

B.I.BioBankTool™ Bruker IVDr BioBankTool (for research use only)

Quality Control under Standardization

While the number of Biobanks worldwide is growing rapidly, quality control of the whole process is a requirement to ensure the value of the biobanks. Standardization is needed to allow researchers to integrate results obtained of specimen tests from 1 or more biobanks.

Standardization also includes the QC Process, which needs to cover all aspects of pre-analytics and sample storage. In addition validation of specimen/donor metaparameters is of additional value. NMR is especially suited to perform QC-analysis of liquid biopsies and can deliver a large number of criteria based on one QC measurement per sample.

In addition to QC Information NMR can deliver a large number of metabolic information using the same spectra generated during the QC process. With this information in urine 150 metabolites in 2 age ranges are quantified. In plasma/serum 115 lipoprotein related parameters (including subclasses) and 41 metabolites/parameters are analyzed and quantified, the whole process is under push button automation and can be handled by a trained medical technical assistant.

NMR based Biobank QC delivers up to 46 criteria (depends on matrix type)



Table 2

Plasma/Serum					Urine					
3.1 Matrix Identity Test The spectral fingerprint of the sample is consistent with EDTA plasma.					3.1 Matrix Identity Test The spectral fingerprint of the sample is consistent with Urine.					
	K-EDTA mmol/L	Ca-EDTA mmol/L	Citic acid B mmol/L	Flag		Creatinine mmol/L	Alanine mmol/L	Fumaric acid mmol/L	Flag	
Sample	5.23	2.04	0.13	●	Sample	1.79	0.30	0.04	●	
EDTA plasma	2.50 - 13.00	1.30 - 3.00	<3.00	●	Urine	0.60 - 29.00	<2.20	<0.07	●	
Citrate plasma	<0.05	<0.01	3.10 - 20.00	○						
Heparine plasma	<0.05	<0.01	<3.00	○						
Serum	<0.05	<0.01	<3.00	○						
3.2 Matrix Integrity Parameters					3.2 Matrix Integrity Parameters					
Compound	Parameter	LOD	Target Value	Measured Value	Flag	Compound	LOD	Range	Measured Value	Flag
Acetic acid	Conc. in mmol/L	<0.01	<0.10	0.03	●	Acetic acid in mmol/L	<0.030	<2.90	<0.030	●
	Shift in ppm	-/-	1.916 - 1.918	1.918	●	Benzoic acid in mmol/L	<0.040	<0.45	<0.040	●
Citic acid B	Conc. in mmol/L	<0.03	<3.00	0.13	●	Citic acid in mmol/L	<0.300	>0.30	1.200	●
	Shift in ppm	-/-	2.657 - 2.659	2.658	●	Formic acid in mmol/L	<0.020	<0.71	2.321	●
Formic acid	Conc. in mmol/L	<0.02	<0.20	0.04	●	Hippuric acid in mmol/L	<0.200	<15.10	<0.200	●
	Shift in ppm	-/-	8.456 - 8.460	8.459	●	Lactic acid in mmol/L	<0.100	<2.00	0.179	●
D-Glucose-alpha	Conc. in mmol/L	<0.20	<3.20	1.50	●	Succinic acid in mmol/L	<0.020	<0.44	0.057	●
	Shift in ppm	-/-	5.237 - 5.239	5.238	●					
Lactic acid	Conc. in mmol/L	<0.03	<0.10	4.45	●					
	Shift in ppm	-/-	1.327 - 1.329	1.329	●					
3.3 Matrix Contamination Parameters					3.3 Matrix Contamination Parameters					
Contamination		LOD	Measured Value	Flag	Contamination	LOD	Measured Value	Flag		
test Based in mmol/L		<0.000	0.009	●	Propylene glycol in mmol/L	<0.020	7.227	●		
Contamination-1.25ppm in mmol/L		<0.008	<0.008	●	Isopropanol in mmol/L	<0.020	<0.020	●		
Isopropanol in mmol/L		<0.020	<0.020	●						

Table 2 : detailed examples extracted from the automatic B.I.BioBankQC-PS and B.I.BioBankQC-UR analysis reports

