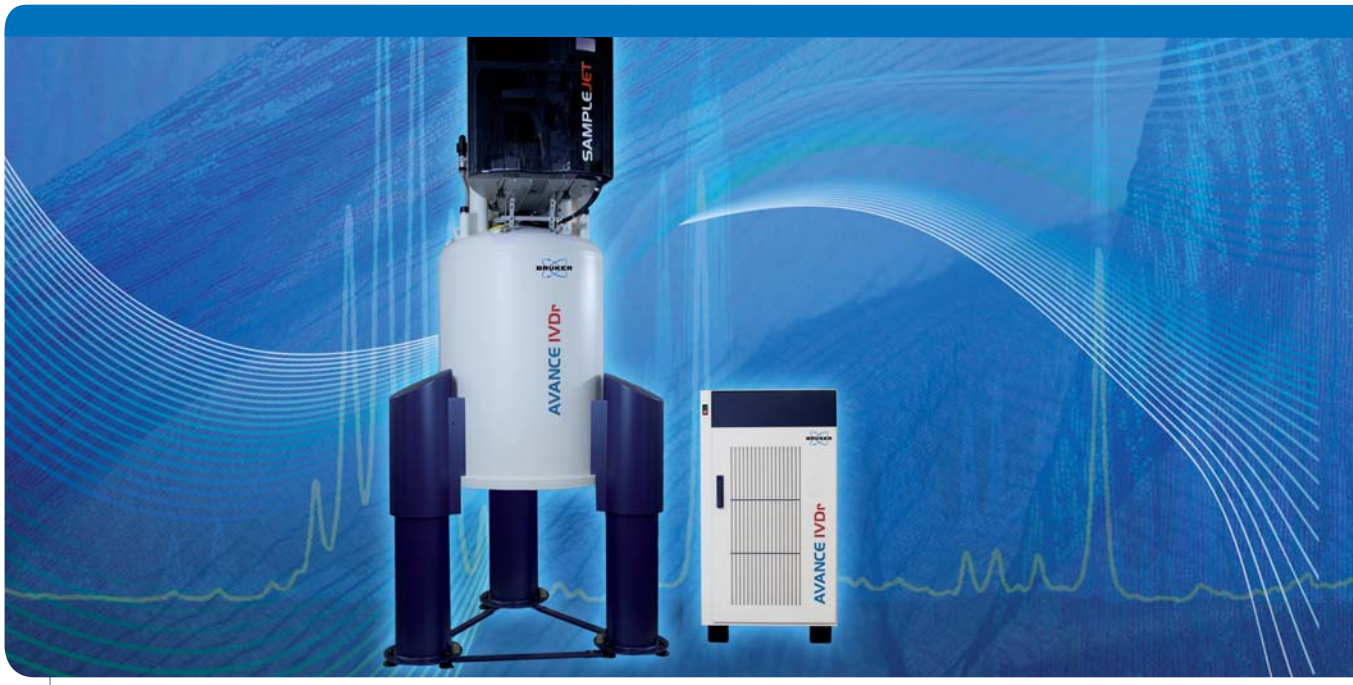

AVANCE™-IVDr

NMR Screening Solution for Translational Metabonomics Research

NMR (Nuclear Magnetic Resonance) is a major analysis tool for all kinds of metabonomics-related work. Its highest result reproducibility and transferability makes it the ideal solution for the integration of results from multiple laboratories across the world, e.g. thanks to NMR, newly developed analytical methods in human biofluid analysis have been transferred to the clinical research field, thereby enabling large epidemiological studies. Based on a 600 MHz superconducting magnet with minimized strayfield and modern digital console technology, Bruker has developed a push button screening solution.

With the AVANCE™-IVDr (IVDr = In-Vitro-Diagnostic-research) screening solution, highest quality NMR data and analytical results can be generated under standardized operating procedures.

Features

- Minimal sample preparation
- Non-destructive measurement
- Full automation in high throughput screening mode
- Highest reproducibility and data quality from sample to sample and instrument to instrument
- Quantification of large sets of metabolites with automated reporting
- Classification and discriminiation using statistical tools with automated reporting
- Low cost per sample and lowest cost per parameter, with small footprint to suit every lab

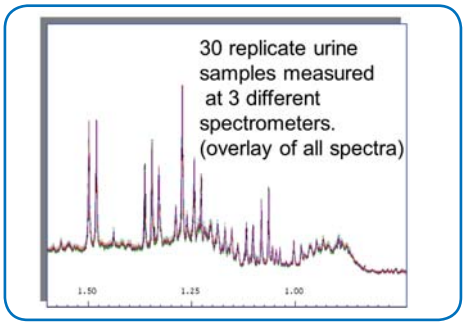

Figure 1 - Reproducibility test on multiple aliquots of one human urine, prepared by 6 people (5 samples each) and measured at 3 different instruments of identical field strength. All spectra shown in overlay.

