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Approach to diagnosis of metabolic diseases

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Abstract. Inborn errors of metabolism are generally categorized as rare diseases. Their presentations are often so subtle and insidious as to cause daunting diagnostic challenges for even the most astute clinicians. Thus, irreversible morbidity and preventable mortality have been unavoidable until recent decades because of delayed diagnoses. This unfortunate circumstance has led to newborn screening programs worldwide for 40 or more hereditary metabolic disorders beginning with the dramatic improvements for patients with phenylketonuria in the 1960's. Increasingly sophisticated testing procedures such as tandem mass spectrometry and other multiplex technologies applied to dried blood spot specimens are now having greater impact without raising costs significantly. The advent of next generation sequencing methods is likely to stimulate further progress and lead to whole genome or exome sequencing as prenatal and neonatal screening expands further. With early diagnosis through screening and expedited therapies better outcomes are routinely possible, and even preventive therapies amounting to "cures" can be anticipated through research.

Keywords: Gene, genetic mutations, inborn errors of metabolism, hyperglycemia

1. Conceptual overview

The term "inborn errors of metabolism" was first used by Sir Archibald Garrod in his Croonian Lectures in 1908 [1] and in his monograph *Inborn Errors of Metabolism* in 1909 [2]. He defined these inborn errors as genetically determined diseases caused by blocks in the metabolic pathways due to deficient activity of an enzyme [3]. From Sir Garrod's observations of patients with alkaptonuria, albinism, cystinuria, and pentosuria, he developed the concept that certain diseases of lifelong duration arise because an enzyme governing a single metabolic step is reduced in activity or missing altogether [4]. Most of these disorders may be classified as rare diseases because newborn screening data show clearly that their incidence ranges from 1:4,000 for congenital hypothyroidism to >1:250,000 (many disorders such as Maple Syrup Urine Disease (branched chain ketoaciduria).

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The definition of an inborn error of metabolism is arbitrary. Scriver et al. [5] include several hundred diseases with definite biochemical genetic bases. McKusick's catalog [6] contains several thousand diseases and disease states whose genetic abnormalities are described or assumed. Scriver et al. [5] solved the problem of exclusivity by adding "molecular" before encompassing every disease of the "textbook of the future." The 2nd Edition of *Metabolic Diseases: Foundations of Clinical Management, Genetics, and Pathology* [7] is limited to those diseases with either: 1) recognized biochemical abnormalities supplemented with pathologic and genetic information, and in which a mutation leads to an enzyme deficiency that causes a metabolic disease such as phenylketonuria (PKU); or 2) disorders associated with known genetic mutations that have altered cellular physiology such as the chloride channel defect in cystic fibrosis or caused severe structural, cellular, or subcellular abnormalities. Emphasis in the book has been given to the more common and/or well defined hereditary biochemical/metabolic disorders. Prototype conditions such as Lesch Nyhan Disease, an excellent example of a nucleotide (purine) metabolism disorder, are also emphasized.

Investigation of the molecular functions of genes has determined that they control the cellular metabolic function in the pathogenesis of disease far beyond that commonly understood as a metabolic disease. The genetics of variant human phenotypes is discussed by Scriver et al. [5] and Champion [8]. The relationship between gene and enzyme was described as "one gene, one enzyme" by Beadle and Tatum [9–11]. Tatum expanded this concept as follows: 1) all biochemical processes in all organisms are under genetic control; 2) these biochemical processes are resolvable into series of individual stepwise reactions; 3) each biochemical reaction is under the ultimate control of a different single gene; and 4) mutation of a single gene results only in an alteration in the ability of the cell to carry out a single primary chemical reaction.

Pauling et al. [12] discovered direct evidence that human mutations actually produce an alteration in the primary structure of proteins. Their seminal research revealed a valine substitution for glutamic acid in sickle cell hemoglobin. Ingram [13] showed that inborn errors of metabolism were caused by mutant genes that produced abnormal proteins whose functional activities were altered.

It is estimated that some 30,000 genes constitute the human genome. A variety of genome maps are available, including some that are disease specific such as the "cancer cell map" [14]. The genome map is being constantly improved, with updated gene sequences and locations of intronic elements, revised lists of benign SNPs, additional reference genomes, databases of variant frequencies that are ethnicity-specific, and associations of specific genes with specific human diseases. In addition, combinations of genes can result in a metabolic error. Thus, although ~7000 hereditary metabolic disorders are currently known, at least the same number of significant genetic errors as the number of genes seems theoretically possible, and an undetermined but large percentage of these may cause biochemical disorders with clinical impact. An estimation of genetic disease frequencies is shown in Table 1.

Table 1
Estimation of genetic disease frequencies

- 1% of live-born infants have monogenic disease
- 5% of individuals under 25 can expect to have a disease due to a genetic component
- 6%–8% of hospitalized children have monogenic disease
- 29%–41% of hospitalized children have gene-influenced disease
- 60% of older individuals have genetically influenced diseases, if multifactorial diseases are included
- 100% of humans carry 6–8 lethal genes
- 20%–30% of all infant deaths are due to genetic disorders
- 30%–50% of post-neonatal deaths are due to congenital malformations
- 50% of mental retardation has a genetic basis

2. Diagnostic strategies and tactics

Clinical diagnosis of metabolic disease is made by specific tests, biochemical analyses, and histologic and genetic studies that are discussed by Leonard et al. [15] and Cleary et al. [16]. New methods such as next generation sequencing of genes [17, 18] and even whole genome sequencing [19, 20] are facilitating diagnoses and other goals such as genetic counseling. Clinicians seek diagnosis, effective treatment, an understanding of prognosis, and the capability to explain and counsel patients and their families. Parents and patients appreciate gaps in knowledge but may be left seriously disappointed or angry without a cure. Fortunately, our increased genetic knowledge and better understanding of molecular pathophysiology of the past two decades has led to dramatic improvements in therapies using novel methods such as small molecule modulators of defective proteins [e.g., CFTR modulators for cystic fibrosis [21], gene therapy [22], and stem cell infusions [23]]. Thus, investments in expedited diagnostic strategies such as newborn screening can pay great dividends when well targeted, highly effective therapies are available.

Identification of inborn errors of metabolism provides the basis for diagnosis, prognosis, genetic counseling, and, in an increasing number of patients, targeted treatments aimed directly at the fundamental defect. Many infants and children present as medical emergencies and life-preserving treatment is begun before a definite diagnosis is available. Diagnosis should be made rapidly and the implications and complexities of treatment explained in detail. Metabolic disease is usually not suspected in patients until more common diseases are considered. Those children with a history of consanguinity or those in families with a history of unexplained death, multiple spontaneous abortions, or previously diagnosed metabolic diseases have an increased likelihood of a metabolic disease. Frequently, children (and some adults) with metabolic diseases are first seen as critically ill patients with non-specific findings. Dehydration, acidosis, vomiting, ammonemia, hypoglycemia, or seizures must be managed aggressively. Inborn metabolic errors may be suspected if response to emergency treatment is not as expected.

