Newborn screening: Test list
Disorders of galactose metabolism
1. Galactose-1-phosphate-uridytranspherase
deficiency* (Gal-1-P)
2. Galaktokinase deficiency* (Gal-Gal-1-P)
3. UDP-glucose-4-epimerase deficiency*
   (Gal-Gal-1-P)

Disorders of amino acid metabolism
(Tandem Mass Spectrometry/TMS: Aminosides)
4. Phenylketonuria/ Hyperphenylalaninemia
5. Maple syrup urine disease (MSUD)
6. Citrullinemia
7. Argininosuccinic aciduria
Organic acidoemias (TMS: acylcarnitines)
8. Propionic acidemia
9. Methylmalonic acidemia
10. Isovaleric acidemia
11. Glutaric acidemia type 1

Disorders of fatty acid oxidation
(TMS: acylcarnitines)
12. Medium-chain acyl-CoA dehydrogenase
   (MCAD) deficiency
13. Very long-chain acyl-CoA dehydrogenase
   (VLCAID) deficiency
14. Long-chain 3-hydroxyacyl-CoA dehydrogenase
   (LCHAD) deficiency
15. Multiple-acyl-CoA dehydrogenase (MADH)
   deficiency

Disorders of carnitine metabolism
(TMS: acylcarnitines)
16. Carnitine transporter deficiency
17. Carnitine palmityl transferase I deficiency
18. Carnitine palmityl transferase II deficiency
19. Carnitine translocase deficiency

Single Tests
23. Hypothyroidism (ELISA, quantitative: TSH)
24. Congenital adrenal hyperplasia
   (ELISA, quantitative: 17-OH-Progesterone)
25. Biotinidase deficiency (enzyme activity)
   * rare disorders which can only be detected if sufficient lactose
   has been ingested
Test: Inborn errors of metabolism to detect
- Congenital hypothyroidism
- Congenital adrenal hyperplasia
- Aminoacidopathies
- Organic acidaemias (or aciduria) including isovaleric acidemia and glutaric acidemia
- Disorders of fatty acid oxidation including medium-chain-acyl-CoA dehydrogenase (MCAD) deficiency
- Biotinidase deficiency
- Gaucher disease

Congenital hypothyroidism
Congenital hypothyroidism occurs sporadically, with an incidence of one in about 4,000 newborns; some familial cases have been described. Dyogenesis or ectopic position of the thyroid gland are common causes of the disease. Treatment is achieved by giving the necessary dose of thyroxine.

Congenital adrenal hyperplasia
A defect in the biosynthesis of cortisol leads to hyperplasia of the adrenal glands, resulting in an overproduction of androgens in a deficiency in mineralocorticoids. An acute salt wasting crisis which is lethal in many cases can result. Measurement of 17-Hydroxyprogesterone in term babies can detect this inborn error of steroid metabolism. Blood samples exceeding the cut off level of the immunoassay will be further analysed by tandem mass spectrometry to distinguish between true and false positive cases.

Aminoacidopathies
Disorders of amino acid metabolism are caused by inherited enzymatic defects in the relevant metabolic pathways. Phenylketonuria (PKU) is the most important one. Without early treatment it leads to severe mental retardation. During the first days and weeks of life these babies show no signs of disease. Diagnosis by clinical means alone is therefore insufficient.

Citrullinemia is a rare disorder of the urea cycle, resulting from argininosuccinate synthetase deficiency. In some cases, it presents as an overwhelming disease on the first days of life. In some other cases late onset of symptoms is observed. Neonatal screening will allow early diagnosis and treatment to prevent metabolic crisis and severe neurological defects at least in late onset cases.

By measuring a spectrum of amino acid concentrations in blood there is a chance to also detect very rare diseases like maple syrup urine disease.

Organic acidaemias (or aciduria)
Organic acidaemias present as acute or more chronic disorders, neonates presenting with seizures, metabolic acidosis or feeding problems and lethargy. The mainstay of long-term treatment consists of reduced intake of branched chain amino acids which lead to production of organic acids. Although it is not possible to detect all known organic acidaemias during the first days of life, there is a good chance to detect isovaleric acidemia and glutaric acidemia before clinical disease becomes obvious.

