

March 2005 · Volume 2 · Issue 7



# eNeonatal Review

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## In this issue...Volume 2, Number 7

One of the most recent technologies for newborn screening is tandem mass spectrometry (MS/MS). This method of screening has the capacity to identify more than 25 distinct biochemical/genetic disorders, and has led to recommendations for a broad expansion of neonate screening. The MS/MS technique — based on methodology developed in the 1970's to directly analyze components of complex mixtures without the requirement for prior chemical separation — involves two mass spectrometers linked in tandem. In the 1980's, Millington et al at Duke University used MS/MS to analyze human fluids for acylcarnitine; in 1990, they reported on the feasibility of using newborn blood filter paper for screening. Since then, MS/MS technology has continued to evolve, expanding to provide both a means of identifying new disorders as well as a way to potentially improve the diagnosis of classical diseases such as congenital adrenal hyperplasia.

In this month's issue, we focus on recent developments in the field of newborn screening using MS/MS. We review experiences from both the US and several other countries, as well as recent studies evaluating the psychological impact(s) of expanded newborn screening.

→ **Commentary**  
Our guest editor opinion

→ **TANDEM MASS SPECTROMETRY: AN OVERVIEW**

→ **STEROID PROFILING BY MS/MS FOR CONGENITAL ADRENAL HYPERPLASIA**

→ **NEWBORN SCREENING AND LYSOSOMAL STORAGE DISEASES**

→ **NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM IN VERY LOW BIRTH WEIGHT INFANTS**

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- Demonstrate an increased understanding of recent developments in newborn screening and tandem mass spectrometry;
- Be able to evaluate the various new recommendations for expanded newborn screening;
- Better understand the psychological impact of newborn screening as it may apply to your own practice.

## Program Information

→ [NEWBORN SCREENING FOR CYSTIC FIBROSIS](#)

→ [NEWBORN SCREENING AND PARENTAL STRESS](#)

### Guest Editors of the Month



Commentary & Reviews:  
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#### Guest Faculty Disclosure

**James F. Padbury, M.D.**  
Faculty Disclosure: No relationship with commercial supporters.

**Chanika Phornphutkul, M.D.**  
Faculty Disclosure: Dr. Phornphutkul has indicated research support with the Charles Hood Foundation.

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0.5 hours

#### EXPIRATION DATE

March 15, 2007

#### NEXT ISSUE

April 15, 2005

## COMMENTARY

"Expanded newborn screening" refers to the emerging opportunity to use sophisticated new technical instrumentation such as MS/MS to identify an increased number of inherited metabolic and genetic disorders. There is, however, a striking regional disparity in MS/MS application, in that:

- only PKU and congenital hypothyroidism are included in the current newborn screening programs of *all* 50 states;
- a *majority* of states have adopted a modestly "expanded" panel of disorders that includes hemoglobinopathies;
- a growing *minority* of states now provide MS/MS-based expanded screening of over 25 disorders.

Recognition of this regional inequity in "health fairness", as well as significant pressure from advocacy groups, has led the Department of Health and Human Services to commission a formal review by the American College of Medical Genetics (ACMG) to develop recommendations for uniform, nation-wide newborn screening criteria. The review has been several years in preparation and will summarize opinions from medical experts, state policy makers, consumers and public health officials. This ACMG consensus statement — scheduled to be issued within the next several months — is expected to include a recommendation for newborn screening by MS/MS of over 30 disorders, including hemoglobinopathies and cystic fibrosis.

Our review is offered in recognition of the significant technical advances in newborn screening and in anticipation of this important consensus recommendation. We also believe it is important to highlight recent insights that will help to optimize newborn screening based diagnoses, e.g. the need for re-screening VLBW infants for hypothyroidism. As newborn screening programs are largely managed under the auspices of regional public health authorities, in order for the benefits of new technologies like MS/MS to be fully realized, each region involved in this important public health intervention needs to have a well-established interdisciplinary infrastructure. This infrastructure is responsible for management of not only this robust new technology but also the mechanisms for patient identification, sample collection and transportation, notification, specialized follow-up, and counseling.

