2010 April/May Newborn Screening Articles

1. J Inherit Metab Dis. 2010 May 8. [Epub ahead of print]

Inborn errors of metabolism in Latin America: challenges and opportunities.

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Abstract
Latin America includes more than 40 countries and possessions, and its population of 570 million has an important representation of the three main human races. The area is experiencing an economic improvement, progressively bringing the inborn errors of metabolism (IEM) to a higher level among health priorities. Challenges to the progress of the IEM field include the huge disparities, the high prevalence of malnutrition and infections, the co-existence of very different models of public health services, the unstable socio-economic and political conditions, and the difficulties in integrating the countries. However, a rapidly changing social and economic environment is presenting many opportunities to the IEM field, like the improvements in infrastructure, the concentration of the population in urban areas, the continuous growth of neonatal screening, the use of filter paper samples, the availability of internet communication, and the interest in IEM by the new population medical genetics discipline. Analyzing this picture, several proposals are presented, such as the development of activities of provision of health services, education and research as an integrated package, the increase in training of human resources, the expansion of access to diagnostic tests, and the use the neonatal screening framework to expand the provision of services. In a continent with few IEM centers, there is a major need for such groups to work in collaboration, complementing each other's capabilities, providing training of human resources, and developing joint projects. The integration of these groups into a large transnational network of reference centers would be a major task for the coming years.

2. J Inherit Metab Dis. 2010 May 6. [Epub ahead of print]

Newborn screening for congenital hypothyroidism: improved assay performance has created an evidence gap.

Pollitt RJ, Wales JK.

3. Eur J Hum Genet. 2010 May 5. [Epub ahead of print]

Molecular characterization of SMN copy number derived from carrier screening and from core families with SMA in a Chinese population.

Zhu S, Xiong F, Chen YJ, Yan TZ, Zeng J, Li L, Zhang YN, Chen WQ, Bao XH, Zhang C, Xu XM.

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Abstract
Screening for carriers of spinal muscular atrophy (SMA) is necessary for effective clinical/prenatal diagnosis and genetic counseling. However, a population-based study of SMA prevalence in mainland China has not yet been conducted. In this study, the copy number of survival motor neuron (SMN) genes was determined in 1712 newborn cord blood samples collected from southern China and from 25 core families, which included 26 SMA patients and 44 parents, to identify SMA carriers. The results presented 13 groups with different SMN1/SMN2 ratios among 1712 newborn individuals, which corresponded to 1535 subjects with two copies of SMN1, 119 with three copies of SMN1, 17 with four copies of SMN1, and 41 with a heterozygous deletion of SMN1 exon 7. Simultaneously, two '2+0' genotypes and two point mutations were found among the 44 obligate carriers in the core families, including a novel SMN1 splice-site mutation that was identified in the junction between intron 6 and exon 7 (c. 835-1G>A). These results indicated that the carrier frequency is 1/42 in the general Chinese population and that duplicated SMN1 alleles and de novo deletion mutations are present in a small number of SMA carriers. In addition, we developed and validated a new alternative screening method using a reverse dot blot assay for rapid genotyping of deletional SMA. Our research elucidated the genetic load and SMN gene variants that are present in the Chinese population, and could serve as the basis for a nationwide program of genetic counseling and clinical/prenatal diagnosis to prevent SMA in China.

4. Genet Med. 2010 May 4. [Epub ahead of print]

Medical foods: Inborn errors of metabolism and the reimbursement dilemma.

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Abstract
PURPOSE:: Medical foods and pharmacological doses of vitamins are used to treat certain genetic diseases for the duration of a patient's lifetime, which necessitates life-long management of the condition and diet by the patient and a health care provider. However, payment for medical foods and health insurance coverage of medical foods is not uniform. METHODS:: A survey of states' newborn screening (NBS) representatives and a review of state policies (as of 2008) were conducted to ascertain payment and insurance coverage of medical foods.

RESULTS:: According to the NBS representatives, 61% of the states provided or guaranteed medical foods for all or a subset of the population detected by NBS, whereas 82% of states provided or guaranteed medical formulas for the same population. Policies for private health insurance coverage existed in 33/50 states, and range from providing medical food for one specific metabolic condition to providing it for any NBS disorder. In addition, there is variability among states in the specificity of defining what conditions qualify for medical foods. CONCLUSION:: This article suggests four options, not mutually exclusive, options for addressing the patchwork of state policies regarding coverage of medical foods, ranging from amending Medicaid legislation to enacting federal legislation, or changing the Food and Drug Administration's stance on oversight of medical foods.

5. J Inherit Metab Dis. 2010 May 4. [Epub ahead of print]

Expanded newborn screening: reducing harm, assessing benefit.

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Abstract
Achieving the goals of newborn screening is, as for any screening, a balancing act: getting the maximum benefit from screening while producing the minimum harm. The advent of "expanded" newborn screening, with a large number of disorders detectable using a single test, has also posed problems, not new, but now more obvious. One is the finding of many more cases by screening, the extra cases being largely patients who have attenuated phenotypes and may remain asymptomatic for many years, even throughout life. These may or may not require active management in the short term, but do need lifelong awareness. Additionally, disorders have been included that are now thought benign or largely so. Babies risk being unnecessarily medicalized. Assessing outcome has also proved difficult because of the rarity of some disorders and the impracticality of randomized controlled trials. The requirements for valid studies include the need for case definitions, comparable comparison groups and probably assessment on a whole-population basis. An Australia-wide study of tandem mass spectrometry newborn screening involving 2 million screened and unscreened babies has demonstrated benefits overall to screened patients at age 6 years. The study was too small to provide conclusions for individual disorders other than for medium-chain acyl-CoA dehydrogenase deficiency.

6. J Inherit Metab Dis. 2010 May 4. [Epub ahead of print]

Useful second-tier tests in expanded newborn screening of isovaleric acidemia and methylmalonic aciduria.

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Abstract
Common use of pivalate-generating antibiotics in newborns in Japan and low cutoff value of C5-acylcarnitine (C5) to detect mild forms of isovaleric acidemia (IVA) led to 1,065 positive results from IVA screening among 146,000 newborns tested by tandem mass spectrometry over the last 3 years. Using our method to determine isovalerylglycine (IVG) levels in dried blood spots (DBS) as a second-tier test with IVG cutoff value of 0.5 nmol/ml in DBS, one patient with severe IVA was identified, and no recall of the second DBS was needed. Retrospective analysis revealed that most patients with moderate to severe forms of IVA have decreased free-carnitine levels shortly after birth and higher levels of IVG than those of C5, which suggests that this method is useful in evaluating the severity of IVA. Another second-tier test, to measure methylmalonic acid (MMA) levels in DBS by gas chromatography/mass spectrometry (GC/MS), has been developed to overcome difficulties in screening methylmalonic aciduria (MMAU) and propionic acidemia. Methanol extract from DBS was dried and derivatized using N-methyl-N-(tert-butyldimethylsilyl)-trifluoroacetamide. GC/MS was performed using splitless injection, electron-impact ionization, and selected ion monitoring for data recording. MMAU patients had much higher DBS concentrations of MMA (24.2-321.9 nmol/ml) than control newborns (0.34 +/- 0.11 nmol/ml). MMA measurement in DBS was thought to provide useful information about the severity of MMAU, as MMAU patients with high levels of MMA had decreased levels of free carnitine and mildly increased levels of propionylcarnitine.

7. Clin Chim Acta. 2010 May 2;411(9-10):684-9. Epub 2010 Feb 1.

Comparison of amino acids and acylcarnitines assay methods used in newborn screening assays by tandem mass spectrometry.

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Abstract
BACKGROUND: The analysis of amino acids (AA) and acylcarnitines (AC) by tandem mass spectrometry (MS/MS) is performed in newborn screening laboratories worldwide. While butyl esterification assays are routine, it is possible to detect AAs and ACs as their native free acids (underivatized). The Centers for Disease Control and Prevention's Newborn Screening Quality Assurance Program provides dried blood spot (DBS) quality control (QC) and proficiency testing (PT) programs for numerous MS/MS analytes. We describe empirical differences between derivatization and non-derivatization techniques for selected AAs and ACs. METHODS: DBS materials were prepared at levels near, above and below mean domestic laboratory cut-offs, and distributed to program participants for MS/MS analysis. Laboratories reported quantitative and qualitative results. QC DBS materials were assayed in-house following established protocols. RESULT: Minor differences (<15%) between quantitative values resulting from butyl esters and free acid techniques were observed for the majority of the analytes. Mass spectrometric response from underivatized dicarboxylic acid acylcarnitines was less intense than their butyl esters. CONCLUSIONS: The use of underivatized techniques may also result in the inability to differentiate isobaric acylcarnitines. Laboratories should establish their own protocols by

focusing on the decisions that identify test results requiring additional follow-up testing versus those that do not.