Metabolic diseases can be divided into 3 main categories as listed in (Table 2). The majority of these disorders are inherited as autosomal recessive traits. Some such as Duchenne muscular dystrophy are X-linked. A few are inherited as dominant traits, and mitochondrial disorders form a genetically separate category. Mitochondrial enzymes are coded by both the maternal nuclear genome and by the mitochondrial DNA.

Clinical findings associated with metabolic diseases are listed in Table 3. It has been well recognized that symptoms may be quite variable, even in a group of patients with the same mutation. Thus, it has become clear that genetic modifiers may alter the expression of signs/symptoms and that gene-environment and nutrition-metabolism relationships can also influence the disease liability of pathologic genetic mutations.

The newborn with a severe metabolic abnormality may present with symptoms of apparent sepsis or asphyxia. These symptoms usually consist of irritability, failure to feed or suck, flaccidity, or coma. Previous miscarriages or sudden unexpected death in a sibling should trigger a screening investigation for metabolic disease. Sophisticated newborn screening using 4-5 blood spots on filter paper [“Guthrie cards” named for Robert Guthrie, the originator of population-based newborn screening with dried blood spots [24]], combined with tandem mass spectrometry as discussed by Ziadeh et al. [25] and Millington et al. [26] or molecular analyses [21] can identify a number of life-threatening diseases with a single, multiplex assay. The hereditary metabolic diseases that can now be screened for from filter paper blood spots in the newborn are listed in Table 4. Recently, severe combined immunodeficiency (SCID) has been added in many regions as well as “point of care” screening methods such as oxygen saturation measurements for critical congenital heart diseases.

Metabolic abnormalities may be suspected in infants with *hydrops fetalis* Table 3, or with placental abnormalities. Routine placental examination may disclose fetal metabolic storage disease by the

Table 2
Categories of metabolic disease (Examples)

Large Complex Molecule Diseases
Complex lipid degradation (Gaucher, Niemann-Pick, Tay-Sachs, metachromatic leukodystrophy)
Glycoprotein degradation (fucosidase and mannosidase deficiency)
Mucopolysaccharidoses (Sanfilippo and Hurler syndrome)
Lipofuscin storage disorders (Batten disease)
Glycogen storage disease type I (von Gierke disease), type II (Pompe disease), type III (debrancher deficiency)
Peroxisomal disorders (Zellweger syndrome)
Small Molecule Diseases
Amino acid metabolism disorders (phenylketonuria, maple syrup urine disease, homocystinuria, tyrosinemia)
Ammonia metabolism disorders (ornithine transcarbamylase deficiency)
Organic acid metabolism disorders (methylmalonic acidemia, propionic acidemia, isovaleric acidemia)
Monosaccharides (galactosemia, hereditary fructose intolerance)
Pyruvic and lactic acid metabolism disorders (primary lactic acidosis, mitochondrial disorders)
Fatty acid metabolism disorders (medium-chain acyl-CoA dehydrogenase deficiency)
Purines and pyrimidine metabolism disorders (Lesch-Nyhan syndrome)
Vitamin and cofactor metabolism disorders (biotinidase deficiency)
Other Diseases
Metal metabolism disorders (Wilson and Menkes disease, hemochromatosis)
Lipoprotein metabolism disorders (Abetalipoproteinemia, familial hypercholesterolemia)
Porphyrin metabolism disorders (porphyria)
Membrane transport disorders (cystinuria, cystinosis)
Intestinal disaccharidases
Collagen and connective tissue disorders (Ehlers-Danlos disease, Marfan syndrome)
Congenital adrenal hyperplasia
Hyperinsulinism

presence of vacuolations of syncytiotrophoblasts, intermediate trophoblasts, and stromal Hofbauer cells. Suspected metabolic errors in the newborn are emergencies and require prompt identification and treatment. After obtaining the appropriate specimens for testing, emergency treatment must be instituted. If the patient dies, regardless of age, preparation should be made for a metabolic disease autopsy as discussed by Ernst et al. [27].

Pregnancy may occur in patients with metabolic diseases. Some of these conditions can be teratogenic. Many such pregnancies can be successfully managed with treatment. Treatment of these disorders is discussed in each chapter.

Examples of inborn errors of metabolism potentially occurring in high frequency among specific ethnic groups are listed in Table 5. However, it should be noted that some of these disorders are quite rare now in the era of prenatal diagnosis. For instance, the incidence of Tay Sachs disease in targeted Jewish populations is extremely low worldwide [28, 29].

The most common presentations of inborn errors are without gross physical anomalies and include disorders of amino acid, fatty acid, organic acid, and carbohydrate metabolism Table 6. Others present with dysmorphic features, neonatal deaths, self-mutilation, abnormal body or urine odor, hypotonia, deafness, or recurrent acidosis with or without ketosis. Failure to recognize and, when possible, treat these infants can result in irreversible neurologic damage.

Diagnostic strategy consists of meticulous attention to history and physical examination followed by appropriate screening tests, including biochemistry, radiology, or other modalities, and specific enzyme, protein, or gene analysis. Special educational services for children with inborn errors of metabolism may be available and therefore accuracy of diagnosis is essential as discussed by Powell et al. [30].

Table 3
Clinical findings associated with specific metabolic diseases

Abdomen
Hepatomegaly
Galactosemia
Glycogen storage disease, type 1
Hereditary fructose intolerance
Fructose-1,6-diphosphatase deficiency
Methylmalonic acidemia
Propionic acidemia
Glutaric acidemia, type II
Very-long-chain acyl-CoA deficiency
Medium-chain acyl-CoA deficiency
Short-chain acyl-CoA deficiency
Long-chain 3-OH acyl-CoA, dehydrogenase deficiency
Carnitine transporter defect
Carnitine palmityl transferase I o II deficiency
Acylcarnitine translocase deficiency
3-hydroxy-3-methylglutaryl-CoA lyase deficiency
Phosphoenolpyruvate carboxykinase deficiency
Mitochondrial respiratory/electron transport chain defects
Hereditary tyrosinemia, type I
Argininosuccinicaciduria
α_1-Antitrypsin deficiency
Smith-Lemli-Opitz syndrome
Zellweger syndrome
Neonatal adrenoleukodystrophy
Nieman-Pick disease, type C
Hepatosplenomegaly
GM_1 gangliosidosis
I-cell disease
Gaucher disease, type I
Niemann-Pick disease, type A, C
Galactosialidosis
Sialidosis
Mucopolysaccharidosis, type VII
Wolman disease
Pancreatitis
Glycogen storage disease, type I
Lipoprotein lipase deficiency
Homocystinuria
Hydroxymethylgiutaryl-CoA lyase deficiency
Methylmalonic acidemia
Propionic acidemia
Pearson syndrome

