Disease	Mode of inheritace	Molecular basis of disease	Symptoms & presentation	Diagnositc testing	Treatment
Amino acid disorders					
Phenylketonuria	Autosomal recessive	Mutation in phenylalanine hydroxylase and conversion to tyrosine is blocked. Phenylalnine is an essential amino acide but the downstream amino acids are not. Build up of phenylalanine is toxic to neurons.	Neonates are usually unaffected but developmental delays begins around 3-4 months.	Phyenylalaine elevated on plasma amino acid quantitation.	Low protein diet
Maple syrup urine disease	Autosomal recessive	A pathologic variant in *BCKDHA, BCKDHB,* and *DBT* can cause failure in a protein complex that catabolize leucine, isoleucine, and valine; rich in milk, meats, and eggs. The incidence is very high among Mennonites of PA, OH, and IN; likely due to genetic drift/founder effect in a small population and social stratification.	Usually detected during neonate screening. Individuals have sweet smelling urine and are also characterized by poor feeding, vomiting, lethargy, abnormal movements, and delayed development. When untreated can lead to seizures, coma, and death.	Elevated leucine levels in newborn blood.	Low protein diet
Organic acid disorders					
Methylmalonic aciduria/emia	Autosomal recessive	Mutations in several genes (usually *MUT*) stop production of methylmalonyl-CoA mutase, which converts methylmalonyl-CoA (a product of protein and lipid metabolism) into succinyl-CoA. This, in turn, causes build up of methylmalonic acid in urine.	Acidosis in early infancy, mild to life-threatening. Vomiting, dehydration, hypotonia, developmental delay, lethargy, hepatomegaly, failure to thrive. Long-term consequences include feeding problems, diminished cognitive function, chronic kidney disease, pancreatitis.	Methylmalonic acid is elevated on urine organic acid quantitation.	Low protein diet
Urea cycle defects					
Ornithine transcarbamylase (OTC) deficiency	X-linked (recessive)	Mutation in *OTC* causes and enzyme deficiency that prevents the combination of carbamyl phsphate and orithine in the liver to form citrulline ultimately stopping normal function of the urea cycle (removal of ammonia). Female carries may have some symptoms due to X-inactivation and insufficient dosage compensation.	Usually leads to an event in the first days of life among males—ammonia is especially toxic to the nervous system: lethargy, unwillingness to eat uncontrolled breathing, temperature, seizures, or comma. Complications include: developmental delays, intellectual disability, progressive liver damage, skin lesions,or brittle hair.	Plasma amino acid quantitation will be elevated save citrulline.	Low protein diet and ammonia scavenger medications
Carbohydrates disorders					
Hereditary fuctose intolerance	Autosomal recessive	Mutation(s) in *ALDOB* causes a deficiency in the aldolase B enzyme which converts fructose-1-phosphate into dihydroxyacetone phospate (DHAP) before entering the gluconeogenesis pathway.	Usually identified in infancy after ingesting fruit or juices. Patients present with nausea, vomiting, abdominal pain, diarrhea, or hypoclycemia. Infants may grow/gain weight slowly.	Clinical suspicion and assay of aldolase B.	Restricted consumption of fructose

Disease	Mode of inheritace	Molecular basis of disease	Symptoms & presentation	Diagnositc testing	Treatment
Purine/Pyrimidine disorders					
Lesch-Nyhan	X-linked recessive	Pathogenic variants in *HPRT1* suppresses synthesis of hypoxanthine phosphoribosyltransferase 1, which is involved in the reclamation of purines causing diversion into the catabolic pathway causing high levels of uric acid. For unknown reasons *HPRT1* is also associated with dopamine and subsequently control of movement and emotion. There are known milder variants.	Excess of uric acid can cause build up in blood, under the skin, and gouty arthritis as well as kidney and balder stones. Patients also present with dystonia, chorea, ballismus, and self-injurious behavior.	Clinical suspicion, elevated uric acid, and molecular analysis of *HGPRT*.	Low purine diet, allopurinol, and behavior modifying drugs.
