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Routine Newborn Screening, Testing the Newborn
Inherited Metabolic Disorders
Update August 2015

Metabolic birth defects can cause physical problems, mental retardation and, in some cases, death. It is the best for the baby and the family if these conditions are detected and treated early. Freiburg Laboratory offers an expanded metabolic screening and can exclude many disorders in the newborn and also in older children (metabolic screen). The accreditation certificates of the single parameters are provided on request.

Please note that the Newborn Screening should be performed:

- **Only in highly standardized and accredited Laboratories!**
- **In units providing control by the Government as well as official Consensus Guidelines by a Paediatric Newborn Screening Commission. This can for example avoid detecting heterozygotes (healthy babies) as 'sick' by setting a reasonable cut-off.**
- **As a 'Screening'! Please note that the procedure does not differentiate between single disorders (for example 'neonatal or adult CPT II deficiency' etc.) therefore a simple listing of all disorders and their synonyms should not be confused with a specific exclusion of a specific disorder, especially if the detection can be missed in neonates.**

The most important timings in Newborn-Screening are:

1st) the early blood collection (preferably 36 hours after birth),

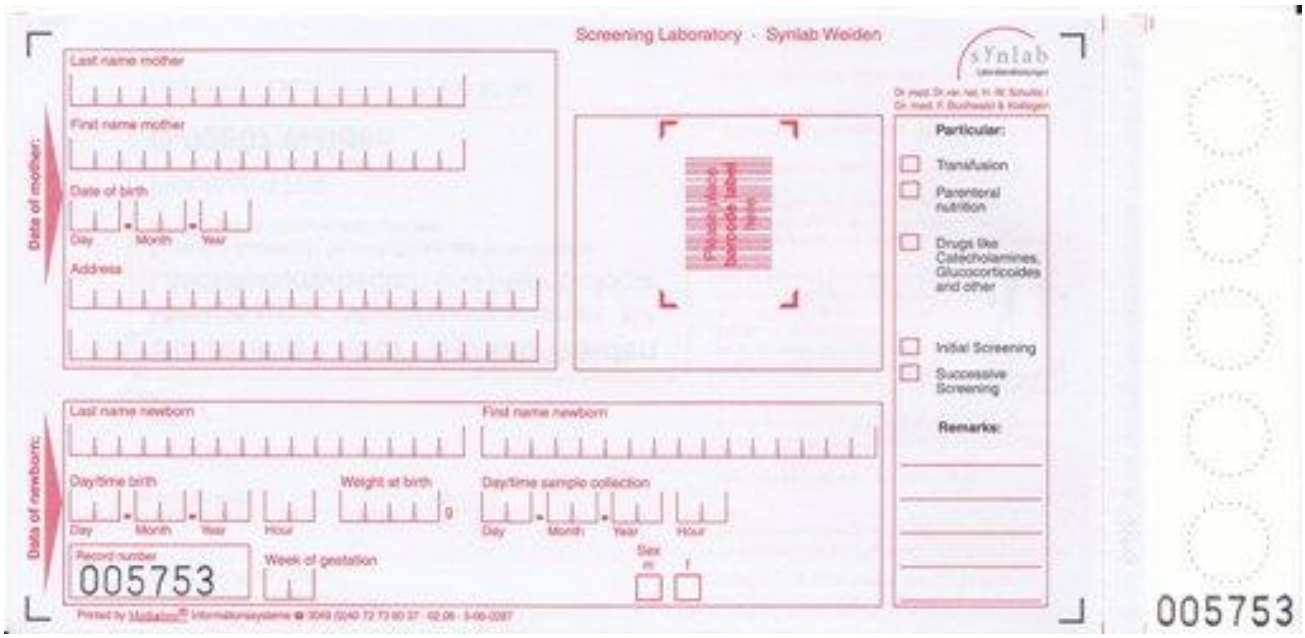
2nd) the fast delivery to the laboratory and

3rd) reasonable turnaround times!

The development of a new screening technique known as **tandem mass spectrometry** (often abbreviated as MS/MS) can detect the blood components that are elevated in certain disorders, and is capable of screening for inherited metabolic disorders with a single test such as phenylketonuria, maple syrup disease, homocystinuria, tyrosinaemia type I, MCAD deficiency, propionic acidaemia, glutaric aciduria type I, isovalerianic acidaemia and methylmalonic acidaemia and other more rare disorders. Furthermore the used method also detects aberrant amino acid concentrations. *See also the Table below*. The same filter-card is used to test other disorders such as hypothyroidism, biotinidase deficiency, galactosaemia, adrenogenital syndrome etc. by using other test methods such as photometry.

How is the screening done?

Special lancets are provided by Freiburg Medical Laboratory.



Capillary blood drops must be placed in the circles of the Filtercard

(provided by Freiburg Medical Laboratory).

The time of withdrawal is **2nd to 6th day of life (optimal is 36-72 hours after birth).**

Blood collection: Do not touch the filters. Collect capillary or venous blood (no EDTA or other additives!). Disinfect the skin (heel). Take a blood lancet (safety lancets will be provided), discard the first blood drop. Fill the filter circles starting at one side until the other side is filled as well. Let it **dry for 2-4 hours**.

