August/September 2009 Newborn Screening Articles

1. Am J Forensic Med Pathol. 2009 Sep;30(3):284-6.

A neonatal death due to medium-chain acyl-CoA dehydrogenase deficiency: utilization of the neonatal metabolic screen in a functional approach to sudden unexplained infant death.

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We report a perinatal death due to medium-chain acyl-CoA dehydrogenase deficiency, which was referred to the Coroner's Physician as sudden unexplained infant death. Detailed death investigation including the autopsy findings, and newborn biochemical and molecular studies revealed the cause and natural manner of death. This disorder affects fatty acid oxidation and results in decreased tolerance for fasting, which can be life threatening. This case illustrates the critical role of newborn screening in the investigation of perinatal death. A brief historical perspective of the origins of newborn biochemical screening is also presented.

2. Ann Trop Paediatr. 2009 Sep;29(3):197-202.

Prevalence of pneumococcal polysaccharide vaccine administration and incidence of invasive pneumococcal disease in children in Jamaica aged over 4 years with sickle cell disease diagnosed by newborn screening.

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BACKGROUND: Patients with sickle cell disease (SCD) are susceptible to bacterial infections, especially those caused by encapsulated organisms such as Streptococcus pneumoniae which is an important cause of morbidity and mortality in early childhood. Preventive measures such as penicillin prophylaxis and immunisation are therefore required. Although penicillin is the mainstay of prophylaxis, pneumococcal vaccination is also important for defence against invasive pneumococcal disease (IPD). AIM: To determine the prevalence of pneumococcal polysaccharide vaccination among patients with SCD diagnosed by newborn screening, and the incidence of IPD in this group of patients. METHODS: In this retrospective study, data were obtained from the pneumococcal polysaccharide vaccine (PPV) log books and the electronic clinic database. Patients' dockets were searched to confirm their vaccine status if

they were over 4 years of age and PPV data had not been found by the above methods. Episodes of invasive pneumococcal disease (sepsis or meningitis) were obtained from the clinic database. Data were analysed using STATA version 9. RESULTS: Ninety-one per cent of participating patients in the study population who were eligible for PPV had been appropriately immunised. Also, 94.8% of patients with a severe form of SCD had appropriately received PPV. The incidence rate of IPD was 480/100,000 person years in the study population and 160/100,000 person years in patients over 4 years of age. CONCLUSION: The high prevalence of PPV administration in children with SCD diagnosed by newborn screening had a significant impact on the incidence of IPD with improved patient outcomes.

3. Clin Chim Acta. 2009 Sep;407(1-2):6-9. Epub 2009 Jun 21.

Improved MS/MS analysis of succinylacetone extracted from dried blood spots when combined with amino acids and acylcarnitine butyl esters.

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BACKGROUND: The utilization of succinylacetone (SUAC) as the primary metabolic marker for tyrosinemia Type I is now well known, thus new methods have been developed to analyze SUAC as a first tier test in newborn screening. One approach is to prepare a SUAC hydrazine derivative from the dried blood spots (DBS) previously utilized in the extraction of acylcarnitine (AC) and amino acids (AA). The final derivatized products of SUAC, AA and AC are combined in a single tandem mass spectrometric (MS/MS) analysis. However, butyl esterification techniques may result in contamination of underivatized acylcarnitines by as much as 20%. We have developed a simple wash step to improve the combined analysis of SUAC, AA and AC in DBS by MS/MS. METHODS: AA and AC were extracted with methanol containing labeled internal standard from 3.2mm punches taken from the DBS specimen. The previously extracted blood spot that remains after removal of the methanol extraction solvent was used in the preparation of SUAC with and without additional washing of the blood spot. The butyl ester eluates of AA and AC, and SUAC hydrazine derivatives were recombined and measured by MS/MS. RESULTS: Three additional methanol wash steps of the remaining DBS punches prior to SUAC derivatization reduced the presence of underivatized acylcarnitines, resulting in a 4-fold reduction of underivatized palmitoylcarnitine. Palmitoylcarnitine butyl ester is detected at m/z 456 while the underivatized species is detected at m/z 400, which is also the mass of dodecanoylcarnitine butyl ester. The linearity of the SUAC assay was unchanged by the additional wash steps. For butyl esterification methods, the preferred analytic procedure, the presence of AC can compromise the results of a newborn screen for the actual concentrations of acylcarnitines. It is essential to remove any underivatized acylcarnitines prior to SUAC analysis. CONCLUSION:

The additional methanol wash steps did not alter SUAC assay results but did remove underivatized acylcarnitines which could result in the incorrect quantification of acylcarnitines.

4. Int J Gynaecol Obstet. 2009 Sep;106(3):273-4. Epub 2009 Apr 15.

Ethical aspects concerning neonatal screening FIGO Committee for the Ethical Aspects of Human Reproduction and Women's Health.

Milliez J.

5. J Laryngol Otol. 2009 Sep;123(9):982-9. Epub 2009 Apr 24.

Initial outcomes from universal newborn hearing screening in Avon.

