

October/November 2009 Newborn Screening Articles

1. J Pediatr. 2009 Dec;155(6):928-930.e1.

The importance of sweat testing for older siblings of patients with cystic fibrosis identified by newborn screening.

Munck A, Houssin E, Roussey M.

French Association for the Screening and Prevention of Infant Handicap AFDPHE, Paris, France.

We report cystic fibrosis (CF) care center instructions for sweat testing in older siblings after implementation of the French nationwide newborn screening program, and we evaluate the incidence of unrecognized CF. Nearly 9% of families with an infant screened for CF were unaware of an affected older sibling. We strongly recommend sweat testing for all first-degree older children.

2. J Pediatr. 2009 Dec;155(6):924-7.

Asymptomatic maternal combined homocystinuria and methylmalonic aciduria (cb1C) detected through low carnitine levels on newborn screening.

Lin HJ, Neidich JA, Salazar D, Thomas-Johnson E, Ferreira BF, Kwong AM, Lin AM, Jonas AJ, Levine S, Lorey F, Rosenblatt DS.

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A symptom-free woman gave birth to a girl with a low carnitine level on newborn screening. The baby was unaffected, but the mother had biochemical abnormalities and mutations characteristic of the cb1C defect of vitamin B(12) metabolism (late-onset form). This patient with cb1C was detected through her infant's newborn screening.

3. J Pediatr. 2009 Dec;155(6):829-33. Epub 2009 Jul 22.

Identification of severe combined immunodeficiency by T-cell receptor excision circles quantification using neonatal Guthrie cards.

Morinishi Y, Imai K, Nakagawa N, Sato H, Horiuchi K, Ohtsuka Y, Kaneda Y, Taga T, Hisakawa H, Miyaji R, Endo M, Oh-Ishi T, Kamachi Y, Akahane K, Kobayashi C, Tsuchida M, Morio T, Sasahara Y, Kumaki S, Ishigaki K, Yoshida M, Urabe T, Kobayashi N, Okimoto Y, Reichenbach J, Hashii Y, Tsuji Y, Kogawa K, Yamaguchi S, Kanegane H, Miyawaki T, Yamada M, Ariga T, Nonoyama S.

Department of Pediatrics, National Defense Medical College, Saitama, Japan.

OBJECTIVE: To assess the feasibility of T-cell receptor excision circles (TRECs) quantification for neonatal mass screening of severe combined immunodeficiency (SCID). STUDY DESIGN: Real-time

PCR based quantification of TRECs for 471 healthy control patients and 18 patients with SCID with various genetic abnormalities (IL2RG, JAK3, ADA, LIG4, RAG1) were performed, including patients with maternal T-cell engraftment (n = 4) and leaky T cells (n = 3). RESULTS: TRECs were detectable in all normal neonatal Guthrie cards (n = 326) at the levels of 10(4) to 10(5) copies/microg DNA. In contrast, TRECs were extremely low in all neonatal Guthrie cards (n = 15) and peripheral blood (n = 14) from patients with SCID, including those with maternal T-cell engraftment or leaky T cells with hypomorphic RAG1 mutations or LIG4 deficiency. There were no false-positive or negative results in this study. CONCLUSION: TRECs quantification can be used as a neonatal mass screening for patients with SCID.

4. Rapid Commun Mass Spectrom. 2009 Dec;23(23):3891-3.

The successful inclusion of succinylacetone as a marker of tyrosinemia type I in Tuscany newborn screening program.

la Marca G, Malvagia S, Funghini S, Pasquini E, Moneti G, Guerrini R, Zammarchi E.

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5. J Cyst Fibros. 2009 Nov 17. [Epub ahead of print]

Pulmonary outcome differences in U.S. and French cystic fibrosis cohorts diagnosed through newborn screening.

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BACKGROUND: A comparison of the longitudinal progression of lung disease in cystic fibrosis patients identified through newborn screening (NBS) in cohorts located in two different countries has never been performed and was the primary objective of this study. METHODS: The study included 56 patients in Brittany diagnosed through NBS between 1989 and 1994 and 69 similar patients in Wisconsin between 1985 and 1994. The onset and progression of lung disease was radiographically quantified using the Wisconsin Chest X-ray (WCXR) scoring system. A single pediatric pulmonologist blinded to all identifiers scored the films. RESULTS: Generalized estimating equation analyses adjusted for age, genotype, sex, pancreatic insufficiency, and meconium ileus showed worse WCXR scores in Brittany patients compared to Wisconsin patients (average score difference=4.48; p<0.001). Percent predicted FEV1 was also worse among Brittany patients (p<0.001). CONCLUSIONS: The finding of milder radiographically-quantified lung disease using the WCXR scoring system, as well as better FEV1 values, may be explained by variations in nutrition, environmental exposures, or healthcare delivery.

6. Int J Lab Hematol. 2009 Nov 16. [Epub ahead of print]

Application of an expanded multiplex genotyping assay for the simultaneous detection of Hemoglobin Constant Spring and common deletional alpha-thalassemia mutations.

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Hemoglobin Constant Spring (HbCS) is the most common nondeletional alpha-thalassemia variant causing HbH disease, making its detection crucial in populations at risk. Universal newborn screening for HbH is carried out in California. Identification of alpha-thalassemia genotypes responsible for HbH and HbH-CS requires rapid, accurate and cost-effective genotyping methods suitable for population screening. We incorporated the HbCS mutation into our existing seven-plex genotyping assay for common alpha-thalassemia deletions. To assess the feasibility and diagnostic utility of this expanded multiplex gap-PCR assay, we determined genotypic frequencies of HbCS in samples referred for alpha-thalassemia testing between 1 January 2006 and 31 December 2008. During the 3-year study period, 1436 samples were genotyped for alpha-thalassemia. HbH-CS accounted for 23 (13%) of the 176 cases of HbH disease identified. In a subset of 145 newborns referred by the California NBS program with an elevated Hb Bart's level at birth, HbH disease was confirmed in 134 (93%) and HbH-CS identified in 13 (10%) of these. This expanded genotyping assay has proven to be a rapid, reliable and clinically useful diagnostic tool for the detection of HbH-CS disease.

7. Semin Fetal Neonatal Med. 2009 Nov 16. [Epub ahead of print]

Fatty acid oxidation disorders: maternal health and neonatal outcomes.

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Mitochondrial fatty acid beta-oxidation (FAO) disorders have become an important group of inherited metabolic disorders causing serious pediatric and maternal morbidity and mortality. More than 20 defects affecting beta-oxidation have been discovered, characterized by distinct enzyme or transporter deficiencies. This growing number of FAO disorders covers a wide spectrum of phenotypes and are characterized by a wide array of clinical presentations. We discuss the major mitochondrial FAO disorders and the impact they have on maternal health and neonatal outcomes; diagnostic tools and the value of genetic screening are reviewed; and current therapeutic approaches and management strategies are discussed.

8. Thyroid. 2009 Nov 16. [Epub ahead of print]

Congenital Hypothyroidism and Late-Onset Goiter: Identification and Characterization of a Novel Mutation in the Sodium/Iodide Symporter of the Proband and Family Members.

Montanelli L, Agretti P, Marco GD, Bagattini B, Ceccarelli C, Brozzi F, Lettierio T, Cerbone M, Vitti P, Salerno M, Pinchera A, Tonacchera M.

