Testing Strategy for Inborn Errors of Metabolism in the Neonate
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Testing Strategy for Inborn Errors of Metabolism in the Neonate

Aditi I. Dagli, MD,* Roberto T. Zori, MD,* Bryce A. Heese, MD*

Author Disclosure
Drs Dagli, Zori, and Heese have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives After completing this article, readers should be able to:

1. List the initial appropriate screening tests when a neonate is suspected of having an inborn error of metabolism.
2. Describe common neonatal presentations of inborn errors of metabolism.
3. Interpret the initial screening test results to formulate a differential diagnosis.
4. Recognize the pitfalls to avoid while ordering metabolic tests.

Abstract
Early detection and management of inborn errors of metabolism (IEMs) can improve the affected infant’s prognosis. Initial screening tests can provide a general overview of the infant’s metabolic status and suggest potential IEMs. Among the clinical findings seen in many IEMs are encephalopathy, hypoglycemia, jaundice and liver disease, cardiac arrhythmias, cardiomyopathy, hypotonia, dysmorphic features, and nonimmune hydrops. Confirmatory testing (enzyme analysis or molecular DNA testing) are required to make the diagnosis. Clinicians should be aware of specific requirements for such testing to obtain the desired results.

Introduction
Many IEMs present in the newborn period, and early detection and management can improve an infant’s prognosis substantially. The advent of extended newborn screening has made presymptomatic diagnosis of a number of these disorders possible. However, not all IEMs are identified on an extended newborn screen, and in some instances, an infant who has an IEM may become ill before the results of newborn screening become available. It is, therefore, important for the neonatologist to consider an inborn error of metabolism in the differential diagnosis for an acutely sick neonate and initiate appropriate testing.

Sudden deterioration after a period of apparent normalcy is highly suggestive of a metabolic disorder. A neonate who has an IEM may present with symptoms that frequently are attributed to more common neonatal conditions, such as sepsis or gastrointestinal pathology, which may lead to a delayed or missed diagnosis. Signs such as an unusual odor (as in maple syrup urine disease), posturing (as in glutaric acidemia type 1), or apnea (as in nonketotic hyperglycinemia) can indicate an IEM. Parental consanguinity or a family history of neonatal death also should alert the physician to the possibility of a genetic disorder.

In this review, we discuss the laboratory testing strategy that may be considered in the initial evaluation of a possible IEM. Discussion of the treatment of metabolic disorders is beyond the scope of this review.

Initial Testing Strategy
All of the tests listed in Table 1 should be obtained for neonates suspected of having IEMs. Understandably, an acutely ill neonate in metabolic crisis requires immediate management, but it is crucial to set aside samples (at least 5 mL plasma and 5 mL urine) before attempting to correct metabolic abnormalities. This is important for certain diseases where abnormal metabolites that are critical in providing a diagnosis are detected only in times of acute decompensation. The initial test results can provide a general overview of the
metabolic status of the neonate and suggest IEMs that might be considered in the differential diagnosis (Table 2).

Some IEMs have characteristic presentations, but initial test results are normal. These presentations and appropriate testing are discussed in the relevant sections of this article.

**Encephalopathy**

An infant who has encephalopathy can present with seizures, lethargy, or poor feeding that may be associated with metabolic abnormalities such as hyperammonemia and metabolic acidosis. Occasionally, an infant who has encephalopathy and an IEM may present with no other supporting laboratory abnormalities.

Encephalopathy associated with hyperammonemia can be a feature of several inborn errors, which can be differentiated based on initial test results (Fig. 1). Elevated ammonia concentration within 24 hours of birth with normal plasma amino acids values suggests the diagnosis of transient hyperammonemia of newborn, a metabolic status of the neonate and suggest IEMs that might be considered in the differential diagnosis (Table 2).