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OBJECTIVE: The Avon Area Health Authority was a first-phase site for introduction of universal newborn screening in the UK. The aims of this study were: to review the programme's results to date; to assess the impact screening would have on other services (e.g. the cochlear implant programme); and to assess the longer term outcome for children identified by the screening programme. PATIENTS: All children identified by the Avon universal newborn hearing screening programme between April 2002 and July 2006. RESULTS: Fifty-four children with a bilateral hearing impairment of worse than 40 dBHL were identified from a screened population of approximately 44 000. Nine of these children were put forward for cochlear implantation, and seven had been implanted at the time of writing. Thirteen of these children were identified with possible auditory neuropathy or dys-synchrony. All the newborn hearing screening programme criteria assessed were met. CONCLUSIONS: The screening programme was effective. Some areas may need review in order to optimise patient care.

6. Nat Rev Endocrinol. 2009 Sep;5(9):490-8.

Neonatal screening for congenital adrenal hyperplasia.

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Congenital adrenal hyperplasia (CAH) caused by steroid 21-hydroxylase deficiency occurs in 1:16,000-1:20,000 births. If not promptly diagnosed and treated, CAH can cause death in early infancy from shock, hyponatremia and hyperkalemia. Affected girls usually have ambiguous genitalia but boys appear normal; therefore, newborn babies are commonly screened for CAH in the US and many other countries. By identifying babies with severe, salt-wasting CAH before they develop adrenal crises, screening reduces morbidity and mortality, particularly among affected boys. Diagnosis is based on elevated levels of 17-hydroxyprogesterone, the preferred substrate for steroid 21-hydroxylase. Initial testing usually involves dissociation-enhanced lanthanide fluorescence immunoassay that has a low positive predictive value (about 1%), which leads to many follow-up evaluations that have negative results. The positive predictive value might be improved by second-tier screening using DNA-based methods or liquid chromatography followed by tandem mass spectrometry, but these methods are not widely adopted. Cost estimates for such screening range from US$20,000 to $300,000 per life-year saved. In babies with markedly abnormal screen results, levels of serum electrolytes and 17-hydroxyprogesterone should be immediately determined, but the most reliable way to diagnose CAH is measurement of levels of steroid precursors after stimulation with cosyntropin.

7. Pediatr Blood Cancer. 2009 Sep;53(3):397-400.

Initial presentation of unscreened children with sickle cell disease: the Toronto experience.

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BACKGROUND: The morbidity and mortality related to sickle cell disease (SCD) has decreased since the introduction of newborn screening in the United States. Given the multicultural nature of the Canadian population and the growing African Canadian population, it is concerning that there is no national neonatal screening program for SCD in Canada. The objective of this study was to evaluate the most common manner in which SCD is diagnosed in children when neonatal screening is not available routinely. PROCEDURE: The study design was a retrospective chart review. All children aged from birth to 18 years with SCD and an admission to the Hospital for Sick Children in Toronto, Canada, between 1978 and 2004 were eligible for inclusion. RESULTS: Fifty-two percent of the children with SCD were diagnosed through some form of screening while 48% were diagnosed with symptoms suggestive of their disease. The median age at time of diagnosis was 0.75 years in the "screened" group, and 2 years in the "symptom" group ($P < 0.05$). The most common symptomatic presentation was with a vaso-occlusive crisis. Fifteen percent presented with more severe symptoms including acute chest syndrome (5.5%), acute splenic sequestration (5%), sepsis (3.3%), aplastic crisis (1%), priapism (0.5%), meningitis (0.5%), stroke (0.5%), and death (1%). CONCLUSIONS: Fifteen percent of children with undiagnosed SCD presented initially with severe

complications of the disease. The morbidity and mortality related to undiagnosed SCD underscores the need for a national neonatal screening program in Canada. (c) 2009 Wiley-Liss, Inc.

8. Pediatr Res. 2009 Sep;66(3):312-6.

Elevated free thyroxine levels detected by a neonatal screening system.

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In Sapporo city of Japan, neonatal screening for congenital hypothyroidism has used the measurement of free thyroxine (T4) and thyroid-stimulating hormone (TSH) in the filter-paper blood spot. This system has enabled us to identify hyperthyroxinemic diseases. Filter papers were collected from neonatal infants born at 4-6 d of age and neonates who showed elevated free T4 (>4.0 ng/dL, 4 SD above the mean) were studied. Between January 2000 and December 2006, 83,232 newborns were screened. Eleven infants demonstrated persistent hyperthyroxinemia. One patient with slightly elevated free T4 and normal TSH was diagnosed as having familial dysalbuminemic hyperthyroxinemia (FDH). The other two patients with elevated free T4 without suppressed TSH were considered as having resistance of thyroid hormone (RTH), and analysis of thyroid hormone receptor (TR) beta gene confirmed the diagnosis. The remaining eight patients were diagnosed as having neonatal Graves' disease (NGD). Seven of eight pregnant women were treated with antithyroid drug and thus only one unrecognized NGD during pregnancy was detected by screening. Our screening system enables for early awareness of RTH and FDH. Regarding Graves' disease, the benefit of elevated free T4 screening is small, because most pregnant women with Graves' disease were managed.

9. Acta Paediatr. 2009 Aug 18. [Epub ahead of print]

Inconclusive Cystic Fibrosis neonatal screening results: long-term psychosocial effects on parents.

