National

Screening Report 2005

DGNS

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Abbreviations:

CAH	Congenital adrenal hyperplasia
CACT- Deficiency	Carnitin-Acylcarnitin-Translocase-Deficiency
CPTI- Deficiency	Carnitin- Palmitoyl-CoA-Transferase I-Deficiency
CPTII- Deficiency	Carnitin- Palmitoyl-CoA-Transferase II-Deficiency
GA I	Glutaric acidemia type I
BW	Birth weight
HPA	Hyperphenylalaninemia
IVA	Isovaleric acidemia
LCHAD-Deficiency	Long-Chain-3-hydroxy-Acyl-CoA-Dehydrogenase-Deficiency
DoL	Day of life
GV 1 bis 3	guide value 1 - 3
MCAD-Deficiency	Medium-Chain-Acyl-CoA-Dehydrogenase-Deficiency
MSUD	Maple syrup urine disease
NBS	New born screening
SP	secondary parameter
PKU	Phenylketonuria
PPV	positivee predictive value
Recall	Recall due to abnormality
WoG	Week of gestation
VLCAD-Deficiency	Very-Long-Chain-Acyl-CoA-Dehydrogenase-Deficiency

1 Introduction

The newborn screening is a medical population based preventive measure with the aim of early and sufficient detection and high quality therapy of all newborns with treatable endocrine or metabolic diseases.

On 21.12.2004 the Federal Joint Committee (G-BA) changed the children's guidelines and cleared the way for financing the ambulant newborn screening from the 1.7.2005. In these guidelines the details of the screening process are outlined. The National Screening Report 2005 was provided by "Deutsche Gesellschaft für Neugeborenenscreening (DGNS)" on request of the screening laboratories. The statistical analysis was prepared according to the newly defined criterias for quality for the newborn screening in Germany. Only the targeted diseases, as defined in the new guidelines, inborn metabolic and endocrine defects, are referred to in this report. A comprehensive statistical summary of screening data, recall rates as well as confirmed diagnoses is presented. Additionally, data for process quality is shown.

Process quality describes the process flow and its evaluation through specialists according to defined indicators. These are the following for the newborn screening:

- Total Survey of the population
    - Collection method and rate
    - Blank card system
- Completeness of the control and the secondary testing
- Collection of test parameters and cut offs
- According to laboratory, age as well as gestational age, stratified rates of recall, positive predictive values and prevalence
- Specificity and sensitivity of diagnostic tests
- Process times (pre analytic and laboratory), age at blood collection, time between blood collections and arrival in the laboratory and until communication of results
- Screening values of newborns for which further testing is emphasized
- Diagnostic for confirmation
    - Type of diagnostic
    - Time of diagnostic
- Final diagnosis
- Start of therapy

In chapter 2, laboratories are listed which have undertaken the screening in 2005 for Germany. From chapter 3 the laboratories are listed scrambled (see chapter 2). Referred to paragraphs are listed according to the altered children's guidelines from 21.12.2004 [1]. Tables are numbered corresponding to the chapters.

We thank all the laboratories for provision of their data. The data was checked for plausibility.

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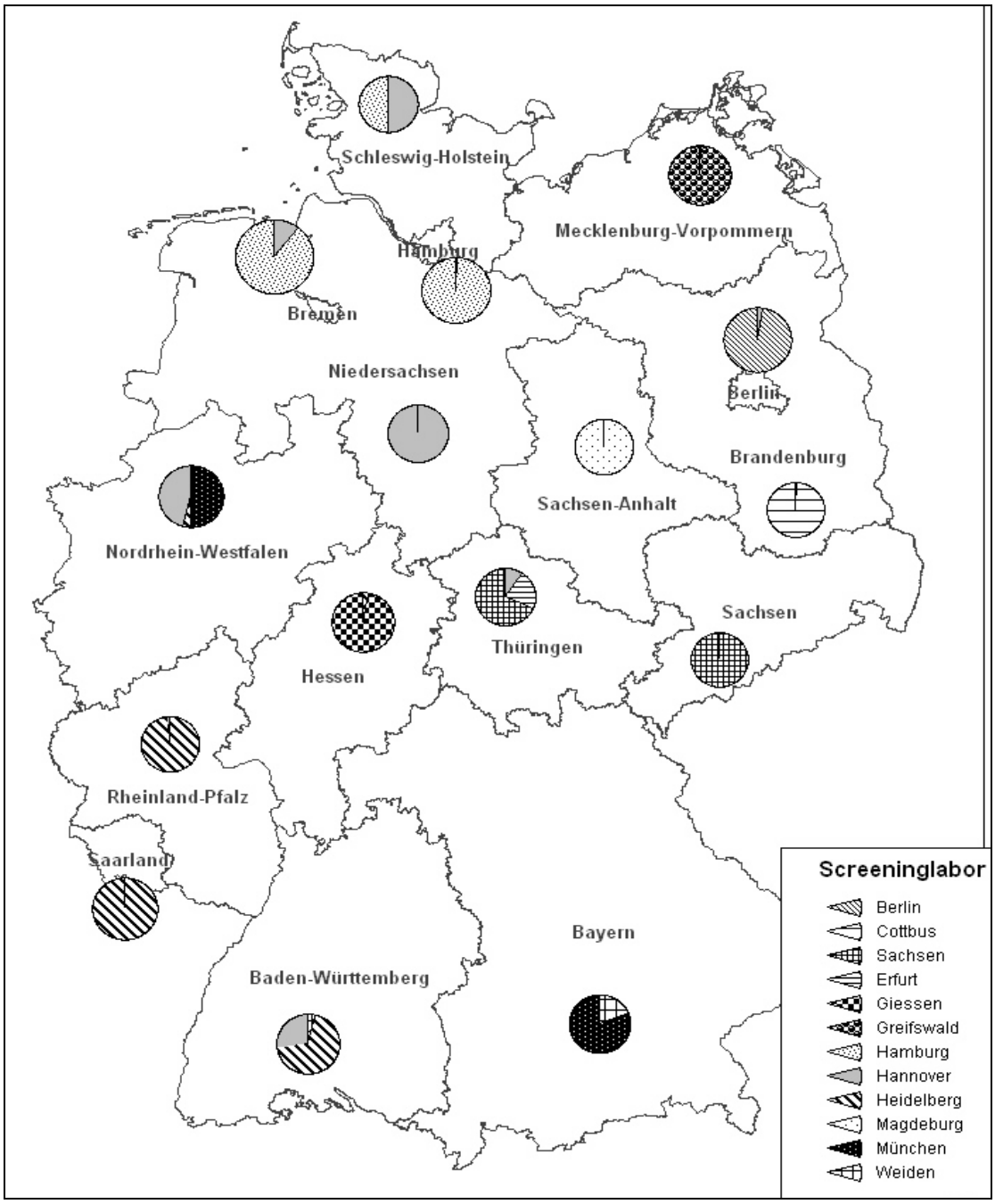
The screening samples of the federal states are spread to the laboratories according to Figure1. Newborn screening is not conducted in Erfurt as from 01.04.2005 and from Cottbus 01.01.2006

Figure 1: sample distribution according to state and laboratory



3 Results 2005

Births (2)	687.963
Primary screening	697.503
Confirmed diagnosis (see Table 3)	490

In the federal states of Baden-Württemberg, Berlin, Bremen, Nordrhein-Westfalen and Saarland the number of screened children out raised the number of newborns, because:

If a repeat screening is sent to a different laboratory than the primary screening, the receiving laboratory will record the test as a primary screening.

In some laboratories primary and repeat screening are not recorded separately.

A secure statement about the rate of participation in NBS can only be made by comparison of person related data of the population. By law this is only legal in the state of Bavaria.

Table 3. Absolute number of detected diseases found by screening

Disease	Confirmed cases	Prevalence
Hypothyroidism	187	1: 3.728
Congenital adrenal hyperplasia (CAH)	59	1: 11.822
BiotinidaseDeficiency	36	1: 19.375
Classic Galactosaemia	7	1: 99.643
Phenylketonurie (PKU)/ Hyperphenylalaninämie (HPA)	118	1: 5.911
Ahornsirupkrankheit (MSUD)	5	1: 139.501
Medium-Chain-Acyl-Coa-Dehydrogenase (MCAD)-Deficiency	54	1: 12.917
Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (LCHAD)-Deficiency	3	1: 232.501
(Very-)Long-Chain-Acyl-CoA-Dehydrogenase (VLCAD)-Deficiency	5	1: 139.501
Carnitin- Palmitoyl- CoA- Transferase I Deficiency (CPTI- Deficiency)	1	1: 697.503
Carnitin- Palmitoyl- CoA- Transferase II Deficiency (CPTII- Deficiency)	2	1: 348.752
Carnitin-Acylcarnitin-Translocase-Deficiency	0	
Glutaric acidemia type I (GA I)	6	1: 116.251
Isovaleric acidemia (IVA)	7	1: 99.643
Total	**490**	**1: 1.423**

3.1 Data of primary screening

According to the guidelines of children, every newborn should be screened before leaving the birth facility. A reliable screening can only be undertaken with blood sampling beyond the completed 32nd gestational week and 36th hour of life. A primary screening before the 36th hour of life or before the completed 32nd week of gestation should be followed by a repeat screening (Section 8 - paragraph 2,4). The following table shows the stratified results of the primary screening according to age and gestational age.

In Table 3.2 the repeat screenings are listed stratified according to their base of request. Repeat screening due to parental nutrition, blood transfusion or medication are not recorded.