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Background: Iodide transport defects (ITDs), rare causes of congenital hypothyroidism (CH), have been shown to arise from abnormalities of the sodium/iodide symporter (NIS). We describe a 16-year-old girl with CH caused by an ITD resulting from a novel mutation of NIS. Summary: A 16-year-old girl with CH

diagnosed by a neonatal screening program received early treatment with L-thyroxine replacement therapy. A ^{123}I scan had failed to reveal any iodide uptake by the thyroid and salivary glands; thus, thyroid agenesis was diagnosed. Thyroglobulin (Tg) was not measured when she was a neonate or infant. Unexpectedly, at the age of 14.5 years, a nodular goiter and high serum Tg concentrations (303 ng/mL; normal, <50) were identified. Her thyroid radioactive iodine uptake was very low as was the saliva to plasma iodide ratio (0.5). Analysis of her NIS gene revealed an in-frame six-nucleotide deletion of the coding sequence (1206-1211delGTCGGC) corresponding to the deletion of amino acids 287 and 288 of the human NIS protein located at the beginning of the VIII transmembrane segment. The proband was homozygous for this deletion, whereas both unrelated parents and her brother were heterozygous. COS-7 cells transfected with the mutant NIS failed to concentrate iodide, confirming that the mutation was the direct cause of the ITD in this patient. Conclusions: We describe a patient with CH caused by a previously not described mutation of the NIS gene that was inherited from her parents. We therefore recommend that thyroid ultrasonography be performed in CH patients with low radioactive iodine uptake and elevated serum Tg.

9. J Pediatr. 2009 Nov 13. [Epub ahead of print]

Newborn Population Screening for Classic Homocystinuria by Determination of Total Homocysteine from Guthrie Cards.

Gan-Schreier H, Kebbewar M, Fang-Hoffmann J, Wilrich J, Abdoh G, Ben-Omran T, Shahbek N, Bener A, Al Rifai H, Al Khal AL, Lindner M, Zschocke J, Hoffmann GF.

OBJECTIVE: To allow early recognition of cystathionine beta-synthase by newborn screening. STUDY DESIGN: Total homocysteine was determined in dried blood spots with a novel, robust high-performance liquid chromatography method with tandem mass spectrometry. Quantification of homocysteine was linear over a working range up to 50 $\mu\text{mol/L}$. For mutation analysis, DNA was tested for 2 mutations common in Qatar. RESULTS: Both methods proved to be suitable for high throughput processing. In 2 years, 7 infants with classic homocystinuria were identified of 12 603 native Qatari infants, yielding an incidence of 1:1800. Molecular screening would have missed 1 patient homozygous for a mutation not previously identified in the Qatari population. Over a period of 3 years, a total of 14 cases of classic homocystinuria were detected by screening of homocysteine from all newborn infants born in Qatar ($n = 46\ 406$). Homocysteine was always elevated, whereas methionine was elevated in only 7 cases. CONCLUSIONS: The study offers a reliable method for newborn screening for cystathionine beta-synthase deficiency, reaching a sensitivity of up to 100%, even if samples are taken within the first 3 days of life.

10. Curr Opin Endocrinol Diabetes Obes. 2009 Nov 6. [Epub ahead of print]

Fetal and neonatal thyroid function: review and summary of significant new findings.

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PURPOSE OF REVIEW: The purpose of this review is to briefly summarize current knowledge of fetal and neonatal thyroid function, and then to summarize the most significant new findings over the last year that add to our knowledge of the cause, diagnosis, and management of fetal and neonatal thyroid

disorders. RECENT FINDINGS: Significant findings from publications in the last year include a report that inadequate iodine intake during pregnancy exists in many parts of the world. Conversely, maternal exposure to iodinated contrast agents did not affect neonatal thyroid function. A small lowering in the screening of thyroid-stimulating hormone cutoff resulted in nearly a doubling of the birth prevalence of congenital hypothyroidism, but more cases had a thyroid gland 'in situ'. Partial iodination defects are relatively common causes of dysmorphogenesis. Tailoring the initial starting levothyroxine dose to severity of hypothyroidism resulted in rapid normalization of thyroid function. Although consensus guidelines recommend an initial starting dose in the 10-15-mug/kg/day range, the Cochrane collaborative did not find sufficient evidence from randomized controlled trials to confirm the high-dose recommendation. Under or overtreatment of childhood hypothyroidism appears to adversely impact adult cardiovascular function. Adults with congenital hypothyroidism are more likely to have quality of life issues. SUMMARY: Investigations of the impact of iodine and thyroid hormone transfer continue to improve our knowledge of maternal-fetal thyroid relationships. Screening programs to detect and treat newborns with congenital hypothyroidism have resulted in a dramatic improvement in neurocognitive outcome. Nevertheless, debate continues on the optimal screening test approach and thyroid hormone treatment.

11. Am J Med Genet A. 2009 Nov;149A(11):2424-9.

Maternal knowledge and attitudes about newborn screening for sickle cell disease and cystic fibrosis.

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Illinois introduced mandatory newborn screening (NBS) for sickle cell disease (SCD) in 1989 and for cystic fibrosis (CF) in 2008. We examined maternal understanding of NBS for SCD and CF, and their knowledge of the genetics, symptoms, and treatments of both conditions. Our methods consisted of conducting interviews of inpatient post-partum women (>18 years and English speaking). Our results showed that of the 388 eligible participants, 34 self-identified as sickle cell carriers, 1 with SCD and 1 as a CF carrier. Almost 3/4 were African American (282/387). Although all but 5 women had prenatal care, only 35% (133/378) recalled their prenatal care provider mentioning NBS, and only 56% (217/388) of participants recalled nursery staff mentioning NBS. There was more self-reported familiarity with SCD (3.32/5) than CF (1.97/5, $P < 0.001$). Over 2/3 (260/388) of participants could not answer CF knowledge questions because they had never heard of CF. Among those who had heard of the conditions, mean knowledge scores were 66% for SCD ($n = 372$) and 63% for CF ($n = 128$). Bivariate analysis identified education, age, race, marital status, and insurance status as statistically significant. After linear regression education remained significant for both conditions. We conclude that in a sample of predominantly African American post-partum women, we found poor understanding of NBS, greater familiarity with SCD, and significant knowledge gaps for both SCD and CF. There are many missed educational opportunities for educating parents about NBS and specific conditions included in NBS panels in both the obstetric clinics and the nursery. Copyright 2009 Wiley-Liss, Inc.

12. Clin Endocrinol (Oxf). 2009 Nov;71(5):739-45. Epub 2009 Mar 28.

A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency of congenital hypothyroidism (CH).

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CONTEXT: The guidelines of the National Academy of Clinical Biochemistry advocated the use of low bloodspot TSH (b-TSH) threshold for newborn screening of congenital hypothyroidism (CH). The impact generated by the application of this indication is largely unknown. OBJECTIVE: To determine the impact on CH epidemiology and classification generated by the introduction of low b-TSH cutoff. DESIGN: Retrospective study of 629,042 newborns screened with b-TSH cutoffs of 12 (years 1999-2002) or 10 mU/l (2003-2005). MEASUREMENTS: Congenital hypothyroidism incidence and classification. Results were compared with those virtually obtained with the previous cutoff (20 mU/l). Clinical re-evaluation after L-T4 withdrawal of a representative group of 140 CH children at 3-5 years. RESULTS: Low b-TSH cutoffs allowed the detection of 435 newborns with confirmed CH (incidence 1:1446). Forty-five percent of CH infants, including 12/141 dysgenesis, would have been missed using the 20 mU/l cutoff. In contrast to current classification, 32% CH newborns had thyroid dysgenesis and 68% had a gland in situ (GIS). Premature birth was present in 20% of cases being associated with a 3-5 fold increased risk of GIS CH. Re-evaluation at 3-5 years showed a permanent thyroid dysfunction in 78% of 59 CH toddlers with GIS. CONCLUSIONS: The use of low b-TSH cutoff allowed the detection of an unsuspected number of children with neonatal hypothyroidism, evolving in mild permanent thyroid dysfunction later in life. The incidence of CH in this Italian population appears to be double than previously thought with a clear-cut prevalence of functional defects over dysgenetic ones.