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Abstract Aim: Cystic Fibrosis (CF) Newborn Screening occasionally identifies neonates where a CF diagnosis can neither be confirmed nor excluded. To assess how parents of these infants cope with this ambiguous situation. Methods: Parents of 11 children with Ambiguous

Diagnosis (group AD) were compared with parents of 11 children diagnosed with CF through neonatal screening [group Cystic Fibrosis Diagnosis (CFD)] and with parents of 11 Healthy Control children (group HC) matched for gender and age. Results: The emotional reaction to the inconclusive result was less pronounced in AD than in CFD ($p = 0.003$), and AD parents considered their infants as healthy as controls. Parents' anxiety about their child's health is stronger in CFD than in AD ($p < 0.05$) and HC ($p < 0.001$). Long-term emotional distress was rated similarly in AD and CFD, and greater than in HC ($p = 0.0003$). The parent/child relationship was less influenced in AD than in the CF group ($p = 0.03$). Seven AD and CFD parents changed their family planning projects. Conclusion: Inconclusive neonatal screening results appear to be understood and associated with lower anxiety levels than CF diagnosis. Concern about the child's health is similar to healthy controls and lower than in parents of CF children.

10. Am J Med Genet C Semin Med Genet. 2009 Aug 15;151C(3):214-34.

Quality assurance in medical and public health genetics services: a systematic review.

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As genetic services grow in scope, issues of quality assessment in genetic services are emerging. These efforts are well developed for molecular and cytogenetic testing and laboratories, and newborn screening programs, but assessing quality in clinical services has lagged, perhaps owing to the small work force and the recent evolution from a few large training programs to multiple training sites. We surveyed the English language, peer-reviewed literature to summarize the knowledge-base of quality assessment of genetics services, organized into the tripartite categories of the Donabedian model of "structure," "process," and "outcome." MEDLINE searches from 1990 to July 2008, yielded 2,143 articles that addressed both "medical/genetic screening and counseling" and "quality indicators, control, and assurance." Of the 2,143 titles, 131 articles were extracted for in-depth analysis, and 55 were included in this review. Twenty-nine articles focused on structure, 19 on process, and seven on outcomes. Our review underscored the urgent need for a coherent model that will provide health care organizations with tools to assess, report, monitor, and improve quality. The structure, process, and outcomes domains that make up the quality framework provide a comprehensive lens through which to examine quality in medical genetics.

11. Am J Med Genet C Semin Med Genet. 2009 Aug 15;151C(3):207-13

Outcomes of genetics services: creating an inclusive definition and outcomes menu for public health and clinical genetics services.

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Third party payers, funding agencies, and lawmakers often require clinicians and public health agencies to justify programs and services by documenting results. This article describes two assessment tools--"Defining Genetics Services Framework" and "Genetics Services Outcomes Menu," created to assist public health professionals, clinicians, family advocates, and researchers to plan, evaluate, and demonstrate the effectiveness of genetics services. The tools were developed by a work group of the Western States Genetics Services Collaborative (WSGSC) consisting of public health genetics and newborn screening professionals, family representatives, a medical geneticist, and genetic counselors from Alaska, California, Hawaii, Idaho, Oregon, and Washington. The work group created both tools by an iterative process of combining their ideas with findings from a literature and World Wide Web review. The Defining Genetics Services Framework reflects the diversity of work group members. Three over-lapping areas of genetics services from public health core functions to population screening to clinical genetics services are depicted. The Genetics Services Outcomes Menu lists sample long-term outcomes of genetics services. Menu outcomes are classified under impact areas of Knowledge and Information; Financing; Screening and Identification; Diagnosis, Treatment, and Management; and Population Health. The WSGSC incorporated aspects of both tools into their Regional Genetics Plan. 2009 Wiley-Liss, Inc.

12. J Inherit Metab Dis. 2009 Aug 14. [Epub ahead of print]

Mental retardation and inborn errors of metabolism.

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In countries where clinical phenylketonuria is detected by newborn screening inborn errors of metabolism are rare causes of isolated mental retardation. There is no international agreement about what type of metabolic tests must be applied in patients with unspecific mental retardation. However, and although infrequent, there are a number of inborn errors of metabolism that can present in this way. Because of the high recurrence risk and the possibility of specific therapies, guidelines need to be developed and adapted to different populations. The

application of a universal protocol may result in a low diagnostic performance in individual ethnic populations. Consideration of associated signs (extraneurological manifestations, psychiatric signs, autistic traits, cerebellar dysfunction, epilepsy or dysmorphic traits) greatly improves the diagnostic fulfilment.

13. Arch Dis Child. 2009 Aug 12. [Epub ahead of print]

Difficulties in selecting an appropriate Neonatal TSH screening threshold.

