A Pathway Genomics White Paper

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Extended Carrier Status Genetic Screening

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PATHWAY GENOMICS

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Introduction

The Case for Screening

Choosing to have a child is one of the most important decisions in a person's life. It is crucial for prospective parents to be equipped with critical information regarding their own genetics when considering conception. Extended carrier status screening provides broader and more useful information to prospective parents than traditional offerings of ethnicity – or family history – based genetic screening.

Ideally, before conceiving a child, both prospective parents would be encouraged by their physicians to participate in extended carrier status testing. Usually when a child is born with, or develops, a serious genetic disease, the parents are otherwise healthy people who will not develop the disease and may not be aware that they carry a recessive mutation, as it may pass silently from generation to generation. Although rare, these disorders become very real when a family has a child born with two disease-causing recessive mutations. Therefore, extended carrier status screening provides prospective parents and their physicians with vital information that will allow them to make the most informed decisions about family planning.

The Problem

Traditionally, pregnancy-related genetic testing has been limited to prospective parents whose family history or ethnicity suggests that they may be at increased risk for a serious genetic condition. The problem with this approach is that it overlooks genetic risks in people who do not fit into particular well-known risk groups, and relies on self-reported ethnicity and family history, which can be incomplete or misleading. Additionally, the ethnic distribution and prevalence of many genetic disease-causing mutations is not known. Moreover, the traditional approach places at a disadvantage the patient who does not possess a complete record of his or her family history or ethnicity. Since carrier traits can be passed silently across generations, each person has the possibility of being a carrier, regardless of any known familial health condition.

The Solution

In contrast with traditional genetic testing, extended carrier status screening provides patients with information about carrier status for known recessive mutations that they may pass to their children, without restriction by ethnicity or family history. Screening both parents allows rapid identification of

potential risks to offspring: if both parents carry mutations for the same recessive disorder, their offspring are at risk for that specific condition.

Advancements in science, medicine and laboratory technology now make it possible to detect an exceptional number of these recessive mutations in prospective parents, using only a saliva sample. Currently, Pathway's *Extended Carrier Status Screening* tests for known mutations causing 76 recessive health conditions. Pathway continually updates its database of recessive health conditions. Additional conditions will be offered as new studies that pass our rigorous criteria for reporting are published.

Pathway's screening includes the traditionally recommended 23 common mutations causing cystic fibrosis (CF), a lung and digestive disease. Screening for these 23 common mutations has been recommended by the American College of Obstetricians and Gynecologists (ACOG). Further, Pathway also screens for an additional 60 mutations.

Established several years ago, ACOG's current criteria for CF and spinal muscular atrophy, a severe neuromuscular disease, are available and recommended for all pregnant couples. Moreover, it is recommended that people of Ashkenazi Jewish descent be offered a genetic test panel of several conditions found with increased frequency in individuals of Ashkenazi descent, including Tay-Sachs and Canavan diseases, progressive neurodegenerative conditions that are usually fatal in childhood.

The Process and Technology

Securing the Sample
The first step of the carrier status genetic screening is to extract DNA from a saliva sample provided by the patient. Because of the high sensitivity of our genetic testing, a simple and painless saliva collection that can be completed in a physician's office provides enough DNA for the extended carrier status screening. This is an improvement over traditional genetic testing, which requires a blood sample drawn by a licensed phlebotomist, causing patient anxiety and discomfort.

Supplied to the physician by Pathway, a Saliva Collection Kit is given to the prospective parent, who activates each kit through Pathway's secure online system.

The Saliva Collection Kit includes all of the necessary supplies for the collection and shipment of the saliva sample. The physician or the patient uses the enclosed envelope to send the saliva sample back to Pathway's laboratory, which is California-state licensed and federally certified in accordance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

Once we receive a sample, it is immediately processed for genetic testing. The remaining DNA not used for testing purposes is stored in Pathway's DNA Lockbox™, a comprehensive system of laboratory controls, for the retention time required by federal and state regulations and in accordance with our standard operating procedures. All work is completed in a CLIA- or CAP-certified laboratory.

Accurate and Safe Analysis
Before being delivered to the physician, the information in each report is crosschecked and validated by our on-staff geneticists and physicians. All samples go through rigorous analysis and quality control. Our reports reflect the best available genetic evidence. We use custom disease-targeted genotyping technologies that are capable of testing for the presence of thousands of mutations in a patient's DNA. The analysis of genetic testing

results is accomplished by our highly trained staff and relayed back to the physician and patient securely and privately in a comprehensive, self-explanatory report. Our privacy and security program protects a patient's saliva sample, DNA, genetic testing and report results, as well as any other personally identifiable information.

Reporting the Findings

Approximately three weeks after our laboratory receives the saliva sample, a comprehensive and easy-to-understand report is available for viewing. The personal genetic report is accessed through a secure website and is available to the referring physician before the patient has access to it. Once the physician receives the patient's report, the appropriate steps can be taken.

Prospective parents in whom no mutations are identified can continue planning a pregnancy with the peace of mind that they are unlikely to carry the set of mutations tested. Should an individual patient's results show that they are a carrier for a known disease-causing mutation, analysis of the other parent's results will be required in order to determine the risk to their offspring of developing that disease.

This information will allow prospective parents to prepare – mentally, emotionally and physically – for making informed decisions before and during pregnancy. In some cases, receiving positive results may lead the parents to consider alternative methods of conception, such as the use of a sperm donor or an egg donor, or other assistive reproductive technologies. Alternatively, if they decide to conceive a child, the pregnancy can be closely monitored for early detection of the health condition and, if necessary, precautions can be taken by the pediatrician.

In rare cases, prospective parents may elect to avail themselves of a technology called pre-implantation genetic diagnosis (PGD), after which only unaffected embryos are selected for the pregnancy.

In any of these scenarios, extended carrier status genetic testing clearly results in prospective parents being more informed and prepared for the journey into parenthood.

Limitations

Although our extended carrier status genetic screening covers a wide range of mutations and health conditions, we do not screen for spinal muscular atrophy (SMA).

Additionally, because there are many very rare mutations that cause recessive disorders, it is also possible to carry a mutation that is not included in our screening. If the patient has a family history or is concerned about his or her status for a particular disease and wishes to find out more, that patient should first consult his or her physician.

In addition, it is not usually possible to determine health prognosis solely from genotype information. There can be a great deal of variability in how diseases are expressed among individuals, even with the same mutations, depending on many other factors, such as environment and lifestyle. Since not all genetic or inherited health conditions affecting people can be detected through genetic testing, a negative result from an extended carrier status genetic screening does not exclude a person from inheriting a genetic disease. Further, while a negative result suggests a reduced likelihood to inherit one of the tested health conditions, it does not eliminate the possibility that a person may inherit one of the conditions.

Physician Assistance – Genetic Counseling

Our expert panel of geneticists and physicians at Pathway offer pre- and post-testing assistance and guidance to physicians and patients at no charge. Our qualified genetic counselors and medical professionals are available to assist physicians in a number of ways. Whether a physician or clinic staff member is in need of information or is interested in sampling, or marketing Pathway's kits, our staff is on-call to assist. Further, our genetic counseling service is staffed by counselors who are board-eligible/certified by the American Board of Genetic Counseling.

Once the physician has reviewed the results, a Pathway genetic counselor is available to assist in the interpretation of report results, patient referral coordination, following up with the patient as needed for further testing options, or for any other assistance the physician requires.

We encourage and recommend that physicians and clinical staff consult with us if there are questions regarding interpretation of results or any other questions or concerns they may have before, during and after the results of the screening.

Counseling for Patients

While we are devoted to making our testing process and reporting as simple as possible, we understand that, for some patients, testing one's genetic makeup can be a daunting experience. It is our goal to make the testing process as worry-free as possible. One of the ways we do this is by offering physicians and their patients a free genetic counseling service. All of our genetic counselors are under the supervision of our on-staff medical doctors. Physicians and their patients are invited and encouraged to use this service for any related questions they may have, which includes pre-purchase questions, as well as individual genetic report interpretation and counseling.

Summary

Because the reports we provide are meant to be educational and informative, the practical information within the reports provides prospective parents with a foundation to begin, or continue, a conversation with their medical providers. The information in the report is not meant to frighten or intimidate people into making hasty decisions, but rather to strengthen the patient-physician relationship through the availability of genetic information.

Moreover, extended carrier status genetic testing informs and educates prospective parents about the possibility of passing on a recessive genetic condition to their children.

By providing physicians with another tool to help personalize the delivery of care while educating customers about their risks, extended carrier status genetic testing holds the promise of providing better, more comprehensive and individualized care at an affordable price.

Appendix A: Genetic Diseases Included in the Report

Pathway Genomics' extended carrier status genetic testing service currently screens for mutations that cause 76 recessive genetic diseases.

Note: this list is subject to change. Please contact a Pathway representative for the most current list.

Recessive Genetic Diseases Included in Pathway's *Extended Carrier Status Screening* Report					
3-Methylcrotonyl-CoA carboxylase deficiency	Citrullinemia type I	Fanconi anemia	Homocystinuria, classic	Phenylketonuria	Tay-Sachs pseudodeficiency
Acrodermatitis enteropathica	Corticosterone methyl oxidase deficiency	Galactokinase deficiency	Hurler syndrome	Polycystic kidney disease	Thrombocytopenia, congenital amegakaryocytic
Alpha-1 antitrypsin deficiency	Crigler-Najjar syndrome	Galactosemia	Krabbe disease	Pompe disease	Tyrosinemia
Amyotrophic lateral sclerosis	Cystic fibrosis	Gaucher disease	Lipoprotein lipase deficiency, familial	Prekallikrein deficiency	Very long-chain acyl-CoA dehydrogenase deficiency
Argininosuccinate lyase deficiency	Diabetes, permanent neonatal	Glutaric acidemia, type 1	Maple syrup urine disease	Propionic acidemia	Von Willebrand disease type 2 Normandy
Autoimmune polyglandular syndrome, type I	Dihydropyrimidine dehydrogenase deficiency	Glycogen storage disease, type 1A	Medium-chain acyl-CoA dehydrogenase deficiency	Prothrombin deficiency	Von Willebrand disease type 3
Bartter syndrome type 4A	Dubin-Johnson syndrome	GM1-gangliosidosis	Methylmalonic acidemia	Rh-null syndrome	
Beta-ketothiolase deficiency	Ehlers-Danlos syndrome, dermatosparaxis	Hearing loss, DFNB1 and DFNB9 nonsyndromic	MTHFR deficiency	Rickets, pseudovitamin D-deficiency	
Beta-thalassemia	Ehlers-Danlos syndrome, hypermobility	Hearing loss, DFNB59 nonsyndromic	Mucolipidosis II	Sandhoff disease	
Biotinidase deficiency	Ehlers-Danlos syndrome, kyphoscoliotic	Hemochromatosis	Mucolipidosis III	Short-chain acyl-CoA dehydrogenase deficiency	
Bloom syndrome	Ethylmalonic aciduria	Hemoglobin C	Mucolipidosis IV	Sick sinus syndrome	
Canavan disease	Factor XI deficiency	Hemoglobin E	Multiple carboxylase deficiency	Sickle cell disease	
Carnitine deficiency, primary systemic	Familial dysautonomia	HMG-CoA lyase deficiency	Nephrotic syndrome, steroid-resistant	Spherocytosis, hereditary	
Cerebrotendinous xanthomatosis	Familial Mediterranean fever	Homocystinuria, cblE type	Niemann-Pick disease	Tay-Sachs disease	