Chest
Cardiomyopathy
Glycogen storage disease, type I
Glycogen storage disease, type II
Glycogen storage disease, type III
Electron transport chain abnormalities
Disorders of fatty acid oxidation
Mucopolysaccharidoses
Myocardial infarction
Familial
Hypocholesterolemia
Fabry disease
Homocystinuria
Menkes disease

Diarrhea
Lysinuric protein intolerance
Shwachman syndrome
Johansson Blizzard syndrome
Pearson syndrome
Congenital chloride diarrhea
Glucose galactose malabsorption
Lactase deficiency
Sucrase deficiency
Abetalipoproteinemia
Wolman disease
Diarrhea (Persistent)
Sucrase isomaltase deficiency
Acrodermatitis enteropathica
Congenital folate malabsorption

Dysmorphic Features
Glutaric aciduria, type II
Glomerulopathy
Renal cystic dysplasia
Cerebral dysgenesis
Facial dysmorphism
Congenital heart disease
Genital anomalies
Pyruvate dehydrogenase deficiency
Microcephaly
"Fetal alcohol" facies
Agenesis of corpus callosum
Peroxisomal Disorders
Zellweger Syndrome
Renal microcysts
Epiphyseal calcification
Facial dysmorphism
Congenital heart disease
Cerebral dysgenesis
Hepatopathy
Infantile Refsum disease
Facial dysmorphism
Hepatopathy
Rhizomelic chondrodysplasia punctata

Table 3
(*Continued*)

Facial dysmorphism
Rhizomelic limb shortening
GM_1 gangliosidosis
Frontal bossing, low-set ears
Congenital adrenal hyperplasia
Ambiguous genitalia
Sialidosis
Coarse facial features, stippled epiphyses
Mucolipidosis II
Coarse facial features
Mucopolysaccharidoses
Coarse facial features
Infantile sialic acid storage disease
Coarse facial features
β-Hydroxyisobutyryl-CoA deacylase deficiency
Congenital heart defects
Agenesis of corpus callosum
Dysmorphic facies
Gaucher-like storage disease
Arthrogryposis
Muscle phosphorylase deficiency
Arthrogryposis
Smith-Lemli-Opitz syndrome
Genital and digital abnormalities

Ears
Otic atrophy
Pyruvate dehydrogenase com plex deficiency
Leigh disease
Zellweger syndrome

Extremities
Arthritis
Alkaptonuria
Gaucher disease, type I
Lesch-Nyhan disease
Farber disease
I-cell disease
Mucolipidosis III
Homocystinuria
Mucopolysaccharidosis IS, HS
Bone or limb deformity
Dyostosis Multiplex
Hurler, Hurler-Scheie disease
Hunter disease
Sanfilippo disease
GM1 gangliosidosis
Mucolipidosis II, I-cell disease
Mucolipidosis III
Galactosialidosis
Maroteaux-Lamy disease
Sly disease
Multiple sulfatase deficiency
Osteoporosis and/or fractures
Propionic acidemia
Methylmalonic acidemia
Glycogen storage disease, type I
Homocystinuria
Adenosine deaminase deficiency
Lysinuric protein intolerance
Menkes disease
Infantile Refsum disease
Gaucher disease
I-cell disease

Eyes
Cataract
Galactosemia
Lowe syndrome
Mitochondrial respiratory electron transport chain defects
Zellweger syndrome
Rhizomelic chondrodysplasia punctata
Mevalonic aciduria
Corneal Clouding
I-cell disease
Steroid sulfatase deficiency
Dislocated lens
Methionine synthetase deficiency
Sulfite oxidase deficiency
Macular cherry-red spot
GM_1 gangliosidosis
Galactosialidosis
Niemann-Pick Disease, type A
Tay-Sachs disease (GM_2 gangliosidosis)
Retinitis pigmentosa
Mitochondrial respiratory electron transport chain defects
Methylmalonic acidemia/Homocystinuria
Sjögren-Larsson syndrome
Zellweger syndrome
Neonatal adrenoleukodystrophy
Infantile Refsum disease
Abetalipoproteinemia
Long-chain 3-OH acyl-CoA dehydrogenase deficiency

Head
Alopecia

Table 3
(*Continued*)

Multiple carboxylase deficiency
Cerebral calcification
Adrenoleukodystrophy
Abnormalities of folate metabolism
L-2-Hydroxyglutaric aciduria
Biopterin abnormalities
Coarse facial features
GM_1 gangliosidosis
I-cell disease
Mucopolysaccharidosis, type VII
Sialidosis
Galactosialidosis
Macrocephaly
4-Hydroxybutyric aciduria
Glutaric aciduria, type I
L-2-Hydroxyglutaric aciduria
Neonatal adrenoleukodystrophy
Tay-Sachs disease
Hurler disease
Krabbe disease
Multiple sulfatase deficiency
Canavan disease
Mannosidosis
3-Hydroxy-3-methylglutaric aciduria
Pyruvate carboxylase deficiency
Multiple acyl-CoA dehydrogenase deficiency
Microcephaly
Short-chain Acyl-CoA dehydrogenase deficiency
Mitochondrial respiratory electron transport chain defects
Leigh disease
Steely hair
Menkes disease

Hematology
Hematologic abnormalities
Leukopenia with or without thrombopenia and anemia
Methylmalonic acidemia
Propionic acidemia
Isovaleric acidemia
3-Oxothiolase deficiency
Abnormalities of folate metabolism
Transcobalamin II deficiency
Shwachman syndrome
Pearson syndrome
Johansson Blizzard syndrome
Megaloblastosis
Cobalamin metabolic errors:
Methylmalonic acidemia
Homocystinuria
Transcobalamin II deficiency
Orotic aciduria
Mevalonic aciduria
Pearson syndrome
Abnormalities of folate metabolism
Shwachman syndrome
Johansson Blizzard syndrome

Hydrops fetalis
Gaucher disease
GM_1 gangliosidosis
Salla disease
Sialidosis
Wolman disease
β-Glucuronidase deficiency
Congenital disorders of protein glycosylation
Deficiencies of red cell glycolytic/pentose phosphate pathway enzymes (eg, G6PDH deficiency, private kinase deficiency)
Farber disease
Fumarase deficiency
GSD IV
MPS VII (Sly disease)
MPS IVA (Morquio type A)
Mucolipidosis I (Sialidosis)
Mucolipidosis II (I-cell disease)
Neonatal hemochromatosis
Niemann-Pick C
Primary carnitine deficiency
Respiratory chain disorders
Sialic acid storage disease
Morquio syndrome
Neuraminidase deficiency
Myotonic dystrophy
Perinatal iron storage syndrome
Carnitine deficiency
Niemann-Pick type C
I-cell disease
Farber disease
Mucopolysaccharidosis type VII
Carbohydrate-deficient glycoprotein storage disease

Mouth and throat
Macroglossia
GM_1 gangliosidosis
Macroglossia

Table 3
(*Continued*)