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BACKGROUND: The UK Newborn Screening Program Centre recommend that a blood-spot TSH cut-off of 10mU/l is used to detect congenital hypothyroidism. The value used varies from 5-10mU/l and so we examined the implications of altering this threshold. METHODS: Our regional blood spot TSH cut-off is 6mU/l. Positive or suspected cases were defined as a TSH >6mU/l throughout the study period (1/4/2005 to 1/3/2007). All term infants (>35 weeks) whose first TSH was 6-20mU/l had a second TSH measured. The biochemical details of infants with a TSH between 6.1-10.0mU/l and then >6mU/l on second sampling were sent to Paediatric Endocrinologists to determine approaches to management. RESULTS: 148 of 65446 infants (0.23%) had a first blood spot TSH >6.0mU/l. 120 were term infants with 67 of these (0.1% of all infants tested) having a TSH between 6.1-10.0mU/l and 53 a TSH >10.0mU/l. Of the 67 term infants with a TSH between 6.1-10.0mU/l on initial testing, 4 continued to have a TSH >6mU/l. One with a TSH greater than 10 mU/l and 1 infant with a TSH <10mU/l on the second blood spot have been diagnosed with congenital hypothyroidism. The survey of endocrinologists highlighted significant differences in practice. CONCLUSIONS: A reduced threshold of 6mU/l will increase the number of false positive 'term' infants by 126% but abnormalities of thyroid function requiring treatment will be detected. We suspect that the additional expense involved in setting a lower threshold is justified.

14. Clin Genet. 2009 Aug 7. [Epub ahead of print]

MCAD mutations identified in newborn screening cause different levels of enzymatic dysfunction.

Ehrnhoefer DE.

15. Genet Med. 2009 Aug 5. [Epub ahead of print]

Impact of false-positive newborn metabolic screening results on early health care utilization.

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PURPOSE:: To analyze the association between false-positive newborn screening results and health care utilization. METHODS:: We surveyed parents regarding their children's health care utilization. Parents of children who received false-positive newborn screening results were primarily enrolled by a screening laboratory in Pennsylvania. Parents of children with normal results were recruited through the Massachusetts birth registry. We used bivariate tests and multivariate regression to assess the association between newborn screening results and primary care utilization, emergency room use, and hospitalization by the age of 6 months. RESULTS:: Our sample included 200 children with false-positive results and 137 with normal results. Variation in recruitment strategies led to sample children with false-positive results being more likely to be non-white, have unmarried parents, and be of lower socioeconomic status. After adjusting for significant covariates, such as age, race, and socioeconomic status, there were no significant associations between newborn screening results and child health care utilization. CONCLUSIONS:: Despite the reported negative psychosocial effects of false-positive results, our study found no impact on early health care utilization. These results may assist in economic analyses of newborn screening as they suggest that medical costs associated with false-positive results are limited to the cost of diagnostic testing and follow-up.

16. Am J Public Health. 2009 Aug;99(8):1348-9. Epub 2009 Jun 18.

Comment in:
Am J Public Health. 2009 Aug;99(8):1349-50.
Comment on:
Am J Public Health. 2009 Feb;99(2):210-5.

Clinical and ethical considerations in managing carrier detection.

17. Am J Public Health. 2009 Aug;99(8):1349-50. Epub 2009 Jun 18.

Comment on:
Am J Public Health. 2009 Aug;99(8):1348-9.

Carrier detection and clinical uncertainty: the case for public health ethics.

Miller FA, Hayeems RZ, Robert JS.

18. Dev Med Child Neurol. 2009 Aug;51(8):642-6. Epub 2009 Mar 24.

Auditory neuropathy: unexpectedly common in a screened newborn population.

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Auditory neuropathy, or dyssynchrony, is defined by an abnormal or absent auditory brainstem response but intact otoacoustic emissions or cochlear microphonics. It is associated with impaired hearing on behavioural pure-tone audiometry, absent acoustic reflexes, and poor speech perception, particularly in noisy environments. These results suggest a disorder of inner hair-cell and or eighth-nerve function. We describe a case-note survey of patients with and without auditory neuropathy, using data from the local newborn hearing screening programme collected prospectively from 2002 to 2007. During this period, 45 050 infants were screened with otoacoustic emissions, 30 patients were diagnosed with suspected severe to profound hearing loss (16 males, 14 females), and 12 of those 30 had auditory neuropathy (six males, six females). Mean gestational age was 33 weeks 1 day in the auditory neuropathy group and 35 weeks in the non-auditory neuropathy group. The most significant risk factors for auditory neuropathy were hyperbilirubinaemia (p=0.018), sepsis (p=0.024), and gentamicin exposure (p=0.024). Children with auditory neuropathy comprise a subgroup of patients with hearing impairment involving different pathologies most commonly associated with the risk factors related to admission to neonatal intensive care units. Improvement is possible with maturity, at least in a minority.

19. Ear Hear. 2009 Aug;30(4):447-57.

Using benefit-cost ratio to select Universal Newborn Hearing Screening test criteria.

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OBJECTIVES: Current protocols presumably use criteria that are chosen on the basis of the sensitivity and specificity rates they produce. Such an approach emphasizes test performance

