Obsah

Stargardt disease (*ABCA4*)

The *ABCA4* gene provides instructions for making a protein that is produced in the retina's light receptor cells (photoreceptors), the specialized light-sensitive tissue that lines the back of the eye. Mutations in this gene are the most common cause of Stargardt disease, also known as Stargardt 1 (STGD1) that is usually characterized by a progressive loss of central vision associated with retinal deposits forming yellow-white retinal flecks.

Worldwide prevalence of STGD1 is estimated at 1/8,000 - 1/10,000. Both sexes are equally affected.

The disease typically presents within the first two decades of life, even though symptoms can also appear during adulthood and as late as the seventh decade. Although disease progression and severity varies widely, STGD1 is usually characterized by a progressive loss of central vision causing blurry vision and, occasionally, an increasing difficulty to adapt in the dark.

Stargardt's disease is experimentally treated by gene therapy.

STGD1 prevalence is estimated at 1/8000 - 1/10000. *ABCA4* mutation carrier frequency is 1/50.

CarrierTest targets frequent mutations in *ABCA4* gene.

More info https://ghr.nlm.nih.gov/condition/stargardt-macular-degeneration.

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/10000	1/50	30	1/70	1/19600

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (*ACADM*)

The *ACADM* gene provides instructions for making an enzyme called medium-chain acyl-CoA dehydrogenase (MCAD). This enzyme functions within mitochondria, the energy-producing centres in cells. MCAD is essential for fatty acid oxidation, which is the multistep process that breaks down (metabolizes) fats and converts them to energy.

Mutations in the *ACADM* gene cause medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. The most common change replaces the amino acid lysine with the amino acid glutamic acid at position 304 in the enzyme (written as Lys304Glu or Lys329Glu). This mutation and other amino acid substitutions alter the enzyme's structure, severely reducing or eliminating its activity.

Deficient MCAD enzyme cannot metabolize medium-chain fatty acids properly. As a result, these fats are not converted to energy, which can lead to some features of this disorder such as lack of energy (lethargy) and low blood sugar (hypoglycaemia). Medium-chain fatty acids or partially metabolized fatty acids may build up in tissues and damage the liver and brain. This abnormal build-up causes the other signs and symptoms of MCAD deficiency.

MCADD presents in early childhood with hypoketotic hypoglycaemia and liver dysfunction, often preceded by periods of fasting or an infection with vomiting. Infants who are exclusively breast-fed may present in this manner shortly after birth, due to poor feeding. In some individuals the first manifestation of MCADD may be sudden death following a minor illness.

Treatment of MCAD deficiency is based on a diet that permits adequate nutrition and avoids any fasting period longer than 4-5 hours.

MCAD deficiency prevalence is 1/17,000 in the general population and increases (1/4000) in individuals originating from northern Europe.

The carrier frequency of *ACADM* mutations is 1/65.

CarrierTest targets frequent mutations in *ACADM* gene. More info at https://ghr.nlm.nih.gov/gene/ACADM

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/17000	1/65	90	1/640	1/1638400

Short-chain acyl-CoA Dehydrogenase Deficiency (*ACADS*)

The *ACADS* gene provides instructions for making an enzyme called short-chain acyl-CoA dehydrogenase (SCAD). This enzyme functions within mitochondria, the energy-producing centres within cells. SCAD is essential for fatty acid oxidation, which is the multistep process that breaks down (metabolizes) fats and converts them to energy.

Mutations in the ACADS gene cause short-chain acyl-CoA dehydrogenase (SCAD) deficiency preventing the enzyme from properly metabolizing short-chain fatty acids. As a result, these fats are not converted into energy, which can lead to the characteristic signs and symptoms of this disorder, including lack of energy (lethargy), low blood sugar (hypoglycaemia), poor muscle tone (hypotonia), and weakness.

Preventive measures if necessary, include avoidance of fasting longer than 12 hours (during childhood) and an age-appropriate heart-healthy diet.

SCAD deficiency prevalence is 1/50000. The carrier frequency of ACADS mutations is 1/112. CarrierTest targets frequent mutations in *ACADS* gene. More info at https://ghr.nlm.nih.gov/gene/ACADS

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/50000	1/112	60	1/280	1/313600

Very long-chain acyl-CoA dehydrogenase deficiency (*ACADVL*)

The *ACADVL* gene provides instructions for making an enzyme called very long-chain acyl-CoA dehydrogenase (VLCAD). This enzyme functions within mitochondria, the energy-producing centres in cells. Very long-chain acyl-CoA dehydrogenase is essential for fatty acid oxidation, which is the multistep process that breaks down (metabolizes) fats and converts them to energy.

Mutations in the ACADVL gene cause very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency with very-long chain fatty acids not metabolized properly. As a result, these fats are not converted to energy, which can lead to signs and symptoms of this disorder such as the lack of energy (lethargy) and low blood sugar (hypoglycaemia). Very long-chain fatty acids or partially metabolized fatty acids may build up in tissues and damage the heart, liver, and muscles.

Individuals with the more severe forms of VLCAD deficiency are typically placed on a low-fat formula, with supplemental calories provided through medium-chain triglycerides.

Birth prevalence of VLCAD deficiency is 1/50000. The carrier frequency of *ACADVL* mutations is 1/100.

CarrierTest targets frequent mutations in *ACADVL* gene. More info at https://ghr.nlm.nih.gov/gene/ACADVL

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/40000	1/100	40	1/170	1/115600

Syndromic hearing loss-Usher syndrome (*ADGVR1*)

The *ADGVR1* gene encodes calcium binding protein expressed in the central nervous system. Mutations in this gene are associated with Usher syndrome type 2 and familial febrile seizures.

Usher syndrome is a condition characterized by partial or total hearing loss and vision loss that worsens over time. The hearing loss is classified as sensorineural, which means that it is caused by abnormalities of the inner ear. Gradually deteriorating loss of vision is caused by an eye disease called retinitis pigmentosa (RP), which affects the layer of light-sensitive tissue at the back of the eye (the retina).

There are three major types of Usher syndrome, designated as types 1, 3, and 3. These types are distinguished by their severity and the age when signs and symptoms appear. The types are further divided into subtypes based on their genetic cause.

Usher syndrome type 2 is characterized by hearing loss from birth and progressive vision loss that begins in adolescence or adulthood. The hearing loss associated with this form of Usher syndrome ranges from mild to severe and mainly affects the ability to hear high-frequency sounds. Unlike the other forms of Usher syndrome, type 2 is not associated with vestibular abnormalities that cause difficulties with balance.

Usher's syndrome prevalence is 1/23000 representing 3 to 6% of hereditary hearing loss, and about 50% deaf-blindness of adults. Usher's syndrome prevalence associated with mutation of ADGVR1 gene is about 1/1 000 000. *ADGVR1* mutation carrier frequency in general population is 1/500.

CarrierTest targets frequent mutations in *ADGVR1* gene. More info at https://ghr.nlm.nih.gov/gene/ADGRV1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/1000000	1/500	30	1/710	1/2016400

Cori disease - GSDIII (*AGL*)

The *AGL* gene provides instructions for making the glycogen debranching enzyme. This enzyme is involved in the breakdown of a complex sugar called glycogen, which is a major source of stored energy in the body. Mutations in the AGL gene results in a non-functional enzyme. Glycogen molecules cannot be removed and abnormal, partially broken down glycogen molecules are stored within cells damaging organs and tissues throughout the body, particularly the liver and muscles and leading to the symptoms of glycogen storage disease type III (also called GSDIII or Cori disease).

Beginning in infancy, individuals with any type of GSDIII may have low blood sugar (hypoglycaemia), excess amounts of fats in the blood (hyperlipidaemia), and elevated blood levels of liver enzymes. As they get older, children with this condition typically develop an enlarged liver (hepatomegaly). Liver size usually returns to normal during adolescence, but some affected individuals develop chronic liver disease (cirrhosis) and liver failure later in life. People with GSDIII often have slow growth because of their liver problems, which can lead to short stature. In a small percentage of people with GSDIII, noncancerous (benign) tumours called adenomas may form in the liver.

Individuals with GSDIIIa may develop muscle weakness (myopathy) later in life. These muscle problems can affect both heart (cardiac) muscle and the muscles that are used for movement (skeletal muscles).

Birth prevalence of GSDIII is 1/20 000. Carrier frequency of *AGL* mutations is 1/70.

Most AGL mutations are private (family specific).

CarrierTest targets frequent mutations in *AGL* gene. More info at: https://ghr.nlm.nih.gov/gene/AGL

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/20000	1/70	40	1/120	1/57600

Hypophosphatasia (ALPL)

The ALPL gene provides instructions for making an enzyme called alkaline phosphatase (ALP). This enzyme plays an important role in the growth and development of bones and teeth. It is also active in many other tissues, particularly in the liver and kidneys.

ALP deficiency allows substances that are normally processed by the enzyme to accumulate in the body. One of these compounds, inorganic pyrophosphate, underlies the defective mineralization of bones and teeth with signs and symptoms of hypophosphatasia. Hypophosphatasia weakens and softens the bones, causing skeletal abnormalities. Affected infants are born with short limbs, an abnormally shaped chest, and soft skull bones. Additional complications in infancy include poor feeding and a failure to gain weight, respiratory problems, and high levels of calcium in the blood (hypercalcemia), which can lead to recurrent vomiting and kidney problems. These complications are life-threatening in some cases.

Currently, there are no specific treatments for hypophosphatasia.

Prevalence of serious forms of Hypophosphatasia is 1/100 000 newborns. Milder cases, such as those that appear in childhood or adulthood, probably occur more frequently. Carrier frequency is 1/158.

CarrierTest targets frequent mutations in *ALPL* gene. More info: https://ghr.nlm.nih.gov/gene/ALPL

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	30	1/230	1/211600

ANXA5 M2 haplotype

The ANXA5 gene encodes a protein ANXA5 forming a protective film on the surface of the villi of the placenta. Haplotype M2 ANXA5 associated with decreased production of protein and an increased tendency for blood clotting in the placenta is formed by four variants ANXA5 gene (rs112782763 (C> T), rs28717001 (T> G), rs28651243 (A> G) and rs113588187 (C> T) that are inherited together. Blood clots in the placenta can reduce the quality of nutrition of the fetus and can lead to complications of pregnancy. CarrierTest has shown M2 haplotype in the heterozygous state (M2 haplotype was inherited from only one parent). M2 haplotype status of both partners together with immunologic status of female partner (e.g. antibodies against annexin and antiphospholipid antibodies) can affect IVF treatment.
More info: https://www.ncbi.nlm.nih.gov/pubmed/27440469

Androgen Insensitivity Syndrome (AR)

The *AR* gene provides instructions for making a protein called an androgen receptor. Androgens are hormones (such as testosterone) that are important for normal male sexual development before birth and during puberty. Androgen receptors allow the body to respond appropriately to these hormones. The receptors are present in many of the body's tissues, where they attach (bind) to androgens. The resulting androgen-receptor complex then binds to DNA and regulates the activity of androgen-responsive genes. By turning the genes on or off as necessary, the androgen receptor helps direct the development of male sexual characteristics. Androgens and androgen receptors also have other important functions in both males and females, such as regulating hair growth and sex drive.

Androgen receptor deficiency results in lower sensitivity to androgens or in severe cases cells are unable to use these hormones at all with signs and symptoms of Androgen Insensitivity Syndrome. People with this condition are genetically male, with one X chromosome and one Y chromosome in each cell. Because their bodies are unable to respond to androgens, they may have mostly female sex characteristics or signs of both male and female sexual development.

Mutations that completely eliminate the function of the androgen receptor cause complete androgen insensitivity syndrome (CAIS). Genetic changes that significantly reduce but do not eliminate the receptor's activity cause partial androgen insensitivity syndrome (PAIS). Mild androgen insensitivity syndrome (MAIS) results from changes that only slightly reduce the activity of the receptor with normal male habitus, mild spermatogenic defect or reduced secondary terminal hair.

To prevent testicular malignancy, treatment of CAIS may include either removal of the testes after puberty when feminization is complete or prepubertal gonadectomy accompanied by oestrogen replacement therapy.

AR deficiency is inherited in an X-linked manner. If an affected male reproduces, none of his sons will be affected and all of his daughters will inherit the pathogenic variant. Heterozygous females have a 50% chance of transmitting the pathogenic variant with each pregnancy: males who inherit the pathogenic variant will be affected; females are healthy carriers.

Prevalence of Androgen Insensitivity Syndrome is 1/10000 men. Female carrier frequency is 1/5000.

CarrierTest targets frequent mutations in AR gene. More info: https://ghr.nlm.nih.gov/gene/AR

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	The risk of son (mother test -ve)
1/10000	1/5000	30	1/7100	1/14200

Metachromatic Leukodystrophy (ARSA)

The *ARSA* gene provides instructions for making the enzyme arylsulfatase a located in lysosomes, which are the cell's recycling centres. Within lysosomes, arylsulfatase A helps process substances known as sulfatide that are important components of cell membranes. Sulfatides are abundant in the nervous system's white matter, consisting of nerve fibres covered by myelin. Myelin, made up of multiple layers of membranes, insulates and protects nerves. Arylsulfatase A deficiency interferes with the breakdown of sulfatides. As a result, these substances can accumulate to toxic levels in the nervous system and destroy the cells that produce myelin. Destruction of myelin leads to the loss of white matter (leukodystrophy) and impairment of nervous system function, resulting in the signs and symptoms of Metachromatic Leukodystrophy.

White matter damage causes progressive deterioration of intellectual functions and motor skills, such as the ability to walk. Affected individuals also develop loss of sensation in the extremities (peripheral neuropathy), incontinence, seizures, paralysis, an inability to speak, blindness, and hearing loss. Eventually they lose awareness of their surroundings and become unresponsive. While neurological problems are the primary feature of metachromatic leukodystrophy, effects of sulfatide accumulation on other organs and tissues have been reported, most often involving the gallbladder.

The most common form of Metachromatic Leukodystrophy, affecting about 50 to 60 percent of all individuals with this disorder, is called the late infantile form. This form of the disorder usually appears in the second year of life. Individuals with the late infantile form of Metachromatic Leukodystrophy typically do not survive past childhood.

In 20 to 30 percent of individuals with Metachromatic Leukodystrophy, onset occurs between the age of 4 and adolescence. In this juvenile form, the first signs of the disorder may be behavioural problems and increasing difficulty with schoolwork. Progression of the disorder is slower than in the late infantile form, and affected individuals may survive for about 20 years after diagnosis.

The adult form of Metachromatic Leukodystrophy affects approximately 15 to 20 percent of individuals with the disorder. In this form, the first symptoms appear during the teenage years or later. Often behavioural problems such as alcoholism, drug abuse, or difficulties at school or work.

Prevalence of Metachromatic Leukodystrophy is 1 /40 000. Carrier frequency is 1/100.

CarrierTest targets frequent mutations in *ARSA* gene.

More info: https://ghr.nlm.nih.gov/gene/ARSA

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/40000	1/100	50	1/200	1/160000

Argininosuccinic Aciduria (ASL)

The *ASL* gene provides instructions for making the protein argininosuccinate lyase. This enzyme participates in the urea cycle. The urea cycle processes excess nitrogen, generated when protein is used by the body, to make a compound called urea that is excreted by the kidneys. Excreting the excess nitrogen prevents it from accumulating in the form of ammonia.

