

351 Inborn Errors of Metabolism

Definition/Cut-Off Value

Inherited metabolic disorders caused by a defect in the enzymes or their co-factors that metabolize protein, carbohydrate, or fat.

Inborn errors of metabolism (IEM) generally refer to gene mutations or gene deletions that alter metabolism in the body, including but not limited to:

Inborn Errors of Metabolism*	
Amino Acid Disorders	Urea Cycle Disorders
Organic Acid Metabolism Disorders	Carbohydrate Disorders
Fatty Acid Oxidation Disorders	Peroxisomal Disorders
Lysosomal Storage Diseases	Mitochondrial Disorders
<i>*For information about additional IEM, please see Clarification.</i>	

Presence of condition diagnosed, documented, or reported by a physician or someone working under physician's orders, or as self reported by applicant/participant/caregiver. See Clarification for more information about self-reporting a diagnosis.

Participant Category and Priority Level

Category	Priority
Infants	I
Children	III
Pregnant Women	I
Breastfeeding Women	I
Non-Breastfeeding Women	III, IV, V or VI

Justification

The inheritance of most metabolic disorders is rare. IEM disorders may manifest at any stage of life, from infancy to adulthood. Early identification of IEM correlates with significant reduction in morbidity, mortality, and associated disabilities for those affected (1).

All States screen newborns for IEM, although the type and number of IEM screened for may vary from State to State. Typically, infants are screened for amino acid disorders, urea cycle disorders, organic acid disorders, and fatty acid oxidation defects. A few States are working toward including lysosomal storage diseases and peroxisomal disorders among their newborn screening panels (2).

In most states, treatment of an IEM is referred to a specialized metabolic treatment facility. Please see Clarification for contact information for treatment facilities. IEM treatment is based on symptomatic therapy which may include the following strategies: substrate restriction; stimulation or stabilization of residual enzyme activity; replacement of deficient products; removal of toxic metabolites or blocking their production; and enzyme replacement therapy (3). Avoidance of catabolism is essential at all treatment stages.

Nutrition therapy is integral to the treatment of IEM. Nutrition therapy should both correct the metabolic imbalance and ensure adequate energy, protein, and nutrients for normal growth and development among affected individuals. Continual monitoring of nutrient intake, laboratory values, and the individual's growth are needed for evaluation of the adequacy of the prescribed diet (4). It is important that caregivers of infants and children with IEM ensure that the patient follows the prescribed dietary regimen. The below embedded links provide the most up-to-date information about the disease state as well as treatment.

Amino Acid Metabolism Disorders (3)

- [Phenylketonuria \(includes clinically significant hyperphenylalaninemia variants\)](#)
- [Maple syrup urine disease](#)
- [Homocystinuria](#)
- [Tyrosinemia](#)

Amino Acid Metabolism Disorders are characterized by the inability to metabolize a certain essential amino acid. The build-up of the amino acid that is not metabolized can be toxic. Treatment of amino acid disorders involves restricting one or more essential amino acids to the minimum required for growth and development and supplying the missing product due to the blocked reaction.

Carbohydrate Disorders (5)

- [Galactosemia](#)
- [Glycogen storage disease type I](#)
- [Glycogen storage disease type II](#) (See also [Pompe disease](#))
- [Glycogen storage disease type III](#)
- [Glycogen storage disease type IV \(Andersen Disease\)](#)
- [Glycogen storage disease type V](#)
- [Glycogen storage disease type VI](#)
- Hereditary Fructose Intolerance ([Fructose 1-phosphate aldolase deficiency](#), Fructose 1, 6, biphosphatase deficiency, fructose kinase deficiency)

This group of disorders includes an enzyme deficiency or its cofactor that affects the catabolism or anabolism of carbohydrate. Carbohydrate disorders are complex and affect neurological, physical, and nutritional status.

