NMR-based Quality Control and Added Value Generation for Biobanks

Spraul M, Cannet C., Fang F., Leiminger.R and Schäfer H. Bruker BioSpin GmbH, Rheinstetten, Germany

Introduction

Quality control, standardization and coverage of relevant metadata are major issues for successful biobanking. Keeping in mind the rapidly increasing number of biobanks worldwide, the solution to solve such issues becomes a high priority. NMR is a technology that has rapidly grown into one of the 2 major tools in mixture analysis. It benefits from its outstanding reproducibility and transferability. Such spectra generated by different groups worldwide, working under standardized NMR conditions, can generate spectra that can go into common statistical analysis. This is a huge advantage for large clinical studies or epidemiology. The NMR (Nuclear Magnetic Resonance) based IVDr platform (In vitro Diagnostic Research) has been developed at 600 MHz with completely standardized hardware and standard operation procedures for the most common body fluids, and is already widely used in clinical and translational research. It also forms the basis of the International Phenome Center Network (IPCN, https://phenomenetwork.org) NMR-based investigations. The intrinsic reproducibility and transferability of NMR is demonstrated in figures 1 and 2.

NMR in Biobanks

1. Advantages beyond reproducibility and transferability

- Minimum sample preparation (buffer addition and mixing)
- Complete push button operation, including report generation in high throughput mode
- Robust and minimum maintenance (sample does not get in contact with detection)
- Detection system with high dynamic range (> 2*105)
- Delivers large number of parameters from each sample
- Targeted and non-targeted analysis in one experiment
- Retrospective analysis (re-analyze spectra with quantification or statistical models)

2. Quality control before input of samples into biobanks

Identifying quality issues can reduce cost or allow a warning
remark on input to avoid wrong interpretation or outliers in future analysis. Such statistical outliers in clinical trials or
epidemiological studies can be explained based on quality
issues.

- Preanalytic conditions (under development: time at room temperature, freezing cycles)
- Control of status description (e.g.fasting, declared drugs, alcohol, food…)
- Unreported drugs
- Accidental mislabeling/exchange of samples
- Differentiate serum/plasma
- Validate type of plasma (e.g. EDTA, Citrate)
- Dilution of plasma/serum
- Contaminations (e.g. disinfectants, cleaning agents,contrast
agents, skin creams, ..)

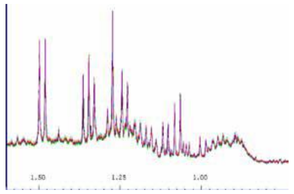

Figure 1: Reproducibility and transferability in urine Left part shows the overlay of 30 spectra generated from 30 aliquots of one urine sample, prepared by 6 people (5 aliquots each) and analyzed on 3 identical NMR platforms

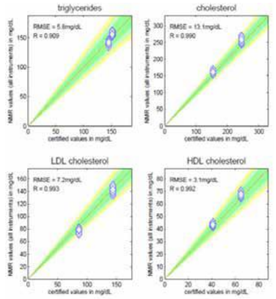

Figure 2: Reproducibility and transferability in plasma/serum Result of an 11 instrument ringtest on 2 NIST standard serum samples (1951c). In green, the error allowed by the NCEP (national cardiovascular education program) is shown, 11 results of each sample are shown as blue squares

3. Added biobank value of NMR beyond QC

After running NMR-based QC, spectra are available for storage into the biobank. Once spectra are generated under the platform SOPs, the analysis tools for urine and plasma/serum can be executed and additional information can be entered into the biobank sample description. Such information can be enriched retrospectively, when updated or new analysis tools become available. Added value by NMR generating additional information for each sample:

- Quantification of 150 metabolites and disease markers in newborn urine
- Classification against healthy newborn urine model
- Quantification of 150 metabolites/disease-markers in urine of children and adults
- Quantification of 115 lipoprotein parameters including subclasses
- Quantification of 20 small molecules in plasma/serum

Figure 4 show excerpts of urine quantification, for all parameters generated reference ranges are given and the actual sample is shown by a black bar. In the newborn samples univariate and multivariate classification is performed and deviating spectral regions are indicated.

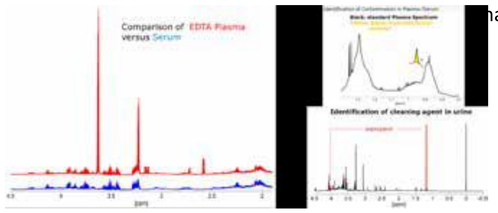

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Figure 3: Visualization of 3 NMR based QC functions in plasma/serum and urine