Finally, we must not lose sight of the immense psychosocial implications surrounding these otherwise unanticipated diagnoses in the seemingly "healthy newborn."

## TANDEM MASS SPECTROMETRY: AN OVERVIEW

**Wilcken B, Wiley V, Hammond J, Carpenter K**  
***Screening newborns for inborn errors of metabolism by tandem mass spectrometry.***

New England Journal of Medicine 2003 Jun  
5;348(23):2304-12.

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**Schulze A, Linder M, Kohlmuller D, Olgemoller K, Mayatepek E, Hoffman GF**  
***Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications.***

Pediatrics 2003 Jun;111(6 Pt 1):1399-406.

*(For non-journal subscribers, an additional fee may apply for full text articles)*

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**Rinaldo P, Tortorelli S, Matern D**  
***Recent developments and new applications of tandem mass spectrometry in newborn screening.***

Current Opinion in Pediatrics 2004, 16:427-433.

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### ***Investigations into the clinical effectiveness of newborn screening.***

The benefits of newborn screening have been proven for many disorders, including PKU and congenital hypothyroidism. With the recent development of MS/MS technology, for the first time, it has become possible to use a single test to screen for many other biochemical and genetic disorders. However, despite numerous clinical experiences and anecdotal descriptions, the systematic, formal evidence of clinical effectiveness of newborn screening has been lacking — a need that these three studies address.

In the Wilcken report, due to the centralized health care system in Australia, the authors were able to compare the incidence and clinical profile of patients diagnosed with 31 metabolic diseases identified through MS/MS versus those who were diagnosed during the period preceding the use of MS/MS. There were ~6 million people in geographic area under study, with 362,000 newborns screened over a period of 4 years (1998-2002). Among the key findings was that the incidence of metabolic diseases, excluding PKU, was 15.7 per 100,000 births, as compared with an adjusted rate of 8.6 to 9.5 per 100,000 births in the four years preceding MS/MS screening (1994-1998). Importantly, the rate of detection was significantly increased for medium-chain acyl-CoA dehydrogenase deficiency (MCAD) and other defects in fatty-acid oxidation. The authors also reported a false positive of ~0.1% — a very low rate

relative to other testing procedures.

Within a similar timeframe, Schulze et al made similar observations from samples collected from 250,000 newborns born between 1998 and 2001. The investigators identified 106 newborns with confirmed metabolic diseases and reported a false positive rate of ~0.33%. In addition, 58% of the confirmed cases were judged to have benefited from screening and treatment, in that a) none of these patients had metabolic crisis, b) none developed psychomotor retardation, and c) none died during the follow up period (which was slightly longer than in the Wilcken study).

The review article by Rinaldo et al discusses the Wilcken and Schultze studies, provides an overview of the technique of MS/MS, and reports on recent developments and new applications of MS/MS. The authors describe several new diseases that can be detected by MS/MS, including ethylmalonic encephalopathy, isobutyryl-CoA and short/branched chain acyl-CoA dehydrogenase deficiency. In addition, they discuss the emerging genotype/phenotype correlations in cases detected by newborn screening, including the known genotype/phenotype correlations in MCAD, VLCAD and Isovaleryl-CoA dehydrogenase deficiency, thereby providing important insight into the apparently common variants that are believed to confer disease susceptibility.

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## STEROID PROFILING BY MS/MS FOR CONGENITAL ADRENAL HYPERPLASIA

**Minutti CZ, Lacey JM, Magera MJ, Hahn SH, McCann M, Schulze A, Cheillan D, Dorche C, Chace DH, Lymp JF, Zimmerman D, Rinaldo P, Matern D.**  
***Steroid profiling by tandem mass spectrometry improves the positive predictive value of newborn screening for congenital adrenal hyperplasia.***

Journal of Clinical Endocrinology and Metabolism 2004  
Aug; 89(8):3687-93.