Table 3.1 Age at primary screening

	Total	>=36h		<36h		<32WoG	
Laboratory	n	n	%	n	%	n	%
1	30.518	28.895	94,68	1.252	4,10	371	1,22
2	15.231	14.752	96,86	302	1,98	177	1,16
3	44.927	43.305	96,39	1.180	2,63	442	0,98
4	3.559	3.506	98,51	33	0,93	20	0,56
5	53.481	52.768	98,67	558	1,04	155	0,29
6	12.345	11.689	94,69	511	4,14	145	1,17
7	39.384	n.s.		n.s.		n.s.	
8	179.304	154.873	86,37	2.587	1,44	1.953	1,09
9	112.064	109.480	97,69	1.256	1,12	1.328	1,19
11	16.972	16.311	96,11	474	2,79	187	1,10
12	171.120	168.676	98,57	2.062	1,21	n.s.	
14	18.598	18.098	97,31	304	1,63	196	1,05
Total	**697.503**	**622.353**	**94,57**	**10.519**	**1,60**	**4.974**	**1,02**

*****Laboratory cannot completely differentiate the timing of blood collection according to age and gestational age and therefore data is not considered for percentage calculation but included in the total

3.2 Data on repeat screening

Table 3.2 base of request of repeat screenings

Laboratory	Total	Recall	primary screening < 36 h	primary screening < 32 WoG
1	1.980	333	1.191	302
2	633	355	n.s.	n.s.
3	2.410	250	1.353	530
4	129	41	33	20
5	2.458	452	421	n.s.
6	641	206	349	131
7*	765	765	n.s.	n.s.
8*	10.183	2.820	n.s.	n.s.
9	2.315	532	907	951
11	665	24	419	134
12*	4.440	1.971	1.987	n.s.
14	685	200	287	182
Total	**27.304**	**7.949**	**6.947**	**2.250**

*Laboratory cannot differentiate age or gestational age at sampling nor the indication for repeat screening, therefore the sum (recall+<36h + <32WoG) does not equal the total of secondary screening.

- **„<32WoG“**: all sample of newborns before 32 WoG, independent of age and result of primary screening
- **„<36h“**: all sample of newborns beyond 32 WoG, but age less than 36h, independent of the result of primary screening
- **Recall**: essential repeat testing due to suspicious primary screening at a gestational age > 32 WoG and age > 36h

3.3 Received and registered blank cards by the laboratory

As stated in section 9 paragraph 6 the Obstetric Units should document on a blank test card if a screening was denied or the newborn was deceased. This test card should be sent to the laboratory.

In 2005 only 6 laboratories received blank testcards, but subtotal. 1300 cards should have been received from children deceased within the first 3 days of life (2). Only 62 were received (Table 3.3). Refusal of screening could be expected in about 1‰ (3) roughly corresponding to 690 blank cards, only 71 were received (Table 3.3).

Table 3.3 Laboratory received blank cards

Laboratory	deceased	Refusal of screening	Transfer to a different Unit	Early testing refused
	n	n	n	n
2				646
3	2	9	1.029	920
5	32	2		2187
6		18		198
9	14	33	16	215
11	14	9	699	353
Total	**62**	**71**	**1.744**	**4.519**

Laboratories who cannot provide data are not listed

3.4 Tracking of Completeness

The newborn screening is a measure of public health and should be received by all Germany-born children. To guarantee that the screening is offered to all newborns tracking of completeness is necessary. For children born in obstetric units, an alignment of the recorded birth number on the screening card with the recorded birth number of the sending unit would be possible, or if legally allowed, by comparing with data from the birth register. As shown in table 3.4 a tracking of completeness wasn't done nationwide.

Table 3.4 Totally screened children due to tracking

Laboratory	alignment by name from Birth Register	blank cards	Recorded birth number
	n	n	n
1		46	
2		5	
3		31	
5		2.000	
6		2	
11			34
12	67		
14	16		
Total	**83**	**2.084**	**34**

*Laboratories who cannot provide data are not listed

4 Recall Rate, Prevalence, Positive predictive value specificity

The excellence of a test is measured by the sensitivity, the specificity as well as the positive predictive value. In a screening, the sensitivity (true-test positives) but more the specificity (true-test negatives) should be high to avoid unnecessary worries and costs. A measure for the specificity in newborn screening is the recall rate. The smaller the recall rate the higher the specificity. The positive predictive value estimates the risk of disease with a positive test result. It depends on the prevalence of the targeted disease.

Table 4 outlines the epidemiologic data of all screened newborns independent of their age and gestational age. Due to the short period of observation and the consecutive unknown number of missed cases, sensitivity cannot be estimated. In the future, data on missed cases will be provided in cooperation with registers from the DGNS, the METAB-NET (Metabolism) and AQUAPE (Endokrinology).

Table 4: Specificity, PPV

Disease	Primary screening	Recall	Recall rate in%	Confirmed cases	PPV in %	specificity in %	false negative
Hypothyroidism	697.119	1.677	0,24	187	11,15	99,79	0
CAH	697.503	5.459	0,78	59	1,08	99,23	2
Biotinidase def.	697.503	200	0,03	36	18,00	99,98	0
Galactosaemia*	697.503	635	0,09	7	1,10	99,91	0
MS/MS	697.503	1931	0,28	201	10,41	99,75	0
Total	**697.503**	**9.902**	**1,42**	**490**	**4,95**	**98,65**	**2**

* only classic galactosaemia, variants are not considered

In case of suspicious screening the chance of disease can be estimated with help of the positive predictive value in relation to the prevalence of the targeted disease.

For hyperphenylalaninaemia including the PKU the PPV of newborns is 67,5% meaning that more than two thirds of recalled children are diseased. For MCAD deficiency more than a third, 34,6% and for hypothyroidism, less than a third (PPV = 29%) of suspected newborns are diseased.

Further, positive predictive values of term babies who were screened after the 36th hour of life are listed in Table 4a. These numbers are different from Table 4.

Table 4a: Recall PPV with a screening > 36 hours of life and >32 weeks of gestation

Disease	Primary screening	Recall	Recall-rate %	Confirmed cases	PPV %
Hypothyroidism	661.353	792	0,12	178	28,99
CAH	661.737	4.113	0,62	47	1,16
Biotinidase deficiency	661.737	187	0,03	34	22,22
Classic galactosaemia	661.737	629	0,10	7	1,13
MS/MS	661.737	1.790	0,27	192	12,02
Total	**661.737**	**7.511**	**1,14**	**458**	**6,49**

* only classic galactosaemia, variants are not considered

4.1 All targeted diseases

The recall rates for the following tables apply only to newborns screened after the 36th hour of life and beyond the 32nd gestational week, and differs from table 4.

The plausibility check allowed graduation in certain and likely positives. Implausible, open or ambiguous cases are not considered for analysis. The number of primary screening tests for hypothyroidism was slightly less since financing took place separately until 1.7.2007. Some hospitals split probes for TSH determination in their own laboratory.

Disease	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	certain positive	likely positive	Prevalence	false negative
Hypothyroidism	697.119	661.353	792	0,12	187	138	49	1: 3.728	0
CAH	697.503	661.737	4.113	0,62	59	45	14	1: 11.822	2
Biotinidase deficiency	697.503	661.737	187	0,03	36	33	3	1: 19.375	0
Classic Galactosaemia	697.503	661.737	629	0,10	7	7	0	1: 99.643	0
PKU/HPA**	518.199	506.864	211	0,03	118	102	16	1: 5.911	0
MSUD**	518.199	506.864	84	0,01	5	5	0	1: 139.501	0
MCAD**	518.199	506.864	140	0,02	54	45	9	1: 12.917	0
LCHAD**	518.199	506.864	32	0,00	3	3	0	1: 232.501	0
VLCAD**	518.199	506.864	231	0,03	5	3	2	1: 139.501	0
CPT I-Deficiency**	518.199	506.864	14	0,00	1	1	0	1: 697.503	0
CPT II-Deficiency**	518.199	506.864	25	0,00	2	1	1	1: 348.752	0
CAT-Deficiency**	518.199	506.864							
GA I**	518.199	506.864	151	0,02	6	6	0	1: 116.251	0
IVA**	518.199	506.864	124	0,02	7	7	0	1: 99.643	0
MS/MS**	179.304	154.873	778	0,50					
Total	**697.503**	**661.737**	**7.511**	**1,14**	**490**	**396**	**94**	**1: 1.423**	**2**

** Laboratory 8 recalled only for MS/MS total. The recall rate equates the sum of recall rates of the targeted diseases (MS/MS) of the remaining laboratories, see tab 4.2.5

4.1.1 Hypothyroidism

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	16	0,06	**8**	8		1: 3.815
2	15.231	14.752	13	0,09	**2**	1	1	1: 7.616
3	44.927	43.305	12	0,03	**8**	6	2	1: 5.616
4	3.175	3.122	6	0,19	**1**	1		1: 3.175
5	53.481	52.768	107	0,20	**15**	12	3	1: 3.565
6	12.345	11.689	10	0,09	**3**	2	1	1: 4.115
7	39.384	39.384	38	0,10	**10**	2	8	1: 3.938
8	179.304	154.873	336	0,22	**52**	37	15	1: 3.448
9	112.064	109.480	86	0,08	**41**	40	1	1: 2.733
11	16.972	16.311	8	0,05	**2**	2		1: 8.486
12	171.120	168.676	141	0,08	**42**	28	14	1: 4.074
14	18.598	18.098	19	0,10	**3**	3		1: 6.199
Total	**697.119**	**661.353**	**792**	**0,12**	**187**	**142**	**45**	**1: 3.728**

4.1.2 Congenital adrenal hyperplasia (CAH)

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	100	0,35	**1**	1		1: 30.518
2	15.231	14.752	185	1,25	**5**	5		1: 3.046
3	44.927	43.305	90	0,21	**5**	3	2	1: 8.985
4	3.559	3.506	15	0,43	**0**			
5	53.481	52.768	162	0,31	**3**	3		1: 17.827
6	12.345	11.689	134	1,15	**0**			
7	39.384	39.384	495	1,26	**5**	0	5	1: 7.877
8	179.304	154.873	846	0,55	**17**	16	1	1: 10.547
9	112.064	109.480	321	0,29	**7**	4.	3	1: 16.009
11	16.972	16.311	5	0,03	**0**			
12	171.120	168.676	1.624	0,96	**13**	10	3	1: 13.163
14	18.598	18.098	136	0,75	**3**	3		1: 6.199
Total	**697.503**	**661.737**	**4.113**	**0,62**	**59**	**45**	**14**	**1: 11.822**

