Jan-Mar 2010 Newborn Screening Articles

1. J Pediatr Nurs. 2010 Apr;25(2):142-3. Epub 2009 Aug 6.
A new horizon for newborn screening.
Monsen RB.

2.Eur J Hum Genet. 2010 Mar 3. [Epub ahead of print]
Reconsidering reproductive benefit through newborn screening: a systematic review of guidelines on preconception, prenatal and newborn screening.
Bombard Y, Miller FA, Hayeems RZ, Avard D, Knoppers BM.

The expansion of newborn screening (NBS) has been accompanied by debate about what benefits should be achieved and the role of parental discretion in their pursuit. The opportunity to inform parents of reproductive risks is among the most valued additional benefits gained through NBS, and assumes prominence where the primary goal of identifying a treatable condition is not assured. We reviewed 53 unique guidelines addressing prenatal, preconception and newborn screening to examine: (1) how generating reproductive risk information is construed as a benefit of screening; and (2) what conditions support the realization of this benefit. Most preconception and prenatal guidelines - where generating reproductive risk information is described as a primary benefit - required that individuals be given a 'cascade of choices', ensuring that each step in the decision-making process was well informed, from deciding to pursue information about reproductive risks to deciding how to manage them. With the exception of three guidelines, NBS policy infrequently attended to the potential for reproductive benefits; further, most guidelines that acknowledged such benefits construed voluntarism narrowly, without attention to the choices attendant on receiving reproductive risk information. This review suggests that prenatal and preconception guidance identifies a coherent framework to support the pursuit of reproductive benefits through population screening programmes. Interestingly, attention to reproductive benefits is increasing among NBS guidance, yet reflection on how such benefits ought to be pursued remains limited. Traditional norms for NBS may require reconsideration where the remit of screening exceeds the primary goal of clinical benefits for infants.

3. J Inherit Metab Dis. 2010 Mar 2. [Epub ahead of print]
Newborn screening strategies for congenital hypothyroidism: an update.
Lafranchi SH.

It is the purpose of this article to briefly review the initial development and subsequent evolution of newborn screening programs to detect infants with congenital hypothyroidism (CH) and then to provide an update of the advantages and disadvantages of the main test strategies. Pilot programs began screening newborn populations in North America in the mid-1970s using either primary thyroxine (T4)-follow-up thyroid stimulating hormone (TSH) or primary TSH testing. Many programs in the United States and around the world continue to prefer a primary T4-follow-up TSH test strategy. This approach has the advantage of detecting infants with primary CH, as well as cases of hypopituitary hypothyroidism, by follow-up of infants with a T4 below an absolute cutoff or with a persistently low T4 level, necessitating a higher recall rate. With increasing assay sensitivity and specificity, several programs in the United States and worldwide

have elected to switch to a primary TSH test strategy. This test strategy has the advantage of detecting primary CH and subclinical hypothyroidism and at a lower recall rate. Programs considering switching to a primary TSH test strategy need to develop age-related TSH cutoffs to maintain an acceptable recall rate. Both test strategies have the potential to detect infants with CH characterized by "delayed TSH rise," but only if they collect a routine or discretionary second specimen, now recommended in low-birth-weight and acutely ill infants. Lastly, a lower TSH cutoff appears to be one of the explanations for the recently described increased incidence of CH.

4. Clin Chem. 2010 Mar;56(3):437-44. Epub 2010 Jan 14.
Newborn screening for galactosemia: a review of 5 years of data and audit of a revised reporting approach.
Freer DE, Ficicioglu C, Finegold D.

BACKGROUND: Availability of the galactose-1-phosphate uridyltransferase (GALT) assay for newborn (NB) screening has improved identification of classic galactosemia. Previously defined critical cutoffs for total galactose (Gal), typically 1.110 mmol/L (20 mg/dL), are still in use in laboratories measuring total Gal for the diagnosis of nonclassic galactosemias. Urgent notification/referral to a treatment center follows, although few of the NBs will need treatment. METHODS: We reviewed all NB galactosemia-screening results and their corresponding clinical outcomes over a 5-year period (first phase, 1.32 x 10(6) NBs) and then over a 2-year period (second phase, 274 960 NBs). Each NB was screened for Gal and GALT. When Gal was increased and/or GALT was deficient, testing for percentage galactose-1-phosphate and/or DNA testing for common GALT mutations were performed. RESULTS: Of 209 reported positive results, 89% did not indicate GALT deficiency. These non-GALT-deficient results represented mostly clinically benign cases with a Gal threshold of >/=1.110 mmol/L (>/=20 mg/dL). The positive predictive value of a GALT cutoff of </=40 mumol/L was 83%. After a protocol change that redefined a critical result as a GALT value </=40 mumol/L and/or a Gal value >/=1.665 mmol/L (>/=30 mg/dL), results were monitored for an additional 2 years. The new protocol dramatically reduced the number of urgent calls/referrals and reduced the total number of referrals by nearly half. CONCLUSIONS: Use of a GALT cutoff of </=40 mumol/L/L and a Gal cutoff of >/=1.665 mmol/L (>/=30 mg/dL) for urgent notification/referral dramatically reduces false positives and unnecessary follow-up, thereby reducing the stress on healthcare resources.

5. Clin Chem. 2010 Mar;56(3):445-50. Epub 2009 Dec 29.
Newborn screening for cystic fibrosis by use of a multiplex immunoassay.
Lindau-Shepard BA, Pass KA.

BACKGROUND: Since its beginnings, newborn screening for cystic fibrosis (CF) using an assay for immunoreactive trypsinogen (IRT) has been plagued by a high rate of false-positive results (screen positive, diagnosis negative), despite attempts to reduce this rate by use of altered cutoffs and second-tier DNA testing. IRT exists as 2 isoforms: IRT1 and IRT2, with IRT2 being more closely aligned with pancreatic disease, including CF. Assay standardization between programs is a continuing problem because the IRT assays currently in use variously recognize either 1 or both isoforms. Here we report the development of a multiplexed assay for both forms of IRT simultaneously. METHODS: Using 2 different Luminex bead sets, we developed assays

for each IRT isoform separately and then combined them. Using the sum of IRT1 and IRT2 values (IRT1+IRT2), we compared the results with a CF kit currently in use. RESULTS: In a sample set consisting of 16 cases confirmed positive for CF, we established a cutoff at >97 mug/L total IRT. Seven of 8 carriers with 1 CF mutation screen-positive by the standard method were also screen-positive by IRT1+IRT2. Of 32 cases screen-positive by standard IRT, 11 were screen-negative by IRT1+IRT2. None of these 11 cases had CF mutations identified by the screening program. CONCLUSIONS: These data indicate that the multiplex method with specificity for 2 isoforms of IRT has performance comparable to that of a standard IRT method and the advantage of improved standardization by detection of the 2 isoforms.

6. Eur J Hum Genet. 2010 Mar;18(3):303-8. Epub 2009 Oct 7.
Understanding sickle cell carrier status identified through newborn screening: a qualitative study.
Miller FA, Paynter M, Hayeems RZ, Little J, Carroll JC, Wilson BJ, Allanson J, Bytautas JP, Chakraborty P.

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.

7.Eur J Pediatr. 2010 Mar 1. [Epub ahead of print]
Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical routine-results from a prospective multicenter study.
Riede FT, Wörner C, Dähnert I, Möckel A, Kostelka M, Schneider P.

Pulse oximetry screening (POS) has been proposed as an effective, noninvasive, inexpensive tool allowing earlier diagnosis of critical congenital heart disease (cCHD). Our aim was to test the hypothesis that POS can reduce the diagnostic gap in cCHD in daily clinical routine in the setting of tertiary, secondary and primary care centres. We conducted a prospective multicenter trial in Saxony, Germany. POS was performed in healthy term and post-term newborns at the age of 24-

72 h. If an oxygen saturation (SpO(2)) of </=95% was measured on lower extremities and confirmed after 1 h, complete clinical examination and echocardiography were performed. POS was defined as false-negative when a diagnosis of cCHD was made after POS in the participating hospitals/at our centre. From July 2006-June 2008, 42,240 newborns from 34 institutions have been included. Seventy-two children were excluded due to prenatal diagnosis (n = 54) or clinical signs of cCHD (n = 18) before POS. Seven hundred ninety-five newborns did not receive POS, mainly due to early discharge after birth (n = 727; 91%). In 41,445 newborns, POS was performed. POS was true positive in 14, false positive in 40, true negative in 41,384 and false negative in four children (three had been excluded for violation of study protocol). Sensitivity, specificity, positive and negative predictive value were 77.78%, 99.90%, 25.93% and 99.99%, respectively. With POS as an adjunct to prenatal diagnosis, physical examination and clinical observation, the percentage of newborns with late diagnosis of cCHD was 4.4%. POS can substantially reduce the postnatal diagnostic gap in cCHD, and false-positive results leading to unnecessary examinations of healthy newborns are rare. POS should be implemented in routine postnatal care.

8. Int J Pediatr Otorhinolaryngol. 2010 Mar;74(3):265-70. Epub 2009 Dec 29.
Qualitative analysis of parents' experience with receiving the news of the detection of their child's hearing loss.
Gilbey P.

OBJECTIVE: Despite the fact that clinicians are responsible for delivering bad news, they have been shown to lack both confidence and skill in performing this basic task. The time immediately after the detection of childhood hearing loss is perceived as stressful. We conducted a qualitative study to assess parents' experiences with receiving the bad news of the detection of their child's hearing loss. STUDY DESIGN: Semi-structured interviews were conducted with families of children with hearing loss identified during early childhood. SETTING: A rehabilitation center treating pre-school children in the north of Israel. PATIENTS: 14 families/parents of children diagnosed prior to the implementation of a universal screening program. MAIN OUTCOME MEASURE: Parents' perceptions of the manner in which the information regarding the detection of their child's hearing loss was given, and what their feelings were at the time. RESULTS: 50% of parents expressed dissatisfaction with the process of the breaking of the bad news. ABR is perceived by parents and health professionals alike as the definitive moment of diagnosis. The emotions experienced by parents at the moment of the breaking of the bad news were predominantly shock and upset. The meaning of the news was perceived differently under different circumstances. Information given bluntly, without empathy, was a frequent complaint. Parents repeatedly stated the importance of the formulation of a plan for the future. CONCLUSIONS: Qualitative enquiry provided valuable information. Effective strategies for the breaking of bad news should become an integral part of universal neonatal screening programs.