but does not include societal implications of the benefit of early identification. The purpose of the present analysis was to evaluate an approach to selecting criteria for use in Universal Newborn Hearing Screening (UNHS) programs that uses benefit-cost ratio (BCR) to demonstrate an alternative method to audiologists, administrators, and others involved in UNHS protocol decisions. DESIGN: Existing data from more than 1200 ears were used to analyze BCR as a function of Distortion Product Otoacoustic Emission (DPOAE) level. These data were selected because both audiometric and DPOAE data were available on every ear. Although these data were not obtained in newborns, this compromise was necessary because audiometric outcomes (especially in infants with congenital hearing loss) in neonates are either lacking or limited in number. As such, it is important to note that the characteristics of responses from the group of subjects that formed the bases of the present analyses are different from those for neonates. This limits the extent to which actual criterion levels can be selected but should not affect the general approach of using BCR as a framework for considering UNHS criteria. Estimates of the prevalence of congenital hearing loss identified through UNHS in 37 states and U.S. territories in 2004 were used to calculate BCR. A range of estimates for the lifetime monetary benefits and yearly costs for UNHS were used, based on data available in the literature. Still, exact benefits and costs are difficult to know. Both one-step (DPOAE alone) and two-step (DPOAE followed by automated auditory brainstem response, AABR) screening paradigms were considered in the calculation of BCR. The influence of middle ear effusion was simulated by incorporating a range of expected DPOAE level reductions into an additional BCR analyses RESULTS: Our calculations indicate that for a range of proposed benefit and cost estimates, the monetary benefits of both one-step (DPOAE alone) and two-step (DPOAE followed by AABR) NHS programs outweigh programmatic costs. Our calculations indicate that BCR is robust in that it can be applied regardless of the values that are assigned to benefit and cost. Maximum BCR was identified and remained stable regardless of these values; however, it was recognized that the use of maximum BCR could result in reduced test sensitivity and may not be optimal for use in UNHS programs. The inclusion of secondary AABR screening increases BCR but does not alter the DPOAE criterion level at which maximum BCR occurs. The model of middle ear effusion reduces overall DPOAE level, subsequently lowering the DPOAE criterion level at which maximum BCR was obtained CONCLUSION: BCR is one of several alternative methods for choosing UNHS criteria, in which the evaluation of costs and benefits allows clinical and societal considerations to be incorporated into the pass/refer decision in a meaningful way. Although some of the benefits of early identification of hearing impairment cannot be estimated through a monetary analysis, such as improved psychosocial development and quality of life, this article provides an alternative to audiologists and administrators for selecting UNHS protocols that includes consideration of societal implications of UNHS screening criteria. BCR suggests that UNHS is a worthwhile investment for society as benefits always outweigh costs, at least for the estimations included in this article. Although the use of screening criteria that maximize BCR results in lower test sensitivity compared with other criteria, BCR may be used to select criteria that result in increased test sensitivity and still provide a high, although not maximal, BCR. Using BCR analysis provides a framework in which the societal implications of NHS protocols are considered and emphasizes the value of UNHS.

20. Eur J Endocrinol. 2009 Aug;161(2):285-92. Epub 2009 May 18.

Transient hyper-17-hydroxyprogesteronemia: a clinical subgroup of patients diagnosed at neonatal screening for congenital adrenal hyperplasia.

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OBJECTIVE: Neonatal screening for congenital adrenal hyperplasia (CAH) is characterized by a high false-positive rate, mainly among preterm and low birth weight infants. The aims of this study were to describe a subgroup of infants with transient serum hyper-17-hydroxyprogesteronemia (hyper-17-OHPemia) and to compare them with false positive and affected by 21-hydroxylase deficiency newborns. METHODS: We retrospectively analyzed the clinical data of all newborns positive at CAH neonatal screening, who were referred to our hospital to confirm the diagnosis from 2002 to 2006. They were submitted to clinical investigations and blood tests to evaluate 17-hydroxyprogesterone (17-OHP), renin, and electrolyte levels. CAH-unaffected newborns with increased serum 17-OHP were submitted to strict follow-up monitoring, which included an ACTH-stimulating test and genetic analysis of the 21-hydroxylase gene, until serum 17-OHP decreased. RESULTS: Thirty-seven newborns with gestational ages ranging from 33 to 40 weeks were studied. Eight infants (three male and five female) were affected by CAH (serum 17-OHP: 277.5 (210-921) nmol/l), 14 (ten male and four female) were false positives (17-OHP: 3.75 (0.3-8.4) nmol/l), and 15 (ten male and five female) showed a serum hyper-17-OHPemia (17-OHP: 15.9 (9.9-33) nmol/l). No mutations of the 21-hydroxylase gene were found in infants with hyper-17-OHPemia and their serum 17-OHP levels were normalized by the third month of life. CONCLUSION: We identified a population of infants with transient serum hyper-17-OHPemia, and no clinical signs of disease or 21-hydroxylase gene mutations. No further investigations are necessary after birth in these newborns if 17-OHP levels decrease, other confirmatory tests such as ACTH-stimulation test or genotyping analysis are necessary only if symptoms appear.

21. Int J Pediatr Otorhinolaryngol. 2009 Aug;73(8):1090-4. Epub 2009 May 12.

Implementation of neonatal screening for hearing impairment: influence on pediatric otitis media surgery in The Netherlands.

