Inborn Errors of Metabolism: From Preconception to Adulthood

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Inborn errors of metabolism (IEM), although individually rare, occur in 1 out of every 1,500 births. The first opportunity to detect IEM occurs during preconception counseling, when pregnant women and couples considering future pregnancies can undergo carrier screening. For individuals of all ethnic backgrounds, the screening includes testing for a variety of IEM and non-IEM. For individuals of Ashkenazi Jewish descent, carrier screening, per the American College of Medical Genetics and Genomics, also includes testing for Tay-Sachs disease and four other IEM. Inborn errors of metabolism can present in utero; in newborns; or in children, adolescents, and adults. Some IEM can be detected in utero with the use of ultrasonography. Most commonly, IEM are detected at newborn screening. Expanded newborn screening, which now includes 34 core conditions, allows for diagnosis in the newborn period and provides the opportunity for early institution of available treatments. However, some newborns present with symptoms consistent with an IEM before the availability of pending newborn screening results or present with symptoms attributable to an IEM not detectable with screening. Such situations are medical emergencies requiring immediate consultation with a metabolic specialist. If a delay occurs in obtaining consultation, initial treatment involves discontinuing feeding and providing high-rate glucose infusions. Some IEM present later in life. Children may develop and present with dysmorphic facial features. In some cases, symptoms may not appear until adolescence or adulthood when patients have residual enzyme activity that allows for slow accumulation of toxic molecules over time. Long-term treatments are effective for some IEM. Treatments include dietary restrictions and enzyme-replacement therapies. (*Am Fam Physician*. 2019;99(1):25-32.

Inborn errors of metabolism (IEM) are genetic conditions that block metabolic pathways involved in the breakdown of nutrients and the generation of energy. Perturbation of these metabolic pathways results in a spectrum of clinical findings affecting multiple organ systems. The diagnosis of IEM is challenging because the clinical presentation is often nonspecific; however, more IEM are now included in recommended newborn screening, which helps for early diagnosis. Therefore, knowledge of IEM has become essential for physicians. Although individual IEM are rare, the combined incidence is 1 out of every 1,500 births.[1] This review discusses IEM disorders from preconception to adulthood.

CME **This clinical content** conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 11.

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Patient information: Handouts on this topic are available at https://familydoctor.org/newborn-screening-tests/ (newborn screening overview, including metabolic disorders) and https://familydoctor.org/condition/phenylketonuria-pku (PKU).

Screening

PRECONCEPTION

The first opportunity to address IEM occurs with testing of asymptomatic future parents. Certain populations have increased carrier rates for IEM, and preconception screening has been shown to decrease disease prevalence.

Carrier testing first began in the Ashkenazi (Eastern European) Jewish population in the early 1970s with preconception screening for carriers of Tay-Sachs disease.[2,3] With the

WHAT IS NEW ON THIS TOPIC

Inborn Errors of Metabolism (IEM)

The American College of Obstetricians and Gynecologists has classified expanded carrier screening as an acceptable pre-pregnancy and prenatal screening strategy for all patients. Expanded screening refers to concurrently screening for as many as several hundred conditions, including both IEM and non-IEM.

The initial treatment for all newborns and children with a suspected IEM comprises ending the buildup of toxic metabolites by discontinuing feeds and by preventing catabolism by giving glucose at a high infusion rate (5 to 10 g per kg per hour).

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Strength of recommendation	References	Comments
The option of carrier screening for IEM should be discussed when providing preconception counseling to women considering pregnancy.	C	7	Consensus
Newborn screening is recommended for 34 disorders, including 25 IEM.	C	14, 15	Consensus
An IEM disorder should always be considered in the differential diagnosis in infants being evaluated or treated for suspected infection, especially if the infant does not respond to antibiotics as expected.	C	24, 25	Expert opinion
Physicians should consult with a metabolic specialist on an emergency basis upon diagnosis of IEM in a newborn.	C	16, 18	Expert opinion
The ACMG ACTion (ACT) sheets and algorithms should be used to further determine appropriate action after a positive newborn screen, particularly if there is a delay in contacting a metabolic specialist.	C	16, 18	Expert opinion

ACMG = American College of Medical Genetics and Genomics; IEM = inborn errors of metabolism.

A = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

advent of carrier screening, the incidence of Tay-Sachs disease decreased by 90% between 1970 and 1993 in the Jewish populations of North America.[3] The American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) have expanded the list of recommended carrier testing for IEM beyond Tay-Sachs disease in the Ashkenazi Jewish population *(Table 1)*.[4-6]

In addition, ACOG has recently classified expanded carrier screening as an acceptable pre-pregnancy and prenatal screening strategy for all patients.[7] Expanded screening refers to concurrent screening for as many as several hundred conditions—both IEM and non-IEM—and is more accessible because of the decreased cost of DNA analysis.

Because of the previous recommendations and decreased testing costs, physicians in family medicine, obstetrics, and maternal fetal medicine are now able to offer preconception screening for inherited disorders; however, preconception screening detects only the most common DNA variants associated with a particular IEM disorder. Thus, a normal

TABLE 1

IEM and Non-IEM Disorder Carrier Screening Recommendations for Adults of Ashkenazi Jewish Descent from the ACMG and the ACOG

Disease	ACMG*†	ACOG†‡§	Carrier frequency‖	Sensitivity
Gaucher disease	Recommended	Consider	1/18	89% to 96%
Tay-Sachs disease	Recommended	Recommended	1/31	95% to 97%
Canavan disease	Recommended	Recommended	1/40	94% to 98%
Familial hyperinsulinism	—	Consider	1/52	—
Glycogen storage disease type 1	—	Consider	1/71	—
Maple syrup urine disease	—	Consider	1/81	—
Niemann-Pick disease type A	Recommended	Consider	1/90	92%
Mucolipidosis IV	Recommended	Consider	1/127	95% to 97%

ACMG = American College of Medical Genetics and Genomics; ACOG = American College of Obstetricians and Gynecologists; IEM = inborn errors of metabolism.

*—ACMG recommends carrier screening in Ashkenazi Jewish individuals for these non-IEM: cystic fibrosis, familial dysautonomia, Fanconi anemia group C, and Bloom syndrome.
†—Both ACMG and ACOG recommend carrier screening for all ethnicities for these non-IEM: cystic fibrosis and spinal muscular atrophy.
‡—ACOG recommends carrier screening in Ashkenazi Jewish individuals for these non-IEM: cystic fibrosis and familial dysautonomia; ACOG recommends considering screening in Ashkenazi Jewish individuals for these non-IEM: Bloom syndrome; Fanconi anemia groups A, C, and G; Joubert syndrome; and Usher syndrome.
§—ACOG recommends that screening should be offered to couples of French Canadian or Cajun descent or with a family history of Tay-Sachs disease.
‖—Carrier frequency for Ashkenazi Jewish population.

Information from references 4 through 6.

screening test does not always eliminate the possibility of an IEM disorder.

NEWBORN

IEM disorder screening began in the 1960s with Dr. Robert Guthrie's development of a screening test for phenylketonuria (PKU) from a blood spot[8]; early knowledge of the disorder allowed for treatment of PKU with diet restriction of the amino acid phenylalanine.[9] Expanded newborn screening beyond PKU has occurred largely as a result of the introduction of tandem mass spectrometry, which allows for testing of multiple metabolic conditions from a single blood spot.[10,11]

Sensitivity for newborn screening using tandem mass spectrometry is 99.9%, and specificities range from 99.9% to 99.99%.[12,13] Because of the low prevalence of these conditions, however, positive predictive values range from 26% to 37%.[12,13]

The Secretary of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children created the Recommended Uniform Screening Panel[14] to indicate the conditions for which screening should occur.[15] The panel lists 34 core conditions, 25 of which are IEM[15] *(Table 2[15,16])*. The Recommended Uniform Screening Panel also lists 26 secondary conditions that can be detected on tandem mass spectrometry that are in the differential diagnosis of the core disorders.[14] A number of criteria must be met for a disease to be added to the Recommended Uniform Screening Panel, including the ability of U.S. states to conduct the screening, evidence of a net benefit from screening, and availability of effective treatments.[17] Individual U.S. states control newborn screening; not all U.S. states screen for all core and secondary conditions.[14,15]