Fatty Acid Oxidation Defects (5)

- [Medium-chain acyl-CoA dehydrogenase deficiency](#)
- [Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency](#)

- [Trifunctional protein deficiency type 1](#) (LCHAD deficiency)
- [Trifunctional protein deficiency type 2](#) (mitochondrial trifunctional protein deficiency)
- [Carnitine uptake defect](#) (primary carnitine deficiency)
- [Very long-chain acyl-CoA dehydrogenase deficiency](#)

Fatty acid oxidation defects include any enzyme defect in the process of mitochondrial fatty acid oxidation (FAO) system. The biochemical characteristic of all FAO defects is abnormal low ketone production as a result of the increased energy demands. This results in fasting hypoglycemia with severe acidosis secondary to the abnormal accumulation of intermediate metabolites of FAO, which can result in death.

Organic Acid Disorders (AKA organic aciduria or organic acidemia) (6)

- [Isovaleric acidemia](#)
- [3-Methylcrotonyl-CoA carboxylase deficiency](#)
- [Glutaric acidemia type I](#)
- [Glutaric acidemia type II](#)
- [3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency](#)
- [Multiple carboxylase deficiency](#) (Biotinidase deficiency, [Holocarboxylase synthetase deficiency](#))
- [Methylmalonic acidemia](#)
- [Propionic acidemia](#)
- [Beta-ketothiolase deficiency](#)

Organic Acid Disorders are characterized by the excretion of non-amino organic acids in the urine. Most of the disorders are caused by a deficient enzyme involving the catabolism of specific amino acid(s). As a result, the non-metabolized substance accumulates due to the blockage of the specific metabolic pathway, which is toxic to certain organs and may also cause damage to the brain (7).

Lysosomal Storage Diseases (6, 8)

- [Fabry disease](#) (α -galactosidase A deficiency)
- [Gauchers disease](#) (glucocerebrosidase deficiency)
- [Pompe disease](#) (glycogen storage disease Type II, or acid α -glucosidase deficiency)

Lysosomal storage diseases are a group of related conditions characterized by increased storage of undigested large molecule in lysosomes. Lysosome is a cellular organelle responsible for intracellular degradation and recycling of macromolecules. Due to a defect in a specific lysosomal enzyme, the macromolecule that normally would be metabolized is not broken down; instead, it accumulates in the lysosomes. This leads to tissue damage, organ failures and premature death. Common clinical features include bone abnormalities, organomegaly, developmental impairment and central, peripheral nervous system disorders.

Mitochondrial Disorders (6, 8)

- [Leber hereditary optic neuropathy](#)

- [Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes \(MELAS\)](#)
- [Mitochondrial neurogastrointestinal encephalopathy disease \(MNGIE\)](#)
- [Myoclonic epilepsy with ragged-red fibers \(MERRF\)](#)
- [Neuropathy, ataxia, and retinitis pigmentosa \(NARP\)](#)
- [Pyruvate carboxylase deficiency](#)

Mitochondrial Disorders are caused by the dysfunction of the mitochondrial respiratory chain, or electron transport chain (ETC). Mitochondria play an essential role in energy production. The ETC dysfunction increases free radical production, which causes mitochondrial cellular damage, cell death and tissue necrosis and further worsens ETC dysfunction and thus forms a vicious cycle. The disorders can affect almost all organ systems. However, the organs and cells that have the highest energy demand, such as the brain and muscles (skeletal and cardiac) are most affected. The clinical features vary greatly among this group of disorders, but most have multiple organ dysfunctions with severe neuropathy and myopathy.

[Peroxisomal Disorders \(6, 8, 9\)](#)

- [Zellweger Syndrome Spectrum](#)
- [Adrenoleukodystrophy \(x-ALD\)](#)

There are two types of peroxisomal disorders: single peroxisomal enzyme deficiencies and peroxisomal biogenesis disorders. These disorders cause severe seizures and psychomotor retardation (9). Peroxisomes are small organelles found in cytoplasm of all cells. They carry out oxidative reactions which generate hydrogen peroxides. They also contain catalase (peroxidase), which is important in detoxifying ethanol, formic acid and other toxins. Single peroxisomal enzyme deficiencies are diseases with dysfunction of a specific enzyme, such as acyl coenzyme A oxidase deficiency. Peroxisomal biogenesis disorders are caused by multiple peroxisome enzymes such as Zellweger syndrome and neonatal adrenoleukodystrophy.