9. J Am Soc Nephrol. 2010 Mar;21(3):413-7. Epub 2010 Jan 7.
High prevalence of sickle cell trait in african americans with ESRD.
Derebail VK, Nachman PH, Key NS, Ansede H, Falk RJ, Kshirsagar AV.

Sickle cell trait (HbAS) associates with impaired urinary concentration, hematuria, and renal papillary necrosis, but its prevalence among African Americans with ESRD is unknown. We

performed a cross-sectional study reviewing available hemoglobin phenotypes for 188 of 206 adult African-American patients receiving renal replacement therapy in four dialysis units. Results from the state newborn screening program in corresponding counties provided the local population prevalence of sickle trait among African Americans. Compared with the general African-American population, HbAS was twice as common among African Americans with ESRD (15% versus 7%, $P < 0.001$). Prevalence of hemoglobin C trait (HbAC) was similarly more common (5% versus 2%, $P < 0.01$). The higher prevalence of HbAS and HbAC in the ESRD population raises the possibility that these hemoglobinopathies contribute to a decline in kidney function, either alone or in conjunction with other known risk factors for renal disease. The potential effect of HbAS on the development and progression of CKD and its effect on the course and management of patients with ESRD deserve further study.

10. J Child Neurol. 2010 Mar;25(3):306-11. Epub 2009 Oct 21.
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.

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.

11. J Cyst Fibros. 2010 Mar;9(2):75-83. Epub 2009 Dec 2.
An overview of international literature from cystic fibrosis registries 2. Neonatal screening and nutrition/growth.
Salvatore D, Buzzetti R, Baldo E, Forneris MP, Lucidi V, Manunza D, Marinelli I, Messore B, Neri AS, Raia V, Furnari ML, Mastella G.

BACKGROUND: This is the second article related to a review of the literature based on data from national cystic fibrosis (CF) registries up to June 2008 and covering a total of 115 studies. It focuses on two topics: neonatal screening (NS) and nutritional status, with particular reference to growth. METHODS: Ten papers meeting the inclusion criteria were found on the topic of NS and its impact on the course of the disease, and were analyzed according to a dedicated grid. The issue of nutrition was addressed by 14 studies, analyzed according to similar criteria. RESULTS: Most of the studies report benefits of early diagnosis by NS, albeit to variable degrees. The benefits were assessed in terms of better nutritional status and growth, but also in terms of lower

overall morbidity rate as compared to subjects diagnosed by symptoms. The main biases of these studies, which partly undermine the validity of their results, are also analyzed. A part of our analysis on nutrition/growth is dedicated to the identification of the most suitable parameters to define malnutrition: in children older than two years the body mass index percentile (BMIp) appears to be the most sensitive and significantly associated with respiratory function. Better nutritional status and satisfactory growth appear to be associated with better lung function and lower risk of death. The relationship between nutritional status and socio-economic status is also of interest. CONCLUSIONS: CF registry studies support the outcome of cohort observational studies i.e. that pre-symptomatic early diagnosis is beneficial, especially in terms of nutritional status and growth. Studies on nutrition indicate that good nutritional status is associated with better respiratory function and prognosis. Regarding methods, the need emerged to manage potential biases of this kind of non randomized studies, resorting to suitable statistical techniques, such as matching and stratification and, above all, to multivariate methods able to provide estimates adjusted for the main covariates tested.

12. J Mol Diagn. 2010 Mar;12(2):147-51. Epub 2010 Jan 14.
Detecting 22q11.2 deletions by use of multiplex ligation-dependent probe amplification on DNA from neonatal dried blood spot samples.
Sørensen KM, Agergaard P, Olesen C, Andersen PS, Larsen LA, Ostergaard JR, Schouten JP, Christiansen M.

The 22q11 deletion syndrome, which is caused by a 1.5- to 3.0-megabase hemizygous deletion in chromosome 22q11.2, has a prevalence of 1/2000 to 1/4000. However, the syndrome presents with highly variable phenotypes and thus may be underestimated among Danish newborns. To establish a true incidence of 22q11.2 deletions among certain manifestations, eg, congenital heart disease, on selected Danes, a multiplex ligation-dependant probe amplification (MLPA) analysis was designed. The analysis was planned to be performed on DNA extracted from dried blood spot samples (DBSS) obtained from Guthrie cards collected during neonatal screening programs. However, the DNA concentration necessary for a standard MLPA analysis (20 ng) could not be attained from DBSS, and a novel MLPA design was developed to permit for analysis on limited amounts of DNA (2 ng). A pilot study is reported here that validates the new MLPA design using nine patients diagnosed with the 22q11.2 deletion and 101 controls. All deletions were identified using DNA extracted from DBSS, and no copy number variations were detected in the controls, resulting in a specificity and sensitivity of 100%. It is thereby concluded that the novel MLPA probe design is successful and reliable using minimal amounts of DNA. This allows for use of DBSS samples in a retrospective study of 22q11.2 deletion among certain manifestations associated with DiGeorge Syndrome.

13. J Pediatr. 2010 Mar;156(3):492-494. Epub 2010 Jan 8.
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency in a Patient with Normal Newborn Screening by Tandem Mass Spectrometry.
Ficicioglu C, Coughlin CR 2nd, Bennett MJ, Yudkoff M.

Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD) can be detected through newborn screening with tandem mass spectrometry. We report a patient who died as a result of

severe brain injury due to hypoglycemia. Newborn screening was normal. Postmortem enzyme analysis and molecular testing confirmed the diagnosis of VLCADD.

14. **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 mumol/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.

15. J Pediatr. 2010 Mar;156(3):420-426. Epub 2009 Nov 14.
Prevalence of Developmental Disabilities and Receipt of Special Education Services among Children with an Inborn Error of Metabolism.
Powell K, Van Naarden Braun K, Singh R, Shapira SK, Olney RS, Yeargin-Allsopp M.

OBJECTIVE: To examine the presence of developmental disabilities and receipt of special education services in children with an inborn error of metabolism. STUDY DESIGN: The study population was children born from 1988 through 2001 in whom a metabolic disorder was diagnosed after identification by newborn screening (n = 97) or after clinical identification (n = 34). These children were linked to the Metropolitan Atlanta Development Disability Surveillance Program (MADDSP) and Special Education Database of Metropolitan Atlanta (SEDMA) to determine developmental outcomes at 8 years of age and 3 through 10 years of age, respectively. Medical and educational records were examined to consider factors contributing to developmental outcomes. RESULTS: Of 97 children with a metabolic disorder identified with newborn screening, 12 (12.4%) were identified by SEDMA as receiving special education services and 2 (2.7%) were identified by MADDSP as having a developmental disability. Of the 34 children with a clinically identified metabolic disorder, 8 (23.5%) were identified with SEDMA, and 5 (17.2%) were identified with a MADDSP developmental disability. CONCLUSION: Early identification and treatment have been successful in limiting the impact of severe developmental disabilities. Continued surveillance and research are needed to monitor less severe developmental outcomes.

16.Matern Child Health J. 2010 Mar;14(2):174-83. Epub 2008 Dec 9.

Pediatricians' attitudes about screening newborns for infectious diseases.
Schittek H, Koopmans J, Ross LF.

In 2002, the U.S. Health Resources and Services Administration (HRSA) commissioned the American College of Medical Genetics (ACMG) to recommend a uniform newborn screening (NBS) panel. The ACMG sent out a survey to stakeholders to evaluate 80 metabolic and genetic conditions and 3 infectious diseases (Human Immunodeficiency Virus (HIV), Toxoplasmosis (Toxo), and Cytomegalovirus (CMV)). In March 2005, the ACMG/HRSA report recommended a panel including 29 metabolic and genetic conditions and 25 secondary targets. This panel was endorsed by the newly-formed U.S. Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (Advisory Committee). Decisions about infectious diseases were deferred by the ACMG/HRSA committee due to limited survey responses and lack of expertise of surveyed stakeholders and committee members. The Advisory Committee has not pursued these conditions further. In this manuscript, we examine the attitudes of U.S. pediatricians toward targeted and universal screening of newborns for these three infectious diseases. Members of the American Academy of Pediatrics (AAP) sections of infectious disease (n = 150) and community pediatrics (n = 150) plus 13 contributors to the AAP Red Book were surveyed by email or fax. Of eligible pediatricians, 113 of 297 (38%) returned surveys. Seventy-four percent supported either targeted or universal NBS for HIV, 57% for Toxo, but only 42% for CMV. The majority of respondents support screening newborns for HIV and Toxo. The Advisory Committee ought to solicit a systematic evaluation of these conditions to determine whether they should be included in the uniform panel.

17. Mol Genet Metab. 2010 Mar;99(3):263-8. Epub 2009 Nov 1.
Lack of genotype-phenotype correlations and outcome in MCAD deficiency diagnosed by newborn screening in New York State.
Arnold GL, Saavedra-Matiz CA, Galvin-Parton PA, Erbe R, Devincentis E, Kronn D, Mofidi S, Wasserstein M, Pellegrino JE, Levy PA, Adams DJ, Nichols M, Caggana M.