8. Brain Dev. 2010 May;32(5):409-11. Epub 2009 Apr 3.

Molecular analysis of a presymptomatic case of carnitine palmitoyl transferase I (CPT I) deficiency detected by tandem mass spectrometry newborn screening in Japan.

Tsuburaya R, Sakamoto O, Arai N, Kobayashi H, Hasegawa Y, Yamaguchi S, Shigematsu Y, Takayanagi M, Ohura T, Tsuchiya S.

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Abstract
Carnitine palmitoyl transferase I (CPT I) deficiency is a rare disorder of long-chain fatty acid oxidation. It is one of the metabolic diseases detectable by tandem mass spectrometry. We report herein a presymptomatic CPT I deficiency detected in a Japanese female newborn by tandem mass spectrometry newborn screening. A mutation analysis of the CPT1A gene revealed two novel mutations, p.R446X and p.G719D.

9. Clin Biochem. 2010 May;43(7-8):691-3. Epub 2009 Oct 22.

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

Al-Dirbashi OY, Fisher L, McRoberts C, Siriwardena K, Geraghty M, Chakraborty P.

10. Clin Chem. 2010 May;56(5):764-71. Epub 2010 Mar 18.

Multiplex enzyme assay for galactosemia using ultraperformance liquid chromatography-tandem mass spectrometry.

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Comment in:

- Clin Chem. 2010 May;56(5):690-2.

Abstract
BACKGROUND: Galactosemia is one of the most important inherited disorders detected by newborn screening tests. Abnormal results in screening tests should be confirmed by enzyme activity assays, but existing methods are time and labor intensive. We developed a novel multiplex enzyme assay for galactosemia using ultraperformance liquid chromatography-tandem

mass spectrometry (UPLC-MS/MS). METHODS: [(13)C6]-galactose, [(13)C2]-galactose-1-phosphate, and UDP-glucose were used as substrates for 3 galactose-metabolizing enzymes. The end products from the combined reaction mixtures, [(13)C6]-galactose-1-phosphate, UDP-[(13)C2]-galactose, and UDP-galactose, were simultaneously measured using UPLC-MS/MS. Linearity, imprecision, ion suppression, and the effects of substrate were evaluated to determine assay performance. Enzyme activities from 35 healthy individuals, 8 patients with enzyme deficiency, and 18 mutant cells were analyzed. RESULTS: Substrates, products, and internal standards from the mixture of 3 enzyme reactions were clearly separated by using UPLC-MS/MS, with an injection cycle time of 10 min. Ion suppression was 0.1%-2.5%, the interassay imprecision of UPLC-MS/MS was 3.3%-10.6% CV, and the linearity of each system was good (R(2) = 0.994-0.999). Patient samples and mutated cells showed consistently low enzyme activities compared with those of normal individuals and wild-type cells. CONCLUSIONS: This method allows for a high-throughput and reproducible multiplex enzyme assay for galactosemia in erythrocytes.

11. Eur J Pediatr. 2010 May;169(5):569-72. Epub 2009 Oct 8.

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

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Abstract
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 micromol/L (norm <5 micromol/L) and increased within 12 h to 87.5 micromol/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.

12. Hear Res. 2010 May;263(1-2):52-65. Epub 2009 Sep 20.

Wideband acoustic-reflex test in a test battery to predict middle-ear dysfunction.

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Abstract
A wideband (WB) aural acoustical test battery of middle-ear status, including acoustic-reflex thresholds (ARTs) and acoustic-transfer functions (ATFs, i.e., absorbance and admittance) was

hypothesized to be more accurate than 1-kHz tympanometry in classifying ears that pass or refer on a newborn hearing screening (NHS) protocol based on otoacoustic emissions. Assessment of middle-ear status may improve NHS programs by identifying conductive dysfunction and cases in which auditory neuropathy exists. Ipsilateral ARTs were assessed with a stimulus including four broadband-noise or tonal activator pulses alternating with five clicks presented before, between and after the pulses. The reflex shift was defined as the difference between final and initial click responses. ARTs were measured using maximum likelihood both at low frequencies (0.8-2.8 kHz) and high (2.8-8 kHz). The median low-frequency ART was elevated by 24 dB in NHS refers compared to passes. An optimal combination of ATF and ART tests performed better than either test alone in predicting NHS outcomes, and WB tests performed better than 1-kHz tympanometry. Medial olivocochlear efferent shifts in cochlear function may influence ARs, but their presence would also be consistent with normal conductive function. Baseline clinical and WB ARTs were also compared in ipsilateral and contralateral measurements in adults

13. J Pediatr Otorhinolaryngol. 2010 May;74(5):510-5. Epub 2010 Mar 19.

The universal newborn hearing screening in Brazil: from identification to intervention.

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Abstract
OBJECTIVE: The objective of the study is to investigate the results of the newborn hearing screening program carried out in a Public Hospital in Brazil, in the first 3 years regarding: (1) the prevalence of hearing impairment; (2) the influence of the universal hearing screening program on the age at which the diagnosis of hearing loss is defined; (3) the cost effectiveness of the program; (4) the outcomes, in terms of the age in which the hearing rehabilitation started. METHODS: A descriptive study of the first 3 years after starting the universal newborn hearing screening in a Public Hospital of Bauru, São Paulo state, Brazil. The screening method consists of a two-stage screening approach with transient otoacoustic emissions (TOAE), conducted by an audiologist. If the outcome in the second-stage screening is REFER, the infant is submitted to diagnostic follow-up testing and intervention at the Audiology and Speech Pathology Clinic at the University of São Paulo, campus of Bauru. The evaluation of the costs of the universal newborn hearing screening program per each screened newborn (around 4000/year) was done based on a proposal by the National Center for Hearing Assessment and Management, of the Utah State University, United States of America. RESULTS: 11,466 newborns were submitted to hearing screening, corresponding to 90.52% of the living newborns. The prevalence of sensorineural hearing loss was 0.96:1000. Of the 11 children with sensorineural hearing loss, eight children received hearing aids and five started the therapeutic process before the age of 1. Currently, four children between the ages of 11 months and 2 years old were submitted to cochlear implant surgery. The cost of hearing screening was US$7.00 and the annual cost of the universal newborn hearing screening program was US$26,940.47. CONCLUSION: The hospital-based universal newborn hearing screening carried out through the Brazilian National Health System is viable, with promising results. However, in a country such as Brazil, which presents

large socio-economic differences, the same type of analyses should be performed in several regions, so as to take into account specific aspects, to implement the newborn hearing screening along with the Public System.

14. J Pediatr. 2010 May;156(5):771-6, 776.e1. Epub 2010 Feb 20.

Psychological effects of false-positive results in cystic fibrosis newborn screening: a two-year follow-up.

Beucher J, Leray E, Deneuville E, Roblin M, Pin I, Bremont F, Turck D, Giniès JL, Foucaud P, Rault G, Derelle J, David V, Journel H, Marchand S, Veillard D, Roussey M.

CF Center University Hospital, Rennes, France.

Abstract
OBJECTIVE: To evaluate parental stress after a false-positive result at the time of the cystic fibrosis (CF) newborn screening (NBS), attributable to heterozygotism or persistent hypertrypsinemia. STUDY DESIGN: A prospective study was conducted in 86 French families at 3, 12, and 24 months after NBS. A psychologist conducted interviews with a questionnaire, the Perceived Stress Scale, and the Vulnerable Child Scale. RESULTS: Overall, 96.5% of parents said they had been anxious at the time of the sweat test. However, 86% felt entirely reassured 3 months after the test. The mean Perceived Stress Scale score did not differ from that observed in the French population. Mean Vulnerable Child Scale scores were high, associated with a low Parental Perception of Child Vulnerability. These results did not differ significantly at 1 and 2 years. In total, 86% to 100% of families no longer worried about CF. All parents stated that they would have the test performed again for another child. CONCLUSIONS: CF NBS can lead to false-positive results, causing parental anxiety, which quickly decreases after a sweat test performed soon after the phone call.

