CE 2.5 HOURS Continuing Education

Deconstructing Black Swans

An Introductory Approach to Inherited Metabolic Disorders in the Neonate

Nicholas Ah Mew, MD; Sarah Viall, MSN, PPCNP; Brian Kirmse, MD; Kimberly A. Chapman, MD, PhD

ABSTRACT

Background: Inherited metabolic disorders (IMDs) are individually rare but collectively common disorders that frequently require rapid or urgent therapy.

Purpose: This article provides a generalized approach to IMDs, as well as some investigations and safe therapies that may be initiated pending the metabolic consult.

Methods/Search Strategy: An overview of the research supporting management strategies is provided. In addition, the newborn metabolic screen is reviewed.

Findings/Results: Caring for infants with IMDs can seem difficult because each of the types is rarely seen; however, collectively the management can be seen as similar.

Implications for Practice: When an IMD is suspected, a metabolic specialist should be consulted for expert advice regarding appropriate laboratory investigations and management. Because rapid intervention of IMDs before the onset of symptoms may prevent future irreversible sequelae, each abnormal newborn screen must be addressed promptly.

Implications for Research: Management can be difficult. Research in this area is limited and can be difficult without multisite coordination since sample sizes of any significance are difficult to achieve.

Key Words: autopsy, inborn errors of metabolism, neonatal screening, neonate, review

Pediatric and neonatal healthcare providers often believe that inherited metabolic disorders (IMDs, or the more archaic and nearly synonymous term, "inborn errors of metabolism") are esoteric and ultra-rare, characterized by obscure but pathognomonic symptoms, and treated with idiosyncratic cocktails of unpronounceable medications. The general sentiment is that metabolism is difficult to learn and seldom relevant, but this is far from true. Whereas individual metabolic disorders are rare, collectively their incidence is approximately 1 in 1000,[1] and therefore the average neonatal intensive care unit (NICU) would be expected to see several cases each year. Most NICU staff are familiar with the newborn metabolic screen, a nationwide state-sponsored program that screens virtually all newborns, sick or well, for treatable IMDs. Therefore, being able to implement a generalized approach to metabolic disorders, rather than being knowledgeable about every IMD that can affect newborns, is important.

Author Affiliation: *Division of Genetics and Metabolism, Children's National Health System, Washington, District of Columbia.*

All authors have reviewed and have contributed significantly to this manuscript. No author claims any conflict of interest. No honorarium, grant, or other form of payment was received for the production of this manuscript.

Correspondence: *Nicholas Ah Mew, MD, Division of Genetics and Metabolism, Children's National Health System, 111 Michigan Ave, NW, Washington, DC 20010 (nahmew@childrensnational.org).*

DOI: 10.1097/ANC.0000000000000206

An IMD is a genetic defect (or mutation) that interferes with normal metabolism. This genetic defect typically results in a deficiency of an enzyme, leading to accumulation of the enzyme's substrates (which may be toxic), and a lack of the enzyme's products (which may be necessary for other chemical reactions). See Table 1 for abbreviations used throughout this article.

The first course of action when an IMD is suspected in a neonate is to consult a metabolic specialist, but neonatal caregivers will also be called on to proceed with appropriate investigations and safe therapies in the acute setting, pending specialist consultation. The objective of this review article is to help neonatal clinicians recognize when symptoms in the newborn might be caused by an IMD and provide guidance for the immediate management of the infant. It also describes a general classification of IMDs, the common clinical manifestations in the newborn period, and the management of abnormal newborn screening (NBS) results in the sick or well child.

CLASSIFICATION OF IMDs

Metabolic disorders may broadly be classified in the following 4 categories, based on the underlying metabolic defect[2,3]:

- Intoxication-type disorders
- Disorders of energy metabolism
- Disorders of complex molecule metabolism

TABLE 1. Abbreviations

ACMG	American College of Medical Genetics
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
GABA	Gamma-aminobutyric acid
IMD	Inherited metabolic disorder
IQ	Intelligence quotient
NICU	Neonatal intensive care unit
PKU	Phenylketonuria

- Disorders of neurotransmission

Examples of disorders in each classification of IMDs are provided in Table 2.

