a million each of red blood cells, EDTA plasma, serum and urine samples. Over 1½ million of these then require a liquid handling step prior to loading onto the analyzers. For these matrices the parent samples are withdrawn from the automated store and a sub-aliquotting process is performed before the parent sample is returned to storage. The daughter aliquots are sent for biomarker measurement. The liquid handling operation is performed on a robotic sample processor (RSP) and the Azenta Tube Auditor is used as part of this process to verify the parent sample volume and then to measure the remaining volume after liquid handling. This volume data is then uploaded to the LIMS to ensure accurate tracking of sample volumes in storage for use in future projects.

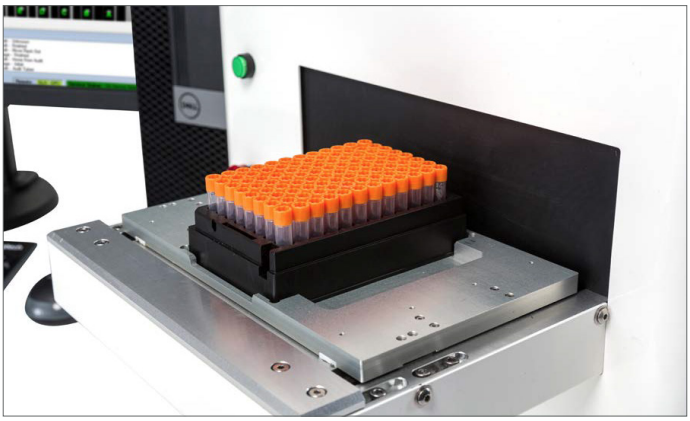
DNA Extraction & Genotyping

The Genotyping project also has a dedicated workflow; in this case dedicated automated work cells perform DNA extraction and sample aliquotting. As with Biochemistry, samples (buffy coat) are first selected from the central store and checked on the Azenta Tube Auditor systems. Following this audit step, DNA is extracted from these samples on custom-built TECAN workstations. DNA is extracted using the Promega Maxwell® 16 Instruments, aliquotted to three destination plates; two in 0.65ml septum sealed tubes (destined for storage) and one in a PCR plate, and then a concentration measurement is made on a Trinean DropSense® 96 instrument.

The Azenta Tube Auditor is employed again at the end of this process to verify the DNA volume in the tube-based samples prior to these being sent to storage. The information is uploaded to the LIMS to ensure an accurate record of the volume available for future projects is maintained.

Sample Auditing With the Azenta Tube Auditor

The Tube Auditors at UK Biobank allow an automated, high throughput process to be maintained for both these projects. In the case of Genotyping, a 24/7 operation performs 30,000 extractions per month (312 plates), requiring almost 1,000 rack audits. For Biochemistry, the processing rate depends on the



project phase but, at its peak, will exceed 100,000 per month, requiring 2,100 rack audits.

The Azenta Tube Auditor audits each sample and can report back on key characteristics such as sample volume, presence (or not) of precipitation, rack and tube barcodes and can even flag if the septa or screw cap is present or missing. This audit task, for a full rack of 96 tubes, is complete within 1.5 minutes, does not require removal of the cap and thus minimizes risk of sample contamination. The Azenta Tube Auditor works by acquiring and then analyzing detailed images of each sample. The sophisticated image processing algorithms combined with calibration curves generated for each sample / tube type allow accurate and reliable artefact detection and volume calculation.

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The information generated can be exported to an Excel ready file or provided to the controlling scheduler to allow LIMS update and/or to inform “real time” decisions regarding downstream processing. At UK Biobank, the reported statistics (volume only in the case of UK Biobank samples) are automatically uploaded to the LIMS or controlling scheduler to ensure the database is always up to date.

Sample auditing during an automated run is an important step in overall quality management of the entire process. UK Biobank recognizes the value in this measurement and has invested in it to ensure accurate tracking both of sample volumes recorded in LIMS and of samples shipped to researchers or partner organizations.

Samantha Murphy, Senior Project Manager at UK Biobank explains: “It is crucial that the volume recorded in the LIMS for each aliquot held at UK Biobank is correct. During the application process for researchers to obtain access to UK Biobank samples, the volume held in LIMS for aliquots is assessed to ensure UK Biobank is able to fulfil the volume requirements for proposed projects. Without an accurate volume measure, UK Biobank would struggle to ensure the volumes requested are available.”

Typically when samples are first introduced to a laboratory’s workflow, great care is taken to identify and characterize the sample. Barcodes are added, plate maps are created and the volume is recorded in the database. In practice, however, as samples are accessed, small liquid handling errors can cause a discrepancy between calculated and actual volumes; these are generally small initially and can go unnoticed. However, over time, and following multiple sample aspirate dispense cycles, these errors can build and may lead to incorrect or missing data as samples with insufficient volume are mistakenly included in downstream analysis or processing. Such errors can be costly and, without timeline auditing, may only be identified following many work-hours in analysis and troubleshooting.