Fill all **data** to the filter card such as day and hour of birth, day of withdrawal and others.

Transport and processing in Freiburg Medical lab

Send the filter card on the same day. Keep it separate and do not stick it to other filters or leave it in putative blood contaminated areas, such as laboratory desks. The turn-around-time (TAT) will be less than 7 days. There are only very few exceptional cases with a possible delay (e.g. EID, Christmas) however the German Newborn Screening Laboratory will work on week-ends as well.

Result, reporting and support

Freiburg Medical Laboratory will send you the final report in case of all parameters are unsuspicious. If there are irregular or positive results or suspicious single parameters the lab will immediately give report to the customers by phone or fax.

Freiburg Medical Laboratory offers a close Network with Metabolic Disease Centres in Germany if a special treatment is required.

What does the screening exclude?

See also:

American College of Medical Genetics. Newborn Screening: Toward a Uniform Screening Panel and System. Final Report, March 8, 2005. http://mchb.hrsa.gov/screening/

Rinaldo P et al. (2008) Newborn Screening of Metabolic Disorders: Recent Progress and Future Developments in Bier et al (eds): Personalized Nutrition for the Diverse Needs of Infants and Children
Karger AG, Basel

Disorder	Method	Frequency
I) Endocrine Disorders		
1. Hypothyroidism (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	Depdg. 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
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!
13. Tyrosinemia Type 3	MS/MS	Tyrosine levels may not be sufficiently elevated for detection!
14. Maple Syrup 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.

	Disorder	Method	Frequency
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
21.	Citrullinemia Type II (ASA)		1:150000
22.	Argininemia	MS/MS	1:250000
	IIIc) Fatty Acid Oxidation Disorders		
23.	Carnitine uptake defect	MS/MS	1:50000
24.	Long Chain 3-OH acyl CoA dehydrogenase deficiency (LCHAD)	MS/MS	1:50000 (see Trifunctional Protein deficiency!)
25.	Medium Chain 3-OH acyl CoA dehydrogenase deficiency (MCAD)	MS/MS	1:11000
26.	Trifunctional Protein Deficiency	MS/MS	See LCHAD!
27.	Very long chain acyl CoA dehydrogenase deficiency	MS/MS	1:75000
28.	Dienoyl reductase deficiency	MS/MS	1: 2000000
29.	Carnitine Palmitoyl Transferase I deficiency	MS/MS	1:300000 May not be realiably detected in the first few days of life
30.	Carnitine Palmitoyl Transferase Type II deficiency	MS/MS	1:250000 (detection as neonatal form is extremely rare)
31.	Glutaric acidemia type II	MS/MS	1:250000
32.	Medium/short chain 3-OH acyl CoA dehydrogenase deficiency	MS/MS	1:2000000
33.	Medium chain ketoacyl CoA dehydrogenase deficiency	MS/MS	1:2000000
34.	Short chain acyl-CoA dehydrogenase deficiency	MS/MS	1:30000
35.	Carnitine/acylcarnitine translocase deficiency	MS/MS	1:300000
	IIId) Organic Acid Disorders		
36.	Glutaric Aciduria Type I	MS/MS	1:100000
37.	Methylmalonic acidemia (A,B)	MS/MS	1:100000
38.	Methylmalonic acidemia (Mut)	MS/MS	1:40000 (combined with A,B)
39.	3-Methyl Crotonyl CoA carboxylase deficiency	MS/MS	1:50000
40.	3-Hydroxy 3-Methylglutaric aciduria	MS/MS	1:250000

	Disorder	Method	Frequency
41.	Beta-Ketothiolase deficiency	MS/MS	1:300000
42.	Multiple carboxylase deficiency	MS/MS	1:250000
43.	Propionic acidemia	MS/MS	1:150000
44.	2-Methyl- 3- hydroxybutyric aciduria	MS/MS	1:1000000
45.	2-Methylbutyryl CoA dehydrogenase deficiency	MS/MS	<1:100000
46.	3-Methylglucaconic aciduria	MS/MS	1:100000
47.	Isobutyryl CoA dehydrogenase deficieny	MS/MS	1:100000
48.	Malonic aciduria	MS/MS	1:300000
49.	Methylmalonic acidemia (Cbl, C,B)	MS/MS	1:100000

Description of some diseases, conditions and the available treatments

PKU (phenylketonuria): Babies with this disorder cannot process the amino acid phenylalanine which is found in most food. Without treatment, phenylalanine accumulates and causes brain damage and mental retardation. If PKU is detected early, mental retardation can be prevented by a special diet.

Analyte Measured: Aminoacid profiling by Tandem Mass Spectrometry.