Many IEM in newborns are medical emergencies, and physicians should take immediate action if a positive newborn screen is received. The

TABLE 2

Inborn Errors of Metabolism for Which Newborn Screening Is Recommended by the Secretary of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children

Condition listed by category	Clinical presentation
Amino acid disorder	
Classic phenylketonuria	Cognitive impairment, seizures, spasticity
Homocystinuria	Marfan-like appearance, lens dislocation, cognitive impairment, thromboembolism
Maple syrup urine disease	Progressive encephalopathy
Tyrosinemia, type I	Liver failure, septicemia, hypoglycemia, Fanconi syndrome (renal tubulopathy)
Fatty acid oxidation disorder	
Carnitine uptake defect/ carnitine transport defect	Hypoketotic hypoglycemia, cardiomyopathy, liver disease
Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency	Hypoketotic hypoglycemia, cardiomyopathy, liver disease, recurrent rhabdomyolysis
Medium-chain Acyl-CoA dehydrogenase deficiency	Reye-like syndrome, metabolic crisis after fasting with lethargy, nausea, vomiting, coma
Trifunctional protein deficiency	Hypoketotic hypoglycemia, cardiomyopathy, liver disease, recurrent rhabdomyolysis
Very long-chain Acyl-CoA dehydrogenase deficiency	Hypoketotic hypoglycemia, cardiomyopathy, liver disease, recurrent rhabdomyolysis
Organic acidemia	
3-hydroxy-3-methylglutaric aciduria	Metabolic decompensation triggered by periods of fasting or infections
3-methylcrotonyl-CoA carboxylase deficiency	Encephalopathy, ketoacidosis, hyperammonemia
ß-ketothiolase deficiency	Ketoacidotic attacks, sometimes leading to coma
Glutaric acidemia type I	Macrocephaly, encephalopathy
Holocarboxylase synthetase deficiency	Metabolic acidosis, neurologic defects, skin rash
Isovaleric acidemia	Encephalopathy, ketoacidosis, hyperammonemia
Methylmalonic acidemia (cobalamin disorders)	Encephalopathy, ketoacidosis, hyperammonemia
Methylmalonic acidemia (methylmalonyl-CoA mutase)	Encephalopathy, ketoacidosis, hyperammonemia
Propionic acidemia	Encephalopathy, ketoacidosis, hyperammonemia
Urea cycle disorders	
Argininosuccinic aciduria	Neurologic and liver abnormalities
Citrullinemia type I	Mild hyperammonemia, failure to thrive
Other	
Biotinidase deficiency	Metabolic acidosis, neurologic defects, skin rash
Classic galactosemia	Liver and renal failure after start of milk feeds in first week of life
Glycogen storage disease type II (Pompe disease)	Failure to thrive, cardiomyopathy, hypotonia
Mucopolysaccharidosis I	Hydrocephalus, cognitive impairment, coarse facies
X-linked adrenoleukodystrophy	Intellectual regression, leukodystrophy, adrenal insufficiency

Information from references 15 and 16.

TABLE 3

Inborn Error of Metabolism Disorders Found in Second Trimester Prenatal Ultrasonography

	Ultrasound findings							
Condition	IUGR	Brain anomalies	Hydrops fetalis	Renal anomaly	Hyperechogenic colon	Polyhydramnios	Liver steatosis	Left ventricular noncompaction
Lysosomal storage diseases			X					
Cholesterol synthesis disorders (Antley-Bixler syndrome, Greenberg dysplasia, CHILD syndrome)	X							
Glycogen storage disease type IV			X			X		
Peroxisomal disorders		X		X				
Fatty acid oxidation disorders		X		X			X	
Organic acidemia (Barth syndrome, methylmalonic acidemia, holocarboxylase synthetase deficiency, mevalonic aciduria)	X	X			X			X
Amino acidopathies	X	X			X			
Congenital disorders of glycosylation	X		X					

CHILD syndrome = congenital hemidysplasia with ichthyosiform erythroderma and limb defects; IUGR = intrauterine growth restriction.