Neurological
MLD, Niemann-Pick A and B, and Gaucher, type III
Gaucher disease, type II
Glutaric acidemia, type I
Krabbe disease
Crigler-Najjar syndrome
Phenylketonuria caused by a biopterin defect
Stroke-like episodes
Carbamoyl phosphate synthetase
MELAS
Carbohydrate deficient glycoprotein storage disease
Ethylmalonic aciduria
Fabry disease
Glutaric aciduria, type I
Homocystinuria
Isovaleric acidemia
Menkes disease
3-MTHF reductase deficiency
Methylmalonic acidemia
Ornithine transcarbamylase deficiency
Propionic acidemia
Purine nucleoside phosphorylase deficiency

Odor
Sweaty feet, strong
Glutaric aciduria (type II)
Isovaleric acidemia
Mousy or musty
Phenylketonuria
Maple syrup
Maple syrup urine disease
Tomcat urine
β-Methylcrotonylglycinuria
Cabbage
Methionine malabsorption
Rotting fish
Trimethylaminuria
Rancid fishy or cabbage
Tyrosinemia
Hoplike
Oasthouse disease
Swimming pool
Hawkinsinuria

Psychiatric
Sanfilippo syndrome (MPS III)
Hunter syndrome (MPS II)

X-linked ALD
Late-onset MLD
Late-onset GM2 gangliosidosis
Lesch-Nyhan syndrome
Porphyria
Wilson disease
Cerebrotendinous xanthomatosis
UCED
Homocystinuria due to MTHF reductase deficiency
Adult-onset NCL

Skin
Angiokeratoma
Fabry disease
GM_1 gangliosidosis
Fucosidosis
Galactosialidosis
Sialidosis
Desquamating, eczematous, or vesiculobullous lesions
Acrodermatitis enteropathica
Multiple carboxylase deficiency
Methylmalonic acidemia
Propionic acidemia
Hepatoerythropoietic porphyria
Congenital erythropoietic porphyria
Ichthyosis
Multiple sulfatase deficiency
X-linked ichthyosis (steroid sulfatase deficiency)
Gaucher disease
Krabbe disease
Refsum disease
Sjögren-Larsson syndrome
Nodules
Farber disease (Ceramidase deficiency)
Thick skin
I-cell disease
GM_2 gangliosidosis
Mucopolysaccharidosis, type VII
Sialidosis
Galactosialidosis
Xanthomas
Familial hypercholesterolemia
Lipoprotein lipase deficiency
Niemann-pick disease

ALD, adrenoleukodystrophy; MLD, metachromatic leukodystrophy; UCED, urea cycle enzyme defects; MTHF, methylenetetrahydrofolate; NCL, neuronal ceroid lipofuscinosis; MELAS, myoclonic epilepsy, lactic acidosis, and stroke.

Table 4
Newborn screening panel: Core panel and secondary targets*

	MS/MS			
Acylcarnitines		Amino acids		
9 Organic Acidemia Disorders	5 Fatty Acid Oxidation Defects	6 Aminoacidopathies	3 Hemoglobinopathies	7 Other Genetic Disorders
		Core panel		
Isovaleric academia	Medium-chain acyl-COA dehydrogenase deficiency	Phenlketonuria	Sickle cell anemia (hemoglobin SS disease)*	Congenital Hypothyroidism
Glutaric acidemia type I	Very long-chain acyl-CoA	Maple syrup disease		Biotinidase deficiency
3-hydroxy-3-methyl glutaric aciduria (HMG)	dehydrogenase deficiency	Homocystinuria* (due to cystathionine beta synthase deficiency)	Hemoglobin S/β-thalassemia*	Congenital adrenal hyperplasia*
Multiple carboxylase deficiency	Long-chain L-3-hydroxy		Hemoglobin S/C disease*	(21-hydroxylase deficiency)
Methylmalonic acidemia (mutase deficiency)*	acyl-CoA dehydrogenase deficiency	Citrullinemia		Classical galactosemia
3-Methylcrotonyl-CoA carboxylase deficiency*	Trifunctional protein deficiency	Argininosuccinic academia		Hearing loss
		Tyrosinemia type I*		Cystic fibrosis
Methylmalonic acidemia (cobalamin disorders A & B)*	Carnitine uptake defect			Severe combined immunodeficiency
Propionic acidemia				
B-Ketothiolase deficiency				
		Secondary targets		
6 More Organic Acidemia Disorders	8 More Fatty Acid Oxidation Defects	8 More Aminioacidopathies	Other Hemoglobinopathies	2 Other Hereditary Metabolic Disorders
Methylmalonic academia* (cobalamin disorders C & D)	Short-chain acyl-CoA dehydrogenase deficiency	Benign hyperphenylalaninemia	Variant hemoglobinopathies* (including hemoglobin E)	Galactokinase deficiency*
	Glutaric acidemia type II	Tyrosinemia type II		Galactose epimerase deficiency
Malonic academia	Medium/short-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency	Defects of biopterin cofactor biosynthesis		

(*Continued*)

Table 4
(*Continued*)

		Secondary targets		
6 More Organic Acidemia Disorders	8 More Fatty Acid Oxidation Defects	8 More Aminioacidopathies	Other Hemoglobinopathies	2 Other Hereditary Metabolic Disorders
Isobutyryl-CoA dehydrogenase deficiency	Medium-chain ketoacyl-CoA thiolase deficiency	Argininemia		
2-Methyl 3-hydroxy butyric aciduria	Carnitine palmitoyltransferase II deficiency	Tyrosinemia type III		
2-Methylbutyryl-CoA dehydrogenase deficiency	Carnitine: acylcarnitine translocase deficiency	Defects of biopterin cofactor regeneration		
3-Methylglutaconic aciduria	Carnitine palmitoyltransferase I deficiency (liver)	Hypermethioninemia		
	Dienoyl-CoA reductase deficiency	Citrullinemia type II		

*From *Newborn Screening: Toward a Uniform Screening Panel and System, Maternal and Child Health Bureau* [Federal Register: March 8, 2005 (Volume 70, Number 44)]. [http://mchb.hrsa.gov/screening/].

Table 5
Ethnic group incidence of inborn errors of metabolism

Inborn Error	Ethnic Group	Estimated Incidence (per 100000 births)
Hepatorenal tyrosinemia	French-Canadians (Saguenay-Lac Saint-Jean region)	54 (before the introduction of preventive prenatal diagnosis)
Tay-Sachs disease	Canavan disease Ashkenazi Jews	33 (before the introduction of preventive prenatal diagnosis)
Gaucher disease, type 1	Canavan disease Ashkenazi Jews	100
Phenylketonuria (PKU)	Canavan disease Ashkenazi Jews	5
	Yemenite Jews	19
	Turkish	38.5
Porphyria variegata	South African (white)	300
Congenital adrenal hyperplasia	Yupik Eskimos	200
Glutaric aciduria, type 1	Ojibway Indians (Canada)	>50
Maple syrup urine disease	Mennonites (Pennsylvania)	568

From: Clarke JTR, (Ed.): A Clinical Guide to Inherited Metabolic Diseases – 3rd ed., Cambridge University Press, 2006.