Table 3

QC criteria	Plasma/Serum	Urine
Check Sample Preparation	<ul style="list-style-type: none"> TSP Protein background intensity Alanine shift position 	<ul style="list-style-type: none"> TSP
Check NMR analysis	<ul style="list-style-type: none"> Shim performance Baseline 	<ul style="list-style-type: none"> Shim performance Baseline
Validate Matrix Identity	<ul style="list-style-type: none"> EDTA plasma Citrate plasma Serum 	<ul style="list-style-type: none"> Urine
Validate Matrix Integrity	<ul style="list-style-type: none"> Degradation Matrix composition out of model reference ranges 	<ul style="list-style-type: none"> Degradation Matrix composition out of model reference ranges
Check Matrix Contamination	<ul style="list-style-type: none"> Cleaning agents Desinfection material 	<ul style="list-style-type: none"> Propylene glycol Isopropanol
Check most frequent medication		<ul style="list-style-type: none"> Drugs Drugs metabolites
Check Protein background		<ul style="list-style-type: none"> Protein concentration beyond reference range
Check further parameter		<ul style="list-style-type: none"> Fasting/non-fasting state

Table 3: Criteria used for the QC analysis depending on matrix type

The methods and solutions described here are for research use only and not for use in clinical diagnostic procedures.

Table 1

Plasma QC Summary			Urine QC Summary		
Test	Result	Flag	Test	Result	Flag
NMR Experiment Parameter Test	not passed	●	NMR Experiment Parameter Test	not passed	●
NMR Experiment Quality Test	passed	●	NMR Experiment Quality Test	not passed	●
NMR Preparation Quality Test	passed	●	NMR Preparation Quality Test	passed	●
Matrix Identity Test	EDTA plasma	●	Matrix Identity Test	not passed	●
Matrix Integrity Test	passed	●	Matrix Integrity Test	not passed	●
Matrix Contamination Test	not passed	●	Matrix Contamination Test	passed	●
			Medication Test	passed	●
			Protein Background Test	passed	●
			Further Indicative Parameter Test	not passed	●

Table 1 : Extract of the summary page of the B.I.BioBankQC-PS and B.I.BioBankQC-UR analysis report

Rich spectral information

Based on the outstanding performance of NMR in reproducibility and transferability, high quality analysis of data is available to deliver additional information for the biobank specimens. Together with the biobank, tool packages are offered for plasma/serum and urine quantification as outlined before. A multitude of disease relevant as well as endogenous metabolites and lipoprotein information is delivered extracted from the QC spectra analysis.

Clinical trials: spectra instead of aliquots

Based on the IVDr Platform concept and its strict standardization for NMR data generation, it is possible to select spectra from multiple biobanks for large epidemiological studies on a worldwide basis or to expand the testing range of clinical trials, providing for example spectra from healthy cohorts out of the biobanks. Instead of generating always new aliquots. This builds a new value proposition for biobanks, allowing to save cost and contribute to big data in an efficient way. New NMR based diagnostic tests can such be validated on a worldwide basis and multiple phenotypes without exploding the cost of the trial. Data generated from a 11 IVDr platform ringtest clearly proof this unique feature of NMR.