Appendix B: Genetic Diseases – Description, Ethnic Prevalence and Frequency

Disease	Description	Ethnic Prevalence and Frequency
3-Methylcrotonyl-CoA carboxylase deficiency	3-methylcrotonyl-coA carboxylase deficiency (MCC deficiency) is an autosomal recessive disease that causes brain damage in infants and young children because of a defect in protein metabolism. In the course of normal metabolism, proteins that we eat are broken down into their amino acid building blocks. These amino acids can be reassembled into new proteins or be further broken down as a source of energy. MCC deficiency results from a defect in an enzyme that breaks down the amino acid leucine. Because of the defect, toxic levels of 3-hydroxy-isovaleric acid and 3-methylcrotonyl glycine accumulate in body fluids and are excreted in the urine. Often, an illness can provoke a crisis in which the brain is damaged by the accumulation of these toxic substances. Other symptoms of the crisis may include poor appetite, nausea, vomiting, extreme sleepiness, irritability, low muscle tone, and muscle weakness. If not treated, breathing problems, seizures, liver failure, coma and sometimes even death can occur. With prompt and lifelong treatment, children with MCC deficiency can often live normal lives. The appearance of clinical symptoms in MCC deficiency is variable; some children with MCC deficiency never have symptoms. Even as adults, some people with MCC deficiency never have symptoms and are only identified when a sibling is diagnosed.	The combined worldwide frequency of MCC deficiency is 1 in 40,000 to 1 in 50,000 infants. In a California newborn screening, the prevalence of MCC deficiency is 1 in 27,000. There is no known ethnic variability.
Acrodermatitis enteropathica	AE is a very rare inherited zinc deficiency disease (PMID 19370757). It occurs in early infancy if the child is fed cow's milk or shortly after weaning from breastfeeding. AE is characterized by periorificial (around the natural orifices) and acral (in the limbs) dermatitis, alopecia (loss of hair), and diarrhea. All of these symptoms are due to zinc deficiency. Generalized zinc deficiency causes immune system impairment, infections and failure to thrive. If not treated, multiple organ failure can cause death. However, zinc supplementation can reverse all symptoms.	AE occurs worldwide with no sex or ethnic predilection. However, about half of AE cases were reported from the countries in the Mediterranean basin. The estimated frequency of AE was 1 in 500,000 people in Denmark but not known in other countries (PMID 2691254).
Alpha-1 antitrypsin deficiency	Alpha-1 antitrypsin (AAT) is a protein in the plasma that helps prevent the lungs from being damaged by a powerful enzyme called neutrophil elastase. Neutrophil elastase functions to help digest bacteria and cell debris. AAT functions to inactivate the enzyme when it is no longer needed. Left unchecked, neutrophil elastase eats away at the inner lining (alveoli) of the lung, leading to emphysema and chronic obstructive pulmonary disease (COPD). 95% of individuals with alpha-1 antitrypsin deficiency (AATD) carry a mutation called the Z allele on both copies of the AAT gene that reduces the level of AAT in the blood. Individuals with AATD may remain healthy throughout their lives. However, AATD leaves the individual at great risk for developing potentially fatal lung and liver disease. Normally alpha1-antitypsin is produced in the liver and travels to the lungs to where it is needed. The Z allele produces an altered AAT protein that accumulates in the liver, leaving the lung unprotected and causing liver damage. In rare cases, some AATD individuals develop a skin disease called panniculitis. Smoking is a major contributor to the development of AATD-associated emphysema. Cigarette smoking exaggerates the defect of AAT variants by decreasing the number of functional AAT molecules available to protect the lung. Non-smokers often have a normal life span. However, for AATD patients with emphysema, the 2-year mortality rate is 40% if lung function has deteriorated.	AATD is one of the most common potentially fatal single-gene diseases in the world. AATD has been identified in virtually all populations and ethnic groups, but is most common in individuals of Northern European (Scandinavian and British) and Iberian (Spanish and Portuguese) descent. About 100,000 Americans have AAT deficiency. It is estimated that one in every 2,500 U. S. Caucasians has AATD. The overall carrier rate among U. S. Caucasians for AATD is 1/33. It is not a rare disease but it is a disease that has been infrequently diagnosed.

Disease	Description	Ethnic Prevalence and Frequency
Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig's disease, is a progressive, lethal disease that affects motor neurons in the brainstem and in the spinal cord. With the deterioration of the neurons that control muscle movement, ALS patients gradually lose their strength, their ability to walk, and the use of their hands and arms. Eventually their muscles become too weak for them to breathe and they die from respiratory failure. The median age of onset is 55 years; death usually occurs within 1-5 years after onset. Most cases of ALS occur in individuals with no family history of ALS (sporadic ALS or SALS). However, 10% of ALS cases can be attributed to an inherited genetic defect (familial ALS or FALS). Single mutations responsible for FALS have been found in at least half a dozen genes. Different types of FALS are classified according to the gene involved, age of onset and disease progression. For persons carrying an ALS mutation, the risk of developing the disease increases with age.	The prevalence of ALS is approximately 4 to 8 per 100,000. There are no populations with an increased prevalence except for the South Pacific Islanders for whom the incidence is higher.
Argininosuccinate lyase deficiency	Argininosuccinate lyase deficiency (ASLD) is a serious inherited disorder which can cause the accumulation of potentially fatal levels of ammonia in the blood of newborn infants (PMID 12384776, PMID 18666241, PMID 15465784). In the more common and serious neonatal form of ASLD, infants which appear normal at birth, start accumulating ammonia and other toxic metabolites shortly thereafter. The affected infant may appear irritable, feed poorly, become lethargic, vomit, show poor muscle tone, suffer seizures and lose consciousness. If not treated promptly, the accumulation of toxic metabolites like ammonia can cause irreversible brain damage, seizures, coma and ultimately death. A milder form of ASLD can develop late in infancy or early childhood with physical signs such as fragile brittle hair, enlarged liver and small head size as well as neurological symptoms such as hyperactivity, behavior problems and learning disabilities. Episodes of excess ammonia in the blood can be triggered by the stress of illness or infection, by long periods of starvation or by high-protein meals. These episodes may give rise to symptoms similar to those described for neonatal ASLD with similar risks of permanent brain damage and mental retardation if not treated promptly.	The incidence of ASLD is estimated to be approximately 1 in 70,000 live births in the U. S. (PMID 15465784). In the Druze community in Israel, which is characterized by marriage between close relatives, the carrier rate for ASL mutations was determined to be 1 in 41 (PMID 19092443).
Autoimmune polyglandular syndrome, type I	Autoimmune polyglandular syndrome 1 is an autoimmune disease that affects the organs of the endocrine system, specifically the parathyroid and adrenal glands, as well as causing ectodermal defects. APS1 is diagnosed when patients present with at least two out of the three main clinical symptoms, mucocutaneous candidiasis (thrush), hypoparathyroidism and adrenocortical insufficiency (Addison's disease). Mucocutaneous candidiasis generally is the first clinical symptom and in many patients is seen in the first five years of life. Typically hypoparathyroidism presents next followed by adrenal insufficiency within the first two decades of life (PMID 9543115). However, the order, age of onset and severity of symptoms can vary. Patients also often develop additional endocrine and ectodermal symptoms well into the fifth decade of life that can include type 1 diabetes, hypothyroidism, hepatitis, ovarian or testicular failure, malabsorption, nail bed pitting, alopecia and vitiligo. Generally, early onset of the three diagnostic symptoms correlates with a higher chance of developing additional symptoms, but this is not true in all cases. Treatment for APS1 typically consists of hormone replacement therapy to compensate for loss of the endocrine function coupled with medications to alleviate symptoms such as candidiasis. Some studies have also suggested that immunosuppressive therapies may be therapeutic in severe cases (PMID 11976729).	APS1 is a rare disease in most populations but the incidence of APS1 is higher in some populations. The incidence of APECED in Finland, Sardinia and among Iranian Jews is 1:25,000, 1:14,400 and 1:9,000, respectively (PMID 15157567).

Disease	Description	Ethnic Prevalence and Frequency
Bartter syndrome type 4A	Bartter syndrome type 4A is a rare, inherited autosomal recessive disease. It is characterized by severe renal salt excretion, too much base in the blood due to reduced blood potassium and elevated calcium in the urine. The syndrome is associated with sensorineural deafness and progression of chronic renal failure, which is an uncommon complication for other types of Bartter Syndrome. The patients have a triangular face, protruding ears and large eyes. Patients also have maternal polyhydramnios (excess amniotic fluid), premature birth and excessive urination after birth. In some cases, children who had Bartter syndrome were from consanguineous families (PMID 16328537).	Information on the prevalence of this type of Bartter syndrome is not available.
Beta-ketothiolase deficiency	Beta-ketothiolase deficiency is a rare disease. Since 1971, there have been only 90 patients reported (PMID 20156697). The symptoms appear between the ages of 6 to 24 months and include intermittent ketoacidotic episodes of vomiting, dehydration, difficulty breathing, extreme fatigue and, occasionally, seizures. There are no clinical symptoms between episodes. The episodes can be induced by infections, fasting or intake of protein-rich foods (PMID 20156697).	The incidence of beta-ketothiolase deficiency is estimated to be fewer than 1 in 1 million newborns (http://ghr.nlm.nih.gov/condition/beta-ketothiolase-deficiency). A higher incidence of the disease is found in Vietnam (1 in 333,000 newborns) (PMID 20156697).
Beta-thalassemia	Beta-thalassemia is an autosomal recessive disease that abolishes or causes a decrease in production of the ß hemoglobin protein. The severity of the disease depends on the severity of the mutation and on whether both copies of the HBB gene (one from the mother and one from the father) are affected. In the most severe form of ß-thalassemia, typically called thalassemia major or Cooley's anemia, the patient requires lifelong blood transfusions to survive. Such patients may live 40 years or longer, but the most common cause of death is heart failure. In the less severe form of ß-thalassemia, called thalassemia intermedia, the patient has significant anemia, but does not require blood transfusions.	Beta-thalassemia is found in people of Mediterranean, Middle Eastern, African, South Asian (Indian, Pakistani, etc.), Southeast Asian and Chinese descent. The high prevalence of the ß-thalassemia mutations in areas of the world where malaria is endemic suggests that mutations associated with ß-thalassemia may confer some protection against malaria.The highest disease incidences are in Cyprus (14%), Sardinia (12%), and Southeast Asia. In certain areas of India and Asia, the prevalence of ß-thalassemia is 1 in 2000 births.
Biotinidase deficiency	Biotinidase deficiency is caused by a defect in the way the body uses the vitamin biotin. Without biotin, multiple metabolic reactions necessary for processing proteins, fats and carbohydrates are compromised. Children with profound biotinidase deficiency will usually show symptoms at about three months of age, but the disease may remain undetected until the age of 10. The most common symptoms are seizures, low muscle tone, vision and hearing problems, delayed development and various skin problems (skin rash, hair loss and yeast infections). The treatment is effective and simple: taking high doses of biotin daily for life. Early diagnosis is important, because the hearing loss, vision loss and delayed development cannot be reversed by biotin supplementation. Some children with a milder form of the disorder called partial biotinidase deficiency may not show signs of the disorder until after a prolonged infection.	The worldwide incidence, as determined by newborn screening, of profound biotinidase deficiency is 1 in 137,401 persons, of partial biotinidase deficiency is 1 in 109,921 and of the combined incidence of profound and partial biotinidase deficiency is 1 in 61,067. The estimated carrier frequency in the general population is 1 in 120. The condition occurs in all ethnic groups.
Bloom syndrome	Bloom syndrome, which is named after the New York City dermatologist who first described it in 1954, is a rare autosomal recessive disease whose most obvious feature is the unusually small size of the individual before and after birth. The small, slender body combined with a long narrow face, small lower jaw and prominent nose and ears, together with a high-pitched voice, give an elfin appearance to the individual. A characteristic red patch may develop on the face after exposure to sunlight. Individuals with Bloom syndrome are more susceptible to infections of the middle ear and lung, to develop diabetes at an earlier than normal age and to develop a broad range of cancers at an earlier than normal age. Cancer is the most common cause of death in people with Bloom syndrome. Men with Bloom syndrome cannot father children, but women with Bloom syndrome have borne children. Some people with this syndrome may have learning disabilities, but many lead successful lives despite difficulties due to their small size.	The carrier rate among Ashkenazi Jews is 1 in 107. The prevalence of Bloom syndrome is 1 in 48,000 in people of Ashkenazi Jewish descent, who comprise about one-third of individuals with Bloom syndrome. Bloom syndrome occurs in all ethnic groups, but one mutation, blm(Ash), is responsible for most instances of Bloom syndrome in Ashkenazai Jews.