INTRODUCTION: Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is one of the most common inborn errors of metabolism. Affected patients have impaired ability to break down medium chain fatty acids during fasting, and typically present in the early years of life with hypoketotic hypoglycemia, Reye syndrome-like symptoms, brain damage or death. The development of newborn screening (NBS) for MCAD deficiency has greatly improved outcome, but some patients still appear at risk for severe complications. We reviewed the outcome of patients identified with MCAD deficiency by the New York State NBS process to identify biochemical or genotypic markers which might predict outcome. METHOD: All eight NBS follow-up centers in New York State contributed the cases of MCAD deficiency diagnosed by newborn screen, who received diagnostic and follow-up care in their clinic. Data reviewed included gender, age, birthweight, initial NBS octanoylcarnitine level (C8) and C8/C2 ratio, follow-up C8 and hexanoylglycine, race/ethnicity, and presence of neonatal or later symptoms. RESULTS: We identified 53 cases of MCAD deficiency. More than one quarter of patients had a post-neonatal symptomatic admission (predominantly lethargy associated with an intercurrent illness). No genotype or C8 level was protective for neonatal or later symptoms. There was a relationship between initial C8 level or C8/C2 ratio and occurrence of later symptoms (7.3 micromol/L in the asymptomatic vs. 19.1 micromol/L in the symptomatic, $p<0.0002$ for C8, and

0.26 vs. 0.6, respectively, for C8/C2 ratio, p<0.012). Four infants had initial C8 level >30 micromol/L; these infants had a high rate of symptomatic or multiple symptomatic episodes or a history of sibling death from "SIDS", and typically had deletion, nonsense or splice sites mutations. Infants having a history of a symptomatic episode were more likely to have higher initial C8 on NBS and a genotype predicted to strongly affect protein function. In our ethnically diverse group of patients, the c.985A>G mutation was rarely found in non-Caucasians. DISCUSSION: No genotype or metabolite profile is protective from symptoms. The strong relationship between initial C8 level and outcome suggests that in at least some cases neonates having high initial C8 levels may be demonstrating an increased susceptibility to catabolic stress, and may merit additional precautions. Our data also suggest that these infants are more likely to carry severe mutations including homozygosity for the common mutation, deletions, nonsense or splice site mutations. The reports of significant lethargy or hypoglycemia during intercurrent illness in over one quarter of cases even when early medical intervention is recommended (and even when initial C8 is not profoundly elevated) underscores the importance of continued vigilance to prevent stressful fasting in this disorder.

18. Pediatr Dev Pathol. 2010 Mar 1. [Epub ahead of print]
EXPANDED NEWBORN SCREENING: A REVIEW FOR THE PEDIATRIC PATHOLOGIST.
Rakheja D, Deberardinis RJ.

19. Pediatr Res. 2010 Mar;67(3):237.
The fate of newborn screening blood spots.
Grody WW, Howell RR.

20. Pediatrics. 2010 Mar;125(3):417-9. Epub 2010 Feb 15.
The lure of treatment: expanded newborn screening and the curious case of histidinemia.
Brosco JP, Sanders LM, Dharia R, Guez G, Feudtner C.

21. Soc Sci Med. 2010 Mar;70(6):926-33. Epub 2010 Jan 12.
Public accountability of newborn screening: collective knowing and deciding.
Wieser B.

A number of European countries have expanded their screening programme considerably during the last decade. Other countries have, however, not expanded their programme substantially. In this paper, I will compare UK and Austria, two countries representing two ends of the European spectrum. Focussing on the decision-making processes behind the design and expansion of newborn screening, I draw on Sheila Jasanoff's concept of "civic epistemology" (Jasanoff, S. (2005). Designs on Nature. Princeton and Oxford: Princeton University Press.) to investigate how the chosen countries provide information in order to give account for their respective screening policies. In particular, I analyse how key institutions in the UK and Austria use scientific expertise to explain and justify national screening programmes. For this purpose, I compare the material that is made available to the public, including policy documents, scientific studies, medical guidelines, legal regulation, advisory committee reports and public engagement exercises. It was found that the observed differences in the accountability practices are rooted in nationally traditional forms of policy making. However, whether or not these repertoires become

indeed realised is a more contingent matter and is often triggered by events which evoke a response from the medical and policy-making actors.

22. J Inherit Metab Dis. 2010 Feb 23. [Epub ahead of print]
Four years of expanded newborn screening in Portugal with tandem mass spectrometry.
Vilarinho L, Rocha H, Sousa C, Marcão A, Fonseca H, Bogas M, Osório RV.

INTRODUCTION: The Portuguese Neonatal Screening Programme (PNSP) was started in 1979 for phenylketonuria (2,590,700 newborns screened; prevalence 1:11,031) and, shortly after, for congenital hypothyroidism (2,558,455 newborns screened; prevalence 1:3,174). In 2004, expanded neonatal screening was implemented in the National Laboratory. The programme is not mandatory and has 99.8% coverage of the country (including Madeira and the Azores islands). MATERIAL AND METHODS: In the past 4 years, 316,243 neonates were screened with the use of tandem mass spectrometry (MS/MS) to test for selected amino acids and acylcarnitines. RESULTS: During this time, 132 patients were identified with 24 different inherited metabolic diseases (classic forms and variants). To date, the global frequency for all disorders integrated into the PNSP is estimated to be 1:1,380, with 1:2,396 for metabolic disorders. A total of 379 tests (0.12%) were classified as having false positive results, yielding an overall specificity of 99.9%. Despite the low frequency of several disorders, the positive predictive value of the overall MS/MS screening was found to be 26%, reflecting high diagnostic specificity of the method. Diagnostic sensitivity of extended screening for the different groups of disorders was 100%. Eight cases of maternal disorders [three glutaric aciduria type I, one carnitine transporter defect, and four 3-methylcrotonyl coenzyme A (CoA) carboxylase deficiency] were also detected through newborn screening. CONCLUSIONS: Our data support the advantage of a centralised laboratory for screening an elevated number of samples and making decisions if relying on a clinical network able to provide fast treatment and a good outcome in the screened cases.

23. J Pediatr. 2010 Feb 18. [Epub ahead of print]
Psychological Effects of False-Positive Results in Cystic Fibrosis Newborn Screening: A Two-Year Follow-up.
Beucher Jd 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.

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.

24. J Inherit Metab Dis. 2010 Feb 17. [Epub ahead of print]
Dermatan sulfate and heparan sulfate as a biomarker for mucopolysaccharidosis I.
Tomatsu S, Montaño AM, Oguma T, Dung VC, Oikawa H, de Carvalho TG, Gutiérrez ML, Yamaguchi S, Suzuki Y, Fukushi M, Sakura N, Barrera L, Kida K, Kubota M, Orii T.

Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by deficiency of alpha-L-iduronidase leading to accumulation of its catabolic substrates, dermatan sulfate (DS) and heparan sulfate (HS), in lysosomes. This results in progressive multiorgan dysfunction and death in early childhood. The recent success of enzyme replacement therapy (ERT) for MPS I highlights the need for biomarkers that reflect response to such therapy. To determine which biochemical markers are better, we determined serum and urine DS and HS levels by liquid chromatography tandem mass spectrometry in ERT-treated MPS I patients. The group included one Hurler, 11 Hurler/Scheie, and two Scheie patients. Seven patients were treated from week 1, whereas the other seven were treated from week 26. Serum and urine DS (DeltaDi-4S/6S) and HS (DeltaDiHS-0S, DeltaDiHS-NS) were measured at baseline, week 26, and week 72. Serum DeltaDi-4S/6S, DeltaDiHS-0S, and DeltaDiHS-NS levels decreased by 72%, 56%, and 56%, respectively, from baseline at week 72. Urinary glycosaminoglycan level decreased by 61.2%, whereas urine DeltaDi-4S/6S, DeltaDiHS-0S, and DeltaDiHS-NS decreased by 66.8%, 71.8%, and 71%, respectively. Regardless of age and clinical severity, all patients showed marked decrease of DS and HS in blood and urine samples. We also evaluated serum DS and HS from dried blood-spot samples of three MPS I newborn patients, showing marked elevation of DS and HS levels compared with those in control newborns. In conclusion, blood and urine levels of DS and HS provide an intrinsic monitoring and screening tool for MPS I patients.

25. J Inherit Metab Dis. 2010 Feb 16. [Epub ahead of print]
The first case of mitochondrial acetoacetyl-CoA thiolase deficiency identified by expanded newborn metabolic screening in Italy: the importance of an integrated diagnostic approach.
Catanzano F, Ombrone D, Di Stefano C, Rossi A, Nosari N, Scolamiero E, Tandurella I, Frisso G, Parenti G, Ruoppolo M, Andria G, Salvatore F.

A pilot expanded newborn screening programme to detect inherited metabolic disorders by means of liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) began in the Campania region, southern Italy, in 2007. By October 2009, >8,800 dried blood samples on filter paper from 11 hospitals had been screened. Within this screening programme, we identified a case of mitochondrial acetoacetyl-coenzyme A (CoA) thiolase deficiency [beta-ketothiolase (beta-KT) deficiency] by analysing the acylcarnitine profile from a dried blood spot with LC-MS/MS. Gas chromatography coupled with mass spectrometry analysis of urinary organic acids and LC-MS/MS analysis of urinary acylcarnitines were in line with this disorder. In fact, concentrations were well beyond the cut-off values of tiglyl carnitine, 3-hydroxybutyrylcarnitine and 2-methyl-3-hydroxybutyrylcarnitine, 2-methyl-3-hydroxybutyric acid and tiglyl glycine. The absence of 2-methylacetoacetic acid in urine may be attributed to: (i) the instability of this beta-ketoacid because it undergoes spontaneous decarboxylation to 2-butanone, which is highly

volatile and thus difficult to detect, and (ii) the good health of the patient in the first days of life. beta-KT deficiency was subsequently diagnosed in the patient's older sister, who showed increased levels of the same metabolites but also small amounts of 2-methylacetoacetic acid, which is considered a key marker for beta-KT diagnosis. Genomic analysis revealed mutation c.1189C >G in exon 12 of the ACAT1 gene, which results in a severe defect because of the p.H397D amino acid change in both alleles of both patients.

26. BMC Pediatr. 2010 Feb 15;10:9.
Discontinuation of thyroid hormone treatment among children in the United States with congenital hypothyroidism: findings from health insurance claims data.
Kemper AR, Ouyang L, Grosse SD.