IVDr Platform Concept

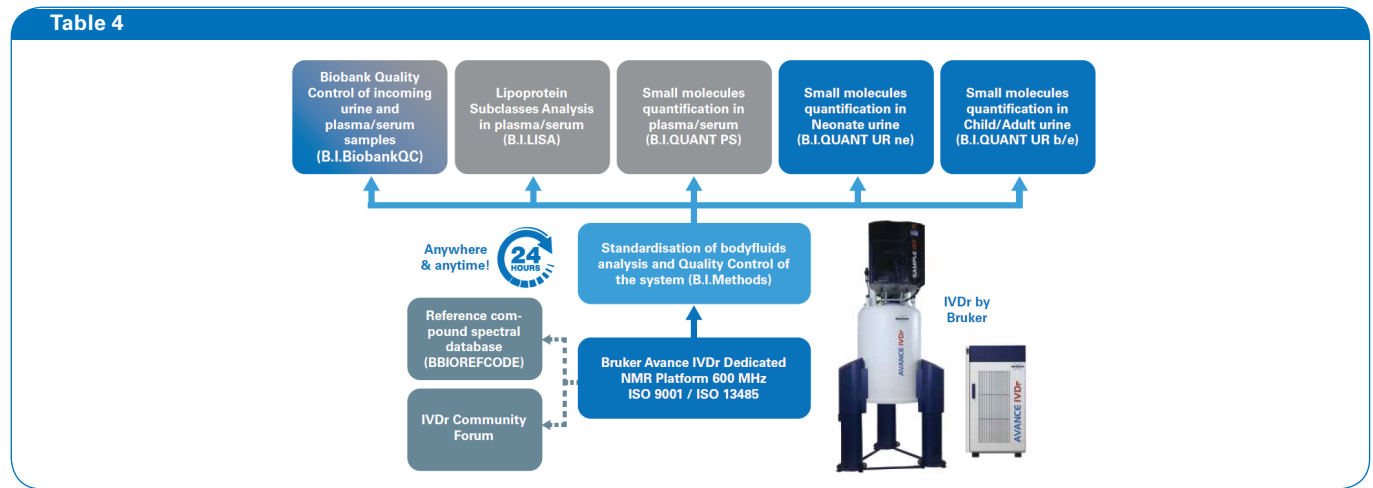


Table 4: Bruker IVDr Platform and embedded solutions

IVDr Platform quantification tools

Table 5

1 Alcohols and derivatives

Compound	Conc. [mmol/L]	LOD [mmol/L]	r	p	Δ	95% Range	Graphics
Etanol	< 0.10	0.10	0.000	0	0	3.355 - 0.82	

2 Amines and derivatives

Compound	Conc. [mmol/L]	LOD [mmol/L]	r	p	Δ	95% Range	Graphics
Trimethylamine N-oxide	2.5	0.08	2.535	100	0.005	< 0.00	

3 Amino acids and derivatives

Compound	Conc. [mmol/L]	LOD [mmol/L]	r	p	Δ	95% Range	Graphics
S-Aminobutyric acid	< 0.05	0.05	0.000	0	0.348	< 0.10	
Alanine	< 0.05	0.05	0.000	0	4.571	< 0.08	
Asparagine	< 0.01	0.01	0.004	98	0.005	< 0.07	
Creatinine	< 0.11	0.01	0.105	98	0.005	0.05 - 0.14	

4 Amino acids and derivatives

Compound	Conc. [mmol/L]	LOD [mmol/L]	r	p	Δ	95% Range	Graphics
S-Methylthioacetate	< 0.01	0.01	0.000	0	0.10	< 0.05	
D-Fenylglycine	< 0.04	0.04	0.000	0	0.08	< 0.05	
S-Aminobutyric acid	< 0.05	0.05	0.000	0	0.348	< 0.10	
S-Methylthiothioacetate	< 0.02	0.02	0.000	0	0.20	< 0.05	
S-Aminopropionic acid	< 0.06	0.06	0.000	0	0.12	< 0.05	
Alanine	0.24	250	10	11	72	< 0.02	
Arginine	< 0.02	0.02	0.000	0	0.08	< 0.05	
Argininosuccinic acid	< 0.03	0.03	0.000	0	0.08	< 0.05	
Asparagine	< 0.01	0.01	0.004	98	0.005	< 0.07	
Citrulline	< 0.06	0.06	0.000	0	0.12	< 0.05	
Cysteine	< 0.05	0.05	0.000	0	0.12	< 0.05	
DL-Alloisoleucine	< 0.05	0.05	0.000	0	0.12	< 0.05	
DL-Tyrosine	< 0.04	0.04	0.000	0	0.08	< 0.05	
Glutamic acid	< 0.44	0.44	0.000	0	0.88	< 0.10	
Glutamine	< 0.42	0.42	0.000	0	0.84	< 0.10	
Glycine	0.72	750	34	38	440	< 0.02	
Guanidinoacetic acid	2.2	2300	100	140	< 0.02	< 0.02	
L-Carnitine	< 0.12	0.12	0.000	0	0.24	< 0.05	
L-Homocysteine	< 0.08	0.08	0.000	0	0.16	< 0.05	
L-Isoleucine	< 0.01	0.01	0.000	0	0.02	< 0.05	
L-Phenylalanine	< 0.11	0.11	0.000	0	0.22	< 0.05	
L-Tyrosine	< 0.09	0.09	0.000	0	0.18	< 0.05	
Methionine	< 0.05	0.05	0.000	0	0.10	< 0.05	
N,N-Dimethylglycine	< 0.06	0.06	0.000	0	0.12	< 0.05	
N-Acetylaspartic acid	< 0.10	0.10	0.000	0	0.20	< 0.05	
N-Acetylglutamate	< 0.04	0.04	0.000	0	0.08	< 0.05	
N-Acetylglutamine	< 0.13	0.13	0.000	0	0.26	< 0.05	
N-Acetylphenylalanine	< 0.02	0.02	0.000	0	0.04	< 0.05	
N-Acetylserine	< 0.03	0.03	0.000	0	0.06	< 0.05	
N-Acetylthreonine	< 0.03	0.03	0.000	0	0.06	< 0.05	
Phenylalanine	< 0.19	0.19	0.000	0	0.38	< 0.05	
Proline	< 0.01	0.01	0.000	0	0.02	< 0.05	
Protein-ketone	< 0.01	0.01	0.000	0	0.02	< 0.05	
Pyroglutamic acid	< 0.01	0.01	0.000	0	0.02	< 0.05	
Sarcosine	< 0.01	0.01	0.000	0	0.02	< 0.05	
Threonine	< 0.02	0.02	0.000	0	0.04	< 0.05	
Tyrosine	< 0.14	0.14	0.000	0	0.28	< 0.05	
Valine	< 0.02	0.02	0.000	0	0.04	< 0.05	