Deficiency of argininosuccinate lyase causes argininosuccinic aciduria (ASA), an inherited disorder that causes ammonia to accumulate in the blood. Ammonia, which is formed when proteins are broken down in the body, is toxic if the levels become too high. The nervous system is especially sensitive to the effects of excess ammonia. ASA usually becomes evident in the first few days of life. An infant with ASA may be lacking in energy (lethargic) or unwilling to eat, and have poorly controlled breathing rate or body temperature. Some babies with this disorder experience seizures or unusual body movements, or go into a coma. Complications from ASA may include developmental delay and intellectual disability. Progressive liver damage, skin lesions, and brittle hair may also be seen.

Occasionally, an individual may inherit a mild form of the disorder in which ammonia accumulates in the bloodstream only during periods of illness or other stress.

Treatment of acute metabolic decompensation with hyperammonemia involves rapid control of hyperammonemia by discontinuing oral protein intake, supplementing oral intake with intravenous lipids and/or glucose, and use of intravenous arginine and nitrogen scavenging therapy. If ammonia levels do not normalize, hemodialysis is the next step.

Prevalence of argininosuccinic aciduria is 1/70 000. Carrier frequency is 1/132.

CarrierTest targets frequent mutations in *ASL* gene. More info: https://ghr.nlm.nih.gov/gene/ASL

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/70000	1/132	30	1/190	1/144400

Canavan disease (ASPA)

The *ASPA* gene provides instructions for making an enzyme called aspartoacylase (ASPA). In the brain, this enzyme breaks down a compound called N-acetyl-L-aspartic acid (NAA) into aspartic acid (an amino acid that is a building block of many proteins) and another molecule called acetic acid.

The production and breakdown of NAA appears to be critical for maintaining the brain's white matter, which consists of nerve fibres surrounded by a myelin sheath.

Aspartoacylase deficiency causes Canavan disease, which is a rare inherited disorder that affects brain development. There are two major forms of this condition: neonatal/infantile Canavan disease, which is the most common and most severe form, and mild/juvenile Canavan disease. Neonatal/infantile Canavan disease is the most common and most severe form of the condition. Affected infants appear normal for the first few months of life, but by age 3 to 5 months, problems with development become noticeable. These infants usually do not develop motor skills such as turning over, controlling head movement, and sitting without support. Other common features of this condition include weak muscle tone (hypotonia), an unusually large head size (macrocephaly), and irritability. Feeding and swallowing difficulties, seizures, and sleep disturbances may also develop.

There is no cure, nor is there a standard course of treatment. Treatment is symptomatic and supportive.

While Canavan disease occurs in people of all ethnic backgrounds, it is most common in people of Ashkenazi (eastern and central European) Jewish heritage.

Prevalence of ASPA deficiency is 1/ 6400 in Ashkenazi population with carrier frequency 1/55. Prevalence in other population is not known.

CarrierTest targets frequent mutations in *ASPA* gene. More info: https://ghr.nlm.nih.gov/gene/ASPA

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/12100	1/55	50	1/110	1/48400

Citrullinemia type I (ASS1)

The ASS1 gene provides instructions for making an enzyme called argininosuccinate synthase 1. This enzyme participates in the urea cycle processing excess nitrogen that is generated as the body uses proteins. The excess nitrogen is used to make a compound called urea, which is excreted from the body in urine.

Deficient argininosuccinate synthase 1 prevents processing excess nitrogen into urea. As a result, nitrogen (in the form of ammonia) and other byproducts of the urea cycle (such as citrulline) build up in the bloodstream. Ammonia is toxic, particularly to the nervous system. An accumulation of ammonia during the first few days of life leads to poor feeding, vomiting, seizures, and the other signs and symptoms of type me citrullinemia (CIT). Less commonly, a milder form of type I citrullinemia can develop later in childhood or adulthood. This later-onset form is associated with intense headaches, partial loss of vision, problems with balance and muscle coordination (ataxia), and lethargy. Some people with gene mutations that cause type I citrullinemia never experience signs and symptoms of the disorder.

Treatment of CIT is based restriction of dietary protein using other nonprotein caloric sources. Long-term management requires close dietary monitoring and oral administration of sodium phenylbutyrate and arginine.

Birth prevalence of type I citrullinemia (CIT) is 1/57000. Carrier frequency is 1/120. CarrierTest targets frequent mutations in *ASS1* gene.

More info: https://ghr.nlm.nih.gov/gene/ASS1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/50000	1/110	50	1/220	1/193600

Ataxia-Telangiectasia (ATM)

The *ATM* gene provides instructions for making a protein that is located primarily in the nucleus of cells, where it helps control the rate at which cells grow and divide. This protein also plays an important role in the normal development and activity of several body systems, including the nervous system and the immune system. Additionally, the ATM protein assists cells in recognizing damaged or broken DNA strands damaged by agents such as toxic chemicals or radiation. The ATM protein coordinates DNA repair by activating enzymes that fix the broken strands. Efficient repair of damaged DNA strands helps maintain the stability of the cell's genetic information.

Cells with deficient ATM protein are hypersensitive to radiation and do not respond normally to DNA damage. Defective ATM protein allows mutations to accumulate in other genes, which may cause cells to grow and divide in an uncontrolled way. In addition, *ATM* mutations can allow cells to die inappropriately, particularly affecting cells in a part of the brain involved in coordinating movements (the cerebellum).

This loss of brain cells causes the movement problems characteristic of Ataxia-Telangiectasia (AT). Progressive difficulty with coordinating movements (ataxia) begins in early childhood, usually before age 5. Affected children typically develop difficulty walking, problems with balance and hand coordination, involuntary jerking movements (chorea), muscle twitches (myoclonus), and disturbances in nerve function (neuropathy). The movement problems typically cause people to require wheelchair assistance by adolescence. People with this disorder also have slurred speech and trouble moving their eyes to look side-to-side (oculomotor apraxia). Small clusters of enlarged blood vessels called telangiectasas, which occur in the eyes and on the surface of the skin, are also characteristic of this condition. People with ataxia-telangiectasia often have a weakened immune system, and many develop chronic lung infections. They also have an increased The risk of developing cancer, particularly cancer of blood-forming cells (leukemia) and cancer of immune system cells (lymphoma). Affected individuals are very sensitive to the effects of radiation exposure, including medical x-rays. The life expectancy of people with ataxia-telangiectasia varies greatly, but affected individuals typically live into early adulthood.

Ataxia-Telangiectasia (AT) prevalence is 1/ 40000. Carrier frequency is 1/100.

CarrierTest targets frequent mutations in *ATM* gene. More info: https://ghr.nlm.nih.gov/gene/ATM

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/40000	1/100	70	1/330	1/435600

Wilson disease (ATP7B)

The ATP7B gene provides instructions for making a protein called copper-transporting ATPase 2. It plays a role in the transport of copper from the liver to other parts of the body and in the removal of excess copper from the body.

Copper-transporting ATPase 2 deficiency causes excessive accumulation of copper in the body, particularly in the liver, brain, and eyes with signs and symptoms of Wilson disease. The features of this condition usually appearing between the ages of 6 and 45 and include a combination of liver disease and neurological and psychiatric problems. Liver disease is typically the initial feature of Wilson disease including jaundice, fatigue, loss of appetite, and abdominal swelling. Nervous system or psychiatric problems commonly occur in young adults. Signs and symptoms of these problems can include clumsiness, tremors, difficulty walking, speech problems, impaired thinking ability, depression, anxiety, and mood swings. In many individuals with Wilson disease, copper deposits in the front surface of the eye (the cornea) form a green-to-brownish ring, called the Kayser-Fleischer ring that surrounds the coloured part of the eye. Treatment with copper chelating agents or zinc – initiated as soon as possible – can reduce hepatic, neurologic, and psychiatric findings in many symptomatic individuals. Treatment is lifelong.

Prevalence of Wilson disease is 1/30000. Carrier frequency is 1/90.

CarrierTest targets frequent mutations in *ATP7B* gene. More info: https://ghr.nlm.nih.gov/gene/ATP7B

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/30000	1/90	90	1/890	1/3168400

Bloom syndrome (BLM)

The *BLM* gene provides instructions for making a member of a protein family called RecQ helicases. Helicases are enzymes that attach (bind) to DNA and unwind the two spiral strands (double helix) of the DNA molecule. This unwinding is necessary for several processes in the cell nucleus, including copying (replicating) DNA in preparation for cell division and repairing damaged DNA. Because RecQ helicases help maintain the structure and integrity of DNA, they are known as the "caretakers of the genome".

More than 70 *BLM* gene mutations have been identified in people with Bloom syndrome, an inherited disorder characterized by short stature, a skin rash that develops after exposure to the sun, and a greatly increased risk of cancer. One particular BLM gene mutation c.2207_2212delATCTGAins7 causes almost all cases of Bloom syndrome among people of Central and Eastern European (Ashkenazi) Jewish descent.

CarrierTest targets frequent mutations in *BLM* gene. More info: https://ghr.nlm.nih.gov/gene/BLM

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/71824	1/134	97	1/4430	1/78499600

Biotinidase Deficiency (BTD)

The *BTD* gene encodes an enzyme biotinidase recycling biotin- a B vitamin - found in foods such as liver, egg yolks, and milk. Biotinidase removes biotin that is bound to proteins in food, leaving the vitamin in its free (unbound) state. The body needs free biotin to activate enzymes called biotin-dependent carboxylases. These carboxylases are involved in many critical cellular functions, including the breakdown of proteins, fats, and carbohydrates.
Untreated young children with profound biotinidase deficiency usually exhibit neurologic abnormalities including seizures, hypotonia, ataxia, developmental delay, vision problems, hearing loss, and cutaneous abnormalities (e.g., alopecia, skin rash, and candidiasis). Older children and adolescents with profound biotinidase deficiency often exhibit motor limb weakness, spastic paresis, and decreased visual acuity. Once vision problems, hearing loss, and developmental delay occur, they are usually irreversible, even with biotin therapy. Individuals with partial biotinidase deficiency may have hypotonia, skin rash, and hair loss, particularly during times of stress.
Signs of deficiency can improve by lifelong treatment with 5-10 mg of oral biotin per day.
Birth prevalence is 1/60 000. Carrier frequency is 1/122.
CarrierTest targets frequent mutations in *BTD* gene. More info: https://ghr.nlm.nih.gov/gene/BTD

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/60000	1/122	90	1/1210	1/5856400

Homocystinuria, classic (CBS)

The *CBS* gene provides instructions for making an enzyme called cystathionine beta-synthase. This enzyme convert amino acid homocysteine and serine to a cystathionine. Cystathionine is then converted to the amino acid cysteine, which is used to build proteins or is broken down and excreted in urine.
Cystathionine beta-synthase deficiency results in accumulation of homocysteine in the blood and homocysteine in excreted in urine. Excess homocysteine leads to the signs and symptoms of homocystinuria. There are multiple forms of homocystinuria, which are distinguished by their signs and symptoms and genetic cause. The most common form of homocystinuria is characterized by nearsightedness (myopia), dislocation of the eye lens, an increased risk ofabnormal blood clotting, brittle bones that are prone to fracture (osteoporosis) or other skeletal abnormalities. Some affected individuals also have developmental delay and learning problems. Less common forms of homocystinuria can cause intellectual disability, failure to thrive, seizures, problems with movement, and a blood disorder called megaloblastic anaemia. The signs and symptoms of homocystinuria typically develop within the first year of life, although some mildly affected people may not develop features until later in childhood or adulthood.

No specific cure is available for homocystinuria; however high doses of pyridoxine, low-sulphur diet, folic acid supplement and cysteine in the diet can be helpful. Betaine is used to reduce concentrations of homocysteine.

Birth prevalence in European population is 1/20 000. Carrier frequency is 1/70.
CarrierTest targets frequent mutations in *CBS* gene. More info: https://ghr.nlm.nih.gov/gene/CBS

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/20000	1/70	60	1/173	1/120000

Syndromic hearing loss-Usher syndrome- USH1D (CDH23)

The *CDH23* gene provides instructions for making cadherin 23, a type of protein that helps cells stick together. Cadherin 23 deficiency can cause Usher syndrome type 1 (USH1D).
Usher syndrome is a condition characterized by partial or total hearing loss and vision loss that worsens over time. The hearing loss is classified as sensorineural, which means that it is caused by abnormalities of the inner ear. Gradually deteriorating loss of vision is caused by an eye disease called retinitis pigmentosa (RP), which affects the layer of light-sensitive tissue at the back of the eye (the retina).
There are three major types of Usher syndrome, designated as types I, II, and III. These types are distinguished by their severity and the age when signs and symptoms appear. The types are further divided into subtypes based on their genetic cause.
Most individuals with Usher syndrome type I are born with severe to profound hearing loss. Progressive vision loss caused by retinitis pigmentosa becomes apparent in childhood. This type of Usher syndrome also causes abnormalities of the vestibular system, which is the part of the inner ear that helps maintain the body's balance and orientation in space. As a result of the vestibular abnormalities, children with the condition have trouble with balance.
Usher syndrome type II is characterized by hearing loss from birth without difficulties with balance and progressive vision loss that begins in adolescence or adulthood. People with Usher syndrome type III experience hearing loss and vision loss beginning somewhat later in life.
All Usher's syndrome types prevalence is 1/23000 representing 3 to 6% of hereditary hearing loss, and about 50% deaf blindness of adults.
CDH23 mutation carrier frequency in general population is 1/500.
CarrierTest targets frequent mutations in *CDH23* gene. More info: https://ghr.nlm.nih.gov/gene/CDH23

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/360000	1/300	30	1/430	1/739600

Cystic fibrosis (CFTR)

CFTR gene encodes a CFTR protein (the transmembrane conductance regulator) which participates in chloride and sodium ions transport across membranes of cells producing mucus, sweat, saliva, tears, and digestive enzymes membranes. Functioning CFTR protein is essential for the production of thin, freely flowing mucus protecting the lining of the airways, digestive system, reproductive system, and other organs and tissues. CFTR deficiency causes abnormally thick and sticky mucus obstructing the airways and glands, leading to the characteristic signs and symptoms of cystic fibrosis. This abnormal mucus can clog the airways, leading to severe problems with breathing and bacterial infections in the lungs. These infections cause chronic coughing, wheezing, and inflammation. Over time, mucus build up and infections result in permanent lung damage, including the formation of scar tissue (fibrosis) and cysts in the lungs.
Most people with cystic fibrosis also have digestive problems. Some affected babies have meconium ileus, a blockage of the intestine that occurs shortly after birth. Other digestive problems result from a build-up of thick, sticky mucus in the pancreas.

Treatment options of cystic fibrosis may include: Antibiotics to treat and prevent lung infections, anti-inflammatory medications to lessen swelling in the airways in lungs, mucus-thinning drugs, inhaled bronchodilators and oral pancreatic enzymes. For those with cystic fibrosis who have certain gene mutations, doctors may recommend a newer medication called ivacaftor (Kalydeco).

CarrierTest targets frequent mutations in *CFTR* gene. Birth prevalence is 1/2,500 to 3,500. Carrier frequency is 1/25.
More info https://ghr.nlm.nih.gov/gene/CFTR

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/4500	1/25	95	1/480	1/920000

Congenital myasthenia (CHRNE)

The *CHRNE* gene provides instructions for making the epsilon subunit of the acetylcholine receptor (AChR) protein. The AChR protein is found in the membrane of skeletal muscle cells and plays a critical role in the neuromuscular junction, which is the area where signaling between nerve and muscle cells occurs.