15. Matern Child Health J. 2010 May;14(3):360-4. Epub 2009 Apr 8.

Methodological innovations in data gathering: newborn screening linkage with live births records, Michigan, 1/2007-3/2008.

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Abstract
OBJECTIVE: To match Michigan birth and newborn screening records to identify and follow-up potentially unscreened infants, assess data quality, and demonstrate the utility of Link Plus linkage software for matching MCH related administrative datasets. METHODS: Birth and newborn screening records maintained by the Michigan Department of Community Health from January 2007 through March 2008 were used in this study. Link Plus, a freely-available

probabilistic record linkage software program developed at the Centers for Disease Control and Prevention, was used to match records. Linkage performance was assessed by the linkage success rate (percentage of valid matches). Follow-up of un-matched records was conducted by the Michigan Newborn Screening Follow-up Program. RESULTS: Nearly all (99.2%) of the 142,178 birth records included in this study were successfully matched to newborn screening records. Following a transition to a web-based electronic birth certificate system and inclusion of a newborn screening card identification number on the birth record in 2008, the linkage success rate increased to 99.6% based on analysis of approximately 18,000 records. Of approximately 600 un-matched records, nearly half had received a newborn screen. Approximately 8% of un-matched records were due to parental refusal of newborn screening. Nine children received an initial screen as a result of this study; one was confirmed as having sickle cell trait. CONCLUSIONS: We have demonstrated that a freely available record linkage software, Link Plus, can be used to successfully match records of MCH databases thereby providing an opportunity for further research and quality assurance investigations.

16. Mol Genet Metab. 2010 May;100(1):24-8. Epub 2010 Feb 4.

Long-term outcome of patients with argininosuccinate lyase deficiency diagnosed by newborn screening in Austria.

Mercimek-Mahmutoglu S, Moeslinger D, Häberle J, Engel K, Herle M, Strobl MW, Scheibenreiter S, Muehl A, Stöckler-Ipsiroglu S.

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Abstract
Twenty-three patients with late onset argininosuccinate lyase deficiency (ASLD) were identified during a 27-year period of newborn screening in Austria (1:95,600, 95% CI=1:68,036-1:162,531). One additional patient was identified outside the newborn screening with neonatal hyperammonemia. Long-term outcome data were available in 17 patients (median age 13 years) ascertained by newborn screening. Patients were treated with protein restricted diet and oral arginine supplementation during infancy and childhood. IQ was average/above average in 11 (65%), low average in 5 (29%), and in the mild intellectual disability range in 1 (6%) patients. Four patients had an abnormal EEG without evidence of clinical seizures and three had abnormal liver function tests and/or evidence of hepatic steatosis. Plasma citrulline levels were elevated in four patients. Plasma ammonia levels were within normal range prior and after a protein load in all patients. Seven different mutations were identified in the 16 alleles investigated. Four mutations were novel (p.E189G, p.R168C, p.R126P, and p.D423H). All mutations were associated with low argininosuccinate lyase activities (0-15%) in red blood cells. Newborn screening might be beneficial in the prevention of chronic neurologic and intellectual sequelae in late onset ASLD, but a proportion of benign variants might have contributed to the overall favorable outcome as well.

17. Mol Genet Metab. 2010 May;100(1):1-5. Epub 2010 Jan 25.

Inborn Errors of Metabolism: the metabolome is our world. Presidential address for the 11th International Congress of Inborn Errors of Metabolism (ICIEM).

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Abstract
Thank you for honoring me by allowing me to serve as president of the 11th International Congress of Inborn Errors of Metabolism (ICIEM). The science brought by the IEM community to the Congress was quite impressive and demonstrated the quality of research within this community. In this address, I will consider briefly the history of IEMs to determine how we have arrived where we are, and will spend more time ascertaining our place in the current biomedical community and our role in determining the future of personalized medicine. In the 1950s-1970s new tools were added to expand our ability to interrogate the metabolome and the result was an explosive increase in the number of IEMs. This set the stage for expanded newborn screening (NBS) by tandem mass spectrometry (MS/MS) to identify these patients and to intervene pre-symptomatically. The complexity of the metabolome has led us to utilize the mathematical algorithms of systems biology to reduce high dimensionality data to low dimensionality output. However, the metabolome does not exist in isolation and we must learn how to integrate the metabolome with other xomics. The metabolome is our world and the IEM community has much to share with the broader xomics communities by integrating what we have learned with the other xomics communities. They are seeking access to the metabolome as a closer measure of phenotype, and we are already extremely comfortable and competent in the metabolomic space. But we should not be insular in our occupation of this space. NBS should be the model for personalized medicine, because it is already functioning as testing system for predictive, preventive and personalized care. We have been working in the area of NBS for nearly a half century and have many lessons learned that will be valuable to the practitioners of personalized medicine - lessons that they should not have to rediscover. We must embrace the international IEM community to meet population trends and to improve the care for individuals - children and adults - with IEMs. Demographic projections indicate the countries with largest population growth during the next four decades will be in Asia and we need to work collaboratively to build capacity in the IEM community in Asia and beyond to other underserved regions of the world.

18. Mol Genet Metab. 2010 May;100(1):6-13. Epub 2010 Jan 11.

Clinical issues and frequent questions about biotinidase deficiency.

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Abstract
Biotinidase deficiency is a biotin-responsive, inherited neurocutaneous disorder. The disorder is readily treatable and is screened for in the newborn period. Over the years since the discovery of the disorder, many practical questions and issues have been raised as to the diagnosis, management, treatment, and newborn screening of the disorder. In this paper, many of these issues are addressed using evidence-based medicine and anecdotal experiences. If adequate answers are not known, the answers to these queries will require future investigations

19. Mol Genet Metab. 2010 May;100(1):46-50. Epub 2009 Dec 28.

Diagnoses of newborns and mothers with carnitine uptake defects through newborn screening.

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Abstract
Carnitine uptake defect (CUD) is an autosomal recessive fatty acid oxidation defect caused by a deficiency of the high-affinity carnitine transporter OCTN2. CUD patients may present with hypoketotic hypoglycemia, hepatic encephalopathy or dilated cardiomyopathy. Tandem mass spectrometry screening of newborns can detect CUD, although transplacental transport of free carnitine from the mother may cause a higher free carnitine level and cause false negatives during newborn screening. From Jan 2001 to July 2009, newborns were screened for low free carnitine levels at the National Taiwan University Hospital screening center. Confirmation tests included dried blood spot free acylcarnitine levels and mutation analyses for both babies and their mothers. Sixteen newborns had confirmation tests for persistent low free carnitine levels; four had CUD, six had mothers with CUD, and six cases were false positives. All babies born to mothers with CUD had transient carnitine deficiency. The six mothers with CUD were put on carnitine supplementation (50-100mg/kg/day). One mother had dilated cardiomyopathy at diagnosis and her cardiac function improved after treatment. Analysis of the SLC22A5 gene revealed that p.S467C was the most common mutation in mothers with CUD, while p.R254X was the most common mutation in newborns and children with CUD. Newborn screening allows for the detection of CUD both in newborns and mothers, with an incidence in newborns of one in 67,000 (95% CI: one in 31,600-512,000) and a prevalence in mothers of one in 33,000 (95% CI: one in 18,700-169,000). Detection of CUD in mothers may prevent them from developing dilated cardiomyopathy.

20. Pediatrics. 2010 May;125(5):e1265-6.

Evidence-based reviews of newborn-screening opportunities.

Botkin JR.

21. Pediatrics. 2010 May;125(5):e1226-35. Epub 2010 Apr 19.

Systematic evidence review of newborn screening and treatment of severe combined immunodeficiency.

Lipstein EA, Vorono S, Browning MF, Green NS, Kemper AR, Knapp AA, Prosser LA, Perrin JM.

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Comment in:

- Pediatrics. 2010 May;125(5):e1265-6.