Disease	Description	Ethnic Prevalence and Frequency
Canavan disease	Canavan disease is a fatal, autosomal recessive disease, which is characterized by a progressive deterioration of the white matter of the brain. It was first described in 1931 by Dr. Myrtelle Canavan, who was one of the first female neuropathologists in the United States. The first symptoms appear when the infant is three to nine months old, and may include weak muscle tone (hypotonia), unusually large head size (macroencephaly), abnormal posture and intellectual disability. Most strikingly, children with Canavan disease cannot crawl, walk, sit or talk. They may suffer seizures, become paralyzed, mentally retarded or blind and have trouble swallowing. There is no cure for Canavan disease and the life expectancy is short. Most children with Canavan disease die before age four, but some children may survive into their teens and twenties.	Canavan disease is a rare disease that affects all ethnic groups, but is more common in people of Ashkenazi Jewish descent. The carrier rate in Ashkenazi Jews is 1 in 41 persons. The prevalence of Canavan disease in Ashkenazi Jews is estimated to be about 1 in 6,400 to 1 in 13,456. The carrier rate in individuals not of Ashkenazi Jewish descent is unknown and assumed to be much lower.
Carnitine deficiency, primary systemic	CDSP is a lethal, autosomal recessive disorder characterized by progressive weakness, heart muscle disease (cardiomyopathy) and recurrent brain disorder (encephalopathy) due to fasting low blood sugar. The affected individuals are usually normal at birth and healthy for several years but develop heart disease and heart failure in late infancy or early childhood. L-carnitine therapy from birth prevents the symptoms. Identification of disease-causing mutations is important because the disorder is progressive and lethal and it may be one of the causes of sudden infant deaths (PMID 15591002).	The frequency of CDSP is about 1 in 40,000 newborns in Japan (PMID 10545605), 1 in 37,000 to 1 in 100,000 newborns in Australia (PMID 11295726) and 1 in 67,000 in Taiwan (PMID 20074989). The frequency is not reported in the United States and Europe, but appears to be similar to the frequency in Japan based on the reported cases (PMID 20027113).
Cerebrotendinous xanthomatosis	CTX is a rare, inherited lipid storage disease characterized by chronic diarrhea during infancy, development of cataracts in the late childhood, formation of tendon fat deposits (xanthomas) in young adults and progressive neurologic dysfunction in the adults. In addition, laboratory tests find high plasma and tissue cholestanol concentrations but normal-to-low plasma cholesterol concentration. People with CTX also have an increased risk of developing cardiovascular disease (PMID 10775536).	The incidence of CTX is estimated to be 3 to 5 per 100,000 people worldwide and is more common in the Moroccan Jewish population with an incidence of 1 in 108 individuals (http://ghr.nlm.nih.gov/condition=cerebrotendinousxanthomatosis). The prevalence of the mutation R395C is about 1 in 50,000 among Caucasians (PMID 16157755).
Citrullinemia type I	Citrullinemia is a serious inherited disorder which can cause the accumulation of potentially fatal levels of ammonia in the blood of newborn infants. In the classical type I form of citrullinemia (CTLN1), infants which appear normal at birth, start accumulating ammonia and other toxic metabolites shortly thereafter. The affected infant may appear irritable, feed poorly, become lethargic, vomit, show poor muscle tone, suffer seizures and lose consciousness. If not treated promptly, the accumulation of toxic metabolites like ammonia and glutamine can cause irreversible brain damage, seizures, coma and ultimately death. A milder form of CTLN1 can develop in children or adults, who may suffer intense headaches, slurred speech, partial loss of vision, problems with balance and muscle coordination and lethargy. Women may also experience a form of CTLN1 during pregnancy or after birth.	Citrullinemia type I affects both sexes. The incidence of citrullinemia type I is estimated to be 1 in 57,000 and it affects 74 of 545 (13.6%) individuals with urea cycle disorders. However, this figure does not include the increasing number of patients identified by modern newborn screening programs.

Disease	Description	Ethnic Prevalence and Frequency
Corticosterone methyl oxidase deficiency	Corticosterone methyl oxidase deficiency is an inherited disorder where patients are unable to make sufficient levels of the hormone aldosterone, resulting in neonatal dehydration and severe loss of salts through the kidneys. Patients with type I disease have been associated with the inability to make any aldosterone and with the accumulation of the precursor of aldosterone synthesis. In addition to severe salt-wasting and increased blood potassium, patients often also have low blood pH, failure to thrive and growth retardation in childhood (PMID 9177280, 15134805). As the kidney matures, sodium resorption becomes more independent of aldosterone and often symptoms improve and become milder (PMID 7852500). The CYP11B2 enzyme converts corticosterone to aldosterone in a 2 step process that generates 18-hydroxycorticosterone as an intermediate product. Type 1 and 2 patients have the same clinical symptoms but are distinguished by whether they have decreased or increased levels of 18-hydroxycorticosterone, respectively.	Corticosterone methyl oxidase deficiency of type 1 is a very rare disease and has been identified in less than 50 patients worldwide. Type 2 deficiency is also very rare among the general population, but has an estimated incidence of 1 in 4,000 births among those of Iranian Jewish ancestry (PMID 8481357).
Crigler-Najjar syndrome	Crigler-Najjar syndrome (CNS) is a serious inherited disease that results in the accumulation of toxic levels of bilirubin in the blood. While almost half of infants develop jaundice due to elevated bilirubin levels, those with CNS do not respond to classical treatments and have severe persistent jaundice (PMID 10091414). Crigler-Najjar syndrome is classified into two types based on responsiveness to phenobarbital treatment, which induces UGT1A1 enzyme activity (PMID 10603107). Type 1 CNS patients have no UGT1A1 enzyme activity and are not responsive to phenobarbital while type 2 CNS patients retain some UGT1A1 enzyme activity and respond to phenobarbital. Type 1 CNS is more severe and patients accumulate large deposits of bilirubin in their organs including the brain. Brain damage due to the accumulation of bilirubin, called kernicterus, can occur within the first weeks to years of life and can be fatal. Type 2 patients typically have lower levels of bilirubin so brain damage is rarely observed, and many type 2 patients survive into adulthood without complications. Treatments for both type 1 and 2 include phototherapy with blue lights in infancy and childhood. Type 1 patients typically require liver transplants for survival past childhood, while type 2 patients can be treated with phenobarbital and other pharmaceuticals (PMID 10091414).	Crigler-Najjar syndrome is a very rare disease. The worldwide incidence of the disease is not known and only a few hundred cases have been reported in the literature (PMID 10603107).
Cystic fibrosis	Cystic fibrosis (CF) is one of the most common genetic diseases, affecting over 70,000 people worldwide. It is a complex disease with involvement of several organs including lung and pancreas, with a median predicted survival age of 37. The main diagnostic indicator of CF is that patients secrete an excess of sodium and chloride ions in their sweat. The most well-known symptoms include thick mucus in the lungs that leads to chronic and persistent respiratory infections, and which may lead to respiratory failure. However, people with CF have a wide range of symptoms. Affected individuals may have combinations of symptoms of chronic pulmonary disease, inflammation of the lower airways, gastrointestinal abnormalities, and salt-loss syndromes to varying degrees. In addition, males with CF are likely to be infertile due to malformations of the vas deferens which are part of the male genital tract. CF is inherited as an autosomal recessive disease, meaning that an individual must have a disease-causing variant (also called a mutation or allele) in each copy of the gene in order to develop the disease. The symptoms of the disease vary widely among individuals from moderate to severe depending on what types of mutations are found in the gene, as well as other genetic and environmental factors. Male infertility due to mutations in the CF gene can occur without other symptoms of CF. An increased prevalence CF gene mutation carriers has been noted in individuals suffering from idiopathic pancreatitis, bronchiectasis, allergic bronchopulmonary aspergillosis, and chronic rhinosinusitis, suggesting that there is a broad spectrum of disease associated with the carriage of CF gene mutations.	The prevalence of CF carriers varies in different populations. In certain groups such as Caucasians and Ashkenazi Jews, CF alleles are found in up to 1 in 25 people. CF has a prevalence of 1 in 2500-3000 live births in Caucasians. In other populations, CF is less frequent. Hispanics have a carrier rate of 1 in 58; 1 in 61 in African Americans, and 1 in 94 Asian Americans. The incidence of CF disease in these three populations is 1 in 13,500 for Hispanic people, 1 in 15,100 for African Americans, and 1 in 35,000 for Asian Americans. In native Asians CF is very rare and occurs in only 1 in 900,000 births.

Disease	Description	Ethnic Prevalence and Frequency
Diabetes, permanent neonatal	Neonatal diabetes (ND) is a rare form of diabetes caused by a mutation in a single gene that reduces or eliminates the production of insulin in the pancreas. The consequence is low birth weight and the appearance of other symptoms within the first six months of life. These other symptoms include high levels of blood glucose (hyperglycemia), excretion of glucose in the urine, dehydration and poor growth and development (failure to thrive). In severe cases, infants may produce an excess of acid (ketoacidosis) which can lead to coma. Once diagnosed, the condition can be corrected by giving insulin. ND can be temporary or permanent. In about 50% of the cases, insulin production resumes within 18 months, although the diabetes may return later in life; this is referred to as transient neonatal diabetes (TND). If the insulin deficiency is permanent, the condition is called permanent neonatal diabetes (PND). Mutations in different genes can give rise to the two conditions, although sometimes different mutations in the same gene can give rise to TND or PND. When first diagnosed, ND cannot be classified as transient or permanent by clinical symptoms alone; genetic testing can provide more definitive information as certain mutations are associated with the transient or the permanent form of ND.	The estimated prevalence of neonatal diabetes is about 1 in 400,000 live births and affects people of all ethnic groups. The rarity of this disease is illustrated by noting that monogenic, or single-gene forms of diabetes, which include ND, only account for about 1-5% of all cases of diabetes in young people.
Dihydropyrimidine dehydrogenase deficiency	Dihydropyrimidine dehydrogenase (DPD) deficiency is a serious inherited disorder that results in the accumulation of pyrimidines in the body. Patients with a complete deficiency have variable symptoms with the most common symptoms being convulsive disorders, mental retardation and motor skill retardation. Less frequently, patients have small heads, dysmorphic features, eye abnormalities and growth retardation (PMID 10071185). Typically symptoms of complete deficiency are first observed in infancy or early childhood. The highly variable presentation of symptoms in DPD deficiency suggests that other factors affect the severity of the disease. In families where siblings have the same DPYD gene mutation, sometimes only one sibling will develop symptoms (PMID 10071185). DPD is also required for the breakdown and clearance of a popular chemotherapeutic drug, 5-fluorouracil (5-FU). In patients with DPD deficiency, administration of 5-FU can result in a toxic buildup of 5-FU and has been associated with severe complications and death in response to treatment. Estimates are that 4-7% of people in the U. S. population have a DPD deficiency which is asymptomatic and not detected unless they are treated with 5-FU (PMID 15377401).	The incidence of DPD deficiency is currently unknown. Severe deficiency that results in neurological symptoms appears to be quite rare. However, mild deficiencies that are typically asymptomatic appear to be more frequent throughout the population.
Dubin-Johnson syndrome	Dubin-Johnson syndrome (DJS) is also known as hyperbilirubinemia Type II. Most individuals with DJS, a rare inherited disorder, have no symptoms (PMID 16549534). However, as teenagers, individuals with DJS may develop jaundice caused by chronic or intermittent conjugated hyperbilirubinemia because mutations in the ABCC2 gene prevent liver cells from excreting a water-soluble form of bilirubin, called conjugated bilirubin. Individuals with DJS have a normal lifespan.	DJS has been found in all ethnic groups, but founder mutations are apparently responsible for the high incidence of DJS in Jews from Iran (estimated at 1:1300) and Morocco (PMID 5532959, PMID 11477083).

Disease	Description	Ethnic Prevalence and Frequency
Ehlers-Danlos syndrome, dermatosparaxis	Ehlers-Danlos syndromes (EDS) comprise a diverse group of diseases that affect the connective tissues of the skin, joints and blood vessels. First recognized by Danish and French dermatologists in the 1930s (Edvard Ehlers and Henri-Alexandre Danlos), EDS is characterized by varying degrees of skin elasticity, easy bruising and delayed wound healing with abnormal scarring, highly-bendable joints and generally fragile tissues (PMID 18328988). Many complications result from these primary symptoms and depending on the overall presentation of the disease in an individual or a family, EDS is further classified into six well-defined subtypes (Classical, Hypermobility, Vascular, Kyphoscoliotic, Arthrochalasis and Dermatosparaxis) and a few variant overlap syndromes. Mutations in many genes can cause EDS, because many genes are involved in the formation of connective tissue, both as enzymes and as structural components. Dermatosparaxis, first described in cattle and other animals, is a condition characterized by extremely fragile skin. The term itself means "torn skin" and is caused by alterations in collagen, a protein molecule found in the skin. Fine structure observations of the affected skin show collagen chains that are larger than usual, and apparently brought about by faulty processing of precursor molecules (procollagen) (PMID 8215498). In humans, a disease with the same presentation was found and initially classified "Ehlers-Danlos syndrome type VIIc" but is now known as Dermatosparaxis Ehlers-Danlos syndrome after the animal condition. Another major symptom that is often observed in patients is sagging, redundant skin (excessive skin that folds). The condition may cause large umbilical and inguinal hernias, and premature rupture of the fetal membrane.	Dermatosparaxis Ehlers-Danlos syndrome is extremely rare; very few individuals have been identified with the condition.
Ehlers-Danlos syndrome, hypermobility	Ehlers-Danlos syndromes describe a diverse group of diseases that affect the connective tissues of the skin, joints and blood vessels. First recognized by Danish and French dermatologists in the 1930s (Edvard Ehlers and Henri-Alexandre Danlos), EDS is characterized by varying degrees of skin elasticity, easy bruising and delayed wound healing with abnormal scarring, highly-bendable joints and generally fragile tissues (PMID 18328988). Many complications result from these primary symptoms and depending on the overall presentation of the disease in an individual or a family, EDS is further classified into six well-defined subtypes and a few variant overlap syndromes. Mutations in multiple genes that encode connective tissue structural and synthetic proteins cause EDS. Hypermobility (or type III) EDS, is considered the least severe EDS. Patients with this disease have pronounced joint hypermobility but show no deformations of their skeletal systems. Skin pathologies are minimal, distinguishing it from Classical EDS. The condition leads to recurring dislocations, even with minimum trauma, and chronic pain.	Hypermobility type EDS is estimated to have a prevalence of 1:5,000-20,000 and is more common in women.

