Clinical Approach to the Diagnoses of Inborn Errors of Metabolism

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KEYWORDS

- Inborn errors of metabolism • Developmental delay
- Replacement therapy • Newborn screening • Phenylketonuria
- Fatty acid oxidation disorders

Inborn errors of metabolism (IEMs) are a set of relatively uncommon complicated medical conditions involving abnormalities in the complex biochemical and metabolic pathways of the human body system. They involve great complexity of the underlying pathophysiology, biochemical workup, and analysis, and have complicated therapeutic options for management. These children are often sick with significant complications and high rates of morbidity and mortality. The understanding of these complex disorders requires special in-depth training and experience. Most primary care physicians are less familiar with these disease conditions, and therefore less willing to deal with them because of the complexity involved. There are metabolic specialists available, mostly in large medical centers, with expertise to deal with these intricate complicated issues. Primary care physicians and pediatricians usually are the first point of contact for most of these newborns, children, or adolescents, however. Therefore, it is important that primary care physicians become comfortable in being able to recognize early signs and symptoms, be able to initiate appropriate diagnostic and therapeutic interventions, and be able to make appropriate referrals.

The following article summarizes the key issues basic to understanding IEMs. The main points of discussion address the following questions:

What are IEMs?
What are the different types of IEMs?
What is the relative frequency of these IEMs?
What is the inheritance pattern of these IEMs?
How can these IEMs be diagnosed in a timely manner?
What is the role of newborn screening (NS) programs in early diagnosis and prevention of morbidity and mortality?

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What are the treatment and management options for these IEMs?
What is the long-term prognosis for patients who have IEMs?

WHAT ARE INBORN ERRORS OF METABOLISM?

The term *metabolism* encompasses the net result of a multitude of complex biochemical processes that occur in living organisms to maintain cellular activities. These processes are organized into specific metabolic pathways with the primary function to maintain daily life activities. Each pathway depends on certain substrates and specific enzymes to ensure smooth functioning. IEMs are a group of heritable genetic disorders interfering with these metabolic pathways in different ways, leading to inadequate functioning of a particular pathway. This interference in the normal enzymatic or metabolic pathway has varying consequences, including deficiency of a particular end product or excessive accumulation of a substrate that may be toxic. Either of these two scenarios leads to significant morbidity and mortality by hampering normal functioning of a particular metabolic pathway.

IEMs have been known for the approximately the past 100 years, with the term being first used by Sir Archibald Garrod in 1902.[1] The initial disorders described were alkaptonuria, benign pentosuria, albinism, and cystinuria at that time, to be followed by description of one of the major IEMs, namely, phenylketonuria (PKU), by Folling in 1934. Since that time, advances in medicine have uncovered more than 500 IEMs.[2]

WHAT ARE THE DIFFERENT TYPES OF INBORN ERRORS OF METABOLISM?

Some of the common metabolic disorders are listed in **Box 1**.[3,4]

WHAT IS THE RELATIVE FREQUENCY OF OCCURRENCE OF INBORN ERRORS OF METABOLISM?

The incidence of IEMs is highly variable among the many specific clinical entities, ranging from 1 in 400 US African Americans for hemoglobinopathies, 1 in 4500 for congenital hypothyroidism, 1 in 15,000 for PKU, to 1 in 100,000 for most of the fatty acid disorders (except MCAD) and organic acidemias. Incidences of some common inborn errors are listed in **Table 1**.[3]

WHAT IS THE INHERITANCE PATTERN OF INBORN ERRORS OF METABOLISM?

Several patterns of inheritance are possible for the different IEMs. It is important to detail a three- to four-generation pedigree to evaluate the mode of inheritance accurately.