Clinical investigation is augmented by a large number of common blood and urine tests (blood, sugar, urine pH, anion gap, cytopenia, liver function tests, sweat test, electroencephalogram, and radiography of bones). Radiologic examination may include X-rays, CT scans, and MR imaging. MRI scans should be substituted for CT scans whenever possible to avoid radiation exposure. Ophthalmologic and neurophysiologic investigations are often important. Laboratory findings in inborn errors of metabolism are listed in Table 7. Abnormal metabolites are shown in Table 8.

Abnormalities in serum electrolytes can be caused by vomiting or diarrhea. Inclusion of bicarbonate and pH assessment may indicate a large anion gap due to the presence of organic acids. Electrolytes, however, may be normal with organic acidemias.

Neutropenia or pancytopenia suggests the presence of one of the organic acidemias. A urinalysis may indicate the presence of reducing substances and the presence or absence of ketones. Ketonuria is not found in normal newborns. Urine pH above 5.0 in an acidotic infant may suggest renal tubular acidosis. Absence of ketones in association with hypoglycemia may indicate an error in fatty acid metabolism. It is helpful to save a small amount of frozen urine and plasma for later evaluation of keto acids, carnitine, and organic acids.

Elevated serum ammonia levels are found in patients with liver disease and in those with errors of the urea cycle and several of the organic acidemias. Transient hyperammonemia occurs in some newborns, and this is reversible when treatment is prompt. Urea cycle errors are frequently associated with very low blood urea levels. Some metabolic disorders cause liver cirrhosis in infants and children and some liver disorders progress to stupor and coma.

Liver function tests commonly indicate primary liver diseases. However, abnormal liver function test findings result from many of the metabolic diseases, including disorders of organic and amino acid metabolism, and many of the storage diseases.

Elevated serum lactate is usually due to hypoxemia or poor perfusion and occurs with sepsis. It may be due, however, to improper technique in drawing blood without good blood flow. Lactic acid is produced in the anaerobic metabolism of glucose through pyruvate, which is then converted in the liver to glucose. Deficiency of pyruvate dehydrogenase complex is the most common error of metabolism that causes lactic acidosis.

Table 6
Laboratory findings in some inborn errors of metabolism

Lactic acidosis ±
Increased anion gap
Methylmalonic acidemia
Propionic acidemia
Isovaleric acidemia
Multiple carboxylase deficiency
Maple syrup urine disease
Glutaric acidemia, type I
Glutaric acidemia, type II
Short-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-OH acyl-CoA dehydrogenase deficiency
Ketothiolase deficiency
Acetoacetate CoA ligase deficiency
3-hydroxy-3-methylglutaryl CoA Iyase deficiency
Pyruvate dehydrogenase complex deficiency
Pyruvate carboxylase deficiency
Phosphoenolpyruvate carboxykinase deficiency
Mitochondrial respiratory/electron transport chain defects
Leigh disease
Hereditary galactosemia
Glycogen storage disease, type I
Hereditary fructose intolerance
Fructose-1,6-diphosphatase deficiency
Hereditary tyrosinemia, type I
Respiratory alkalosis
Omithine transcarbamylase deficiency
Carbamoyl phosphate synthetase deficiency
Argininosuccinicaciduria
Citrullinemia

Hyperammonemia
Ornithine transcarbamylase deficiency
Carbamoyl phosphate synthetase deficiency
Argininosuccini-caciduria
Citrullinemia
Methylmalonic acidemia
Propionic acidemia
Isovaleric acidemia
Multiple carboxylase deficiency
Glutaric acidemia, type II
Very-long-chain acyl-CoA dehydrogenase deficiency
Medium-chain acyl-CoA dehydrogenase deficiency
Short-chain acyl-CoA dehydrogenase deficiency
Acylcarnitine translocase deficiency
Ketosis
Methylmalonic acidemia
Propionic acidemia
Isovaleric acidemia
Multiple carboxylase deficiency
Maple syrup urine disease
Glutaric acidemia, type II
Short-chain acyl-CoA dehydrogenase deficiency
Ketothiolase deficiency
Acetoacetate-CoA ligase deficiency
Pyruvate carboxylase deficiency
Glycogen storage disease, type I

Fructose-1,6-diphosphatase deficiency
Hypoglycemia
Hyperinsulinism
Glycogen storage disease, type I
Hereditary fructose intolerance
Fructose-1,6-diphosphatase deficiency
Glutaric acidemia, type I
Glutaric acidemia, type II
Very-long-chain acyl-CoA dehydrogenase deficiency
Medium-chain acyl-CoA dehydrogenase deficiency
Short-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-OH acyl-CoA dehydrogenase deficiency
Carnitine transporter defect
Carnitine palmitoyl transferase I deficiency
Carnitine palmitoyl transferase II deficiency
Acylcarnitine translocase deficiency
Ketothiolase deficiency
Acetoacetate-CoA ligase deficiency
3-hydroxy-3-methylglutaryl-CoA Iyase deficiency
Hereditary galactosemia
Neonatal hemochromatosis
Mitochondrial respiratory/electron transport chain defects
Lipemia
Glycogen storage disease, type I

Myopathy can be caused by a few of the glycogen storage diseases or mitochondrial disorders. Muscle biopsy or fibroblast cultures may be diagnostic. Myoglobinuria may be present, and serum free carnitine may be decreased.

Peroxisomal action is responsible for β-oxidation of fatty acids, and deficiency results in developmental retardation. Peroxisomal disorders with such manifestations include Zellweger syndrome,

Table 7
Laboratory evaluation for suspected inborn errors of metabolism

	Comments
Initial Evaluation*	
Blood tests	
CBC with differential	
Blood glucose	
Electrolytes, BUN, creatinine, uric acid	
Arterial blood gas	
Serum ammonia	Should be obtained from artery or vein without a tourniquet; the tube should be placed on ice for transport to the laboratory and analyzed immediately. If the plasma ammonia concentration is >100 micromol/L (1.7 mcg/mL), the measurement should be repeated immediately
AST, ALT, bilirubin, PT	If the patient has signs or symptoms of myopathy
LDH, aldolase, creatine, kinase	
Urine Tests	
Color, odor	
Urinalysis	
Reducing substances	
Myoglobin	If the patient has signs or symptoms of myopathy
Specialized Tests	
Blood tests	
Quantitative plasma amino acids	Plasma amino acid analysis must be performed quantitatively rather than qualitatively
Lactate and pyruvate	Lactate and pyruvate should be measured in arterial blood that is, transported on ice
Acylcarnitine profile	Analysis of acylcarnitine conjugates is performed by tandem mass spectrometry and can be measured in a plasma sample or a filter-paper bloodspot; serum is preferred because of inherent problems in quantitating compounds from a filter-paper blood spot
Urine Tests	
Qualitative urine organic acids	Minimum of 2 to 5 mL in sterile container without preservative

CBC: complete blood count; ALT: alanine aminotransferase; BUN: blood urea nitrogen; PT: prothrombin time; AST: aspartate aminotransferase; LDH: lactate dehydrogenase. *If possible, blood and urine samples should be obtained for both the initial and specialized tests at the time of presentation. Samples for specialized tests should be processed and stored appropriately for further testing if indicated.

adrenoleukodystrophy, and oxalosis [31]. Very-long-chain fatty acids are elevated in the serum with most forms of peroxisomal disorders.