Disease	Description	Ethnic Prevalence and Frequency
Ehlers-Danlos syndrome, kyphoscoliotic	Ehlers-Danlos syndromes (EDS) describe a diverse group of diseases that affect connective tissues of the skin, joints and blood vessels. First recognized by Danish and French dermatologists in the 1930s (Edvard Ehlers and Henri-Alexandre Danlos), EDS is characterized by varying degrees of skin elasticity, easy bruising and delayed wound healing with abnormal scarring, highly-bendable joints and generally fragile tissues (PMID 18328988). Many complications result from these primary symptoms and depending on the overall presentation of the disease in an individual or a family, EDS is further classified into six well-defined subtypes (Classical, Hypermobility, Vascular, Kyphoscoliotic, Arthrochalasis and Dermatosparaxis) and a few variant overlap syndromes. Mutations in many genes can cause EDS, because many genes are involved in the formation of connective tissue, both as enzymes and as structural components. Kyphoscoliotic (or type VI) Ehlers-Danlos syndrome may overlap in symptoms with classical EDS (extensible skin, easy bruising, abnormal scarring, highly bendable joints) and vascular EDS (arterial rupture and complications), but it is mainly recognized by progressive scoliosis, or the bending or curving of the spine, and severely limited muscle tone that are evident, often, as soon as after birth (PMID 9557891). In some patients the globe of the eye is also very fragile. Orthopedic surgery can be performed to correct scoliosis while physiotherapy, including swimming, is recommended to increase tone in the large muscle groups. Surveillance for possible ocular and arterial rupture should be constant because severe complications, including blindness and death, may occur thereafter.	Kyphoscoliotic EDS is a rare disorder with an estimated prevalence of 1:100,000 which does not vary by ethnicity. The estimated carrier frequency is 1:150.
Ethylmalonic aciduria	The majority of people carrying two copies of the 625G>A and 511C>T variants are healthy and have no visible symptoms. However, in studies of a rare inherited fatty acid oxidation disorder called short-chain acyl-CoA dehydrogenase (SCAD) deficiency, it was found that 60 out of 67 patients carried two copies of these common variants or one copy of the common variant together with a copy of a rare inactivating mutation in the ACADS gene (PMID 18523805). SCAD deficiency is rare, with an incidence of 1 in 50,000 live births (PMID 16926354). The association of these common variants with a rare, inherited disease suggests that the 625G>A and 511C>T variants may make an individual susceptible to SCAD deficiency, but only in the presence of other genetic or environmental factors (PMID 18523805). Thus, these common variants may be necessary, but not sufficient for the development of SCAD deficiency.	In a U. S. study with 694 subjects, the carrier rates of 625G>A and 511C>T were 1/5 and 1/33, respectively (PMID 12706374). As much as 14% of the normal population may carry two copies of these variants (PMID 18523805).
Factor XI deficiency	Bleeding disorders like hemophilia are caused when blood cells do not clot normally after injury. This is usually due to genetic variations in coagulation proteins that reduce their ability to clot. Factor XI deficiency, also called hemophilia C, is a mild form of hemophilia that was first described in 1953 by Rosenthal et al. in 3 members of an American Jewish family (PMID 13037836). Two sisters and a maternal uncle all bled after dental extractions; the sisters also bled after tonsillectomy. These incidents encapsulate the essential characteristics of factor XI deficiency: it is an inherited condition, it affects both females and males, it is especially prevalent among Ashkenazi Jews, and it occurs more frequently after surgery or trauma in tissues with mucosal surfaces (e.g. the mouth, nose, urinary tract, genital tract). In contrast to hemophilia A and B, spontaneous bleeding, deep muscle bleeding and joint bleeding are uncommon in factor XI deficiency. Individuals with factor XI deficiency are more likely to have bruises, nosebleeds and blood in the urine. Women may have abundant menstrual flow and prolonged bleeding after childbirth. Also in contrast to hemophilia A and B, the severity of bleeding does not correspond to the level of coagulation factor activity in the blood. No factor XI concentrates are available in the U. S., but fresh-frozen plasma or antifibrinolytic agents such as Amicar (aminocaproic acid) or Cyklokapron (tranexamic acid) can be used to control bleeding. Most factor XI deficiency variants have an autosomal recessive inheritance pattern, though some are autosomal dominant.	The estimated prevalence of factor XI deficiency in the American population is 1 in 100,000. The frequency is much higher in certain ethnic groups. 1 in 11 Ashkenazi Jews is a carrier for either one of the two most common factor XI mutations (E117X and F283L). Fewer common mutations have been found in non-Jewish population groups. In a study of 116 ethnically diverse factor XI deficient patients in the UK, Mitchell et al. (PMID 16835901) found that 40% of the mutations were one of the three common mutations (E117X, F283L and C128X). The remaining 60% of mutations included 31 novel mutations and whole gene deletions.

Disease	Description	Ethnic Prevalence and Frequency
Familial dysautonomia	Familial dysautonomia (FD) is an autosomal recessive disease, found almost exclusively in Ashkenazi Jews. FD affects the development and survival of nerve cells in the autonomic and sensory nervous systems. There is a wide range of symptoms that can be caused by the progressive deterioration of nerve cells. In infants with FD, the most distinctive symptom is the absence of overflow tears with emotional crying. Older children may display delayed speech and walking, excessive drooling and sweating, frequent lung infections, and dry eyes. Life expectancy is shortened. Lung disease and unexplained sudden death are the main causes of death. At present, there is no cure and only 60% of FD patients survive to age 20 while 50% survive to age 40.	This disease is almost exclusively found in individuals of Eastern European Jewish descent (Ashkenazi Jews). 90% of American Jews are of Ashkenazi descent. The incidence of FD is 1 per 3900 births; about 1 in 31 Ashkenazi Jews is a carrier of the most common FD mutation.
Familial Mediterranean fever	Familial Mediterranean fever (FMF) causes recurrent episodes of fever and painful inflammation of the membranes that enclose several body cavities. Membranes in the abdomen, joints, and chest are most commonly affected. FMF patients typically experience their first inflammation episode as children, but the first attack can also happen later in life. Although the symptoms usually resolve within 1-4 days, the acute inflammation induces a buildup of immune response proteins in the plasma. In some patients this buildup causes a condition called amyloidosis in the kidneys and other organs. Some people with FMF may have amyloidosis without fever or inflammation episodes. Kidney failure caused by amyloidosis is the major life-threatening complication of FMF. FMF is usually inherited in a recessive manner.	Most FMF cases are found in people descended from Eastern Mediterranean regions. In non-Ashkenazi Jewish, Armenian, Arab and Turkish populations, prevalence of FMF varies from 1 in 200 to 1 in 1,000. Carriers of recessive disease-causing mutations can be found at a rate of one in every 3-7 people in Armenian, Turkish, North African Jewish, and Iraqi Jewish populations.
Fanconi anemia	Fanconi anemia (FA) is a rare autosomal recessive disease, first described by Swiss pediatrician Guido Fanconi in 1927. Features of the disease include aplastic anemia, an increased risk for cancer and leukemia, and cellular hypersensitivity to drugs or agents that act by crosslinking DNA.. Aplastic anemia is a decrease in red blood cell count due to inadequate red blood cell production in the bone marrow. FA patients may have short stature, developmental delay and congenital anomalies of the limbs, heart and/or kidney. Other FA patients are free from any visible disorder except for bone marrow failure that typically occurs before the age of 10. The median survival age of FA patients is 30 years. At least 20% of FA patients also develop cancer. The definitive test for FA is a chromosome breakage test.	Although FA is found in all ethnic groups, one specific mutation, IVS4+4A>T, is unique to FA patients of Ashkenazi Jewish background and has a carrier frequency of greater than 1 in 100 in this population. In the U.S. and Canada, 50% of FA patients are Ashkenazi Jews.
Galactokinase deficiency	Galactokinase deficiency, also called galactosemia type 2, is one of the three inborn errors of metabolism that results in hypergalactosemia and the subsequent buildup of galactose and galactitol in the lens of the eye. The major clinical symptom is the development of cataracts in children not maintained on a lactose-free diet and the appearance of presenile cataracts in adults. The disease is preventable in infants through early diagnosis and treatment with a galactose-restricted diet which includes the avoidance of all milk products since milk sugar (lactose) is a major source of galactose.	Galactokinase deficiency affects all ethnic groups and occurs in about 1 in 1,000,000 in Europe, the U. S. and Asia. The birth incidence of the disease was reported as 1 in 52,000 in Bulgaria, 1 in 153,000 in Austria, 1 in 157,000 in Germany and I in 2,200,000 in Switzerland (PMID 10521295). A high incidence of the disease was found among the Romani Gypsy population from some regions of eastern Europe.

Disease	Description	Ethnic Prevalence and Frequency
Galactosemia	Galactosemia is an autosomal recessive disorder named for high levels of galactose in the blood, which is the primary biochemical finding of the disease. Galactose is a type of simple sugar molecule and is usually coupled with another simple sugar molecule called glucose to form a larger molecule called lactose, which is present in many foods, especially in the milk. Normally ingested galactose is processed to produce energy or used by the body as components in building complex biomolecules. People suffering from galactosemia cannot process galactose efficiently, and as a result, galactose accumulates at toxic levels in their blood and their cells. Because breast milk or dairy products are usually the primary source of nutrition for newborns, galactosemia can cause life-threatening and irreversible damages in affected infants immediately after birth. Common symptoms of untreated patients include feeding difficulties, diarrhea, vomiting, failure to gain weight, liver failure, bleeding, severe bacterial infection, cataracts, and mental retardation. Severe symptoms and complications can be avoided if the diagnosis is prompt and sources of lactose or galactose are immediately eliminated from food intake. Due to newborn screening programs, most galactosemia cases can be diagnosed soon enough for prompt medical intervention. However, even with early diagnosis and adequate treatment, many affected individuals still present with complications later in life, including developmental delays, speech difficulties, learning difficulties, impaired motor functions, and ovarian failure (in females). Depending on the causative genetic change, galactosemia can be categorized into classic galactosemia and a milder form called “Duarte variant galactosemia”, which typically does not cause complications as severe as is seen in the classic form of the disease.	The prevalence of classic galactosemia is about 1 in 30,000 live births, whereas Duarte variant galactosemia has an incidence of about 1 in 16,000 live births.
Gaucher disease	Gaucher disease (GD) is a recessive genetic disorder that is characterized by a variety of symptoms including enlarged spleen and liver, anemia due to the spleen breaking down blood cells, osteoporosis, and yellowish-brown skin pigmentation. Some forms of GD can affect the nervous system. GD is a type of lysosomal storage disease, which occurs when defective enzymes are unable to perform their normal function to clear metabolites from cells. As a consequence, the cells become damaged and produce the symptoms of the disease. Gaucher disease is classified as one of three types based on clinical symptoms and degree of neurological involvement. Type I is characterized by the above-listed symptoms and does not involve the nervous system, with onset from early life into adulthood. Types II and III have neurological involvement and vary from early to late onset, with moderate to severe symptoms. Types I and III GD can be treated with enzyme replacement therapy to reduce symptoms. Gaucher disease is highly variable both in penetrance and expression. Some people with two type I GD mutations may not know that they have the condition because they experience few, if any, of the symptoms. In addition, the symptoms vary from very mild to severe even in people with the same genotype for GD, so the expert advice of physician-geneticist experienced in GD should be sought by anyone concerned about their status for GD based on genetic results.	Gaucher disease is a rare genetic disorder that is exhibited at varied frequencies in the population. Type I is the most common form and is found in approximately 1 in 50,000 live births, with approximately 1 in 100 people estimated to carry a type I mutation. Gaucher disease has the highest carrier rate among people of Ashkenazi Jewish descent where the carrier rate for type I mutations is 1 in 15, with an incidence of about 1 in 1,000. Type II and III are more rare and each is observed in about 1 in 100,000 live births.