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### ***Investigating the utility and potential advantages in diagnosing CAH in newborns.***

Currently, only 35 states in the US screen for congenital adrenal hyperplasia. One primary reason for this incomplete implementation is the high rate of false-positive results. Newborn screening for CAH is based on measuring 17-hydroxyprogesterone by immunoassay; despite attempts to adjust cutoff levels for birth weight, gestational age and stress factors, the positive predictive value remains <1%. Minutti et al studied the application of MS/MS technology in steroid profiling, in an attempt to develop a methodology based on MS/MS to measure 17-hydroxyprogesterone, androstenedione, and cortisol in blood spots.

Using MS/MS in a blinded fashion, the authors retrospectively re-analyzed 1222 blood spots collected between the 2nd and 5th day of life in four countries. Of the samples collected, 31 were from babies with CAH, 190 had yielded false-positive results by immunoassay, and the remaining 1001 samples were from babies with normal screening results. When steroid profiling was performed by MS/MS, it resulted in 100% true positive identification, an 89% reduction of false-positive results, and improvement in the positive predictive value to 4.7%. The only noted limitation of steroid profiling was the length of time required for sample analysis, leading to the suggestion that steroid profiling be used as second-tier test of blood spots with "positive results" by immunoassay. The authors also note that the 89% reduction in the false-positive rate would significantly reduce unnecessary blood draws, the need for additional medical evaluation, and stress to families.

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## NEWBORN SCREENING AND LYSOSOMAL STORAGE DISEASES

Li Y, Scott CR, Chamoles NA, Ghavami A, Pinto BM, Turecek F, Gelb MH.

***Direct multiplex assay of lysosomal enzymes in dried blood spots for newborn screening.***

Clin Chem. 2004 Oct;50(10):1785-96.

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### ***Developing a methodology to screen for lysosomal enzyme deficiencies.***

Lysosomal storage diseases are a group of disorders that affect both somatic organs and the central nervous system, and can manifest from birth through adulthood. Until recently, there have been few therapeutic interventions available to alter the natural course of the disorders. However, with recombinant enzyme replacement therapy proven efficacious in recent clinical trials, newborn screening for deficiency of the lysosomal enzymes that cause Fabry, Gaucher, Krabbe, Niemann-Pick A/B, and Pompe diseases is now warranted.

Li et al recently reported a multiplex screening method for all five of these lysosomal storage diseases from newborn blood spots. They first rehydrated the dry blood spots with buffer containing substrates for five lysosomal enzymes, then used tandem mass spectrometry for multiplex detection of the enzymatic products that are relevant to each specific diagnosis. They analyzed dried blood spots from 5 patients with Gaucher, 5 with Niemann-Pick A/B, 11 with Pompe, 5 with Fabry, and 12 with Krabbe disease: in all cases, the measured enzymatic activities were below the minimum activity measured in a collection of heterozygous carriers and healthy non-carrier individuals. The authors report that this approach offers the potential to allow screening programs to expand their coverage to include selected lysosomal storage disorders, and discuss the added costs of the screening process.

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## NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM IN VERY LOW BIRTH WEIGHT INFANTS

Larson C, Hermos R, Delaney A, Daley D, Mitchell M.

***Risk factors associated with delayed thyrotropin elevations in congenital hypothyroidism.***

J Pediatr. 2003 Nov; 143(5):587-91.

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### ***Investigating the hypothalamic-pituitary-thyroid axis in VLBW infants.***

The benefits of newborn screening for congenital hypothyroidism have been extensively documented. With the recent improvement in survival of very low birth weight infants (VLBW), it has become clear that the hypothalamic-pituitary-thyroid axis is different in VLBW infants compared to term infants. Of particular note is the delayed elevation of thyrotropin in hypothyroid VLBW infants.