4.1.3 Biotinidase deficiency

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	7	0,02	**1**	1		1: **30.518**
2	15.231	14.752	3	0,02	**0**			
3	44.927	43.305	9	0,02	**2**	2		1: **22.464**
4	3.559	3.506	8	0,23	**0**			
5	53.481	52.768	5	0,01	**1**	1		1: **53.481**
6	12.345	11.689	3	0,03	**0**			
7	39.384	39.384	17	0,04	**0**			
8	179.304	154.873	108	0,07	**27**	24	3	1: **6.641**
9	112.064	109.480	8	0,01	**3**	3		1: **37.355**
11	16.972	16.311	1	0,01	**0**			
12	171.120	168.676	17	0,01	**1**	1		1: **171.120**
14	18.598	18.098	1	0,01	**1**	1		1: **18.598**
Total	**697.503**	**661.737**	**187**	**0,03**	**36**	**33**	**3**	**1: 19.375**
Complete deficiency					**8**	**8**		**0 87.188**

4.1.4 Galactosaemia

Galactosaemia incl. variants

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	21	0,07	**8**	8		1: 3.815
2	15.231	14.752	40	0,27	**2**		2	1: 7.616
3	44.927	43.305	60	0,14	**3**	3		1: 14.976
4	3.559	3.506	6	0,17	**2**	2		1: 1.780
5	53.481	52.768	34	0,06	**3**	3		1: 17.827
6	12.345	11.689	7	0,06	**0**			
7	39.384	39.384	44	0,11	**10**	10		1: 3.938
8	179.304	154.873	319	0,21	**39**	10	29	1: 4.598
9*	112.064	109.480	25	0,02	**2**	2		1: 56.032
11	16.972	16.311	1	0,01	**0**			
12	171.120	168.676	52	0,03	**7**	5	2	1: 24.446
14	18.598	18.098	20	0,11	**1**		1	1: 18.598
Total	**697.503**	**661.737**	**629**	**0,10**	**77**	**43**	**34**	**1: 9.058**
Classic					**7**	**7**		**1: 99.643**

4.1.5 MS/MS MS/MS Total

Disease	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
MS/MS	697.503	661.737	1.790	0,27	**201**	173	28	1: 3470

4.1.5.1 PKU / HPA

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	30	0,10	**10**	10		1: 3.052
2	15.231	14.752	8	0,05	**1**	1		1: 15.231
3	44.927	43.305	26	0,06	**10**	9	1	1: 4.493
4	3.559	3.506	5	0,14	**0**			
5	53.481	52.768	36	0,07	**12**	11	1	1: 4.457
6	12.345	11.689	3	0,03	**1**		1	1: 12.345
7	39.384	39.384	19	0,05	**2**	2		1: 19.692
8**	179.304	154.873	n.s.	n.s.	**29**	17	12	1: 6.183
9	112.064	109.480	37	0,03	**19**	19		1: 5.898
11	16.972	16.311	0		**0**			
12	171.120	168.676	33	0,02	**28**	28		1: 6.111
14	18.598	18.098	14	0,08	**6**	5	1	1: 3.100
Total	**697.503**	**661.737**	**211**	**0,03**	**118**	**102**	**16**	**1: 5.911**
PKU					**56**	**8**	**8**	**1: 12.455**

** Laboratory declares recall rates only for MS/MS total

4.1.5.2 MSUD

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	18	0,06	**1**	1		1: 30.518
2	15.231	14.752	7	0,05	**0**			
3	44.927	43.305	4	0,01	**0**			
4	3.559	3.506	0		**0**			
5	53.481	52.768	17	0,03	**0**			
6	12.345	11.689	8	0,07	**0**			
7	39.384	39.384	15	0,04	**0**			
8**	179.304	154.873	n.s.	n.s.	**1**	1		1: 179.304
9	112.064	109.480	8	0,01	**3**	3		1: 37.355
11	16.972	16.311	2	0,01	**0**			
12	171.120	168.676	4	0,00	**0**			
14	18.598	18.098	1	0,01	**0**			
Total	**697.503**	**661.737**	**84**	**0,01**	**5**	**5**		**1: 139.501**
Classic					**2**			**1: 348.752**

** Laboratory declares recall rates only for MS/MS total

4.1.5.3 MCAD-Deficiency

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	24	0,08	**5**	5		1: 6.104
2	15.231	14.752	22	0,15	**0**			
3	44.927	43.305	12	0,03	**1**	1		1: 44.927
4	3.559	3.506	0	0,00	**0**			
5	53.481	52.768	28	0,05	**7**	6	1	1: 7.640
6	12.345	11.689	3	0,03	**1**	1		1: 12.345
7	39.384	39.384	13	0,03	**6**	2	4	1: 6.564
8**	179.304	154.873	n.s.	n.s.	**15**	13	2	1: 11.954
9	112.064	109.480	8	0,01	**6**	6		
11	16.972	16.311	2	0,01	**0**			
12	171.120	168.676	24	0,01	**12**	10	2	1: 14.260
14	18.598	18.098	4	0,02	**1**	1		1: 18.598
Total	**697.503**	**661.737**	**140**	**0,02**	**54**	**45**	**9**	**1: 12.917**

** Laboratory declares recall rates only for MS/MS total

4.1.5.4 LCHAD-Deficiency

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	4		**0**			
2	15.231	14.752	4		**0**			
3	44.927	43.305	6		**0**			
4	3.559	3.506	0		**0**			
5	53.481	52.768	7		**0**			
6	12.345	11.689	4		**0**			
7	39.384	39.384	0		**0**			
8**	179.304	154.873	n.s.	n.s.	**1**	1		1: 179.304
9	112.064	109.480	0		**0**			
11	16.972	16.311	1		**1**	1		1: 16.972
12	171.120	168.676	5		**1**	1		1: 171.120
14	18.598	18.098	1		**0**			
Total	**697.503**	**661.737**	**32**	**<0.01**	**3**	**3**		**1: 232.501**

** Laboratory declares recall rates only for MS/MS total

4.1.5.5 VLCAD-Deficiency

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	certain positive	likely positive	Prevalence
1	30.518	28.895	29	0,10	**0**			
2	15.231	14.752	14	0,09	**0**			
3	44.927	43.305	10	0,02	**1**		1	1: 44.927
4	3.559	3.506	0		**0**			
5	53.481	52.768	22	0,04	**0**			
6	12.345	11.689	3		**0**			
7	39.384	39.384	104	0,26	**0**			
8**	179.304	154.873	n.s.	n.s.	**2**	2		1: 89.652
9	112.064	109.480	26	0,02	**0**			
11	16.972	16.311	1		**0**			
12	171.120	168.676	19	0,01	**2**	1	1	1: 85.560
14	18.598	18.098	3		**0**			
Total	**697.503**	**661.737**	**231**	**0,03**	**5**	**3**	**2**	**1: 139.501**

** Laboratory declares recall rates only for MS/MS total

4.1.5.6 CPT I - Deficiency

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	2		**0**			
2	15.231	14.752	2		**0**			
3	44.927	43.305	1		**0**			
4	3.559	3.506	0		**0**			
5	53.481	52.768	2		**0**			
6	12.345	11.689	6		**0**			
7	39.384	39.384	0		**0**			
8**	179.304	154.873	n.s.	n.s.	**0**			
9	112.064	109.480	1		**1**	1		1: 112.064
11	16.972	16.311	0		**0**			
12	171.120	168.676	0		**0**			
14	18.598	18.098	0		**0**			
Total	**697.503**	**661.737**	**14**		**1**	**1**		**1: 697.503**

** Laboratory declares recall rates only for MS/MS total

4.1.5.7 CPT II - Deficiency

Laboratory	Primary screening	Primary screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	9		**0**			
2	15.231	14.752	3		**0**			
3	44.927	43.305	7		**0**			
4	3.559	3.506	0		**0**			
5	53.481	52.768	1		**0**			
6	12.345	11.689	3		**0**			
7	39.384	39.384	1		**0**			
8**	179.304	154.873	n.s.	n.s.	**2**	1	1	1: 89.652
9	112.064	109.480	0		**0**			
11	16.972	16.311	0		**0**			
12	171.120	168.676	1		**0**			
14	18.598	18.098	0		**0**			
Total	**697.503**	**661.737**	**25**		**2**	**1**	**1**	**1: 348.752**

** Laboratory declares recall rates only for MS/MS total

4.1.5.8 Glutaric acidaemia

Laboratory	Primary screening	P.screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	44	0,15	**0**			
2	15.231	14.752	26	0,18	**0**			
3	44.927	43.305	4	0,01	**0**			
4	3.559	3.506	0		**0**			
5	53.481	52.768	27	0,05	**0**			
6	12.345	11.689	21	0,18	**0**			
7	39.384	39.384	6	0,02	**0**			
8**	179.304	154.873	n.s.	n.s.	**1**	1		1: 179.304
9	112.064	109.480	9	0,01	**0**			
11	16.972	16.311	1	0,01	**0**			
12	171.120	168.676	13	0,01	**5**	5		1: 34.224
14	18.598	18.098	0	0,00	**0**			
Total	**697.503**	**661.737**	**151**	**0,02**	**6**	**6**		**1: 116.251**

** Laboratory declares recall rates only for MS/MS total

4.1.5.9 Isovaleric acidemia

Laboratory	Primary screening	P.screening >=36h	Recall >=36h	Recall-rate %	Confirmed cases	Certain positive	Likely positive	Prevalence
1	30.518	28.895	29	0,10	**1**	1		1: 30.518
2	15.231	14.752	28	0,19	**0**			
3	44.927	43.305	6	0,01	**0**			
4	3.559	3.506	1	0,03	**0**			
5	53.481	52.768	4	0,01	**1**	1		1: 53.481
6	12.345	11.689	1	0,01	**0**			
7	39.384	39.384	13	0,03	**1**	1		1: 39.384
8**	179.304	154.873	n.s.	n.s.	**2**	2		1: 89.652
9	112.064	109.480	2	0,00	**2**	2		1: 56.032
11	16.972	16.311	2	0,01	**0**			
12	171.120	168.676	37	0,02	**0**			
14	18.598	18.098	1	0,01	**0**			
Total	**697.503**	**661.737**	**124**	**0,02**	**7**	**7**		**1: 99.643**

** Laboratory declares recall rates only for MS/MS total

4.2 Recall rate stratified according to age of primary screening

The number of positives, especially false positive screening results and therefore the recall rate depends on age and gestational age. Earlier testing than the 36th hour of life and a gestational age of <32 weeks increase the risk of false negative and false positive results. Since this is different for the individual diseases we show the recall rate stratified to targeted disease and age / gestational age. For statistical reasons recall rates n<10 were not calculated.