Disease	Description	Ethnic Prevalence and Frequency
Glutaric acidemia, type 1	Glutaric acidemia type 1 (GA1) is an autosomal recessive disease that causes brain damage in infants and young children because of a defect in protein metabolism. In the course of normal metabolism, proteins that we eat are broken down into their amino acid building blocks. These amino acids can be reassembled into new proteins or be further broken down as a source of energy. GA1 results from a defect in an enzyme that breaks down certain amino acids (lysine, hydroxylysine and tryptophan). Because of the defect, toxic levels of glutaric acid and 3-hydroxyglutaric acid accumulate in body fluids and are excreted in the urine. Often an illness can provoke a crisis in which the brain is damaged by the accumulation of these toxic substances. Other symptoms of the crisis may include poor appetite, nausea, vomiting, extreme sleepiness, irritability, low muscle tone and muscle weakness. If not treated, breathing problems, seizures, swelling of the brain, blood in the brain (subdural hematoma), coma and sometimes even death can occur. With prompt and lifelong treatment, children with GA1 can often live normal lives. Some people with GA1 have very mild or no symptoms and are only identified when a sibling is diagnosed.	The combined worldwide frequency of GA1 is 1 in 100,000 infants. It is very frequent (up to 1 in 300) among certain ethnic groups such as the Old-Order Amish community of Pennsylvania and the North American Ojibway-Cree in Canada. In Sweden, it affects 1 in 30,000 newborns and about 1 in 50,000 in the U.S. In California newborn screening, the prevalence of GA1 was 1 in 354,000. In the North American Ojibway-Cree, the carrier rate for GA1 is about 1 in 10.
Glycogen storage disease, type 1A	Glycogen storage disease type Ia (GSDIa) is caused by impaired metabolism of glucose and glycogen. Mutations in the G6PC gene which abolish or reduce the activity of the G6PC enzyme result in low levels of glucose in the blood (hypoglycemia), which may cause seizures. G6PC enzyme deficiency also results in the accumulation of glycogen and fat in the liver and kidneys, leading to enlargement of these organs (hepatomegaly and renomegaly). Other biochemical changes in the blood include abnormally high levels of lactate (lactic acidosis), uric acid (hyperuricemia) and lipids (hyperlipidemia). Some affected newborns may present with severe hypoglycemia, but symptoms are more commonly noticed at 3-4 months of age. Affected patients usually have fat faces, thin legs and arms, short stature and suffer from bleeding problems. Untreated patients can have severe complications in multiple organs; however, normal growth and survival to adulthood can be achieved with proper treatment.	The incidence of GSDIa is about 1 in 100,000 in the general population. In Ashkenazi Jewish people, the prevalence is 1 in 20,000, mostly due to the relatively high presence of a mutation (R83C) in this population.
GM1-gangliosidosis	GM1-gangliosidosis is a lysosomal storage disease affecting the central nervous system. There are three clinical phenotypes of GM1-gangliosidosis. The infantile type shows symptoms, at birth or in early infancy, which include low muscle tone, cherry-red spots on the skin, severe degeneration of the CNS and death by the age of 1 to 2. The late-infantile/juvenile type presents between the age of 7 months and 3 years, with slower progression of psychomotor deterioration. The adult/chronic type has late onset and is mostly found in Japanese, with normal neurologic development early on and slow development of dementia with features of Parkinson's syndrome. Only supportive therapy is available for GM1-gangliosidosis patients, including bone marrow transplantation, gene therapy and substrate reduction therapy (PMID 18524657).	GM1-gangliosidosis is very rare, occurring in 1 in 100,000 to 1 in 200,000 live births worldwide (PMID 18524657). Higher incidences of the disease have been found in Brazil (1 in 17,000 births) (PMID 10517258, PMID 9266201), in the Roma people (1 in 10,000 births) (PMID 16941474, PMID 16466959) and in the Maltese islands (1 in 3,700 births) (PMID 9323577).

Disease	Description	Ethnic Prevalence and Frequency
Hearing loss, DFNB1 and DFNB9 nonsyndromic	Hearing loss is the most common sensory disorder and it is categorized in many ways. The severity of hearing loss is graded as mild, moderate, severe or profound. The sound frequencies affected can be low (less than 500 Hz), middle (500-2000 Hz), or high (greater than 2000 Hz), and the impairment can be in only one ear (unilateral) or both ears (bilateral). The defects can be found in the inner ear (sensorineural hearing loss), in the outer or middle ear (conductive hearing loss), or a combination of the two. The symptoms can be progressive (worsening over time) or stable. Hearing loss can begin during any period of life. The impact of hearing loss is most significant if it is prelingual, which refers to hearing loss that begins before the critical period of language acquisition. Most prelingual hearing loss is congenital, which can now be detected by newborn hearing screening programs. Hearing loss can be caused by both external and internal factors. Environmental factors like exposure to loud noises, viral infection, premature birth, use of certain medications, and physical trauma can all contribute to this condition. More than half of hearing loss cases have genetic causes and are considered hereditary. About 1% of genes in the human genome are believed to function in the hearing process. Hereditary hearing loss can be syndromic, meaning that the hearing loss is associated with additional clinical features in other tissues or organs. There are more than 400 syndromes in which hearing loss is a recognized finding, and these make up about 30% of hereditary hearing loss cases. Nonsyndromic hearing loss (NSHL) accounts for the remaining 70% of hereditary hearing loss cases and is predominantly sensorineural. NSHL is usually caused by mutations in a single gene (monogenic), which may be autosomal dominant (a defect in one of a person's two copies of a gene is enough to cause the condition) or autosomal recessive (both copies of the gene must have a mutation in order for the person to exhibit the condition). In some rare cases, mutations are found on the X chromosome (X-linked) or in mitochondrial DNA (PMID 18804553). Genetic hearing loss is highly heterogeneous, meaning that symptoms vary substantially among people with the condition, and the gene variant(s) found are not the only factors that determine the course or severity of the condition. The individual's family history, genetic background and environmental factors play a major role. It is important to consult with the appropriate physicians including audiologists and otolaryngologists if you suspect you have hearing loss. Your genotype may provide important information for your diagnosticians.	In developed countries, hearing loss is the most common birth defect, with one in 500 newborns affected. Because some types of hearing loss are progressive, the prevalence figure gradually reaches 3.5 per 1,000 by adolescence. According to a recent survey in the United States (PMID 18663164), 16.1% of adults have hearing loss in speech frequencies. Men are 5.5 times more likely to have impaired hearing than women. Risk of hearing loss is 70% lower in African-Americans compared to people of European ancestry, whereas Mexican-Americans have the highest odds of both high-frequency hearing loss and bilateral hearing loss. The risk of hearing loss also increases with age.
Hearing loss, DFNB59 nonsyndromic	Auditory neuropathy is a hearing loss caused by a problem in the nerves that transmit sound from the ear to the brain. DFNB59 nonsyndromic hearing loss is a type of auditory neuropathy that was originally discovered in families from different regions in Iran carrying nonsyndromic, bilateral (both ears affected), prelingual sensorineural hearing impairment. Nonsyndromic deafness means the hearing loss is not associated with symptoms affecting other parts of the body. Sensorineural hearing loss is a type of hearing loss in which the cause is associated with the cranial nerve, the inner ear, or the central processing centers of the brain. Prelingual onset of deafness means that a child was born with insufficient hearing or lost his hearing prior to the age at which speech is acquired. The affected individuals have a profound deafness involving all sound frequencies and have trouble learning to speak (PMID 16804542).	Hearing loss due to defects in the DFNB59 gene is a very rare familial disease. DFNB59 mutations have been identified in Iranian, Turkish and Moroccan families (PMID 16804542, PMID 17373699, PMID 17301963). In some cases DFNB59 mutations have been found in deaf Dutch patients with nonsyndromic hearing impairment (PMID 17373699).

Disease	Description	Ethnic Prevalence and Frequency
Hemochromatosis	Hereditary hemochromatosis is a potentially fatal disorder caused by autosomal recessive mutations in any one of several genes that result in abnormally high absorption of iron into the body. The body normally adjusts levels of iron by regulating the intake of iron from the intestines. Because there is no mechanism for excreting iron, any failure to limit the level of iron intake can lead to a dangerous accumulation of iron in the body. Excess iron can damage many organ systems including the liver, skin, pancreas, endocrine glands, joints, and heart. The only way to remove the excess iron is by bloodletting (therapeutic phlebotomy). If such treatment is started in time, the affected individuals will have a normal lifespan. Therefore, early diagnosis is essential.	The prevalence of hereditary hemochromatosis associated with mutations in the HFE gene (HFE-HHC) is 1 in 200 for Caucasians, 1 in 6667 for non-Hispanic blacks and 1 in 3333 for Mexican Americans. Compared to HFE-HHC, hereditary hemochromatosis from mutations in other genes such as HFE2 and TFR2 is rare.
Hemoglobin C	Hemoglobin C disease is an inherited disorder characterized by a mild hemolytic anemia and mild to moderate enlargement of the spleen. The high prevalence (10-20%) of the HbC mutation in certain West Africa populations is likely due to the protection against malarial infection conferred by the two copies of the HbC variant in individuals with HbC disease. Diabetics should be aware that hemoglobin variants such as HbC may give misleading results in the A1C test that is used to measure average blood glucose levels. False A1C test results can lead to false diagnosis, over-treatment or under-treatment of diabetes in people with hemoglobin variants (hemoglobinopathies).	From 1990 to 2003, nearly 7.5 million babies in California were screened for the hemoglobin C trait. The following carrier rates were found for different ethnic groups: 1 in 52 for African-Americans, 1 in 489 for Native Americans, 1 in 1517 for Hispanics, 1 in 5475 for Middle Eastern populations, 1 in 2756 for Caucasians, 1 in 4768 for Asian Indian populations, 1 in 4775 for Filipinos, 1 in 6607 for Asians, and 1 in 14,200 for Southeast Asians. From 1998-2006 in California, the incidence of HbC disease (two copies of the HbC variant) was 1 per 100,000 infants screened.
Hemoglobin E	Hemoglobin E (HbE) disease is an inherited, autosomal recessive disorder characterized by a mild, hemolytic anemia, abnormally small red blood cells (microcytosis) and mild enlargement of the spleen. The high prevalence of the HbE mutation in areas of the world where malaria is endemic is likely due to the protection against malarial infection conferred by the presence of one copy of HbE variant in carriers of hemoglobin E disease. Diabetics should be aware that hemoglobin variants such as HbE may give misleading results in the A1C test that is used to measure average blood glucose levels. False A1C test results can lead to false diagnosis, over-treatment, or under-treatment of diabetes in people with hemoglobin variants (hemoglobinopathies).	HbE is the second most common abnormal hemoglobin disease after sickle cell disease (HbS). HbE is common in Southeast Asia where its prevalence can reach 30-40% in some parts of Thailand, Cambodia and Laos. HbE is also found in Sri Lanka, Northeast India, Bangladesh, Pakistan, Nepal, Vietnam and Malaysia. From 1998-2006 in California, the incidence of HbE disease (two copies of the HbE variant) was 11 per 100,000 infants screened.
HMG-CoA lyase deficiency	HMG-CoA lyase deficiency, also known as 3-hydroxy-3-methyl glutaric aciduria, is a rare and severe disease that disrupts two important biochemical processes inside cells, causing damage to many organs, especially the brain. First, HMG-CoA lyase-deficient patients cannot make small molecules called ketone bodies, which are used as fuel for many organs, particularly the brain, when the body experiences a shortage of sugar-based energy sources. As a result, if sugar-based energy sources are depleted, people with this deficiency have a metabolic crisis because they cannot rely on the alternative energy supply based on ketone bodies. This crisis is usually triggered by a period of feeding disruption or a common infection. The first episode usually occurs within the first year of life and typical symptoms include vomiting, sleepiness and muscle weakness. The symptoms can quickly worsen and result in life-threatening seizures and coma. The second process that is affected by HMG-CoA lyase deficiency is the processing of an amino acid called leucine. Amino acids are the fundamental building blocks of proteins and normally their processing is well balanced inside the body. When leucine cannot be processed normally, acidic byproducts can accumulate to toxic levels, causing a condition called metabolic acidosis, which can damage many types of cells, including brain cells in particular.	Fewer than 100 individuals in the world have been diagnosed with this disease and the vast majority of those cases are from Saudi Arabia, Spain and Portugal.