Intoxication-type Disorders

Intoxication-type disorders are characterized by the accumulation of toxic small molecules, which may transit through cell membranes, and produce pathology at a distant site. In the developing fetus, the toxin is completely removed via placental exchange; therefore, there is an expectation of normal intrauterine development (no dysmorphism, structural abnormalities, or impaired organ development). No symptoms are seen in the first hours of life, and presentation typically occurs only after exposure to the toxin or its precursors, between days 2 and 7 of extra-uterine life at the earliest.[2,4]

Disorders of Energy Metabolism

The common feature of these disorders is a deficiency in energy production or energy utilization. Because most energy is derived *in vivo* from carbohydrate or fat, disorders in this category primarily result from defects in the enzymes that process these macronutrients. Disorders of energy metabolism frequently present with hypoglycemia, with or without lactic acidosis, particularly in response to a prolonged fast. Hypoketonuria in the setting of hypoglycemia is a hallmark biochemical finding in these disorders.[2]

The intracellular organelle—the mitochondrion—is required for both carbohydrate and fat metabolism. Impaired mitochondria, as in the disorders of the mitochondrial electron transport chain, may result in symptoms of both dysfunctional carbohydrate and fat metabolism. Mitochondrial disorders may present as early as the first day of life and affect

TABLE 2. Broad Categories of IMDs and Examples of Specific Disorders

Classification	Examples
Intoxication-type disorders	Galactosemia
• Aminoacidopathies	Tyrosinemia, maple syrup urine disease
• Organic acidopathies	Propionic acidemia, methylmalonic acidemia
• Urea cycle disorders	Ornithine transcarbamylase deficiency, citrullinemia
Disorders of energy metabolism	
Carbohydrate metabolism	
• Disorders of glycogen metabolism	Glycogen storage disease type 0 or type Ia
• Disorders of glucose utilization	Pyruvate dehydrogenase deficiency
• Disorders of gluconeogenesis	Fructose 1,6-bisphosphatase deficiency
Fat metabolism	
• Fatty acid oxidation disorders	Medium-chain acyl CoA dehydrogenase deficiency Carnitine uptake deficiency
• Disorders of ketone metabolism	β-ketothiolase deficiency
Impaired mitochondria	
• Electron transport chain disorders	Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) Myoclonic epilepsy with ragged-red fibers (MERRF) Leigh disease
Disorders of complex molecule metabolism	
Lysosomal disorders	Niemann-Pick type C, mucopolysaccharidoses, Pompe
Peroxisomal disorders	Zellweger, neonatal adrenoleukodystrophy
Glycosylation disorders	Congenital disorder of glycosylation, type 1a
Disorders of sterol metabolism	Smith-Lemli-Opitz
Disorders of neurotransmission	
Disorders of GABA metabolism	GABA-transaminase deficiency, succinic semialdehyde dehydrogenase deficiency
Disorders of sulfite metabolism	Sulfite-oxidase deficiency, Molybdenum cofactor deficiency
Disorders of glycine metabolism	Glycine encephalopathy (nonketotic hyperglycinemia)

Abbreviations: GABA, γ-aminobutyric acid; IMD, Inherited metabolic disorder.

the most energy-dependent organs, such as the brain, heart, muscle, and liver.

Disorders of Complex Molecule Metabolism

These disorders result from accumulation of large molecular-weight compounds that cannot easily cross membranes, and therefore, they collect and cause pathology at the site of production. This gives rise to several common features of these disorders. In contrast to the intoxication-type disorders, in complex molecule metabolism disorders, detoxification by the placenta is not possible. Accumulation begins *in utero*, and depending on the rapidity of collection, the disorder may present prenatally or postnatally. Hypertrophy of the organs in which the large-molecule compounds accumulate is often an early sign, and the accumulation can lead to dysmorphism, dysplasia, or malformations. This category of disorders includes the lysosomal disorders, peroxisomal disorders, congenital disorders of glycosylation, and disorders of sterol metabolism.