Deficiency of AChR protein causes Congenital Myasthenic Syndrome (CMS) characterized by muscle weakness (myasthenia) that worsens with physical exertion. The muscle weakness typically begins in early childhood but can also appear in adolescence or adulthood. Facial muscles, including muscles that control the eyelids, muscles that move the eyes, and muscles used for chewing and swallowing, are most commonly affected. Due to muscle weakness, affected infants may have feeding difficulties. Development of motor skills such as crawling or walking may be delayed. Some individuals have episodes of breathing problems that may be triggered by fevers or infection. Severely affected individuals may also experience short pauses in breathing (apnoea) that can lead to a bluish appearance of the skin or lips (cyanosis).

About 60% cases of AChR deficiency is caused by mutations of *CHRNE* gene.

AChR deficiency associated with 1327delG mutation is typical for gypsy, Indian and south European population with carrier frequency 1/33.

CarrierTest targets 1327delG mutation in *CHRNE* gene. More info: https://ghr.nlm.nih.gov/gene/CHRNE

Syndromic hearing loss-Usher syndrome (CLRN1)

The *CLRN1* gene provides information for making a protein called clarin 1. Clarin 1 has been found in several areas of the body, including sensory cells in the inner ear called hair cells. These cells help transmit sound and motion signals to the brain. Mutations in the *CLRN1* gene have been identified in people with Usher syndrome type 3.

Usher syndrome is a condition characterized by partial or total hearing loss and vision loss that worsens over time. The hearing loss is classified as sensorineural, which means that it is caused by abnormalities of the inner ear. Gradually deteriorating loss of vision is caused by an eye disease called retinitis pigmentosa (RP), which affects the layer of light-sensitive tissue at the back of the eye (the retina).

People with Usher syndrome type 3 experience hearing loss and vision loss beginning somewhat later in life. Unlike the other forms of Usher syndrome, type 3 is usually associated with normal hearing at birth. Hearing loss typically begins during late childhood or adolescence, after the development of speech, and becomes more severe over time. By middle age, most affected individuals have profound hearing loss. Vision loss caused by retinitis pigmentosa also develops in late childhood or adolescence. Some people with Usher syndrome type 3 have vestibular abnormalities that cause problems with balance.

Usher's syndrome prevalence is 1/23000 representing 3 to 6% of hereditary hearing loss, and about 50% deafblindness of adults.

CLRN1 mutation carrier frequency in general population is 1/500.

CarrierTest targets frequent mutations in *CLRN1* gene. More info: https://ghr.nlm.nih.gov/gene/CLRN1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/1000000	1/500	50	1/1000	1/4000000

Alport syndrome (COL4A5)

The *COL4A5* gene provides instructions for making one component of type IV collagen, which is a flexible protein. Type IV collagen plays an especially important role in the basement membranes of the kidney, inner ear, and eye.

Deficiency of type IV collagen causes Alport syndrome characterized by kidney disease, hearing loss, and eye abnormalities. People with Alport syndrome experience progressive loss of kidney function. Almost all affected individuals have blood in their urine (hematuria), which indicates abnormal functioning of the kidneys. Many people with Alport syndrome also develop high levels of protein in their urine (proteinuria). The kidneys become less able to function as this condition progresses, resulting in end-stage renal disease (ESRD). People with Alport syndrome frequently develop sensorineural hearing loss, which is caused by abnormalities of the inner ear, during late childhood or early adolescence. Affected individuals may also have misshapen lenses in the eyes (anterior lenticonus) and abnormal coloration of the light-sensitive tissue at the back of the eye (retina).

Significant hearing loss, eye abnormalities, and progressive kidney disease are more common in males with Alport syndrome than in affected females.

About 80 percent of Alport syndrome cases are caused by mutations in the COL4A5 gene located on the X chromosome (XLAS form). In males having only one X chromosome one altered copy of the COL4A5 gene in each cell is sufficient to cause symptoms of the disorder. In females (who have two X chromosomes), a mutation in one copy of the COL4A5 gene usually only results in haematuria, but some women experience more severe symptoms. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons. Heterozygous females (usually with haematuria only) have a 50% chance of transmitting the pathogenic variant with each pregnancy: males who inherit the pathogenic variant will be fully affected; females who inherit the pathogenic variant may develop moderate clinical findings (haematuria) related to the disorder.

Birth prevalence of XLAS je 1/60000. Female carrier frequency is 1/30000.

CarrierTest targets frequent mutations in *COL4A5* gene.

More info: https://ghr.nlm.nih.gov/gene/COL4A5

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	The risk of son (mother test -ve)
1/60000	1/30000	50	1/60000	1/120000

Cystinosis (CTNS)

The *CTNS* gene provides instructions for making a protein called cystinosin. Cystinosin is a transport protein that specifically moves the amino acid cystine out of the lysosomes which are compartments in the cell that digest and recycle materials.

Cystinosin deficiency results in accumulation of cystine within cells. Excess cystine damages cells and often forms crystals that can build up and cause problems in many organs and tissues with signs and symptoms of cystinosis. The kidneys and eyes are especially vulnerable to damage; the muscles, thyroid, pancreas, and testes may also be affected.

There are three distinct types of cystinosis. In order of decreasing severity, they are nephropathic cystinosis, intermediate cystinosis, and non-nephropathic or ocular cystinosis. Nephropathic cystinosis begins in infancy, causing poor growth and a particular type of kidney damage (renal Fanconi syndrome) leading to the loss of important minerals, salts, fluids, and many other nutrients. The loss of nutrients impairs growth and may result in soft, bowed bones (hypophosphatemic rickets), especially in the legs. The nutrient imbalances in the body lead to increased urination, thirst, dehydration, and abnormally acidic blood (acidosis). By about the age of 2, cystine crystals may be present in the clear covering of the eye (cornea). The buildup of these crystals in the eye causes pain and an increased sensitivity to light (photophobia). Untreated children will experience complete kidney failure by about the age of 10. Other signs and symptoms that may occur in untreated people, especially after adolescence, include muscle deterioration, blindness, inability to swallow, diabetes, thyroid and nervous system problems, and an inability to father children (infertility) in affected men.

The signs and symptoms of intermediate cystinosis are the same as nephropathic cystinosis, but they occur at a later age. People with non-nephropathic or ocular cystinosis typically experience photophobia due to cystine crystals in the cornea, but usually do not develop kidney malfunction or most of the other signs and symptoms of cystinosis. Due to the absence of severe symptoms, the age at which this form of cystinosis is diagnosed varies widely.

With renal dialysis, kidney transplantation, and pharmacologic treatment, individuals with cystinoisis are now surviving into adulthood. The most effective medical treatment for cystinosis is the use of cysteamine converting accumulated cystine into a form that can be easily excreted from the lysosome.

Prevalence of cystinosis is 1/100 000 (in Bretagne 1/25000). Carrier frequency is 1/158. CarrierTest targets frequent mutations in *CTNS* gene.

More info: https://ghr.nlm.nih.gov/gene/CTNS

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	30	1/230	1/211600

21-hydroxylase deficiency (CYP21A2)

The *CYP21A2* gene provides instructions for making an enzyme called 21-hydroxylase, which is part of the cytochrome P450 family of enzymes. Cytochrome P450 enzymes are involved in many processes in the body, such as assisting with reactions that break down drugs and helping to produce cholesterol, certain hormones, and fats (lipids). 21-hydroxylase plays a role in producing hormones called cortisol and aldosterone. Cortisol helps maintain blood sugar levels, protects the body from stress, and suppresses inflammation. Aldosterone is sometimes called the salt-retaining hormone because it regulates the amount of salt retained by the kidneys. The retention of salt affects fluid levels in the body and blood pressure.

There are three clinical forms of 21-hydroxylase deficiency (21-OHD). Individuals with a form of the disorder called the salt-wasting type have *CYP21A2* mutations that result in a completely non-functional enzyme. People with the simple virilising type of this condition have *CYP21A2* gene mutations that allow the production of low levels of functional enzyme. Individuals with the non-classic type of this disorder have *CYP21A2* mutations that result in the production of reduced amounts of the enzyme. All types of 21-OHD interfere with the production of cortisol and aldosterone. The substances that are usually used to form these hormones instead build up in the adrenal glands and are converted to androgens, which are male sex hormones. The excess production of androgens leads to abnormalities of sexual development in people with 21-OHD.

Approximately 75 percent of individuals with classic 21-OHD deficiency have the salt-wasting type. Affected individuals lose large amounts of sodium in their urine, which can be life-threatening in early infancy. Babies with the salt-wasting type can experience poor feeding, weight loss, dehydration, and vomiting. Individuals with the simple virilising form do not experience salt loss.

Males and females with either classic form of 21-OHD tend to have an early growth spurt, but their final adult height is usually shorter than others in their family. Additionally, affected individuals may have a reduced ability to have biological children (decreased fertility). Females may also develop excessive body hair growth (hirsutism), male pattern baldness, and irregular menstruation. In both the salt-wasting and simple virilising forms of this disorder, females typically have external genitalia that do not look clearly male or female (ambiguous genitalia). Males usually have normal genitalia, but the testes may be small. Females with the non-classic type of 21-OHD have normal female genitalia. As affected females get older, they may experience hirsutism, male pattern baldness, irregular menstruation, and decreased fertility. Males with the non-classic type may have early beard growth and small testes. Some individuals with this type of 21-OHD have no symptoms of the disorder.

The principles of treatment of 21-OHD are to supplement insufficient glucocorticoid and mineralocorticoid levels, inhibit enhanced adrenal androgen production, and maintain growth and maturation similar to those of healthy children. Treatment continues for life.

Birth prevalence of 21-OHD is 1/8000. Carrier frequency is 1/55.

CarrierTest targets frequent mutations in *CYP21A2* gene.More info: https://ghr.nlm.nih.gov/gene/ CYP21A2

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/8000	1/55	50	1/110	1/48500

Cerebrotendinous xanthomatosis (CYP27A1)

The *CYP27A1* gene provides instructions for producing an enzyme called sterol 27-hydroxylase. This enzyme is located in the energy-producing centres of cells (mitochondria), where it is involved in the pathway that breaks down cholesterol to form acids used to digest fats (bile acids). Specifically, sterol 27-hydroxylase breaks down cholesterol to form a bile acid called chenodeoxycholic acid. The formation of bile acids from cholesterol is the body's main pathway for cholesterol removal.

Sterol 27-hydroxylase deficiency causes abnormal storage of fats. A molecule called cholestanol, which is similar to cholesterol, is produced and accumulates in blood and tissues.The accumulation of cholesterol and cholestanol throughout the body's tissues causes the signs and symptoms of cerebrotendinous xanthomatosis (CTX).

People with cerebrotendinous xanthomatosis often develop neurological problems in early adulthood that are thought to be caused by an abnormal accumulation of fats and an increasing number of xanthomas in the brain. These neurological problems include recurrent seizures (epilepsy), movement disorders, impaired speech (dysarthria), loss of sensation in the arms and legs (peripheral neuropathy), decline in intellectual function (dementia), hallucinations, and depression.

Other features of cerebrotendinous xanthomatosis include clouding of the lenses of the eyes (cataracts) and chronic diarrhea in childhood; a reduced ability to produce and release a digestive fluid called bile (cholestasis), which can lead to a yellowing of the skin or whites of the eyes (jaundice); and progressively brittle bones that are prone to fracture (osteoporosis). People with cerebrotendinous xanthomatosis are also at an increased risk ofdeveloping cardiovascular disease or respiratory failure because of lipid accumulation in the heart or lungs, respectively.

For treatment of cerebrotendinous xanthomatosis is used chenodeoxycholic acid replacement therapy and statins if necessary.

CarrierTest targets frequent mutations in *CYP27A1* gene.Prevalence CTX is 1/50000. Carrier frequency is 1/110.

More info: https://ghr.nlm.nih.gov/gene/CYP27A1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/50000	1/110	50	1/220	1/193600

Smith-Lemli - Opitz SLOS (DHCR7)

The *DHCR7* gene provides instructions for making an enzyme called 7-dehydrocholesterol reductase. This enzyme is responsible for the final step in cholesterol production in many types of cells converting molecule called 7-dehydrocholesterol to cholesterol. Cholesterol is fat-like substance that is produced in the body and obtained from foods that come from animals (particularly egg yolks, meat, poultry, fish, and dairy products). Cholesterol plays a critical role in embryonic development by interacting with development of the brain, limbs, genital tract, and other structures. It is also a structural component of cell membranes and myelin, the fatty covering that insulates nerve cells. Additionally, cholesterol is used to make certain hormones and is important for the production of acids used in digestion (bile acids). Deficiency of 7-dehydrocholesterol reductase reduces its ability to convert 7-dehydrocholesterol to cholesterol. In addition, potentially toxic by-products of cholesterol production (such as 7-dehydrocholesterol) can build up in the blood and other tissues leading to the specific features of Smith-Lemli-Opitz syndrome (SLOS). Smith-Lemli-Opitz syndrome is a developmental disorder that affects many parts of the body. This condition is characterized by distinctive facial features, small head size (microcephaly), intellectual disability or learning problems, and behavioural problems. Many affected children have the characteristic features of autism, a developmental condition that affects communication and social interaction. Malformations of the heart, lungs, kidneys, gastrointestinal tract, and genitalia are also common. Infants with Smith-Lemli-Opitz syndrome have weak muscle tone (hypotonia), experience feeding difficulties, and tend to grow more slowly than other infants. Most affected individuals have fused second and third toes (syndactyly), and some have extra fingers or toes (polydactyly). For most affected foetuses (80%) SLOS is lethal in utero. The signs and symptoms of Smith-Lemli-Opitz syndrome vary widely. Mildly affected individuals may have only minor physical abnormalities with learning and behavioural problems.
Cholesterol supplementation may result in clinical improvement.
Birth prevalence of SLOS is 1 / 20 000 - 60000 with higher prevalence in Czechoslovakia. Carrier frequency is 1/30-50. CarrierTest targets frequent mutations in *DHCR7* gene.
More info: https://ghr.nlm.nih.gov/gene/DHCR7

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/10000	1/50	80	1/250	1/242064

Prothrombin thrombophilia (F2)

The *F2* gene encodes a blood protein prothrombin (coagulation factor II), whose active form (thrombin) is a major component of blood clots. The mutation that causes most cases of prothrombin thrombophilia changes nucleotide guanine with the nucleotide adenine at position 20210 (written G20210A or 20210G>A). This mutation causes the gene to be overactive and leads to the production of too much prothrombin. An abundance of prothrombin leads to increased tendency to form abnormal blood clots in blood vessels (thrombophilia).

People who have prothrombin thrombophilia are at somewhat higher than average risk ofa type of clot which typically occurs in the deep veins of the legs (deep venous thrombosis). Affected people also have an increased risk ofdeveloping a pulmonary embolism, which is a clot that travels through the bloodstream and lodges in the lungs. Most people with prothrombin thrombophilia never develop abnormal blood clots, however.

Prothrombin thrombophilia is associated with a somewhat increased risk ofpregnancy loss (miscarriage) and may also increase the risk ofother complications during pregnancy. These complications may include pregnancy-induced high blood pressure (preeclampsia), slow foetal growth, and early separation of the placenta from the uterine wall (placental abruption). However most women with prothrombin thrombophilia have normal pregnancies.

CarrierTest is targeted on G20210A mutation of *F2* gene.

More info: https://ghr.nlm.nih.gov/gene/F2

Factor V Leiden thrombophilia (F5)

The *F5* gene provides instructions for making a protein called coagulation factor V. Coagulation factors are a group of related proteins that make up the coagulation system, a series of chemical reactions that form blood clots. After an injury, clots seal off blood vessels to stop bleeding and trigger blood vessel repair.