Disease	Description	Ethnic Prevalence and Frequency
Homocystinuria, cblE type	Homocystinuria of the cblE type is an inherited disorder, which results in the accumulation of homocysteine in the blood. Symptoms of this type of homocystinuria include megaloblastic anemia, developmental delay, failure to thrive, and a variety of neurological defects including cerebral atrophy accompanied by white matter abnormalities. Most patients exhibit symptoms in the first weeks to first two years of life (PMID 15714522). Patients typically respond to treatments including vitamin B12 supplementation, but as with other progressive diseases, are managed better when treatment begins early in life.	Homocystinuria of the cblE type is an extremely rare disease with only 17 diagnosed and reported cases worldwide as of 2005 (PMID 15714522).
Homocystinuria, classic	Classic homocystinuria (PMID 20301697) is an inherited disorder that results in the accumulation of homocysteine and methionine in the blood and urine. The clinical manifestations of homocystinuria include dislocation of the lens of the eyes which usually occurs after the age of 2, skeletal abnormalities including scoliosis and long, thin extremities that give patients a Marfan-like appearance, mental retardation, developmental delay and vascular disorders including thromboembolitic events and accelerated atherosclerosis (PMID 3872065). Patient symptoms vary greatly in their severity, with lens dislocation often being the first classic symptom, leading to a diagnosis in patients who are not detected by newborn screening. Newborn screening using the Guthrie blood spot card can identify hypermethioninemia, one symptom of homocystinuria, which can then be diagnosed upon further testing. Homocystinuria of the classic type is treatable with a combination of therapies including dietary restrictions of certain amino acids, supplementation with vitamin B6 and B12 and betaine treatment. Such treatments ideally are started at birth to prevent any clinical manifestations. When patients are treated they are classified as being vitamin B6 responsive or non-responsive based on whether supplementation with vitamin B6 alone results in the lowering of homocysteine levels. B6-responsiveness can then determine treatment options. The I278T mutation is generally indicative of being B6-responsive, while the G307S mutation is generally indicative of B6 non-responsiveness (PMID 10338090). Patients who are B6 responsive typically have milder clinical manifestations. However, newborn screening typically identifies B6 non-responsive patients more frequently than B6-responsive patients possibly due to a lack of elevated methionine in the blood in the first few days of life in B6-responsive patients (PMID 20301697).	Classic homocystinuria is a rare disease with the worldwide incidence of the disease estimated to be approximately 1 in 200,000 to 1 in 300,000. In some populations the incidence is higher with rates as high as 1 in 20,000 to 1 in 60,000 in Irish, German, Dutch and Australian populations (PMID 10338090). Conversely the incidence in Japan is estimated at 1 in 1,000,000 (PMID 16307898). These figures may be underestimates based on the heterozygous carrier rates observed in a number of populations, suggesting that some patients may be asymptomatic (PMID 19819175).
Hurler syndrome	Hurler syndrome is the most severe form of a condition called mucopolysaccharidosis type I (MPS I) (PMID 20301341). Clinically, Hurler syndrome affects many systems due to the ubiquitous nature of lysosomal degradation of GAGs (PMID 12838287). The symptoms for Hurler syndrome are progressive with age and often begin to occur in early life (ages 1-2). These include skeletal dysplasia (abnormal bone growth), hearing loss, mental retardation, and severe cardiopulmonary failure. Some therapeutic intervention such as enzyme therapy has been reported for this disease (PMID 12517274).	Hurler syndrome is present in all ethnic populations studied but the types and prevalence of each mutation vary considerably. The disease is generally rare and affects about 1:100,000 people.
Krabbe disease	Krabbe disease, which takes its name from the Danish neurologist Knud Haraldsen Krabbe, is a rare and fatal neurological disorder affecting the central and peripheral nervous systems. The severe, rapidly progressing infantile form is the most common type of the disease. Infants are normal at birth but symptoms appear between the ages of 3 and 6 months with muscle weakness, irritability, fevers, limb stiffness, feeding difficulties and slowing of mental and motor development. At a later stage, increasing muscle weakness affects chewing, swallowing and breathing. Infants also have vision loss and seizures. 85-90% of infant patients die before the age of two. Krabbe disease can also occur in children, adolescents or adults. They have similar symptoms but a slower progression. These patients can live significantly longer.	Krabbe Disease affects all ethnic groups and occurs in about 1 in 100,000 births. In Scandinavian countries, higher rates of the disease have been found (1 in 50,000 births). In some Arab communities in Israel, the incidence of the disease was reported to be as high as 1 in 100 to 1 in 150 live births.

Disease	Description	Ethnic Prevalence and Frequency
Lipoprotein lipase deficiency, familial	Hypertriglyceridemia, a condition in which fat (triglyceride) levels in the blood are elevated, is commonly diagnosed. However, genetically inherited defects in the LPL gene that result in lipoprotein lipase deficiency are rarely identified. Lipoprotein lipase deficiency is a severe disease which is usually diagnosed in childhood (PMID 18275685). The affected child may have abdominal pain, inflammation of the pancreas (pancreatitis), an enlarged liver and spleen (hepatosplenomegaly) and fatty deposits in the skin (eruptive xanthomas) (PMID 20301485). The condition is easily treated by following a low-fat diet and avoiding alcohol and medications known to increase fat levels in the blood.	Lipoprotein lipase deficiency is rare and affects approximately 1 in 1 million people. Racial predisposition has not been defined for this genetically inherited disorder.
Maple syrup urine disease	Maple syrup urine disease (MSUD) is characterized by a sweet, maple syrup-like odor in earwax and urine. The smell is from byproducts that are generated when certain amino acids are not processed normally. Amino acids are the fundamental building blocks of proteins and normally their processing is well balanced inside the body. In people with MSUD, an enzyme that is essential for breaking down three amino acids, namely leucine, isoleucine and valine, is lacking or defective. These three amino acids are called branched-chain amino acids because of their common structural features. As a result, these amino acids cannot be removed even when they are accumulated to abnormally high levels in the body, which results in toxicity in many organs, especially the nervous system. MSUD is classified into several types. The most severe and also most common type is classic MSUD, which typically affects newborns. The characteristic sweet smell can be detected in affected newborns within the first day of birth. If untreated, affected infants quickly develop symptoms including poor feeding, vomiting, and lack of energy. By 10 days of age, patients may suffer from life-threatening symptoms such as coma and seizures. Variant types of MSUD usually present milder symptoms at a later age of onset, but they can still lead to severe symptoms and complications if not properly monitored. Mental retardation and psychiatric disorders are the major long-term complications of MSUD, especially in patients whose brain development in early years is affected by long periods of amino acid imbalance.	MSUD affects about one in 185,000 newborns in the general population. Higher incidences are seen in some ethnic groups. In the Ashkenazi Jewish population, the incidence is approximately one in 27,600, and in the Old Order Mennonite population in the US, the frequency is about one in 380.
Medium-chain acyl-CoA dehydrogenase deficiency	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is a genetic disease that disrupts the breakdown of a type of fat molecules called medium-chain fatty acids. The normal breakdown of fats in cells creates smaller molecules that can be used by the brain and other organs as an energy source. Fats as energy sources are important when the body has a strong demand for energy or is depleted of other more readily available sources of energy such as glucose. In individuals with MCAD deficiency, energy cannot be generated from medium-chain fatty acids. Consequently, when they use up other energy sources, they may experience an episode of “energy crisis”, in which they cannot rely on certain fats stored in their own body. Usual symptoms include vomiting, drowsiness, and low blood sugar (hypoglycemia). Such crises usually occur after a long period of fasting or a common infection that causes fever and reduced appetite. The crisis can quickly worsen, causing seizures, coma and even death. Sudden death, usually unexpected for these otherwise healthy individuals, is often the first and only presentation of the disease. Episodes of energy shortage can lead to long-term complications including damage to the brain and muscles. In addition, people with MCAD deficiency often have problems in the liver, the main site for breaking down fatty acids. People with MCAD deficiency typically experience their first episode in infancy, between 3 months to 2 years of age, but the initial attack can also happen later in life.	In the United States, the estimated prevalence is 1 in 17,000 in the general population. MCAD deficiency is more common among individuals of northern European ancestry than people of other ethnic groups. This disease is one of the most frequently diagnosed diseases in newborn screening programs.

Disease	Description	Ethnic Prevalence and Frequency
Methylmalonic acidemia	Methymalonic acidemia causes brain damage in infants and young children because of a defect in protein and fat metabolism. Methylmalonic acidemia results from a defect in one step of a pathway for the degradation of certain amino acids (valine, isoleucine, methionine, threonine) and fats (odd-chain fatty acids, cholesterol). Because of the defect, toxic levels of methylmalonic acid and its by-products accumulate in body fluids and are excreted in the urine. Often times, an illness can provoke a crisis in which the brain is damaged by the accumulation of these toxic substances. Other symptoms of the crisis may include poor appetite, nausea, vomiting, extreme sleepiness, irritability, low muscle tone and muscle weakness. If not treated, breathing problems, seizures, stroke, coma and sometimes even death can occur. With prompt and lifelong treatment, children with methylmalonic acidemia can often live normal lives. A small number of people with methylmalonic acidemia never show symptoms.	In the U.S., the prevalence of methylmalonic acidemia is 1 in 80,000 infants. The prevalence is 1 in 115,000 in Italy and 1 in 169,000 in Germany.
MTHFR deficiency	Severe methylenetetrahydrofolate reductase (MTHFR) deficiency (less than 20% enzyme activity) leads to developmental delays, mental retardation, seizures, and motor and gait dysfunction often early in life (Rosenblatt DS, loc. cit.). However severe deficiency is very rare and has been documented in fewer than 100 cases worldwide. Mutations associated with mild MTHFR deficiency are very common in the general population. Mild deficiency that results in increased homocysteine in the blood, such as in C677T homozygotes, has been linked to an increased risk of cardiovascular diseases as well as to congenital abnormalities such as neural tube closure defects. However, the severity or impact of the disease in people with mild enzyme deficiency has been strongly linked to diet, specifically folic acid intake. Sufficient folic acid intake in C677T homozygotes often reduces blood levels of homocysteine to normal (PMID 12083967). It has also been shown that women who have folic acid supplementation around conception reduce the risk of neural tube closure defects by 50-70%, suggesting that folic acid supplementation may decrease the risk for neural tube defects even in carriers of mild MTHFR mutations (PMID 16672082).	The prevalence of MTHFR carriers varies widely in different populations. The most common variant, known as C677T, leads to mild deficiency and is most prevalent in Mediterranean and Hispanic populations followed by Chinese, Caucasian, other Asian populations and African/African-Americans. In North American populations, the C677T variant is carried by 30% of the population with at least 10% of the population being homozygous, or having two copies of the variant (PMID 12920077, PMID 9545406, PMID 8837319). The second most common mutation known as A1298C is also associated with mild deficiency and is carried by 11-30% of the population with <1%-13% of the population being homozygous (PMID 9719624).
Mucolipidosis II	Mutations in the GNPTAB gene with a complete loss of GNPT enzyme activity cause a severe, neonatal form of mucolipidosis called MLII alpha/beta. MLII alpha/beta is a fatal, inherited disorder caused by a defect in the cell's garbage disposal and recycling system that results in the abnormal accumulation of carbohydrates and lipids in a cellular structure called the lysosome (http://www.ninds.nih.gov/disorders/mucolipidoses/detail_mucolipidoses.htm) (PMID 19617216, PMID 19945768). Cells in the skeletal system are the most sensitive to this defect. At birth, infants with MLII alpha/beta may show abnormal skeletal development, restricted joint movement, and coarse facial features (flat nasal bridge, puffy eyelids, enlarged gums and tongue (PMID 19617216)). The liver, spleen and heart may be enlarged. Affected children fail to grow and develop, have eye problems and suffer respiratory tract infections. There is no cure for MLII alpha/beta. Children with MLII alpha/beta usually die of congestive heart failure or respiratory tract infections before the age of seven.	The incidence of MLII alpha/beta is rare in most populations, with incidences of 1 in 123,457 live births in Portugal, 1 in 252,525 live births in Japan, and 1 in 625,000 live births in the Netherlands (PMID 18190596). In the northeastern part of Quebec, the incidence of MLII alpha/beta is 1 in 6184 live births in a French-Canadian population, but this high incidence is due to the presence of the 3503_3504delTC mutation in the GNPTAB gene in ancestors of this population (PMID 18190596). In this population the carrier rate, which is the highest in the world, is estimated to be 1 in 39.
Mucolipidosis III	Mutations in the GNPTAB gene with a partial loss of GNPT enzyme activity cause a mild, late-onset form of mucolipidosis called MLIII alpha/beta. At 3-5 years of age, children with MLIII alpha/beta begin showing symptoms such as skeletal abnormalities, coarse facial features, short stature and eye problems. Individuals with MLIII alpha/beta may live into their forties (http://www.ninds.nih.gov/disorders/mucolipidoses/detail_mucolipidoses.htm, PMID 19617216, PMID 19945768). Mutations in the GNPTG gene cause a mild, late-onset form of mucolipidosis called MLIII gamma, which is clinically indistinguishable from MLIII alpha/beta (PMID 18203164, PMID 20034096, PMID 19370764).	The incidence of MLIII has been reported as 1 in 52,910 live births in Portugal and 1 in 1,250,000 live births in the Netherlands PMID 14685153).