Information from references 19 and 20.

following actions should be taken: (1) contact the parents of the newborn to inform them of the situation; (2) assess the newborn's clinical condition; and (3) provide prompt referral to a metabolic specialist.[16,18] The ACMG provides ACTion (ACT) sheet resources that describe the short-term actions a health professional should follow in communicating with the family and in determining the appropriate steps for an infant who has screened positive for an IEM disorder (see Medical Genetic Practice Resources at http://www.acmg.net).

Clinical Presentation

Various IEM can present throughout a patient's life span, from the prenatal period through adulthood.

PRENATAL

Some IEM present in pregnancy, with abnormalities detected on ultrasound. For example, hydrops fetalis (fluid accumulation in multiple body areas, such as ascites, pleural or pericardial effusions, or skin edema) may be seen on prenatal ultrasonography after 26 weeks' gestation in lysosomal storage diseases. Lysosomal storage diseases are a group of disorders that result from an enzyme deficiency that blocks the ability of lysosomes to digest large cellular molecules. The most common lysosomal storage diseases are mucopolysaccharidosis VII, Gaucher disease, and GM1 gangliosidosis.[19] Other IEM presenting in utero on ultrasonograpy during the second trimester are shown in *Table 3*.[19,20]

Maternal history, examination, and laboratory findings may be used in addition to fetal ultrasonography for indicators of IEM for two particular conditions. In ornithine transcarbamylase, the pregnant mother may be symptomatic with hyperammonemia, coma, and psychiatric symptoms.[21] In long-chain hydroxyacyl dehydrogenase deficiency, the mother can present with an acute fatty liver; hyperemesis; and a syndrome with symptoms of hemolysis, elevated liver enzymes, and low platelet count.[22]

For all prenatal genetic diseases, whether detected with ultrasonography or suspected from clinical findings, a definitive diagnosis can be accomplished with chorionic villi sampling or amniocentesis.[23]

NEWBORN

Many IEM present in the first month of life. Often, the newborn will initially appear healthy because metabolites occurring in the IEM disorder have been cleared via placental circulation during the intrauterine period. Those metabolites accumulate only after birth; thus, a symptom-free period after birth is a vital component of the medical history.[16]

Symptoms of IEM in newborns are typically nonspecific, such as lethargy, poor feeding, vomiting, abnormal breathing, seizures, and/or hypotonia. Although these signs also signal infection (including sepsis), which is more common, IEM must be considered in the differential diagnosis. Additional findings that should raise concern about the possibility of an IEM disorder are metabolic acidosis, unexplained hypoglycemia, constitutional liver dysfunction, and encephalopathy.[16]

All newborns being evaluated for these presentations should have an ammonia level and urine ketone tests performed in addition to the evaluation for possible infection or sepsis. If acidosis is a concern (i.e., urine pH is low, respiratory rate is abnormal), a confirmation blood gas measurement should be performed, even if the pulse oximetry is normal. If any one of these tests is abnormal or if the newborn does not respond to antibiotics as expected,[24,25] an IEM disorder should be considered, and a metabolic specialist should be consulted. If obtaining support from a metabolic specialist is delayed, plasma amino acids, acylcarnitine profile, and urine organic acids should be measured *(Table 4[16])*.

Whereas many IEM present after a period during which the newborn appears healthy, some IEM may clinically present before the physician has received the IEM disorder screening test results. Additionally, a normal newborn metabolic screen should not deter physicians from performing a metabolic workup in a sick newborn because not all variations of metabolic diseases are covered in newborn screening tests.

CHILDREN

Most conditions that present in the newborn period can present during childhood in a similar or less severe manner and in some cases are linked with dysmorphic physical