4.2.1 Hypothyroidism

	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
Laboratory	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	16	28.895	0,06	35	1.252	2,8	1	371	
2	13	14.752	0,09	68	302	22,52	2	177	
3	12	43.305	0,03	56	1.180	4,75	4	442	
4	6	3.122		5	33		0	20	
5	107	52.768	0,2	2	558		0	155	
6	10	11.689	0,09	0	511		0	145	
7*	38	39.384	0,1						
8	336	154.873	0,22	370	2.587	14,3	11	1.953	0,56
9	86	109.480	0,08	13	1.256	1,04	7	1.328	
11	8	16.311		71	474	14,98	0	187	
12	141	168.676	0,08	124	2.062	6,01	4	*	
14	19	18.098	0,1	10	304	3,29	1	196	
Total	**792**	**661.353**	**0,12**	**754**	**10.519**	**7,17**	**30**	**4.974**	**0,60**

*Laboratory cannot differentiate age at sampling from their database

4.2.2 Congenital adrenal hyperplasia (CAH)

	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
Laboratory	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	100	28.895	0,35	20	1.252	1,6	25	371	6,74
2	185	14.752	1,25	136	302	45,03	20	177	11,3
3	90	43.305	0,21	26	1.180	2,2	89	442	20,14
4	15	3.506	0,43	6	33		1	20	
5	162	52.768	0,31	5	558		0	155	
6	134	11.689	1,15	0	511		0	145	
7*	495	39.384	1,26						
8	846	154.873	0,55	329	2.587	12,72	203	1.953	10,39
9	321	109.480	0,29	33	1.256	2,63	16	1.328	1,2
11	5	16.311		10	474	2,11	4	187	
12	1.624	168.676	0,96	90	2.062	4,36	195	*	
14	136	18.098	0,75	7	304		13	196	6,63
Total	**4.113**	**661.737**	**0,62**	**662**	**10.519**	**6,29**	**566**	**4.974**	**11,38**

* Laboratory cannot differentiate age at sampling from their database

4.2.3 Biotinidase deficiency

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	7	28.895		1	1.252		2	371	
2	3	14.752		0	302		0	177	
3	9	43.305		0	1.180		0	442	
4	8	3.506		0	33		0	20	
5	5	52.768		0	558		0	155	
6	3	11.689		0	511		0	145	
7*	17	39.384	0,04						
8	119	154.873	0,08	7	2.587		7	1.953	
9	8	109.480		0	1.256		1	1.328	
11	1	16.311		0	474		0	187	
12	17	168.676	0,01	0	2.062		2	*	
14	1	18.098		0	304		0	196	
Total	**198**	**661.737**	**0,03**	**8**	**10.519**		**12**	**4.974**	**0,24**

* Laboratory cannot differentiate age at sampling from their database

4.2.4 Galactosaemia

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	21	28.895	0,07	0	1.252		0	371	
2	40	14.752	0,27	0	302		0	177	
3	60	43.305	0,14	1	1.180		0	442	
4	6	3.506		0	33		0	20	
5	34	52.768	0,06	0	558		0	155	
6	7	11.689		0	511		0	145	
7*	44	39.384	0,11						
8	347	154.873	0,22	2	2.587		0	1.953	
9	25	109.480	0,02	3	1.256		0	1.328	
11	1	16.311		0	474		0	187	
12	52	168.676	0,03	0	2.062		0	*	
14	20	18.098	0,11	0	304		0	196	
Total	**657**	**661.737**	**0,10**	**6**	**10.519**		**0**	**4.974**	

* Laboratory cannot differentiate age at sampling from their database

4.2.5 MS/MS Total

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	189	28.895	0,65	13	1.252	1,04	26	371	7,01
2	114	14.752	0,77	0	302		14	177	7,91
3	76	43.305	0,18	13	1.180	1,1	17	442	3,85
4	6	3.506		0	33		2	20	
5	144	52.768	0,27	0	558		1	155	
6	52	11.689	0,44	0	511		0	145	
7*	171	39.384	0,43						
8	778	154.873	0,5	23	2.587	0,89	86	1.953	4,4
9	91	109.480	0,08	4	1.256		7	1.328	
11	9	16.311		0	474		3	187	
12	136	168.676	0,08	5	2.062		6	*	
14	24	18.098	0,13	2	304		0	196	
Total	**1.790**	**661.737**	**0,27**	**60**	**10.519**	**0,57**	**162**	**4.974**	**3,26**

* Laboratory cannot differentiate age at sampling from their database

For the following targeted diseases, totals cannot be calculated, since one laboratory did only deliver data for recall MS/MS total.

4.2.5.1 PKU/HPA

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	30	28.895	0,10	6	1252		6	371	
2	8	14.752		0	302		0	177	
3	26	43.305	0,06	4	1180		10	442	2,26
4	5	3.506		0	33		1	20	
5	36	52.768	0,07	0	558		1	155	
6	3	11.689		0	511		0	145	
7*	19	39.384	0,05						
9	37	109.480	0,03	4	1256		2	1328	
11	0	16.311		0	474		2	187	
12	33	168.676	0,02	1	2062		2	*	
14	14	18.098	0,08	0	304		0	196	

* Laboratory cannot differentiate age at sampling from their database
Laboratory 8 does not differentiate recall with MS/MS according to suspected diagnosis

4.2.5.2 MSUD

Lab-oratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall rate
1	18	28.895	0,06	1	1.252		0	371	
2	7	14.752		0	302		1	177	
3	4	43.305		1	1.180		0	442	
4	0	3.506		0	33		0	20	
5	17	52.768	0,03	0	558		0	155	
6	8	11.689		0	511		0	145	
7*	15	39.384	0,04						
9	8	109.480		0	1.256		2	1.328	
11	2	16.311		0	474		1	187	
12	4	168.676		0	2.062		0	*	
14	1	18.098		0	304		0	196	

* Laboratory cannot differentiate age at sampling from their database
Laboratory 8 does not differentiate recall with MS/MS according to suspected diagnosis

4.2.5.3 MCAD-Deficiency

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	24	28.895	0,08	0	1.252		0	371	
2	22	14.752	0,15	0	302		3	177	
3	12	43.305	0,03	0	1.180		0	442	
4	0	3.506		0	33		1	20	
5	28	52.768	0,05	0	558		0	155	
6	3	11.689		0	511		0	145	
7*	13	39.384	0,03						
9	8	109.480		0	1.256		0	1.328	
11	2	16.311		0	474		0	187	
12	24	168.676	0,01	0	2.062		1	*	
14	4	18.098		0	304		0	196	

* Laboratory cannot differentiate age at sampling from their database
Laboratory 8 does not differentiate recall with MS/MS according to suspected diagnosis

4.2.5.4 LCHAD-Deficiency

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	4	28.895		0	1.252		0	371	
2	4	14.752		0	302		0	177	
3	6	43.305		0	1.180		0	442	
4	0	3.506		0	33		0	20	
5	7	52.768		0	558		0	155	
6	4	11.689		0	511		0	145	
7*	0	39.384							
9	0	109.480		0	1.256		0	1328	
11	1	16.311		0	474		0	187	
12	5	168.676		0	2.062		0	*	
14	1	18.098		1	304		0	196	

* Laboratory cannot differentiate age at sampling from their database
Laboratory 8 does not differentiate recall with MS/MS according to suspected diagnosis

4.2.5.5 VLCAD-Deficiency

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	29	28.895	0,10	2	1.252		2	371	
2	14	14.752	0,09	0	302		2	177	
3	10	43.305	0,02	6	1.180		0	442	
4	0	3.506		0	33		0	20	
5	22	52.768	0,04	0	558		0	155	
6	3	11.689		0	511		0	145	
7*	104	39.384	0,26						
9	26	109.480	0,02	0	1.256		1	1.328	
11	1	16.311		0	474		0	187	
12	19	168.676	0,01	0	2.062		0	*	
14	3	18.098		1	304		0	196	

* Laboratory cannot differentiate age at sampling from their database
Laboratory 8 does not differentiate recall with MS/MS according to suspected diagnosis

4.2.5.6 CPT I-Deficiency

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	2	28.895		3	1.252		4	371	
2	2	14.752		0	302		2	177	
3	1	43.305		0	1.180		0	442	
4	0	3.506		0	33		0	20	
5	2	52.768		0	558		0	155	
6	6	11.689		0	511		0	145	
7*	0	39.384							
9	1	109.480		0	1.256		0	1.328	
11	0	16.311		0	474		0	187	
12	0	168.676		0	2.062		0	*	
14	0	18.098		0	304		0	196	

* Laboratory cannot differentiate age at sampling from their database
Laboratory 8 does not differentiate recall with MS/MS according to suspected diagnosis

4.2.5.7 CPT II-Deficiency

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	9	28.895		0	1.252		0	371	
2	3	14.752		0	302		1	177	
3	7	43.305		2	1.180		4	442	
4	0	3.506		0	33		0	20	
5	1	52.768		0	558		0	155	
6	3	11.689		0	511		0	145	
7*	1	39.384							
9	0	109.480		0	1.256		0	1.328	
11	0	16.311		0	474		0	187	
12	1	168.676		0	2.062		0	*	
14	0	18.098		0	304		0	196	

* Laboratory cannot differentiate age at sampling from their database
Laboratory 8 does not differentiate recall with MS/MS according to suspected diagnosis