The factor V protein is made primarily by cells in the liver. The protein circulates in the bloodstream in an inactive form until the coagulation system is activated by an injury that damages blood vessels. When coagulation factor V is activated, it interacts with coagulation factor X. The active forms of these two coagulation factors (written as factor Va and factor Xa, respectively) form a complex that converts an important coagulation protein called prothrombin to its active form, thrombin. Thrombin then converts a protein called fibrinogen into fibrin, which is the material that forms the clot.

Coagulation factor V has another role in regulating the coagulation system through its interaction with activated protein C (APC). APC normally inactivates coagulation factor V by cutting (cleaving) it at specific sites. This inactivation slows down the clotting process and prevents clots from growing too large. When coagulation factor V is cleaved at a particular site (protein position 506), it can work with APC to inactivate factor VIIIa, which is another protein that is essential for normal blood clotting.

Factor V Leiden (FVL) is the name of a specific mutation in the *F5* gene. This mutation replaces the amino acid arginine with the amino acid glutamine at F5 protein position 506 (written as Arg506Gln or G1691A). Leiden mutation slows the rate at which APC inactivates this factor. As a result, both the activated form of coagulation factor V and coagulation factor VIIIa persist longer in circulation, increasing the risk ofdeveloping an abnormal blood clot. This tendency to form abnormal clots that can block blood vessels is known as thrombophilia. The presence of the factor V Leiden mutation in one or both copies of the *F5* gene can cause thrombophilia; two copies of the mutation lead to a higher risk ofdeveloping abnormal blood clots than a single copy of the mutation.

CarrierTest is targeted on Leiden mutation Arg506Gln (G1691A) of *F5* gene.

More info: https://ghr.nlm.nih.gov/gene/F5

Tyrosinemia type I (FAH)

The *FAH* gene provides instructions for making an enzyme called fumarylacetoacetate hydrolase which is the part of enzymatic system breaking down the amino acid tyrosine into smaller molecules that are either excreted by the kidneys or used to produce energy or make other substances in the body.

The consequence of fumarylacetoacetate hydrolase deficiency is toxic accumulation of fumarylacetoacetate in the liver and kidneys with signs and symptoms of tyrosinemia type I.

The most severe form of tyrosinemia type I begins in the first few months of life. Affected infants have failure to thrive due to poor food tolerance because high-protein foods lead to diarrhea and vomiting. Affected infants may also have jaundice, a cabbage-like odor, and an increased tendency to bleed (particularly nosebleeds). Tyrosinemia type I can lead to liver and kidney failure, softening and weakening of the bones (rickets), and an increased risk ofliver cancer (hepatocellular carcinoma). Some affected children have repeated neurologic crises that consist of changes in mental state, reduced sensation in the arms and legs (peripheral neuropathy), abdominal pain, and respiratory failure. These crises can last from 1 to 7 days. Untreated, children with tyrosinemia type I often do not survive past the age of 10.

Nitisinone (Orfadin) which prevents the accumulation of fumarylacetoacetate and dietary management with controlled intake of phenylalanine and tyrosine should be started immediately after diagnosis.

Birth prevalence of tyrosinemia type I is 1/100000. Carrier frequency is 1/158.

CarrierTest targets frequent mutations in *FAH* gene.More info: https://ghr.nlm.nih.gov/gene/FAH

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	60	1/390	1/608400

FSHr polymorphism Ser680Asn (FSHR)

FSHR gene encodes a protein FSHr acting as a receptor of follicle stimulating hormone (FSH) in ovarian and testicular cells. Binding capacity of FSHr and general sensitivity to gonadotropins is affected by a single-nucleotide polymorphism (SNP) changing the amino acid serine (Ser) to asparagine (Asn) at position 680 of the FSHr protein chain (Ser680Asn). Genotype Ser680Ser (wild homozygote) with population frequency 18% is associated with a lower sensitivity of FSHr to gonadotropins. Genotype Asn680Asn is associated with a higher sensitivity of FSHr to gonadotropins. Asn680Asn homozygotes have a lower relative risk (0.63) for polycystic ovary syndrome (PCOS) as well.
More info: https://www.ncbi.nlm.nih.gov/gene/2492

Glycogen storage disease, type 1A (G6PC)

The *G6PC* gene provides instructions for making an enzyme called glucose 6-phosphatase. This enzyme is found on the membrane of the endoplasmic reticulum, which is a structure inside cells that is involved in protein processing and transport. Glucose 6-phosphatase is involved in breaking down a type of sugar molecule called glucose 6-phosphate to simple sugar glucose, which is the primary source of energy for most cells. The glucose 6-phosphatase enzyme is expressed (active) in the liver, kidneys, and intestines, and is the main regulator of glucose production in the liver.

Mutations in the *G6PC* gene impair the function of the glucose 6-phosphatase enzyme. Glucose 6-phosphate that is not broken down to glucose is converted to fat and glycogen, a complex sugar that is stored within cells. Too much fat and glycogen stored within a cell can be toxic. This build up damages organs and tissues throughout the body, particularly the liver and kidneys, leading to the signs and symptoms of Glycogen storage disease, type 1A (GSDIa).

Signs and symptoms of this condition typically appear around the age of 3 or 4 months. Affected infants may have low blood sugar (hypoglycaemia), which can lead to seizures. They can also have a build up of lactic acid in the body (lactic acidosis), high blood levels of a waste product called uric acid (hyperuricemia), and excess amounts of fats in the blood (hyperlipidaemia). As they get older, children with GSDI have thin arms and legs and short stature. An enlarged liver may give the appearance of a protruding abdomen. The kidneys may also be enlarged. Affected individuals may also have diarrhea and deposits of cholesterol in the skin (xanthomas).

People with GSDI may experience delayed puberty. Beginning in young to mid-adulthood, affected individuals may have thinning of the bones (osteoporosis), a form of arthritis resulting from uric acid crystals in the joints (gout), kidney disease, and high blood pressure in the blood vessels that supply the lungs (pulmonary hypertension). Females with this condition may also have abnormal development of the ovaries (polycystic ovaries). In affected teens and adults, tumors called adenomas may form in the liver. Adenomas are usually benign, but occasionally these tumors can become malignant.

Young infants require continuous nasogastric tube feedings to sustain blood sugar levels. Older children can usually be switched to raw corn starch feedings, which sustain blood glucose values for 4-6 hours.

Birth prevalence of GSDIa is 1/100 000. Birth prevalence is higher - 1/20 000 in Ashkenazi population. General carrier frequency is 1/158.

CarrierTest targets frequent mutations in *G6PC* gene. More info: https://ghr.nlm.nih.gov/gene/G6PC

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	70	1/520	1/1081600

Galactosemia (GALT)

The *GALT* gene provides instructions for making an enzyme called galactose-1-phosphate uridylyltransferase (GALT) converting galactose which is found in all dairy products and many baby formulas to glucose. Glucose is the main energy source for most cells. This chemical reaction also produces galactose-containing proteins and fats. These modified proteins and fats play critical roles in chemical signaling, building cellular structures, transporting molecules, and producing energy.

Deficient galactose-1-phosphate uridylyltransferase prevents cells from processing galactose obtained from the diet. As a result, galactose-1-phosphate and related compounds can build up to toxic levels in the body. The accumulation of these substances damages tissues and organs, leading to the serious medical problems associated with classic galactosemia.

Classic galactosemia, also known as type I, is the most common and most severe form of the condition. If infants with classic galactosemia are not treated promptly with a low-galactose diet, life-threatening complications appear within a few days after birth. Affected infants typically develop feeding difficulties, a lack of energy (lethargy), failure to thrive, jaundice, liver damage, and abnormal bleeding. Other serious complications of this condition can include overwhelming bacterial infections (sepsis) and shock. Affected children are also at increased risk ofdelayed development, clouding of the lens of the eye (cataract), speech difficulties, and intellectual disability. Females with classic galactosemia may develop reproductive problems caused by an early loss of function of the ovaries (premature ovarian insufficiency). Galactosemia type II and type III are rarer and cause fewer medical problems than the classic type.

Birth prevalence of classic galactosemia is 1/30000. Carrier frequency is 1/63.

CarrierTest targets frequent mutations in *GALT* gene. A particular *GALT* mutation Asn314Asp or N314D called the Duarte variant results in a form of galactosemia with less serious complications than the classic type.

More info: https://ghr.nlm.nih.gov/gene/GALT

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/16000	1/64	80	1/320	1/409600

Gaucher disease (GBA)

The *GBA* gene provides instructions for making enzyme called beta-glucocerebrosidase present in lysosomes. Beta-glucocerebrosidase I helps break down a large molecule called glucocerebroside into a sugar (glucose) and a simpler fat molecule (ceramide).
Deficiency of beta-glucocerebrosidase results in accumulation of glucocerebroside in white blood cells called macrophages in the spleen, liver, bone marrow, and other organs. The abnormal accumulation and storage of these substances damages tissues and organs, causing the characteristic features of gaucher disease.
Type 1 Gaucher disease is the most common form of this condition. Major signs and symptoms include enlargement of the liver and spleen (hepatosplenomegaly), a low number of red blood cells (anaemia), easy bruising caused by a decrease in blood platelets (thrombocytopenia), lung disease, and bone abnormalities such as bone pain, fractures, and arthritis. The brain and spinal cord are usually not affected. The features of this condition range from mild to severe and may appear anytime from childhood to adulthood.
More rare types 2 and 3 gaucher disease are known as neuronopathic forms of the disorder because they are characterized by problems that affect the central nervous system.
There are two types of Gaucher disease treatments currently available: enzyme replacement therapy (ERT) and substrate reduction therapy (SRT).
Gaucher disease prevalence is between 1/50 000 and 1/100 000 in the general population. Type 1 occurs more frequently in people of Ashkenazi Jewish heritage than in those with other backgrounds. This form of the condition affects 1 in 500 to 1,000 Ashkenazi people. The other forms of gaucher disease are uncommon without population differences. Carrier frequency is 1/110.
CarrierTest targets frequent mutations in *GBA* gene. More info: https://ghr.nlm.nih.gov/gene/GBA

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/50000	1/110	70	1/360	1/518400

Glutaric acidemia, type 1 (GCDH)

The *GCDH* gene provides instructions for making the enzyme glutaryl-CoA dehydrogenase. This enzyme is found in mitochondria, the energy-producing centres of cells. The GCDH enzyme is involved in the breakdown of the amino acids lysine, hydroxylysine, and tryptophan, which are building blocks of proteins.

Glutaryl-CoA dehydrogenase deficiency results in inadequate break down and toxic accumulation the amino acids lysine, hydroxylysine and tryptophan in the brain with signs and symptoms of glutaric acidemia type I.

The severity of glutaric acidemia type I varies widely; some individuals are only mildly affected, while others have severe problems. In most cases, signs and symptoms first occur in infancy or early childhood, but in a small number of affected individuals, the disorder first becomes apparent in adolescence or adulthood.

Some babies with glutaric acidemia type I are born with unusually large heads (macrocephaly). Affected individuals may have difficulty moving and may experience spasms, jerking, rigidity, or decreased muscle tone. Some individuals with glutaric acidemia have developed bleeding in the brain or eyes that could be mistaken for the effects of child abuse.

Strict dietary control may help limit progression of the neurological damage. Stress caused by infection, fever or other demands on the body may lead to worsening of the signs and symptoms, with only partial recovery.

Birth prevalence of glutaric acidemia type I in European population is 1/40000. Carrier frequency is 1/100.

CarrierTest targets frequent mutations in *GCDH* gene.More info: https://ghr.nlm.nih.gov/gene/GCDH

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/40000	1/100	50	1/200	1/160000

Hearing loss, DFNB1 nonsyndromic (GJB2)

The *GJB2* gene provides instructions for making a protein called connexin 26. Connexins proteins form channels called gap junctions that permit the transport of nutrients, charged atoms (ions), and signalling molecules between adjoining cells. Connexin 26 deficiency causes congenital nonsyndromic hearing loss, which is loss of hearing that is not associated with other signs and symptoms. Connexin 26 deficiency causes about 50% cases of inherited hearing loss. Mutation 35delG (p.Gly12Valfs) represents more than 80% of *GJB2* mutations. Birth prevalence is 1/3600. Carrier frequency is 1/30.
CarrierTest targets frequent mutations in *GJB2* gene, including the most common mutations 35delG, Trp24Ter and 313_326del.
More info https://ghr.nlm.nih.gov/gene/GJB2

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/3600	1/30	90	1/290	1/336400

Fabry disease (GLA)

The *GLA* gene provides instructions for making an enzyme called alpha-galactosidase A. This enzyme is breaks down a molecule called globotriaosylceramide in lysosomes. As a result of alpha-galactosidase a deficiency globotriaosylceramide is accumulated and damages cells particularly cells lining blood vessels in the skin and cells in the kidneys, heart, and nervous system. The progressive accumulation of globotriaosylceramide leading to the varied signs and symptoms of Fabry disease. Classic form of Fabry disease typically begins in childhood. Characteristic features of Fabry disease include episodes of pain, particularly in the hands and feet (acroparesthesias); clusters of small, dark red spots on the skin called angiokeratomas; a decreased ability to sweat (hypohidrosis); cloudiness of the front part of the eye (corneal opacity); problems with the gastrointestinal system; ringing in the ears (tinnitus); and hearing loss. Fabry disease also involves potentially life-threatening complications such as progressive kidney damage, heart attack, and stroke. Some affected individuals have milder forms of the disorder that appear later in life and affect only the heart or kidneys.

Fabry disease is inherited in an X-linked manner. Males who inherit the pathogenic variant will be fully affected. Females who inherit the pathogenic variant may or may not develop clinical findings related to the disorder. The most common symptom of Fabry disease seen in heterozygous females is corneal dystrophy, which occurs in around 70% of females. Other symptoms that have been reported in females with Fabry disease include: angiokeratomas, acroparesthesias, anhidrosis, and gastrointestinal disturbances, vascular lesions in the conjunctiva and retina, kidney disease, autonomic and other neurological complications such as tinnitus and vertigo, cardiovascular abnormalities, cerebrovascular abnormalities, fatigue. If an affected male reproduces, none of his sons will be affected and all of his daughters will inherit the pathogenic variant and may or may not develop clinical symptoms related to the disorder. Heterozygous females have a 50% chance of transmitting the pathogenic variant with each pregnancy.

For treatment of Fabry disease Enzyme Replacement Therapy (ERT) has been introduced in 2003.

Prevalence of Fabry disease is 1/3000 (Milder, late-onset forms) - 1/40000 (severe forms). Female carrier frequency of milder forms is 1/1500.

CarrierTest targets frequent mutations in *GLA* gene.More info https://ghr.nlm.nih.gov/gene/GLA

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	The risk of son (mother test -ve)
1/3000	1/1500	60	1/3800	1/7600

GM1-gangliosidosis (GLB1)

The *GLB1* gene provides instructions for producing an enzyme called beta-galactosidase (ß-galactosidase) located in lysosomes. Within lysosomes, ß-galactosidase helps break down certain molecules, including substances called GM1 ganglioside and keratan sulphate. GM1 ganglioside is important for normal functioning of nerve cells in the brain, and keratan sulphate is particularly abundant in cartilage and the clear covering of the eye (cornea). The GLB1 gene also provides instructions for making the elastin-binding protein which is a component of the connective tissue that forms the body's supportive framework.