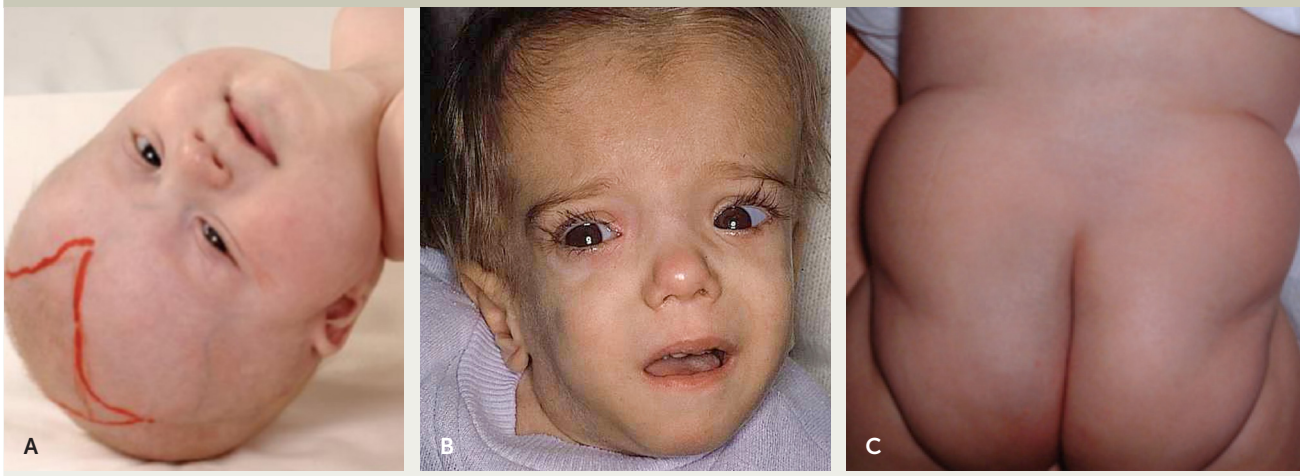
TABLE 4

Metabolic Laboratory Testing when Inborn Errors of Metabolism Are Suspected

Test	Significance	Examples of inborn errors of metabolism associated with abnormal values
Urine		
Ketones	Sign of ketosis	Ketouria found in organic acidemias, hypoketotic hypoglycemia in fatty acid oxidation disorders
Organic acids	Elevated organic acids in urine especially when patient is in a fasting or catabolic state	Amino acidopathies, organic acidemias, fatty acid oxidation disorders
Blood		
Electrolytes, creatine kinase, creatinine	Acid-base analysis	Anion gap in organic acidemias (i.e., methylmalonic acidemia and propionic acidemia)
Creatine kinase	Cardiomyopathy	Fatty acid oxidation disorders, organic acidemias, mitochondrial disorders, glycogen storage disorders
Coagulation studies, alanine aminotransferase, aspartate aminotransferase	Liver disease	Fatty acid oxidation disorders, tyrosinemia type I, mitochondrial defects, hereditary fructose intolerance
Glucose	Hypoglycemia	Glycogen storage diseases and fatty acid oxidation disorders
Ammonia	Elevated levels cause encephalopathy	Urea cycle disorders, organic acidemias
Arterial/venous gas (pH, bicarbonate, CO_2)	pH, acid base analysis	Acidosis (organic acidemias), elevated pH (occasionally in urea cycle disorders)
Acylcarnitines	Quantifies carbon chains esterified to carnitine	Organic acidemias and fatty acid oxidation disorders
Amino acids	Elevated amino acid levels	Maple syrup urine disease, phenylketonuria, tyrosinemia type 1, some urea cycle disorders, elevated glycine in organic acidemias
Lactate	Hypoxia and tissue perfusion problems	Mitochondrial disorders, pyruvate dehydrogenase or carboxylase deficiency, organic acidemias, glycogen storage diseases

Information from reference 16.

FIGURE 1



Recognizable dysmorphic features associated with inborn errors of metabolism disorders.

(A) Six-month-old girl with Zellweger syndrome,[26] which is a leukodystrophy caused by a peroxisome biogenesis defect. Clinical features include epicanthal folds, high forehead, broad nasal bridge, hypoplastic supraorbital ridges, and enlarged anterior fontanel.

Reprinted with permission from Klouwer FC, Berendse K, Ferdinandusse S, et al. Zellweger spectrum disorders. Orphanet J Rare Dis. *2015;10:151.*

(B) A 21-month-old child with mevalonic aciduria displaying typical dysmorphic features to include down-slanting eyes, blue sclerae, low set ears, and long face.[27] Mevalonic aciduria presents with developmental delay, progressive ataxia, failure to thrive, visual defects, and periodic fevers.