Autosomal recessive (AR) inheritance is the most common mode of inheritance for metabolic disorders. In this case, both the parents are heterozygous for the mutant gene; hence, they do not express the disorder, but the offspring are homozygous for that particular gene defect; hence, they express the defect and present clinically with the disorder. The family history is generally negative in the parents, but there may be a history of early neonatal deaths or a clinical disorder expressed as a concern. Consanguinity has an increased chance of expression of an AR disorder. Rarely, these mutations may occur de novo.[5]

X-linked recessive inheritance may also be seen in some IEMs, in which one copy of the mutated gene on the X-chromosome is sufficient for causing the disorder. Therefore, in this mode of inheritance, the disorder is transmitted from a carrier mother to her male offspring. Also, de novo mutations are observed with a much higher incidence in this pattern of inheritance.[5]

Autosomal dominant (AD) inheritance is a less common mode of inheritance for IEMs. The incidence of de novo mutations causing AD disorders is much higher than in other patterns of inheritance. AD transmission generally means that one of

Box 1
Some common disorders of inborn errors of metabolism

Disorders of carbohydrate metabolism

- Glycogen storage diseases
- Galactosemia

Disorders of amino acid metabolism (aminoacidurias)

- PKU
- Maple syrup urine disease
- Homocystinuria
- Tyrosinemia
- Nonketotic hyperglycemia

Disorders of organic acids metabolism (organic acidemias)

- Methylmalonic acidemia
- Propionic acidemia

Disorders of fatty acid oxidation

- Short-chain acyl coenzyme A (CoA) dehydrogenase (SCAD)
- Medium-chain acyl CoA dehydrogenase (MCAD)
- Long-chain acyl CoA dehydrogenase (LCAD)
- Very long-chain acyl CoA dehydrogenase (VLCAD)

Disorders of mitochondrial metabolism

- Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Glutaric aciduria
- Pyruvate dehydrogenase deficiency

Disorders of urea cycle

- Carbamyl phosphate synthetase deficiency
- Ornithine transcarbamylase deficiency
- Arginosuccinate deficiency

Peroxisomal disorders

- Adrenoleukodystrophy
- Zellweger syndrome
- Chondrodysplasia punctata
- Adult Refsum disease

Disorders of the steroid pathway

- Congenital adrenal hyperplasia
- Smith Lemli Opitz syndrome

Disorders of lipid storage

- Tay-Sachs disease
- Gaucher's disease
- Metachromatic leukodystrophy

Disorders of purine metabolism

- Lesch-Nyhan syndrome

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Box 1
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Transport disorders

- Cystinosis
- Hypercholesterolemia

Lysosomal disorders

- Mucopolysaccharidoses (MPS)
- MPS I (Hurler and Scheie disease)
- MPS II (Hunter disease)
- MPS III (Sanfilippo disease)
- MPS IV (Morquio disease)
- MPS VI
- MPS VII
- Glycoproteinosis
- Sphingolipidosis
- Combined defects
- I-cell disease

Disorders of metal metabolism

- Wilson disease
- Hemochromatosis
- Menkes disease

Others

- Hypothyroidism
- Hemoglobinopathies
- MELAS

the parents has the disease; 50% of the progeny have the disorder, and there is an equal gender distribution.[5]

A mitochondrial mode of inheritance is also seen in some IEMs. It is interesting to note that the mitochondrial DNA is always natural in origin; therefore, a mutation in

Table 1
Incidence of some inborn errors of metabolism

Congenital hypothyroidism	1:4500
Congenital adrenal hyperplasia	1:10,000
PKU	1:15,000
Galactosemia	1:30,000
Other aminoacidurias Homocystinuria MSUD	1:100,000
Organic acidemias	1:100,000
Fatty acid oxidation disorders	1:100,000
MCAD	1:15,000

Abbreviation: MSUD, maple syrup urine disease.

the mitochondrial DNA is inherited only from the mother. Mitochondrial DNA is prone to de novo mutations; hence, diseases transmitted in this manner may be found to be sporadic in occurrence.[5]

Box 2 lists the modes of inheritance of some common IEMs.[5]

HOW CAN YOU DIAGNOSE INBORN ERRORS OF METABOLISM IN A TIMELY MANNER?

Clinical Signs and Symptoms

IEMs may present early in the newborn period, later on in early or late childhood, or much later in adulthood. A high index of suspicion needs to be maintained for IEMs, because the symptomatology of these disorders is often nonspecific, and hence may lead to a workup for other medical conditions. The clinical presentation attributable to IEMs may be subclassified into a few broad categories.

Early-onset disorders

These present in the newborn period and can be further subgrouped into the following categories.