4.2.5.8 Glutaric acidaemia type I

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	44	28895	,15	1	1252		0	371	
2	26	14752	,18	0	302		2	177	
3	4	43305		0	1180		0	442	
4	0	3506		0	33		0	20	
5	27	52768	,05	0	558		0	155	
6	21	11689	,18	0	511		0	145	
7*	6	39384							
9	9	109480		0	1256		1	1328	
11	1	16311		0	474		0	187	
12	13	168676	,01	1	2062		1	*	
14	0	18098		0	304		0	196	

* Laboratory cannot differentiate age at sampling from their database
Laboratory 8 does not differentiate recall with MS/MS according to suspected diagnosis

4.2.5.9 Isovaleric acidemia

Laboratory	Primary screening >=36hours			Primary screening <36hours			Primary screening <32WoG		
	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate	Recall	Primary screening	Recall-rate
1	29	28.895	0,10	0	1.252		14	371	3,77
2	28	14.752	0,19	0	302		3	177	
3	6	43.305		0	1.180		3	442	
4	1	3.506		0	33		0	20	
5	4	52.768		0	558		0	155	
6	1	11.689		0	511		0	145	
7*	13	39.384	0,03						
9	2	109.480		0	1.256		0	1.328	
11	2	16.311		0	474		0	187	
12	37	168.676	0,02	3	2.062		2	*	
14	1	18.098		0	304		0	196	

* Laboratory cannot differentiate age at sampling from their database
Laboratory 8 does not differentiate recall with MS/MS according to suspected diagnosis

5 Process periods

5.1 Period from birth to sampling

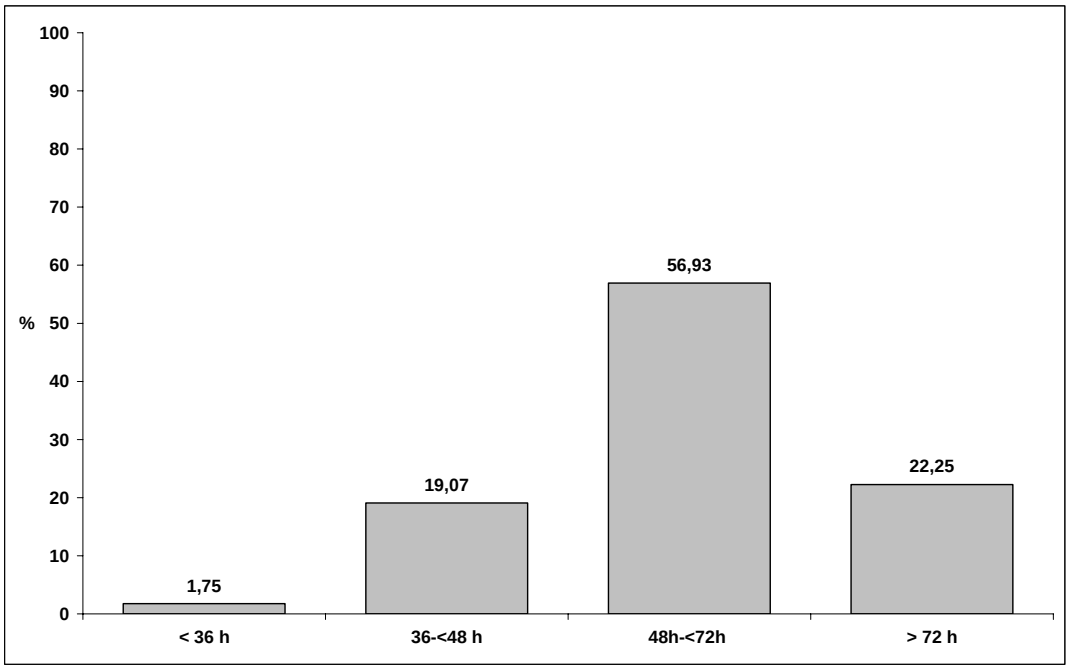
According to the screening guidelines (§8.1) blood should be sampled between the 36th and 72nd hour of life. In 76,5% of cases with declaration of sampling time the collection was according to the guidelines, in 22,2% (14,93-42%) beyond the 72nd hour, in 1,75% (0,96-4,26%) before the 36th hour of life (Tab.5.1 and Fig.2).

Table 5.1: Age at blood collection, primary screening

Laboratory*	Total	<36h		36h-<48h		48h-<72h		>72h	
	n	n	%	n	%	n	%	n	%
1	30.518	1.300	4,26	2.731	8,95	16.558	54,26	9.929	32,53
2	15.231	302	1,98	1.611	10,58	6.921	45,44	6.397	42,00
3	44.041	1.157	2,63	5.384	12,22	30.925	70,22	6.575	14,93
4	3.433	33	0,96	684	19,92	1.823	53,10	893	26,01
5	53.020	558	1,05	16.530	31,18	27.219	51,34	8.713	16,43
6	12.236	511	4,18	2.085	17,04	6.068	49,59	3.572	29,19
8	131.066	2.587	1,97	35.853	27,35	67.559	51,55	25.067	19,13
9	110.883	1.256	1,13	10.274	9,27	61.511	55,47	37.842	34,13
11	16.972	474	2,79	2.067	12,18	11.665	68,73	2.766	16,30
12	167.718	2.090	1,25	34.487	20,56	101.950	60,79	29.191	17,40
14	18.405	310	1,68	3.411	18,53	11.410	61,99	3.274	17,79
Total	**603.523**	**10.578**	**1,75**	**115.117**	**19,07**	**343.609**	**56,93**	**134.219**	**22,25**

* laboratories, who cannot differentiate process periods are not listed.
For all laboratories the number of probes with a time stamp is less than the total number of probes

Figure 2: Age at blood collection for primary screening



5.2 Period from sampling to laboratory receipt

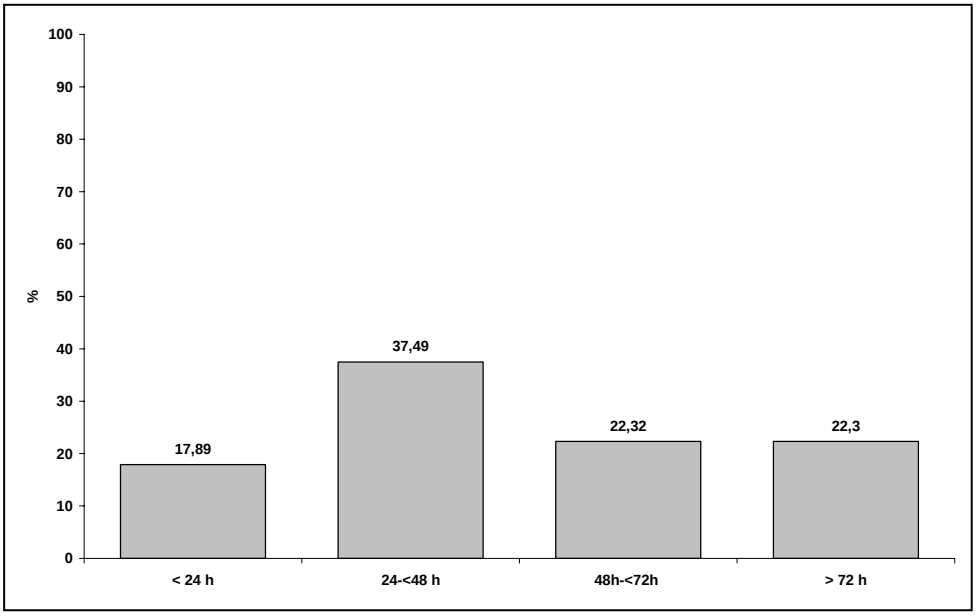
The time span between sampling and conveyance of suspect results should not exceed 72 hours (section 6, paragraph 3). In 22,3% (3,25-46,7%) of cases with statement of the delivery time the probe was received after 72 hours of sampling. In further 22,3% (10,2-46,8%) of the cases in a period between 48 and 72 hours. Shorter periods of delivery times are desirable, especially on the weekends.

Table 5.2: Period between sampling and laboratory receipt

Laboratory*	Total	<24h		24h-<48h		48h-<72h		>72h	
	n	n	%	n	%	n	%	n	%
1	30.518	13.324	43,66	10.463	34,28	4.269	13,99	2.462	8,07
2	15.227	788	5,18	2.003	13,15	7.125	46,79	5.311	34,88
3	44.041	5.001	11,36	18.128	41,16	11571	26,27	9.341	21,21
4	3.559	117	3,29	743	20,88	1.037	29,14	1.662	46,70
5	53.020	2.227	4,20	35.874	67,66	8.828	16,65	6.091	11,49
6	12.236	1.612	13,17	3.384	27,66	2.631	21,50	4.609	37,67
8	134.860	9.068	6,72	52.351	38,82	31.801	23,58	4.1640	30,88
9	110.868	6.804	6,14	32.844	29,62	28.879	26,05	42.341	38,19
11	16.972	1.465	8,63	7.603	44,80	4.689	27,63	3.215	18,94
12	167.925	59.245	35,28	58.901	35,08	32.377	19,28	17.402	10,36
14	13.907	8.238	59,24	3.798	27,31	1.419	10,20	452	3,25
Total	**603.133**	**107.889**	**17,89**	**226.092**	**37,49**	**134.626**	**22,32**	**134.526**	**22,30**

* Laboratories which cannot differentiate the progress are not listed.
The amount of probes with known time stamps are less than the total number of probes.