The Larson study, a retrospective review of the experience of the New England Newborn Screening Program, assessed the rationale for re-screening VLBW infants still in the intensive care unit. Critical findings from this study included recognition that the incidence of congenital hypothyroidism was 14-fold higher in VLBW infants than their term counterparts.

Importantly, two thirds of the VLBW infants with congenital hypothyroidism were not detected on the initial screen, but became apparent on re-screening at 2, 6, and 10 weeks postnatal age. Also, among the non-VLBW infants with a delayed diagnosis of congenital hypothyroidism, 45% had congenital cardiac anomalies.

The authors conclude that re-screening of VLBW babies in the neonatal intensive care unit is necessary, and that special attention should be paid to follow-up testing of newborns known to have cardiac disease.

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## NEWBORN SCREENING FOR CYSTIC FIBROSIS

**Grosse SD, Boyle CA, Botkin JR, Comeau AM, Kharrazi M, Rosenfeld M, Wilfond BS.**  
***Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs.***

MMWR Recomm Rep. 2004 Oct 15;53(RR-13):1-36.

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### ***Reporting on new research findings in CF.***

This recent report from the Centers for Disease Control and the Cystic Fibrosis Foundation provides a comprehensive review of the justification for newborn screening for cystic fibrosis (CF). The report summarizes the long-term benefits of screening and early nutritional treatment, which include: improved growth, improved cognitive development, reduced hospitalization, and improved survival. Note, however, that pulmonary outcomes were mixed.

The report also points out that the clinical diagnosis of cystic fibrosis is still delayed, in that many/most patients have been seen prior to eventual diagnosis by many specialists, especially for "failure to thrive." While newborn screening would clearly result in earlier diagnosis as well as decreased expense and anxiety associated with the workup for failure to thrive (and similar symptoms), it is nonetheless important to also recognize the psychosocial risks and burdens placed on carrier children and their families (e.g. anxiety and misunderstanding) associated with newborn screening.

The report concludes that newborn screening for cystic fibrosis is justified. Realizing that implementation of newborn screening is a regional decision, the authors recommend that the states should consider the magnitude of the benefits versus the costs and the need to minimize risks through careful planning and implementation, including ongoing collection and evaluation of outcomes data.

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## NEWBORN SCREENING AND PARENTAL STRESS

**Waisbren SE, Albers S, Amato S, Ampola M, Brewster TG, Demmer L, Eaton RB, Greenstein R, Korson M, Larson C, Marsden D, Msall M, Naylor EW, Pueschel S, Seashore M, Shih V, Levy HL.**  
***Effect of expanded newborn screening for biochemical genetic disorders on child outcomes and parental stress.***

JAMA 2003 Nov 19;290(19):2564-72.

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### ***Assessing the psychological impacts of false-positive results on parents and children.***

The objective of this study was to assess the psychological impact of false-positive screening on the family by comparing identification of newborn disorders by expanded screening versus clinical identification. Waisbren et al interviewed the families of: 50 affected children identified through expanded newborn screening, 33 children whose diagnosis was based on delayed clinical identification, 94 children with false-positive screening results, and 81 children with normal results. Assessment criteria included the child's health and development, and their parental stress index. Key findings were a higher hospitalization rate and poorer mental outcome in children who were identified after becoming clinically symptomatic; in addition, mothers of the children whose diagnoses were made by newborn screening were found to have a lower parental stress index when compared to the clinically identified group.

These results demonstrate clear health and psychological disadvantages in the clinically identified group. However, it is important to note that the children with false-positive results were hospitalized more frequently than children with normal screening results. Moreover, the mothers of the false-positive group had a higher parental stress index and parent/child dysfunctional subscales.

The authors conclude that the identification of a child as having a false-positive result may place families at risk for increased stress and parent/child dysfunction, and recommend that clinicians be prepared to provide additional support family support as needed.

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- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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