Silent disorders IEMs in this category do not cause life-threatening signs and symptoms in infancy but present later on in the early childhood period with mental retardation and developmental delay. This group includes PKU and congenital hypothyroidism.[6]

Disorders presenting with acute metabolic encephalopathy This group includes urea cycle disorders, organic acidemias, and aminoacidurias. These conditions may present with

Box 2
Modes of inheritance in some common inborn errors of metabolism

AR inheritance

- PKU
- Maple syrup urine disease
- Glycogen storage disease
- Galactosemia
- Organic acidurias
- MCAD
- Zellweger syndrome

X-linked recessive (XLR) inheritance

- Ornithine carbamylase deficiency
- Fabry disease
- Pyruvate dehydrogenase deficiency

AD inheritance

- Marfan syndrome
- Acute intermittent porphyria
- Familial hypercholesterolemia

Mitochondrial inheritance

- Kearns-Sayre syndrome
- Leigh syndrome

metabolic disturbances caused by accumulations of precursors or metabolites, which are reflected early in the newborn period with poor feeding, lethargy, persistent vomiting, seizures, hypotonia, apnea, respiratory distress, tachypnea, and tachycardia. These newborns usually end up getting a workup for sepsis with this type of presentation.[6]

These features are attributed to the toxic effect of metabolites on the central nervous system, causing a picture of a metabolic encephalopathy. The biochemical features are significant for metabolic acidosis, hyperammonemia, or other metabolic abnormalities.

Disorders presenting with metabolic acidosis This group generally includes organic acidemias. These neonates exhibit severe metabolic acidosis with an increased anion gap along with elevated organic acid intermediates specific for the defect or lactate. Lactic acidosis is present in disorders of pyruvate metabolism including pyruvate dehydrogenase deficiency, defects in gluconeogenesis, pyruvate carboxylase deficiency, and mitochondrial disorders.[7]

Disorders presenting with hyperammonemia Many newborns with defects in the urea cycle, organic acidemias, and transient hyperammonemia of the newborn (THAN) present with metabolic encephalopathy and hyperammonemia.

Disorders presenting later on in childhood

This group of IEMs includes lysosomal storage disorders, Tay-Sachs disease, Gaucher's disease, and metachromatic leukodystrophy. These disorders generally present with progressive neurologic deterioration.[8]

Other clinical signs and symptoms, including generalized nonspecific manifestations; neurologic signs and symptoms; developmental disorders; dysmorphic phenotypes; and disorders in the gastrointestinal, hematologic, and dermatologic systems, are summarized in **Box 3**.[6,7,9]

One of the most unique and intriguing features of IEMs is the presence of specific odors in some of these metabolic disorders. Some of these are listed in **Table 2**.[7,9–11]

HOW TO MAKE A TIMELY DIAGNOSIS

Clinical presentation should raise suspicion of an IEM. Details of history, including a family history of consanguinity, similar disorders in close and extended family, and any neonatal deaths, should be sought. Details of relation of symptoms to eating in terms of timing and in relation to specific type of food consumption, cyclic pattern of vomiting, lethargy, and behavioral changes should be inquired about. Signs manifested on clinical examination, including hepatosplenomegaly, skin lesions, and neurologic deficits, should guide one toward an initial laboratory workup. In children who may be critically ill, it is important to consider and then rule out options in the differential diagnosis of the specific clinical scenario. General laboratory investigations indicated are listed in **Box 4**.[6,12] Additional specific biochemical workup should be decided on based on details of the history, clinical presentation, results of preliminary laboratory investigations, and suspicion of a specific IEM. It is preferred that extra blood and urine samples be drawn and saved for later investigations. A second tier of laboratory workup that may be indicated is listed in **Box 5**. Special precautions may be needed in the drawing and processing of some of these samples. The samples for plasma ammonia, lactate, and pyruvate should be obtained without the use of a tourniquet and need to be transported on ice for immediate analysis in the laboratory; pyruvate samples should be collected in perchlorate to prevent degradation.[12]

Box 3
Important clinical signs and symptoms of inborn errors of metabolism

Dysmorphism

- Peroxisomal disorders
- Zellweger syndrome
- Lysosomal storage disorders
- Mucopolysaccharidosis
- Mucolipidosis
- Gangliosidosis
- Homocystinuria
- Smith-Lemli-Opitz syndrome

