

# 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 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 Contamination Test	not passed	●
Matrix Contamination Test	not passed	●	Medication Test	passed	●
			Protein Background Test	passed	●
			Further Indicative Parameter Test	not passed	●

Table1 : Extract of the summary page of the B.I.BioBankQC-PS and B.I.BioBankQC-UR analysis report



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Table2 : 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"> <li>TSP</li> <li>Protein background intensity</li> <li>Alanine shift position</li> </ul>	<ul style="list-style-type: none"> <li>TSP</li> </ul>
Check NMR analysis	<ul style="list-style-type: none"> <li>Shim performance</li> <li>Baseline</li> </ul>	<ul style="list-style-type: none"> <li>Shim performance</li> <li>Baseline</li> </ul>
Validate Matrix Identity	<ul style="list-style-type: none"> <li>EDTA plasma</li> <li>Citrate plasma</li> <li>Serum</li> </ul>	<ul style="list-style-type: none"> <li>Urine</li> </ul>
Validate Matrix Integrity	<ul style="list-style-type: none"> <li>Degradation</li> <li>Matrix composition out of model reference ranges</li> </ul>	<ul style="list-style-type: none"> <li>Degradation</li> <li>Matrix composition out of model reference ranges</li> </ul>
Check Matrix Contamination	<ul style="list-style-type: none"> <li>Cleaning agents</li> <li>Desinfection material</li> </ul>	<ul style="list-style-type: none"> <li>Propylene glycol</li> <li>Isopropanol</li> </ul>
Check most frequent medication		<ul style="list-style-type: none"> <li>Drugs</li> <li>Drugs metabolites</li> </ul>
Check Protein background		<ul style="list-style-type: none"> <li>Protein concentration beyond reference range</li> </ul>
Check further parameter		<ul style="list-style-type: none"> <li>Fasting/non-fasting state</li> </ul>

Table3: 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.

## 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

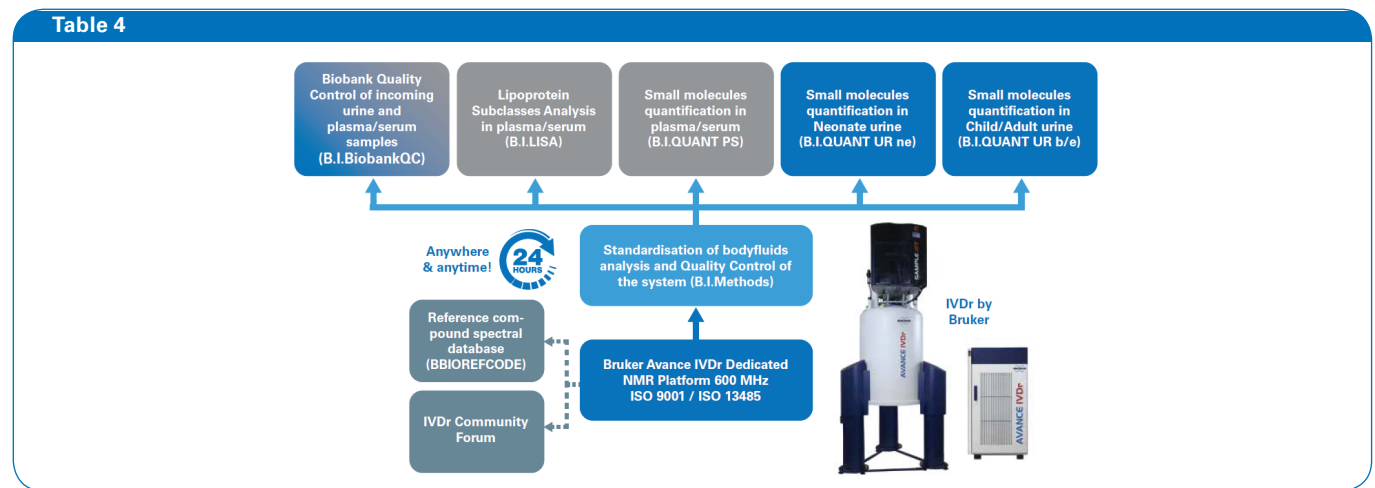


Table 4: Bruker IVDr Platform and embedded solutions

## IVDr Platform quantification tools

**Table 5**

**1 Alcohols and derivatives**

Compound	Conc. [mmol/L]	LOD [mmol/L]	r	p	Δ	95% Range	Graphics
Ethanol	< 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	0.006	< 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	66	0.005	< 0.07	
Creatinine	< 0.11	0.01	0.105	98	0.005	0.06 - 0.14	