Hypothyroidism: Babies with this disorder have a hormone deficiency that slows growth and brain development. If it is detected early, a baby can be treated with oral doses of the hormone to permit normal development. Most countries screen for hypothyroidism. **Analyte Measured:** TSH

Galactosemia: Babies with this disorder cannot convert galactose, a sugar present in milk into glucose, which is essential as energy source. Galactosemia can cause death in infancy, or blindness and mental retardation. The treatment for the condition is to eliminate milk and all other dairy products from the baby's diet.

Analyte Measured: Galactose and Enzyme activity (GALT).

Congenital adrenal hyperplasia (CAH): Babies who have this disorder are deficient in certain hormones. CAH affects genital development and, in severe cases, can disturb kidney function and cause death. Lifelong treatment with the missing hormones suppresses the disease.

Analyte Measured: 17-OH-Progesterone

Biotinidase deficiency: Babies with this condition do not have enough biotinidase, an enzyme that recycles biotin (one of the B vitamins) in the cell. The deficiency may cause seizures, poor muscle control, immune system impairment, hearing loss, mental retardation, coma, and even death. If the deficiency is detected in time, symptoms can be prevented by biotin.

Analyte Measured: Biotinidase Enzyme activity.

Homocystinuria: This metabolic disorder results from a deficiency of one of several enzymes for normal development. If untreated, it can lead to dislocated lenses of the eyes, mental retardation, skeletal abnormalities, and abnormal blood clotting. However, a special diet combined with dietary supplements may help prevent most of these problems.

Analyte Measured: Aminoacid profiling by Tandem Mass Spectrometry.

Maple syrup urine disease (MSUD): Babies with MSUD are missing an enzyme needed to process three amino acids that are essential for the body's normal growth. When these amino acids are not processed properly, they can accumulate and cause abnormal urine smell like maple syrup or sweet, burnt sugar. These babies usually have little appetite and are

extremely irritable. If not detected and treated early, MSUD can cause mental retardation, physical disability, and even death. A carefully controlled diet that avoids certain high-protein foods containing those amino acids can prevent the outcomes. Similar to patients with PKU, patients with MSUD are often treated by a formula that supplies the necessary nutrients.

Analyte Measured: Aminoacid profiling by Tandem Mass Spectrometry.

Tyrosinemia: Babies with this disorder have trouble processing the amino acid tyrosine. If it accumulates in the body, it can cause mild retardation, language skill difficulties, liver problems, and even death from liver failure. A special diet and sometimes a liver transplantation are needed to treat the condition. Early diagnosis and treatment seem to prevent long-term problems, however more information is needed. Some babies have a mild self limited form of tyrosinemia.

Analyte Measured: Aminoacid profiling by Tandem Mass Spectrometry.

Homocystinuria & Hypermethioninemia: Autosomal recessive amino acid disorder. A deficiency in cystathionine beta synthase enzyme activity causing the accumulation of the amino acid methionine in blood is found. Early detection and treatment can prevent associated mental retardation, seizures, motor development delays, weakening of bones, and venous and arterial blood clots. **Analyte Measured:** Aminoacid profiling by Tandem Mass Spectrometry.

Organic Acidemia Disorders (GA-1, PA, MMA, IVA, 3-MCC, MAD, HMG): Organic Acidemias (OA) are a class of inherited metabolic disorders that lead to accumulation of organic acids in biological fluids (blood and urine). This, in turn, produces disturbances in the acid-base balance and causes alterations in pathways of intermediary metabolism. Clinical

symptoms of OA disorders may include vomiting, metabolic acidosis, ketosis, dehydration or coma, hyperammonemia, lactic acidosis, hypoglycemia, failure to thrive, hypotonia, global developmental delay, sepsis, and hematological disorders. **Analyte Measured:** Acylcarnitine profiling by Tandem Mass Spectrometry.

Fatty Acid Oxidation Disorders (MCAD, VLCAD, LCHAD, CPT1, CPT2, CAT): Fatty Acid Oxidation Disorders (FOD) are a class of inborn errors of metabolism where there is an enzyme defect in the fatty acid metabolic pathway (use of dietary and stored fat). Clinical symptoms of FOD disorders include hypotonia, lethargy, and vomiting; the hypoglycemia can lead to coma, encephalopathy, hepatic failure, or death. **Analyte Measured:** Acylcarnitine profiling by Tandem Mass Spectrometry.

Argininosuccinic Acidemia (ASA): Autosomal recessive urea cycle disorder caused primarily by a deficiency in argininosuccinic acid (ASA) lyase enzyme activity. Clinical symptoms include lack of appetite, vomiting, hearing loss, seizures, and coma. NOTE: Newborn Screening can not differentiate ASA from Citrullinemia.

Analyte Measured: Aminoacid profiling by Tandem Mass Spectrometry.

Cystic Fibrosis: Newborns are screened for CF using a test called immunoreactive trypsin (IRT). Infants with CF may have elevated levels of IRT. Any false- positive elevations in IRT will usually fall to normal from day 21st onwards. Please note that the re-call rate is high (1:100). Sweat tests and reconfirmation of IRT on day 21 should be performed in such cases.**Analyte Measured:** Immunoreactive Trypsin.