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OBJECTIVE: Screening for hearing impairment in the Netherlands took place at the age of 9 months for many years but was recently moved to the neonatal period. Since otitis media has its highest prevalence at the age of 9 months, it might be that screening for hearing impairment at this age is linked to treatment of otitis media. We were interested in what the impact would be on the number of children treated with ventilation tubes or adenoidectomy when they were no longer screened at the age of 9 months. METHODS: National birth rates, data regarding screening for hearing impairment at the age of 9 months and at the neonatal period, as well as data regarding adenoidectomy and tube placement were used to study treatment of otitis media in children aged 0-2 years in the Netherlands. RESULTS: The percentage of children treated with ventilation tubes after implementation of neonatal screening for hearing impairment did not decline (OR 1.198-1.112), and more children were treated at a younger age. The number of children treated with adenoidectomy did however decline (OR 0.724-0.890). CONCLUSION: There seems to be an association between the implementation of neonatal screening for hearing impairment and the treatment of otitis media. During the whole studied period there was a slight but statistical significant increase in the odds for tube placement in all children aged 0-23 months. After implementation of the neonatal screen there was a distinct increase in the number of children aged 6-11 months treated with tubes. In the same period a statistical significant decline in the odds of undergoing adenoidectomy was observed.

22. J Chromatogr B Analyt Technol Biomed Life Sci. 2009 Aug 1;877(23):2412-7. Epub 2008 Nov 13.

Analytical validation based on total error measurement and cut-off interpretation of a neonatal screening TSH-immunoassay.

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To prevent the severe developmental and physical morbidities associated with congenital hypothyroidism, we developed a home-made Enzyme-Linked Immunosorbent Assay (ELISA) method to quantify Thyroid Stimulating Hormone (TSH) levels on newborn dried blood spots. In order to agree with actual clinical laboratory quality referential (ISO 15189), we desired to update our analytical validation protocol. For this purpose, an approach using accuracy profiles based on tolerance intervals for the total error measurement was for first time applied to an immunological assay. According to acceptance limits fixed at +/-30%, the method was found accurate over a concentration range from 17.48 to 250 mIU/L. Based on 99.5 percentile of a 16,459 newborn population, cut-off was fixed at 20.1 mIU/L and validated against normal and pathologic neonatal populations. Additionally, uncertainty regions around this value were obtained applying four different approaches. Finally, we demonstrated here our in-house immunological technique fulfils criterions of a neonatal screening policy.

23. J Inherit Metab Dis. 2009 Aug;32(4):459-71. Epub 2009 Jul 7.

Inherited disorders in the conversion of methionine to homocysteine.

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During the last decade much important new information relating to the metabolic pathway from methionine to homocysteine has been gained. Interest has been stimulated by the discovery of two novel disorders, glycine N-methyltransferase deficiency and S-adenosylhomocysteine hydrolase deficiency. Another disorder in this pathway, methionine adenosyltransferase deficiency, has been increasingly detected, thanks to the expansion of newborn screening programmes by tandem mass spectrometry technology. These significant steps allow important insight into the pathogenesis of these three disorders, as well as into the mechanisms of damage to various organs (liver, brain, muscle) and point to the relevance of these disorders for crucial biological processes such as methylation, transsulfuration or carcinogenesis in mammals, the pathogenesis of numerous pathological conditions, in particular those associated with hyperhomocysteinaemia, the action and possible toxicity of some drugs or consequences of nutritional variations. This review summarizes current knowledge of three inherited disorders in this metabolic pathway and draws attention to their much broader significance for human health and understanding of important biological processes.

24. J Inherit Metab Dis. 2009 Aug;32(4):498-505. Epub 2009 Apr 28.

Treatment recommendations in long-chain fatty acid oxidation defects: consensus from a workshop.

Spiekerkoetter U, Lindner M, Santer R, Grotzke M, Baumgartner MR, Boehles H, Das A, Haase C, Hennermann JB, Karall D, de Klerk H, Knerr I, Koch HG, Plecko B, Röschinger W, Schwab KO, Scheible D, Wijburg FA, Zschocke J, Mayatepek E, Wendel U.

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Published data on treatment of fatty acid oxidation defects are scarce. Treatment recommendations have been developed on the basis of observations in 75 patients with long-chain fatty acid oxidation defects from 18 metabolic centres in Central Europe. Recommendations are based on expert practice and are suggested to be the basis for further multicentre prospective studies and the development of approved treatment guidelines.

Considering that disease complications and prognosis differ between different disorders of long-chain fatty acid oxidation and also depend on the severity of the underlying enzyme deficiency, treatment recommendations have to be disease-specific and depend on individual disease severity. Disorders of the mitochondrial trifunctional protein are associated with the most severe clinical picture and require a strict fat-reduced and fat-modified (medium-chain triglyceride-supplemented) diet. Many patients still suffer acute life-threatening events or long-term neuropathic symptoms despite adequate treatment, and newborn screening has not significantly changed the prognosis for these severe phenotypes. Very long-chain acyl-CoA dehydrogenase deficiency recognized in neonatal screening, in contrast, frequently has a less severe disease course and dietary restrictions in many patients may be loosened. On the basis of the collected data, recommendations are given with regard to the fat and carbohydrate content of the diet, the maximal length of fasting periods and the use of l-carnitine in long-chain fatty acid oxidation defects.

25. J Inherit Metab Dis. 2009 Aug;32(4):488-97. Epub 2009 Apr 29.

Management and outcome in 75 individuals with long-chain fatty acid oxidation defects: results from a workshop.

Spiekerkoetter U, Lindner M, Santer R, Grotzke M, Baumgartner MR, Boehles H, Das A, Haase C, Hennermann JB, Karall D, de Klerk H, Knerr I, Koch HG, Plecko B, Röschinger W, Schwab KO, Scheible D, Wijburg FA, Zschocke J, Mayatepek E, Wendel U.