Disorders of Neurotransmission

These disorders result from abnormal metabolism of neurotransmitters. The onset is often prenatal, with a history of prenatal seizures or hiccups. After birth, the primary manifestation is seizures refractory to antiepileptics. Prompt diagnosis is important, because affected infants may respond to pharmacological doses of a vitamin or cofactor. This classification includes disorders of γ-aminobutyric acid, sulfite, and glycine metabolism.

CLINICAL PRESENTATIONS OF IMDS IN THE NEONATE

The sick neonate has limited responses to illness.[2,5,6] Many of the symptoms of an IMD are consistent with sepsis; therefore, a workup for sepsis should be considered and, if appropriate, conducted concurrently with a metabolic workup. The severely ill neonate may have multiple secondary diagnoses, which can obscure an underlying primary metabolic condition. To recognize an IMD, it is important to isolate the *primary* or *initial* presentation of the neonate. A noncomprehensive differential diagnosis by predominant presenting feature is found in Table 3.

"Neurological" Presentation

A deterioration in neurological status is a common response of neonates to illness. The neonate may initially exhibit poor feeding, which may progress to irritability, lethargy, episodes of apnea and bradycardia, and if untreated, unexplained coma and death. Although hypotonia more often suggests a nonmetabolic cause of neurologic deterioration, low tone does not rule out a metabolic disorder. However,

TABLE 3. Sample IMDs by Predominant Presenting Feature

Presenting Feature	Differential Diagnosis of Common IMDs
Altered mental status	*Intoxication-type disorder* Aminoacidopathy Maple syrup urine disease Organic acidopathy Propionic acidemia Methylmalonic acidemia Urea cycle disorder *Disorder of energy metabolism* Mitochondrial disorder
Seizures	*Disorders of neurotransmission* Pyridoxine-dependent seizures Disorder of GABA metabolism Glycine encephalopathy Sulfite oxidase deficiency *Disorders of energy metabolism* (secondary to hypoglycemia) *Intoxication-type disorders* (with altered mental status)
Metabolic acidosis	*Intoxication-type disorder* Organic acidopathy Propionic acidemia Methylmalonic acidemia Isovaleric acidemia *Disorder of energy metabolism* Mitochondrial disorder Disorder of ketolysis Glycogen storage disorder
Respiratory alkalosis	*Intoxication-type disorders* Urea cycle disorder Ornithine transcarbamylase deficiency
Hypoglycemia	*Disorders of energy metabolism* Fatty acid oxidation disorder Glycogen storage disorder Disorder of ketogenesis and ketolysis Mitochondrial disorder
Liver dysfunction	*Intoxication-type disorder* Aminoacidopathy (eg, tyrosinemia) Galactosemia *Disorders of energy metabolism* Mitochondrial disorders Fatty acid oxidation disorder Glycogen storage disorder *Disorders of complex molecules* Peroxisomal disorder Disorders of glycosylation
Cardiac dysfunction	*Disorders of energy metabolism* Fatty acid oxidation disorder Mitochondrial disorder *Disorders of complex molecules* Lysosomal storage disorder (eg, Pompe disease)

Abbreviations: GABA, γ-aminobutyric acid; IMD, Inherited metabolic disorder.

normal tone or hypertonicity in a comatose neonate should raise suspicion for a metabolic problem.[4]

Altered mental status points most strongly to an intoxication-type disorder, particularly with an onset within a few days to weeks of life, or when accompanied by involuntary movements, such as pedaling of the limbs. Disorders of energy metabolism, in particular, the mitochondrial disorders, are possible causes of altered mental status, although they are less likely. Lactic acidemia and the lack of a symptom-free period following delivery support the diagnosis of a mitochondrial disorder.

An *isolated* initial presentation of seizures is highly suggestive of a disorder of neurotransmission. Seizures can also occur in infants with disorders of energy metabolism, particularly the mitochondrial disorders. More often, however, the neonate with a disorder of energy metabolism will also have associated hepatic, ophthalmologic, myocardial, or muscular signs and symptoms. Infants with intoxication-type disorders may also present with seizures, but rarely as the initial or only symptom. Seizures may also occur as a secondary manifestation of hypoglycemia.