5 Benzene and substituted derivatives

Compound	Conc. [mmol/L]	LOD [mmol/L]	r	p	Δ	95% Range	Graphics
S-Hydroxyphenylacetic acid	< 0.05	0.05	0.000	0	0.10	< 0.05	
S-Phenylacetic acid	< 0.09	0.09	0.000	0	0.18	< 0.05	
S-Aminopropionic acid	< 0.26	0.26	0.000	0	0.52	< 0.05	
S-Ethylmalonic acid	< 0.01	0.01	0.000	0	0.02	< 0.05	
S-Hydroxybutyric acid	< 0.03	0.03	0.000	0	0.06	< 0.05	
S-Hydroxyphenylacetic acid	< 0.02	0.02	0.000	0	0.04	< 0.05	
Benzoic acid	0.04	42	14	14	< 0.02	< 0.02	
D-Malic acid	0.02	25	8	8	< 0.02	< 0.02	
Hydroxy acid	< 0.04	0.04	0.000	0	0.08	< 0.05	
Phenylacetic acid	< 0.07	0.07	0.000	0	0.14	< 0.05	
Phenylpyruvic acid	< 0.09	0.09	0.000	0	0.18	< 0.05	
Pyruvic acid	< 0.17	0.17	0.000	0	0.34	< 0.05	
Synvalic acid	< 0.04	0.04	0.000	0	0.08	< 0.05	

6 Carboxylic acids

Compound	Conc. [mmol/L]	LOD [mmol/L]	r	p	Δ	95% Range	Graphics
S-Aminovaleric acid	< 0.02	0.02	0.000	0	0.04	< 0.05	
Acetic acid	0.03	32	5	5	< 0.02	< 0.02	
Citric acid	0.58	600	330	330	< 0.02	< 0.02	
E-Glutaric acid	< 0.04	0.04	0.000	0	0.08	< 0.05	
Ethylmalonic acid	< 0.03	0.03	0.000	0	0.06	< 0.05	
Fumaric acid	0.04	42	14	14	< 0.02	< 0.02	
Formic acid	< 0.01	0.01	0.000	0	0.02	< 0.05	
Glutaric acid	< 0.16	0.16	0.000	0	0.32	< 0.05	
Isobutyric acid	< 0.05	0.05	0.000	0	0.10	< 0.05	
Lactic acid	0.16	170	140	140	< 0.02	< 0.02	
Malic acid	0.01	6	2	2	< 0.02	< 0.02	
Methylmalonic acid	< 0.02	0.02	0.000	0	0.04	< 0.05	
Pyruvic acid	< 0.01	0.01	0.000	0	0.02	< 0.05	
Succinic acid	0.03	32	5	5	< 0.02	< 0.02	
Tartaric acid	< 0.01	0.01	0.000	0	0.02	< 0.05	
Triglycolic acid	< 0.03	0.03	0.000	0	0.06	< 0.05	
Nonanoic acid	< 0.02	0.02	0.000	0	0.04	< 0.05	

Selected lipoprotein parameters plasma/serum

Key	Parameter	Value	Unit	95% Range of Model	Graphics
LDL	LDL-1	7	mg/dL	3 - 14	
LDL	LDL-2	3	mg/dL	1 - 6	
LDL	LDL-3	3	mg/dL	1 - 6	
LDL	LDL-4	3	mg/dL	1 - 6	
LDL	LDL-5	3	mg/dL	1 - 6	
LDL	LDL-6	3	mg/dL	1 - 6	

Selected small molecule metabolites

Key	Parameter	Value	Unit	95% Range of Model	Graphics
CHOL	CHOL-1	13	mg/dL	8 - 20	
CHOL	CHOL-2	13	mg/dL	2 - 48	
CHOL	CHOL-3	17	mg/dL	3 - 46	
CHOL	CHOL-4	18	mg/dL	4 - 49	
CHOL	CHOL-5	13	mg/dL	5 - 49	
CHOL	CHOL-6	13	mg/dL	6 - 54	

Table 5: Extract of the packages for plasma/serum and urine