Newborn Screening

General:

Examination parameters: TSH-neonatal (hypothyreosis), 17-OH progesterone (AGS), galactose (galactosemia), galactose-uridyl transferase (galacto-semia), biotinidase (biotinidase deficiency), phenylalanine (PKU), amino acid screening (please note: not the full panel of amino acids is investigated), acylcarnitines (> 30 inherited disorders), G6PDH and immunoreactive trypsin (Cystic Fibrosis). Blood collection on the 3rd to 6th day.

Please note that a certain number of disorders are recognized well, whereas others show a questionable sensitivity. Summarizing all detectable and published reports about Newborn-Screening, we currently might discuss about 50 inherited metabolic disorders – however the pediatricians must be aware of the – sometimes low - sensitivities. A few selected and well detectable disorders are discussed below.

Method:	Tandem MS/MS, FIA, Photometry, Capillary Electrophoresis
Preanalytics:	collection between 36th hour and 3rd day after birth.
TAT:	5-7 days*
Note:	The possibility of 'Metabolic Screening' at any age has to be considered in specific disorders such as CPT II deficiency, MCAD deficiency and others. Please contact the laboratory.

The following tests are available:

- **TSH-neonatal**

General:

The innate (primary) hypothyroidism is a result of dysgenesis and affects 1 in 4,000 newborns. It occurs 3 times more frequently in girls than in boys. Early symptoms: drinking weakness, muscular hypotonia, icterus prolongatus, open small fontanel. Symptoms usually appear later, from 8-12th week: myxedema, blunt facial expression, macroglossia, wide open large fon-tanel, broad flat nose, scanty growth of hair, cool dry skin, constipation, muscular hypotonia, ubilical hernia, delayed psychomotor development. Substitution therapy is required.

- **17-OH progesterone**

General:

Hydroxyprogesterone is directly synthesized from progesterone or indirectly from 17α-OH-pregnelonone. As an intermediate product of glucocorticoids and sexual hormone pathway,

hydroxyprogesterone is accumulated in inherited enzyme deficiencies (hydroxylase deficiencies). Most common is the congenital adrenogenital syndrome (AGS) or congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency.

- **Galactose metabolism deficiency**

General:

inherited deficiency of galactose-1-phosphate uridyltransferase in erythrocytes, frequency 1:40,000.

Clinical symptoms: icterus, lethargy and vomiting, cataract formation from 1st to 12th month. Drinking weakness, prospering disturbance, dystrophy, cerebral damage possible. Prognosis without early diagnosis: most of the patients die in infancy. A galactose-free diet is required depending on residual enzyme activity.

Note:

Blood collection immediately after breast-feeding can result in increased galactose values. Further pathological laboratory values: bilirubinemia (direct), transaminases increased, hypoproteinemia. Galactose in urine is posi-tive as long as the baby is breastfed or fed with cow's milk. A lac-tose-free (galactose free: Lactose consists out of one molecule galactose and one molecule glucose) diet is required.

- **Phenylalanine (Phenylketonuria)**

General:

Possible reasons for hyperphenylalaninemia are: deficiencies of the phenylalanine-hydroxylase, disturbances in synthesis of tetrahydrobiopterin, temporary enzyme maturation disturbances. Frequency: 1:10,000.

Clinical symptoms: mostly after 6 months, psychomotor retardation and neurological symptoms occur. Psychomotor disability, lack of pigments (fair-haired and blue-eyed), aggressive behavior, muscular hypertonia, extrapyramidal symptoms, convulsions, and microcephaly point to PKU. Once symptoms occur, a healing therapy is not possible anymore. The disorder must be detected in the newborn. Dietic restriction of phenylalanine supply is required.

- **Biotinidase**

General:

The frequency is 1:60,000. First symptoms can be cramp attacks within the first 2 weeks. Prognosis without early therapy: mental retardation, lifelong biotin supply is required.

Clinical symptoms of biotinidase deficiency ("3 H-syndrome") appear after weeks or months: developmental retardation, hypotonia, ataxia, seborrhoic dermatitis, ceratoconjunctivitis, alopecia, candidiasis and occasional acidosis (metabolic acidosis; overlapped by respiratory alcalosis), cramps, laryngeal stridor, deafness.

- **Leucine**

General:

the amino acids leucine, isoleucine and valine are transformed into α-keto acids and then metabolized with vitamin B1 as cofactor. Deficiency of α-keto acids degrading enzymes leads to increase in the concentration of leucine, isoleucine and valine. Frequency: 1:200,000. Disorders and conditions are the “maple syrup disease”, leucine-isoleucinemia, a high protein supply or amino acid infusion as well as a postnatal adaption disturbance.

Symptoms: in the second week of life: drinking weakness, vomiting, lethargy, main symptom: urine smells like maple syrup, consciousness up to coma, muscle hypertonia and cramps. Prognosis without early therapy: death in infancy or severe brain damage. Leucine-isoleucine-valine-poor diets are required.