ß-galactosidase deficiency causes toxic accumulation of GM1 ganglioside and keratan sulphate in many tissues and organs. In the brain, progressive damage caused by the build up of GM1 ganglioside leads to the destruction of nerve cells, which causes many of the signs and symptoms of GM1 gangliosidosis. Elastin-binding protein deficiency contributes to the weakened heart muscle (cardiomyopathy) found in some people with GM1 gangliosidosis.

The signs and symptoms of the most severe form of GM1 gangliosidosis, called type I or the infantile form, usually become apparent by the age of 6 months. Infants with this form of the disorder typically appear normal until their development slows and muscles used for movement weaken. Affected infants eventually lose the skills they had previously acquired (developmentally regress) and may develop an exaggerated startle reaction to loud noises. As the disease progresses, children with GM1 gangliosidosis type I develop an enlarged liver and spleen (hepatosplenomegaly), skeletal abnormalities, seizures, profound intellectual disability, and clouding of the clear outer covering of the eye (the cornea). Loss of vision occurs as the light-sensing tissue at the back of the eye (the retina) gradually deteriorates. An eye abnormality called a cherry-red spot, which can be identified with an eye examination, is characteristic of this disorder. In some cases, affected individuals have distinctive facial features that are described as "coarse," enlarged gums (gingival hypertrophy), and an enlarged and weakened heart muscle (cardiomyopathy). Individuals with GM1 gangliosidosis type I usually do not survive past early childhood. Type II GM1 gangliosidosis consists of intermediate forms of the condition, also known as the late infantile and juvenile forms. The third type of GM1 gangliosidosis is known as the adult or chronic form, and it represents the mildest end of the disease spectrum.

Treatment for patients with GM1 gangliosidosis is symptomatic and supportive.

Birth prevalence of GM1 gangliosidosis is 1/100000 - 1 200000 with higher rate at roma ethnic group (1/10000) with carrier frequency 1/50. CarrierTest targets frequent mutations in *GLB1* gene.

More info: https://ghr.nlm.nih.gov/gene/GLB1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/10000	1/50	60	1/120	1/57600

Mucolipidosis II/III (GNPTAB)

The *GNPTAB* gene provides instructions for making two different parts, the alpha and beta subunits, of an enzyme called GlcNAc-1-phosphotransferase (GNPT), which is involved in transport of different compounds in lysosomes. Lysosomes are compartments in the cell that digest and recycle materials.

GNPT deficiency causes large molecules to accumulate in lysosomes with signs and symptoms of mucolipidoses II alpha/beta and III alpha/beta called as „lysosomal storage disorders".

Mucolipidosis II alpha/beta (also known as I-cell disease) is a progressively debilitating disorder that affects many parts of the body. Most affected individuals do not survive past early childhood. At birth, children with mucolipidosis II alpha/beta are small and have weak muscle tone (hypotonia) and a weak cry. Affected individuals grow slowly after birth and usually stop growing during the second year of life. Development is delayed, particularly the development of speech and motor skills such as sitting and standing. Children with mucolipidosis II alpha/beta typically have several bone abnormalities, many of which are present at birth. Affected individuals may have an abnormally rounded upper back (kyphosis), feet that are abnormally rotated (clubfeet), dislocated hips, unusually shaped long bones, and short hands and fingers. People with this condition also have joint deformities (contractures) that significantly affect mobility. Most children with mucolipidosis II alpha/beta do not develop the ability to walk independently. Affected individuals have dysostosis multiplex, which refers to multiple skeletal abnormalities seen on x-ray.

Mucolipidosis III alpha/beta is a disorder similar to mucolipidosis II. Signs and symptoms of this condition are typically milder, appearing around age 3 and worsen slowly over time.

As yet, there is no *cure* for individuals affected by these diseases.

Birth prevalence of Mucolipidoses II/III is 1/100 000. Carrier frequency is 1/158. In Quebec province (Canada) carrier frequency is 1/39.

CarrierTest targets frequent mutations in *GNPTAB* gene.More info: https://ghr.nlm.nih.gov/gene/GNPTAB

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	50	1/320	1/409600

Long-chain acyl-CoA dehydrogenase deficiency (HADHA)

The *HADHA* gene provides instructions for making long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) forming a part of an enzyme complex called mitochondrial trifunctional protein. This enzyme complex functions in mitochondria (the energy-producing centres within cells) and is essential for fatty acid oxidation, which is the multistep process that breaks down (metabolizes) fats and converts them to energy. Mitochondrial trifunctional protein is required to metabolize a group of fats called long-chain fatty acids. Long-chain fatty acids are found in foods such as milk and certain oils. These fatty acids are stored in the body's fat tissues. Fatty acids are a major source of energy for the heart and muscles.

LCHAD deficiency prevents the body from converting certain fats to energy, particularly during periods without food (fasting). Signs and symptoms of LCHAD deficiency typically appear during infancy or early childhood and can include feeding difficulties, lack of energy (lethargy), low blood sugar (hypoglycaemia), weak muscle tone (hypotonia), liver problems, and abnormalities in the light-sensitive tissue at the back of the eye (retina). Later in childhood, people with this condition may experience muscle pain, breakdown of muscle tissue, and a loss of sensation in their arms and legs (peripheral neuropathy). Individuals with LCHAD deficiency are also at risk of serious heart problems, breathing difficulties, coma, and sudden death. Problems related to LCHAD deficiency can be triggered by periods of fasting or by illnesses such as viral infections. Mothers of foetuses with LCHAD deficiency are at risk ofacute fatty liver of pregnancy (AFLP) or HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome.

The management of affected patients is directed at the avoidance of fasting. Most patients also are provided with uncooked corn starch and medium-chain triglyceride (MCT) oil supplementation to further decrease exposure to fasting. Oral supplementation with docosahexaenoic acid ethyl ester (DHA) may be considered to improve visual function.

Birth prevalence of LCHAD deficiency is 1/56000. Carrier frequency of *HADHA* mutations is 1/118. CarrierTest targets frequent mutations in *GNPTAB* gene.

More info: https://ghr.nlm.nih.gov/gene/HADHA

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/56000	1/118	90	1/1170	1/5500000

Beta-thalassemia (HBB)

The *HBB* gene provides instructions for making a protein called beta-globin. Beta-globin is a component (subunit) of haemoglobin. Haemoglobin within red blood cells binds to oxygen molecules in the lungs. These cells then travel through the bloodstream and deliver oxygen to tissues throughout the body.

Beta-globin deficiency reduce or eliminate the haemoglobin production and disrupts the normal development of red blood cells. A shortage of mature red blood cells can reduce the amount of oxygen that is delivered to tissues. A lack of oxygen in the body's tissues can lead to poor growth, organ damage, and other health problems associated with beta thalassemia. Partial beta-globin deficiency results in a type of the condition called beta-plus (B^+) thalassemia. Mutations that prevent cells from producing any beta-globin result in beta-zero (B^0) thalassemia.

Three clinical and haematological conditions are recognized: Thalassemia major (Cooley's Anaemia), Thalassemia intermedia and Beta-thalassemia carrier state. Thalassemia major is a severe transfusion-dependent anaemia. Thalassemia intermedia comprehends a clinically and genotypically very heterogeneous group of thalassemia-like disorders, ranging in severity from the asymptomatic carrier state to the severe transfusion-dependent type. The beta-thalassemia carrier state, which results from heterozygosity for beta-thalassemia, is clinically asymptomatic and is defined by specific haematological features.

The signs and symptoms of thalassemia major appear within the first 2 years of life. Children develop life-threatening anaemia. They do not gain weight and grow at the expected rate (failure to thrive) and may develop yellowing of the skin and whites of the eyes (jaundice). Affected individuals may have an enlarged spleen, liver, and heart, and their bones may be misshapen. Some adolescents with thalassemia major experience delayed puberty.

Thalassemia intermedia is milder than thalassemia major. The signs and symptoms of thalassemia intermedia appear in early childhood or later in life. Affected individuals have mild to moderate anaemia and may also have slow growth and bone abnormalities.

Regular blood transfusions are the only treatment available to patients with thalassemia. While regular transfusions greatly contribute to the quality and length of life of thalassemia major patients, they also leave patients with an excess of iron in their bodies resulting in liver, heart, and hormone problems. It is necessary that this excess iron be removed, or chelated.

Birth prevalence of thalassemia in Central European population is about 1/100 000. Carrier frequency is 1/158. Birth prevalence is much higher in Mediterranean area and some African an Asian populations. CarrierTest targets frequent mutations in *HBB* gene. More info: https://ghr.nlm.nih.gov/gene/HBB

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	80	1/790	1/2496400

Haemoglobin E disease (HBB)

The *HBB* gene provides instructions for making a protein called beta-globin. Beta-globin is a component (subunit) haemoglobin. Haemoglobin within red blood cells binds to oxygen molecules in the lungs. These cells then travel through the bloodstream and deliver oxygen to tissues throughout the body.
Beta-globin deficiency reduce or eliminate the haemoglobin production and disrupts the normal development of red blood cells. A shortage of mature red blood cells can reduce the amount of oxygen that is delivered to tissues. A lack of oxygen in the body's tissues can lead to poor growth, organ damage, and other health problems associated with beta thalassemia.
Haemoglobin E (HbE) is an abnormal haemoglobin caused by a single point HBB gene mutation Glu26Lys. At position 26 there is a change in the amino acid, from glutamic acid to lysine. Amount of haemoglobin E at homozygotes increases in the first months of life so the subjects start to have a mild Beta-thalassemia with mild haemolytic anaemia and mild enlargement of the spleen.
Haemoglobin E has been one of the less well known variants of normal haemoglobin. It is very common in Southeast Asia but has a low frequency amongst other ethnicities.

People can inherited one *HBB* mutation for haemoglobin E from one parent and one *HBB* mutations for β-thalassemia from the other parent. Haemoglobin E/β-thalassemia is a severe and frequent disease. It affects more than a million people in the world.

Haemoglobin E is most prevalent in Southeast Asia (Thailand, Myanmar, Cambodia, Laos, Vietnam, India), where its prevalence can reach from 30 or 70%. In Europe there have been found cases of families with haemoglobin E.

CarrierTest targets frequent mutations in *HBB* gene. More info: https://rarediseases.info.nih.gov/diseases/2641/hemoglobin-e-disease

Sickle Cell Disease (HBB)

The *HBB* gene provides instructions for making a protein called beta-globin. Beta-globin is a component (subunit) of haemoglobin. Haemoglobin within red blood cells binds to oxygen molecules in the lungs. These cells then travel through the bloodstream and deliver oxygen to tissues throughout the body.

Sickle cell disease is haemoglobin disorder caused by Glu6Val mutation of *HBB* gene. People with this disorder have atypical haemoglobin molecules called haemoglobin S, which can distort red blood cells into a sickle, or crescent, shape particularly when exposed to low-oxygen condition.

Signs and symptoms of sickle cell disease usually begin in early childhood. Characteristic features of this disorder include a low number of red blood cells (anaemia), repeated infections, and periodic episodes of pain. The severity of symptoms varies from person to person. The signs and symptoms of sickle cell disease are caused by the sickling of red blood cells. When red blood cells sickle, they break down prematurely, which can lead to anaemia. Anaemia can cause shortness of breath, fatigue, and delayed growth and development in children. The rapid breakdown of red blood cells may also cause yellowing of the eyes and skin, which are signs of jaundice. Painful episodes can occur when sickled red blood cells, which are stiff and inflexible, get stuck in small blood vessels. These episodes deprive tissues and organs of oxygen-rich blood and can lead to organ damage, especially in the lungs, kidneys, spleen, and brain. A particularly serious complication of sickle cell disease is high blood pressure in the blood vessels that supply the lungs (pulmonary hypertension). Pulmonary hypertension occurs in about one-third of adults with sickle cell disease and can lead to heart failure. Other mutations in the *HBB* gene lead to additional abnormal versions of beta-globin such as haemoglobin C (HbC) and haemoglobin E (HbE). *HBB* gene mutations can also result in beta thalassemia.

Therapy is mostly symptomatic: pain relief, hydratation and treatment of infections. Stem cell or bone marrow transplants are the only cure in some cases.

Sickle cell disease affects millions of people worldwide. It is most common among people whose ancestors come from Africa; Mediterranean countries, the Arabian Peninsula; India; and Spanish-speaking regions in South America, Central America, and parts of the Caribbean. Heterozygotes of Glu6Val mutation - sickle cell trait carriers with mild symptoms - possess a resistance to malarial infection.

CarrierTest targets frequent mutations in *HBB* gene. More info: https://ghr.nlm.nih.gov/condition/sickle-cell-disease

Tay-Sachs disease (HEXA)

The *HEXA* gene provides instructions for making one part (subunit) of an enzyme called beta-hexosaminidase A. Specifically, the protein produced from the *HEXA* gene forms the alpha subunit of this enzyme. One alpha subunit joins with one beta subunit (produced from the *HEXB* gene) to form a functioning enzyme.

Beta-hexosaminidase A plays a critical role in the brain and spinal cord (central nervous system). This enzyme is found in lysosomes, which are structures in cells that break down toxic substances and act as recycling centres. Within lysosomes, beta-hexosaminidase A forms part of a complex that breaks down a fatty substance called GM2 ganglioside.

Deficient Beta-hexosaminidase A prevents breaking down GM2 ganglioside with its accumulation in nerve cells in the brain and spinal cord. Progressive damage caused by the buildup of GM2 ganglioside leads to the destruction of these cells, which causes the signs and symptoms of Tay-Sachs disease.

The most common form of Tay-Sachs disease becomes apparent in infancy. Infants with this disorder typically appear normal until the age of 3 to 6 months, when their development slows and muscles used for movement weaken. Affected infants lose motor skills such as turning over, sitting, and crawling. They also develop an exaggerated startle reaction to loud noises. As the disease progresses, children with Tay-Sachs disease experience seizures, vision and hearing loss, intellectual disability, and paralysis. An eye abnormality called a cherry-red spot, which can be identified with an eye examination, is characteristic of this disorder. Children with this severe infantile form of Tay-Sachs disease usually live only into early childhood.

Other forms of Tay-Sachs disease are very rare. Signs and symptoms can appear in childhood, adolescence, or adulthood and are usually milder than those seen with the infantile form. Characteristic features include muscle weakness, loss of muscle coordination (ataxia) and other problems with movement, speech problems, and mental illness. These signs and symptoms vary widely among people with late-onset forms of Tay-Sachs disease. Treatment for Tay-Sachs disease is only symptomatic.

Birth prevalence of Tay-Sachs disease is 1/300 000. Carrier frequency is 1/270.

CarrierTest targets frequent mutations in *HEXA* gene. More info: https://ghr.nlm.nih.gov/gene/HEXA

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/300000	1/274	95	1/5641	N/S

Hemochromatosis (HFE)

The *HFE* gene provides instructions for producing a protein regulating iron absorption. As a result of HFE protein deficiency too much iron is absorbed from the diet. This increase in the absorption of dietary iron leads to the iron overload characteristic of type 1 hemochromatosis (*HFE*-HH).

Two particular *HFE* mutations are responsible for most cases of this disorder. One - more significant mutation replaces the amino acid cysteine with the amino acid tyrosine at position 282 in the protein's chain of amino acids (written as Cys282Tyr). The other *HFE* mutation His63Asp is associated with a mild picture of HFE-haemochromatosis mostly in compound heterozygous state with Cys282Tyr mutation.

The vast majority of patients who have hereditary hemochromatosis are Cys282Tyr homozygotes.