Biochemical Abnormalities and Liver Dysfunction

Acid-base disturbances are common in infants with IMDs. In neonates, primary acidosis results from the accumulation of an acid (which contributes to a widened anion gap) rather than the loss of bicarbonate. The acid may be lactic acid, ketones, or another organic acid. Metabolic acidosis is most typical of intoxication-type disorders, but can also be a sign of a disorder of energy metabolism. Renal tubular acidosis is a feature of several IMDs, but rarely as a presenting symptom. Tachypnea and respiratory alkalosis are characteristic of urea cycle disorders, because hyperammonemia is a brainstem respiratory stimulant.

Hypoglycemia is a hallmark of disorders of energy metabolism, in particular the disorders of fatty acid oxidation. Low blood glucose, typically in conjunction with such biochemical abnormalities as acidosis or hyperammonemia, is also seen in intoxication-type disorders.

Liver dysfunction is a presenting symptom in intoxication-type disorders, disorders of energy metabolism, and disorders of complex molecule metabolism. In the intoxication-type disorders, acute liver failure is caused by the infant's inability to metabolize a nondextrose carbohydrate (eg, galactose, fructose) or an amino acid (eg, tyrosine). In disorders of complex molecule metabolism, the liver and spleen may be enlarged.

Cardiac Dysfunction

An isolated cardiomyopathy may result from either a disorder of energy metabolism or a disorder of complex molecule metabolism. Infants with disorders of energy metabolism may also develop arrhythmias. Intoxication-type disorders (particularly the organic acidemias) may present with cardiomyopathy in the neonatal period, but typically in association with pronounced acidosis and ketosis.

Laboratory Investigations

In the absence of input from a metabolic expert, the investigations in Table 3 should be considered. Diagnosis of a suspected disorder of neurotransmission requires fastidious collection of cerebrospinal fluid (CSF), ideally guided by a metabolic specialist or pediatric neurologist. These special investigations require the first sample of CSF obtained immediately after lumbar puncture, and the CSF must be frozen within minutes of collection. Blood-contaminated samples should be centrifuged as soon as possible, and the clear fluid transferred to new tubes.

Treatment of IMDs

Caloric management is the cornerstone of immediate management of the neonate with many IMDs. In intoxication-type disorders, reversal of catabolism is essential to correct the biochemical abnormalities. In disorders of energy metabolism, the profound hypoglycemia must be corrected.

In general, dextrose infusion at a higher than 5% concentration and a rate faster than the maintenance rate is recommended.[6] If administration of a high dextrose concentration results in hyperglycemia, an insulin drip can be administered to promote anabolism. If the serum lactate level rises with a high dextrose concentration, infusing 5% dextrose at or less than the maintenance rate is appropriate. An intravenous lipid emulsion may also be added[6] to increase caloric intake, because a dextrose infusion alone does not meet caloric needs for a neonate. However, supplemental lipid should be avoided if a fatty acid oxidation disorder is suspected.

Protein or amino acids are the precursors to many of the toxins responsible for intoxication-type disorders. Therefore, when such an intoxication-type disorder is suspected, all protein or amino acids sources, including regular infant formula or breast milk, should be initially withheld. However, because protein is essential to growth and anabolism, this protein-free period should not exceed 24 to 48 hours. A metabolic specialist and dietitian should be consulted on how best to reintroduce protein.

In the intoxication disorders, effective therapy is predicated upon rapid removal of the toxin. In fact, dialysis may be a life-saving measure and should be discussed with the metabolic specialist and nephrologist. Bicarbonate supplementation may be appropriate to temporarily improve pH, but long-term pH correction will require addressing underlying metabolic defect and reducing acid production.