13. J Med Genet. 2009 Nov;46(11):752-8. Epub 2009 Jun 29.

The very low penetrance of cystic fibrosis for the R117H mutation: a reappraisal for genetic counselling and newborn screening.

Thauvin-Robinet C, Munck A, Huet F, Génin E, Bellis G, Gautier E, Audrézet MP, Férec C, Lalau G, Georges MD, Claustres M, Bienvenu T, Gérard B, Boisseau P, Cabet-Bey F, Feldmann D, Clavel C, Bieth E, Iron A, Simon-Bouy B, Costa C, Medina R, Leclerc J, Hubert D, Nové-Josserand R, Sermet-Gaudelus I, Rault G, Flori J, Leroy S, Wizla N, Bellon G, Haloun A, Perez-Martin S, d'Acromont G, Corvol H, Clément A, Houssin E, Binquet C, Bonithon-Kopp C, Alberti-Boulmé C, Morris MA, Faivre L, Goossens M, Roussey M; Collaborating Working Group on R117H and E Girodon.

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BACKGROUND: Cystic fibrosis (CF) is caused by compound heterozygosity or homozygosity of CF transmembrane conductance regulator gene (CFTR) mutations. Phenotypic variability associated with certain mutations makes genetic counselling difficult, notably for R117H, whose disease phenotype varies from asymptomatic to classical CF. The high frequency of R117H observed in CF newborn screening has also introduced diagnostic dilemmas. The aim of this study was to evaluate the disease penetrance for R117H in order to improve clinical practice. METHODS: The phenotypes in all individuals identified in France as compound heterozygous for R117H and F508del, the most frequent CF mutation, were described. The allelic prevalences of R117H (p(R117H)), on either intron 8 T5 or T7 background, and F508del (p(F508del)) were determined in the French population, to permit an evaluation of the penetrance of CF for the [R117H]+[F508del] genotype. RESULTS: Clinical details were documented for 184

[R117H]+[F508del] individuals, including 72 newborns. The disease phenotype was predominantly mild; one child had classical CF, and three adults' severe pulmonary symptoms. In 5245 healthy adults, p(F508del) was 1.06%, p(R117H;T7) 0.27% and p(R117H;T5)<0.01%. The theoretical number of [R117H;T7]+[F508del] individuals in the French population was estimated at 3650, whereas only 112 were known with CF related symptoms (3.1%). The penetrance of classical CF for [R117H;T7]+[F508del] was estimated at 0.03% and that of severe CF in adulthood at 0.06%.
CONCLUSIONS: These results suggest that R117H should be withdrawn from CF mutation panels used for screening programmes. The real impact of so-called disease mutations should be assessed before including them in newborn or preconceptional carrier screening programmes.

14. J Pediatr. 2009 Nov;155(5):605-6.

Cystic fibrosis: refining the approach to newborn screening.

Wilcken B.

Comment on:

- J Pediatr. 2009 Nov;155(5):618-22.

15. J Pediatr. 2009 Nov;155(5):623-8.e1. Epub 2009 Jul 19.

Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening.

Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, Gangell CL, De Klerk N, Linnane B, Ranganathan S, Robinson P, Robertson C, Sly PD; Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF).

Collaborators (19)

Balding E, Berry LJ, Calogero C, Carlin JB, Carzino R, Hall GL, Kicic A, Laing IA, Logie KM, Massie J, Mott LS, Mullane D, Nolan G, Pillarisetti N, Poreddy SR, Robins-Browne R, Skoric B, Sutanto EN, Williamson E.

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Comment in:

- J Pediatr. 2009 Nov;155(5):629-33.

OBJECTIVES: To determine the prevalence of bronchiectasis in young children with cystic fibrosis (CF) diagnosed after newborn screening (NBS) and the relationship of bronchiectasis to pulmonary inflammation and infection. STUDY DESIGN: Children were diagnosed with CF after NBS. Computed tomography and bronchoalveolar lavage were performed with anesthesia (n = 96). Scans were analyzed for the presence and extent of abnormalities. RESULTS: The prevalence of bronchiectasis was 22% and increased with age (P = .001). Factors associated with bronchiectasis included absolute neutrophil count

($P = .03$), neutrophil elastase concentration ($P = .001$), and *Pseudomonas aeruginosa* infection ($P = .03$).
CONCLUSIONS: Pulmonary abnormalities are common in infants and young children with CF and relate to neutrophilic inflammation and infection with *P. aeruginosa*. Current models of care for infants with CF fail to prevent respiratory sequelae. Bronchiectasis is a clinically relevant endpoint that could be used for intervention trials that commence soon after CF is diagnosed after NBS.

16. J Pediatr. 2009 Nov;155(5):646-50. Epub 2009 Jul 19.

Evaluation of hearing loss after failed neonatal hearing screening.

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OBJECTIVE: We evaluated the causes of hearing loss found after failed universal newborn hearing screening and compared the results with the previously used behavioral observation test (Ewing/CAPAS).
STUDY DESIGN: Hearing loss in neonates, born between September 1999 and October 2007 and referred to our center after failed screening, was determined by audiologic testing and physical examination.
RESULTS: In 340 included neonates the results of hearing tests were as follows: normal hearing 21.2%, conductive hearing loss 20.3%, and sensorineural hearing loss (SNHL) 57.9%. Children referred from the neonatal intensive care unit were more at risk of SNHL (71%) than those from the well-baby clinics (54%). Hearing aids were provided at a median age of 8 months. The positive predictive value of SNHL screening was 54% for a child from a well-baby clinic and 71% for a child from the neonatal intensive care unit.
CONCLUSION: The use of universal newborn hearing screening results in a lower proportion of infants positive because of otitis media with effusion than the previously used Ewing/CAPAS test (20% vs 59-81%). Second, screening leads to identification of hearing loss and intervention at a younger age (8 months vs 15-18 months). Third, the positive predictive value for SNHL has improved (54% vs 2%).

17. J Pediatr. 2009 Nov;155(5):618-22. Epub 2009 Jun 21.

A new cystic fibrosis newborn screening algorithm: IRT/IRT1 upward arrow/DNA.

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Comment in:

- J Pediatr. 2009 Nov;155(5):605-6.

OBJECTIVE: To evaluate an immunoreactive trypsinogen (IRT) IRT/IRT1 upward arrow/DNA algorithm, aimed at improving sensitivity while decreasing cystic fibrosis (CF) carrier identification.
STUDY DESIGN: New technologies allow the measurement of the second IRT level solely in infants with an elevated first IRT level. Specimens with an elevated second IRT level undergo mutation analysis.

We tested the projected efficacy with retrospective data from Colorado. RESULTS: All known infants with CF would have been identified with our proposed IRT cutoff points, and 3 would have been missed with our mutation panel. Two of 3 missed cases would have been identified by using a failsafe method (IRT >99.9th percentile), yielding a sensitivity rate of 99.7% (95% CI, 98.4-99.9). Estimated reduction in carrier detection was 80% compared with IRT/DNA. CONCLUSION: IRT/IRT1 upward arrow/DNA appears to improve cystic fibrosis newborn screen sensitivity while decreasing carrier identification, providing an alternative to IRT/IRT in states that obtain 2 blood spots.

18. J Public Health Manag Pract. 2009 Nov-Dec;15(6):451-8.

Integrating child health information systems in public health agencies.