The phenotypic spectrum of *HFE*-HH includes:

- Those with clinical *HFE*-HH, in which manifestations of end-organ damage secondary to iron storage are present;
- Those with biochemical *HFE*-HH, in which the only evidence of iron overload is increased transferrin-iron saturation and increased serum ferritin concentration;
- Non-expressing p.Cys282Tyr homozygotes, in whom neither clinical manifestations of *HFE*-HH nor iron overload is present.

Clinical *HFE*-HH is characterized by excessive storage of iron in the liver, skin, pancreas, heart, joints, and testes. In untreated individuals, early symptoms may include: abdominal pain, weakness, lethargy, and weight loss; the risk of cirrhosis is significantly increased when the serum ferritin is higher than 1,000 ng/mL; other findings may include progressive increase in skin pigmentation, diabetes mellitus, congestive heart failure, and/or arrhythmias, arthritis, and hypogonadism. Clinical *HFE*-HH is more common in men than women. Men with type 1 hemochromatosis typically develop symptoms between the ages of 40 and 60, and women usually develop symptoms after menopause.

Transferrin saturation corresponding to the ratio of serum iron and total iron-binding capacity (TIBC) greater than 45% together with genetic testing can confirm the diagnosis.

Treatment: Phlebotomy is the best method for removing excess iron from the body. In men, testosterone hormone therapy can help improve the loss of sexual desire and changes in secondary sexual characteristics.

Hereditary hemochromatosis is probably the most common inherited disorder of people of northern European ancestry.

Prevalence of Cys282Tyr homozygotes is 1/400 and carrier frequency of Cys282Tyr mutation is 1/10. But only about 25% (1 in 4) Cys282Tyr homozygous men and 3, 5% (1 in 28) menopausal women will present with clinical *HFE*-HH.

CarrierTest is targeted on Cys282Tyr mutation of the *HFE* gene.

More info: https://ghr.nlm.nih.gov/gene/HFE

Mucopolysaccharidosis type I - MPS I-H. (IDUA)

The *IDUA* gene provides instructions for producing lysosomal enzyme called alpha-L-iduronidase, which is essential for the breakdown of large sugar molecules called glycosaminoglycans (GAGs) called heparan sulphate and dermatan sulphate. Lysosomes are compartments within cells that digest and recycle different types of molecules.

Alpha-L-iduronidase deficiency leads to the accumulation of heparan sulphate and dermatan sulphate within the lysosomes. Accumulated GAGs may interfere with the functions of the lysosomes and disrupt the movement of molecules inside the cell with signs and symptoms of Mucopolysaccharidosis type me (MPS I-H – Hurler syndrome.

People with severe MPS I-H generally begin to show signs and symptoms of the disorder within the first year of life, while those with the attenuated form have milder features that develop later in childhood. Individuals with MPS I-H may have a large head (macrocephaly), accumulation of cerebrospinal fluid within the brain. (Hydrocephalus), heart valve abnormalities, distinctive-looking facial features that are described as "coarse," an enlarged liver and spleen (hepatosplenomegaly), and a large tongue (macroglossia). Vocal cords can also enlarge, resulting in a deep, hoarse voice. The airway may become narrow in some people with MPS I-H, causing frequent upper respiratory infections and short pauses in breathing during sleep (sleep apnoea). Clouding of cornea) can cause significant vision loss. Affected individuals may also have hearing loss and recurrent ear infections.

Some individuals with MPS I-H have short stature, joint deformities, multiple skeletal abnormalities and narrowing of the spinal canal.

People with severe MPS I-H experience a decline in intellectual function. Heart disease and airway obstruction are major causes of death.

Treatment: Laronidase (Aldurazyme) is used for enzyme replacement therapy.

Birth prevalence of MPS I-H id 1/100 000. Carrier frequency is 1/158.

CarrierTest targets frequent mutations in *IDUA* gene. More info: https://ghr.nlm.nih.gov/gene/IDUA

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	70	1/520	1/1080000

Mucopolysaccharidosis type IIIA - MPS IIIA. (SGSH)

The *SGSH* gene provides instructions for producing an enzyme called sulphamidase.
This enzyme is located in lysosomes, compartments within cells that digest and recycle different types of molecules. Sulphamidase is involved in the step-wise breakdown of large molecules called glycosaminoglycans (GAGs) removing a chemical group known as a sulphate from a sugar called glucosamine when it is at the end of the GAG chain.
Sulphamidase deficiency disrupts the breakdown of a subset of GAGs called heparan sulphate. As a result, partially broken down heparan sulphate accumulates within lysosomes mostly in the central nervous system cells with signs and symptoms of mucopolysaccharidosis type IIIA (MPS IIIA - Sanfilippo syndrome A).
People with MPS III generally do not display any features of the condition at birth, but they begin to show signs and symptoms of the disorder during early childhood. Affected children often initially have delayed speech and behaviour problems. They may become restless, destructive, anxious, or aggressive. Sleep disturbances are also very common in children with MPS III. This condition causes progressive intellectual disability and the loss of previously acquired skills (developmental regression). In later stages of the disorder, people with MPS III may develop seizures and movement disorders. Individuals with MPS III typically have mildly"coarse" facial features, a large head (macrocephaly), a slightly enlarged liver (mild hepatomegaly), and a soft out-pouching around the belly-button (umbilical hernia) or lower abdomen (inguinal hernia). Some people with MPS III have short stature, joint stiffness, or mild dysostosis multiplex, which refers to multiple skeletal abnormalities seen on x-ray. Affected individuals often develop chronic diarrhoea and recurrent upper respiratory and ear infections. People with MPS III may also experience hearing loss and vision problems.
There is currently no cure or standard treatment for people with mucopolysaccharidosis type IIIA (MPS IIIA).
Birth prevalence of MPS IIIA je 1/100 000. Carrier frequency is 1/158.

CarrierTest targets frequent mutations in *SGSH* gene. More info: https://ghr.nlm.nih.gov/gene/SGSH

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	60	1/390	1/608000

Familial dysautonomia (IKBKAP)

The *IKBKAP* gene provides instructions for making a protein called IKK complex-associated protein (IKAP). This protein is important for the transcription of proteins that affect the cell's structural framework (the cytoskeleton) and cell movement (motility).

IKAP deficiency may impair the growth and development of nerve cells by disrupting the cytoskeleton and cell motility and causes familial dysautonomia (FD) affecting cells in the autonomic nervous system, which controls involuntary actions such as digestion, breathing, production of tears, and the regulation of blood pressure and body temperature. It also affects the sensory nervous system, which controls activities related to the senses, such as taste and the perception of pain, heat, and cold. Familial dysautonomia is also called hereditary sensory and autonomic neuropathy, type III.

Problems related to this disorder first appear during infancy. Early signs and symptoms include poor muscle tone (hypotonia), feeding difficulties, poor growth, lack of tears, frequent lung infections, and difficulty maintaining body temperature. Older infants and young children with familial dysautonomia may hold their breath for prolonged periods of time, which may cause a bluish appearance of the skin or lips (cyanosis) or fainting. This breath-holding behaviour usually stops by age 6. Developmental milestones, such as walking and speech, are usually delayed, although some affected individuals show no signs of developmental delay.

Additional signs and symptoms in school-age children include bed wetting, episodes of vomiting, reduced sensitivity to temperature changes and pain, poor balance, abnormal curvature of the spine (scoliosis), poor bone quality and increased risk ofbone fractures, and kidney and heart problems. Affected individuals also have poor regulation of blood pressure. Familial dysautonomia occurs primarily in Ashkenazi people. Familial dysautonomia is extremely rare in the general population.

Prevalence of Familial disautonomia in Ashkenazi is 1/3700. Carrier frequency is 1/30.

CarrierTest targets frequent mutations in *IKBKAP* gene. More info: https://ghr.nlm.nih.gov/gene/IKBKAP

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/4000	1/32	95	1/640	1/1638400

X-linked severe combined immunodeficiency (SCID) (IL2RG)

The *IL2RG* gene provides instructions for making a protein called the common gamma chain receptor. This protein is a component of several different receptors that are involved in immune system. The receptors span the cell membrane, with one end outside the cell like an antenna and the other end inside to transmit signals to the nucleus. Other proteins attach to these receptors, like a key in a lock, to trigger a series of chemical reactions inside the cell. Receptors containing the common gamma chain are located on the surface of immature blood-forming cells in bone marrow. They partner with other proteins to direct blood-forming cells to form lymphocytes (a type of white blood cell). The receptors also regulate the growth and maturation of several subtypes of lymphocytes: T cells, B cells, and natural killer cells. These cells kill viruses, make antibodies, and help regulate the entire immune system.

Common gamma chain deficiency results in impaired development of lymphocytes. A lack of functional mature lymphocytes prevents the immune system from fighting off infections with signs and symptoms of X-linked severe combined immunodeficiency (SCID) occurring almost exclusively in males.

Boys with X-linked SCID are prone to recurrent and persistent infections because they lack the necessary immune cells to fight off certain bacteria, viruses, and fungi. Many infants with X-linked SCID develop chronic diarrhoea, a fungal infection called thrush, and skin rashes. Affected individuals also grow more slowly than other children. Without treatment, males with X-linked SCID usually do not live beyond infancy.

SCID can be treated by bone marrow transplantation or gene replacement therapy is required for survival. SCID management includes treatment of infections, immunoglobulin infusions and prophylactic antibiotics.

X-linked SCID is inherited in an X-linked manner. If an affected male reproduces, none of his sons will be affected and all of his daughters will inherit the pathogenic variant and may or may not develop clinical symptoms related to the disorder. Heterozygous females have a 50% chance of transmitting the pathogenic variant with each pregnancy: males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant may or may not develop clinical findings related to the disorder.

Birth prevalence of X-linked SCID is 1/50000. Female carrier frequency is 1/25000.

CarrierTest targets frequent mutations in *IL2RG* gene. More info: https://ghr.nlm.nih.gov/gene/IL2RG

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	The risk of son (mother test –ve)
1/50000	1/25000	40	1/41700	1/83400

3-Methylcrotonyl-CoA carboxylase deficiency (MCCC1)

The *MCCC1* gene provides instructions for making one part (the alpha subunit) of an enzyme called 3-methylcrotonoyl-CoA carboxylase or 3-MCC. Alpha subunits join with smaller beta subunits made from the *MCCC2* gene forming a functioning enzyme. The 3-MCC enzyme is found in mitochondria, which are the energy-producing centres inside cells and plays a critical role in breaking down leucine, an amino acid that is a building block of many proteins. As a result of 3-MCC deficiency leucine cannot be broken down properly, and by-products of leucine processing build up to toxic levels in the body. These toxic substances can damage the brain, causing the characteristic signs and symptoms.

Infants with 3-MCC deficiency appear normal at birth but usually develop signs and symptoms in infancy or early childhood. The characteristic features of this condition, which can range from mild to life-threatening, include feeding difficulties, recurrent episodes of vomiting and diarrhoea, excessive tiredness (lethargy), and weak muscle tone (hypotonia). If untreated, this disorder can lead to delayed development, seizures, and coma.

Many of these complications can be prevented with early detection and lifelong management with a low-protein diet and appropriate supplements. Some people with gene mutations that cause 3-MCC deficiency never experience any signs or symptoms of the condition.

Birth prevalence of 3-MCC deficiency is 1/27000. Carrier frequency of *MCCC1* or *MCCC2* mutations is 1/82. CarrierTest targets frequent mutations in *MCCC1* gene.

More info: https://ghr.nlm.nih.gov/gene/MCCC1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/27000	1/82	40	1/140	1/78400

3-Methylcrotonyl-CoA carboxylase deficiency (MCCC2)

MCCC2 and *MCCC1* genes provide instructions for making beta and alpha subunits of an enzyme called 3-methylcrotonoyl-CoA carboxylase or 3-MCC. The 3-MCC enzyme is found in mitochondria, which are the energy-producing centres inside cells and plays a critical role in breaking down leucine, an amino acid that is a building block of many proteins.

As a result of 3-MCC deficiency leucine cannot be broken down properly, and by-products of leucine processing build up to toxic levels in the body. These toxic substances can damage the brain, causing the characteristic signs and symptoms.

Infants with 3-MCC deficiency appear normal at birth but usually develop signs and symptoms in infancy or early childhood. The characteristic features of this condition, which can range from mild to life-threatening, include feeding difficulties, recurrent episodes of vomiting and diarrhoea, excessive tiredness (lethargy), and weak muscle tone (hypotonia). If untreated, this disorder can lead to delayed development, seizures, and coma.

Many of these complications can be prevented with early detection and lifelong management with a low-protein diet and appropriate supplements. Some people with gene mutations that cause 3-MCC deficiency never experience any signs or symptoms of the condition.

Birth prevalence of 3-MCC deficiency is 1/27000. CarrierTest targets frequent mutations in *MCCC2* gene.

More info: https://ghr.nlm.nih.gov/gene/MCCC2

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/27000	1/82	40	1/140	1/78400

Familial Mediterranean fever (MEFV)

The *MEFV* gene provides instructions for making a protein called pyrin (also known as marenostrin). Pyrin is produced in white blood cells that play a role in inflammation and in fighting infection. Pyrin deficiency causes inappropriate or prolonged inflammatory response with symptoms of Familial Mediterranean Fever (FMF).

FMF is characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints. These episodes are often accompanied by fever and sometimes a rash or headache. Occasionally inflammation may occur in other parts of the body, such as the heart; the membrane surrounding the brain and spinal cord; and in males, the testicles. The first episode of illness in Familial Mediterranean Fever usually occurs in childhood or the teenage years, but in some cases, the initial attack occurs much later in life. Typically, episodes last 12 to 72 hours and can vary in severity. Without treatment of severe forms a buildup of protein deposits (amyloidosis) in the body's organs and tissues may occur, especially in the kidneys, which can lead to kidney failure. Untreated individuals with FMF, especially those with multiple attacks and/or amyloidosis, have a higher chance of infertility.

Febrile and inflammatory episodes are usually treated with nonsteroidal anti inflammatory drugs. Individuals who are homozygous for the mutation Met694Val or compound heterozygous for Met694Val and another disease - causing allele should be treated with colchicine as soon as the diagnosis is confirmed.

Familial Mediterranean fever primarily affects populations originating in the Mediterranean region, particularly people of Armenian, Arab, Turkish, or Jewish ancestry. The disorder affects 1 in 200 to 1,000 people in these populations with corresponding carrier frequency 1/16. It is less common in other populations.

CarrierTest targets frequent mutations in *MEFV* gene. More info: https://ghr.nlm.nih.gov/gene/MEFV

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/1000	1/16	90	1/150	1/90000

MTHFR deficiency (MTHFR)

The *MTHFR* gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase (MTHFR) involved in converting the amino acid homocysteine to methionine. CarrierTest is targeted on C677T polymorphism of MTHFR gene which in homozygous state significantly reduces enzyme activity. Deficient methylenetetrahydrofolate reductase results in elevated homocysteine blood and urine levels (hyperhomocysteinemia, homocysteinuria). Elevated homocysteine is a known risk factor for cardiovascular disease and thrombosis.
More info: https://ghr.nlm.nih.gov/gene/MTHFR

Myotubular myopathy (MTM1)

The *MTM1* gene provides instructions for producing an enzyme myotubularin. Myotubularin is involved in the development and maintenance of muscle cells.

Deficient myotubularin causes X-linked myotubular myopathy primarily affecting muscles used for movement (skeletal muscles) and occurs almost exclusively in males. People with this condition have muscle weakness (myopathy) and decreased muscle tone (hypotonia) that are usually evident at birth.