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<table>
<thead>
<tr>
<th>Tests</th>
<th>Key Finding</th>
<th>IEM Consideration</th>
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<td>Complete blood count with differential count</td>
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<td>Blood ammonia</td>
<td></td>
<td>UCD, OA, FAO, PDH, PC</td>
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<td>Serum uric acid</td>
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<tr>
<td>Plasma acylcarnitine profile</td>
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</tr>
<tr>
<td>Plasma (free and total) carnitine</td>
<td></td>
<td>FAA, OA</td>
</tr>
<tr>
<td>Plasma amino acids</td>
<td></td>
<td>UCD, OA</td>
</tr>
<tr>
<td>Urine organic acids</td>
<td></td>
<td>OA, FAO, Mito, PDH, PC</td>
</tr>
<tr>
<td>Urine reducing substances</td>
<td></td>
<td>Galac, HFI, Tyr I</td>
</tr>
<tr>
<td>Very long-chain fatty acids</td>
<td></td>
<td>Peroxisomal disorders</td>
</tr>
<tr>
<td>Urine mucopolysaccharides</td>
<td></td>
<td>Lysoosomal storage disorders</td>
</tr>
<tr>
<td>Urine oligosaccharides</td>
<td></td>
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</tr>
<tr>
<td>7-dehydrocholesterol</td>
<td></td>
<td>Smith–Lemli–Opitz syndrome</td>
</tr>
<tr>
<td>Serum transferrin glycoforms</td>
<td></td>
<td>CDG</td>
</tr>
</tbody>
</table>

CDG = congenital disorder of glycosylation, FAA = fatty acid oxidation defect, Galac = galactosemia, GSD I = glycogen storage disease type I, G6PD = glucose-6-phosphate dehydrogenase, HFI = hereditary fructose intolerance, IEM = inborn error of metabolism, Mito = mitochondrial energy metabolism defects, OA = organic aciduria, PC = pyruvate carboxylase deficiency, PDH = pyruvate dehydrogenase deficiency, Tyr I = tyrosinemia type I, UCD = urea cycle defect.
poorly understood condition that is believed to have a nongenetic cause.

Encephalopathy associated with metabolic acidosis due to inborn errors of metabolism usually is characterized by an increased anion gap. It is important to determine the source of this increase. Lactic acidosis is encountered commonly and if mild, usually is due to cardiovascular compromise. Unexplained elevation of lactic acid requires the consideration of a metabolic disorder (Fig. 2). In addition, an acylcarnitine profile can aid in the diagnosis of fatty acid oxidation disorders and organic acidemias.

Some IEMs can present with an encephalopathic picture without hyperammonemia or metabolic acidosis. Maple syrup urine disease (MSUD) is caused by an inability to break down branched-chain amino acids such as leucine, isoleucine, and valine, and a plasma amino acid profile is diagnostic. Ketoacidosis is observed in MSUD but may be absent at initial presentation. Nonketotic hyperglycinemia is caused by an inability to breakdown glycine in the liver and is characterized by a severe encephalopathy with no other associated abnormalities. Plasma amino acids may show an elevated glycine, and supporting laboratory results may be noncontributory. In this clinical scenario, it is essential to obtain cerebrospinal fluid to measure glycine concentrations, which can be diagnostic.

Pyridoxine-dependent seizures present as severe, intractable seizures within the first few hours of birth. This disorder is marked by a dramatic response to vitamin B6 administration. Severe seizures and encephalopathy usually developing in the first postnatal week also can suggest molybdenum cofactor deficiency. This is associated with combined deficiencies of the two enzymes that depend on molybdenum: xanthine oxidase and sulfite oxidase. In xanthine oxidase deficiency, uric acid is markedly decreased (not seen in isolated sulfite oxidase deficiency). The presence of sulfite in a fresh urine sample using a special dipstick test may be suggestive of this condition. However, elevated S-sulfocysteine concentrations in urine are more definitive.

**Hypoglycemia**

Hypoglycemia is a relatively common neonatal concern. Unexplained hypoglycemia may be caused by IEMs due to defects in carbohydrate metabolism and fatty acid oxidation. Occasionally, protein metabolism defects can have associated hypoglycemia, but other metabolic disturbances predominate.