ABSTRACT: BACKGROUND: Thyroid hormone treatment in children with congenital hypothyroidism can prevent intellectual disability. Guidelines recommend that children diagnosed with congenital hypothyroidism through newborn screening remain on treatment to at least 3 years of age, after which a trial off therapy can determine which children have transient hypothyroidism. The purpose of this study was to describe the rate at which children with congenital hypothyroidism in the United States discontinue thyroid hormone treatment in early childhood. METHODS: Retrospective analysis of the 2002-2006 MarketScan(R) Commercial Claims and Encounters research databases and the 2001-2005 MarketScan Multi-State Medicaid databases. Children were classified as having congenital hypothyroidism based on billing codes and having filled a prescription for thyroid hormone treatment. Kaplan-Meier curve analysis was used to determine discontinuation rates. RESULTS: There were a total of 412 Medicaid-enrolled children and 292 privately-insured children with presumed congenital hypothyroidism included in this study. The overall birth prevalence of congenital hypothyroidism across both datasets was about 1 per 2,300. By 36 months, the percentage who had discontinued thyroid replacement treatment was 38% (95% Confidence Interval: 32%-44%). Medicaid-enrolled children had a more rapid decline in the first 24 months of treatment compared to those with private insurance (P = 0.02). CONCLUSIONS: More than one-third of children treated for congenital hypothyroidism discontinued treatment within 36 months, which is inconsistent with current guidelines. It is not known how many of these children required continued treatment or experience adverse effects from discontinuation. These findings emphasize the critical need for follow-up systems to monitor the outcome of newborn screening.

27. J Inherit Metab Dis. 2010 Feb 12. [Epub ahead of print]
Classical galactosemia in Estonia: selective neonatal screening, incidence, and genotype/phenotype data of diagnosed patients.
Ounap K, Joost K, Temberg T, Krabbi K, Tõnisson N.

28. Eur Arch Otorhinolaryngol. 2010 Feb 11. [Epub ahead of print]
Evaluation of an automated auditory brainstem response in a multi-stage infant hearing screening.
Guastini L, Mora R, Dellepiane M, Santomauro V, Mora M, Rocca A, Salami A.

An automated auditory brainstem response (AABR) method, the Maico MB-11 with BERAphone((R)), has been developed for hearing screening in newborns. The aim of this study

was to test the validity of this automated ABR screening method in a multistage newborn hearing screening (NHS). We applied a "five level" protocol using transient evoked otoacoustic emission (TEOAE), AABR-MB-11 with BERAphone((R)) and conventional auditory brainstem response (ABR). TEOAE, AABR, and conventional ABR testing were performed by ENT specialists experienced in neonatal screening techniques. Among the 8,671 newborns tested (males 3,889; females 4,782), only 42 newborns were lost to follow-up and the final false-positive rate was of 0.03%. Our experience highlights that for the neonatal period, conventional auditory brainstem response is the most reliable method for assessing the hearing level and minimizing the false-positive rate. Although AABR (performed by ENT specialists experienced in neonatal screening techniques) is easy to use, fast and with a good compliance, the device is unable to provide accurate and certain diagnosis on the degree of hearing loss to allow a proper treatment.

29. Genet Med. 2010 Feb 11. [Epub ahead of print]
An evidence development process for newborn screening.
Perrin JM, Knapp AA, Browning MF, Comeau AM, Green NS, Lipstein EA, Metterville DR, Prosser L, Queally D, Kemper AR.

30.Genet Test Mol Biomarkers. 2010 Feb 7. [Epub ahead of print]
DNA Carrier Testing and Newborn Screening for Maple Syrup Urine Disease in Old Order Mennonite Communities.
Carleton SM, Peck DS, Grasela J, Dietiker KL, Phillips CL.

Maple syrup urine disease (MSUD) is an inherited metabolic disorder caused by mutations in the branched chain alpha-keto acid dehydrogenase complex. Worldwide incidence of MSUD is 1:225,000 live births. However, within Old Order Mennonite communities, the incidence is 1:150 live births and results from a common tyrosine to asparagine substitution (Y438N) in the E1alpha subunit of branched chain alpha-keto acid dehydrogenase. We developed a new DNA diagnostic assay utilizing TaqMan((R)) technology and compared its efficacy, sensitivity, and duration with an existing polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. Carrier testing was performed by both TaqMan technology and PCR-RFLP on DNA isolated from buccal swabs of 160 individuals as well as from buccal swabs and blood spots of nine at-risk newborns; assay time, sensitivity, and reliability were also evaluated. The TaqMan assay, like the PCR-RFLP assay, accurately determined Y438N E1alpha allele status. However, the TaqMan assay appeared (1) more sensitive than the PCR-RFLP assay, requiring 10-fold less DNA (10 ng) to reliably determine genotype status and (2) faster, reducing the assay time required for diagnosis from approximately 12 to 5 h. TaqMan technology allowed more rapid DNA diagnoses of MSUD in the neonate, thereby reducing the likelihood of neurological impairment while enhancing health and prognosis for affected infants.

31. Genet Med. 2010 Feb 4. [Epub ahead of print]
Newborn screening-the unique role of unique evidence.
Fleischman AR, Howse JL.

32. J Genet Couns. 2010 Feb 4. [Epub ahead of print]

Long-term Evaluation of Genetic Counseling Following False-Positive Newborn Screen for Cystic Fibrosis.
Cavanagh L, Compton CJ, Tluczek A, Brown RL, Farrell PM.

This cross-sectional mixed method study was a long-term follow-up evaluation of families who participated in an earlier survey of their understanding of cystic fibrosis (CF) genetics and their infants' false-positive CF newborn screening (NBS) results. Thirty-seven of the original 138 parents participated in the follow-up telephone survey. Results showed parents who received genetic counseling at the time of their infants' diagnostic sweat tests had significantly higher long-term retention of genetic knowledge than those without genetic counseling. However, both groups still had misconceptions and lacked accurate information about the actual risk associated with being a CF carrier. Most parents either had already informed (65%) or planned to inform (19%) their children about the child's carrier status. Mean child age at the time of disclosure was 9.2 years. Situational prompts were the most common reasons for informing their children. Neither parental knowledge, medical literacy, nor parental education predicted whether parents informed their children about their carrier status. False-positive NBS results for CF were not associated with parental perceptions of child vulnerability 11-14 years after the testing. Although the sample from this study was small, these findings underscore the benefits of genetic counseling at the time of the diagnostic sweat test and offer information that can assist parents in talking with their children about the implications of having one CFTR mutation.

33. Arch Dis Child. 2010 Feb;95(2):130-5. Epub 2009 Mar 26.
Hearing screening in newborns: systematic review of accuracy, effectiveness, and effects of interventions after screening.
Wolff R, Hommerich J, Riemsma R, Antes G, Lange S, Kleijnen J.

BACKGROUND: The authors aimed to evaluate the benefits and harms of universal newborn hearing screening programmes in the detection of hearing impairment. OBJECTIVES: In the absence of randomised trials evaluating whole screening programmes, the study divided the objective into three systematic reviews of non-randomised controlled studies of diagnostic accuracy of screening tests, screening versus no screening, and therapeutic effect of early versus later treatment. METHODS: The authors searched 11 bibliographic databases, and included 17 studies (diagnostic: 9, screening: 2, and treatment: 6). All studies apart from one treatment study showed major quality deficits. Eight diagnostic studies comparing otoacoustic emissions with auditory brainstem response showed sensitivities (and specificities) between 50% (49.1%) and 100% (97.2%). RESULTS: The studies comparing screening versus no screening showed an improvement of speech development of children in the screening group compared with the group without screening. Early treatment was associated with better language development in comparison to children with later treatment. CONCLUSIONS: The authors concluded that there is a lack of high-quality evidence regarding all elements of newborn hearing screening. Early identification and early treatment of children with hearing impairments may be associated with advantages in language development. Other patient-relevant parameters, such as social aspects, quality of life, and educational development, have not been adequately investigated.

34. Best Pract Res Clin Endocrinol Metab. 2010 Feb;24(1):63-75.

Neonatal TSH screening: is it a sensitive and reliable tool for monitoring iodine status in populations?
Li M, Eastman CJ.

Iodine deficiency is the most common cause of preventable brain damage in the newborn. The indicators for assessing iodine nutritional status include urinary iodine excretion, thyroid size, thyroid stimulating hormone (TSH) and thyroglobulin (Tg) concentrations in the blood. Neonatal TSH concentration is increased when the supply of thyroid hormone and iodine from the maternal circulation to the foetus has been compromised. The World Health Organization (WHO) has suggested that when a sensitive assay is used on samples collected 3-4 days after birth, a <3% frequency of TSH concentrations >5 mIUl(-1) indicates iodine sufficiency in a population. However, many studies have attempted to apply the frequency of neonatal TSH values >5 mIUl(-1) in determining population iodine status and monitoring intervention programmes, and although some have proven to be successful, most have provided conflicting or uncertain data. This is due to the many technical issues that remain unresolved on the use of neonatal TSH screening for monitoring iodine status, making it doubtful as a sensitive and reliable quantitative tool. More research is required to resolve these issues. In the interim, WHO should consider withdrawing its current guidelines for neonatal TSH screening for monitoring iodine deficiency in populations.

35. Braz J Med Biol Res. 2010 Feb;43(2):134-8. Epub 2010 Jan 15.
Frequency of 8 CFTR gene mutations in cystic fibrosis patients in Minas Gerais, Brazil, diagnosed by neonatal screening.
Perone C, Medeiros GS, del Castillo DM, de Aguiar MJ, Januário JN.

The nature and frequency of cystic fibrosis mutations in Brazil is not uniform due to the highly varied ethnic composition of the population. The average frequency of the F508del mutation has been reported to be 48.6%. Other common mutations in Brazil are G542X, R1162X, and N1303K. The aim of this study was to analyze the frequency of 8 mutations (F508del, G542X, R1162X, N1303K, W1282X, G85E, 3120+1G>A, and 711+1G>T) in a sample of 111 newborn patients with cystic fibrosis diagnosed by the Cystic Fibrosis Neonatal Screening Program of Minas Gerais State. The mutations were tested by allele-specific oligonucleotide PCR with specially designed primers. An allele frequency of 48.2% was observed for the F508del mutation, and allele frequencies of 5.41, 4.50, 4.05, and 3.60% were found for the R1162X, G542X, 3120+1G>A, and G85E mutations, respectively. The genotypes obtained were in Hardy-Weinberg equilibrium. These data demonstrate that the 8-mutation panel studied here has extensive coverage (68%) for the cystic fibrosis mutations in Minas Gerais. These data improve our knowledge of cystic fibrosis in Brazil, particularly in this region. In addition, this investigation contributed to the establishment of a sensitive and population-specific mutation panel, which can be helpful for molecular diagnosis of cystic fibrosis.