Corticosteroids can promote catabolism, often exacerbating IMDs associated with altered mental status, such as the intoxication-type disorders. Therefore, higher-dose systemic corticosteroids, although not strictly contraindicated, should be avoided if possible in infants diagnosed with or suspected of having these disorders.[7-9] Similarly, valproic acid should be avoided in most intoxication-type disorders.[10]

Imminent Death in an Infant With a Suspected IMD

When death is imminent in a critically ill neonate without a definitive diagnosis, an effort should be made to collect samples for postmortem analysis. The diagnosis of an IMD, even postmortem, is critical for future preconceptual or prenatal genetic counseling. Any of the investigations listed in Table 4 that have not yet been obtained should be considered. Furthermore, frozen samples of urine and plasma (isolated from whole blood and stored in a heparin tube) should be obtained for additional studies. A separate vial of blood in an EDTA tube should be collected for later DNA isolation. Finally, a snippet of skin should be obtained under sterile conditions and stored in tissue culture medium or sterile saline at room temperature. Such a sample may be used to grow fibroblasts for future enzymatic or DNA studies. A more comprehensive description of the metabolic autopsy has been described elsewhere.[11]

Newborn Screening: A Chance to Treat Before Symptom Onset

Not all IMDs present with symptoms at birth. Therefore, there is a brief window of time during which otherwise asymptomatic infants may be screened for IMDs before the apparent onset of pathology. Newborn screening is a national public health program whose mandate is to identify infants with disorders that can cause irreversible disability or death in the first days to weeks of life. Screening began in 1963 with the disorder phenylketonuria (PKU), which, if left untreated, results in

TABLE 4. List of Initial Investigations to Be Considered Pending a Metabolic Consult

Blood gases
Electrolytes
Liver enzymes
Plasma lactate
Plasma ammonia
Urinalysis (with urine ketones)
Plasma amino acids
Plasma acylcarnitine profile
Urine organic acids

TABLE 5. Recommended Uniform Screening Panel, Core Conditions

Metabolic disorders
Organic acid disorders
Propionic acidemia
Methylmalonic acidemia (methylmalonyl-CoA mutase)
Methylmalonic acidemia (cobalamin disorders)
Isovaleric acidemia
3-Methylcrotonyl-CoA carboxylase deficiency
3-Hydroxy-3-methylglutaric aciduria
Holocarboxylase synthase deficiency
Beta-ketothiolase deficiency
Glutaric acidemia type I
Fatty acid oxidation disorders
Carnitine uptake defect/carnitine transport defect
Medium-chain acyl-CoA dehydrogenase deficiency
Very long-chain acyl-CoA dehydrogenase deficiency
Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Amino acid disorders
Argininosuccinic aciduria
Citrullinemia, type I
Maple syrup urine disease
Homocystinuria
Classic phenylketonuria
Tyrosinemia, type I
Other disorders
Biotinidase deficiency
Classic galactosemia
Endocrine disorders
Primary congenital hypothyroidism
Congenital adrenal hyperplasia
Hemoglobin disorders
S, S disease (Sickle cell anemia)
S, Beta-thalassemia
S, C disease
Other disorders
Critical congenital heart disease
Cystic fibrosis
Hearing loss
Severe combined immunodeficiencies

progressive, severe intellectual disability. With the implementation of national PKU screening, affected children were identified and treated from birth, before the onset of symptoms, resulting in normal growth, development, and IQ.[12]

In the last 2 decades, state NBS programs have rapidly expanded their panels to include many other metabolic and nonmetabolic conditions. Prompt recognition via the NBS makes it possible to avoid not only intellectual disabilities but metabolic acidosis, seizures, neurological deterioration, coma, and even death.[4]

Although each state determines the disorders on their NBS panel, most states screen for a core panel of 31 disorders (Table 5) recommended by the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children.[13] These range from disorders that take months to years to present, to disorders that may be fatal in the first few days of life, such as maple syrup urine disease. Although all positive newborn screens should be followed up on quickly, the basics of when, where, and how to refer are different for every disorder. Consensus documents were created by the American College of Medical Genetics for use by nonmetabolic specialist providers to help with the triage of an abnormal screening result. These documents can be helpful tools in determining next steps.[14] Moreover, most birthing hospitals and NICUs can obtain recommendations from a local or regional medical geneticist, a physician specially trained in metabolic disorders, by contacting the state NBS program and asking for the contact information of this individual.