The tests listed in Table 1 should be ordered, with the addition of urine for reducing substances (Fig. 3). If nonglucose reducing substances are present in the urine, galactosemia, hereditary fructose intolerance, or tyrosinemia should be considered. Abnormally low ketones in the presence of hypoglycemia may be indicative of a fatty acid oxidation disorder. Fatty acid oxidation disorders are important because of their relatively high prevalence and usually are identified based on acylcarnitine profile abnormalities. Affected infants have an impaired capacity to use stored fats in periods of extended fasting. The presentation may be similar to Reye syndrome, with metabolic acidosis, hyperammonemia, and elevated liver enzymes, particularly transaminases.

Hepatic glycogen storage diseases (GSDs), especially type I, cause hypoglycemia during periods of fasting. The diagnosis of GSD type I may be missed in the neonatal period because the hypoglycemia resolves when regular feeding is established. The liver is mildly enlarged in the first 2 postnatal days but can be markedly enlarged by the end of the first week. Abnormal laboratory study results that indicate the diagnosis of GSD type I include lactic acidosis, hyperuricemia, and hypoglycemia.

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Figure 1. Algorithm for evaluation of hyperammonemia in a neonate who has a suspected inborn error of metabolism. metab.=metabolism.
Jaundice and Liver Disease

Unconjugated hyperbilirubinemia may be seen in inborn errors of erythrocyte and bilirubin metabolism. Glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency can present in the newborn period with unconjugated hyperbilirubinemia due to hemolysis. Nonspherocytic hemolytic anemia, as noted on peripheral smear, helps in diagnosis, which can be confirmed by enzymatic analysis. Disorders of bilirubin metabolism, such as Gilbert, Crigler Najjar, Dubin-Johnson, and Lucey Driscoll syndromes, present with unconjugated hyperbilirubinemia and normal values for other liver function tests. Most of these disorders are benign. However, hyperbilirubinemia in type I Crigler Najjar syndrome may be severe enough to cause kernicterus.

Most newborn screening programs include evaluation for classic galactosemia. It presents in the newborn period with unconjugated hyperbilirubinemia due to hemolysis. Nonspherocytic hemolytic anemia, as noted on peripheral smear, helps in diagnosis, which can be confirmed by enzymatic analysis. Disorders of bilirubin metabolism, such as Gilbert, Crigler Najjar, Dubin-Johnson, and Lucey Driscoll syndromes, present with unconjugated hyperbilirubinemia and normal values for other liver function tests. Most of these disorders are benign. However, hyperbilirubinemia in type I Crigler Najjar syndrome may be severe enough to cause kernicterus.

Most newborn screening programs include evaluation for classic galactosemia. It presents in the neonatal period with unconjugated hyperbilirubinemia that is unconjugated in the early stages and predominantly conjugated in the later stages. If the neonate continues to be fed lactose-containing formula or human milk, the jaundice worsens, hepatomegaly appears, transaminases become elevated, and coagulopathy and hypoalbuminemia can occur. When classic galactosemia is suspected, urine and blood samples should be reserved for confirmatory testing, and the patient should be switched to a nongalactose-containing soy formula. The collected urine should be tested simultaneously with Benedict solution and a glucose oxidase method (urine dipsticks). A negative glucose oxidase test result and positive Benedict reagent reaction suggests the presence of a nonglucose reducing substance, and confirmatory testing can be undertaken.

Aminoacidopathies such as tyrosinemia type 1 and citrullinemia type 2 may present with severe liver disease and an abnormal plasma amino acid profile. Excretion of succinylacetone in the urine is diagnostic for tyrosinemia type 1. Fatty acid oxidation disorders also may present with hepatocellular dysfunction and are diagnosed based on an abnormal acylcarnitine profile.