Figure 3: Period from sampling to laboratory receipt



5.3 Period between laboratory receipt and conveyance

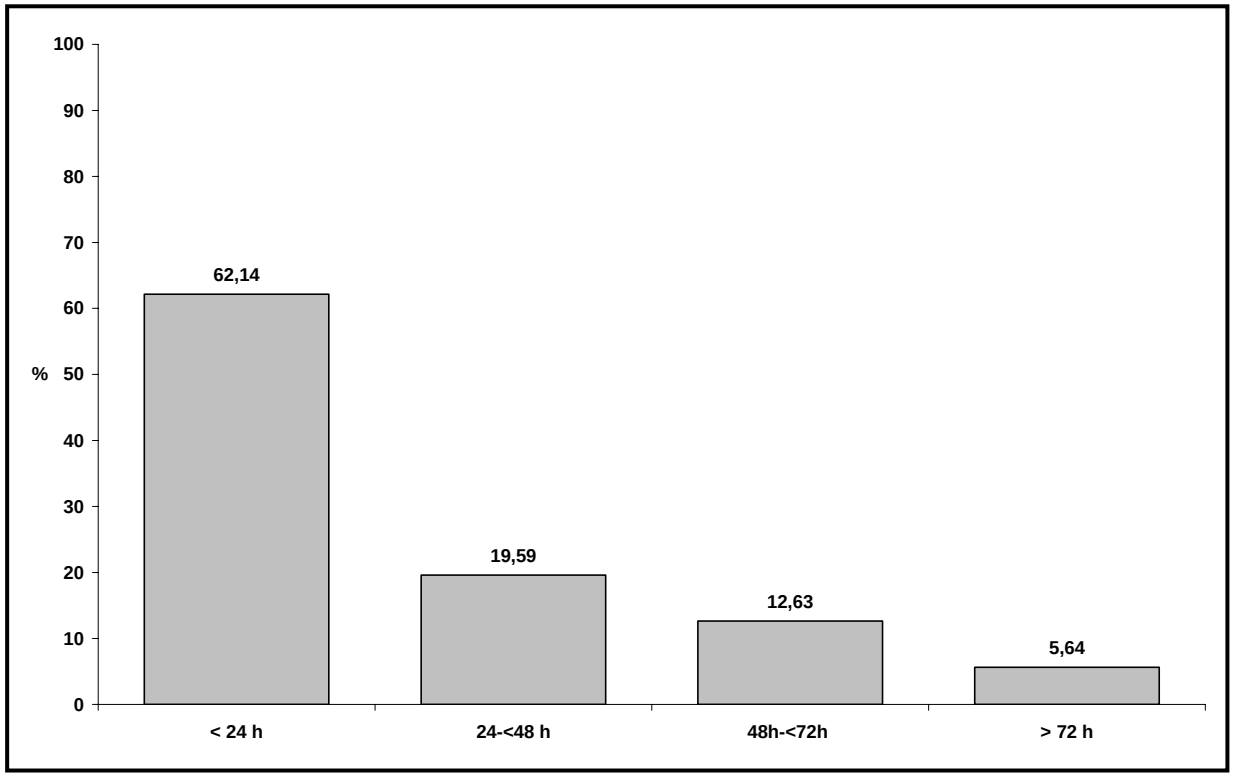
With pathological results it has to be assured that testing and reporting of probes is done on the day of laboratory receipt. (§14.3). Usually, this reporting is done via Telephone or Fax. Data made available by the laboratories does not indicate if the first telephone conveyance or the written report after internal repeat evaluation is analysed. Due to this, the listed periods are probably shorted than stated.

Table 5.3 Period between laboratory receipt and conveyance

Laboratory*	Total	<24h		24h-<48h		48h-<72h		>72h	
	n	n	%	n	%	n	%	n	%
1	30.518	13.667	44,78	14.008	45,90	2.108	6,91	735	2,41
3	44.086	30.932	70,16	8.747	19,84	3.695	8,38	712	1,62
4	3559	2	0,06	0		2.392	67,21	1.165	32,73
5	53.021	3.191	6,02	14.622	27,58	27.579	52,02	7.629	14,39
8	179.304	153.001	85,33	8.817	4,92	14.927	8,32	2.559	1,43
9	110.462	46.434	42,04	35.300	31,96	9.372	8,48	19.356	17,52
11	16.702	10.746	64,34	5.528	33,10	371	2,22	57	0,34
12	170.369	116.514	68,39	32.923	19,32	18.065	10,60	2.867	1,68
14	18.332	14.731	80,36	2.760	15,06	583	3,18	258	1,41
Total	**626.353**	**389.218**	**62,14**	**122.705**	**19,59**	**79.092**	**12,63**	**35.338**	**5,64**

- Laboratories which cannot differentiate the progress are not listed.
  The amount of probes with known time stamps are less than the total number of probes.

Figure 4: Period between laboratory receipt and conveyance



6 Time of screening in the confirmed cases

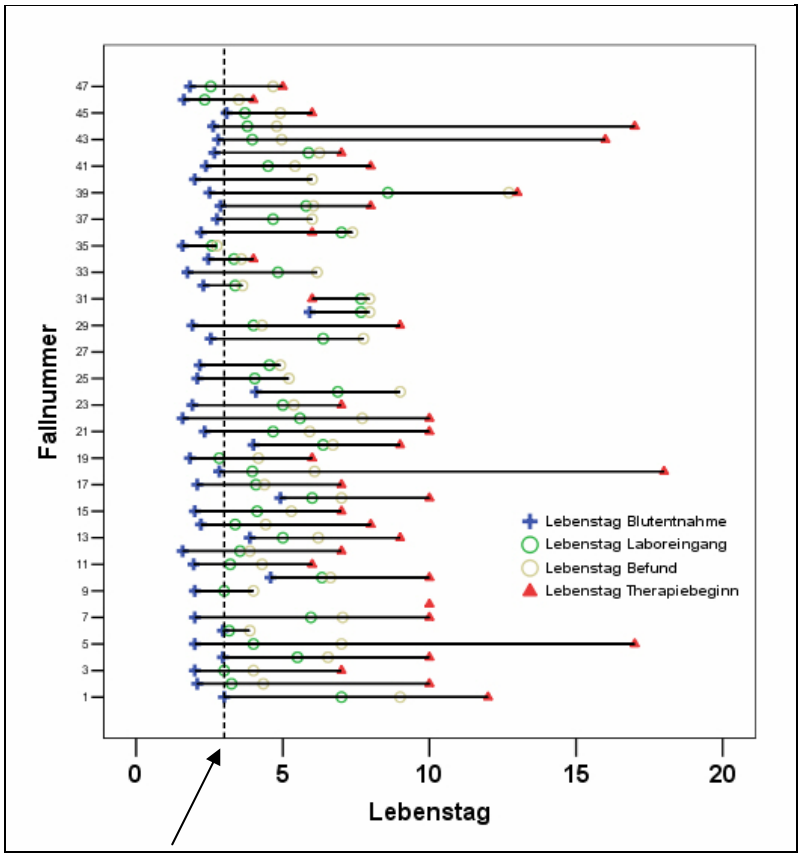
6.1 Primary screening

Crucial for successful screening is the reliability of results and the promptness of further diagnostic evaluation and therapy in suspect cases. The optimal sampling time is the 48th to the 72nd hour of life (§6.1). The probe should not be sampled before the 36th and not after the 72nd hour of life. Laboratories which have no positive screening for some targeted diseases are not listed. Exemplary the age of the children and the time of sampling, laboratory receipt, reporting and start of therapy is shown for children with PKU and CAH (in figure 5 and 6). For clarity reasons the description >72 hours of age is reported in days, calculated from hours of life.

Tab. 6.1 Time of primary screening in confirmed cases

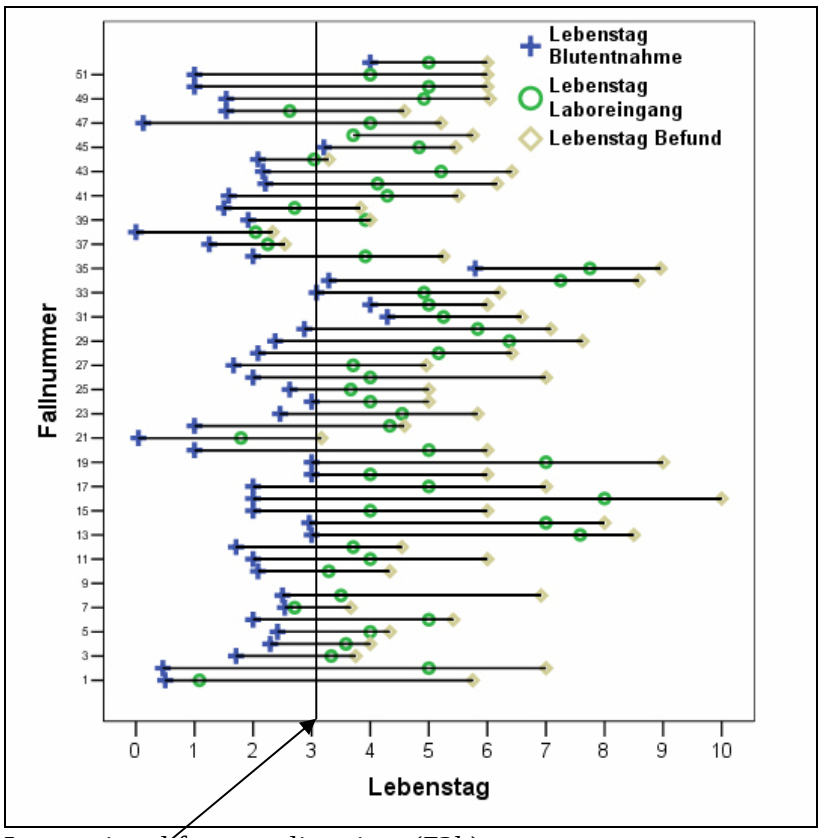
Targeted diseases	36-72 h.	4-7 Day	> 7 Day	< 36 h.	< 32 WoG	n.s.	Total
Hypothyroidism	100	24	1	3	6	53	**187**
CAH	31	7		10	2	9	**59**
Biotinidase deficiency	28	2		2		4	**36**
Classic Galactosaemia	4	1				2	**7**
PKU/HPA**	77	15	1	1	3	21	**118**
MSUD**	2		3				**5**
MCAD**	36	7		1	2	8	**54**
LCHAD**	1	1		1			**3**
VLCAD**	5						**5**
CPT I-Deficiency**						1	**1**
CPT II-Deficiency**	2						**2**
CAT-Deficiency**							**0**
GA I**	4	1		1			**6**
IVA**	4	1				2	**7**
Total	**294**	**59**	**5**	**19**	**13**	**100**	**490**

Figure 5: newborns with PKU, age at sampling etc



Latest aimed for sampling time (72h)

Figure 6: newborn with CAH, age at sampling time etc



Latest aimed for sampling time (72h)

6.2 Indication for request of repeat testing in the confirmed cases.

An indication for a second screening could be early sampling before the 32nd week of pregnancy or before the 36th hour of life, even in children with confirmed diagnosis. In Table 6.2 the indications for repeat testing are shown. Occasionally, the confirmation diagnostics are undertaken without sending the repeat screening to the laboratory as stated in the guidelines (§6 paragraph 2).