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Public health agencies at state and local levels are integrating information systems to improve health outcomes for children. An assessment was conducted to describe the extent to which public health agencies are currently integrating child health information systems (CHIS). Using online technology information was collected, to assess completed and planned activities related to integration of CHIS, maturity of these systems, and factors that influence decisions by public health agencies to pursue integration activities. Of the 39 public health agencies that participated, 18 (46%) reported already integrating some or all of their CHIS, and 13 (33%) reported to be planning to integrate during the next 3 years. Information systems most commonly integrated include Early Hearing Detection and Intervention (EHDI), immunization, vital records, and Newborn Dried Bloodspot Screening (NDBS). Given the high priority that has been placed on using technology to improve health status in the United States, the emphasis on expanding the capability for the electronic exchange of health information, and federal support for electronic health records by 2014, public health agencies should be encouraged and supported in their efforts to develop, implement, and maintain integrated CHIS to facilitate the electronic exchange of health information with the clinical healthcare sector.

19. Mol Genet Metab. 2009 Nov;98(3):273-7. Epub 2009 Jun 25.

Argininosuccinate lyase deficiency: longterm outcome of 13 patients detected by newborn screening.

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Argininosuccinate lyase deficiency is a urea cycle disorder which can present in the neonatal period with hyperammonemic encephalopathy, or later in childhood with episodic vomiting, growth and developmental delay. Abnormal hair, hepatomegaly, and hepatic fibrosis are unique features of this disorder. Twelve patients with argininosuccinate lyase deficiency were ascertained between 4 and 6

weeks of age by urine amino acid screening. One infant in a previously identified family was diagnosed shortly after birth. Diagnosis was confirmed by enzyme assay in red blood cells and/or skin fibroblasts. At the time of last follow-up, patients had been followed for 13-33 years. All patients were asymptomatic at detection, 7 had slightly increased blood ammonia, and all were initially treated with low-protein diet. Utilization of (14)C-citrulline by intact skin fibroblasts measured by (14)C incorporation into macromolecules was 74-135% of the control mean for 7 of the 8 patients studied. Nine patients had normal development, 4 had learning disability, 6 had EEG abnormalities, 3 had seizure disorder. None had any episodes of hyperammonemic coma. None had hepatomegaly. Patients detected by screening had higher enzyme activity measured by the (14)C-citrulline incorporation assay than comparison groups of patients with neonatal-onset and with late-onset detected by clinical disease. The ability to utilize (14)C-citrulline by intact fibroblasts seems to correlate with clinical outcome and may have prognostic value. It is likely that early diagnosis and treatment contributed to the relatively mild clinical course of the study group.

20. Clin Chem Lab Med. 2009 Oct 28. [Epub ahead of print]

Quantitation of RNA decay in dried blood spots during 20 years of storage.

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Abstract Background: Diseases with an onset during childhood or adult life can have their origin during fetal life or at birth. Neonatal blood dried on filter paper (Guthrie cards) collected for screening purposes is routinely stored for decades. In addition to clinical use, these filters in combination with patient registers constitute an invaluable resource for epidemiological and pathophysiological research. Although RNA has been successfully recovered from such filters even after decades of storage, the potential decay of RNA over time has not previously been investigated using quantitative methods. Methods: Filter papers (n=5) with dried blood spots from the Swedish National PKU register, stored for 1, 5, 10, 15 or 20 years were randomly selected. RNA was isolated from each sample, quantitated by spectrophotometry and reverse transcribed following DNase I treatment. Amplifiable cDNA was subsequently detected by real-time PCR using primers specific for transcripts encoding beta-actin. Results: Transcripts encoding beta-actin were detected in all 25 samples analyzed at a mean threshold cycle (Ct) of 25 (SD 1.9). A one-way ANOVA indicated no significant effect of storage time on Ct values. Conclusions: The lack of significant decay of RNA in dried blood filters stored for up to 20 years suggests that such filters are useful for studies of RNA determinants of diseases with an onset in childhood as well as adult life. Clin Chem Lab Med 2009;47.

21. Clin Biochem. 2009 Oct 22. [Epub ahead of print]

Identification of a neonate with hepatorenal tyrosinemia by combined routine newborn screening for succinylacetone, acylcarnitines and amino acids.

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22. Clin Chem. 2009 Oct 22. [Epub ahead of print]

Preliminary Proficiency Testing Results for Succinylacetone in Dried Blood Spots for Newborn Screening for Tyrosinemia Type I.

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BACKGROUND: Succinylacetone (SUAC) is the primary metabolite accumulated in tyrosinemia type I—an inborn error of metabolism that, if untreated, can cause death from liver failure during the first months of life. Newborn screening laboratories measure SUAC in dried blood spot (DBS) samples to detect asymptomatic tyrosinemia type I. We used panels of SUAC-enriched DBSs to compare and evaluate the performance of these screening tests. **METHODS:** We prepared sets of DBS materials enriched with predetermined SUAC concentrations and distributed samples of these materials, along with a screening practices questionnaire, to laboratories that perform SUAC tests. We compared their reported SUAC concentrations and questionnaire responses to identify screening practices that affect SUAC test outcomes. **RESULTS:** Data from 2 pilot surveys showed large differences among laboratories in SUAC recoveries, reproducible within-laboratory recoveries, and stable performance of the DBS materials. Results from 257 proficiency test analyses contained a total of 6 false-negative misclassifications. Reported recoveries of added SUAC ranged from 0 to >200%. Low-biased SUAC recoveries were associated with 1 method used by 5 laboratories. All laboratories that reported SUAC recoveries $\geq 100\%$ used DBS matrix calibrators. **CONCLUSIONS:** The wide ranges of SUAC concentrations reported for pilot and proficiency testing specimens demonstrate a need to harmonize quantitative results among laboratories. Although DBS matrix calibrators are important for optimizing SUAC recoveries, the preparation of these calibrators is not standardized among laboratories. Certified DBS-based SUAC calibrators are needed for accuracy and harmonization.

23. J Child Neurol. 2009 Oct 21. [Epub ahead of print]

Utilization of Blood Spot Testing for Metabolic-Genetic Disorders in Honduras: Is it Time for Newborn Screening?

Slaughter JL, Espinoza L, Molinero I, Wood TC, Duron C, Flores A, Porter R, Tomashitis K, Holden KR.

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Honduran infant mortality (20/1000) has fallen below the Latin American newborn screening target rate (<30/1000). The authors report 2 Honduran maple syrup urine disease cases and a newborn screening pilot study. The first infant, diagnosed by plasma/urine testing in the U.S., prompted this study. Although marked clinical/radiological improvement occurred after treatment, moderate neurodevelopmental delays persist at 5 years. This 1-month, prospective study used blood spot specimens from hospitalized term Honduran neonates shipped overnight to South Carolina for routine newborn screening with electronic

result submission to Honduras for follow-up. Of 88 consecutive neonates (mean age: 4.2 days, standard deviation: 4.2 days) tested, 24 (0.6%) of 3837 completed tests were positive. Another infant with maple syrup urine disease, diagnosed after study completion by blood spot testing, later died. The study findings indicate that collaborative blood spot testing aids in the diagnosis of Honduran metabolic-genetic disease. Newborn screening is now needed to diagnose and treat these diseases before morbidity/mortality develops.

24. Pediatrics. 2009 Oct 19. [Epub ahead of print]

Heel-Lancing in Newborns: Behavioral and Spectral Analysis Assessment of Pain Control Methods.