Traditionally, hereditary fructose intolerance does not present in the neonatal period. However, affected infants who are exposed to fructose-containing feedings (as in sucrose-containing soy formulas) may develop acute hepatocellular failure, lactic acidosis, hyperuricemia, hyperchloremia, hypophosphatemia, and metabolic acidosis.

Alpha-1-antitrypsin deficiency presents with jaundice and cholestasis that may resolve spontaneously by 2 months of age only to present later with cirrhosis. The disorder is identified by low plasma concentrations of alpha-1-antitrypsin and is confirmed by protein phenotyping and mutation analysis. The perinatal form of GSD type IV presents with fetal hydrops and severe hypotonia. It often is rapidly fatal and is diagnosed by a liver biopsy. Niemann-Pick disease type C is a progressive neurodegenerative disease that can involve self-resolving jaundice and hepatomegaly in the neonatal period. Diagnosis often requires specialized studies on fibroblast cultures. Neonatal hemochromatosis can cause rapidly progressive liver failure and requires a liver biopsy for diagnosis.
Cardiac Presentation

In the newborn period, cardiac presentations of IEM include cardiac arrhythmias and cardiomyopathy. Neonates who have fatty acid oxidation disorders may present with an arrhythmia or cardiomyopathy. An abnormal plasma acylcarnitine profile establishes the diagnosis. Primary and secondary carnitine deficiency can result in a cardiomyopathy. Free and total carnitine concentrations can be diagnostic. In rare cases, abnormally low carnitine values lead to false-negative acylcarnitine profile results. Cardiomyopathy with elevated plasma lactate and abnormal lactate/pyruvate ratios suggests a mitochondrial electron transport chain disorder. Pompe disease may present in the neonatal period with significant hypotonia and cardiomyopathy. Initial testing shows a characteristic pattern on electrocardiography, an abnormal pattern of oligosaccharides in urine, and vacuolated lymphocytes. Enzyme analysis confirms diagnosis.

Hypotonia

Newborns who have metabolic disorders may exhibit hypotonia and generally have associated clinical features such as encephalopathy, metabolic acidosis, cardiomyopathy, or dysmorphic features. In addition to the initial tests, relevant additional metabolic tests include measurement of very long-chain fatty acids for peroxisomal disorders, urine oligosaccharides for Pompe disease, and transferrin isoforms for congenital disorders of glycosylation. Elevated lactate values suggest a mitochondrial disorder or pyruvate metabolism defects.

Dysmorphic Features

Subtle or overt dysmorphic features are observed in several metabolic disorders. Some disorders have a constellation of findings that can be diagnostic.

Smith-Lemli-Opitz syndrome is a disorder of cholesterol synthesis associated with dysmorphic features, cleft palate, congenital heart disease, hypospadias, polydactyly, and syndactyly of the second and third toe. Serum cholesterol concentrations may be abnormally low or normal. An elevated plasma 7-dehydrocholesterol value is diagnostic.

Zellweger syndrome is a peroxisomal disorder. Newborns have flat, expressionless faces with epicanthal folds and can be suspected initially to have Down syndrome. Hypotonia, cataracts, camptodactyly, and stippled epiphyses and patellae are observed. Zellweger syndrome, neonatal adrenoleukodystrophy, and other peroxisomal disorders are diagnosed by abnormal plasma very long-chain fatty acid values.

Congenital disorders of glycosylation are rare conditions caused by abnormalities in glycoprotein synthesis. Several different types are described and have varying clinical features involving multiple organ systems. Type 1a is characterized by a broad nasal bridge, prominent jaw and forehead, and large ears as well as abnormal fat distribution, especially of the buttocks and thighs. The diagnosis is based on an isoelectric focusing pattern of transferrin isoforms.