Many chemical screening programs such as determination of organic and amino acids, oligosaccharides, and glycosaminoglycans in blood and urine are available for diagnostic workup of suspected progressive degenerative metabolic diseases. Distinguishing biochemical findings of inborn errors of metabolism are shown in Table 9.

Some inherited metabolic diseases significantly increase the risk of intercurrent illness. For example, recurrent treatment-resistant otitis media is a common problem in children with mucopolysaccharide storage diseases because distortion of the Eustachian tube and production of particularly tenacious

Table 8
Abnormal metabolites in metabolic disorders

Disorder	Abnormal Metabolite (s)*
Organic Acidemias	
Methylmalonic academia	Methylmalonic and methylcitric acids
Propionic academia	3-Hydroxpropionic acid propionylglycine, methylcitric acid
Isovaleric academia	Isovalerylglycine
Glutaric academia type I	Glutaric and 3-hydroxyglutaric acids
3-Methylglutaconic aciduria	3-Methylglutaconic acid
2-Hydroxy-3-methylbutyryl-CoA dehydrogenase deficiency	2-Hydroxy-3-methylblutyric acid, tiglyglycine, 2-methyl-3-hydroxyacetoacetic acid
2-Hydroxyglutaric aciduria	2-Hydroxyglutaric acid
Disorders of Ketogenesis	
Medium chain acyl-CoA dehydrogenase (MCAD) deficiency	Hexanoylglycine and suberylglycine
3-ketothiolase deficiency	2-hydroxy-3-methylbutyric acid, tiglyglycine, 2-methyl-3-hydroxyacetoacetic acid
3-Hydroxy-3-methylglutaryl (HMG)-CoA lyase deficiency	3-Hydroxy-3-methylglutaric, 3-methylglutaric and 3-methylglutaconic acids
Other Disorders	
Canavan disease	N-acetylaspartic acid
Glutaric academia type II (multiple acyl-CoA dehydrogenase deficiency)	Glutaric and 2-hydroxyglutaric acids
Mevalonate kinase deficiency	Mevalonic acid
Maple syrup urine disease	2-Hydroxyisovaleric and 2-hydroxy-3-methylvaleric
Phenylketonuria	Phenylpyruvic and phenyllactic acids
Fumarase deficiency	Fumaric acid
Glutathione synthetase deificneyc	5-Oxoproline (pyroglutamic acid)
Biotinidase deficiency*	3-Hydroxyisovaleric acid, methylcitric acid, 3-methylcrotonlglycine, propionylglycine
Holocarboxylase synthetase deficiency*	3-Hydroxyisovaleric acid, methylcitric acid, 3-methylcrotonylglycine, propionylglycine
Glycerol kinase deficiency	Glycerol
Ethylmalonic encephalopathy	Ethylmalonic and methylsuccinic acids
Disorders of Uncertain Consequence	
3-methylcrotonyl-CoA carboxlase deficiency	3-methylcrotonylglycine
Short chain acyl-CoA dehydrogenase deficiency	Ethylmalonic acid, butyrylglycine

*Other abnormal metabolites may be seen in these disorders but those listed are the most characteristic for the diagnosis.

mucus combine to create a favorable environment for bacterial colonization of the middle ear. The neutropenia that is a prominent feature of glycogen storage disease type Ib, and some of the organic acidopathies, predisposes to pyogenic infections. Classic galactosemia predisposes infants to neonatal *Escherichia coli* sepsis [32].

Major congenital malformations, such as meningomyelocele, complex congenital heart disease, and major congenital limb deformities, are not generally considered signs of an underlying inherited metabolic disease; however, some inherited metabolic conditions occur with dysmorphism so characteristic that a strong presumptive diagnosis can be made on physical examination alone [32]. A large

Table 9
Distinguishing biochemical findings of inborn errors of metabolism

Findings	MSUD	OA	UCD	DCM	FAO	MD	PD	LSD
Metabolic acidosis	±	++	–	±	±	±	–	–
Respiratory alkalosis	–	–	+	–	–	–	–	–
Hyperammonemia	±	+	++	–	±	–	–	–
Hypoglyclemia	±	±	–	+	+	±	–	–
Ketones	A/H	H	A	A/H	A/L	A/H	A	A
Lactic acidosis	±	±	–	+	±	++	–	–

MSUD: maple syrup urine disease; OA: organic acidemias' UCD: urea cycle disorders; DCM: disorders of carbohydrate metabolism; FAO: fatty acid oxidation disorders; MD: mitochondrial disorders; PD: peroxisomal disorders; LSD: lysosomal storage disorder. –: usually absent; ±: sometimes present; +: usually present; ++: always present. A: appropriate; H: inappropriately high; L: inappropriately low. Adapted from: Weiner DL, Metabolic Emergencies. In: Textbook of Pediatric Emergency Medicine, 5th ed. Fleisher GR, Ludwig S, Henretig FM (Eds). Lippincott, Williams & Wilkins, Philadelphia, 2006.

number of metabolic diseases present with gross abnormalities of appearance Table 10A and 10B. Many of these have lysosomal defects, and most will have hepatosplenomegaly. These include such diseases as mucopolysaccharidoses, sphingolipidoses, and other lysosomal storage diseases. These diseases are not acutely life-threatening. Children with these conditions commonly have developmental delay. Many appear normal at birth and progressively deteriorate Table 3.

An important step between the clinical findings and the biochemical findings is the anatomic pathology, including histology, histochemistry, immunochemistry, and electron microscopy (EM). For example, screening peripheral blood for cytoplasmic vacuoles in the lymphocytes as shown in Fig. 1 may be the first indication of a storage disorder.

Some metabolic disorders present as acute encephalopathy. The earliest signs of encephalopathy may be no more obvious than excessive drowsiness, unusual behavior, or some unsteadiness of gait. Acute or intermittent ataxia is a common sign of acute encephalopathy in older children with inborn errors of metabolism. A history of recurrent attacks of unsteadiness of gait or ataxia, especially when associated with vomiting or deterioration of consciousness, should stimulate investigation of a possible inherited metabolic disease Table 11 [25].

In addition to the biochemical tests of blood and urine, solid tissues and cell cultures may be needed for biochemical assays. A biopsy specimen should be divided for biochemical analysis and morphologic investigation. This is particularly important in liver, muscle, and intestinal biopsies and in skin biopsies made for the fibroblast cultures.