Abstract
CONTEXT: Severe combined immunodeficiency (SCID) is a group of disorders that leads to early childhood death as a result of severe infections. Recent research has addressed potential newborn screening for SCID. OBJECTIVE: To conduct a systematic review of the evidence for newborn screening for SCID, including test characteristics, treatment efficacy, and cost-effectiveness. METHODS: We searched Medline and the OVID In-Process & Other Non-Indexed Citations databases. We excluded articles if they were reviews, editorials or other opinion pieces, or case series of fewer than 4 patients or if they contained only adult subjects or nonhuman data. The remaining articles were systematically evaluated, and data were abstracted by 2 independent reviewers using standardized tools. For topics that lacked published evidence, we interviewed experts in the field. RESULTS: The initial search resulted in 719 articles. Twenty-six met inclusion criteria. The results of several small studies suggested that screening for SCID is possible. Interviews revealed that 2 states have begun pilot screening programs. Evidence from large case series indicates that children receiving early stem-cell transplant for SCID have improved outcomes compared with children who were treated later. There is some inconclusive evidence regarding the need for donor-recipient matching and use of pretransplant chemotherapy. Few data on the cost-effectiveness of a SCID-screening program. CONCLUSIONS: Evidence indicates the benefits of early treatment of SCID and the possibility of population-based newborn screening. Better information on optimal treatment and the costs of treatment and screening would benefit policy makers deciding among competing health care priorities.

22. J Inherit Metab Dis. 2010 Apr 29. [Epub ahead of print]

Clinical aspects of short-chain acyl-CoA dehydrogenase deficiency.

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Abstract

Short-chain acyl-CoA dehydrogenase deficiency (SCADD) is an autosomal recessive inborn error of mitochondrial fatty acid oxidation. SCADD is biochemically characterized by increased C4-carnitine in plasma and ethylmalonic acid in urine. The diagnosis of SCADD is confirmed by DNA analysis showing SCAD gene mutations and/or variants. SCAD gene variants are present in homozygous form in approximately 6% of the general population and considered to confer susceptibility to development of clinical disease. Clinically, SCADD generally appears to present early in life and to be most frequently associated with developmental delay, hypotonia, epilepsy, behavioral disorders, and hypoglycemia. However, these symptoms often ameliorate and even disappear spontaneously during follow-up and were found to be unrelated to the SCAD genotype. In addition, in some cases, symptoms initially attributed to SCADD could later be explained by other causes. Finally, SCADD relatives of SCADD patients as well as almost all SCADD individuals diagnosed by neonatal screening remained asymptomatic during follow-up. This potential lack of clinical consequences of SCADD has several implications. First, the diagnosis of SCADD should never preclude extension of the diagnostic workup for other potential causes of the observed symptoms. Second, patients and parents should be clearly informed about the potential lack of relevance of the disorder to avoid unfounded anxiety. Furthermore, to date, SCADD is not an optimal candidate for inclusion in newborn screening programs. More studies are needed to fully establish the relevance of SCADD and solve the question as to whether SCADD is involved in a multifactorial disease or represents a nondisease.

23. Clin Chem. 2010 Apr 22. [Epub ahead of print]

Relationship of Octanoylcarnitine Concentrations to Age at Sampling in Unaffected Newborns Screened for Medium-Chain Acyl-CoA Dehydrogenase Deficiency.

Khalid JM, Oerton J, Besley G, Dalton N, Downing M, Green A, Henderson M, Krywawych S, Wiley V, Wilcken B, Dezateux C; on behalf of the UK Collaborative Study of Newborn Screening for MCADD.

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Abstract
BACKGROUND: Although octanoylcarnitine (C8) concentrations measured from newborn screening dried blood spots are used to identify those at high risk of medium-chain acyl-CoA dehydrogenase deficiency (MCADD), age-related reference values are currently not available for unaffected newborn populations. Because age at sampling may vary within and between screening programs, variations in C8 concentrations by age may affect screening program performance. We determined whether C8 concentrations vary by age at sampling, sex, birth weight, or gestational age in unaffected newborns. METHODS: We analyzed C8 concentrations from 227 098 unaffected newborns, including 179 729 from 6 English laboratories participating in a multicenter study and 47 369 from the single laboratory serving the New South Wales (NSW) Newborn Screening Program in Australia. In England, the majority of samples were collected at age 5-8 days and analyzed underivatized by use of tandem mass spectrometry (MS/MS); in NSW, samples were obtained at a median age of 3 days and analyzed derivatized by MS/MS. Information on infants' sex, birth weight, gestation, hospitalization, and transfusion

status was recorded at time of sampling. RESULTS: C8 concentrations did not vary significantly by age at sampling, sex, birth weight, or gestational age and remained relatively constant during the first 2 weeks of life in unaffected babies being screened for MCADD. CONCLUSIONS: Newborn MCADD screening programs using this biomarker for screening samples collected after the first day and during the first 14 days of life do not need to adjust cutoff values to account for postnatal age, prematurity, or size at birth.

24. Genome Med. 2010 Apr 22;2(4):25. [Epub ahead of print]

Carrier detection in childhood: a need for policy reform.

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Abstract
ABSTRACT: Current policy statements discourage identification of disease carrier status in minors on the grounds that carrier information is of mainly reproductive significance. Such policies fail to consider that the carrier state may have important health implications for minors. They also fail to consider that carrier status of newborns is routinely discovered as an incidental finding in newborn screening programs. Finally, such policies fail to take into account that it may not be parents but adolescents who are seeking out this information and that adolescence may be a valid time to learn about one's reproductive risks. Here, I consider the issues that need to be addressed in revising current policies about the carrier detection of minors.

25. Arch Dis Child. 2010 Apr 19. [Epub ahead of print]

Declining prevalence of cystic fibrosis since the introduction of newborn screening.

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Abstract
Objectives Newborn screening for cystic fibrosis (CF) facilitates early diagnosis and genetic counselling for parents of affected infants. Many parents elect to use prenatal testing for subsequent pregnancies, and this may affect the prevalence of CF. The aim of this study was to assess the evidence for changes in the live-birth prevalence of CF since the introduction of newborn screening for CF. Methods The authors reviewed the records of the Victorian newborn screening programme and the clinical records of the three centres caring for patients with CF in Victoria, Australia, in order to determine the live-birth prevalence of patients with CF; before (1979-1988) and after (1989-2006) the introduction of newborn screening. The authors reviewed the records of the Victorian Clinical Genetics Service to ascertain the number and outcome of prenatal tests for CF (1979-2006). Live births in Victoria were obtained from the state birth register. Findings Between 1979 and 1988, the live-birth prevalence of CF was 3.96 (95% CI

3.48 to 4.49) per 10 000 live births. Following the introduction of newborn screening (1989-2006) the live-birth prevalence of CF was 3.28 (95% CI 2.97 to 3.63) per 10 000 live births, representing a reduction of 17% (95% CI 2% to 29%, p=0.025). In the prescreening period, there were 10 prenatal tests, which identified three affected pregnancies, all of which were terminated. In the later period, there were 304 prenatal tests (mean 17/year), of which 76 were affected, and 70 of these pregnancies were terminated. Conclusion The authors observed a modest reduction in the live-birth prevalence of CF since the introduction of newborn screening. This is principally due to at-risk couples detected by newborn screening electing to use prenatal testing on subsequent pregnancies.

26. J Pediatr. 2010 Apr 16. [Epub ahead of print]

Maternal and Neonatal Vitamin B12 Deficiency Detected through Expanded Newborn Screening-United States, 2003-2007.

Hinton CF, Ojodu JA, Fernhoff PM, Rasmussen SA, Scanlon KS, Hannon WH.

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Abstract
The incidence of neonatal vitamin B(12) (cobalamin) deficiency because of maternal deficiency was determined by surveying state newborn screening programs. Thirty-two infants with nutritional vitamin B(12) deficiency were identified (0.88/100 000 newborns). Pregnant women should be assessed for their risk of inadequate intake/malabsorption of vitamin B(12).

27. J Pediatr. 2010 Apr 16. [Epub ahead of print]

Use of Screening Dried Blood Spots for Estimation of Prevalence, Risk Factors, and Birth Outcomes of Congenital Cytomegalovirus Infection.