36. Clin Chim Acta. 2010 Feb 1. [Epub ahead of print]
Comparison of amino acids and acylcarnitines assay methods used in newborn screening assays by tandem mass spectrometry.
De Jesús VR, Chace DH, Lim TH, Mei JV, Hannon WH.

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.

37. Clin Chim Acta. 2010 Feb;411(3-4):222-8. Epub 2009 Nov 24.
Serum steroid profiling for Congenital Adrenal Hyperplasia using liquid chromatography-tandem mass spectrometry.
Rossi C, Calton L, Hammond G, Brown HA, Wallace AM, Sacchetta P, Morris M.

BACKGROUND: Diagnosis of Congenital Adrenal Hyperplasia (CAH) is based on the quantification of 17-hydroxyprogesterone (17-OHP), usually by immunoassay. During the neonatal period the specificity of screening for CAH by blood spot 17-OHP immunoassay is low. High false-positive rates result in a relatively high demand for a second-tier serum confirmation test. A robust, specific and selective method for measurement of cortisol, 21-deoxycortisol, 11-deoxycortisol, 4-androstene-3,17-dione (A4) and 17-OHP in serum has been developed. The method involves a simple extraction procedure and a fast analysis using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC/MS/MS). METHODS: The steroids were extracted from 50microl of serum using methyl-tert-butyl-ether. Analysis was performed on a UPLC tandem quadrupole mass spectrometer system in positive mode electrospray ionization and multiple reaction monitoring acquisition. RESULTS: The assay was linear over each analyte concentration range with all correlation coefficients (r(2))>0.996. Inter- and intra-day CVs were <or=10% across the analytical range. In addition simultaneous measurement of the full range of steroids on the pathway to cortisol allows confirmation of the affected steroidogenic enzyme. CONCLUSIONS: A second-tier test for the confirmation of CAH has been developed. The method allows for detection and quantification of 5 steroids related to CAH over the range of the clinical assay with good linearity, sensitivity and precision

38. Int J Pediatr Otorhinolaryngol. 2010 Feb;74(2):188-91. Epub 2009 Dec 5.
Newborn hearing screening in a developing country: results of a pilot study in Abidjan, Côte d'ivoire.
Tanon-Anoh MJ, Sanogo-Gone D, Kouassi KB.

OBJECTIVE: To investigate the feasibility of neonatal hearing impairment in newborn babies in Abidjan, Côte d'Ivoire. METHODS: It is a cross-sectional study in which all infants aged from 3 to 28 days, attending for Bacille Calmette-Guerin (BCG) immunization in primary care centers or hospitalized in neonatal intensive care units (NICU), between July 2007 and March 2008, were included. Screening followed a two-stage strategy with transient evoked otoacoustic emissions (TEOAE). Infants referred after the second-stage screening were scheduled for diagnostic evaluation by diagnostic auditory brainstem response (ABR). The variables analyzed were: screening coverage, referral rates; return rates for second-stage screening and diagnostic evaluation, incidence of permanent hearing loss and age at diagnosis. RESULTS: 1306 newborns, of a total of 1495, were successfully screened, giving a screening coverage of 87.4%. The average age was 4.5 days (S.D.: 2.7), with 5.85 days (S.D.: 3.17) for the immunization group and 3.20 days (S.D.: 0.40) for the neonatal unit group. In total, 286 out of the 1306 infants (21.9%) were referred after the first-stage screening; out of which 193 (67.5%) return for the second stage. After the second-stage screening, 48 (16.8%) were scheduled for diagnostic evaluation (45 from NICU and 3 from primary care centers). The overall referral rate for diagnostic evaluation was 3.7% (48/1306). Only 18.75% of those referred (9/48) returned for evaluation, and seven of them (77.8%) were confirmed with hearing loss (2 from immunization group and 5 from neonatal unit group). The prevalence of permanent hearing loss in this screened population was 5.96 per 1000 (7/1174 babies who completed the screening) [95% I.C.: 5.62-6.30 per 1000]. The mean age at diagnosis was 22 weeks (S.D.: 8.3). The reasons for non-completed screening were, according to 62 mothers: no financial means, absence of hearing loss, fear of spouse reactions, lack of information about this test and deafness. CONCLUSION: The incidence of permanent and early hearing impairment identified by this screening program was about 6 per 1000. Routine hearing screening of infants for the early detection of hearing loss is necessary in Côte d'Ivoire. It is possible to implement such a hearing screening, targeting all newborns, in primary health care centers and neonatal intensive care units.

39. J Inherit Metab Dis. 2010 Feb;33(1):43-50. Epub 2009 Dec 23.
Diagnostic efficacy of the fluorometric determination of enzyme activity for Pompe disease from dried blood specimens compared with lymphocytes-possibility for newborn screening.
Lukacs Z, Nieves Cobos P, Mengel E, Hartung R, Beck M, Deschauer M, Keil A, Santer R.

BACKGROUND: Pompe disease is a rare, autosomal-recessive disorder which results from a defect in the lysosomal enzyme acid alpha-glucosidase (GAA). The onset of this disease is highly variable, with infantile types being the most severe. Traditionally, lymphocytes, fibroblasts or muscle biopsies were necessary for enzyme activity measurement, because these materials do not express maltase-glucoamylase (MGA) that interferes with the assay. Recently, acarbose was found to inhibit MGA activity selectively, so that dried blood became accessible for GAA assessment. AIM: To evaluate the diagnostic efficacy of GAA measurement in dried blood specimens (DBSs) in comparison with lymphocytes. If DBSs provided reliable results, the diagnosis of Pompe disease could be facilitated, and high-throughput screening would become possible. METHODS AND RESULTS: GAA activity was measured in DBSs of known patients at pH 3.8 (with and without acarbose) and at pH 7.0. Additionally, lymphocytes were obtained from the same patients, and the enzyme activity was determined at pH 4 to pH 7. In total, seven infantile patients and 29 patients with late-onset variants were investigated. All patients were reliably identified by both methods. Furthermore, a simplified protocol was established for

neonatal screening. CONCLUSION: The fluorometric technique for the assessment of GAA activity in DBS provides a reliable diagnosis for all variants of Pompe disease. The assay protocol could be simplified for neonatal screening, without increasing the false positive rate significantly or burdening the laboratory with time-consuming procedures.

40. Mol Genet Metab. 2010 Feb;99(2):116-23. Epub 2009 Sep 27.
Newborn screening and early biochemical follow-up in combined methylmalonic aciduria and homocystinuria, cblC type, and utility of methionine as a secondary screening analyte.
Weisfeld-Adams JD, Morrissey MA, Kirmse BM, Salveson BR, Wasserstein MP, McGuire PJ, Sunny S, Cohen-Pfeffer JL, Yu C, Caggana M, Diaz GA.

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 13.4mumol/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.

41. Pediatrics. 2010 Feb;125(2):e286-94.
Projected costs, risks, and benefits of expanded newborn screening for MCADD.
Prosser LA, Kong CY, Rusinak D, Waisbren SL.

OBJECTIVE: To evaluate the cost-effectiveness of newborn screening for medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD) incorporating quality-of-life effects for false-positive newborn screens and recommended dietary treatment. METHODS: A computer simulation model was developed to predict costs and health outcomes for expanded newborn screening for MCADD compared with clinical identification. The modeled target population was a hypothetical cohort of 100 000 newborns in the United States. Probabilities, costs, and quality-of-life weights were derived from a long-term follow-up study of newborn screening compared with clinical identification, primary data collection, published data, and expert opinion. We used a lifetime time horizon and the societal perspective. The main outcome measure was the

incremental cost-effectiveness ratio in dollars per quality-adjusted life-year (QALY) gained. Secondary outcomes included averted deaths and hospitalizations. RESULTS: Using base-case assumptions, the cost-effectiveness of newborn screening for MCADD was $21 273 per QALY gained. The cost-effectiveness ratio increased to $21 278/QALY when the loss in quality of life associated with false-positive test results was incorporated and to $27 423/QALY when the quality of life associated with lifelong dietary recommendations for treating MCADD was incorporated. Results were sensitive to the false-positive rate for the newborn screening test and the cost of the initial screen. CONCLUSIONS: Expanded newborn screening for MCADD is cost-effective compared with well-accepted pediatric health interventions. Losses in quality of life associated with dietary treatment for MCADD, however, may offset some of the gains in QALYs from newborn screening. Consideration of new disorders for expanded newborn screening panels should include the potential reduction in quality of life associated with treatments.

42. J Endocrinol Invest. 2010 Jan 22. [Epub ahead of print]
ESTIMATION OF GENETIC RISK FOR TYPE 1 DIABETES MELLITUS IN NEWBORNS ON DRIED BLOOD SPOT.
Giannattasio A, Caruso U, Salina A, Aloi C, Lorini R, d'Annunzio G.

Background. The main contribution to genetic susceptibility for Type 1 Diabetes Mellitus (T1DM) is conferred by the Human Leukocyte Antigens (HLA). Aim. We evaluated the feasibility of large scale screening on Dried Blood Spot (DBS) to estimate the genetic risk for T1DM in newborns. Subjects and Methods. Peripheral blood DBS samples from 256 newborns, were genotyped for HLA DRB1 and DQB1 alleles identification by a commercially available assay based on a dissociation enhancer lanthanide fluorescence system available in many newborn screening laboratories. Results were compared with those obtained in two wide multicentric studies on cord blood (DIABFIN and PREVEFIN). Results. Genotyping on DBS revealed 6 subjects at high risk for T1DM, 99 at moderate risk for T1DM and the remains at low risk for T1DM. We found 100% concordance between both techniques for HLADQB1 and DRB1 determination, confirming the feasibility of large scale screening on DBS. Conclusions. DBSs represent a resource for future studies about new genetics markers. This assay for estimate the genetic risk of T1DM on DBS showed an excellent sensitivity, specificity and accuracy compared with conventional techniques. Moreover, this assay resulted less expensive, and it could be easily performed on material already collected for newborn screening programs.

43. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD003731.
Universal neonatal hearing screening versus selective screening as part of the management of childhood deafness.
Puig Reixach MT, Municio A, Medà MC.
Update of:
Cochrane Database Syst Rev. 2005;(2):CD003731.

BACKGROUND: The principal factors that decide how deafness affects a child's development are the degree of hearing impairment and the age at which it is diagnosed. A number of factors are thought to increase the risk of hearing impairment: low birth weight, prematurity, perinatal hypoxia and jaundice, among others. The high incidence of deafness in children without risk

factors and the introduction of simple new screening tests of high sensitivity and specificity have led many prestigious bodies to recommend universal early detection programmes for deafness rather than screening targeted only at high-risk groups. OBJECTIVES: To compare the long-term effectiveness of a universal neonatal screening and early treatment programme for hearing impairment with: a) screening and treatment only of high-risk neonates and b) opportunistic screening and treatment. SEARCH STRATEGY: Databases searched included MEDLINE (1966 to 2006), EMBASE (1974 to 2006), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2006) and registers of health technology assessment agencies as well as registers of clinical guidelines. The date of the last search was June 2006. SELECTION CRITERIA: Randomised controlled trials comparing universal neonatal screening with either high-risk screening or opportunistic screening for hearing impairment. DATA COLLECTION AND ANALYSIS: Two review authors independently screened the search results to identify suitable trials. MAIN RESULTS: No studies were identified which fulfilled the inclusion criteria. AUTHORS' CONCLUSIONS: The long-term effectiveness of universal newborn hearing screening programmes has not been established to date. There is a need for controlled trials and before and after studies to address this issue further.

44. Med J Aust. 2010 Jan 18;192(2):107.
The case for newborn screening for congenital adrenal hyperplasia in Australia.
Warne GL, Armstrong KL, Faunce TA, Wilcken BM, Boneh A, Geelhoed E, Craig ME.

45. Am Fam Physician. 2010 Jan 15;81(2):191.
Universal screening for hearing loss in newborns.
Lin KW, Camp M.

46.Am Fam Physician. 2010 Jan 15;81(2):124.
Universal newborn hearing screening and beyond.
Biernath KR, Montero DP, Mehl A, Toomey KE.

47. Genet Med. 2010 Jan 12. [Epub ahead of print]
Newborn screening programs: Should 22q11 deletion syndrome be added?
Bales AM, Zaleski CA, McPherson EW.

The highly variable 22q11 deletion syndrome has been proposed for addition to newborn screening panels. A literature review investigated the incidence and prevalence, clinical features, and prognosis of 22q11 deletion syndrome and other issues related to newborn screening. Severe complications that could potentially be helped by screening include cardiac defects in 80% (with 20% having no outward signs to aid detection), hypocalcemia that can lead to seizures in 20% (though hypocalcemia is routinely investigated in sick newborns), and severe immune deficiency in <1% (which would be identified by some states' severe combined immunodeficiency screens). Other benefits that do not fit traditional goals of newborn screening include treatment for complications such as failure to thrive and developmental delay or preventing a "diagnostic odyssey." Although universal screening may prove the incidence to be >1:5000, undetected life-threatening effects occur in a minority of 22q11 deletion syndrome patients. Concerns include an untested screening technique, difficulty obtaining results in time for cardiac intervention, the chance of "vulnerable child syndrome" in mild cases, and possibly detecting congenital heart

disease more efficiently by other means. Because addition of tests for highly variable conditions such as 22q11 deletion syndrome is likely to set a precedent for other syndromes, reevaluation of newborn screening criteria should be considered.

48. Heart Rhythm. 2010 Jan 4. [Epub ahead of print]
Posthumous diagnosis of long QT syndrome from neonatal screening cards.
Gladding PA, Evans CA, Crawford J, Chung SK, Vaughan A, Webster D, Neas K, Love DR, Rees MI, Shelling AN, Skinner JR.

BACKGROUND: Molecular autopsy in sudden unexplained death in the young (SUDY) victims cannot usually be performed if tissue suitable for DNA extraction is not retained at autopsy. OBJECTIVE: The purpose of this study was to assess the feasibility and clinical value of posthumous genetic testing for long QT syndrome (LQTS) using residual material from the neonatal screening (Guthrie) card in SUDY victims. METHODS: Twenty-one cases were investigated up to 13 years after death. Deaths occurred at <1 year in one, 1-18 years in 18, and 19-35 years in two patients. Guthrie cards were 3-39 years old. DNA was extracted, and amplicons corresponding to the coding regions of the LQTS genes 1, 2, 3, 5, and 6 underwent either denaturing high-performance liquid chromatography screening or direct DNA sequencing. RESULTS: Adequate DNA was extracted in every case, although repeated purification and amplification was often required. Rare variants were detected in six of 19 cases undergoing diagnostic screening. Four (21%) are considered to be pathological and have been used for family screening: R243C and H455Y in KCNQ1 in 12-year-old and 13-year-old boys, respectively, and Q81H and S621R in KCNH2 in 21-month and 28-year-old females, respectively. Variants of uncertain significance were R1047L in KCNH2 in a 2-year-old girl and S38G in KCNE1 in a 19-month-old boy. Point mutation tests for previously identified familial LQTS mutations revealed a positive result in both cases: E146K in KCNQ1 and exon 6-4del in KCNH2. CONCLUSION: Residual material from Guthrie cards collected for newborn metabolic screening can be used as a reliable source of DNA for the posthumous diagnosis of LQTS decades after SUDY, although purification and amplification of DNA is time intensive.

49. Genet Med. 2010 Jan;12(1):19-24.
Maternal systemic primary carnitine deficiency uncovered by newborn screening: clinical, biochemical, and molecular aspects.
El-Hattab AW, Li FY, Shen J, Powell BR, Bawle EV, Adams DJ, Wahl E, Kobori JA, Graham B, Scaglia F, Wong LJ.

BACKGROUND: Systemic primary carnitine deficiency is an autosomal recessive disorder of the carnitine cycle caused by mutations in the SLC22A5 gene that encodes the carnitine transporter, organic cation transporter. Systemic primary carnitine deficiency typically presents in childhood with either metabolic decompensation or cardiomyopathy. We report five families in which low free carnitine levels in the infants' newborn screening have led to the diagnosis of maternal systemic primary carnitine deficiency. METHODS: Blood samples from the infants and /or their family members were used to extract the DNA. The entire coding regions of the SLC22A5 gene were sequenced. The clinical data were obtained from the referring metabolic specialists. RESULT: Sequencing the SLC22A5 gene allowed molecular confirmation with identification of three novel mutations: c.1195C>T (p.R399W), c.1324_1325GC>AT (p.A442I),

and c.43G>T (p.G15W). All infants were asymptomatic at the time of diagnosis, and one was found to have systemic primary carnitine deficiency. Three mothers are asymptomatic, one had decreased stamina during pregnancy, and one has mild fatigability and developed preeclampsia. DISCUSSION: These findings provide further evidence that systemic primary carnitine deficiency presents with a broad clinical spectrum from a metabolic decompensation in infancy to an asymptomatic adult. The maternal systemic primary carnitine deficiency was uncovered by the newborn screening results supporting the previous notion that newborn screening can identify some of the maternal inborn errors of metabolism. It also emphasizes the importance of maternal evaluation after identification of a low free carnitine level in the newborn screening.

50. J Am Med Inform Assoc. 2010 Jan-Feb;17(1):13-8.
Improving newborn screening laboratory test ordering and result reporting using health information exchange.
Downs SM, van Dyck PC, Rinaldo P, McDonald C, Howell RR, Zuckerman A, Downing G.

Capture, coding and communication of newborn screening (NBS) information represent a challenge for public health laboratories, health departments, hospitals, and ambulatory care practices. An increasing number of conditions targeted for screening and the complexity of interpretation contribute to a growing need for integrated information-management strategies. This makes NBS an important test of tools and architecture for electronic health information exchange (HIE) in this convergence of individual patient care and population health activities. For this reason, the American Health Information Community undertook three tasks described in this paper. First, a newborn screening use case was established to facilitate standards harmonization for common terminology and interoperability specifications guiding HIE. Second, newborn screening coding and terminology were developed for integration into electronic HIE activities. Finally, clarification of privacy, security, and clinical laboratory regulatory requirements governing information exchange was provided, serving as a framework to establish pathways for improving screening program timeliness, effectiveness, and efficiency of quality patient care services.

51. J Cyst Fibros. 2010 Jan;9(1):44-50. Epub 2009 Nov 18.
Pulmonary outcome differences in U.S. and French cystic fibrosis cohorts diagnosed through newborn screening.
Walsh AC, Rault G, Li Z, Scotet V, Duguépéroux I, Férec C, Roussey M, Laxova A, Farrell PM;

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.

53. J Pediatr. 2010 Jan;156(1):139-44.
An ethical and policy analysis of elective transplantation for metabolic conditions diagnosed by newborn screening.
Ross LF.

54. Klin Padiatr. 2010 Jan-Feb;222(1):35-7. Epub 2010 Jan 18.
Compliance to clinical guidelines determines outcome in glutaric aciduria type I in the era of newborn screening.
Höliner I, Simma B, Reiter A, Sass JO, Zschocke J, Huemer M.

We report on a 4.5-year-old patient diagnosed with Glutaric aciduria type I (GAI), an autosomal recessive inborn error of lysine, hydroxylysine and tryptophan metabolism. Enzymatic assay in cultivated skin fibroblasts revealed complete absence of glutaryl-CoA dehydrogenase activity. All 11 Exons of the GCDH-Gen were sequenced and homozygosity for a yet undescribed mutation was identified. The patient was treated following the recently published guidelines for GA-I. Following this treatment regimen, the child developed normally without any manifest clinical crises. Our patient provides evidence that early commencement and strict adherence to treatment improves clinical outcome even in patients with complete absence of enzyme activity.

55. Pediatr Pulmonol. 2010 Jan;45(1):55-61.
Pseudomonas aeruginosa serological analysis in young children with cystic fibrosis diagnosed through newborn screening.
Hayes D Jr, Farrell PM, Li Z, West SE.