Disorder	**Method**	**Frequency**
I) Endocrine Disorders		
1. Hypothyreoidism (TSH)	Photometry	1: 4000
2. Adrenogenital Syndrome (17-OH Progesterone)	Photometry	1: 11000
II) Hemoglobinopathies		
3. HbS, beta-Thal, HbH etc.	CA	Depending on the country up to >1:10
III) Others		
4. G6PDH Deficiency	Photometry	Depending on the country: >1:10
5. Galactosemia	Photometry	1: 60000
6. Biotinidase Deficiency	Photometry	1: 75000
7. Cystic Fibrosis (Immuno Reactive Trypsin)	Photometry	1: 4000
IIIa) Disorders of Amino Acid Metabolism		
8. PKU (Phenylketonuria) Hyperphenylalaninemia	MS/MS	1:5.500

Disorder	Method	Frequency
9. Disorders of biopterin cofactors biosynthesis (Hyperphenylalaninemia)	MS/MS	1: 500000
10. Disorders of biopterin cofactors regeneration (Hyperphenylalaninemia)	MS/MS	1:250000
11. PBGS Deficiency (Porphobilinogen Synthase); (Tyrosinemia Type 1)	Photometry	<1: 100000
12. Tyrosinemia Type 2	MS/MS	Tyrosine levels may not be sufficiently elevated for detection!
Disorder	**Method**	**Frequency**
13. Tyrosinemia Type 3	MS/MS	Tyrosine levels may not be sufficiently elevated for detection!
14. Maple Sirup Disease (MSUD)	MS/MS	1:150000
15. Hypermethioninemia/ Homocystinuria	MS/MS	<1:100000
16. Arginase Deficiency	Ms/MS	n.a
17. Argininosuccinate Synthase Deficiency	MS/MS	n.a.
18. Argininosuccinate Lyase Deficiency	MS/MS	n.a.
IIIb) Urea Cycle Disorders		
19. Ornithine Aminotransferase Deficiency	MS/MS	The diagnosis in the neonatal presentation of OAT deficiency is difficult as hyperornithinaemia is absent
20. Citrullinemia Type I	MS/MS	1<100000

Disorder	Method	Frequency
21. Citrullinemia Type II (ASA)		1:150000
22. Argininemia	MS/MS	1:250000
IIIc) Fatty Acid Oxidation Disorders		
1. Carnitine uptake defect	MS/MS	1:50000
2. Long Chain 3-OH acyl CoA dehydrogenase deficiency (LCHAD)	MS/MS	1:50000 (see Trifunctional Protein deficiency!)
3. Medium Chain 3-OH acyl CoA dehydrogenase deficiency (MCAD)	MS/MS	1:11000
4. Trifunctional Protein Deficiency	MS/MS	See LCHAD!
5. Very long chain acyl CoA dehydrogenase deficiency	MS/MS	1:75000
6. Dienoyl reductase deficiency	MS/MS	1: 2000000
7. Carnitine Palmitoyl Transferase I deficiency	MS/MS	1:300000 May not be realiably detected in the first few days of life
8. Carnitine Palmitoyl Transferase Type II deficiency	MS/MS	1:250000 (detection as neonatal form is extremely rare)
9. Glutaric academia type II	MS/MS	1:250000
10. Medium/short chain 3-OH acyl CoA dehydrogenase deficiency	MS/MS	1:2000000
11. Medium chain ketoacyl CoA dehydrogenase deficiency	MS/MS	1:2000000
12. Short chain acyl-CoA dehydrogenase deficiency	MS/MS	1:30000

Disorder	Method	Frequency
13. Carnitine/acylcarnitine translocase deficiency	MS/MS	1:300000
IIId) Organic Acid Disorders		
14. Glutaric Aciduria Type I	MS/MS	1:100000
15. Methylmalonic acidemia (A,B)	MS/MS	1:100000
16. Methylmalonic academia (Mut)	MS/MS	1:40000 (combined with A,B)
17. 3-Methyl Crotonyl CoA carboxylase deficiency	MS/MS	1:50000
18. 3-Hydroxy 3-Methylglutaric aciduria	MS/MS	1:250000
19. Beta-Ketothiolase deficiency	MS/MS	1:300000
20. Multiple carboxylase deficiency	MS/MS	1:250000
21. Propionic acidemia	MS/MS	1:150000
22. 2-Methyl- 3- hydroxybutyric aciduria	MS/MS	1:1000000
23. 2-Methylbutyryl CoA dehydrogenase deficiency	MS/MS	<1:100000
24. 3-Methylglucaconic aciduria	MS/MS	1:100000
25. Isobutyryl CoA dehydrogenase deficieny	MS/MS	1:100000
26. Malonic aciduria	MS/MS	1:300000
27. Methylmalonic acidemia (Cbl, C,B)	MS/MS	1:100000

For complete list of laboratory test offered at Freiburg Medical Laboratory, please visit http://www.fml-dubai.com/parameter-listings/