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Abstract
OBJECTIVES: To determine the birth prevalence of cytomegalovirus (CMV) in a population-based sample of newborns by use of dried blood spots compared with previous studies that used established detection methods, and to evaluate risk factors and birth outcomes for congenital CMV infection. STUDY DESIGN: A total of 3972 newborn dried blood spots collected for the California Newborn Screening Program were tested for presence of CMV DNA. Demographic and pregnancy data were obtained from linked newborn screening and live-birth records. RESULTS: CMV prevalence among newborns by maternal race and ethnicity was 0.9% for blacks, 0.8% for Hispanics, 0.6% for whites, and 0.6% for Asians. Among Hispanics (n = 2053), infants who were infected had younger mothers (23 vs 26 years, P = .03), and prevalence was higher for children with no father information provided (2.6% vs 0.6%, P = .03). Overall CMV infection was associated with low birth weight (prevalence ratios [95% CI]: 3.4 [1.4-8.5]) and

preterm birth (2.7 [1.4-5.1]). CMV viral loads were inversely related to birth weight and gestational age (both P = .03). CONCLUSIONS: CMV prevalence measured with dried blood spots was similar to reports using standard viral culture methods. Dried blood spots may be suitable for detection of CMV infection in newborns and warrant further evaluation. Congenital CMV infection may contribute to low birth weight and preterm birth.

28. Kasper DC, Herman J, De Jesus VR, Mechtler TP, Metz TF, Shushan B.

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Abstract
Lysozomal storage disorders are just beginning to be routinely screened using enzyme activity assays involving dried blood spots and tandem mass spectrometry (MS/MS). This paper discusses some of the analytical challenges associated with published assays including complex sample preparation and potential interference from excess residual substrate. Solutions to these challenges are presented in the form of on-line two-dimensional chromatography to eliminate off-line liquid-liquid extraction (LLE) and solid-phase extraction (SPE), the use of ultra-high-performance liquid chromatography (UHPLC) to separate excess substrate from all other analytes and multiplexed sample introduction for higher throughput required of a population screening assay. High sensitivity, specificity and throughput were demonstrated using this novel method.

29. JAMA. 2010 Apr 14;303(14):1425-6.

Screening newborns for congenital cytomegalovirus infection.

Bale JF Jr.

Comment on:

- JAMA. 2010 Apr 14;303(14):1375-82.

30. JAMA. 2010 Apr 14;303(14):1375-82.

Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection.

Boppana SB, Ross SA, Novak Z, Shimamura M, Tolan RW Jr, Palmer AL, Ahmed A, Michaels MG, Sánchez PJ, Bernstein DI, Britt WJ, Fowler KB; National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) Study.

Collaborators (58)

Arora N, Bey A, Blackstone B, Blumenthal J, Brown V, Brumbach A, Chowdhury N, Febres-Cordero S, Jackson M, Kempf M, Kimberlin D, Le Lievre N, McCollister F, Mixon E, Purser M, Woodruff J, Cox E, Courtney J, Flores N, Ricart M, Schneider L, West J, Colaberardino J, Jeffrey N, Maracek A, Probst GE, Rosenberg C, Sabo D, Calderon M, Class M, Feja K, Schwab M, Choo D, Catalanotto K, Jamison L, Kern P, Schibler K, Sullivan-Mahoney M, Wethington S, Irving K, Owens D, Roark S, Ware M, Boatman C, Esquivel J, Jackson GL, Katz-Gaynor K, Liehr Townsley A, Mejías A, Owen KE, Roland PS, Rosado O, Shoup AG, Sosa D, Santoyo J, Stehel EK, Torres L, Zeray F.

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Comment in:

- JAMA. 2010 Apr 14;303(14):1425-6.

Abstract

CONTEXT: Reliable methods to screen newborns for congenital cytomegalovirus (CMV) infection are needed for identification of infants at increased risk of hearing loss. Since dried blood spots (DBS) are routinely collected for metabolic screening from all newborns in the United States, there has been interest in using DBS polymerase chain reaction (PCR)-based methods for newborn CMV screening. OBJECTIVE: To determine the diagnostic accuracy of DBS real-time PCR assays for newborn CMV screening. DESIGN, SETTING, AND PARTICIPANTS: Between March 2007 and May 2008, infants born at 7 US medical centers had saliva specimens tested by rapid culture for early antigen fluorescent foci. Results of saliva rapid culture were compared with a single-primer (March 2007-December 2007) and a 2-primer DBS real-time PCR (January 2008-May 2008). Infants whose specimens screened positive on rapid culture or PCR had congenital infection confirmed by the reference standard method with rapid culture testing on saliva or urine. MAIN OUTCOME MEASURES: Sensitivity, specificity, and positive and negative likelihood ratios (LRs) of single-primer and 2-primer DBS real-time PCR assays for identifying infants with confirmed congenital CMV infection. RESULTS: Congenital CMV infection was confirmed in 92 of 20,448 (0.45%; 95% confidence interval [CI], 0.36%-0.55%) infants. Ninety-one of 92 infants had positive results on saliva rapid culture. Of the 11,422 infants screened using the single-primer DBS PCR, 17 of 60 (28%) infants had positive results with this assay, whereas, among the 9026 infants screened using the 2-primer DBS PCR, 11 of 32 (34%) screened positive. The single-primer DBS PCR identified congenital CMV infection with a sensitivity of 28.3% (95% CI, 17.4%-41.4%), specificity of 99.9% (95% CI, 99.9%-100%), positive LR of 803.7 (95% CI, 278.7-2317.9), and negative LR of 0.7 (95% CI, 0.6-0.8). The positive and negative predictive values of the single-primer DBS PCR were 80.9% (95% CI, 58.1%-94.5%) and 99.6% (95% CI, 99.5%-99.7%), respectively. The 2-primer DBS PCR assay identified infants with congenital CMV infection with a sensitivity of 34.4% (95% CI, 18.6%-53.2%), specificity of 99.9% (95% CI, 99.9%-100.0%), positive LR of 3088.9 (95% CI, 410.8-23 226.7), and negative LR of 0.7 (95% CI, 0.5-0.8). The positive and negative predictive values of the 2-primer DBS PCR were 91.7% (95% CI, 61.5%-99.8%) and 99.8% (95% CI, 99.6%-99.9%), respectively. CONCLUSION: Among newborns, CMV testing with

DBS real-time PCR compared with saliva rapid culture had low sensitivity, limiting its value as a screening test.

31. J Pediatr. 2010 Apr 13. [Epub ahead of print]

Two-Tier Approach to the Newborn Screening of Methylenetetrahydrofolate Reductase Deficiency and Other Remethylation Disorders with Tandem Mass Spectrometry.

Tortorelli S, Turgeon CT, Lim JS, Baumgart S, Day-Salvatore DL, Abdenur J, Bernstein JA, Lorey F, Lichter-Konecki U, Oglesbee D, Raymond K, Matern D, Schimmenti L, Rinaldo P, Gavrilov DK.

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Abstract
OBJECTIVE: To validate a 2-tier approach for newborn screening (NBS) of remethylation defects. STUDY DESIGN: The original NBS dried blood spots of 5 patients with a proven diagnosis of a remethylation disorder and 1 patient with biochemical evidence of such disorder were analyzed retrospectively to determine disease ranges for methionine (Met; 4.7-8.1 mumol/L; 1 percentile of healthy population, 11.1 mumol/L), the methionine/phenylalanine ratio (Met/Phe; 0.09-0.16; 1 percentile of healthy population, 0.22), and total homocysteine (tHcy; 42-157 mumol/L; 99 percentile of normal population, 14.7 mumol/L). These preliminary disease ranges showed a sufficient degree of segregation from healthy population data, allowing the selection of cutoff values. A simple algorithm was then developed to reflex cases to a second-tier testing for tHcy, which has been applied prospectively for 14 months. RESULTS: A total of 86 333 NBS samples were tested between January 2007 and March 2008, and 233 of them (0.27%) met the criteria for second-tier testing of tHcy. All cases revealed concentrations of tHcy <15 mumol/L and were considered unaffected. No false-negative results have been reported with a state-wide system based on 2 combined metabolic clinics and laboratories that cover the entire Minnesota population and border areas of neighboring states. CONCLUSIONS: Pending more conclusive evidence from the prospective identification of additional true-positive cases, NBS for remethylation disorders appears to be feasible with existing methodologies, with only a marginal increase of the laboratory workload.

32. Mol Genet Metab. 2010 Apr 8. [Epub ahead of print]

Allelic diversity in MCAD deficiency: The biochemical classification of 54 variants identified during 5years of ACADM sequencing.