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Objective: Pain experience can alter clinical outcome, brain development, and subsequent behavior in newborns, primarily in preterm infants. The aims of this study were (1) to evaluate several simple, commonly used methods for pain control in newborns and (2) to evaluate the concordance between behavioral and autonomic cardiac reactivity to pain in term neonates during heel-lancing. Methods: A prospective study was conducted of 180 term newborn infants who were undergoing heel-lancing for routine neonatal screening of phenylketonuria and hypothyroidism. Newborns were assigned to 6 groups: (1) control (no pain relief intervention); (2) nonnutritive sucking; (3) holding by mother; (4) oral glucose solution; (5) oral formula feeding; or (6) breastfeeding. Outcome measures included the Neonatal Facial Coding System score; cry duration; and autonomic variables obtained from spectral analysis of heart rate variability before, during, and after heel-lancing. Results: Infants with no pain control showed the highest pain manifestation compared with newborns to whom pain control was provided. Infants who breastfed or received an oral formula showed the lowest increase in heart rate (21 and 23 beats per minute, respectively, vs 36; $P < .01$), lowest neonatal facial score (2.3 and 2.9, respectively, vs 7.1; $P < .001$), lowest cry duration (5 and 13 seconds, respectively, vs 49; $P < .001$), and lowest decrease in parasympathetic tone (-2 and -2.4, respectively, vs 1.2; $P < .02$) compared with the other groups. Conclusions: Any method of pain control is better than none. Feeding and breastfeeding during heel-lancing were found to be the most effective methods of pain relief.

25. J Inherit Metab Dis. 2009 Oct 11. [Epub ahead of print]

Adult presentations of medium-chain acyl-CoA dehydrogenase deficiency (MCADD).

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Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive disorder of mitochondrial fatty acid oxidation which is usually diagnosed in infancy or through neonatal screening. In the absence of population screening, adults with undiagnosed MCADD can be expected. This review discusses 14 cases that were identified during adulthood. The mortality of infantile patients is approximately 25% whereas in this adult case series it was shown to be 50% in acutely presenting patients and 29% in total. Therefore, undiagnosed individuals are at risk of sudden fatal metabolic

decompensation with high mortality. This review illustrates the need to consider the possibility of a fatty acid oxidation defect in an adult who presents with unexplained sudden clinical deterioration, particularly if precipitated by fasting or alcohol consumption. A history of unexplained sibling death may also raise the index of suspicion. There also needs to be appropriate clinical support for those patients identified clinically or as a result of family studies (sibling or parent).

26. Eur J Pediatr. 2009 Oct 8. [Epub ahead of print]

Significant increase of succinylacetone within the first 12 h of life in hereditary tyrosinemia type 1.

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INTRODUCTION: In most countries, hereditary tyrosinemia type 1 is not included in routine newborn screening. **DISCUSSION:** We present the case of a female newborn with prenatal diagnosis of hereditary tyrosinemia type 1 and clear identification of this disorder by succinylacetone measurement in cord blood and peripheral blood immediately after birth. Succinylacetone was 44 $\mu\text{mol/L}$ (norm $<5 \mu\text{mol/L}$) and increased within 12 h to 87.5 $\mu\text{mol/L}$. **CONCLUSION:** With the high toxic potential of downstream metabolites, these data clearly point out the necessity of early nitisinone treatment to prevent symptomatic disease.

27. Pediatr Infect Dis J. 2009 Oct 8. [Epub ahead of print]

Detection of Cytomegalovirus DNA in Dried Blood Spots of Minnesota Infants Who Do Not Pass Newborn Hearing Screening.

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BACKGROUND:: Up to 15% of infants with asymptomatic congenital cytomegalovirus (CMV) infection will experience some degree of sensorineural hearing loss. Many infants who fail newborn hearing screening (NHS) are likely to have congenital CMV infection, but may escape definitive virologic identification because diagnostic evaluation may not commence until several weeks or months of age, making differentiation between congenital and postnatal CMV infection difficult. Early diagnosis linking virologic identification of congenital CMV infection to infants failing NHS may improve diagnostic precision and enhance opportunities for therapeutic intervention. **METHODS::** The goal of this study was to compare newborn dried blood spots from Minnesota infants who had failed NHS, and were designated for referral, with control infants who passed NHS, for the presence of CMV DNA by real-time PCR, using hybridization probes for the CMV gene UL54. **RESULTS::** Of 479 infants with a failed NHS (bilateral failure), 13 had CMV DNA present in the blood spot (2.7%). This compared with only 2/479 positive results from a control group of infants who passed the NHS (0.4%; $P = 0.007$, Fisher exact test).

Analysis of the glycoprotein B (gB) genotype revealed that these PCR positive samples represented separate, distinct clinical isolates. The mean viral load among the 13 positive samples was 1.8×10 genomes/microgram of total DNA. CONCLUSIONS:: Newborn bloodspot CMV screening by real-time PCR may be a useful and rapid adjunct to functional NHS and may enable more rapid etiologic diagnosis of sensorineural hearing loss in newborns.

28. Eur J Hum Genet. 2009 Oct 7. [Epub ahead of print]

Understanding sickle cell carrier status identified through newborn screening: a qualitative study.

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The expansion of newborn screening (NBS) is increasing the generation of incidental results, notably carrier results. Although carrier status is generally understood to be clinically benign, concerns persist that parents may misunderstand its meaning, with deleterious effects on children and their families. Expansion of the NBS panel in Ontario, Canada in 2006 to include sickle cell disorders drew attention to the policy challenge of incidental carrier results. We conducted a study of consumer and provider attitudes to inform policy on disclosure. In this paper, we report the results of (i) qualitative interviews with health-care providers, advocates and parents of carrier infants and (ii) focus groups with new parents and individuals active with the sickle cell community. Lay and provider participants generally believed that carrier results were clinically insignificant. However, some uncertainty persisted among lay consumers in the form of conjecture or doubt. In addition, consumers and advocates who were most informed about the disease articulated insistent yet dissonant claims of clinical significance. Meanwhile, providers referenced research knowledge to offer an equivocal assessment of the possibility and significance of clinically symptomatic carrier status. We conclude that many interpretations of carrier status are in circulation, failing to fit neatly into the categories of 'clinically significant' or 'benign.' This creates challenges for communicating clearly with parents - challenges exacerbated by inconsistent messages from screening programs regarding the significance of sickle cell carrier status. Disclosure policy related to incidentally generated infant carrier results needs to account for these complex realities

29. Genet Test Mol Biomarkers. 2009 Oct 7. [Epub ahead of print]

High-Risk Fragile X Screening in Guatemala: Use of a New Blood Spot Polymerase Chain Reaction Technique.

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Background: Because fragile X syndrome (FXS) is prevalent, it has become the subject of newborn and high-risk screening efforts. International screening, however, can be financially and logistically prohibitive, particularly in countries where resources may be scarce. Recently, we have developed a screening test on blood spot that can detect expanded alleles from the normal through the full mutation range in both males and females. It is accurate, rapid, inexpensive, and applicable on blood spots and therefore ideal for international screening. The use of this blood spot screening technique was piloted in

"a high-risk screening" study of individuals in Guatemala. Methods: One hundred and five blood spots from subjects from Guatemala were screened for the Fragile X Mental Retardation 1 mutation. They were classified as "high-risk" through placement into one of the following five categories: (a) relatives of someone with a previous FXS diagnosis, (b) individuals with confirmed autism, (c) individuals with confirmed intellectual disability, (d) individuals with Parkinson's-like presentation, and (e) individuals with a family history of intellectual disability but no confirmed cases of FXS. Results: Fifteen of the individuals tested yielded an expanded allele, 10 premutations and 5 full mutations. All 15 expansions were found in individuals with a relative with a confirmed FXS diagnosis. No expansions were found in the other clinical groups. Conclusions: Blood spot polymerase chain reaction screening is an effective, cost-efficient method to conduct cascade testing in families with a known history of FXS, even in small screening cohorts.

