Global Infrastructure for Clinical Trials
Through Integrated Biorepository Services and
Harmonized Quality Assurance Platforms

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ABSTRACT

Statement of the problem

Global clinical trials require consistent sample collection, processing, handling and storage. Variation in these pre-analytical processes are amplified when samples are managed by different laboratories and different service providers at diverse locations. A formal program for transferring technology and validating protocols as well as a routine proficiency testing programs are required to successfully manage nucleic acid, cell and analytical services around the globe.

Proposed solution

To provide a comprehensive solution for biobanking platforms in research, and in clinical arenas, we created a validation model that integrates sample collection, processing and analytical platforms to enable global management of critical biobanking and analysis pipelines. This approach incorporates principles from both ISBER/NCI best practices, along with regulatory benchmarks from the College of American Pathologists (CAP) with assay validation standard guidelines established by the States of New York and California. We have successfully applied this model across laboratories of the Brooks Life Sciences Laboratory Services (BLS), which spans three continents. This approach consists of three key areas. First, the selection and validation of robust technologies that can be deployed and managed from a central location. Second, the establishment of a training and validation platform that allows for the ongoing support of processing and analytical technologies in a regulatory compliant manner. Third, a harmonized quality assurance program that allows multiple sites across vast distances to perform complex procedures with the same level of efficiency and sensitivity. We have applied this strategy across two sites in the US, Europe, and Asia in order to demonstrate successful implementation of nucleic acid extraction, cryopreservation of primary cells, and high-throughput genomic analysis in the context of samples used for both discovery and clinical applications. This presentation describes data from experiments conducted across four sites on different days, and by different operators within each site in order to assess intra and inter assay consistency for a given processing service.
PARTICIPATING LOCATIONS

METHODS

Four laboratories across the Brooks Life Sciences (BLS) participated in a series of experiments to test an approach that would allow for the transfer and validation of a variety of sample processing and analytical technologies at our laboratories around the world. This process utilizes our global laboratory infrastructure that is driven by standardized technology implementations, SOPs, quality control assessment and quality assurance. Our most comprehensive bioprocessing laboratory is located in New Jersey and served as the reference lab in this particular study. We chose three different service segments (nucleic acid extraction, PBMC cell processing, and microarray analysis) across three different global sites to validate our process of technology transfer, assay validation/verification and quality assessment. The goal was to compare the results of these service segments at one site for each service to our reference lab in New Jersey. The design of the study was similar across service segments requiring multiple primary samples to be processed/analyzed across days and across technicians in order to measure the robustness of our technology transfer and service management process. It is important to note that the same SOPs were deployed at each site and the same training/verification process was followed. Independent samples from different donors were used for each service segment for the data provided below.
RESULTS

Automated DNA Extraction

The New Jersey site has standardized against Chemagen chemistry for bead based nucleic acid extraction and uses a fully automated ChemagicSTAR solution from Hamilton/Chemagen for both small and large scale gDNA extractions. All protocols were created and validated at New Jersey prior to transfer and training and Germany. Following onsite verification of technology and lab processes DNA was extracted from 96 different donor samples across both laboratories. Three 8 mL K2-EDTA tubes were collected from each donor to ensure that both laboratories extracted DNA from the same sample set. Identical extraction chemistry and instrumentation was used at all sites. Concentration and purity of DNA was assessed using the Trinean DropSense by cuvetteless spectroscopy, and yield was calculated based on measured volume of the extracted DNA samples. Functional QC was performed on every DNA sample to determine it quality and suitability. Fluidigm’s SNPTraceTM was used to assess the uniqueness, gender, ethnicity and downstream performance characteristics of each sample. Data presented is an average of all tubes tested across subjects, days processed and technicians.

There were no significant differences between these sites when comparing the concentration, purity or yield of extracted DNA, or the rate of successful calls when assaying DNA using SNP trace.
Cryopreserved PBMC

A standard SOP was created and validated at New Jersey. The protocol was transferred to Indianapolis and series of validations run were performed to standardize this potentially highly variable process. PBMCs are created using a Ficoll gradient approach with cell counts and viability measured by both hemocytometer and ViCell analyses. PBMCs were isolated from 9 mL of whole blood collected in sodium-heparin tubes using density gradient centrifugation described in the Brooks Life Sciences SOP. A total of 48 tubes from 6 donors were collected for both laboratories, and each technician isolated PBMCs from 24 tubes. Cell concentration, yield and viability were evaluated before and after cryopreservation using manual and automated counting procedures described above.

FIGURE 5: PBMC VIABILITY

![Chart showing PBMC viability comparison between New Jersey and Indianapolis.]

PRE-FREEZE
POST-THAW

FIGURE 6: ISOLATED VIABLE PBMCs

![Chart showing isolated viable PBMCs concentration comparison between New Jersey and Indianapolis.]

Microarray

New Jersey is the largest service provider of Affymetrix services in the US. Until recently all sample processing and array analysis was performed centrally at New Jersey. In order to meet the needs of our global studies and given some of the challenges of transferring samples to specific countries it was important to expand our technology/SOP transfer approach to analytical services. For this study we engaged our partner lab in mainland China to participate in this exercise. 96 HapMap DNA samples that have defined genotype profiles were used to compare assay performance and genotype concordance across two separate microarray plates with two different technicians on two different days. We used the Affymetrix Biobank array which contains over 800K SNPs to measure assay specificity and sensitivity. DNAs were shipped to China along with lot controlled reagents to remove any variability that could be derived from samples or reagents. Data was analyzed using standard Affymetrix analysis tools to generate genotypes for comparative analysis.

FIGURE 7: CALL RATE ACROSS 96 SAMPLES

![Chart showing call rate comparison between New Jersey and China.]

FIGURE 8: REPLICATE CONCORDANCE

![Chart showing replicate concordance comparison between New Jersey and China.]

![New Jersey](image1.png)

![Indianapolis](image2.png)

![China](image3.png)
CONCLUSIONS

The results validate and verify a truly harmonized platform for integrated biobanking services including and not limited to nucleic acid extraction, cellular cryopreservation and genomic analytical services which are all regulatory compliant and can be applied to both research and clinical programs. In addition:

- Brooks Life Sciences has created a formal process for technology transfer and training that yields robust and reproducible results.
- Brooks Life Sciences has created a central QA/QC pipeline for managing processes and data across national and international sites.
- Brooks Life Sciences is setting up a service specific proficiency testing program to keep all Brooks Life Sciences laboratories on the same performance level.
- Brooks Life Sciences is expanding its service set across regional, national and international labs to offer a comprehensive and harmonized service offering for academic and industry studies that require site specific processing and analysis.
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CONTRIBUTIONS

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