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Abstract
Medium-chain acyl-coA dehydrogenase (MCAD) deficiency is a commonly detected fatty acid oxidation disorder and its diagnosis relies on both biochemical and molecular analyses. Over a 5-year period, sequencing all 12 exons of the MCAD gene (ACADM) in our laboratory revealed a total of 54 variants in 549 subjects analyzed. As most molecular ACADM testing is referred for the follow-up of an abnormal newborn screening result obtained from an asymptomatic newborn, the identification of a novel DNA variant, or "variant of unknown significance (VUS)," presents clinicians with a dilemma. Frequently, the results of molecular analyses are correlated to biochemical findings, such as the concentration of octanoylcarnitine (C8) in plasma and the excretion of hexanoylglycine (HG) in urine. Here, we describe the classification of genotypes harboring at least one VUS through the comparison of C8 and HG values measured in individuals who are carriers of, or affected with, MCAD deficiency on the basis of the following genotypes: c.985A>G/wildtype, c.199T>C/c.985A>G and c.985A>G/c.985A>G. Our findings emphasize the importance of obtaining both plasma and urine when following up positive newborn screening results and may influence the way physicians counsel their asymptomatic patients about MCAD deficiency after genetic analysis.

33. J Inherit Metab Dis. 2010 Apr 7. [Epub ahead of print]

Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting.

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Abstract
Experience with new-born screening (NBS) for disorders of fatty-acid oxidation (FAOD) is now becoming available from an increasing number of programs worldwide. The spectrum of FAOD differs widely between ethnic groups. Incidence calculations from reports from Australia, Germany, and the USA of a total of 5,256,999 newborns give a combined incidence of all FAOD of approximately 1:9,300. However, it appears to be much lower in Asians. Consequently, a significant prevalence and evidence for a clear benefit of NBS is proven for medium-chain acyl-CoA dehydrogenase deficiency (MCAD) only in countries with a high percentage of Caucasians, with very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD) and long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency (LCHAD) being additional candidates. The long-term benefit for many disorders has still to be evaluated and will require international collaboration, especially for the rarest disorders. Short-chain acyl-CoA dehydrogenase deficiency (SCAD) [as well as Systemic carnitine transporter deficiency (CTD) and dienoyl-CoA reductase deficiency (DE-RED)] are conditions of uncertain clinical significance, but most FAOD have a spectrum of clinical presentations (healthy-death). Confirmatory diagnostic procedures should be agreed upon to ensure international comparability of results and evidence-based modifications. The case of short-chain acyl-CoA dehydrogenase deficiency (SCAD) deficiency shows that even inclusion of conditions without a clearly known natural course may prove useful with respect to gain of knowledge and consecutive exclusion of a biochemical abnormality without clinical significance,

although this line of argument implies the existence of structured follow-up programs and bears ethical controversies. As a final conclusion, the accumulated evidence suggests all FAOD should to be included into tandem mass spectrometry (MS/MS)-based NBS programs provided sufficient laboratory performance is guaranteed.

34. Am J Prev Med. 2010 Apr;38(4 Suppl):S522-7.

Newborn screening follow-up within the lifespan context: Michigan's experience.

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Abstract
Experience in using various data sources for surveillance systems and studies complements the growing knowledge base regarding requirements for newborn screening follow-up, which include integration with services other than clinical subspecialties. A proposed model for utilizing state resources to develop sickle cell disease surveillance across the lifespan is presented. This surveillance process should help evaluate the burden of sickle cell disease across the lifespan, and it could be used as a model for other hemoglobinopathies as well as other newborn screening disorders. Through the continued assessment and monitoring of prevalence, comorbidities, service utilization, cost, and patient outcomes, the newborn screening follow-up program will be able to inform public health policy.

35. Am J Prev Med. 2010 Apr;38(4 Suppl):S512-21.

Population estimates of sickle cell disease in the U.S.

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Abstract
BACKGROUND: The number of individuals with sickle cell disease (SCD) in the U.S. is unknown. Determination of burden of disease, healthcare issues, and policies is best served by representative estimations of the SCD population. PURPOSE: To update SCD population estimates by using recent U.S. Census and birth-cohort SCD prevalence for at-risk populations as available through the centralized reporting of universal newborn screening for hemoglobinopathies, with an effort to demonstrate the potential effect of early mortality. METHODS: National and state SCD populations were estimated based on the 2008 U.S. Census, using total, African-American, and Hispanic birth-cohort disease prevalence derived from the National Newborn Screening Information System. Estimates were corrected for early mortality for sickle cell anemia using data from the CDC's Compressed Mortality Report and published patient-cohort survival information. RESULTS: National SCD population estimates ranged from

104,000 to 138,900, based on birth-cohort disease prevalence, but from 72,000 to 98,000 when corrected for early mortality. Several limitations were noted in the available data, particularly for SCD mortality in adults. CONCLUSIONS: The number of individuals with SCD in the U.S. may approach 100,000, even when accounting for the effect of early mortality on estimations. A paucity of high-quality data limits appropriate estimation. State-to-state variability may preclude application of state-specific information to other states or to the nation as a whole. Standardized collection and centralized reporting, a surveillance system, will be necessary to assess the size and composition of the U.S. SCD population.

36. Eur Arch Otorhinolaryngol. 2010 Apr;267(4):495-9. Epub 2009 Aug 29.

Effects of background noise on recording of portable transient-evoked otoacoustic emission in newborn hearing screening.

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Abstract
Transient-evoked otoacoustic emission (TEOAE) is a well-established screening tool for universal newborn hearing screening. The aims of this study are to measure the effects of background noise on recording of TEOAE and the duration required to complete the test at various noise levels. This study is a prospective study from June 2006 until May 2007. The study population were newborns from postnatal wards who were delivered at term pregnancy. Newborns who were more than 8-h old and passed a hearing screening testing using screening auditory brainstem response (SABRe) were further tested with TEOAE in four different test environments [isolation room in the ward during non-peak hour (E1), isolation room in the ward during peak hour (E2), maternal bedside in the ward during non-peak hour (E3) and maternal bedside in the ward during peak hour (E4)]. This study showed that test environment significantly influenced the time required to complete testing in both ears with $F [534.23] = 0.945$; $P < 0.001$ on the right ear and $F [636.54] = 0.954$; $P < 0.001$ on the left. Our study revealed that TEOAE testing was efficient in defining the presence of normal hearing in our postnatal wards at maternal bedside during non-peak hour with a specificity of 96.8%. Our study concludes that background noise levels for acceptable and accurate TEOAE recording in newborns should not exceed 65 dB A. In addition, when using TEOAE assessment in noisy environments, the time taken to obtain accurate results will greatly increase.

37. Genet Med. 2010 Apr;12(4 Suppl):S194-211.

Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis.

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Abstract
Cystic fibrosis is one of the most commonly tested autosomal recessive disorders in the United States. Clinical cystic fibrosis is associated with mutations in the CFTR gene, of which the most common mutation among Caucasians, DeltaF508, was identified in 1989. The University of Michigan, Johns Hopkins University, and the Hospital for Sick Children, where much of the initial research occurred, hold key patents on cystic fibrosis genetic sequences, mutations, and methods for detecting them. Several patents, including the one that covers detection of the DeltaF508 mutation, are jointly held by the University of Michigan and the Hospital for Sick Children in Toronto, with Michigan administering patent licensing in the United States. The University of Michigan broadly licenses the DeltaF508 patent for genetic testing with >60 providers of genetic testing to date. Genetic testing is now used in newborn screening, diagnosis, and for carrier screening. Interviews with key researchers and intellectual property managers, a survey of laboratories' prices for cystic fibrosis genetic testing, a review of literature on cystic fibrosis tests' cost-effectiveness, and a review of the developing market for cystic fibrosis testing provide no evidence that patents have significantly hindered access to genetic tests for cystic fibrosis or prevented financially cost-effective screening. Current licensing practices for cystic fibrosis genetic testing seem to facilitate both academic research and commercial testing. More than 1000 different CFTR mutations have been identified, and research continues to determine their clinical significance. Patents have been nonexclusively licensed for diagnostic use and have been variably licensed for gene transfer and other therapeutic applications. The Cystic Fibrosis Foundation has been engaged in licensing decisions, making cystic fibrosis a model of collaborative and cooperative patenting and licensing practice.

38. JAAPA. 2010 Apr;23(4):30-5.

Newborn screening tests in the 21st century: what PAs need to know.

DelRosario G, Gottesman GS

39. Mol Genet Metab. 2010 Apr;99(4):379-83. Epub 2009 Dec 28.

Genetic heterozygosity and pseudodeficiency in the Pompe disease newborn screening pilot program.