Determining the risk for a true positive neonatal screening result can be particularly difficult in the NICU setting, because abnormal screens in this population are more common.[15] False positive screens are more frequent owing to such neonatal factors as prematurity and liver dysfunction, as well as certain common treatments, such as transfusions, aminoglycoside administration, or parenteral nutrition administration. However, the risk for a missed diagnosis is real and potentially perilous. Providers must appreciate the possibility of a true positive in every abnormal screen to ensure the best outcomes for the neonates who have an IMD.[16]

It is not uncommon for the nonspecific signs and symptoms that prompt the transfer of a newborn to the NICU to be caused by an as yet unidentified metabolic disorder. If there are concerns about metabolic disease in a neonate prior to the receipt of an official NBS report, NICU providers can contact the state NBS program directly. These programs, which are often housed in public health departments, are staffed by knowledgeable personnel (typically nurses) who may have access to preliminary results and follow-up recommendations. Their contact information can be obtained online through the respective Department of Health Web sites or at www.babysfirsttest.org.[17]

Decades ago, this program tested only for PKU, but it has now expanded far beyond this 1 condition. Therefore, calling it the "PKU test" is no longer accurate or appropriate. This misnomer also often leads to confusion among providers and, more significantly, among families who believe that their child has screened positive for PKU. When discussing results, referring to the "newborn screen" or "newborn metabolic screen" is the expected standard.

Establishing a Plan

Each NICU should have a predetermined basic plan of action for when a patient is suspected to have an IMD or when an abnormal newborn metabolic screening result is received. A metabolic specialist or service should be identified beforehand, and contact information for potential day or nighttime consults should be displayed in an easily visualized location, along with contact information for the state NBS laboratory.

CONCLUSION

To the unprepared NICU, care of a critically ill infant with a suspected IMD can come as a surprise, with

Summary of Recommendations for Practice and Research

What we know:	• If untreated, inherited metabolic disorders may result in clinical deterioration, coma, and possibly death. • Newborn metabolic screening has identified many affected infants before the onset of symptoms, improving survival and intellectual outcome.
What needs to be studied:	• Newer methods for more rapid identification of metabolic disorders. • Strategies that support obtaining homeostasis faster and more stably for the infant.
What we can do today:	• Establish a system for day and nighttime consultation with a metabolic specialist, a physician board certified in clinical genetics or clinical biochemical genetics. • Address abnormal NBS results promptly. • Contact the state NBS program with any queries regarding abnormal NBS results and for management recommendations.

disastrous consequences. The primary vulnerabilities are the lack of preparedness and knowledge, and this basic precis addresses both of those issues by providing an overview of metabolism, highlighting key investigations, and describing therapies that may be safely initiated pending consultation with a metabolic specialist. It also underscores that each positive newborn screen must be addressed promptly to minimize or prevent irreversible sequelae.

Further Reading

Saudubray JM, Nassogne MC, de Lonlay P, Touati G. Clinical approach to inherited metabolic disorders in neonates: an overview. *Semin Neonatol*. 2002;7(1):3-15.

Ogier de Baulny H. Management and emergency treatments of neonates with a suspicion of inborn errors of metabolism. *Semin Neonatol*. 2002;7(1):17-26.

Zschocke J, Hoffmann G. *Vademecum Metabolicum: Manual of Metabolic Paediatrics*. 2011 ed: Milupa GmbH. ISBN: 978-3540747222.

Clarke JTR. *A Clinical Guide to Inherited Metabolic Diseases*. 3rd ed. Cambridge, UK; New York: Cambridge University Press; 2006. ISBN 978-0521614993.