In X-linked myotubular myopathy, muscle weakness often disrupts normal bone development and can lead to fragile bones, an abnormal curvature of the spine (scoliosis), and joint deformities (contractures) of the hips and knees. People with X-linked myotubular myopathy may have a large head with a narrow and elongated face and a high, arched roof of the mouth (palate). They may also have liver disease, recurrent ear and respiratory infections, or seizures.

Because of their severe breathing problems, individuals with X-linked myotubular myopathy usually survive only into early childhood; however, some people with this condition have lived into adulthood.

Birth prevalence of X-linked myotubular myopathy is 1/50000 males. Female carrier frequency is 1/25000. CarrierTest targets frequent mutations in *MTM1* gene.

Heterozygous females have a 50% chance of transmitting the pathogenic variant with each pregnancy: males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant may or may not develop clinical findings related to the disorder.

More info: https://ghr.nlm.nih.gov/gene/MTM1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	The risk of son (mother test –ve)
1/50000	1/25000	40	1/41700	1/83400

Syndromic hearing loss-Usher syndrome type 1 (MYO7A)

The *MYO7A* gene provides instructions for making a protein called myosin VIIA which helps to transport molecules within cells. Myosin interacts with actin, a protein that is important for cell movement and shape. Mutations in the *MYO7A* gene can cause Usher syndrome type 1.

Usher syndrome is a condition characterized by partial or total hearing loss and vision loss that worsens over time. The hearing loss is classified as sensorineural, which means that it is caused by abnormalities of the inner ear. Gradually deteriorating loss of vision is caused by an eye disease called retinitis pigmentosa (RP), which affects the layer of light-sensitive tissue at the back of the eye (the retina).

There are three major types of Usher syndrome, designated as types 1, 2, and 3. These types are distinguished by their severity and the age when signs and symptoms appear. The types are further divided into subtypes based on their genetic cause.

Most individuals with Usher syndrome type 1 are born with severe to profound hearing loss. Progressive vision loss caused by retinitis pigmentosa becomes apparent in childhood. This type of Usher syndrome also causes abnormalities of the vestibular system, which is the part of the inner ear that helps maintain the body's balance and orientation in space. As a result of the vestibular abnormalities, children with the condition have trouble with balance.

Usher syndrome type 2 is characterized by hearing loss from birth and progressive vision loss that begins in adolescence or adulthood. People with Usher syndrome type 3 experience hearing loss and vision loss beginning somewhat later in life. 7

Usher's syndrome prevalence is 1/23000 representing 3 to 6% of hereditary hearing loss, and about 50% deaf blindness of adults.

MYO7A mutation carrier frequency in general population is 1/166.

CarrierTest targets frequent mutations in *MYO7A* gene. More info: https://ghr.nlm.nih.gov/gene/MYO7A

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/110000	1/166	40	1/280	1/313600

Nijmegen Breakage Syndrome (NBN)

The *NBN* gene provides instructions for making a protein called nibrin. This protein is involved in several critical cellular functions, including the repair of damaged DNA.
Nibrin deficiency causes Nijmegen breakage syndrome (NBS) characterized by progressive microcephaly, intrauterine growth retardation and short stature, recurrent sinopulmonary infections, an increased risk of cancer, and premature ovarian failure in females. Carrier of mutation in this gene has higher risk of cancer development, especially breas cancer (in women) and prostate cancer (in men). Some studies report a slightly risen risk of other cancers - melanoma, ovarian cancer, leukemia and lymphoma. Concrete monitoring plan is not outlined in the current literature. For woman, there is tha same monitoring plan as in breast cancer susceptibility group or according to empirical risk from family hystory (Claus model). For men a screening for prostate cancer starting at the age of 45 is recommended. Moreover antioxidants in diet and protection against ionizing radiation (RTG, UV) is recommended.
Most NBS individuals are homozygous for the single most common Eastern European pathogenic variants, 657_661del5 and R215W. In the US, about 70% of affected individuals tested to date are homozygous for the common allele, 15% are heterozygous for c.657_661del5 and a second unique pathogenic variant, and 15% are homozygous for a unique pathogenic variant.
NBS prevalence is estimated to 1/50000 - 1/100000. Carrier frequency is 1/155.
CarrierTest targets frequent mutations in *NBN* gene.
More info: https://ghr.nlm.nih.gov/gene/NBN

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/75000	1/155	70	1/514	1/1060000

Niemann-Pick disease (NPC1)

The *NPC1* gene provides instructions for making a protein that is located within the membrane of compartments in the cell called lysosomes and endosomes, which digest and recycle materials. It plays a role in the movement of cholesterol and other types of fats (lipids) within cells and across cell membranes. Mutations in the *NPC1* gene cause Niemann-Pick disease type C1. This type of Niemann-Pick disease is characterized by a buildup of fat within cells that leads to movement problems, neurological impairment, lung and liver disease, and speech and feeding problems.

Niemann-Pick disease is divided into four main types: type a, type B, type C1, and type C2. These types are classified on the basis of genetic cause and the signs and symptoms of the condition.

Niemann-Pick disease types C1 usually become apparent in childhood, although signs and symptoms can develop at any time. People with these types usually develop difficulty coordinating movements (ataxia), an inability to move the eyes vertically (vertical supranuclear gaze palsy), poor muscle tone (dystonia), severe liver disease, and interstitial lung disease. Individuals with Niemann-Pick disease types C1 and C2 have problems with speech and swallowing that worsen over time, eventually interfering with feeding. Affected individuals often experience progressive decline in intellectual function and about one-third have seizures. People with these types may survive into adulthood. Specific treatment is not available.

Birth prevalence of all types of Niemann-Pick disease is 1/60000. Prevalence is higher in the Ashkenazi population. NPC1 mutation carrier frequency in general population is approximately 1/235.

CarrierTest targets frequent mutations in *NPC1* gene. More info: https://ghr.nlm.nih.gov/gene/NPC1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/220000	1/235	60	1/586	1/1374000

Niemann-Pick disease (NPC2)

The *NPC2* gene provides instructions for making a protein that is located inside lysosomes, which are compartments in the cell that digest and recycle materials. The NPC2 protein attaches (binds) to cholesterol. NPC2 protein plays an important role in moving cholesterol and certain other fats (lipids) out of the lysosomes to other parts of the cell. Mutations in the NPC2 gene cause Niemann-Pick disease type C2.

Niemann-Pick disease type C2 usually become apparent in childhood, although signs and symptoms can develop at any time. People with these types usually develop difficulty coordinating movements (ataxia), an inability to move the eyes vertically (vertical supranuclear gaze palsy), poor muscle tone (dystonia), severe liver disease, and interstitial lung disease. Individuals with Niemann-Pick disease type C2 have problems with speech and swallowing that worsen over time, eventually interfering with feeding. Affected individuals often experience progressive decline in intellectual function and about one-third have seizures. Specific treatment is not available.

Birth prevalence of all types of Niemann-Pick disease is 1/60000. Prevalence is higher in the Ashkenazi population. *NPC2* mutation carrier frequency in general population is 1/235.

CarrierTest targets frequent mutations in *NPC2* gene. More info: https://ghr.nlm.nih.gov/gene/NPC2

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/220000	1/235	60	1/586	1/1374000

Ornithine transcarbamylase deficiency (OTC)

The *OTC* gene provides instructions for making the enzyme ornithine transcarbamylase (OTC). This enzyme participates in the urea cycle, a series of reactions that occurs in liver cells. The urea cycle processes excess nitrogen, generated when protein is used by the body, into a compound called urea that is excreted by the kidneys. Excreting the excess nitrogen prevents it from accumulating in the form of ammonia, which is toxic, especially to the nervous system.

OTC deficiency can occur as a severe neonatal-onset disease in males (but rarely in females) and as a post-neonatal-onset (partial deficiency) disease in males and females. An infant with ornithine transcarbamylase deficiency may be lacking in energy (lethargic) or unwilling to eat, and have poorly-controlled breathing rate or body temperature. Some babies with this disorder may experience seizures or unusual body movements, or go into a coma. Complications from ornithine transcarbamylase deficiency may include developmental delay and intellectual disability. Progressive liver damage, skin lesions, and brittle hair may also be seen. In some affected individuals, signs and symptoms of ornithine transcarbamylase may be less severe, and may not appear until later in life.

OTC deficiency is inherited in an X-linked manner. If an affected male reproduces, none of his sons will be affected and all of his daughters will inherit the pathogenic variant and may or may not develop clinical symptoms related to the disorder. Heterozygous females have a 50% chance of transmitting the pathogenic variant with each pregnancy: males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant may or may not develop clinical findings related to the disorder. Prevalence of OTC deficiency is 1/40000. Female carrier frequency is 1/20000 CarrierTest targets frequent mutations in *OTC* gene. More info: https://ghr.nlm.nih.gov/gene/OTC

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	The risk of son (mother test –ve)
1/40000	1/20000	30	1/28600	1/57200

Phenylketonuria (PAH)

The *PAH* gene provides instructions for making an enzyme called phenylalanine hydroxylase (PAH) which is responsible for the conversion of phenylalanine to another amino acid, tyrosine. Tyrosine is used to make several types of hormones, certain chemicals that transmit signals in the brain (neurotransmitters), and a pigment called melanin, which gives hair and skin their colour. Tyrosine can also be broken down into smaller molecules that are used to produce energy.

PAH deficiency is preventing processing phenylalanine effectively. As a result, this amino acid can build up to toxic levels in the blood and other tissues with particularly sensitive nerve cells in the brain. Excessive amounts of phenylalanine can cause brain damage with signs of classic phenylketonuria (PKU). People with untreated classic PKU have levels of phenylalanine high enough to cause severe brain damage and other serious medical problems. Mutations in the *PAH* gene that allow the enzyme to retain some activity result in milder versions of this condition, such as variant PKU or non-PKU hyperphenylalaninemia.

The signs and symptoms of PKU vary from mild to severe. The most severe form of this disorder is known as classic PKU. Infants with classic PKU appear normal until they are a few months old. Without treatment, these children develop permanent intellectual disability. Seizures, delayed development, behavioural problems, and psychiatric disorders are also common. Untreated individuals may have a musty or mouse-like odour as a side effect of excess phenylalanine in the body. Children with classic PKU tend to have lighter skin and hair than unaffected family members and are also likely to have skin disorders such as eczema.

Babies born to mothers with PKU and uncontrolled phenylalanine levels (women who no longer follow a low-phenylalanine diet) have a significant risk ofintellectual disability because they are exposed to very high levels of phenylalanine before birth.

The treatment for phenylketonuria includes a lifetime diet with very limited intake of protein, because foods with protein contain phenylalanine and a special nutritional supplements containing essential protein (without phenylalanine) and nutrients that are crucial for growth and general health.

Birth prevalence of PKU in Czech Republic is 1/6500. Carrier frequency is 1 /40.

CarrierTest targets frequent mutations in *PAH* gene. More info: https://ghr.nlm.nih.gov/gene/PAH

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/6500	1/40	90	1/390	1/608400

Syndromic hearing loss-Usher syndrome 1 (PCDH15)

PCDH15 gene provides instructions for making cadherin, a type of protein that helps cells stick together. It plays an essential role in maintenance of normal retinal and cochlear function.

Mutations in the *PCDH15* gene can cause Usher syndrome type 1.

Usher syndrome is a condition characterized by partial or total hearing loss and vision loss that worsens over time. The hearing loss is classified as sensorineural, which means that it is caused by abnormalities of the inner ear. Gradually deteriorating loss of vision is caused by an eye disease called retinitis pigmentosa (RP), which affects the layer of light-sensitive tissue at the back of the eye (the retina).

There are three major types of Usher syndrome, designated as types 1, 2, and 3. These types are distinguished by their severity and the age when signs and symptoms appear. The types are further divided into subtypes based on their genetic cause.

Most individuals with Usher syndrome type I are born with severe to profound hearing loss. Progressive vision loss caused by retinitis pigmentosa becomes apparent in childhood. This type of Usher syndrome also causes abnormalities of the vestibular system, which is the part of the inner ear that helps maintain the body's balance and orientation in space. As a result of the vestibular abnormalities, children with the condition have trouble with balance.

Usher syndrome type 2 is characterized by hearing loss from birth and progressive vision loss that begins in adolescence or adulthood. Unlike the other forms of Usher syndrome, type 2 is not associated with vestibular abnormalities that cause difficulties with balance.

People with Usher syndrome type 3 experience hearing loss and vision loss beginning somewhat later in life.

Usher's syndrome prevalence is 1/23000 representing 3 to 6% of hereditary hearing loss, and about 50% deafblindness of adults.

CarrierTest targets frequent mutations in *PCDH15* gene. More info: https://ghr.nlm.nih.gov/gene/PCDH15

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/810000	1/450	50	1/900	1/3240000

Zellweger Syndrome Spectrum (PEX1)

Zellweger spectrum disorder is a group of conditions that have overlapping signs and symptoms and affect many parts of the body. This group of conditions includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease. Zellweger syndrome is the most severe form of the Zellweger spectrum disorder, NALD is intermediate in severity, and infantile Refsum disease is the least severe form.

Mutations in at least 12 genes have been found to cause Zellweger spectrum disorder (eg *PEX1, PEX2, PEX6, PEX10, PEX12, PEX13, PEX14 and PEX16*).

Mutations in the *PEX1* gene are the most common cause of Zellweger spectrum disorder and are found in nearly 70 percent of affected individuals.

The PEX1 gene provides instructions for making a protein called peroxisomal biogenesis factor 1 (Pex1p), which is part of a group of proteins called peroxins operating in cell structures called peroxisomes. Peroxisomes are sac-like compartments that contain enzymes needed to break down many different substances, including fatty acids and certain toxic compounds.

Pex1p protein deficiency results in empty peroxisomes that cannot carry out their usual functions with signs and symptoms of Zellweger spectrum disorder.

Individuals with Zellweger syndrome, at the severe end of the spectrum, develop signs and symptoms of the condition during the newborn period. These infants experience weak muscle tone (hypotonia), feeding problems, hearing and vision loss, and seizures. These problems are caused by the breakdown of myelin, which is the covering that protects nerves and promotes the efficient transmission of nerve impulses. The part of the brain and spinal cord that contains myelin is called white matter. Destruction of myelin (demyelination) leads to loss of white matter (leukodystrophy). Children with Zellweger syndrome also develop life-threatening problems in other organs and tissues, such as the liver, heart, and kidneys. They may have skeletal abnormalities, including a large space between the bones of the skull (fontanels) and characteristic bone spots known as chondrodysplasia punctata that can be seen on x-ray. Affected individuals have distinctive facial features, including a flattened face, broad nasal bridge, and high forehead. Children with Zellweger syndrome typically do not survive beyond the first year of life.

People with NALD or infantile Refsum disease may have many of the features of Zellweger syndrome; however, their condition typically progresses more slowly.

Because no curative therapy for patients with a ZSD exists, intervention is supportive and based on symptoms.

Total birth prevalence of Zellweger spectrum disorders is 1/50000. Total carrier frequency is 1/80. *PEX1* mutations are involved in 70 percent cases of Zellweger syndrome with birth prevalence 1/72000 and carrier frequency 1/135.