Neurologic manifestations

- Seizures: seen in any IEM because of toxic metabolites
- Pyridoxine dependent
- Folinic acid dependent
- Secondary to hypoglycemia
- Peripheral neuropathy
- Mitochondrial disorders
- Lysosomal storage disorders
- Hypotonia
- Fatty acid oxidation disorders
- Peroxisomal disorders
- Urea cycle disorders
- Mitochondrial disorders
- Pompe's disease
- Glycogen storage disorders
- Myopathy
- Glycogen storage diseases
- Fatty acid oxidation disorders
- Mitochondrial disorders
- Ataxia
- Peroxisomal disorders
- Mitochondrial disorders
- Lysosomal storage disorders
- Lethargy or coma
- Aminoacidurias
- Organic acidemias
- Urea cycle disorders
- Fatty acid oxidation defects
- Mitochondrial disorders

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Box 3
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Developmental delay

- May occur in all IEMs: rare

Gastrointestinal manifestations

- Hepatomegaly or splenomegaly
- Lysosomal storage disorders
- Glycogen storage diseases
- Jaundice or liver dysfunction
- Galactosemia
- Fatty acid oxidation disorders
- Tyrosinemia
- Peroxisomal disorders
- α_1-Antitrypsin deficiency
- Niemann-Pick disease

Cardiac manifestations

- Hypertrophic cardiomyopathy
- Glycogen storage disease: type 2
- Pompe's disease
- Mucopolysaccharidosis
- Dilated cardiomyopathy
- Fatty acid oxidation disorders
- Organic acidemias
- Mitochondrial disorders

Ophthalmologic manifestations

- Lenticular cataracts
- Galactosemia
- Mitochondrial disorders
- Corneal opacities
- Fabry disease
- Mucopolysaccharidosis
- Cystinosis
- Cherry red macular spots
- Tay Sachs disease
- Galactosialidosis
- Niemann-Pick disease
- GM1 gangliosidosis
- Dislocated lens
- Homocystinuria
- Marfan syndrome
- Molybdenum cofactor deficiency

- Sulfite oxidase deficiency
- Retinitis pigmentosa
- Abetelipoprotemia
- Peroxisomal disorders
- Mitochondrial disorders

Hydrops fetalis: nonimmune

- Lysosomal storage disorders
- Mitochondrial disorders
- Neonatal hemochromatosis
- Glycogen storage disease type IV

Dermatologic manifestations

- Skin rash
- Acrodermatitis enteropathica
- Ichthyosis
- X-linked ichthyosis
- Sjögren-Larsson syndrome
- Angiokeratomas
- Fabry disease
- Lysosomal storage disorders

Table 3 lists correlations with some alterations in laboratory evaluations with possible IEMs.[12]

WHAT IS THE ROLE OF NEWBORN SCREENING PROGRAMS IN EARLY DIAGNOSIS AND PREVENTION OF MORBIDITY AND MORTALITY?

NS for genetic disorders for all newborns endeavors to make early and timely diagnosis of otherwise potentially life-threatening or debilitating inherited disorders. For a genetic disorder to be considered for NS, several criteria should be justified. These include the following: the particular genetic disorder should result in significant morbidity or mortality; should have a known mechanism of pathogenesis; should offer

Table 2
Odors characteristic of some inborn errors of metabolism

Odor	Metabolic Disorder
Fruity odor	Methylmalonic acidemia Propionic acidemia
Burnt sugar/maple syrup-like	Maple syrup urine disease
Mousy/musty	Phenylketonuria
Sweaty socks, cheese-like	Isovaleric acidemia
Malt-like	Methionine malabsorption
Cat urine	3-Methylcrotonic acidemia 3-Hydroxy, 3-methyl glutaric aciduria
Fish-like	Trimethylaminuria Carnitine excess
Cabbage-like	Tyrosinemia

Box 4
Initial laboratory investigations for inborn errors of metabolism

Blood

- Complete blood cell count
- Comprehensive metabolic panel, including
  - Liver and kidney function
  - Electrolytes
  - Uric acid
  - Serum ammonia
  - Arterial blood gas

Urine

- Urinalysis
- pH
- Color
- Odor
- Specific gravity
- Ketones
- Urine-reducing substances

Box 5
Additional laboratory investigations for inborn errors of metabolism

Blood or plasma

- Quantitative amino acids
- Lactate
- Aldolase, creatine kinase
- Acyl carnitine profile
- Lipid profile