Disease	Description	Ethnic Prevalence and Frequency
Mucolipidosis IV	Mucolipidosis IV (MLIV) is a devastating inherited disease of the nervous system in which most patients never develop the ability to speak or walk and remain at a developmental level of age 1-2 years. Virtually all MLIV patients lose their eyesight by their early teens as a result of retinal degeneration. There is no cure for MLIV, and it follows an autosomal recessive inheritance pattern.	Two MLIV mutations are especially prevalent in the Ashekenazi Jewish population. This accounts for an MLIV carrier rate of 1 in 103 in Ashkenazi Jews and for an MLIV population prevalence of 1 in 42,436 in Ashkenazi Jews.
Multiple carboxylase deficiency	Multiple carboxylase deficiency (MCD) is a potentially life-threatening inherited disease of newborns caused by a defect in the way the body uses the vitamin biotin. Without biotin, multiple metabolic reactions necessary for processing proteins, fats and carbohydrates are compromised. The consequences can be severe. MCD can develop anytime from soon after birth to 15 months of age and involves an episode of illness called a metabolic crisis. The symptoms may include poor appetite, vomiting, lack of energy, irritability, low muscle tone and severe peeling skin rash. If not treated, breathing problems, seizures, swelling of the brain, coma and sometimes even death can occur. The treatment is effective and simple: high doses of biotin daily for life. Even without metabolic crises, untreated children can suffer mental retardation, hearing loss or vision loss that cannot be reversed by biotin supplementation. The mode of inheritance of MCD is autosomal recessive.	The incidence of MCD is less than 1 per 100,000 births and affects all ethnic groups.
Nephrotic syndrome, steroid-resistant	Steroid-resistant nephrotic syndrome occurs mainly in early childhood (PMID 16291839, PMID 12761252). SRNS is a subgroup of idiopathic nephrotic syndrome, identified on the basis of the patient's response to a standard steroid therapy (PMID 18216321). Steroid-resistant nephrotic syndrome is defined when patients remain unresponsive to the therapy after 8 weeks of treatment (PMID 11733743). The symptoms of the disease include progressive kidney failure, excessive amount of protein in the urine (proteinuria), bloating of the body (edema), abnormally low concentrations of albumin in the blood serum (hypoalbuminemia), and high concentrations of lipid in the blood (hyperlipidemia). Additional complications include infections, anemia, and high blood pressure (hypertension) (PMID 11733743).	Steroid-resistant nephrotic syndrome affects people of different races and ethnic backgrounds (PMID 11733743). Nephrotic syndrome has a prevalence of 16 cases per 100,000 children, and SRNS accounts for approximately 20% of these patients (PMID 11733743).
Niemann-Pick disease	Niemann-Pick disease (NPD) is an autosomal recessive disease that causes organ damage because of a defect in fat metabolism. In NPD patients, some types of lipids are not properly transported to cellular organelles called lysosomes or are not degraded efficiently in the lysosomes. These undegraded lipids accumulate in cells and cause symptoms in multiple organs, including liver, lung, spleen, and the nervous system. NPD is categorized into three main types according to the genetic basis and symptoms. NPD type A is the most severe form and refers to affected individuals who develop neurologic symptoms during infancy. Enlargement of the liver is usually noticed in NPD type A patients by three months of age. Such patients usually do not survive beyond age three. NPD type B generally has a later age at onset compared with type A and has milder symptoms. Type B patients usually do not present neurologic symptoms or the nervous system is affected only later in life. Survival into adulthood is common for NPD type B patients. NPD type C typically manifests first in childhood, but infant or adult onset is also possible. Type C patients can usually survive to late second or third decade when pneumonia is the most life-threatening complication.	Mutations causing NPD type A are especially prevalent in the Ashkenazi Jewish population (Jewish people descended from central and eastern Europe), in which the three most common type A mutations have a combined carrier frequency of 1 in 80 to 1 in 100. Because of implementation of carrier screening programs, birth incidence in this population has been significantly reduced. NPD type B has a wider ethnic and regional distribution and is found more frequently in people of Turkish, Arabic and North African descent. The combined incidence of types A and B in non-Ashkenazi Jewish populations is about 1 in 250,000. Incidence of NPD type C is 1 in 150,000 in Western Europe.

Disease	Description	Ethnic Prevalence and Frequency
Phenylketonuria	Phenylketonuria (PKU) is the most common hereditary disorder of amino acid metabolism, inherited in an autosomal recessive manner. It is diagnosed when a harmful level of an amino acid called phenylalanine is measured in the blood. The disease is named for the finding of increased levels of phenylketone that is converted from accumulated phenylalanine and detected in the urine. Amino acids are building blocks of proteins and phenylalanine is one of the essential amino acids for humans that can only be acquired from the diet. However, excessive phenylalanine is toxic to the brain and impairs cognitive development. Classical PKU is the most severe form of the disease. Untreated newborns with classical PKU can develop irreversible mental retardation, psychiatric problems and seizures. Symptoms are usually noticed several months after birth. Milder forms of the disease, including non-PKU hyperphenylalaninemia and variant PKU, also present high blood levels of phenylalanine, but they have lower risks for neuropsychiatric disorders. The implementation of newborn screening programs for PKU has significantly reduced the damage of the disease. PKU can be successfully diagnosed during newborn screening and treated by restricting phenylalanine intake. However, haphazard compliance of dietary restriction, especially during childhood, can still result in cognitive impairment.	Reported incidence of PKU at birth varies among ethnic groups. Generally, the incidence is 1 in 10,000 for Caucasians and East Asians, and about 1 in 100,000 for people of African descent. Newborn screening can detect most PKU cases. Consequently, most patients are treated immediately upon diagnosis and severe symptoms are prevented.
Polycystic kidney disease	Infants with autosomal recessive polycystic kidney disease (ARPKD) develop large numbers of fluid-filled sacs (called cysts) in enlarged kidneys. Most people with ARPKD are identified before birth or during the neonatal period. The cysts can be detected in fetuses or infants by ultrasound imaging. Cysts can also be found in liver, spleen and other organs. A major complication of the kidney disease before birth is a lack of amniotic fluid. Since the amniotic fluid is essential for the development of lungs, ARPKD infants are often born with underdeveloped lungs. About a third of ARPKD newborns die and their malfunctioning respiratory system is the major cause of death in this period. More than half of the ARPKD patients who survive infancy die from end-stage renal disease, usually before 10 years of age. Because of improved treatment and kidney transplantation, many patients can now survive to the second decade. ARPKD is less common than the autosomal dominant form of polycystic kidney disease.	The incidence of ARPKD at birth is about 1 in 10,000 to 1 in 40,000. However, because many newborns that die from ARPKD have not been correctly diagnosed, the actual incidence may be higher.
Pompe disease	Pompe disease is a type of glycogen storage disease. Glycogen molecules are large carbohydrates consisting of repeating units of glucose and normally serve to store energy in the body. In people with Pompe disease, glycogen accumulates inside the cell to abnormal levels because an important enzyme required for breaking down glycogen is lacking or does not function efficiently. Muscles are most prominently affected in Pompe disease patients. Typical symptoms of Pompe disease include muscle weakness, low muscle tone, feeding difficulties, labored breathing, coughing, and slowed growth rate. In severe cases, accumulated glycogen in heart muscle cells causes enlargement of the heart. Pompe disease is classified into two general subtypes according to the age when the symptoms appear. The infantile-onset Pompe disease typically has a poor outcome. Symptoms may even be detected during pregnancy, but more commonly are noticed within the first year of life. Although symptoms worsen at variable rates in infantile-onset cases, untreated patients usually die early in childhood. In contrast, late-onset cases usually have milder symptoms and people with this form of Pompe disease generally do not develop heart problems.	The combined incidence of all forms of Pompe disease in the United States is about 1 in 40,000 persons. Incidences vary among ethnic groups and are relatively high in African Americans (1 in 14,000). In people of European ancestry, the incidence is 1 in 60,000 for late-onset cases and 1 in 100,000 for infantile-onset cases.

Disease	Description	Ethnic Prevalence and Frequency
Prekallikrein deficiency	Prekallikrein deficiency was first described in 1965. It is known to cause mild to severe bleeding symptoms with extended clotting times. In some cases, patients can present with routine nose bleeds in childhood and later show severe hematomas and recurrent mucosal bleeding episodes. These symptoms can often be confused with other hemophilia-like disorders (PMID 14652634).	Prekallikrein deficiency (PKD) is a rare congenital disorder that is often confused with hemophilia and can be misdiagnosed. PKD is not known to be biased in terms of race or ethnicity, age, or sex.
Propionic acidemia	Propionic acidemia is an autosomal recessive disease that causes brain damage in infants and young children because of a defect in protein and fat metabolism. Propionic acidemia results from a defect in one step of a pathway for the degradation of certain amino acids (valine, isoleucine, methionine, threonine) and fats (odd-chain fatty acids, cholesterol). Because of the defect, toxic levels of propionic acid and its by-products accumulate in body fluids and are excreted in the urine. Often times, an illness can provoke a crisis in which the brain is damaged by the accumulation of these toxic substances. Other symptoms of the crisis may include poor appetite, nausea, vomiting, extreme sleepiness, irritability, low muscle tone and muscle weakness. If not treated, breathing problems, seizures, swelling of the brain, stroke, coma and sometimes even death can occur. With prompt and lifelong treatment, children with propionic acidemia can often live normal lives. A small number of people with propionic acidemia never show symptoms.	The incidence of propionic acidemia is very low worldwide (about 1 in 50,000) but highly variable: 1 in 1000 in the Inuit people of Greenland, 1 in 17,400 in Japan, 1 in 27,264 in Saudi Arabia, 1 in 129,000 in the U.S., and 1 in 250,000 in Germany.
Prothrombin deficiency	Prothrombin deficiency, also known as factor II deficiency, is characterized by increased bleeding tendency. Inherited prothrombin deficiency is very rare. Other (non-genetic) risk factors for prothrombin deficiency include severe liver disease and low levels of vitamin K. Symptoms range from severe to mild bleeding. Hypoprothrombinemia (type I) is associated with severe bleeding, while dysprothrombinemia (type II) is associated with variable bleeding tendency (PMID 12149217). Severe symptoms include bleeding into a joint (hemarthrosis) or bleeding outside of a blood vessel (hematoma). Mild symptoms include nose bleeding and prolonged oozing after medical procedures (PMID 11154146).	Prothrombin deficiency has been identified in patients with diverse ethnic origins. The disease prevalence is 1 in 2,000,000 in the general population (PMID 19598065). Higher frequencies of the disease have been detected in Puerto Rico (PMID 14629473). Prothrombin deficiency is often associated with parental consanguinity (parents with common ancestors) (PMID 11154146, PMID 16543981).
Rh-null syndrome	Rh-null syndrome has been described in a few cases where abnormal red blood cells (RBCs) have been characterized from people, typically when receiving or donating blood. RBCs are devoid of Rh factor and exhibit a distinctive morphology pattern which includes cell swelling. Rh-null syndrome caused by RHAG defects is extremely rare and is often found in consanguineous families (closely related parents). Clinically, Rh-null syndrome can result in mild anemia.	Rh-null syndrome is a very rare congenital disorder that may affect only 1 in 6 million people (PMID 6036671, PMID, 4627672). This disease is not known to be biased in terms of race or ethnicity, age, or sex.
Rickets, pseudovitamin D-deficiency	Pseudovitamin D-deficiency rickets, also known as vitamin D-dependent rickets type I, is a rare inherited disorder characterized by muscle weakness, failure to thrive and early onset of rickets with hypocalcemia (low blood calcium). The patients have normal concentrations of 25(OH)D but very low amounts of 1,25(OH)2D. The disease can be treated with physiological doses of 1,25(OH)2D or 1-alpha(OH)D (PMID 17488797).	Pseudovitamin D-deficiency rickets is common in French Canadians with a carrier rate of 1/26 in the Charlevoix-Seguenay-Lac Saint Jean area in Quebec (PMID 1937486). The incidence of the disease in Denmark is 0.4 per 100,000 (PMID 19095780).

Disease	Description	Ethnic Prevalence and Frequency
Sandhoff disease	Sandhoff disease is an inherited disorder characterized by a gradual deterioration of the central nervous system. Depending on the symptoms and the age of onset, there are three clinical forms of the disease (infantile, juvenile and adult forms). The infantile form is the most severe. The disease onset is during the first 5-6 months of life and the manifestations include developmental delay, seizures, partial or complete vision loss (amaurosis) and appearance of cherry-red spots on the retina. The child in terminal stages of Sandhoff disease regresses to an unresponsive, vegetative state. Death occurs by 3-4 years of age and is usually caused by respiratory infections (PMID 1531140, PMID 7557963) (http://www.ninds.nih.gov/disorders/sandhoff/sandhoff.htm). The juvenile form and the adult form have milder clinical symptoms. The manifestations for the juvenile form appear at 3-10 years of age. The patients can survive into adulthood. The symptoms include progressive muscle degeneration and weakness (muscular atrophy), uncoordinated muscle movement (ataxia), and mental illness (PMID 1531140, PMID 7557963).	Unlike Tay-Sachs disease, which is highly prevalent among Ashkenazi Jews, Sandhoff disease is not limited to any ethnic group (http://www.ninds.nih.gov/disorders/sandhoff/sandhoff.htm). However, a high incidence of Sandhoff disease is found in some geographically isolated populations in northern Saskatchewan (Metis Indians), in the Argentinean province of La Roija (PMID 1390948) and in the Maronite community in Cyprus (PMID 10982028). In the U. S., the carrier rate of Sandhoff disease has been estimated to be 1 in 278 in the non-Jewish population and to be 1 in 500 in the Jewish population (PMID 2955697).
Short-chain acyl-CoA dehydrogenase deficiency	Short-chain acyl-CoA dehydrogenase (SCAD) deficiency is a rare inherited fatty acid oxidation disorder (PMID 18977676). Clinical symptoms may appear during infancy or early childhood; these include failure to thrive, lack of energy, poor muscle tone, seizures, developmental delay and acute acidosis (PMID 18977676). In laboratory tests, people with SCAD deficiency exhibit elevated levels of ethylmalonic acid in the urine . In some patients, the symptoms do not appear until adulthood. Other patients may never develop any symptoms.	The incidence of SCAD deficiency is approximately 1 in 40,000 to 100,000 newborns. In the Netherlands, the incidence of SCAD deficiency was determined to be 1 in 50,000 live births (PMID 16926354).
Sick sinus syndrome	Sick sinus syndrome (SSS) is a condition caused by malfunction of a structure in the heart called the sinus node (also known as the sinoatrial node), which plays an important role as the heart's pacemaker. The rhythm of normal heartbeats is controlled by regular electrical signals sent out from the sinus node. In SSS, the sinus node fails to function properly or the impulses from the sinus node fail to transmit to adjacent heart muscle cells. As a result, the heart rate may slow to an abnormal level (bradycardia) and the heartbeat may even pause or stop. Sometimes the heart rate may alternate between abnormally fast and slow periods. In some patients, the heart rate does not show proper response to exercise, stress or emotional changes. Frequent dizziness and fainting are usual symptoms. The majority of SSS cases are seen in older people and are caused by age-related degeneration of the cells in the sinus node. In cases of which the genetic causes are known, SSS is often associated with other heart conditions such as Brugada syndrome, cardiac conduction defect and long QT syndrome (PMID 18436145). However, SSS is also found as a congenital form in children who do not have other underlying heart problems.	Prevalence of SSS is about 3 per 10,000 in the general population, and is higher with advanced age. Men and women are equally affected.