Disorders of fatty acid oxidation
Generation of energy from fat is necessary in situations of high metabolic turnover or when other sources of energy are failing which happens in fasting periods or during infectious diseases. The body uses fat mainly by stepwise degradation of long chain fatty acids to short chains via the so-called β-oxidation pathway, located in mitochondria. A large number of enzymes are involved, many of which may show inherited functional defects thus causing specific diseases. Not all of them produce detectable biochemical abnormalities, but some can be discovered rather easily by tandem mass spectrometry during the first days of life. The incidence of disorders of β-oxidation shows a great variability among populations and races. The defect of enzymatic degradation of medium chain fatty acids (MCAD-defect) however is the most important one. Although some of the children carrying this defect will never develop a clinical disease, others may die after acute metabolic decompensation. Therapy does not require any aggressive treatment. However, it is necessary to ensure sufficient carbohydrate intake at all times, especially at times of metabolic stress.

Biotinidase deficiency
Biotin, also called Vitamin H, is the functional group of four important enzymes. If biotinidase is lacking sufficient activity the body loses biotin via urine in form of biocytin; in addition, not all of the biotin contained in food can be absorbed. The resulting disease, which can be prevented easily by oral application of free biotin, is called late onset multiple carboxylase deficiency. The incidence is rather low. However, clinical diagnosis is very difficult though treatment is easily achieved and prevents severe (neurological) symptoms. Therefore, many screening laboratories have added the test to their programs.

Gaucher disease
Three different forms of galactosia are known. The incidence is about one in 40,000 newborns. In galactosia deficiency dietary treatment is proven to be more effective than enzyme replacement therapy. The latter is expensive and not always available in all countries. Therefore, dietary therapy is preferred in most centers. It is based on a low-galactose diet, which can be tolerated by most children. The diet is individualized by a dietitian or nutritionist and reviewed regularly. The mainstay of long-term treatment consists of reduced intake of galactose which lead to production of organic acids. Although it is not possible to detect all known organic acidaemias during the first days of life, there is a good chance to detect isovaleric acidemia and glutaric acidemia before clinical disease becomes obvious.

Table: Inborn errors of metabolism

<table>
<thead>
<tr>
<th>Analyte or procedure</th>
<th>Results</th>
<th>Normal range</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible Quality of blood card</td>
<td>good</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH)</td>
<td>unremarkable</td>
<td>&lt; 15</td>
<td>mIU/ml</td>
</tr>
<tr>
<td>17-OH-Progesterone</td>
<td>unremarkable</td>
<td>&lt; 0.02</td>
<td>nmol/l</td>
</tr>
<tr>
<td>Galactose (GAL, GAL-1-P)</td>
<td>unremarkable</td>
<td>&lt; 0.3</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Biotinidase</td>
<td>unremarkable</td>
<td>&gt; 50</td>
<td>Activity %</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>unremarkable</td>
<td>&lt; 3.0</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Spectrum and ratios of 7 amino acids</td>
<td>unremarkable</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spectrum and ratios of acylcarnitines</td>
<td>unremarkable</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The analysis did not give any indication of
- Congenital hypothyroidism (TSH)
- Congenital adrenal hyperplasia (17-OH-progesterone)
- Galectosia (GAL, GAL-1-P)
- profound biotinidase deficiency (Biotinidase)
- phenylketonuria, maple syrup urine disease or citrullinemia (amino acids: Phe, Tyr, Leu, Ileu, Val, Citi) = propionic-, isovaleric-, methylmalonic- or glutaric acidemia, or MCAD deficiency (acylcarnitines: carnitine and 32 acylcarnitines, tandem mass spectrometry)

It is important to bear in mind that neonatal screening will not reveal inborn errors of metabolism or endocrinopathies when biological processes or therapy keep analytes in vivo in a normal range. An exact medical examination is mandatory if any symptoms of such diseases occur. The results are valid only when the infant was at least 36 hours old and has not received any blood transfusion prior to blood collection. Please note that the cutoff for 17-OH-progesterone depends on gestational age and/or birth weight.