**4 Amino acids and derivatives**

Compound	Conc. [mmol/L]	LOD [mmol/L]	r	p	Δ	95% Range	Graphics
3-Methylcrotonic acid	< 0.01	0.01	0.000	0	0.10	< 0.10	
β-Phenylglycine	< 0.04	0.04	0.000	0	0.10	< 0.10	
γ-Aminobutyric acid	< 0.08	0.08	0.000	0	0.10	< 0.10	
β-Aminobutyric acid	< 0.02	0.02	0.000	0	0.10	< 0.10	
α-Aminopropionic acid	< 0.06	0.06	0.000	0	0.10	< 0.10	
Alanine	0.24	250	10	11	72	< 0.10	
Arginine	< 0.72	750	750	750	750	< 0.10	
Argininosuccinic acid	< 0.03	0.03	0.000	0	0.10	< 0.10	
Aspartic acid	0.44	400	110	110	110	< 0.10	
Citrulline	< 0.66	660	660	660	660	< 0.10	
Cystine	< 0.66	660	660	660	660	< 0.10	
Cysteine	< 0.66	660	660	660	660	< 0.10	
DL-Alloisoleucine	< 0.05	0.05	0.000	0	0.10	< 0.10	
DL-Tyrosine	< 0.06	0.06	0.000	0	0.10	< 0.10	
Glutamic acid	< 0.44	440	440	440	440	< 0.10	
Glutamine	< 0.42	420	420	420	420	< 0.10	
Glycine	0.72	750	34	38	440	< 0.10	
Gamma-aminobutyric acid	2.2	2300	100	140	140	< 0.10	
Glutamic acid	< 0.12	120	120	120	120	< 0.10	
L-Carnitine	< 0.12	120	120	120	120	< 0.10	
L-Homocysteine	< 0.08	0.08	0.000	0	0.10	< 0.10	
L-Isoleucine	< 0.01	0.01	0.000	0	0.10	< 0.10	
Gamma-aminobutyric acid	< 0.12	120	120	120	120	< 0.10	
L-Tyrosine	< 0.09	0.09	0.000	0	0.10	< 0.10	
Leucine	< 0.03	0.03	0.000	0	0.10	< 0.10	
Methionine	< 0.05	0.05	0.000	0	0.10	< 0.10	
N,N-Dimethylglycine	< 0.06	0.06	0.000	0	0.10	< 0.10	
N-Acetylglycine	< 0.10	0.10	0.000	0	0.10	< 0.10	
N-Acetylglutamate	< 0.04	0.04	0.000	0	0.10	< 0.10	
N-Acetylphenylalanine	< 0.13	130	130	130	130	< 0.10	
N-Acetylserine	< 0.10	100	100	100	100	< 0.10	
N-Hydroxyglycine	0.00	0	0	0	0	< 0.10	
Phenylalanine	< 0.19	190	200	200	200	< 0.10	
Proline	< 0.03	0.03	0.000	0	0.10	< 0.10	
Protein-ketone	< 0.01	0.01	0.000	0	0.10	< 0.10	
Sarcosine	< 0.01	0.01	0.000	0	0.10	< 0.10	
Taurine	< 0.14	140	140	140	140	< 0.10	
Threonine	< 0.02	0.02	0.000	0	0.10	< 0.10	
Tyrosine	< 0.03	0.03	0.000	0	0.10	< 0.10	
Valine	< 0.03	0.03	0.000	0	0.10	< 0.10	

**5 Benzene and substituted derivatives**

Compound	Conc. [mmol/L]	LOD [mmol/L]	r	p	Δ	95% Range	Graphics
3-Hydroxyphenylacetic acid	< 0.05	0.05	0.000	0	0.10	< 0.10	
3-Phenylacetic acid	< 0.09	0.09	0.000	0	0.10	< 0.10	
4-Aminobenzoic acid	< 0.26	270	270	270	270	< 0.10	
4-Ethylphenol	< 0.01	0.01	0.000	0	0.10	< 0.10	
4-Hydroxyphenol	< 0.03	0.03	0.000	0	0.10	< 0.10	
4-Hydroxyphenylacetic acid	< 0.02	0.02	0.000	0	0.10	< 0.10	
4-Hydroxyphenylacetic acid	< 0.04	0.04	0.000	0	0.10	< 0.10	
Benzoic acid	0.04	42	14	14	14	< 0.10	
D-Mandelic acid	0.02	25	8	8	8	< 0.10	
Hypoxanthine	< 0.16	170	170	170	170	< 0.10	
Phenylacetic acid	< 0.07	72	72	72	72	< 0.10	
Phenylglyoxylic acid	< 0.09	90	90	90	90	< 0.10	
Pyruvic acid	< 0.17	170	170	170	170	< 0.10	
Synvalic acid	< 0.04	0.04	0.000	0	0.10	< 0.10	

**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	0.10	< 0.10	
Acetic acid	0.03	32	5	5	5	< 0.10	
Citric acid	0.58	600	330	330	330	< 0.10	
ε-Gluconic acid	< 0.04	0.04	0.000	0	0.10	< 0.10	
Ethylmalonic acid	< 0.03	0.03	0.000	0	0.10	< 0.10	
Fumaric acid	0.04	42	10	10	10	< 0.10	
Formic acid	< 0.01	0.01	0.000	0	0.10	< 0.10	
Glutaric acid	< 0.16	170	170	170	170	< 0.10	
Isobutyric acid	< 0.05	0.05	0.000	0	0.10	< 0.10	
Lactic acid	0.16	170	140	140	140	< 0.10	
Malic acid	0.01	6	2	2	2	< 0.10	
Methylmalonic acid	< 0.02	0.02	0.000	0	0.10	< 0.10	
Pyruvic acid	< 0.01	0.01	0.000	0	0.10	< 0.10	
Succinic acid	0.03	32	5	5	5	< 0.10	
Tartaric acid	0.01	6	2	2	2	< 0.10	
Triglycolic acid	< 0.03	0.03	0.000	0	0.10	< 0.10	
Nonanoic acid	< 0.02	0.02	0.000	0	0.10	< 0.10	

**Selected lipoprotein parameters plasma/serum**

Key	Parameter	Value	Unit	95% Range of Model	Graphics
LDL	LDL-1 Particle Number	214	nmol/L	36 - 367	
LDL	LDL-2 Particle Number	147	nmol/L	47 - 427	
LDL	LDL-3 Particle Number	386	nmol/L	51 - 499	
LDL	LDL-4 Particle Number	218	nmol/L	77 - 577	
LDL	LDL-5 Particle Number	165	nmol/L	66 - 615	
LDL	LDL-6 Particle Number	219	nmol/L	91 - 815	

**Selected small molecule metabolites**

**Tyrosine**

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