Labrousse P, Chien YH, Pomponio RJ, Keutzer J, Lee NC, Akmaev VR, Scholl T, Hwu WL.

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Abstract
Pompe disease is an autosomal recessive lysosomal storage disorder (LSD) caused by deficiency of lysosomal acid alpha-glucosidase (GAA) activity. This is the first LSD in which newborn screening has been shown to improve clinical outcomes. Newborn screening also identified multiple rare gene variants in this population. Among 132,538 newborns screened, 107 babies (1

in 1239) who had low dried blood spot GAA activity were genotyped. Sixty-nine (64.5%) babies had a total of 54 mutations and 35 novel predictably pathogenic mutations; 36 babies (33.6%) who had no mutation were homozygous for the c.[1726A; 2065A] pseudodeficiency allele. Because 81% of the chromosomes (14% in the controls) were in haplotype *03, we found a link between the pseudodeficiency allele and other mutated alleles. The newborns with Pompe disease detected by screening had lymphocyte GAA activities 0.45 to 1.65 nmol/mg/h (normal 66.7+/-33.8), while only 2 of the 100 false-positive cases had GAA activity less than 2.00 nmol/mg/h (or 3% of the normal mean). Therefore, newborn screening for Pompe disease could be successfully conducted by including genotyping and lymphocyte GAA assay, even in a population with mutation heterozygosity and pseudodeficiency

40. Semin Perinatol. 2010 Apr;34(2):170-9.

The evolution of early hearing detection and intervention programs in the United States.

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Abstract
Identifying and treating children with congenital hearing loss during the first few months of life is a relatively new concept. To assist states in the development of statewide Early Hearing Detection and Intervention programs, the federal government provides grants and/or cooperative agreements to almost all states and has established "National Goals, Program Objectives and Performance Measures" to guide the development and implementation of those systems. This article reviews the history of newborn hearing screening programs in the United States, summarizes the content of legislation and regulations passed by states related to universal newborn hearing screening, and describes how well each National Goal has been addressed. Although substantial progress has been made in the percentage of infants screened for hearing loss before hospital discharge, significant improvement is needed with respect to the availability of pediatric audiologists, implementation of effective tracking and data management systems, program evaluation and quality assurance, availability of appropriate early intervention programs, and linkages with medical home providers.

41. Semin Perinatol. 2010 Apr;34(2):163-9.

Digital microfluidics: a future technology in the newborn screening laboratory?

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Abstract

Expansion of newborn screening for inherited metabolic disorders using tandem mass spectrometry has generated interest in screening for other treatable conditions, including lysosomal storage diseases. Limitations to expansion include labor and equipment costs. We describe a cost-effective new platform that reduces the time to result reporting and can perform multiplexing assays requiring different platforms. Immunoassays and enzyme activity assays currently used in newborn screening have been translated to a disposable microchip programmed to dispense, transport, mix, wash, and incubate individual microdroplets from specimens, including dried blood spot extracts, and reagents all under software control. The specimen and reagents consumed are approximately 1% of those required by equivalent bench assays. In addition to immunologic and enzymatic assays, DNA amplification, amplicon detection, and sequencing have been demonstrated using the same microchips and control equipment. Recently, the multiplexing of 4 different enzyme activities has also been demonstrated with negligible cross-contamination. We review assays relevant to newborn screening.

42. Semin Perinatol. 2010 Apr;34(2):156-62.

Enhancing the quality and efficiency of newborn screening programs through the use of health information technology.

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Abstract

A variety of efforts are underway at national, state, regional, and local levels to enhance the performance of programs for early detection of inherited diseases and conditions of newborn infants. Newborn screening programs serve a vital purpose in identifying nonsymptomatic clinical conditions and enabling early intervention strategies that lessen morbidity and mortality. Currently, the programs of most intense focus are early hearing detection and intervention, using physiological techniques for audiology screening and use of newborn dried blood spots for detection of metabolites or proteins representing inherited disorders. One of the primary challenges to effective newborn screening programs to date has been the inability to provide information in a timely and easily accessible way to a variety of users. Other challenging communication issues being faced include the complexity introduced by the diversity of conditions for which testing is conducted and laboratory methods being used by each state's screening programs, lack of an electronic information infrastructure to facilitate information exchange, and variation in policies that enable access to information while protecting patient privacy and confidentiality. In this study, we address steps being taken to understand these challenges, outline progress made to date to overcome them, and provide examples of how electronic health information exchange will enhance the utility of newborn screening. It is likely that future advances in science and technology will bring many more opportunities to prevent and preempt disabilities among children through early detection programs. To take their advantage, effective communication strategies are needed among the public health, primary care practice, referral/specialty service, and consumer advocacy communities to provide continuity of

information required for medical decision-making throughout prenatal, newborn, and early childhood periods of patient care.

43. Semin Perinatol. 2010 Apr;34(2):145-55.

Newborn screening progress in developing countries--overcoming internal barriers.

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Abstract
Newborn screening is an important public health measure aimed at early identification and management of affected newborns thereby lowering infant morbidity and mortality. It is a comprehensive system of education, screening, follow-up, diagnosis, treatment/management, and evaluation that must be institutionalized and sustained within public health systems often challenged by economic, political, and cultural considerations. As a result, developing countries face unique challenges in implementing and expanding newborn screening that can be grouped into the following categories: (1) planning, (2) leadership, (3) medical support, (4) technical support, (5) logistical support, (6) education, (7) protocol and policy development, (8) administration, (9) evaluation, and (10) sustainability. We review some of the experiences in overcoming implementation challenges in developing newborn screening programs, and discuss recent efforts to encourage increased newborn screening through support networking and information exchange activities in 2 regions-the Asia Pacific and the Middle East/North Africa.

44. Semin Perinatol. 2010 Apr;34(2):134-44.

History and current status of newborn screening for hemoglobinopathies.

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Abstract
The impact of hemoglobinopathies on healthcare in the United States, particularly sickle cell disease (SCD), has been significant. Enactment of the Sickle Cell Anemia Control Act in 1972 significantly increased the federal interest in the SCDs and other hemoglobinopathies. Only since May 1, 2006, have all states required and provided universal newborn screening for SCD despite a national recommendation to this effect in 1987. In this article, we review the history of screening for SCD and other hemoglobinopathies, along with federal and state activities that have contributed to improved health outcomes for patients with SCD, as well as current newborn screening practices. We also chronicle the federal activities that have helped to shape and to refine laboratory screening and diagnostic proficiency. Finally, we review molecular testing

strategies that have evolved and outline their possible future impacts on disease detection and outcome improvement.

45. Semin Perinatol. 2010 Apr;34(2):125-33.

Improving and assuring newborn screening laboratory quality worldwide: 30-year experience at the Centers for disease Control and Prevention.

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Abstract
Newborn screening is the largest population-based genetic screening effort in the United States. The detection of treatable, inherited congenital disorders is a major public health responsibility. The Centers for Disease Control and Prevention's (CDC's) Newborn Screening Quality Assurance Program helps newborn screening laboratories ensure that testing accurately detects these disorders, does not delay diagnosis, minimizes false-positive reports, and sustains high-quality performance. For over 30 years, the CDC's Newborn Screening Quality Assurance Program has performed this essential public health service, ensuring the quality and accuracy of screening tests for more than 4 million infants born each year in the United States and millions more worldwide. The Program has grown from 1 disorder in 1978 for 31 participants to more than 50 disorders for 459 participants in 2009.

46. Semin Perinatol. 2010 Apr;34(2):121-4.

From developing guidelines to implementing legislation: actions of the US Advisory Committee on Heritable Disorders in Newborns and Children toward advancing and improving newborn screening.

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Abstract
Federal advisory committees (or commissions, councils, or task forces) are created either by congressional action or a federal department to bring together a variety of viewpoints on specific policy issues. The committees or advisory bodies are generally directed to advise various bodies within the government, either by congressional mandate, government decree, or executive order. The committees are often created to aid the government in subject matters with difficult issues. In the Department of Health and Human Services (HHS), current advisory committees range from advising the Secretary, Department of Health and Human Services, on immunization practices, to organ donation, blood safety, to issues related to newborn and child screening. This article describes the Secretary's Advisory Committee on Heritable Disorders in Newborns and

Children. Its history offers insight into connection of the development of policy guidelines and the creation of legislation to implement that policy. Its current activities have affected and will continue to affect not only state newborn screening programs but also the policy and practice of screening children for heritable disorders.