Reprinted with permission from Haas D, Hoffmann GF. Mevalonate kinase deficiencies: from mevalonic aciduria to hyperimmoglobulinemia D syndrome. Orphanet J Rare Dis. *2006;1:13.*

(C) Congenital disorders of glycosylation are a group of disorders with a disturbed ability to glycosylate certain tissue proteins and/or lipids, resulting in myriad presentations including seizures, ataxia, failure to thrive, liver disease, and brain anomalies. Lipodystrophy in a congenital disorder of glycosylation syndrome type 1a is shown.[28]

Reprinted with permission from Freeze HH, Eklund EA, Ng BG, Patterson MC. Neurology of inherited glycosylation disorders. Lancet Neurol. *2012;11(5):453-466.*

examination findings *(Figure 1)*.[26-28] Two of the most well-known examples are lysosomal storage disorders, Hunter syndrome and Hurler syndrome.[29,30] The dysmorphic features may not present at birth, but they become more pronounced over time as the storage molecule accumulates.

ADOLESCENTS AND ADULTS

Primary care physicians occasionally encounter IEM in adolescents and adults *(Table 5[31])*. Some children with IEM are living longer because of new treatments and a better understanding of how to avoid metabolic decompensation (e.g., avoiding high-protein diets in organic acidemia and urea cycle disorders). Also, some IEM have their onset in adults, for example, adult-onset lysosomal storage disorders. Patients with these IEM have residual enzyme activity that allows for slow accumulation of toxic molecules over time, and symptoms may not appear until adulthood. Some of these disorders (e.g., Gaucher disease) can be treated with enzyme replacement therapy.[32]

Treatment

When physicians encounter a newborn or infant with acute decompensation that is attributable to an IEM disorder, the most important intervention is arranging urgent transfer to a center with a metabolic specialist.[16,18] While awaiting transfer, the initial treatment is the same for all newborns and children with a suspected IEM disorder: stopping the buildup of toxic metabolites by discontinuing feedings and preventing catabolism by providing glucose at a high infusion rate (5 to 10 g per kg per hour).[33,34] This is the equivalent of 10% dextrose in an electrolyte solution at 1.5 times maintenance rate or 5% dextrose at twice the maintenance rate. If this infusion leads to an elevation of serum lactate levels, it suggests the possibility of a mitochondrial disorder. If this occurs, the 10% dextrose fluid should be replaced with a lower glucose load, such as 5% dextrose.[16]

Although long-term treatment of IEM is beyond the scope of this review, note that chronic therapy is available for many IEM. The best known examples that respond to long-term management are the prototypical IEM disorder, PKU, and Gaucher disease. PKU can be treated with a restricted phenylalanine diet, and Gaucher disease can be treated with enzyme replacement. This demonstrates why accurate diagnosis is important.

This article updates a previous article on this topic by Raghuveer, et al.[35]