Urine

- Quantitative amino acids
- Organic acids
- Myoglobin

Imaging

- MRI: brain
- Echocardiogram

Biopsy

- Muscle biopsy
- Skin biopsy

Genetic studies

- As specifically indicated

Table 3
Laboratory findings in inborn errors of metabolism

Metabolic Acidosis with Increased Anion Gap	Organic Acidemias
Respiratory alkalosis	Urea cycle disorders
Hyperammonemia	Urea cycle disorders Organic acidemias
Lactic acidosis	Mitochondrial disorders Glycogen storage diseases Disorders of Glyconeogenesis Pyruvate metabolism Organic acidemias Fatty acid oxidation disorders Aminoacidurias
High lactate/pyruvate ratio (normal: 10:1 to 20:1)	Mitochondrial disorders Pyruvate carboxylase deficiency
Acylcarnitine profile abnormalities	Fatty acid oxidation disorders Organic acidemias
Hypoglycemia With ketosis Without ketosis	Glycogen storage disease Organic acidemias Maple syrup urine disease Fatty acid oxidation disorders Disorders of ketogenesis
Quantitative amino acid profiles	Specific defects in amino acid metabolism have specific patterns
Urine organic acids	Specific defects in amino acid metabolism have specific patterns

the potential of prevention or adequate treatment; should have an easy, inexpensive, and rapid test available for screening; should have reliable follow-up confirmatory testing available; and the cost-to-benefit ratio of incorporating the testing in the NS should be less than cost of diagnosing, testing, and managing the condition otherwise.[3,13]

NS was initially stated for PKU in 1959 by Guthrie; since then, it has expanded to include an extended list of predominantly IEMs and some hematologic and endocrine disorders.[8] Advances in biochemical testing with tandem mass spectrometry have facilitated the incorporation of many genetic disorders in the NS. Common disorders screened for are listed in **Box 6**.[3,14,15] Most NS programs in the United States are state controlled and state specific, and different states include different disorders in their specific NS programs. Many other countries worldwide offer variable genetic NS programs as well. It is therefore important to remember to look into the specific screening program that a particular newborn underwent. Moreover, it is imperative to realize that a normal newborn screen does not rule out all inborn or inherited disorders. The aim of the NS is to make an early diagnosis for the conditions being screened for. There may be false-positive and false-negative results. Once positive NS is obtained for an IEM, the primary care physician or pediatrician should perform a clinical examination and make an assessment and then seek consultation with the metabolic or genetic specialist who has expertise in the field for initiating further diagnostic testing and implementing the required therapeutic measures. These patients should be closely followed, preferably by the metabolic specialists. Early therapeutic intervention can lower morbidity and mortality significantly.

Box 6
Genetic disorders available for screening on the newborn screening programs

Amino acid disorders
- PKU
- Homocystinuria
- Tyrosinemia
- Maple syrup urine disease
- Nonketotic hyperglycinemia
- Citrullinemia
- Arginosuccinate deficiency
- Hyperornithinemia

Carbohydrate disorders
- Galactosemia

Fatty acid oxidation disorders
- SCAD
- MCAD
- LCAD
- VLCAD
- Carnitine palmityl transferase (CPT) deficiency

Organic acidemias
- Methyl malonic acidemia
- Propionic acidemia
- Isovaleric acidemia
- Glutaric acidemia
- β-methyl crotonyl CoA carboxylase (MCC) deficiency

Other IEMs
- Biotinidase deficiency

Endocrine disorders
- Hypothyroidism
- Congenital adrenal hyperplasia

Hematologic disorders
- Various hemoglobinopathies

The aim of the NS is to make an early diagnosis for the previously mentioned conditions. There may be false-positive and false-negative results. Once positive NS is obtained for an IEM, the primary care physician or pediatrician should initiate dialog with the metabolic or genetic specialist who has expertise in the field for initiating further clinical examination and assessment, diagnostic testing, and implementation of the required therapeutic measures. These patients should preferably be followed closely by the metabolic specialist. With this early intervention, morbidity and mortality can be significantly lowered.

WHAT ARE THE PRINCIPLES OF TREATMENT FOR INBORN ERRORS OF METABOLISM?