Hypoglycemia occurs with starvation in young infants but also may indicate an error in gluconeogenesis, errors in fat metabolism and defects in hormone metabolism. A rapid response to glucose, especially in the presence of hepatomegaly, may suggest glycogen storage disease or fructose-1,6-diphosphatase deficiency. An approach to diagnosis when a patient presents with hypoglycemia is shown in Fig. 2. This algorithm will guide clinicians toward a proper sequence of diagnostic tests.

Even after death, some of the techniques used in the living can be helpful in detecting inborn errors of metabolism. For example, even small amounts of urine may remain in the bladder and should be aspirated and saved. Tissues and body fluids should be obtained and maintained in a state suitable for the tests desired. New diseases and diagnostic tests are identified at a surprisingly rapid rate. Very few laboratories perform all the tests.

Table 10A
Physical examination findings as clues to inborn errors of Metabolism

Finding	Potential Inborn Error
General	
Tall, long-limbed body habitus	Homocysturia
Head	
Coarse facial features (eg, hirsuitism prominent brow ridge, and gingival hypertrophy)	Oligosaccharidoses, mucopolysaccharidoses, mucolipidoses
Microcephaly	Untreated phenylketonuria (PKU), maternal PKU syndrome, congenital disorders of protein glycosylation, leukodystrophies (late, organic acidemias, urea cycle disorders, maple syrup urine disease
Macrocephaly	Canavan disease, glutaric academia type I, oligosaccharidoses, mucopolysaccharidoses, mucolipidoses, Tay-Sachs (early)
Hair	
Alopecia	Biotinidase deficiency, vitamin D resistant rickets
Sparse	Biotinidase deficiency, Menkes disease
Kinky, brittle	Argininosuccinic aciduria and citrullinemia (due to arginine deficiency), Menkes disease, mucopolysaccharidoses
Eyes	
Cataracts	Oligosaccharidoses, Fabry diseiase, neuronal ceroid lipofuscinosis, galactosemia, Smith-Lemli-Opitz syndrome peroxisome bioigenesis defects, rhizomelic chondrodysplasia punctata, Wilson disease, errors of mitochondrial oxidative phosphorylation
Cherry red spot	Tay-Sachs disease, Sandhoff disease, Sialidosis type I and type II, GM1-gangliosidosis, Niemann-Pick disease type A, Gaucher disease type 2, metachromatic leukodystrophy, galactosialidosis
Corneal clouding	Oligosaccharidoses, mucopolysaccharidoses, mucolipidoses, Tangier, sialidosis
Corneal opacity	Oligosaccharidoses, Fabry disease, steroid sulfatase deficiency (X-linked ichthyosis), Tangier, molybdenum cofactor deficiency, sulfite oxidase deficiency
Dislocated lens	Homocystinuria, sulfite oxidase deficiency
Kayser-Fleischer rings	Wilson disease
Retitinitis pigmentosa	Abetalipoproteinemia, peroxisome biogenesis disorders of protein glycosylation, fatty acid oxidation defects, mitochondrial defects, mucopolysaccharidoses, Krabbe disease, Menkes disease, disorders of cobalamin (vitamin B12) transport and synthesis, ornithine aminotransferase deficiency

Adapted from Wappner Rs, Hainline BE. Inborn errors of metabolism. In: Oski's Pediatrics, Principles and Practice, 3rd ed., McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB (Eds), Lippincott, Williams and Wilkins, Philadelphia, 1999. Saudubray JM, Chappentier C. Clinical phenotypes: Diagnosis/algorithms. In: Metabolic and Molecular Bases of Inherited Disease, 8th ed, Scriver CR, Beaudet AL, Sly WS, Valle D (Eds), McGrall-Hill, New York, 2001.Lindor NM, Karnes PS. Initial assessment of infants and children with suspected inborn errors of metabolism. Mayo Clin Proc 70:987, 1995. Cleary MA, Green A. Developmental delay: when to suspect and how to investigate for an inborn error of metabolism, Arch Dis Child 90:1128, 2005.

Table 10B
Physical examination findings as clues to inborn errors of Metabolism

Finding	Potential Inborn Error
Hearing loss	Peroxisomal disorders, mitochondrial disorders, lysosomal storage disorders, mucopolysaccharidoses
Mouth	
Gingival hyperplasia	Oligosaccharidoses, mucopolysaccharidoses, mucolipidoses
Chest	
Inverted nipples	Congenital disorders of protein glycosylation
Abdomen	
Hepatosplenomegaly	Lysosomal storage disease
Hepatomegaly	Glycogen storage diseases, carnitine palmitoyltransferase II deficiency (infantile form), peroxisomal disorders, mitochondrial DNA depletion disorders, tyrosinemia type I (hepatorenal), mucolipidoses, congenital disorders of protein glycosylation, longer chain fatty acid oxidation disorders
Musculoskeletal	
Arthritis	Farber disease, purine metabolism disorders
Neurologic	
Dystonia	Glutaric acidemia I, organic acidemias, Wilson disease, mitochondrial disorders
Myopathy	Fatty acid oxidation defects, mitochondrial disorders, Pompe disease and other glycogen storage diseases
Paresthesia	Fabry disease, sialidosis
Peripheral neuropathy	Congenital disorders of protein glycosylation, leukodystrophies, peroxisomal disorders, Tangier disease
Psychoses	Adult MLD Tay-Sachs, homocystinuria, porphyrias, purine metabolism disorders
Skin	
Hypopigmentation or absent pigment	Cystinosis, Menkes disease, phenylketonuria, sialidosis
Angiokeratoma	Fabry, fucosidosis, galactosialidosis, beta-mannosidosis, sialidosis
Dermatitis	Biotinidase deficiency, Hartup disease, phenylketonuria, prolidase deficiency
Edema	GM1 gangliosidosis, prolidase deficiency
Hirsutism	Oligosaccharidoses, mucopolysaccharidoses, mucolipidoses
Ichthyosis	Multiple sulfatase deficiency, isolated steroid sulfatase deficiency
Photosentization	Porphyrias
Xanthomas	Hyperlipoproteinemias and other disorders of lipoproteins

Adapted from Wappner Rs, Hainline BE. Inborn errors of metabolism. In: Oski's Pediatrics, Principles and Practice, 3rd ed., McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB (Eds), Lippincott, Williams and Wilkins, Philadelphia, 1999. Saudubray JM, Chappentier C. Clinical phenotypes: Diagnosis/algorithms. In: Metabolic and Molecular Bases of Inherited Disease, 8th ed, Scriver CR, Beaudet AL, Sly WS, Valle D (Eds), McGrall-Hill, New York, 2001.Lindor NM, Karnes PS. Initial assessment of infants and children with suspected inborn errors of metabolism. Mayo Clin Proc 70:987, 1995. Cleary MA, Green A. Developmental delay: when to suspect and how to investigate for an inborn error of metabolism, Arch Dis Child 90:1128, 2005.