Lipid disorders					
Medium chain acyl-CoA dehydrogenase (MCAD) deficiency	Autosomal recessive	Deficiency in the enzyme responsible for catabolism of MCAD in the cytoplasm and mitochondrial matrix is a result of a pathogenic variant in *ACADM*. MCFAs are an important source of energy for the heart and brain; failure of digestion thereof can lead to energy deficiency and toxic accumulation.	Patients typically present in early childhood with vomiting, lethargy, hypoglycemia, seizures, breathing difficulty, liver problems, brain damage, coma, and sudden death. MCAD can be misdiagnosed as Reye syndrome and SIDS	Fatty acid intermediates present on urine organic acid quantitation and acylcarnitine analysis	Avoidance of fasting and treatment of hypoglycemia
Vitamin disorders					
Biotinidase deficiency	Autosomal recessive	A pathogenic variant of *BTD* causes deficiency in biotinidase, an enzyme involved in recycling of biotin—an essential B vitamin. This impairs activity of biotin-dependent carboxylase.	Individuals typically present in first months of life or in childhood with seizures, hypotonia, breathing problems, hearing/vision loss, ataxia, rashes, alopecia, candidiasis. Biotin deficiency may also cause delayed development.	Enzyme assay of biotinidase	Biotin supplementation
Mineral disorders					
Menke disease	X-linked recessive	A pathogenic variant in *ATPA7A* results in an inability to absorb copper across the intestinal epithelium and a buildup of Copper in the kidneys. Copper is an essential element for many enzymes in all tissues.	Failure to thrive, sparse kinky hair, deterioration of nervous system, hypotonia, sagging facial features. Children often do not survive past 3 years of age.	Molecular analysis of *ATPA7A*	—

Disease	Mode of inheritace	Molecular basis of disease	Symptoms & presentation	Diagnositc testing	Treatment
Lysosomal storage disorders					
Mucopolysaccharidosis type II (MPSII) Hunter syndrome	X-linked recessive	A pathogenic variant in *IDS* results in failure of α-iduronidase sulfatase: an enzyme involved in the breakdown of glycosaminoglycans leading to their accumulation in lysosomes.	Individuals typically present between ages 2-4, as diets change, with characteristic facial features (full lips, large round cheeks, broad nose, and macroglossia). Vocal cords may be enlarged and a narrow airway may cause sleep apnea and upper respiratory infections. Additionally they may have macrocephaly, hydrocephalurs, hepatosplenomegaly, umbilical/inguinal hernia.	Enzyme assay of α-iduronidase sulfatase	Enzyme replacement therapy: idursulfase (elaprase)
Tay-Sachs disease (G_{M2}-gangliosidosis)	Autosomal recessive	A pathogenic variant in the *HEXA* gene causes disruption of the activity of the β-hexosaminidase A, a lysosomal enzyme that breaks down G_{M2} gangliosides (a fatty substance). Accumulation of these lysosomes becomes toxic to the neurons in the brain and spinal cord.	Symptoms typically manifest in the first 6 months of life. Affected individuals lose motor skills such as turning over, sitting, and crawling; are excessively startled by loud noises; and experience seizures, vision/hearing loss, paralysis, and intellectual disability. A "cherry-red spot" in the retina is characteristic of the disorder.	Genetic testing	—
Peroxisomal disorders					
Zellweger syndrome	Autosomal recessive	There are at least 12 different genes with pathogenic variants that cause peroxisomal disorders consistent with Zellweger syndrome—the most common of which is *PEX1*. The mutations cause the disruption of the formation of peroxisomes, which are essential to peroxide metabolism, catabolism long chain fatty acids, bile acids, and synthesis of complex lipids.	Apparent at birth with characteristic facial features (high forehead, depressed nasal bridge, small face, large fontanelles). Infants have hypertonia, feeding problems, seizures, as a result of demyelination. Individuals do not usually live beyond the first year of life.	Elevated plasma VLC fatty acids, enzymatic assay	—
Mitochondrial disorders					
Navajo neurohepatopathy	Autosomal recessive	*MPV17* codes for a protein that is likely responsible for the maintenance of mtDNA as the pathogenic variants of *MPV17* causes a loss of function in or post translational silencing of MPV17-protein causing hepatocerebral mtDNA depletion syndrome. Reduced mitochondrial function is especially taxing to liver and brain, tissues with high energy demands. While there are only roughly 30 documented cases, the variant is very high among the Navajo (1 in 1,600) a result of genocide and population isolation due to removal and relocation.	Signs and symptoms begin in infancy and are indicative of errors in metabolism: vomiting, diarrhea, failure to thrive, lactic acidosis, hypoglycemia, hepatomegaly, hypotonia, and cholestasis. Affected individuals typically develop liver disease in the first weeks of life, which quickly develops into liver failure during infancy or early childhood.	Clinical suspicion, genetic testing	—