Table 6.2 *:* **Indication for request of repeat testing in the confirmed cases**

Targeted diseases	recall	< 36 Std.	< 32 WoG	n.s.	No repeat test	Total
Hypothyroidism	92	2	6	41	46	**187**
CAH	33	8	2	7	9	**59**
Biotinidase deficiency	27	1		3	5	**36**
Classic Galactosaemia	5			2		**7**
PKU/HPA**	73	1	3	19	22	**118**
MSUD**	5					**5**
MCAD**	36		2	6	10	**54**
LCHAD**	2	1				**3**
VLCAD**	5					**5**
CPT I-Deficiency**				1		**1**
CPT II-Deficiency**	2					**2**
CAT-Deficiency**						**0**
GA I**	5	1				**6**
IVA**	5			2		**7**
Total	**290**	**14**	**13**	**81**	**92**	**490**

7 Confirmation of pathological results

The plausibility of the laboratory reported results were checked by a Pediatric Endocrinologist or by experts in metabolic disease (see above). The following chapter outlines the diagnostic measures for confirmation of the suspected diagnosis as known to the laboratories. This information is used for quality control by the individual laboratories; unfortunately feedback by the Clinicians is not always warranted. No detailed information regarding confirmation diagnostics in 69 of 490 cases is available for 2005, in further 86 cases communication of the final diagnosis to the screening laboratory did not happen.

7.1.1 Hypothyroidism

Laboratory	Patient	TSH	T3	fT3	T4	fT4	Ultrasound	Thyroid antibodies
1	8	8	6	1	7	4	7	7
2	2	1	1		1			
3	8	2		1		1	2	2
4	1	1			1	1		
5	15	14	4	7	2	9	14	14
6	3		2	4	1	3		
7	10	3		1		4	1	
8	52	41	11	24	8	27	26	18
9	41	32	10	18	13	24		
11	2	2		2	1	2	2	
12	42	34	12	17	9	22	19	
14	3	3	3	2		4	2	
Total	**187**	**141**	**49**	**77**	**43**	**101**	**73**	**41**

7.1.2 Congenital adrenal hyperplasia (CAH)

Laboratory	Confirmed cases	17-OHP (Serum)	Serum-steroids	Urinary steroids	Molecular genetic testing
1	1	1	1		1
2	5	3	3		3
3	5	2	2		2
5	3	3	1	2	1
7	5	2	1		
8	17	9	12	6	5
9	7	5			
12	13	4	4	1	7
14	3	2	2		3
Total	**59**	**31**	**26**	**9**	**22**

7.1.3 Biotinidase deficiency

Laboratory	Confirmed cases	Serum Biotinidase	Molecular genetic testing
1	1	1	
3	2	1	
5	1	1	
8	27	20	1
9	3	3	
12	1	1	
14	1	1	
Total	**36**	**28**	**1**

7.1.4 Galactosaemia

Classic

Laboratory	Confirmed cases	GALT(Ery)	Molecular genetic testing
1	1	1	1
4	1		1
8	1		1
9	2	2	
12	2	2	
Total	**7**	**5**	**3**

Incl. Variants

Laboratory	Patient	Galactose	GALT(Ery)	Molecular genetic testing
1	8			5
2	2			1
3	3		3	3
4	2			2
7	10		2	8
8	39			8
9	2	2	2	
12	10		4	
14	1			
Total	**77**	**2**	**11**	**27**

7.1.5 PKU / HPA

Laboratory	Confirmed cases	Phe (Serum)	Phe/ Tyr	BH4-Test	BH4 sensitive	Molecular genetic testing	Pterine im Urin	DHPR in dried blood
1	10	10	7	4		10	10	10
2	1	1						
3	10	6	8	8	3	1	3	2
5	12	11	8	9	2	1	2	9
6	1			1				
7	2	1		1	1		1	
8	29	11	5	17	6	4	5	6
9	19	19					1	
12	28	18	9	26	4	1	15	18
14	6	6	2	5	4		4	2
Total	**118**	**83**	**39**	**71**	**20**	**17**	**41**	**47**

7.1.6 MSUD

Laboratory	Patient	Serum leucine	Serum isoleucine	Serum valine	Serum alloisoleucine	Urinary organic acids
1	1	1	1	1	1	1
8	1	1	1	1	1	
9	**3**	**3**	**3**	**3**	**3**	
Total	**5**	**5**	**5**	**5**	**5**	**1**

7.1.7 MCAD

Laboratory	Confirmed cases	GV1	GV2	GV3	Molecular genetic testing	Urinary organic acids
1	5				4	5
3	1	1	1		1	
5	7	4	3	3	2	5
6	1					1
7	6				4	4
8	15				10	5
9	6					5
12	12				12	1
14	1				1	
Total	**54**	**5**	**4**	**3**	**34**	**26**

7.1.8 LCHAD

Laboratory	Patient	GV1	GV2	GV3	Molecular genetic testing	Urinary organic acids	Fibroblast enzyme activity
8	1				1	1	1
11	1	1	1	1	1	1	
12	1				1		
Total	**3**	**1**	**1**	**1**	**3**	**2**	**1**

7.1.9 VLCAD

Laboratory	Patient	GV1	Molecular genetic testing	Fibroblast enzyme activity
3	1	1		
8	2		1	1
12	2		1	
Total	**5**	**1**	**2**	**1**

7.1.10 CPT I Deficiency

Laboratory	Patient	GV1	Molecular genetic testing
9	**1**	**1**	**1**

7.1.11 CPT II Deficiency

Laboratory	Patient	Fibroblast enzyme activity
8	2	1

7.1.12 Glutaric acidaemia type I

Laboratory	Patient	GV1	Urinary organic acids
8	1		1
12	5	2	5
Total	**6**	**2**	**6**

7.1.13 Isovaleric acidemia

Laboratory	Patient	Molecular genetic testing	Urinary organic acids
1	1		1
5	1		
7	1	1	
8	2		1
9	2		2
Total	**7**	**1**	**4**

8 Laboratory organisation

Paragraphs 13 to 15 verify organisation issues like accreditation, period of sample custody, etc.

8.1 Custody of testcards

Laboratory	Testcard custody > 3 months	accreditation	Health insurance authorisation	Federal state screeningcentre
1	Yes	DACH	1.08.2005	Yes
2	Yes	DACH		
3*	Yes	DACH	April 2005	
3a*		ZLG	1.04.2005	
4	Yes		until 3/2005	
5	Yes	DACH	1.7.2005	Yes
6	Yes	DACH	2003	
7		ZLG		No
8		ZLG	1978	
9	Yes	DACH	1.4.2005	
11	Yes	DACH		
12*	No	DACH	1999	Yes
12a*	No	DACH	1999	No
14	No	DACH	2003	Yes

* differs in regions

8.2 Aquisition of completeness

Laboratory	No aquisition of completeness	Comparison with birth records	Namebased Comparison with birth registry
1	x		
2		x	
3*		x	
4	x		
5		x	
6		x	
7	x		
8		x	
9	x		
11		x	
12*			x
12a*	x		
14			x
Total	**5**	**6**	**2**

* differs in regions

8.3 Tracking

When necessary laboratories or regional screening centres do tracking in the listed situations.

Laboratory	Suspicious primary screening	Primary screening < 36.Std.	Primary screening < 32 WoG	Empty cards	Bad sample quality	confirmation	Therapy
1	Yes	Yes		Yes	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes				Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Yes			Yes	Yes	Yes	Yes
8	Yes				Yes	Yes	Yes
9	Yes	Yes			Yes	Yes	
11	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	Yes	Yes	Yes		Yes	Yes	Yes

9 Methods and cutoffs in the screening

9.1 Filter paper for sampling

Laboratory	Filter paper
1	WS 903
2	WS 903
3	WS 903
4	WS 903
5	WS 902
6	WS 903
7	WS 903
8	WS 903
9	WS 903
11	WS 903
12	WS 2992
14	WS 903

9.2 Hypothyroidism

Laboratory	Parameter	Cut off [mU/l]	Method
1	TSH	15	AutoDELFIA
2	TSH	12	AutoDELFIA
3	TSH	15	AutoDELFIA
4	TSH	15	DELFIA
5	TSH	n.s.	AutoDELFIA
6	TSH	15	DELFIA
7	TSH	15	AutoDELFIA
8	TSH	< 15	DELFIA
9	TSH	15	AutoDELFIA
11	TSH	15	DELFIA
12	TSH	until 4. LT: 20 5.-6. LT: 15 from 7. LT: 10	AutoDELFIA
14	TSH	< 20	AutoDELFIA

9.3 Biotinidase deficiency

Laboratory	Parameter	Cut off	Method
1	Biotinidase	30% board mean	Colorimetry qualitative
2	Biotinidase	30 %	Colorimetry qualitative
3	Biotinidase	30 % day mean	Colorimetry qualitative
4	Biotinidase	35%	Colorimetry quantitative
5	Biotinidase	% board mean	Colorimetry quantitative
6	Biotinidase	30% day mean	Colorimetry quantitative
7	Biotinidase	2,7 U/g Hb	Colorimetry quantitative
8	Biotinidase	< 30% day mean	Colorimetry quantitative
9	Biotinidase	0,2	Colorimetry qualitative
11	Biotinidase	-	Colorimetry qualitative
12	Biotinidase	< 30%	Fluorometry quantitative
14	Biotinidase	< 30 %	Colorimetry quantitative