References

1. Hendriksz CJ. Inborn errors of metabolism for the diagnostic radiologist. *Pediatr Radiol*. 2009;39:211-220.
2. Saudubray JM, Nassogne MC, de Lonlay P, Touati G. Clinical approach to inherited metabolic disorders in neonates: an overview. *Semin Neonatol*. 2002;7:3-15.
3. Hoffmann GF, Nyhan WL, Zschocke J, Kahler SG. *Inherited Metabolic Diseases*. New York: Lippincott Williams and Wilkins; 2002
4. Saudubray JM, Van den Berghe G, Walter J. *Inborn Metabolic Diseases: Diagnosis and Treatment*. Berlin, Germany: Springer; 2012.
5. Burton BK. Inborn errors of metabolism in infancy: a guide to diagnosis. *Pediatrics*. 1998;102:E69.
6. Ogier de Baulny H. Management and emergency treatments of neonates with a suspicion of inborn errors of metabolism. *Semin Neonatol*. 2002;7:17-26
7. Lipskind S, Loanzon S, Simi E, Ouyang DW. Hyperammonemic coma in an ornithine transcarbamylase mutation carrier following antepartum corticosteroids. *J Perintaol*. 2011;31:682-684.
8. Schimanski U, Krieger D, Horn M, Stremmel W, Wermuth B, Theilmann L. A novel two-nucleotide deletion in the ornithine transcarbamylase gene causing fatal hyperammonia in early pregnancy. *Hepatology*. 1996;24:1413-1415.
9. Atiq M, Holt AF, Safdar K, et al. Adult onset urea cycle disorder in a patient with presumed hepatic encephalopathy. *J Clin Gastroenterol*. 2008;42:213-214.
10. Schreiber J, Chapman KA, Summar ML, et al. Neurologic considerations in propionic acidemia. *Mol Genet Metab*. 2012;105:10-15.
11. Ernst LM, Sondheimer N, Deardorff MA, Bennett MJ, Pawel BR. The value of the metabolic autopsy in the pediatric hospital setting. *J Pediatr*. 2006;148:779-783.
12. Donlon J, Levy H, Scriver CR. Hyperphenylalaninemia: phenylalanine hydroxylase deficiency. In: Scriver CR, Sly WS, Childs B, eds. *The Metabolic and Molecular Bases of Inherited Disease*. New York, NY: McGraw-Hill; 2015: Chapter 77.
13. Health Resources Services Administration. Recommended uniform screening panel core conditions. http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/uniformscreeningpanel.pdf. Published 2013. Accessed March 3, 2015.
14. American College of Medical Genetics. Newborn screening conditions ACT sheets and confirmatory algorithms. www.acmg.net/ACMG/Publications/ACT_Sheets_and_Confirmatory_Algorithms/NBS_ACT_Sheets_and_Algorithm_Table/ACMG/Publications/ACT_Sheets_and_Confirmatory_Algorithms/NBS_ACT_Sheets_and_Algorithms_Table.aspx. Accessed March 3, 2015
15. Slaughter JL, Meinzen-Derr J, Rose SR, et al. The effects of gestational age and birth weight on false-positive newborn-screening rates. *Pediatrics*. 2010;126:910-916.
16. Balk KG. Recommended newborn screening policy change for the NICU infant. *Policy Polit Nurs Pract*. 2007;8:210-219.
17. Baby's First Test. 2015. http://www.babysfirsttest.org./. Accessed March 3, 2015.

CE Test Instructions:

- Read the article. The test for this CE activity can only be taken online at www.nursingcenter.com/ce/ANC. Tests can no longer be mailed or faxed . You will need to create (its free!) and login to your personal CE Planner account before taking online tests. Your planner will keep track of all your Lippincott Williams & Wilkins online CE activities for you.
- There is only one correct answer for each question. A passing score for this test is 13 correct answers. If you pass, you can print your certificate of earned contact hours and access the answer key. If you fail, you have the option of taking the test again at no additional cost.
- For questions, contact Lippincott Williams & Wilkins: 1-800-787-8985.

Registration Deadline: August 31, 2017

Disclosure Statement: The authors and planners have disclosed that they have no financial relationships related to this article.

Provider Accreditation:

Lippincott Williams & Wilkins, publisher of *Advances in Neonatal Care,* will award 2.5 contact hours for this continuing nursing education activity.

Lippincott Williams & Wilkins is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 2.5 contact hours. Lippincott Williams & Wilkins is also an approved provider of continuing nursing education by the District of Columbia and Florida, CE Broker #50-1223. Your certificate is valid in all states.

This article has been approved by the National Association for Neonatal Nurses Certification Board for Category B credit toward recertification as an NNP.

Payment:

The registration fee for this test is $15.95 for NANN members and $22.95 for nonmembers.

DOI: 10.1097/ANC.0000000000000219