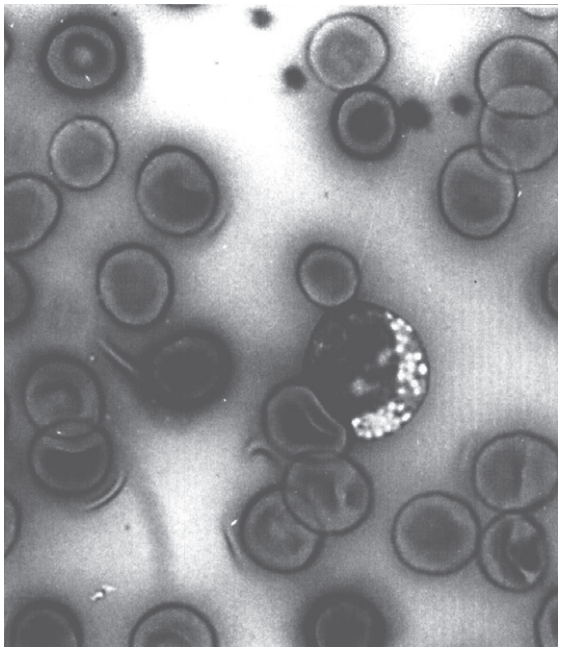

Fig. 1. Vacuolated lymphocyte in the peripheral blood of a patient with mannosidosis.

Table 11
Differential diagnosis of acute encephalopathy in metabolic diseases

	UCED	MSUD	OAuria	FAOD	ETC Defects
Metabolic acidosis	0	±	+++	±	++
Plasma glucose	N	N or ↓	↓↓	↓↓↓	N
Urinary ketones	N	↑↑	↑↑	0	0
Plasma ammonia	↑↑↑	N	↑↑	↑	N
Plasma lactate	N	N	↑	±	↑↑↑
Liver function	±N	N	N	↑↑	N
Plasma carnitine	N	N	↓↓↓	↓↓	N
Plasma amino acids	Abnormal	↑ BCAA	↑ glycine	±	↑ alanine
Urinary organic acids	N	Abnormal	Abnormal	Abnormal	N

UCED, urea cycle enzyme defect; MSUD, maple syrup urine disease; OAuria, organic aciduria; FAOD, fatty acid oxidation defect; ETC, mitochondrial electron transport chain; BCAA, branched-chain amino acids; ↑, elevated; ↓ decreased;+, present; ±, variably present; N, normal; O, not present. From: Clarke JTR, (Ed.): A Clinical Guide to Inherited Metabolic Diseases – 3rd ed., Cambridge University Press, 2006.

3. Further development of prenatal and neonatal screening

As techniques such as next generation sequencing [17, 18] and whole genome sequencing are developed further for routine use, there will be many more commercial laboratories offering comprehensive testing as has already proved helpful for newborn intensive care units [19, 20]. However, reporting and ethical issues need to be resolved before whole genome sequencing can be used widely [33].

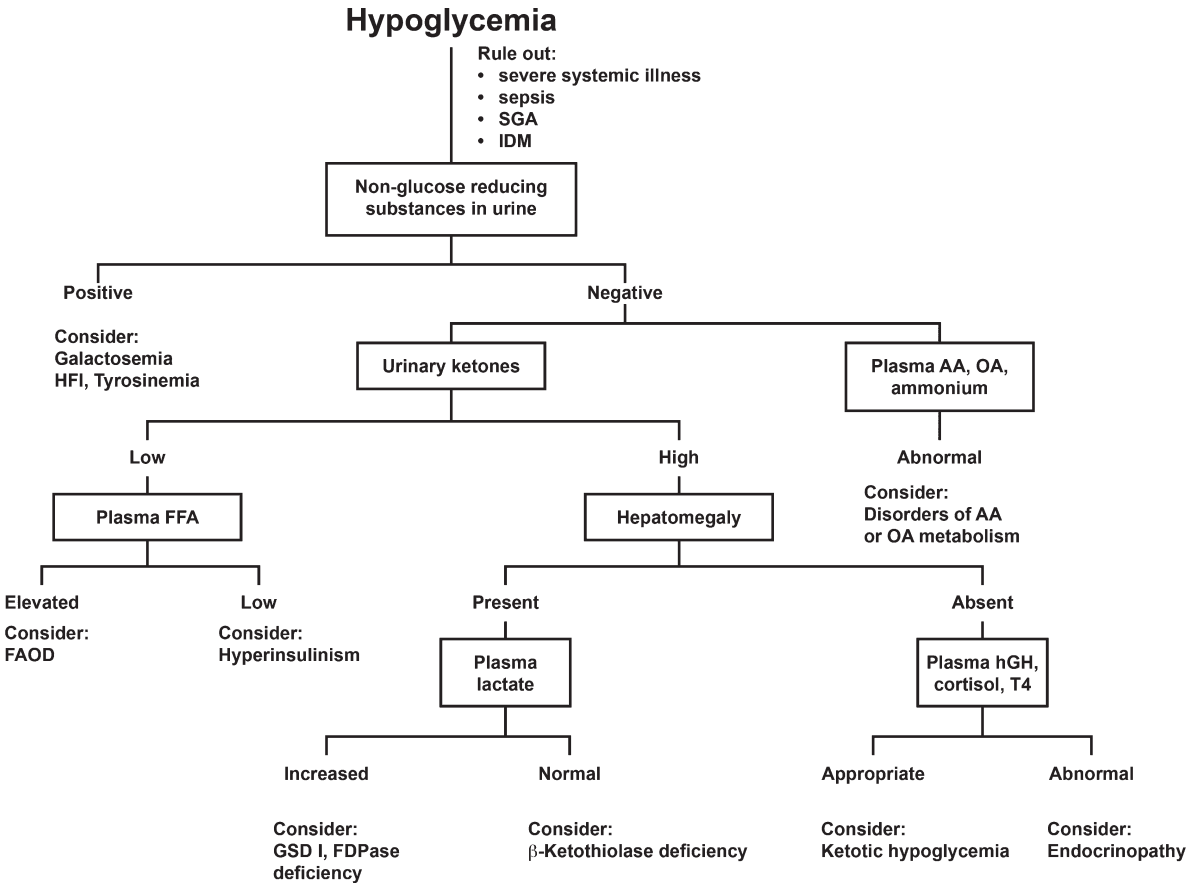

Fig. 2. Approach to the differential diagnosis of hypoglycemia. Abbreviations: SGA, small for gestational age; IDM, infant of diabetic mother; HFI, hereditary fructose intolerance; AA, amino acids; OA, organic acids; FFA, free fatty acids; FAOD, fatty acid oxidation defect; hGH, human growth hormone; T4, thyroxine; GSD, glycogen storage disease; FDPase, fructose-6-diphosphatase. Clarke JTR, (Ed.): A Clinical Guide to Inherited Metabolic Diseases – 3rd ed., Cambridge University Press, 2006.

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