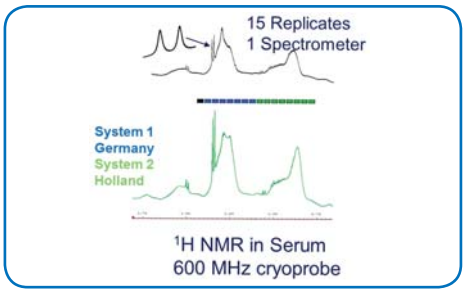

Figure 2 - Reproducibility on serum NMR

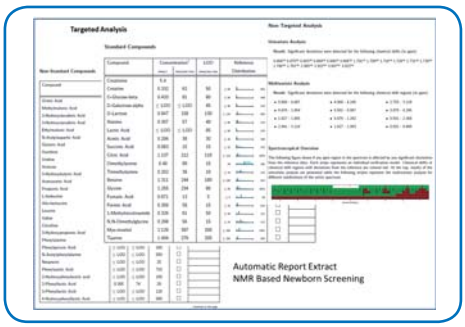

Figure 3 - Sections of NMR based newborn prescreening report showing extracts from targeted and non-targeted analysis

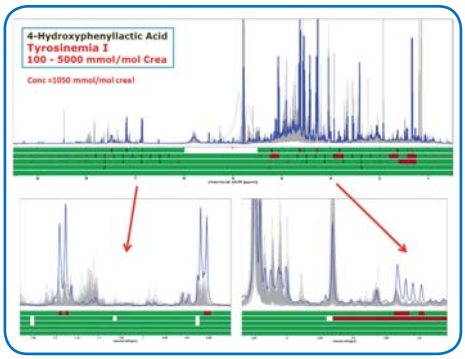

Figure 4 - Result of an automatic Procedure for verification of a new sample against a normal model for healthy newborns in Turkey and breakdown of the spectrum into deviating sections (red), example 4-hydroxyphenyllactic acid as part of Tyrosinemia Type I

Figure 1 shows the result of individually prepared and measured multiple aliquots of the same urine sample, measured by 6 different people (5 samples each) using 3 identical NMR spectrometers.

The spectrum shown above is the overlay of all 30 spectra generated as part of the Metabonomics Trainings course for Beginners. It is immediately evident that the spectra are identical and only differ by noise.

Figure 2 shows the reproducibility obtained on serum of 15 replicate aliquots, prepared and measured in one lab and with overlay of all spectra (upper spectrum).

The lower spectrum shows 8 aliquots of serum, again prepared and measured on two 600 MHz systems in Holland and Germany, under identical standard operating procedures, and with the spectra overlayed, again the spectra are clearly identical.

This performance is achieved through the strict standard operating procedures for sample collection, preparation, measurement and analysis that was especially developed for NMR screening, as delivered by the AVANCE™-IVDr .

Such performance forms the basis for statistical analysis with highest specifity, and delivers the ability to detect even the smallest multiple changes in compound concentration of mixtures, such as urine, with the minimimum of effort. It also provides the basis for robust quantification of individual metabolites that are indicative of disease.

NMR is the ideal tool for integrated, targeted and non-targeted analysis. With just one NMR measurement, for example, hundreds of metabolites in human urine are visible.

The investigation of newborn urine is a successful non-invasive example, proven on a study performed in Turkey. Together with INFAI GmbH Cologne, integrating 14 hospitals under the supervision of Prof. Selda Bülbül, a model for normal babies has been developed against which new samples can be compared. All NMR visible deviations will lead to outliers that are detected automatically independent of whether deviations are known or unknown.

Figure 3 shows elements of a report generated automatically by the Inborn Error of Metabolism (IEM) prescreening procedure. Figure 4 shows the superposition of a new sample to the Turkish normal model, representing a Tyrosinemia case on top of the normal model for Turkey. The figure also illustrates how the automated analysis finds the deviating regions by segmenting the spectra into ever smaller fractions using uni- and multivariate approaches.

Currently the quantification part comprises 64 compounds, 44 of which are indicative of inborn errors. This number is subject to constant enhancement.

IEM-Screening is just one example of the analysis pos¬sible using the AVANCE™-IVDr system. Bruker is connected to many research groups working on other applications, including the following research projects:

- Generation of invariant personalized metabolic profiles on humans
- Prediction of organ rejection
- Coronary heart disease risk assessment
- Lipoprotein subclass analysis
- Influence of gut microflora on human health and metabolic profile
- Prediction of treatment outcome
- Epidemiological studies and phenotyping of human populations
- Effects of nutrition and stress on the human metabolic profile