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At present, long-chain fatty acid oxidation (FAO) defects are diagnosed in a number of countries by newborn screening using tandem mass spectrometry. In the majority of cases, affected newborns are asymptomatic at time of diagnosis and acute clinical presentations can be avoided by early preventive measures. Because evidence-based studies on management of long-chain FAO defects are lacking, we carried out a retrospective analysis of 75 patients from 18 metabolic centres in Germany, Switzerland, Austria and the Netherlands with special regard to treatment and disease outcome. Dietary treatment is effective in many patients and can prevent acute metabolic derangements and prevent or reverse severe long-term complications such as cardiomyopathy. However, 38% of patients with very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency had intermittent muscle weakness and pain despite adhering to therapy. Seventy-six per cent of patients with disorders of the mitochondrial trifunctional protein (TFP)-complex including long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, had long-term myopathic symptoms. Of these, 21% had irreversible peripheral neuropathy and 43% had retinopathy. The main principle of treatment was a fat-reduced and fat-modified diet. Fat restriction differed among patients with different enzyme defects and was strictest in disorders of the TFP-complex. Patients with a medium-chain fat-based diet received supplementation of essential long-chain fatty acids. l-Carnitine was

supplemented in about half of the patients, but in none of the patients with VLCAD deficiency identified by newborn screening. In summary, in this cohort the treatment regimen was adapted to the severity of the underlying enzyme defect and thus differed among the group of long-chain FAO defects.

26. J Pediatr. 2009 Aug;155(2):271-5.e2. Epub 2009 May 31.

Reversal of cardiac dysfunction after enzyme replacement in patients with infantile-onset Pompe disease.

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OBJECTIVE: To compare the effects of enzyme replacement therapy (ERT) on cardiac performance in symptomatic and symptom-free infants with Pompe disease. STUDY DESIGN: Patients diagnosed between 1983 and 2008 were identified. Before the initiation of ERT, systolic dysfunction appeared only in patients > or = 5 months; thus we used this cut-point in age to divide clinically symptomatic patients into early and late treatment groups (Clin-E and Clin-L). Newborn screening (NBS) identified symptom-free patients. RESULTS: Among a total of 40 patients, 14 received ERT: 5 in the Clin-L, 4 in the Clin-E, and 5 in the NBS groups. All patients showed cardiomegaly, hypertrophic myocardium, and elevated B-type natriuretic peptide (measured in the Clin-E and NBS groups). ERT improved the survival and outcomes. Regressed myocardial hypertrophy and lowered B-type natriuretic peptide level occurred after 1 to 6 months of ERT. Nonetheless, there were 2 deaths and 2 survivors requiring ventilator support in the Clin-L group. Despite the regressed QRS voltage and shortened QT dispersion, life-threatening arrhythmias were still observed in 3, but none in the NBS group. CONCLUSION: ERT may restore the cardiac function in both symptomatic and symptom-free patients, but the beneficial effect may be unpredictable if given after the age of 5 months

27. Pediatr Neurol. 2009 Aug;41(2):156.

Comment on:
Genet Med. 2009 Jun;11(6):411-3.
Pediatr Neurol. 2009 Apr;40(4):245-52; discussion 253-5.
Pediatr Neurol. 2009 Apr;40(4):256-7.

A model in response to newborn screening mandates.

Duffner PK.

28. Pediatr Res. 2009 Aug;66(2):230-5.

Use of steroid profiling by UPLC-MS/MS as a second tier test in newborn screening for congenital adrenal hyperplasia: the Utah experience.

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Newborn screening allows the diagnosis of congenital adrenal hyperplasia (CAH) before symptoms appear, preventing the severe and potentially life-threatening crisis associated with this disease in infancy. Traditional screening by enzyme immunoassay results in a large number of false positives. To reduce the number of unnecessary tests, anxiety to families and physicians, and the burden to the newborn screening follow-up program, we implemented a second-tier test for CAH using steroid profiling by an ultra-performance liquid chromatography-tandem mass spectrometry. We measured three steroids: 17-hydroxyprogesterone, androstenedione, and cortisol and correlated them with the age of infant at the time of sample collection and birth weight. Both age at collection and birth weight affected the levels of adrenal steroids, but the use of appropriate cut offs and analyte ratios allowed the identification of infants with CAH. This approach was effective in identifying infants with CAH, with both salt-wasting and simple virilizing forms, while reducing the false-positive rate from 2.6 to 0.09%.

29. Pediatrics. 2009 Aug;124(2):e241-8. Epub 2009 Jul 20.

Expanded newborn screening: outcome in screened and unscreened patients at age 6 years.

Wilcken B, Haas M, Joy P, Wiley V, Bowling F, Carpenter K, Christodoulou J, Cowley D, Ellaway C, Fletcher J, Kirk EP, Lewis B, McGill J, Peters H, Pitt J, Ranieri E, Yaplito-Lee J, Boneh A.