Menkes disease is an X-linked disorder that should be suspected in a neonate who has hypothermia, hypotonia, jaundice, and characteristic facial features. Infants have macrocephaly with high foreheads and large anterior fontanelles. The hair is sparse and has a steely, kinky appearance. Skeletal radiographs show wormian bones, osteopenia, and metaphyseal widening. Copper and ceruloplasmin concentrations are decreased.
Certain organic acidemias may be associated with multiple dysmorphic features. Neonates who have glutaric acidemia type II can have dysmorphic features, cerebral malformations, and cystic renal disease. Newborns affected by pyruvate dehydrogenase deficiency may have the facial features of fetal alcohol syndrome, agenesis of the corpus callosum, and cerebral atrophy. Because abnormal eye findings are seen in IEMs, an eye examination by an ophthalmologist is recommended.

Nonimmune Hydrops
Several disorders, including a number of IEMs, have been associated with nonimmune hydrops (Table 3). It is important to note that in spite of a thorough evaluation, the cause of hydrops often is not identified.

Confirmatory Testing
Although metabolic screening tests are highly sensitive and specific for a particular diagnosis, confirmatory testing may be necessary. This often includes enzyme analysis or molecular DNA testing. Enzyme testing can be performed in various tissues such as leukocytes, skin fibroblasts, muscle, or liver. Prior to obtaining and sending out samples, it is important to review special criteria for collection and transport. Molecular testing to identify mutations in the gene coding for the enzyme may be available for certain disorders. Molecular testing is not always essential for making the diagnosis, but this information may help identify specific disease-causing mutations and aid in clinical correlation. Molecular testing is also useful in genetic counseling for at-risk family members and prenatal diagnosis.

Potential Testing Pitfalls
1. Although acutely ill neonates in metabolic crisis need immediate management, it is imperative to remember that the event provides a window of opportunity for optimal metabolic testing. At least 5 mL plasma and 5 mL urine should be set aside before correction of metabolic abnormalities. Blood spots dropped onto a filter paper (such as newborn screening cards), completely dried and stored with a desiccant, also may be saved for further analysis.
2. Expanded newborn screening provides valuable information but is still only a screen. When a metabolic disorder is suspected, the newborn screen results should not be the sole diagnostic evaluation; more definitive testing should be initiated.
3. When studies such as plasma amino acids, plasma acylcarnitine profile, and urine organic acids need to be sent to a specialized laboratory, they should be sent by overnight courier. Delay can affect results.
4. When ordering measurements of plasma amino acids, it is important to ask for a quantitative analysis. Analysis of amino acids generally is more informative in plasma rather than urine. Therefore, care must be taken to specify plasma amino acid analysis.
5. Free and total carnitine measurements often are ordered erroneously instead of the plasma acylcarnitine profile. The profile provides necessary information on different acylcarnitine moieties that can aid in diagnosis of fatty acid oxidation disorders.
6. Ammonia values can be significantly elevated if the sample is not immediately rushed on ice to the laboratory and analyzed. Accurate results rely on collecting a free-flowing blood sample and avoiding the use of a tight tourniquet.
7. Lactate and pyruvate concentrations must be obtained simultaneously for comparison. The same phlebotomy precautions should be taken as described for ammonia measurement.

Table 3. Inborn Errors of Metabolism Associated With Hydrops Fetalis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic Abnormality</td>
<td>Complete blood count with peripheral smear for hemolytic anemia</td>
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<tr>
<td>G6PD deficiency</td>
<td></td>
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<tr>
<td>Pyruvate kinase deficiency</td>
<td></td>
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<tr>
<td>Lysosomal Storage Disease</td>
<td>Urine screen for mucopolysaccharides and oligosaccharides</td>
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<tr>
<td>Mucopolysaccharidoses, sphingolipidoses, mucolipidoses</td>
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<tr>
<td>Disorders of Steroid Metabolism</td>
<td>7-dehydrocholesterol</td>
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<tr>
<td>Smith–Lemli–Opitz syndrome</td>
<td>Urine organic acids</td>
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<tr>
<td>Mevalonic aciduria</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Zellweger syndrome</td>
<td>Plasma very long-chain fatty acids</td>
</tr>
<tr>
<td>Congenital disorders of glycosylation</td>
<td>Serum transferrin isofoms</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
<td>Serum lactate</td>
</tr>
<tr>
<td>Glycogen storage disease type IV</td>
<td>Enzyme studies, liver biopsy</td>
</tr>
<tr>
<td>G6PD = glucose-6-phosphate dehydrogenase</td>
<td></td>
</tr>
</tbody>
</table>
8. When the clinical condition of a neonate suspected of having a metabolic disorder deteriorates significantly and death is imminent, various samples should be set aside for future testing (Table 4). This can present a stressful situation for the medical staff and family members, and a protocol should be established to help the process flow smoothly. When it is not feasible to retrieve such samples, a blood spot, dried on filter paper as described previously, should be obtained for possible metabolic or genetic testing. It is important to make every attempt to establish a diagnosis in a terminal newborn because such information is very important to the family for making future reproductive decisions.