Treatment Options for Inborn Errors of Metabolism Broadly Include Two Main Options

General principles of treatment

The general measures of treatment are put into place before a definitive diagnosis of a specific IEM is made. Some of these interventions include withholding of all dietary oral intake until some specific investigations and guidelines can be established, preferably after consultation with metabolic specialists. In most cases, intravenous dextrose fluid with saline may be initiated after adequate hydration with normal saline. Acidosis may also need correction by replacement with bicarbonate.[16]

Specific therapeutic measures

The specific therapeutic options are disease specific and are instituted once a particular IEM is diagnosed. These measures are geared toward addressing the specific concerns of the particular underlying defect. **Fig. 1** represents the underlying approaches to treatment strategies for various IEMs.[8]

Table 4 outlines some of the specific therapeutic options available for various metabolic disorders.[8]

WHAT IS THE LONG-TERM PROGNOSIS?

The clinical outcome of children depends on multiple factors. These include severity of the underlying metabolic defect, ability to make the diagnosis early, availability of specific adequate treatment options, and appropriate institution of the therapeutic measures. Depending on all these variables, some IEMs have a relatively better prognosis than others. Many of these children are living longer but many may be at high risk for developing progressive neurologic deficits, learning disabilities, and mental retardation. A study done to evaluate response to treatment in IEMs revealed

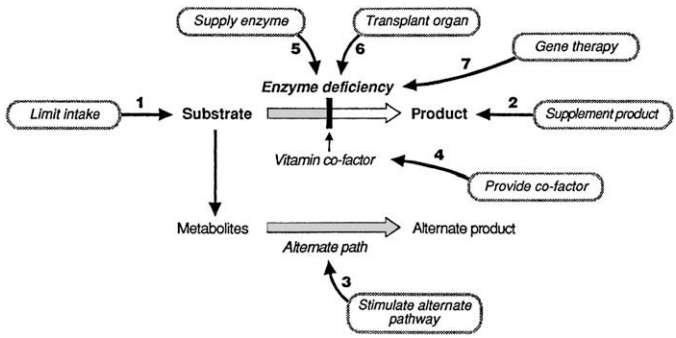

Fig. 1. Approaches to treatment of IEMs. Treatment can be directed at (1) limiting the intake of a potentially toxic compound, (2) supplementing the deficient product, (3) stimulating an alternate metabolic pathway, (4) providing a vitamin cofactor to activate residual enzyme activity, (5) supplying the enzyme itself, (6) transplanting a body organ containing the deficient enzyme, and (7) gene therapy. (*From* Batshaw ML, Tuchman M. PKU and other inborn errors of metabolism. In: Batshaw ML, editor. Children with disabilities. 5th edition. Baltimore: Paul H. Brookes Publishing Co.; 2002. p. 339; with permission.)

Table 4
Examples of treatment approaches for inborn errors of metabolism

Approaches	Disorder	Specific Treatment
Restrict diet	PKU	Phenylalanine restriction
	Maple syrup urine disease	Branch chain amino acid restriction
	Galactosemia	Galactose restriction
Supplement deficient product	Congenital hypothyroidism	Synthroid
	Glycogen storage disease	Cornstarch
	Urea cycle disorders (except argininemia)	Arginine
Stimulate alternate pathway	Urea cycle disorders	Sodium phenylbutyrate
	Organic acidemias	Carnitine
	Isovaleric acidemia	Glycine
	Wilson disease	Penicillamine
Supply vitamin cofactor	Multiple carboxylase deficiency	Biotin
	Homocystinuria	Pyridoxine
	Methylmalonic acidemia	Vitamin B_{12}
Replace enzyme	Severe combined immunodeficiency (SCID)	PEG-ADA
Transplant organ	Metachromatic leukodystrophy	Bone marrow
	Ornithine transcarbamylase deficiency	Liver
	Tyrosinemia	Liver
	Glycogen storage disease	Liver
Use gene therapy	SCID	Retrovirus gene transfer
Use other therapies or emerging technologies	Inhibit pathway: tyrosinemia	NTBC
	Use substrate deprivation: PKU	Recombinant enzyme

From Batshaw ML, Tuchman M. PKU and other inborn errors of metabolism. In: Batshaw ML, editor. Children with disabilities. 5th edition. Baltimore: Paul H. Brookes Publishing Co.; 2002. p. 340; with permission.

improvement in clinical parameters in approximately half of the patients who have metabolic disorders.[17]

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