[Urea Cycle Disorders \(6, 5\)](#)

- [Citrullinemia](#)
- [Argininosuccinic aciduria](#)
- [Carbamoyl phosphate synthetase I deficiency](#)

Urea Cycle Disorders occur when any defect or total absence of any of the enzymes or the cofactors used in the urea cycle results in the accumulation of ammonia in the blood. The urea cycle converts waste nitrogen into urea and excretes it from the kidneys. Since there are no alternate pathways to clear the ammonia, dysfunction of the urea cycle results in neurologic damages.

[Implications for WIC Nutrition Services](#)

WIC can provide exempt infant formulas and WIC-eligible medical foods, including those specifically formulated for IEM. Most of the dietary regimens for IEM require a combination of medical food (special formula in most cases) and standard infant formula or prescribed conventional foods. For example, participants with IEM related to essential amino acid metabolism (such as PKU, MSUD), who are not developmentally ready for conventional foods; require both medical food without the offending amino acid(s), and human milk or standard infant formula.

It is recommended that WIC nutritionists collaborate with the clinical dietitians at the metabolic treatment facility, where available, to prescribe WIC food packages (Food Package III) according to the therapeutic diet ordered by the metabolic team, monitor the compliance of the restricted diet, and follow up on the growth and developmental status of the participants with IEM.

Note: Infants with classic galactosemia cannot be breastfed due to lactose in human milk.

References

1. Metabolic backgrounder: The Ross metabolic formula system for meeting special nutrition needs. Columbus, OH: Ross Products Division; 2007.
2. Levy PA. Inborn Errors of Metabolism: part 1: Overview. *Pediatr Rev.* 2009Apr; 30(4):131-7.
3. Wilcken B. An introduction to nutritional treatment in Inborn errors of metabolism – different disorders, different approaches. *Southeast Asian J Trop med Public Health.* 2003; 34 Suppl 3: 198-201.
4. Hendricks KM, Duggan C. *Manual of pediatric nutrition*, 4th ed. 2005; 626-657.
5. Ekvall S, Ekvall, VK, editors. *Pediatric nutrition in chronic diseases and developmental disorders: prevention, assessment and treatment*. 2nd ed. Oxford University Press; 2005. Part III. Chapters 37-59.
6. GeneReviews are expert-authored, peer-reviewed, current disease descriptions that apply genetic testing to the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions. Available at: <http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=GeneTests> (last accessed 8/5/2010).
7. Stanley CA. Disorders of fatty acid oxidation. In: Fernandes J, et al editors. *Inborn metabolic diseases*. Berlin Springer; 2000. p. 141-150.
8. Agamanolis D. *Inherited metabolic disorders in neuropathology: an illustrated interactive course for medical students and residents*. Akron OH: Akron Children's Hospital, Northeastern Ohio University College of Medicine. Available at: <http://www.neuropathologyweb.org/chapter10/chapter10aLSDgeneral.html>.
9. Van Veldhoven, PP, Leuven KU. Biochemistry and genetic disorders of inherited disorders of peroxisomal fatty acid metabolism. *J Lipid Res.* 2010 June. Available at: <http://www.jlr.org/cgi/rapidpdf/jlr.R005959v1>.

Clarification

IEM not listed within this write-up may be found under: <http://rarediseases.info.nih.gov/GARD>. Please keep in mind these additional resources are not meant for medical advice nor to suggest treatment.

Self-reporting of a diagnosis by a medical professional should not be confused with self-diagnosis, where a person simply claims to have or to have had a medical condition without any reference to professional diagnosis. A self-reported medical diagnosis ("My doctor says that I have/my son or daughter has...") should prompt the CPA to validate the presence of the condition by asking more pointed questions related to that diagnosis.



The link below lists newborn screening coordinators. The coordinator can direct families to appropriate metabolic treatment facilities based on the newborn screening result: http://genes-r-us.uthscsa.edu/State_contacts.pdf.