30. Braz J Med Biol Res. 2009 Oct;42(10):973-8. Epub 2009 Sep 4.

Neonatal screening for cystic fibrosis in São Paulo State, Brazil: a pilot study.

Rodrigues R, Magalhaes PK, Fernandes MI, Gabetta CS, Ribeiro AF, Pedro KP, Valdetaro F, Santos JL, de Souza RM, Pazin Filho A, Maciel LM.

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Cystic fibrosis is one of the most common autosomal recessive hereditary diseases in the Caucasian population, with an incidence of 1:2000 to 1:3500 liveborns. More than 1000 mutations have been described with the most common being F508del. It has a prevalence of 23-55% within the Brazilian population. The lack of population-based studies evaluating the incidence of cystic fibrosis in São Paulo State, Brazil, and an analysis concerning the costs of implantation of a screening program motivated the present study. A total of 60,000 dried blood samples from Guthrie cards obtained from April 2005 to January 2006 for neonatal screening at 4 reference centers in São Paulo State were analyzed. The immunoreactive trypsinogen (IRT)/IRT protocol was used with the cut-off value being 70 ng/mL. A total of 532 children (0.9%) showed IRT >70 ng/mL and a 2nd sample was collected from 418 (80.3%) of these patients. Four affected children were detected at two centers, corresponding to an incidence of 1:8403. The average age at diagnosis was 69 days, and 3 of the children already showed severe symptoms of the disease. The rate of false-positive results was 95.2% and the positive predictive value for the test was 8%. The cost of detecting an affected subject was approximately US\$8,000.00 when this cystic fibrosis program was added to an existing neonatal screening program. The present study clearly shows the difficulties involved in cystic fibrosis screening using the IRT/IRT protocol, particularly in a population with no long-term tradition of neonatal screening.

31. Can Fam Physician. 2009 Oct;55(10):1001.

Genetics: Newborn screening for sickle cell anemia.

Meschino WS, Gibbons CA, Allanson J, Blaine SM, Cremin C, Dorman H, Honeywell C, Permaul J, Wilson BJ, Carroll JC.

32. Genet Med. 2009 Oct;11(10):716-21.

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.

33. Hum Mutat. 2009 Oct;30(10):1397-405.

Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A (IVS4+919G>A).

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Fabry disease (alpha-galactosidase A (alpha-Gal A, GLA) deficiency) is a panethnic inborn error of glycosphingolipid metabolism. Because optimal therapeutic outcomes depend on early intervention, a pilot program was designed to assess newborn screening for this disease in 171,977 consecutive Taiwanese newborns by measuring their dry blood spot (DBS) alpha-Gal A activities and beta-galactosidase/alpha-Gal A ratios. Of the 90,288 male screenees, 638 (0.7%) had DBS alpha-Gal A activity <30% of normal mean and/or activity ratios >10. A second DBS assay reduced these to 91 (0.1%). Of these, 11 (including twins) had <5% (Group-A), 64 had 5-30% (Group-B), and 11 had >30% (Group-C) of mean normal leukocyte alpha-Gal A activity. All 11 Group-A, 61 Group-B, and 1 Group-C males had GLA gene mutations. Surprisingly, 86% had the later-onset cryptic splice mutation c.936+919G>A (also called IVS4+919G>A). In contrast, screening 81,689 females detected two heterozygotes. The novel mutations were expressed in vitro, predicting their classical or later-onset

phenotypes. Newborn screening identified a surprisingly high frequency of Taiwanese males with Fabry disease (approximately 1 in 1,250), 86% having the IVS4+919G>A mutation previously found in later-onset cardiac phenotype patients. Further studies of the IVS4 later-onset phenotype will determine its natural history and optimal timing for therapeutic intervention.

34. J Inherit Metab Dis. 2009 Oct;32(5):597-608. Epub 2009 Aug 14.

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.

35. J Matern Fetal Neonatal Med. 2009 Oct;22(10):943-8.

Undiagnosed maternal phenylketonuria: own clinical experience and literature review.

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Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine (Phe) metabolism resulting from deficiency of phenylalanine hydroxylase (PAH). Most forms of PKU are caused by mutations in the PAH gene. Untreated PKU is associated with an abnormal phenotype, which includes growth failure, seizures, global developmental delay and severe intellectual impairment. The maternal PKU (MPKU) syndrome is caused by high blood Phe concentrations during pregnancy and presents with serious foetal anomalies, especially microcephaly, congenital heart disease and mental retardation. However, since the introduction of newborn screening programs and with early dietary intervention, children born with PKU can now expect to lead relatively normal lives. We present the case of a 33-year-old woman who had been diagnosed as having PKU only after a pregnancy with MPKU embryopathy, to emphasize that undiagnosed maternal phenylketonuria still exists. On that ground, we reviewed updated literature on the pathogenesis of this syndrome, possibility of prophylaxis and treatment.

36. J Med Ethics. 2009 Oct;35(10):626-34.

Clinical obligations and public health programmes: healthcare provider reasoning about managing the incidental results of newborn screening.

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BACKGROUND: Expanded newborn screening generates incidental results, notably carrier results. Yet newborn screening programmes typically restrict parental choice regarding receipt of this non-health serving genetic information. Healthcare providers play a key role in educating families or caring for screened infants and have strong beliefs about the management of incidental results. **METHODS:** To inform policy on disclosure of infant sickle cell disorder (SCD) carrier results, a mixed-methods study of healthcare providers was conducted in Ontario, Canada, to understand attitudes regarding result management using a cross-sectional survey (N = 1615) and semistructured interviews (N = 42). **RESULTS:** Agreement to reasons favouring disclosure of SCD carrier results was high (65.1%-92.7%) and to reasons opposing disclosure was low (4.1%-18.1%). Genetics professionals expressed less support for arguments favouring disclosure (35.3%-78.8%), and more agreement with arguments opposing disclosure (15.7%-51.9%). A slim majority of genetics professionals (51.9%) agreed that a reason to avoid disclosure was the importance of allowing the child to decide to receive results. Qualitatively, there was a perceived "duty" to disclose, that if the clinician possessed the information, the clinician could not withhold it. **DISCUSSION:** While a majority of respondents perceived a duty to disclose the incidental results of newborn screening, the policy implications of these attitudes are not obvious. In particular, policy must balance descriptive ethics (ie, what providers believe) and normative ethics (ie, what duty-based principles oblige), address dissenting opinion and consider the relevance of moral principles grounded in clinical obligations for public health initiatives.

37. J Perinat Neonatal Nurs. 2009 Oct-Dec;23(4):326-34.

Newborn screening: an appeal for improved parent education.

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OBJECTIVE: The purpose of this study, which was part of a larger investigation of newborn screening (NBS) for cystic fibrosis (CF), was to learn how parents were informed about NBS and obtain their suggestions for improving the process of educating parents about NBS. **METHOD:** Qualitative study using directed and summative content analyses was conducted on 100 interviews with 193 parents of 100 newborns recruited from 4 clinical populations including parents of infants with (1) a CF diagnosis, (2) one CF mutation and therefore CF carriers, (3) congenital hypothyroidism, and (4) normal screening results. **RESULTS:** Parents described much inconsistency in the timing of and methods used to inform them about NBS. Mothers with higher income were 3.69 times more likely to receive information before their infants' births than mothers with lower income. Parents recommended improving verbal and written communication with parents about NBS at multiple junctures from preconception to the infant's first few days of life. Parents suggested that providers take time to explain the purpose and importance of NBS,

which diseases are included in testing, and when parents can expect results. CONCLUSION: These findings suggest a need to establish evidence-based guidelines for informing parents about NBS.