9.4 Galactosaemia

Laboratory	Parameter	Cut off	Method
1	Galactose	15 mg/dl	BIORAD Quantase
	GALT	3,5 U/gHb	Fluorometry(PE)
2	GALT/Galactose	15 mg/dl	Enzymatic / Fluorometric
3	GALT/Galactose	2,3 Ug/Hb 20 mg/dl	BIORAD Quantase**!**
4	GALT	3,5 U/g Hb	Fluorometry quantitative
5	GALT/Galactose		Colorimetry quantitative Fluorometry quantitative
6	GALT	3,5 U/g Hb	Fluorometry quantitative
7	GALT	3,5 U/g Hb	Fluorometry quantitative
8	GALT/Galactose	> 15 mg/dl < 20 % Tagesmittel	Colorimetry non Kit / Fluoro quant non kit
9	GALT/Galactose	20mg/dl 2,3U/gHb	BiORAD Quantase / BIORAD Quantase
11	GALT	3,5 U/g Hb	Fluorometry quantitative
12	GALT/Galactose	15 mg/dl < 2,3 U/g Hb	Colorimtrie non Kit / Fluoro. quant.(non-kit)
14	GALT/Galactose	>15mg/dl < 2,3 U/g Hb	BIORAD Quantase / BIORAD Quantase

9.5 MS/MS

Laboratory	Method
1	derivatised non Kit
2	derivatised non Kit
3*	nicht derivat.PE Kit
3*	derivatised non Kit
4	keine MS/MS
5	derivatised non Kit
6	nicht derivat.PE Kit
7	derivatised non Kit
8	derivatised non Kit
9	derivatised non Kit
11	nicht derivat.PE Kit
12	derivatised non Kit
14	derivatised non Kit

* differs in regions

9.6 Congenital adrenal hyperplasia (CAH)

Term babies

Laboratory	Parameter	Method	Dependent on age	Dependent on WoG	Dependent on BW	Formula	Constant value
1	17 OHP	AutoDELFIA	Yes			ln(OHP)=2,90798-0,40653ln(age in days)	
2	17 OHP	AutoDELFIA					30
3	17 OHP	AutoDELFIA	Yes			ln(OHP) = 2,90798 –0,40653* ln(age in days)	
4	17 OHP	DELFIA					40
5	17 OHP	AutoDELFIA B015112		Yes		value * 0,75	40
6	17 OHP	DELFIA		Yes			40
7	17 OHP	AutoDELFIA					40
8	17 OHP	DELFIA					50
9	17 OHP	AutoDELFIA		Yes			50
11	17 OHP	DELFIA	Yes			ln(OHP)=2,90798-0,40653ln(age in days)	
12	17 OHP	AutoDELFIA	Yes		Yes		
14	17 OHP	AutoDELFIA	Yes		Yes		40

Preterm babies

Laboratory	Parameter	Method	Dependent on age	Dependent on WoG	Dependent on BW	Formula	Constant value
1	17 OHP	AutoDELFIA	Yes	Yes		ln(OHP)=3,470-0,121ln(age in days)	
2	17 OHP	AutoDELFIA		Yes			
3	17 OHP	AutoDELFIA	Yes	Yes		ln(OHP) = 3,470 –0,121* ln(age in days) (STOPSACK / KOCH 2005)	
4	17 OHP	DELFIA		Yes			
5	17 OHP	AutoDELFIA B015112		Yes		Before discharge, i.e. 36-38.corrected-WoG *0,75	40
6	17 OHP	DELFIA		Yes			
7	17 OHP	AutoDELFIA			Yes		
8	17 OHP	DELFIA		Yes	Yes		
9	17 OHP	AutoDELFIA		Yes			
11	17 OHP	DELFIA	Yes	Yes		ln(OHP)=3,470-0,121ln(age in days)	
12	17 OHP	AutoDELFIA	Yes		Yes		
14	17 OHP	AutoDELFIA	Yes		Yes		

9.7 MS/MS Parameter

If possible cut off values are stated for guide values (GV), secondary parameters (SP)

9.7.1 PKU

Parameter /Cut off	1	3	5	6	7	8	9	11	12	14
Phe	120	150	150	172,02	150	150	123	126	120	129
Tyr				SP						
Phe/Tyr	SP	SP	SP	SP	2.5	2,5	SP	2,2	2,0	SP

9.7.2 MSUD

Parameter / Cut off	1	3	5	6	7	8	9	11	12	14
Ala				SP					GV	
Val	266	SP	SP	SP	280	SP	SP	241	GV	SP
Leu/Ile	276	314	z >= 3,5	316,4	300	400	299	307	GV	300
Fischer-Q	SP			SP					GV	
Leu/Ile:Phe	SP		z >= 3,5			10			GV	SP
Val/Phe			SP						GV	SP
Leu Ile/Ala	SP	SP	z >= 3,5	SP			SP	SP	GV	

9.7.3 MCAD

Parameter / Cut off	1	3	5	6	7	8	9	11	12	14
C6	SP	SP	SP	SP	0.18	SP	SP	SP	GV	SP
C8	0,29	0,3	z >= 3,5	0,394	0.40	0,3	0.28	0,18	GV	0,34
C8/C10		GV	SP			5,0	SP	2,79	GV	SP
C8/C12			SP	SP			SP	SP	GV	
C8/C16					SP					
C10	SP	SP	SP	SP		SP	SP	SP	GV	SP
C10:1	SP	SP	SP	SP	.15	0,15	SP	SP	GV	SP
C8/C2	SP			SP		0,02	SP			SP
C8/C6			SP				SP		GV	

9.7.4 LCHAD

Parameter / Cut off	1	3	5	6	7	8	9	11	12	14
C14:1			SP	SP		SP		SP	SP	
C14OH			SP	SP		SP	SP	SP	GV	
C16OH	0,09	0,15	z >= 3,5	0,205	0.11	0,06	0.1	0,075	GV	0,60
C16:1OH			SP	SP			SP		GV	SP
C18OH	0,04	SP		0,167	0.1	SP	0.07	0,039		SP
C18:1OH	0,05	SP	z >= 3,5	SP	0.1	0,06	0.11	0,058	GV	SP
C18:2OH						SP				SP
C16OH/C16		SP	SP					0,025		

Laboratory Gießen: Z-value based on > 10.000 primary screening (see MCAD)

9.7.5 VLCAD

Parameter / Cut off	1	3	5	6	7	8	9	11	12	14
C12									GV	
C14	SP	SP	SP	SP	0.65	SP	SP	SP	GV	SP
C 14:1	0,44	0,240	z >= 3,5	0,19	0.4	0,3	0.43	0,19	GV	0,25
C16:1							SP			
C14:2	SP	SP		SP	SP	SP		SP	GV	SP
C14:1/C16	SP	0,070	SP	SP				0,070		
C14/C4										SP
C14:1/C4			SP				SP		GV	SP

9.7.6 CPT I Deficiency

Parameter / Cut off	1	3	5	6	7	8	9	11	12	14
C0	SP	GV	SP	57,884	70	80	65.49	SP	SP	SP
C8				SP						
C16	0,91	GV	SP	0,32	<0.6		7.65	0,73	GV	<1
C18	0,22	SP	SP	0,112	<0.3		2.34	0,24	GV	SP
C18:1	0,33							0,36	GV	
C16/C2										
(C16+C18:1)/C2										
C0/(C16+C18)	SP	SP	>= 70	SP		40	1/0.28	14,03	GV	SP

9.7.7 CPT II Deficiency

Parameter / Cut off	1	3	5	6	7	8	9	11	12	14
C0	SP	SP		57,84	<10			5,1	SP	SP
C16	7,43	8,83	SP	8,276	8.0	8	7.65	9,1	GV	>6
C16:1				SP	0.6		0.67		GV	SP
C18	2,16	3,65		2,756	2.6		2.34	2,37	GV	>2,5
C18:1	2,92	GV	SP	GV	3.5	3,4	1.92	3,87	GV	SP
(C16+C18:1)/C2	SP	SP	z >= 3,5	SP		0,35		SP		
C18:2									GV	
C0/(C16+C18)				SP						

9.7.8 CAT Deficiency

Parameter / Cut off	1	3	5	6	7	8	9	11	12
AC ges							SP		
C0	8,4	5,1		SP		< 25	SP	GV	SP
C16	7,43	91	SP	8,276	8.0	8,0	8,83	GV	>6
C16:1							SP	GV	SP
C18	2,16	2,37		2,576	2.6	2,5	2,65	GV	SP
C18:1	2,92	3,87	SP	GV	3.5		3,9	GV	SP
(C16+C18:1)/C2	SP	SP					SP	GV	SP
C18:2			z >= 3,5						
C0/(C16+C18)								GV	
C0/(C16+C18:1)				SP			SP		

9.7.9 Glutaric acidaemia

Parameter / Cut off	1	3	5	6	7	8	9	11	12	14
C5DC (Glut)	0,12	0,25	z >= 3,0	0,407	0.33	0,20	0.17	0,51	GV	<0,15
C5DC/C8	SP	SP	SP	SP	5.9		SP	SP		SP
C5DC/C16			SP	SP			SP			SP
C5DC/C2	SP									
C5DC/C4	SP		SP						GV	
C5DC/C12	SP	SP	SP	SP				SP	GV	
C5DC/C18										

9.7.10 Isovaleric acidemia

Parameter / Cut off	1	3	5	6	7	8	9	11	12	14
C5	0,33	0,6	z >= 3,5	0,965	1	0,5	0.63	0,38	GV	0,6
C5/C2			SP	SP		0,02	SP			
C5/C3										SP
C5/C8	SP	SP		SP	SP			SP	GV	
C5/C4	SP	SP	SP	SP				SP	GV	

10 Literature

1 Beschluss über eine Änderung der Richtlinien des Bundesausschusses der Ärzte und Krankenkassen über die Früherkennung von Krankheiten bei Kindern bis zur Vollendung des 6. Lebensjahres (Kinder-Richtlinien) zur Einführung des erweiterten Neugeborenen-Screenings vom 21. Dezember 2004; Dt. Ärzteblatt 2005, 102: A1158-63

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3 Nennstiel-Ratzel U, Liebl B, Zapf A. Modellprojekt zur Neuordnung des Neugeborenen-Screening in Bayern. Gesundheitswesen 2003 Mar;65 Suppl 1:S31-5.

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