TABLE 5

Inborn Errors of Metabolism Presenting in Adolescents and Adults

Condition	Incidence	Pathophysiology	Child presentation	Adult/adolescent presentation
Hemochromatosis	1:200 to 1:400 in Caucasians	High absorption of iron	Rare before age 40	Liver disease, diabetes mellitus, renal failure, arthritis
Gaucher disease type 1	1:855 (Ashkenazi Jewish)	Deficiency of lysosomal enzyme glucocerebrosidase	Bone disease, hepatosplenomegaly, anemia, thrombocytopenia	Similar to early presentation with the addition of osteoporosis and Parkinson disease
X-linked adrenoleukodystrophy	1:20,000 to 1:50,000	Peroxisomal disorder; very long-chain fatty acid accumulation resulting in destruction of myelin and adrenal cortex	Visual and hearing impairment, leukodystrophy, cerebellar ataxia, dementia	Males: onset 20 to 30 years of age with gait disturbance, spastic paraparesis, dementia, psychosis, adrenal insufficiency Females: onset after 30 years of age, spastic paraparesis, peripheral neuropathy
Wilson disease	1:30,000	Copper accumulation disorder	Liver failure	Tremor, Parkinson-like symptoms, dysarthria, renal failure, dementia
3-methylcrotonyl CoA carboxylase deficiency	1:36,000	Leucine metabolism disorder	Infants present with seizures and feeding difficulties	Asymptomatic mother identified after her newborn has abnormal newborn screening test because of mother's metabolites in infant's blood
Fabry disease	1:50,000 to 1:117,000 males	X-linked lysosomal storage disease from deficiency of the enzyme alpha-galactosidase A (α-Gal A)	Males with less than 1% α-Gal A present in childhood or adolescence with acroparesthesia, angiokeratoma, renal and heart disease	Heterozygous females typically present later in life than males with milder symptoms
Ornithine transcarbamylase deficiency	1:70,000	Most common urea cycle disorder; X-linked inheritance	Often fatal in newborn males	Adolescent females with dietary protein aversion, abdominal pain, and headaches
Homocystinuria	1:200,000	Reduced activity of the cystathionine ß-synthase enzyme, which is involved in the conversion of the essential amino acid methionine to another amino acid (cysteine)	Developmental delay	Osteoporosis, dislocated ocular lenses, thrombophilia
Carnitine palmitoyltransferase II deficiency	Rare	Fatty acid metabolism disorder	Newborns present with cardiomyopathy and liver failure	Rhabdomyolysis, muscle weakness, and myopathy in adolescents and adults after physical activity
GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease)	Rare	Lysosomal storage disease	Progressive weakness, decreased attentiveness, blindness, and death in year 2 or 3 of life	Motor neuron disease, dystonia, cerebellar degeneration, bipolar disease, psychosis
Porphyria	Rare	Abnormally high levels of porphyrins and porphyrin precursors because of deficiency of the enzyme hydroxymethylbilane synthase	Rare before puberty	Seizures, extremity pain, chest pain, abdominal pain, photosensitivity

Information from reference 31.

Data Sources: A PubMed search was completed in Clinical Queries using the key terms inherited metabolic disorders, genetic carrier screening, prenatal genetic testing, newborn screening, inborn errors of metabolism, and adults. The search included meta-analyses, clinical trials, and reviews. Also searched were the Agency for Healthcare Research and Quality evidence reports, the Cochrane database, the National Guideline Clearinghouse, Bandolier, and Essential Evidence Plus. Search date: May 1, 2017.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Department of Health and Human Services.