38. Nat Rev Genet. 2009 Oct;10(10):666-7.

The expansion of newborn screening: is reproductive benefit an appropriate pursuit?

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39. 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.

40. Clin Chem. 2009 Sep;55(9):1615-26. Epub 2009 Jul 2.

National academy of clinical biochemistry laboratory medicine practice guidelines: follow-up testing for metabolic disease identified by expanded newborn screening using tandem mass spectrometry; executive summary.

Dietzen DJ, Rinaldo P, Whitley RJ, Rhead WJ, Hannon WH, Garg UC, Lo SF, Bennett MJ.

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BACKGROUND: Almost all newborns in the US are screened at birth for multiple inborn errors of metabolism using tandem mass spectrometry. Screening tests are designed to be sufficiently sensitive so that cases are not missed. The NACB recognized a need for standard guidelines for laboratory confirmation of a positive newborn screen such that all babies would benefit from equal and optimal follow-up by confirmatory testing. **METHODS:** A committee was formed to review available data pertaining to confirmatory testing. The committee evaluated previously published guidelines, published methodological and clinical studies, clinical case reports, and expert opinion to support optimal confirmatory testing. Grading was based on guidelines adopted from criteria derived from the US

Preventive Services Task Force and on the strength of recommendations and the quality of the evidence. Three primary methods of analyte measurement were evaluated for confirmatory testing including measurement of amino acids, organic acids, and carnitine esters. The committee graded the evidence for diagnostic utility of each test for the screened conditions. RESULTS: Ample data and experience were available to make strong recommendations for the practice of analyzing amino acids, organic acids, and acylcarnitines. Likewise, strong recommendations were made for the follow-up test menu for many disorders, particularly those with highest prevalence. Fewer data exist to determine the impact of newborn screening on patient outcomes in all but a few disorders. The guidelines also provide an assessment of developing technology that will fuel a refinement of current practice and ultimate expansion of the diseases detectable by tandem mass spectrometry. CONCLUSIONS: Guidelines are provided for optimal follow-up testing for positive newborn screens using tandem mass spectrometry. The committee regards these tests as reliable and currently optimal for follow-up testing. .

41. 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.

42. Genet Med. 2009 Sep;11(9):663-8.

Conference report: second conference of the Middle East and North Africa newborn screening initiative: Partnerships for sustainable newborn screening infrastructure and research opportunities.

Krotoski D, Namaste S, Raouf RK, El Nekhely I, Hindi-Alexander M, Engelson G, Hanson JW, Howell RR; MENA NBS Steering Committee.

Collaborators (21)

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The second conference of the Middle East and North Africa newborn screening initiative: partnerships for sustainable newborn screening infrastructure and research opportunities was held in Cairo, Arab Republic of Egypt on April 12 to 14, 2008. Policy makers, health ministry representatives, health care providers, and experts from the region, Europe, Asia, and North America participated. The primary outcome was development of country plans of action to implement or expand newborn screening programs. Country representatives were grouped by current levels of national newborn screening activities based on a Needs Assessment Survey for national newborn screening programs and assisted by international technical experts. The Needs Assessment Survey provided information on the level of newborn screening in each country, strengths and barriers to implementation of newborn screening programs, and identified areas for research. Newborn screening programs require an integrated system of laboratories, health care providers, and educators, thus, the infrastructure put in place to screen for one condition should support expansion to other conditions. Congenital hypothyroidism was selected for initiating newborn screening programs because of its high prevalence, availability of screening methods, and cost-effective intervention. To this end, the conference provided technical sessions on screening and treatment of congenital hypothyroidism, performance standards, quality assurance, follow-up interventions, and patient management. In addition, presentations highlighted the value of integrating research into newborn screening programs as they are established and in evaluating outcomes. Research opportunities were identified at a postconference workshop sponsored by the US Civilian Research Development Foundation.

43. Lancet Oncol. 2009 Sep;10(9):920-5.

Highly prevalent TP53 mutation predisposing to many cancers in the Brazilian population: a case for newborn screening?

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The unusually high population frequency of a germline TP53 mutation (R337H) predisposing to early cancer has led to mass newborn testing for this mutation in the State of Paraná, southern Brazil. Newborn screening for inherited cancer risk is complex and controversial. In this paper, we discuss the justifications for this screening by considering the medical and scientific evidence for this mutation. R337H has been identified in Brazilian families with Li-Fraumeni or related syndromes predisposing to

cancers in childhood (ie, brain, renal, and adrenocortical carcinomas), adolescence (ie, soft tissue and bone sarcomas), and young adulthood (ie, breast cancer). R337H has also been detected in children with adrenocortical carcinoma without a documented family history of cancer. The mutation is estimated to occur in about 0.3% of the population in southern Brazil and is associated with increased cancer risk throughout life. Cancer patterns in families positive for R337H suggest strong genetic modifying effects, making it difficult to predict individual risk. Because protocols for cancer-risk management in Li-Fraumeni or related syndromes are debatable, extreme care should prevail in predictive testing of children for R337H. A detailed assessment of the risks, benefits, and costs is needed to ensure that medical, social, and ethical justifications for newborn screening are met.

44. Int J Pediatr Otorhinolaryngol. 2009 Sep 29. [Epub ahead of print]

Newborn hearing screening on infants at risk.

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OBJECTIVES: This article presents the results of newborn hearing screenings on infants at risk of hearing impairment at the French University Hospital of Besançon from 2001 to 2007. **MATERIALS AND METHODS:** All newborns at risk of hearing impairment were tested according to the method recommended by the Joint Committee on Infant Hearing (JCIH): a two-step automated oto-acoustic emissions (AOAE) program, completed by an auditory brainstem response (ABR) for the positive diagnosis of hearing impairment. The screening started with AOAE on the third day of life, at the earliest. If one or both ears did not have AOAE, the infant was re-tested at which time, should the AOAE again be positive, ABR was performed. When the ABR threshold was 40dB or more, the infant was referred to an audiologist specialized in infant deafness for diagnosis confirmation and management. **RESULTS:** Over the period, 1461 infants were screened, among whom 4.55% were diagnosed as deaf or hard of hearing. Nearly 10% of the infants were lost to follow up. Forty-six children had a sensorineural hearing impairment, of which 34 were bilateral and were managed before the age of 6 months. The risk factors for sensorineural hearing loss were (in order of statistical significance): severe birth asphyxia; neurological disorder; syndromes known to be associated with hearing loss; TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes) infections; family history of deafness; age at the time of screening; and the association of 2 or more risk factors. However, birth weight inferior to 1500g and premature birth before the 34th week of pregnancy did not show a statistically significant influence on sensorineural hearing loss. Craniofacial anomalies (mostly cleft palate and ear aplasia) were a significant factor for conductive hearing loss. **CONCLUSION:** Our selected hearing screening on infants at risk allowed 60 deaf children access to early management. However, too many children were lost to follow up; which revealed that better information regarding risk of hearing loss must be provided to parents and paramedics and universal newborn screening needs to be performed. The most important result of this study is that in a population of hearing impaired children, with an impairment incidence close to what is commonly reported, the association of several risk factors proves to be a significant additional risk factor for hearing impairment.

45. BMJ. 2009 Sep 28;339:b3984.

Doctors explore research potential of blood samples from newborns.

Roehr B.

46. Mol Genet Metab. 2009 Sep 27. [Epub ahead of print]

Newborn screening and early biochemical follow-up in combined methylmalonic aciduria and homocystinuria, cblC type, and utility of methionine as a secondary screening analyte.