Disease	Description	Ethnic Prevalence and Frequency
Sickle cell disease	Sickle cell disease is an inherited disorder, which is chronic, lifelong, and is associated with a decreased lifespan (PMID 20301551, PMID 12580362, PMID 11792081). In sickle cell disease, the red blood cells become crescent-shaped or "sickled" and clump together and stick to blood vessel walls. Aggregation blocks blood flow within limbs and organs. This can cause painful episodes and permanent damage to the eyes, brain, heart, lungs, kidneys, liver, bones, and spleen. Infections and lung disease are the leading causes of death for people with sickle cell disease. The high prevalence of the Hemoglobin S (HbS) variant in areas of the world where malaria occurs is due to the protection against malarial infection conferred by the presence of just one HbS variant (carriers of the sickle cell trait just have one copy of HbS) (PMID 18410566). Diabetics should be aware that hemoglobin variants such as HbS may give misleading results in the A1C test, which is used to measure average blood glucose levels (PMID 11159762). False A1C test results can lead to false diagnosis or over-treatment or under-treatment of diabetes in people with hemoglobin variants (hemoglobinopathies).	Sickle cell disease occurs in 1/500 African American births and in 1/1000 to 1/4000 Hispanic American/Latino births. It is the most common inherited blood disorder in the U. S. About one in 12 African Americans is a carrier of the sickle cell trait. About one in 100 Hispanic Americans/Latinos is a carrier of the sickle cell trait. From 1990 to 2003, nearly 7.5 million babies in California were screened for the sickle cell trait. The following carrier rates were found for different ethnic groups: 1/15 (Black), 1/150 (Native American), 1/203 (Hispanic), 1/478 (Middle Eastern), 1/642 (White), 1/652 (Asian Indian), 1/879 (Filipino), 1/1315 (Asian), 1/2365 (Southeast Asian) (http://www.cdph.ca.gov/programs/NBS/Documents/NBS-HbTraitFactSheetJuly04.pdf)
Spherocytosis, hereditary	Hereditary spherocytosis (HS) is a very heterogeneous disease with symptoms that range from mild to very severe and life-threatening (PMID 18940465, PMID 18757847). Although HS may develop at any age, most cases are diagnosed in infancy or childhood. Most cases of HS are mild to moderate. About 10% of HS patients require occasional blood transfusions and only 3-4% of patients have a life-threatening anemia that requires regular transfusions (PMID 15071790). The disease gets its name from the characteristic spherical shape assumed by red blood cells (RBC) in patients with spherocytosis. The spherical RBC are more fragile and are destroyed in the spleen. All the major symptoms of HS (anemia, spleen enlargement, jaundice, reticulocytosis and gallstone formation) are consequences of the biological defect in HS. Anemia or lack of RBC is caused by the increased destruction of RBC in the spleen; the spleen becomes in enlarged because of the increased volume of defective RBC to process. Increased breakdown of RBC releases more bilirubin which is the cause of jaundice. In response to anemia, more immature RBC appear (reticulocytosis) because more replacement RBC are needed. The increased in bilirubin is believed to precipitate the formation of gallstones. Removal of the spleen can cure HS, because the spherical RBC have a nearly normal lifespan when there is no spleen to remove them (PMID 15071790).	Hereditary spherocytosis (HS) is found in all ethnic groups, but is the most common inherited anemia in individuals of northern European descent with a frequency of about 1:5000 (PMID 18940465). About 1% of the population in the U. S. is estimated to be a silent carrier of a mutation for recessive HS (PMID 15071790). About 40-65% of HS cases in northern European populations are due to defects in the ANK1 gene. In contrast, only 5-10% of HS cases in Japan are due to defects in the ANK1 gene. Less than 5% of HS cases are caused by defects in the EPB42 gene in northern European populations. In contrast, in Japan, 45-50% of HS cases are caused by defects in the EPB42 gene.
Tay-Sachs disease	Tay-Sachs disease, also known as GM2 Gangliosidosis, is a severe genetic disease that causes degeneration of nerves and can result in the loss of motor function, mental retardation, and ultimately death depending on the classification of the disease (PMID 20301397). The infantile onset form is the most serious. Neurodegeneration occurs in Tay-Sachs disease due to the lack of an enzyme called hexosaminidase A, which is required to break down fatty acids as part of cellular maintenance. When the enzyme is missing or nonfunctional, these fatty acids accumulate and damage the cell. These fatty acids are most prevalent in neurons and thus the lack of the enzyme most severely affects neurons. The severity and onset of the disease are related to the amount of enzyme activity present in the body. There is currently no cure or treatment for Tay-Sachs disease. Tay-Sachs screening programs are a model for the success of genetic screening and genetic counseling (PMID 10464605, PMID 11216898). Since screening began for Tay-Sachs enzyme levels and known Tay-Sachs mutations, the incidence of the disease has been drastically reduced in populations with increased carrier rates.	The incidence of Tay-Sachs in US populations is approximately 1 in 320,000 live births, with the carrier rate of Tay-Sachs mutations in the general population being approximately 1 in 250. Tay-Sachs disease risk is much greater among certain populations such as Ashkenazi Jews where the carrier rate is 1 in 27 with the disease affecting 1 in 3600 live births (PMID 18197058, PMID 20301397). French-Canadian Catholics and Louisiana Cajuns also have a carrier rate of approximately 1 in 27. Individuals with Irish ancestry show increased risk for the disease with the Irish American carrier rate being 1 in 50.

Disease	Description	Ethnic Prevalence and Frequency
Tay-Sachs pseudodeficiency	Tay-Sachs pseudodeficiency is not a disease. Tay-Sachs enzyme screening programs (as opposed to DNA testing) detect carriers by testing the activity of the HEXA enzyme. A deficiency in HEXA enzyme activity most often means that a person is a carrier for Tay-Sachs disease (PMID 20301397). However, there are known changes in the HEXA gene that do not cause the disease, but can cause positive results in the enzyme screening test because the test uses a synthetic substrate. The synthetic substrate does not react with the HEXA protein that has these gene changes, leading to a false-positive enzyme test result. These HEXA gene changes are called "pseudodeficiency" alleles because they affect test results but not disease or carrier status.	Up to 35% of non-Ashkenazi people who test positive for Tay-Sachs carrier status in the enzyme test actually have a pseudodeficiency allele and are not at risk of passing a disease-causing variation to offspring (PMID 20301397). In contrast, about 2% of people of Ashkenzai Jewish descent who test positive for Tay-Sachs carrier status in the enzyme test are found to carry a pseudodeficiency allele.
Thrombocytopenia, congenital amegakaryocytic	CAMT is an extremely rare inherited bone marrow failure disease (PMID 16219544, PMID 10077649). Patients have a severe low platelet count (thrombocytopenia) at birth, but no physical anomalies. Based on the course and outcome of the disease, CAMT is classified into two types: CAMT type I is characterized by early onset of severe pancytopenia (shortage of red and white blood cells as well as platelets), decreased bone marrow activity, and very low platelet counts. CAMT type II is characterized by transient increases of platelet count up to nearly normal counts during the first year of life and an onset of bone marrow failure at age 3 or later. Platelet transfusion is an effective treatment to CAMT patients but the only curative therapy to date is hematopoietic stem cell transplantation.	CAMT is an extremely rare disease and there is no information available concerning its prevalence.
Tyrosinemia	Tyrosinemia is an inherited genetic disorder that disrupts the breakdown of an amino acid called tyrosine. Amino acids are the fundamental building blocks of proteins. Normally the construction (anabolism), breakdown (catabolism) and conversion of amino acids are well balanced inside the body. Tyrosine is normally broken into smaller, nontoxic molecules in five successive steps with the assistance of multiple enzymes. In people with tyrosinemia type I, the enzyme that is responsible for the last step of this process is lacking or defective. As a result, the stepwise reactions cannot be completed, whereas tyrosine and intermediate products generated during this process are accumulated. Some accumulated intermediate products are converted to other molecules that normally should not be present at high levels. The accumulated tyrosine, intermediate products and byproducts are toxic to many cells and lead to a variety of clinical manifestations found in tyrosinemia type I patients. Infants with tyrosinemia type I typically show symptoms within the first year of life, although the age at onset of the initial symptoms, the organs involved and the progression of the disease vary significantly among affected individuals. Common symptoms of tyrosinemia type I include liver failure, liver cancer, kidney dysfunction, delayed growth, rickets, and recurrent crises of the nervous system. Untreated children usually die before 10 years of age.	The incidence of tyrosinemia type I at birth is about one in 100,000 to 120,000.

Disease	Description	Ethnic Prevalence and Frequency
Very long-chain acyl-CoA dehydrogenase deficiency	Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is an autosomal recessive genetic disease that disrupts the breakdown of types of fat molecules called very long-chain fatty acids. The breakdown of fats creates smaller molecules that can be used by the brain, muscles and other organs as an energy source. Fats as energy sources are important when the body has a strong demand for energy or is depleted of other more readily available sources of energy. In individuals with VLCAD deficiency, energy cannot be generated from very long-chain fatty acids. Consequently, when they use up other energy sources, they may experience an episode of "energy crisis" in which they cannot rely on certain fats stored in their own body. About 50% of people with VLCAD deficiency have severe symptoms within the first year of life. Symptoms start with vomiting, drowsiness, and low blood sugar (hypoglycemia), and can quickly worsen, leading to a life-threatening crisis with seizures and coma. Such crises usually occur after the infant goes without food for a long period of time or has a common infection that causes fever and reduced appetite. In addition, these patients usually suffer from severe complications in the heart and liver. About a third of VLCAD deficiency patients have their first crises of hypoglycemia between 1 to 13 years of age, but these cases usually do not involve heart problems. The remaining 20% cases are milder and show first symptoms in their adolescent or adult years. The typical symptoms of these cases are recurrent muscle pain and breakdown of muscles, usually triggered by strenuous exercise or a long period of fasting.	The estimated prevalence of VLCAD deficiency is about 1 in 40,000 to 120,000 people.
Von Willebrand disease type 2 Normandy	Von Willebrand disease, first described by Erik von Willebrand in 1926, is a congenital bleeding disorder that shows varying symptoms which may range from a propensity for easy bruising and routine nosebleeds to excessive bleeding after trauma or surgery, or severe joint and internal bleeding. The disease is classified into three general types (PMID 18786008). Type 2 is uncommon and is seen in 15-20% of VWD cases. It typically results in a mild to moderate phenotype and is characterized by a qualitative loss of function. Subtype 2N differs from the other Type 2 diseases in that it is inherited as autosomal recessive and shows symptoms which include mild-moderate mucocutaneous bleeding, prolonged bleeding occurrences, and excessive bleeding after surgery or trauma (PMID 19506358, PMID 19506360, PMID 19085651).	In the general population, VWD can affect up to one in 100 people. The overall prevalence of Type 2N Von Willebrand disease is uncommon, accounting for <5% of all forms of VWD. This disease is not known to be biased in terms of race or ethnicity, age, or sex.
Von Willebrand disease type 3	Von Willebrand disease, first described by Erik von Willebrand in 1926, is a congenital bleeding disorder that shows varying symptoms which may range from a propensity for easy bruising and routine nosebleeds to excessive bleeding after trauma or surgery, or severe joint and internal bleeding. The disease is classified into three general types (PMID 18786008). Type 3 VWD is very rare, results in complete loss of VWF function and shows the most severe clinical symptoms with excessive and prolonged bleeding episodes. Type 3 VWD is typically diagnosed in childhood (PMID 16977572).	The overall prevalence of Type 3 VWD in the general population is less than one in 250,000. This disease is not known to be biased in terms of race or ethnicity, age, or sex.