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References

1. Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969-1996. *Pediatrics*. 2000;105(1):e10.
2. Vallance H, Ford J. Carrier testing for autosomal-recessive disorders. *Crit Rev Clin Lab Sci*. 2003;40(4):473-497.
3. Kaback M, Lim-Steele J, Dabholkar D, et al. Tay-Sachs disease—carrier screening, prenatal diagnosis, and the molecular era. An international perspective, 1970 to 1993. *JAMA*. 1993;270(19):2307-2315.
4. Committee on Genetics. Committee Opinion No. 691: carrier screening for genetic conditions. *Obstet Gynecol*. 2017;129(3):e41-e55.
5. Gross SJ, Pletcher BA, Monaghan KG; Professional Practice and Guidelines Committee. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med*. 2008;10(1):54-56.
6. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine-points to consider. *Obstet Gynecol*. 2015;125(3):653-662.
7. Committee on Genetics. Committee Opinion No. 690: carrier screening in the age of genomic medicine. *Obstet Gynecol*. 2017;129(3):e35-e40.
8. Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics*. 1963;32:338-343.
9. Poustie VJ, Wildgoose J. Dietary interventions for phenylketonuria. *Cochrane Database Syst Rev*. 2010;(1):CD001304.
10. Chace DH, Sherwin JE, Hillman SL, et al. Use of phenylalanine-to-tyrosine ratio determined by tandem mass spectrometry to improve newborn screening for phenylketonuria of early discharge specimens collected in the first 24 hours. *Clin Chem*. 1998;44(12):2405-2409.
11. Millington DS, Kodo N, Norwood DL, Roe CR. Tandem mass spectrometry. *J Inherit Metab Dis*. 1990;13(3):321-324.
12. Lund AM, Hougaard DM, Simonsen H, et al. Biochemical screening of 504,049 newborns in Denmark, the Faroe Islands and Greenland. *Mol Genet Metab*. 2012;107(3):281-293.
13. Vilarinho L, Rocha H, Sousa C, et al. Four years of expanded newborn screening in Portugal with tandem mass spectrometry. *J Inherit Metab Dis*. 2010;33(suppl 3):S133-S138.
14. Kemper AR, Green NS, Calonge N, et al. Decision-making process for conditions nominated to the recommended uniform screening panel. *Genet Med*. 2014;16(2):183-187.
15. Advisory Committee on Heritable Disorders in Newborns and Children. Recommended Uniform Screening Panel. https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/index.html. Accessed July 1, 2017.
16. Zschocke J, Hoffmann GF. *Vademecum Metabolicum: Diagnosis and Treatment of Inborn Errors of Metabolism*. 3rd ed. http://evm.health2media.com/#/detail-view/about/0/0. Accessed August 31, 2018.
17. Perrin JM, Knapp AA, Browning MF, et al. An evidence development process for newborn screening. *Genet Med*. 2010;12(3):131-134.
18. Weismiller DG. Expanded newborn screening: information and resources for the family physician. *Am Fam Physician*. 2017;95(11):703-709.
19. Gimovsky AC, Luzi P, Berghella V. Lysosomal storage disease as an etiology of nonimmune hydrops. *Am J Obstet Gynecol*. 2015;212(3):281-290.
20. Vianey-Saban C, Acquaviva C, Cheillan D, et al. Antenatal manifestations of inborn errors of metabolism: biological diagnosis. *J Inherit Metab Dis*. 2016;39(5):611-624.
21. Mendez-Figueroa H, Lamance K, Sutton VR, Aagaard-Tillery K, Van den Veyver I. Management of ornithine transcarbamylase deficiency in pregnancy. *Am J Perinatol*. 2010;27(10):775-784.
22. Walter JH. Inborn errors of metabolism and pregnancy. *J Inherit Metab Dis*. 2000;23(3):229-236.
23. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. *Obstet Gynecol*. 2007;110(6):1459-1467.
24. Saudubray JM, Garcia-Cazorla À. Inborn errors of metabolism overview. *Pediatr Clin North Am*. 2018;65(2):179-208.
25. Cook P, Walker V. Investigation of the child with an acute metabolic disorder. *J Clin Pathol*. 2011;64(3):181-191.
26. Klouwer FC, Berendse K, Ferdinandusse S, et al. Zellweger spectrum disorders. *Orphanet J Rare Dis*. 2015;10:151.
27. Haas D, Hoffmann GF. Mevalonate kinase deficiencies: from mevalonic aciduria to hyperimmoglobulinemia D syndrome. *Orphanet J Rare Dis*. 2006;1:13.
28. Freeze HH, Eklund EA, Ng BG, Patterson MC. Neurology of inherited glycosylation disorders. *Lancet Neurol*. 2012;11(5):453-466.
29. Campos D, Monaga M. Mucopolysaccharidosis type I. *Metab Brain Dis*. 2012;27(2):121-129.
30. Martin R, Beck M, Eng C, et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). *Pediatrics*. 2008;121(2):e377-e386.
31. Gray RG, Preece MA, Green SH, et al. Inborn errors of metabolism as a cause of neurological disease in adults: an approach to investigation. *J Neurol Neurosurg Psychiatry*. 2000;69(1):5-12.
32. Pastores GM, Hughes DA. *Gaucher Disease*. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle: University of Washington, Seattle; July 27, 2000 [updated June 21, 2018]:1993-2018.
33. Singh RH, Rhead WJ, Smith W, et al. Nutritional management of urea cycle disorders. *Crit Care Clin*. 2005;21(4 suppl):S27-S35.
34. Chapman KA, Gropman A, MacLeod E, et al. Acute management of propionic acidemia. *Mol Genet Metab*. 2012;105(1):16-25.
35. Raghuveer TS, Garg U, Graf WD. Inborn errors of metabolism in infancy and early childhood: an update. *Am Fam Physician*. 2006;73(11):1981-1990.