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INTRODUCTION: Combined methylmalonic aciduria and homocystinuria, cobalamin C (cblC) type, is an inherited disorder of vitamin B(12) metabolism caused by mutations in MMACHC. CblC typically presents in the neonatal period with neurological deterioration, failure to thrive, cytopenias, and multisystem pathology including renal and hepatic dysfunction. Rarely, affected individuals present in adulthood with gait ataxia and cognitive decline. Treatment with hydroxocobalamin may ameliorate the clinical features of early-onset disease and prevent clinical late-onset disease. Propionic acidemia (PA), methylmalonic acidemia (MMA), and various disorders of cobalamin metabolism are characterized by elevated propionylcarnitine (C3) on newborn screening (NBS). Distinctions can be made between these disorders with secondary analyte testing. Elevated methionine is already routinely used as a NBS marker for cystathionine beta-synthase deficiency. We propose that low methionine may be useful as a secondary analyte for specific detection of cbl disorders among a larger pool of infants with elevated C3 on NBS. **METHODS:** Retrospective analysis of dried blood spot (DBS) data in patients with molecularly confirmed cblC disease. **RESULTS:** Nine out of ten patients with confirmed cblC born in New York between 2005 and 2008 had methionine below 13.4 $\mu\text{mol/L}$ on NBS. Elevated C3, elevated C3:C2 ratio, and low methionine were incorporated into a simple screening algorithm that can be used to improve the specificity of newborn screening programs and provide a specific and novel method of distinguishing cblC from other disorders of propionate metabolism prior to recall for confirmatory testing. **CONCLUSIONS:** It is anticipated that this algorithm will aid in early and specific detection of cobalamin C, D, and F diseases, with no additional expense to NBS laboratories screening for organic acidemias and classical homocystinuria.

47. J Clin Virol. 2009 Sep 25. [Epub ahead of print]

Newborn screening for congenital cytomegalovirus: Options for hospital-based and public health programs.

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BACKGROUND: Congenital cytomegalovirus (CMV) infection is a leading cause of sensorineural hearing loss (SNHL) and developmental disability in children. Early identification of infected children through screening could allow for early intervention and improvement in functional outcomes among the

subset who develop sequelae. OBJECTIVES: To outline potential options and strategies for screening newborns for congenital CMV infection and to discuss barriers to screening and data needs to inform future policy decisions. STUDY DESIGN: Commentary based on the literature and expert opinion on newborn dried blood spot screening, newborn hearing screening/Early Hearing Detection and Intervention (EHDI) programs, and congenital CMV. RESULTS: Although no population-based screening for congenital CMV is underway, pilot newborn screening studies using a variety of assays with urine or dried blood spot specimens are underway. Challenges to screening are both practical-uncertain sensitivity of blood spot assays suitable for large-scale screening and lack of infrastructure for collection of urine specimens; and evidentiary-the need to demonstrate improved outcomes and value of screening to offset the expense and potential adverse psychosocial consequences for children and families whose children require periodic monitoring but never develop sequelae. CONCLUSIONS: Screening for congenital CMV infection is a potentially important intervention that merits additional research, including the logistical feasibility of different screening options and psychosocial consequences for families.

48. J Clin Virol. 2009 Sep 23. [Epub ahead of print]

Evaluation of DNA extraction methods for dried blood spots in the diagnosis of congenital cytomegalovirus infection.

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BACKGROUND: Dried blood spots (DBS) may be valuable in the diagnosis of congenital cytomegalovirus (CMV) infection. However, the 2007 European Quality Control for Molecular Diagnostics (QCMD) proficiency testing programme showed that CMV DNA detection in DBS was lacking sensitivity in a considerable number of participating laboratories. OBJECTIVE: To compare DNA extraction methods for DBS for detecting CMV. Sensitivity and applicability of the methods for high-throughput usage were assessed. STUDY DESIGN: Guthrie cards were spotted with CMV DNA-positive whole blood (n=15). DNA was extracted from the DBS using different extraction methods, followed by CMV amplification by means of real-time PCR. RESULTS: Significant differences between the extraction methods with respect to the sensitivity were found. Optimal sensitivity was achieved when samples were tested in triplicate, demonstrating that the methods in general operated around their detection limits. Triplicate testing using the protocol by Barbi et al. [Barbi M, et al. Cytomegalovirus DNA detection in Guthrie cards: a powerful tool for diagnosing congenital infection. *J Clin Virol* 2000;17:159-65], representing the most sensitive methods, resulted in sensitivities of 100%, 86%, and 50% for DBS with CMV DNA loads of 5-4, 4-3, and 3-2log(10)copies/ml, respectively. This indicates that sensitivity limitations apply in the clinically relevant concentration range. Few methods appeared suitable for 96-well format high-throughput testing. DISCUSSION: When considering universal neonatal screening for congenital CMV infection, an assay which is both sensitive and applicable for high-throughput testing is required. The protocol by Barbi et al. and the BioRobot Universal System appear appropriate candidates currently available for 96-well format application in neonatal screening using DBS.

49. Public Health Genomics. 2009 Sep 22. [Epub ahead of print]

Consent for Newborn Screening: The Attitudes of Health Care Providers.

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Background: As newborn screening (NBS) expands to meet a broader definition of benefit, the scope of parental consent warrants reconsideration. Methods: We conducted a mixed methods study of health care provider attitudes toward consent for NBS, including a survey (n = 1,615) and semi-structured interviews (n = 36). Results: Consent practices and attitudes varied by provider but the majority supported mandatory screening (63.4%) and only 36.6% supported some form of parental discretion. Few health care providers (18.6%) supported seeking explicit consent for screening condition-by-condition, but a larger minority (39.6%) supported seeking consent for the disclosure of incidentally generated sickle cell carrier results. Qualitative findings illuminate these preferences: respondents who favored consent emphasized its ease while dissenters saw consent as highly complex. Conclusion: Few providers supported explicit consent for NBS. Further, those who supported consent viewed it as a simple process. Arguably, these attitudes reflect the public health emergency NBS once was, rather than the public health service it has become. The complexity of NBS panels may have to be aligned with providers' capacity to implement screening appropriately, or providers will need sufficient resources to engage in a more nuanced approach to consent for expanded NBS. Copyright © 2009 S. Karger AG, Basel

50. J Inherit Metab Dis. 2009 Sep 7. [Epub ahead of print]

High incidence of profound biotinidase deficiency detected in newborn screening blood spots in the Somalian population in Minnesota.

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Newborns identified with profound biotinidase deficiency (BTD) by the Minnesota Newborn Screening Program (MN NBS) between 1 October 2004 and 30 May 2008 were all from new immigrant groups. Thirty-three positive cases of BTD were identified out of 264 727 infants screened by the Wolf colorimetric system during the period of this study by MN NBS. Five cases of profound BTD (0.1 to <0.6 nmol/min per ml) and 26 cases of partial BTD (0.9 to 2.3 nmol/min per ml) were later confirmed through measurement of serum biotinidase activity. The incidence of combined partial and profound BTD of 1/8540 and that of profound BTD of 1/52 945 in Minnesota are unusually high in comparison with the reported worldwide numbers of 1/61 067 for combined BTD and 1/137 401 for profound BTD. Four out of the 5 cases of profound BTD ascertained in the MN NBS cohort were of Somali ethnic background, and the remaining case was of Asian (Pakistani/Indian) ethnic background. All four Somali patients have the P497S mutation, with one of the four being homozygous for the mutation. The three compound heterozygotes all have a novel mutation (P142T) and two of them have another change (Y428Y) that has never been described. Within the last two decades, Minnesota has become home to an estimated 40 000 Somali immigrants and their children (<1% of the total Minnesota population). New population demographics prompt careful analysis of case cohorts to identify specific groups at risk for rare inborn errors of metabolism.