47. Semin Perinatol. 2010 Apr;34(2):105-20.

Newborn Screening System Performance Evaluation Assessment Scheme (PEAS).

Therrell BL Jr, Schwartz M, Southard C, Williams D, Hannon WH, Mann MY; PEAS Organizing and Working Groups.

Collaborators (37)
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Abstract
Newborn screening (NBS) reaches approximately all of the 4 million newborns in the United States each year and has been effective in significantly reducing the morbidity and mortality that results from certain congenital conditions. The comprehensive NBS system can be divided into preanalytic (education and screening), analytic (laboratory testing), and postanalytic (reporting, short-term follow-up/tracking, diagnosis, treatment/management, ancillary services, and outcome evaluation) activities. To monitor and improve the screening system, there has been increasing emphasis on evaluation models. Federal sponsorship of a model performance evaluation and assessment scheme (PEAS) has resulted in a comprehensive listing of quality indicators for system self-assessment. We review the PEAS evolution process in an effort to illustrate the necessary infrastructure considerations in a well-functioning NBS system. Readers are encouraged to identify their role in the system and to interact appropriately at the local level. The comprehensive PEAS indicator list is provided as an Appendix.

48. J Pediatr. 2010 Mar 23. [Epub ahead of print]

Breastfeeding effects on newborn screening.

Porta F, Mussa A, Ponzone A.

49. Clin Chim Acta. 2010 Mar 22. [Epub ahead of print]

Newborn screening for Fabry disease by measuring GLA activity using tandem mass spectrometry.

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Abstract
BACKGROUND: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by the deficiency of alpha-galactosidase A (GLA). We evaluated a tandem mass spectrometry method to measure GLA activity. METHODS: One 3.2mm punch from a dried blood spot sample (DBS) was incubated with substrate and internal standard in the reaction buffer for 22h. The resulting product was quantified against internal standard using MS/MS. RESULTS: The median GLA activity of male newborn DBS (N=5051) was 9.85+/-6.4micromol/h/l (CI 95% is 9.67-10.02micromol/h/l); The median GLA activity of female newborns (N=4707) was 10.2+/-6.3micromol/h/l (CI 95% is 10.02-10.38micromol/h/l). The difference between the two subgroups is within assay analytical variation. The GLA activities in the DBS samples from 9 juvenile and adult males with previously identified FD were below 1.64micromol/h/l. The GLA activities from 32 juvenile and adult females with confirmed FD were below 4.73micromol/h/l. In 5 (16%) females GLA activities were above the 0.5th percentile of lower limit of CI 95% at 3.18micromol/h/l. CONCLUSIONS: The MS/MS method for Fabry disease newborn screening is robust can be readily multiplexed with other lysosomal disorders such as Pompe, Gaucher, Niemann-Pick, and Krabbe diseases

50. Am J Respir Crit Care Med. 2010 Mar 15;181(6):539-44.

Update in cystic fibrosis 2009.

Mogayzel PJ Jr, Flume PA.

51. J Pediatr. 2010 Mar 10. [Epub ahead of print]

Newborn Screening Results in Children with Central Hypothyroidism.

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Abstract
OBJECTIVE: To investigate newborn screening results in children with congenital hypopituitarism, including central hypothyroidism, and to determine whether there were differences between children who had abnormal results and children with normal newborn screening results. STUDY DESIGN: Medical records of children with central hypothyroidism observed in our pediatric endocrinology clinics from 1990 to 2006 were reviewed. RESULTS: Forty-two subjects (22 boys) were identified. Eight children (19%) had a low total thyroxine level (<5.0 mcg/dL) on the newborn screening test. The average total thyroxine level in the

remaining 34 subjects was 9.8 +/- 3.4 mcg/dL. Thyrotropin levels were within the reference range in all children. No differences were found in the 2 groups for birth history, jaundice (53% overall), hypoglycemia (36% overall), or micropenis (43% of boys). Fifty-seven percent of children had septo-optic dysplasia, and 98% had multiple pituitary hormone deficiencies. Children with an abnormal newborn screening results were initially examined by a pediatric endocrinologist at an average age of 4.6 +/- 5.0 months, and children with normal newborn screening results were initially examined at an average age of 16.9 +/- 26.7 months (P = .037). CONCLUSIONS: Most children with congenital central hypothyroidism have normal thyroid function at birth. Normal newborn screening results can be falsely reassuring and may contribute to a delay in diagnosis of hypopituitarism despite classic clinical features.

52. Indian Pediatr. 2010 Mar 7;47(3):219-24.

Newborn screening in India: current perspectives.

Kapoor S, Kabra M.

53. MMWR Morb Mortal Wkly Rep. 2010 Mar 5;59(8):220-3.

Identifying infants with hearing loss - United States, 1999-2007.

Centers for Disease Control and Prevention (CDC).

Erratum in:

- MMWR Morb Mortal Wkly Rep. 2010 Apr 23;59(15):460.

Abstract
Congenital hearing loss affects two to three infants per 1,000 live births. Undetected hearing loss can delay speech and language development. A total of 41 states, Guam, and the District of Columbia have statutes or regulatory guidance to identify infants with hearing loss. All states and U.S. territories also have established Early Hearing Detection and Intervention (EHDI) programs, which embody evidence-based public health policy for addressing infant hearing loss. EHDI programs help ensure that newborns and infants are screened and receive recommended follow-up through data collection and outreach to hospitals, providers, and families. To determine the status of efforts to identify newborns and infants with hearing loss, CDC analyzed EHDI surveillance data from 1999-2007. Differences in how data were reported and collected limit comparability between 1999-2004 and 2005-2007 data; however, available data indicated an increase in infants screened from 46.5% in 1999 to 97.0% in 2007. In addition, the number of infants documented with hearing loss in 2007 increased by nearly 500 infants among the same 21 states reporting data in 2001 (1,736 identified in 2001 versus 2,212 in 2007). These findings demonstrate progress toward achieving benchmarks for screening, evaluation, and intervention and document the continued need to ensure infants receive recommended services in a timely manner.

54. J Am Acad Audiol. 2010 Mar;21(3):169-75.

Effects of universal newborn hearing screening on an early intervention program for children with hearing loss, birth to 3 yr of age.

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Abstract
Background: Universal Newborn Hearing Screening (UNHS) was introduced in Kansas in 1999. Prior to UNHS a small percentage of newborns were screened for and identified with hearing loss. Purpose: The purpose of this study was to determine the effects of UNHS on a local early intervention (EI) program for young children with hearing loss. Research Design: This was a retrospective study based on the chart review of children enrolled in the EI program during target years before and after the establishment of UNHS. Study Sample: Charts for 145 children were reviewed. Data Collection and Analysis: The chart review targeted the following aspects of the EI program: caseload size, percentage of caseload identified by UNHS, age of diagnosis, age of enrollment in EI, degree of hearing loss, etiology of hearing loss, late onset of hearing loss, age of hearing aid fit, percentage of children fit with hearing aids by 6 mo, percentage of children with profound hearing loss with cochlear implants, and percentage of children with additional disabilities. Results: Changes in the EI program that occurred after UNHS were increases in caseload size, percentage of caseload identified by UNHS, percentage of children fit with hearing aids by 6 mo of age, and percentage of children with profound hearing loss with cochlear implants. There were decreases in age of diagnosis, age of enrollment in EI, and age of hearing aid fit. Before UNHS, the majority of children had severe and profound hearing loss; after UNHS there were more children with mild and moderate hearing loss. The percentage of known etiology and late-onset hearing loss was approximately the same before and after UNHS, as was the percentage of children with additional disabilities. Conclusion: UNHS had a positive impact on caseload size, age of diagnosis, age of enrollment in EI, and age of hearing aid fit. The percentage of the caseload identified in the newborn period was about 25% before UNHS and over 80% after its implementation. After UNHS, the EI caseload included as many children with mild and moderate hearing loss as with severe and profound loss. By the last reporting year in the study (academic year 2005-2006) all children with profound hearing losses had cochlear implants.

55. Rapid Commun Mass Spectrom. 2010 Apr 15;24(7):986-94.

The application of multiplexed, multi-dimensional ultra-high-performance liquid chromatography/tandem mass spectrometry to the high-throughput screening of lysosomal storage disorders in newborn dried bloodspots.