BACKGROUND: With newborn screening (NBS) for cystic fibrosis (CF), eradication of Pseudomonas aeruginosa (PA) is possible if PA detection occurs early. A serological response to infection likely precedes culture positivity in CF patients, so PA serological testing is very appealing in this population. However, controversies continue to exist about serology testing, titer cutoffs for enzyme-linked immunosorbent assay (ELISA) antibody tests, and their value in children with CF. METHODS: This longitudinal, prospective study collected respiratory secretions as oropharyngeal swabs or expectorated sputum for culture and also sera over 6 years in 69 patients diagnosed by NBS. Serology assessed PA antibody titers against cell lysate, exotoxin A, and elastase. A novel statistical approach with weighted receiver operating characteristic (ROC) curves was used to determine best antibody titer cutoff values to predict subsequent PA positive cultures. RESULTS: Using these weighted ROC curves, the order of sensitivity was found to be cell lysate, exotoxin A, and then elastase while age-specific cutoffs were better than fixed cutoffs previously used. Age-specific serological cutoffs both predict and detect PA respiratory infections with a higher sensitivity and specificity. Serological responses to the PA antigens determined that a response to cell lysate occurs significantly earlier than culture positivity. CONCLUSIONS: Age-specific serological cutoffs rather than fixed values against common PA antigens improve early PA identification in infants and young children diagnosed with NBS. Regular serological assessment with age-specific cutoffs in these children appears to be a worthy diagnostic tool.

56. Pediatrics. 2010 Jan;125(1):e99-106. Epub 2009 Dec 21.
Neonatal screening for treatable and untreatable disorders: prospective parents' opinions.
Plass AM, van El CG, Pieters T, Cornel MC.

OBJECTIVE: In the Netherlands, in 2007, the national newborn screening program was expanded from 3 to 17 disorders that met the World Health Organization's Wilson and Jungner screening criteria, especially regarding treatability. The decision of whether to add diseases to the program is generally based on experts' advice, whereas the opinion of those whom it concerns--prospective parents--remains unknown. In this study, we investigated the opinion of prospective parents concerning newborn screening for disorders that are incurable yet treatable to some extent or even untreatable. METHODS: A structured questionnaire that consisted of 3 parts in which similar questions were posed about treatable, less treatable, and untreatable childhood-onset disorders was posted on the Web site of a national pregnancy fair. RESULTS: A total of 1631 prospective parents filled out the questionnaire, 259 of whom were excluded. In contrast to current policy, respondents showed a positive attitude toward inclusion of less treatable (88%) or untreatable childhood-onset disorders (73%) within the national newborn screening program. Respondents who already had children at the time of completing the questionnaire were even more in favor of screening for especially untreatable disorders. The most important reason mentioned was to prevent a long diagnostic quest. Obtaining information to enable reproductive choices in future pregnancies was hardly mentioned. CONCLUSIONS: Prospective parents in the Dutch population seem interested in newborn screening for untreatable childhood-onset disorders; therefore, we argue that additional debate of pros and cons is needed among policy makers, health care professionals, and consumers.

57. Public Health Genomics. 2010;13(3):181-90. Epub 2009 Sep 22.
Consent for newborn screening: the attitudes of health care providers.
Miller FA, Hayeems RZ, Carroll JC, Wilson B, Little J, Allanson J, Bytautas JP, Paynter M, Christensen R, Chaktraborty P.

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.

58. Public Health Genomics. 2010;13(3):125-30. Epub 2009 Jul 11.
Not without my permission: parents' willingness to permit use of newborn screening samples for research.
Tarini BA, Goldenberg A, Singer D, Clark SJ, Butchart A, Davis MM.

BACKGROUND: State newborn screening (NBS) programs are considering the storage and use of NBS blood samples for research. However, no systematic assessment of parents' attitudes exists. METHODS: We conducted an Internet-based survey of a nationally representative parent sample. We examined parents' willingness (1) to permit use of their children's NBS samples for research with/without their permission and (2) to allow NBS sample storage. Using bivariate and multinomial logistic regression, we examined the association of parent and child characteristics with parents' willingness to permit NBS sample storage and use for research, respectively. RESULTS: The response rate was 49.5%. If permission is obtained, 76.2% of parents were 'very or somewhat willing' to permit use of the NBS sample for research. If permission is not obtained, only 28.2% of parents were 'very or somewhat willing'. Of parents surveyed, 78% would permit storage of their children's NBS sample. Parents who refused NBS sample storage were also less willing to permit use of the NBS sample for research. CONCLUSIONS: Three-quarters of parents would permit use of their children's NBS samples for research - if their permission is obtained. Parents not in favor of storing NBS samples often opposed the use of NBS samples for research.

59. Public Health Genomics. 2010;13(2):106-15. Epub 2009 Jun 29.
Population screening for genetic disorders in the 21st century: evidence, economics, and ethics.
Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ.

BACKGROUND: Proposals for population screening for genetic diseases require careful scrutiny by decision makers because of the potential for harms and the need to demonstrate benefits commensurate with the opportunity cost of resources expended. METHODS: We review current evidence-based processes used in the United States, the United Kingdom, and the Netherlands to assess genetic screening programs, including newborn screening programs, carrier screening, and organized cascade testing of relatives of patients with genetic syndromes. In particular, we address critical evidentiary, economic, and ethical issues that arise in the appraisal of screening tests offered to the population. Specific case studies include newborn screening for congenital adrenal hyperplasia and cystic fibrosis and adult screening for hereditary hemochromatosis. RESULTS: Organizations and countries often reach different conclusions about the suitability of screening tests for implementation on a population basis. Deciding when and how to introduce pilot screening programs is challenging. In certain cases, e.g., hereditary hemochromatosis, a consensus does not support general screening although cascade screening may be cost-effective. CONCLUSION: Genetic screening policies have often been determined by technological capability, advocacy, and medical opinion rather than through a rigorous evidence-based review process. Decision making should take into account principles of ethics and opportunity costs

60. Mol Genet Metab. 2009 Dec 28. [Epub ahead of print]

Diagnoses of newborns and mothers with carnitine uptake defects through newborn screening.
Lee NC, Tang NL, Chien YH, Chen CA, Lin SJ, Chiu PC, Huang AC, Hwu WL.

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.

61. J Inherit Metab Dis. 2009 Dec 23. [Epub ahead of print]
False-positive newborn screening mimicking glutaric aciduria type I in infants with renal insufficiency.
Hennermann JB, Roloff S, Gellermann J, Grüters A, Klein J.

Glutaric aciduria type I (GA I), an autosomal-recessive deficiency of glutaryl-CoA-dehydrogenase, leads to encephalopathic crises resulting in irreversible neurological damage. As early diagnosis and implementation of appropriate treatment has significant benefit for these patients, GA I has been implemented in the extended newborn screening program in several countries. Screening parameter is glutarylcarnitine (C5DC) with its ratios. From 1 January 2005 until 31 December 2008, 173,846 newborns were examined by neonatal screening in our screening center. C5DC and/or at least three C5DC/acylcarnitine ratios were increased in 53 newborns (0.03%) and persisted in 11 infants after recall. GA I was not confirmed in any of these infants, but all 11 infants were suffering from renal insufficiency due to congenital (5/11) or acquired (6/11) renal disease. C5DC was shown to be significantly associated with renal affection and was significantly higher in infants with congenital renal insufficiency than in those with acquired renal insufficiency ($p = 0.011$). Creatinine correlated significantly with C5DC ($p = 0.001$) and all C5DC/acylcarnitine ratios, mainly with C5DC/(C8 + C10), C5DC/C0, C5DC/C2, C5DC/C4, and C5DC/C8 (for all: $p = 0.001$). Glutarylcarnitinemia associated with renal insufficiency has not yet been studied systematically. Renal damage in neonates might lead to disturbances in renal transporter systems of glutaric acid and its metabolites and a decreased excretion of C5DC, thus resulting in an increase of plasma C5DC. Therefore, newborns

presenting with a positive screening indicating GA I may be considered not only to suffer from GA I but from renal insufficiency as well.

62. Child Care Health Dev. 2009 Dec 10. [Epub ahead of print]
Newborn hearing screening programme outcomes in a research hospital from Turkey.
Tasci Y, Muderris II, Erkaya S, Altinbas S, Yucel H, Haberal A.

Abstract Background Universal neonatal hearing screening programmes are encouraged to define and manage hearing loss in early ages of life. The aim of this study is to introduce our 14-month three-step hearing screening programme results with 16 975 births in Turkey. Methods In healthy neonates, Transient Evoked Otoacoustic Emission (TEOAE) is served as the initial screening in the first day of life. In newborns that did not meet pass criteria TEOAE was repeated in 10-day period. If the second test was 'refer' again, the screening was completed with auditory brainstem response (ABR). Additionally, ABR was performed for the neonates with neonatal intensive care unit (NICU) requirement and at high audiologic risk. Neonates who failed the screening test with ABR were referred for further evaluation. Results A total of 15 323 newborns and 1652 NICU infants were tested. The screening coverage was 94.4%; 14 521 neonates (94.7%) passed the first screening step (TEOAE), while 802 (5.2%) neonate failed. In total, 322 (40.1%) of the neonates out of 802 was subjected to the second TEOAE after 10 days have failed and ABR was applied. From the neonates participated the third step (ABR) totalling 1974, 43 (2.17%) of neonates obtained a 'refer' response. Out of these 43 neonates, 17 neonates were (39.5%) NICU infants. From the 43 neonates, 38 cases (88.4%) were found to have hearing impairment. The false-positive rate for first step screening with TEOAE was 4.9%; second step with TEOAE was 1.85% and for ABR was 0.25%. Conclusions It is apparent that three step national hearing screening programme which has been applied for the latest years in Turkey is an accurate and non-invasive method to determine the congenital hearing loss. In the future, screening programmes could be rearranged with two steps as initial with TEOAE and retest with ABR and the coverage of the screening programme can be extended.

63. JAMA. 2009 Dec 9;302(22):2465-70.
Statewide newborn screening for severe T-cell lymphopenia.
Routes JM, Grossman WJ, Verbsky J, Laessig RH, Hoffman GL, Brokopp CD, Baker MW.