Conclusion
Diagnosis of IEMs can be challenging. The testing strategy presented in this review aims to simplify the initial clinical approach to the diagnosis of these disorders. A clinical geneticist should be involved when the initial test results are suggestive of a particular IEM to provide valuable assistance for confirmatory testing and management.

Suggested Reading

<table>
<thead>
<tr>
<th>Table 4. Samples That Should Be Collected in a Dying Neonate Who Has an Undiagnosed Inborn Error of Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Samples Set Aside for Future Testing</strong></td>
</tr>
<tr>
<td>- Plasma (at least 5 mL) frozen</td>
</tr>
<tr>
<td>- Urine (at least 5 mL) frozen</td>
</tr>
<tr>
<td>- Dried blood spot on a newborn screening filter paper card</td>
</tr>
<tr>
<td>- Skin biopsy in sterile saline or in culture medium at room temperature. (Caution: Povidone-iodine is toxic to cell growth)</td>
</tr>
<tr>
<td><strong>With Proper Consent, Postmortem Samples</strong></td>
</tr>
<tr>
<td>- Liver tissue unfixed, immediately frozen below −20°C</td>
</tr>
<tr>
<td>- Muscle biopsy, immediately frozen below −20°C</td>
</tr>
<tr>
<td>- Skin biopsy if not obtained previously</td>
</tr>
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</table>
NeoReviews Quiz

4. A neonate who has an inborn error of metabolism may present with symptoms and signs that often are nonspecific and attributed to other, more common neonatal disorders such as sepsis. However, specific symptoms and signs may distinguish specific inborn errors of metabolism. Of the following, abnormal posturing is most likely to indicate:

A. Fatty acid oxidation defect.
B. Glutaric acidemia type I.
C. Maple syrup urine disease.
D. Nonketotic hyperglycinemia.
E. Pyruvate kinase deficiency.

5. A 48-hour-old term male newborn is lethargic and feeding poorly. He has had a brief episode of generalized tonic-clonic seizures. Physical examination reveals obtunded consciousness, generalized hypotonia, and depressed reflexes. Laboratory data include normal values for blood gases, blood counts, and C-reactive protein. Cultures of blood, urine, and cerebrospinal fluid are pending. Antibiotics are administered and other supportive care is offered. Metabolic studies reveal a markedly elevated blood ammonia concentration and a highly abnormal plasma amino acid profile. Of the following, the most likely inborn error of metabolism in this infant is:

A. Mitochondrial energy disorder.
B. Organic acidemia.
C. Pyruvate metabolism defect.
D. Transient hyperammonemia of the newborn.
E. Urea cycle defect.

6. A 7-day-old term female newborn is lethargic and feeding poorly. Her blood glucose concentration is 7.0 mg/dL (0.39 mmol/L). Other laboratory tests reveal mild metabolic acidosis, elevated liver enzymes and blood ammonia, low urine ketones, and an abnormal plasma acylcarnitine profile. Chest radiography reveals a markedly enlarged heart. Of the following, the most likely inborn error of metabolism in this infant is:

A. Fatty acid oxidation defect.
B. Galactosemia.
C. Glycogen storage disease.
D. Hereditary fructose intolerance.
E. Organic acidemia.
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