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OBJECTIVE: Tandem mass spectrometry is widely applied to routine newborn screening but there are no long-term studies of outcome. We studied the clinical outcome at six years of age in Australia. METHODS: In a cohort study, we analyzed the outcome at 6 years for patients detected by screening or by clinical diagnosis among >2 million infants born from 1994 to 1998 (1,017,800, all unscreened) and 1998 to 2002 (461,500 screened, 533,400 unscreened) recording intellectual and physical condition, school placement, other medical problems, growth, treatment, diet, and hospital admissions. Results were analyzed separately for

medium-chain acyl-CoA dehydrogenase deficiency (MCADD) and other disorders, and grouped patients as those who presented clinically or died in the first 5 days of life; patients presented later or diagnosed by screening, and those with substantially benign disorders. RESULTS: Inborn errors, excluding phenylketonuria, were diagnosed in 116 of 1,551,200 unscreened infants (7.5/100,000 births) and 70 of 461,500 screened infants (15.2/100,000 births). Excluding MCADD, 21 unscreened patients with metabolic disorders diagnosed after 5 days of life died or had a significant intellectual or physical handicap (1.35/100,000 population) compared with 2 of the screened cohort (0.43/100,000; odds ratio: 3.1 [95% CI: 0.73-13.32]). Considering the likely morbidity or mortality among the expected number of never-diagnosed unscreened patients, there would be a significant difference. Growth distribution was normal in all cohorts. CONCLUSION: Screening by tandem mass spectrometry provides a better outcome for patients at 6 years of age, with fewer deaths and fewer clinically significant disabilities.

30. Steroids. 2009 Aug;74(8):662-5. Epub 2009 Mar 9.

False positive rate in newborn screening for congenital adrenal hyperplasia (CAH)-ether extraction reveals two distinct reasons for elevated 17alpha-hydroxyprogesterone (17-OHP) values.

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BACKGROUND: While the sensitivity of newborn screening for the salt wasting form of congenital adrenal hyperplasia (CAH) is good, the positive predictive value is poor due to the high false positive rate of the immunological assays for 17-OHP. Cross-reactivity with steroid sulfates is one of the main causes for false positive results. Several approaches have been described to improve CAH screening: adjusting cut-off levels to gestational age or birth weight, and second-tier molecular genetic analysis or second-tier liquid chromatography-tandem mass spectrometry (TMS). METHODS: 17-OHP was extracted with diethyl ether from dried blood spots in order to separate 17-OHP from polar steroids (like steroid sulfates). The dried ether extracts of calibrators, controls, and patient samples were redissolved and measured with the 17-OHP test kit (Wallac). RESULTS: 760 normal, 1049 false positive, and 232 samples of confirmed cases with CAH were analysed. Mean 17-OHP values were significantly lower after extraction: Normal samples: 17.5 nmol/L vs. 3.2 nmol/L; false positive samples: 97.0 nmol/L vs. 25.9 nmol/L; CAH: 275 nmol/L vs. 205 nmol/L. With a cut-off value of 11.9 nmol/L (mean+3 SD of the normal values), 404 of the false positives turned out to be normal. Ether extraction revealed two distinct subgroups of initially false positives rather than a continuum with normal distribution of 17-OHP values. CONCLUSION: Diethyl ether extraction provided evidence for two causes of false positive results in CAH screening. It reduced the rate of false positives by about 40% without loss of sensitivity.

31. PLoS One. 2009 Jul 30;4(7):e6449.

A novel tandem mass spectrometry method for rapid confirmation of medium- and very long-chain acyl-CoA dehydrogenase deficiency in newborns.

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BACKGROUND: Newborn screening for medium- and very long-chain acyl-CoA dehydrogenase (MCAD and VLCAD, respectively) deficiency, using acylcarnitine profiling with tandem mass spectrometry, has increased the number of patients with fatty acid oxidation disorders due to the identification of additional milder, and so far silent, phenotypes. However, especially for VLCADD, the acylcarnitine profile can not constitute the sole parameter in order to reliably confirm disease. Therefore, we developed a new liquid chromatography tandem mass spectrometry (LC-MS/MS) method to rapidly determine both MCAD- and/or VLCAD-activity in human lymphocytes in order to confirm diagnosis. METHODOLOGY: LC-MS/MS was used to measure MCAD- or VLCAD-catalyzed production of enoyl-CoA and hydroxyacyl-CoA, in human lymphocytes. PRINCIPAL FINDINGS: VLCAD activity in controls was 6.95+/-0.42 mU/mg (range 1.95 to 11.91 mU/mg). Residual VLCAD activity of 4 patients with confirmed VLCAD-deficiency was between 0.3 and 1.1%. Heterozygous ACADVL mutation carriers showed residual VLCAD activities of 23.7 to 54.2%. MCAD activity in controls was 2.38+/-0.18 mU/mg. In total, 28 patients with suspected MCAD-deficiency were assayed. Nearly all patients with residual MCAD activities below 2.5% were homozygous 985A>G carriers. MCAD-deficient patients with one other than the 985A>G mutation had higher MCAD residual activities, ranging from 5.7 to 13.9%. All patients with the 199T>C mutation had residual activities above 10%. CONCLUSIONS: Our newly developed LC-MS/MS method is able to provide ample sensitivity to correctly and rapidly determine MCAD and VLCAD residual activity in human lymphocytes. Importantly, based on measured MCAD residual activities in correlation with genotype, new insights were obtained on the expected clinical phenotype.