CONTEXT: A newborn blood screening (NBS) test that could identify infants with a profound deficiency of T cells may result in a reduction in mortality. OBJECTIVE: To determine if quantitating T-cell receptor excision circles (TRECs) using real-time quantitative polymerase chain reaction on DNA extracted from dried blood spots on NBS cards can detect infants with T-cell lymphopenia in a statewide program. DESIGN, SETTING, AND PARTICIPANTS: Between January 1 and December 31, 2008, the Wisconsin State Laboratory of Hygiene screened all infants born in Wisconsin for T-cell lymphopenia by quantitating the number of TRECs contained in a 3.2-mm punch (approximately 3 microL of whole blood) of the NBS card. Flow cytometry to enumerate the number of T cells was performed on full-term infants and preterm infants when they reached the equivalent of at least 37 weeks' gestation with TREC values of less than 25/microL. Infants with T-cell lymphopenia were evaluated by a clinical immunologist. MAIN OUTCOME MEASURES: The number of infants with TREC values of less than 25/microL with T-cell lymphopenia confirmed by flow cytometry. RESULTS: Exactly

71,000 infants were screened by the TREC assay. Seventeen infants aged at least 37 weeks' gestation had at least 1 abnormal TREC assay (TREC values < 25/microL), 11 of whom had samples analyzed by flow cytometry to enumerate T cells. Eight infants demonstrated T-cell lymphopenia. The causes of the T-cell lymphopenia included DiGeorge syndrome (n = 2), idiopathic T-cell lymphopenia (n = 2), extravascular extravasation of lymphocytes (n = 3), and a Rac2 mutation (n = 1). The infant with the Rac2 mutation underwent successful cord blood transplantation. CONCLUSION: In a statewide screening program, use of the TREC assay performed on NBS cards was able to identify infants with T-cell lymphopenia.

64. Pediatr Int.. [Epub ahead of print]
Extended use and long-term storage of newborn screening blood spots in Japan.
Fujii C, Sato Y, Harada S, Kakee N, Gu YH, Kato T, Shintaku H, Owada M, Hirahara F, Umehashi H, Yoshino M.

Abstract Background: Residual dried blood spots (DBS) remaining after routine newborn screening (NBS) tests are candidate specimens for extended uses such as quality assurance and the development of new technology. A trial of NBS by tandem mass-spectrometry was launched in 2004 in Japan. We designed the present research to analyze the attitudes of the public, patients' families, and medical professionals toward the extended use and long-term storage of residual DBS, and to construct a standardized informational brochure. Methods: A questionnaire was sent to randomly selected members of the public, members of the Japanese phenylketonuria (PKU) association, medical staff of a general hospital, staff of a children's hospital, obstetricians and gynecologists, pediatricians and NBS personnel. Associated responses which were given in a free comment format were analyzed by text mining. Results: The awareness ratio of NBS was low in the public (26.6%), but despite this, when a brief explanatory note on NBS was provided, 71.7% of them recognized the necessity of NBS. They were less positive than medical professionals and PKU patients' families regarding the extended use of DBS for forensic investigation, for the study of health problems, or long-term storage of residual DBS, regardless of whether these factors affected them personally or not. Among the medical professionals, obstetricians and pediatricians exhibited a higher ratio of negative responses toward the extended use and long-term storage of DBS than others. Conclusion: The general public is more conservative than PKU patients and their families or medical professionals about the extended use or long-term storage of residual DBS. Presentation to the public, particularly to couples of childbearing age, of appropriate explanatory information on NBS itself, or the extended use or long-term storage of residual DBS, is recommended.

65. Acta Paediatr. 2009 Dec;98(12):1927-34. Epub 2009 Aug 18.
Inconclusive cystic fibrosis neonatal screening results: long-term psychosocial effects on parents.
Perobelli S, Zanolla L, Tamanini A, Rizzotti P, Maurice Assael B, Castellani C.
Verona Cystic Fibrosis Centre, Ospedale Civile Maggiore, Verona, Italy.

AIM: Cystic Fibrosis (CF) Newborn Screening occasionally identifies neonates where a CF diagnosis can neither be confirmed nor excluded. To assess how parents of these infants cope with this ambiguous situation. METHODS: Parents of 11 children with Ambiguous Diagnosis (group AD) were compared with parents of 11 children diagnosed with CF through neonatal

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

66. Am J Audiol. 2009 Dec;18(2):89-98. Epub 2009 Aug 24.
Universal newborn hearing screening follow-up: a university clinic perspective.
Krishnan LA.

PURPOSE: To evaluate the referral and follow-up procedures at a university clinic to determine whether the early intervention program is achieving the goals of diagnosis of hearing loss by 3 months, amplification within 1 month of diagnosis, and intervention services by 6 months, as outlined in the Joint Committee on Infant Hearing (JCIH; 2007) position statement. METHOD: Files for 142 infants were examined, and the following data were collected from each file: date of birth, birth hospital, hometown, parents' ages, ethnicity, nursery status (well baby or neonatal intensive care unit), medical history, age at initial evaluation and at diagnosis, results of evaluation(s), and age at hearing aid fitting and start of early intervention services. RESULTS: Results revealed that 17% of infants were older than 3 months at the initial evaluation, and 18% of infants who needed further evaluation were lost to follow-up. None of the infants identified with hearing loss received amplification within 1 month of diagnosis or early intervention services by the age of 6 months. CONCLUSIONS: The findings provide further evidence of the challenges of early intervention programs as stated by the JCIH (2007), and they emphasize the importance of communication between practitioners and implementation of monitoring systems and checks and balances to improve the efficacy of early intervention programs.

67. Am J Med Genet A. 2009 Dec;149A(12):vii-viii.
HHS ponders policy on bloodspot use and storage: HRSA advisory committee considers parental permission for research.
Levenson D.

68. Clin Biochem. 2009 Dec;42(18):1780-5. Epub 2009 Sep 3.
A brief review on newborn screening methods for hemoglobinopathies and preliminary results selecting beta thalassemia carriers at birth by quantitative estimation of the HbA fraction.
Mantikou E, Arkesteijn SG, Beckhoven van JM, Kerkhoffs JL, Harteveld CL, Giordano PC.

OBJECTIVES: We present in a brief summary the basic aspects of the most rational technologies used for new born screening (NBS) of the hemoglobinopathies and we report the preliminary results for the identification of beta-thalassemia carriers at birth by measuring the

expression of the HbA fraction. DESIGN AND METHODS: Separation and measurement of the Hb fractions in 1.500 cord blood samples collected among the multi-ethnic Dutch population using different methods. RESULTS: By using a cut of <15% HbA we have found 4 carriers of point mutations defects 3 of which among a group of 34 newborns of ethnic origin and one among 120 north Europeans. DISCUSSION: All methods for NBS summarized in this paper provide identification at practically 100% sensitivity and high specificity. However, all methods should be followed by routine parent's analysis to confirm the provisional results. Taking into consideration the gestation age and the HbA expression, we believe that carriers of beta-thalassemia can be preselected at birth with a reasonable degree of sensitivity and be confirmed by parent analysis.

69. Clin Chem. 2009 Dec;55(12):2207-13. Epub 2009 Oct 22.
Preliminary proficiency testing results for succinylacetone in dried blood spots for newborn screening for tyrosinemia type I.
Adam BW, Lim TH, Hall EM, Hannon WH.

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 > or =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.

70. Clin Genet. 2009 Dec;76(6):503-10.
Molecular analysis of CYP21A2 can optimize the follow-up of positive results in newborn screening for congenital adrenal hyperplasia.
Silveira EL, Elnecave RH, dos Santos EP, Moura V, Pinto EM, van der Linden Nader I, Mendonca BB, Bachega TA.

Neonatal screening for congenital adrenal hyperplasia (CAH) is useful in diagnosing salt wasting form (SW). However, there are difficulties in interpreting positive results in asymptomatic

newborns. The main objective is to analyze genotyping as a confirmatory test in children with neonatal positive results. Patients comprised 23 CAH children and 19 asymptomatic infants with persistently elevated 17-hydroxyprogesterone (17OHP) levels. CYP21A2 gene was sequenced and genotypes were grouped according to the enzymatic activity of the less severe allele: A1 null, A2 < 2%, B 3-7%, C > 20%. Twenty-one children with neonatal symptoms and/or 17OHP levels > 80 ng/ml carried A genotypes, except two virilized girls (17OHP < 50 ng/ml) without CAH genotypes. Patients carrying SW genotypes (A1, A2) and low serum sodium levels presented with neonatal 17OHP > 200 ng/ml. Three asymptomatic boys carried simple virilizing genotypes (A2 and B): in two, the symptoms began at 18 months; another two asymptomatic boys had nonclassical genotypes (C). The remaining 14 patients did not present CAH genotypes, and their 17OHP levels were normalized by 14 months of age. Molecular analysis is useful as a confirmatory test of CAH, mainly in boys. It can predict clinical course, identify false-positives and help distinguish between clinical forms of CAH.

71. Genet Test Mol Biomarkers. 2009 Dec;13(6):855-9.
High-risk fragile x screening in Guatemala: use of a new blood spot polymerase chain reaction technique.
Yuhas J, Walichiewicz P, Pan R, Zhang W, Casillas EM, Hagerman RJ, Tassone F.

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.

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Neonatal screening program for G6PD deficiency in India: need and feasibility.
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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common genetic disorder affecting approximately 400 million people worldwide. In India, 390,000 children are born annually with this disorder causing significant morbidity and mortality in childhood. A National Neonatal Screening program for presumptive screening of all neonates using modified Formazan ring test

method could be introduced. The test requires blood sample obtained using simple heel prick in the first 48 hours of life, and can be carried out using basic laboratory equipment and reagents. The screening program could be introduced in all institutional deliveries at tertiary hospitals in the major metropolitan cities and then gradually scaled up to cover institutional deliveries over the entire country. After field trials, the program can be expanded to cover home deliveries as well. Increased funding for the health sector under the National Rural Health Mission can provide the required financial support to the program.

73. Int J Pediatr Otorhinolaryngol. 2009 Dec;73(12):1691-5. Epub 2009 Sep 30.
Newborn hearing screening on infants at risk.
Ohl C, Dornier L, Czajka C, Chobaut JC, Tavernier L.

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.