CarrierTest targets frequent mutations in *PEX1*, *PEX2, PEX6, PEX10,PEX12, PEX13,PEX14 and PEX16 genes.*

More info: https://ghr.nlm.nih.gov/gene/PEX1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/72000	1/135	80	1/670	1/1795600

Zellweger Syndrome Spectrum (PEX6)

The PEX6 gene provides instructions for making a predominantly cytoplasmic protein which is part of a group of proteins called peroxins operating in cell structures called peroxisomes. Peroxisomes are sac-like compartmentts that contain enzymes needed to break down many different substances, including fatty acids and certain toxic compounds. Peroxisomal proteins deficiency result in empty peroxisomes that cannot carry out their usual functions with signs and symptoms of Zellweger spectrum disorder, a group of conditions that have overlapping signs and symptoms and affect many parts of the body. This group of conditions called peroxisome biogenesis disorders includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease. Zellweger syndrome is the most severe form of the Zellweger spectrum disorder, NALD is intermediate in severity, and infantile Refsum disease is the least severe form. Mutations in at least 12 genes have been found to cause Zellweger spectrum disorder. (eg. PEX1, PEX2, PEX6, PEX10, PEX12, PEX13, PEX14 and PEX16). Individuals with Zellweger syndrome, at the severe end of the spectrum, develop signs and symptoms of the condition during the newborn period. These infants experience weak muscle tone (hypotonia), feeding problems, hearing and vision loss, and seizures. These problems are caused by the breakdown of myelin, which is the covering that protects nerves and promotes the efficient transmission of nerve impulses. The part of the brain and spinal cord that contains myelin is called white matter. Destruction of myelin (demyelination) leads to loss of white matter (leukodystrophy). Children with Zellweger syndrome also develop life-threatening problems in other organs and tissues, such as the liver, heart, and kidneys. They may have skeletal abnormalities, including a large space between the bones of the skull (fontanels) and characteristic bone spots known as chondrodysplasia punctata that can be seen on x-ray. Affected individuals have distinctive facial features, including a flattened face, broad nasal bridge, and high forehead. Children with Zellweger syndrome typically do not survive beyond the first year of life. People with NALD or infantile Refsum disease may have many of the features of Zellweger syndrome; however, their condition typically progresses more slowly. Because no curative therapy for patients with a ZSD exists, intervention is supportive and based on symptoms.

Total birth prevalence of Zellweger spectrum disorders is 1/50000. Total carrier frequency is 1/80. Carrier frequency of PEX6 mutations is 1/350.

Carrier Test is targeted on 24 mutations of PEX1,PEX2,PEX6,PEX10, PEX12,PEX13,PEX14 and PEX16 genes.

More info: https://ghr.nlm.nih.gov/gene/PEX6

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/490000	1/350	30	1/500	1/1000000

Zellweger Syndrome Spectrum (PEX2 , PEX10, PEX12, PEX13, PEX14 and PEX16)

PEX2, PEX10, PEX12, PEX13, PEX14 and PEX16 genes provide instructions for making a cytoplasmic proteins which are part of a group of proteins called peroxins operating in cell structures called peroxisomes. Peroxisomes are sac-like compartments that contain enzymes needed to break down many different substances, including fatty acids and certain toxic compounds. Peroxisomal proteins deficiency result in empty peroxisomes that cannot carry out their usual functions with signs and symptoms of Zellweger spectrum disorder, a group of conditions that have overlapping signs and symptoms and affect many parts of the body. This group of conditions called peroxisome biogenesis disorders includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease. Zellweger syndrome is the most severe form of the Zellweger spectrum disorder, NALD is intermediate in severity, and infantile Refsum disease is the least severe form. Mutations in at least 12 genes have been found to cause Zellweger spectrum disorder. (eg. PEX1, PEX2, PEX6, PEX10, PEX12, PEX13, PEX14 and PEX16). Individuals with Zellweger syndrome, at the severe end of the spectrum, develop signs and symptoms of the condition during the newborn period. These infants experience weak muscle tone (hypotonia), feeding problems, hearing and vision loss, and seizures. These problems are caused by the breakdown of myelin, which is the covering that protects nerves and promotes the efficient transmission of nerve impulses. The part of the brain and spinal cord that contains myelin is called white matter. Destruction of myelin (demyelination) leads to loss of white matter (leukodystrophy). Children with Zellweger syndrome also develop life-threatening problems in other organs and tissues, such as the liver, heart, and kidneys. They may have skeletal abnormalities, including a large space between the bones of the skull (fontanels) and characteristic bone spots known as chondrodysplasia punctata that can be seen on x-ray. Affected individuals have distinctive facial features, including a flattened face, broad nasal bridge, and high forehead. Children with Zellweger syndrome typically do not survive beyond the first year of life. People with NALD or infantile Refsum disease may have many of the features of Zellweger syndrome; however, their condition typically progresses more slowly. Because no curative therapy for patients with a ZSD exists, intervention is supportive and based on symptoms.

Total birth prevalence of Zellweger spectrum disorders is 1/50000. Total carrier frequency is 1/80. Carrier frequency of PEX2, PEX10, PEX12, PEX13, PEX14 or PEX16 mutations is 1/500. Carrier Test is targeted on 24 mutations of PEX1, PEX2, PEX6, PEX10, PEX12, PEX13, PEX14 and PEX16 genes.

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/1000000	1/500	30	1/710	1/2016400

Chondrodysplasia punctata (PEX7)

The *PEX7* gene provides instructions for making a protein called peroxisomal biogenesis factor 7 (Pex7p), which is part of a group known as the peroxisomal assembly (PEX) proteins. Within cells, PEX proteins are responsible for importing certain enzymes into structures called peroxisomes. The enzymes in these sac-like compartments break down many different substances, including fatty acids and certain toxic compounds. They are also important for the production (synthesis) of fats (lipids) used in digestion and in the nervous system.
Pex7p deficiency can cause rhizomelic chondrodysplasia punctata type 1 (RCDP1) or rarely Refsum disease.
Rhizomelic chondrodysplasia punctata is characterized by distinctive facial features (prominent forehead, widely set eyes , a sunken appearance of the middle of the face , a small nose with upturned nostrils and full cheeks) and shortening of the bones in the upper arms and thighs (rhizomelia) with specific picture on x-rays. People with rhizomelic chondrodysplasia punctata often develop joint deformities (contractures) that make the joints stiff and painful. Additionally, almost all affected individuals have clouding of the lenses of the eyes (cataracts). The cataracts are apparent at birth (congenital) or develop in early infancy. Rhizomelic chondrodysplasia punctata is associated with significantly delayed development and severe intellectual disability. Most children with this condition do not achieve developmental milestones such as sitting without support, feeding themselves, or speaking in phrases. Affected infants grow much more slowly than other children their age, and many also have seizures. Recurrent respiratory infections and life-threatening breathing problems are common. Because of their severe health problems, most people with rhizomelic chondrodysplasia punctata survive only into childhood. Refsum disease - an inherited condition that causes vision loss, absence of the sense of smell (anosmia), and a variety of other signs and symptoms are more frequently associated with mutations of other genes than *PEX7*.
Birth prevalence of RCDP1 is 1/100000. Carrier frequency is 1/158. CarrierTest targets frequent mutations in *PEX7* gene.
More info: https://ghr.nlm.nih.gov/gene/PEX7

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	70	1/520	1/1081600

Congenital disorder of glycosylation- CDG (PMM2)

The *PMM2* gene provides instructions for making an enzyme called phosphomannomutase 2 (PMM2). This enzyme is involved in a process called glycosylation, which attaches groups of sugar molecules (oligosaccharides) to proteins. Glycosylation modifies proteins so they can perform a wider variety of functions. PMM2-congenital disorder of glycosylation (PMM2-CDG, also known as congenital disorder of glycosylation type Ia) is an inherited condition that affects many parts of the body. The type and severity of problems associated with PMM2-CDG vary widely among affected individuals, sometimes even among members of the same family.

Individuals with PMM2-CDG typically develop signs and symptoms of the condition during infancy. Affected infants may have weak muscle tone (hypotonia), retracted (inverted) nipples, an abnormal distribution of fat, eyes that do not look in the same direction (strabismus), developmental delay, and a failure to gain weight and grow at the expected rate (failure to thrive). Infants with PMM2-CDG also frequently have an underdeveloped cerebellum, which is the part of the brain that coordinates movement. Distinctive facial features are sometimes present in affected individuals, including a high forehead, a triangular face, large ears, and a thin upper lip. Children with PMM2-CDG may also have elevated liver function test results, seizures, fluid around the heart (pericardial effusion), and blood clotting disorders. About 20 percent of affected infants do not survive the first year of life due to multiple organ failure. The most severe cases of PMM2-CDG are characterized by hydrops fetalis, a condition in which excess fluid builds up in the body before birth. Most babies with hydrops fetalis are stillborn or die soon after birth.

People with PMM2-CDG who survive infancy may have moderate intellectual disability, and some are unable to walk independently. Affected individuals may also experience stroke-like episodes that involve an extreme lack of energy (lethargy) and temporary paralysis. Recovery from these episodes usually occurs over a period of a few weeks to several months. During adolescence or adulthood, individuals with PMM2-CDG have reduced sensation and weakness in their arms and legs (peripheral neuropathy), an abnormal curvature of the spine (kyphoscoliosis), impaired muscle coordination (ataxia), and joint deformities (contractures). Some affected individuals have an eye disorder called retinitis pigmentosa that causes vision loss. Females with PMM2-CDG have hypergonadotropic hypogonadism, which affects the production of hormones that direct sexual development. As a result, females with PMM2-CDG do not go through puberty. Affected males experience normal puberty but often have small testes.

Birth prevalence of PMM2-CDG is about 1/75000. Carrier frequency is 1/137.

CarrierTest targets frequent mutations in *PMM2* gene. More info: https://ghr.nlm.nih.gov/gene/PMM2

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/75000	1/137	50	1/273	1/300000

Alpha-1 antitrypsin deficiency (SERPINA1)

The SERPINA1 gene provides instructions for making a protein called alpha-1 antitrypsin (AAT) produced in the liver and then transported to the lungs. Alpha-1 antitrypsin inhibits different enzymes including neutrophil elastase which can damage lung tissue if not properly controlled. Smoking or exposure to tobacco smoke accelerates damage to the lungs. The clinical manifestations may widely vary between patients, ranging from asymptomatic in some to fatal liver or lung disease in others.

People with alpha-1 antitrypsin deficiency usually develop the first signs and symptoms of lung disease between ages 20 and 50. The earliest symptoms are shortness of breath following mild activity, reduced ability to exercise, and wheezing. Other signs and symptoms can include unintentional weight loss, recurring respiratory infections, fatigue, and rapid heartbeat upon standing. Affected individuals often develop emphysema, which is a lung disease caused by damage to the small air sacs in the lungs (alveoli).

About 10 percent of infants with alpha-1 antitrypsin deficiency develop liver disease.

The basic treatment for AAT deficiency is a stay in a dust-free environment and no smoking. Treatment of severe pulmonary complications is possible by administration of alpha-1 antitrypsin (PROLASTIN®-C).

CarrierTest is targeted on most important mutation associated with AAT deficiency: Glu366Lys mutation called „Z mutation"(rs28929474). Homozygotes of mutations Glu366Lys („Z") account for 95% of patients with AAT deficiency.

Prevalence AAT deficiency is 1/3,500 to 1/5000. Carrier frequency of Glu366Lys („Z") mutation is 1/43.

More info: https://ghr.nlm.nih.gov/gene/SERPINA1

Pended syndrome (SLC26A4)

The *SLC26A4* gene provides instructions for making a protein called pendrin. This protein transports negatively charged particles (ions), including chloride, iodide, and bicarbonate, across cell membranes. Pendrin is produced in several organs and tissues, particularly the inner ear and thyroid gland.

Pendrin deficiency influences development of inner ear structures and production of thyroid hormones with signs and symptoms of Pendred syndrome (PS). This condition is characterized by congenital hearing loss, and other abnormalities of the inner ear, including an enlarged vestibular aqueduct and later on by enlargement of the thyroid gland (goiter) in the second decade of life - in most cases without thyroid malfunction. An inner ear abnormality called an enlarged vestibular aqueduct (EVA) is a characteristic feature of Pendred syndrome. The vestibular aqueduct is a bony canal that connects the inner ear with the inside of the skull. Some affected individuals also have an abnormally shaped cochlea, which is a snail-shaped structure in the inner ear that helps process sound. The combination of an enlarged vestibular aqueduct and an abnormally shaped cochlea is known as Mondini malformation. Some affected individuals also have problems with balance caused by dysfunction of the vestibular system.

Total birth prevalence of Pendred syndrome is 1/14000. *SLC26A4* mutations cause about 50% of PS cases. *SLC26A4* mutations carrier frequency is 1/84.

CarrierTest targets frequent mutations in *SLC26A4* gene. More info: https://ghr.nlm.nih.gov/gene/SLC26A4

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/28000	1/84	70	1/280	1/313600

Spinal muscular atrophy (SMN1)

The *SMN1* gene provides instructions for making the survival motor neuron (SMN) protein. This protein is particularly important for the maintenance of specialized nerve cells called motor neurons, which are located in the spinal cord and the part of the brain that is connected to the spinal cord (the brainstem). Deficiency of SMN protein causes loss of motor neurons with clinical picture of Spinal Muscular Atrophy (SMA). The loss of motor neurons leads to weakness and wasting (atrophy) of muscles used for activities such as crawling, walking, sitting up, and controlling head movement. In severe cases of spinal muscular atrophy (Werdnig - Hofmann disease), the muscles used for breathing and swallowing are affected. There are many types of spinal muscular atrophy distinguished by the pattern of features, severity of muscle weakness, and age when the muscle problems begin. About 95 percent of individuals with spinal muscular atrophy have mutations that delete a section called exon8 in both copies of the SMN1 gene in each cell. As a result, little or no SMN protein is made.

Birth prevalence of Spinal Muscular Atrophy is 1/10 000. Carrier frequency is 1/50.

CarrierTest is targeted on exon8 deletion.

More info: https://ghr.nlm.nih.gov/gene/SMN1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/10000	1/50	95	1/780	1/2500000

Niemann-Pick disease (SMPD1)

The *SMPD1* gene provides instructions for making an enzyme called acid sphingomyelinase. Acid sphingomyelinase is responsible for the conversion of a fat (lipid) called sphingomyelin into another type of lipid called ceramide. Deficient acid sphingomyelinase allows sphingomyelin to accumulate in cells with signs and symptoms of Niemann-Pick disease types A and B.

Infants with Niemann-Pick disease type A usually develop an enlarged liver and spleen (hepatosplenomegaly) by age 3 months and fail to gain weight and grow at the expected rate (failure to thrive). The affected children develop normally until around age 1 year when they experience a progressive loss of mental abilities and movement (psychomotor regression). Children with Niemann-Pick disease type A also develop widespread lung damage (interstitial lung disease) that can cause recurrent lung infections and eventually lead to respiratory failure. All affected children have an eye abnormality called a cherry-red spot. Children with Niemann-Pick disease type A generally do not survive past early childhood. Niemann-Pick disease type B usually presents in mid-childhood. The signs and symptoms of this type are similar to type A, but not as severe.

Niemann-Pick disease is divided into four main types: type A, type B, type C1, and type C2. These types are classified on the basis of genetic cause and the signs and symptoms of the condition.

At present, no specific *treatment* is available for patients with any *Niemann-Pick disease.*

Birth prevalence of all types of Niemann-Pick disease is 1/60000. Prevalence is higher in the Ashkenazi population. SMPD1 mutation carrier frequency in general population is 1/158.

CarrierTest targets frequent mutations in *SMPD1* gene. More info: https://ghr.nlm.nih.gov/gene/SMPD1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	60	1/390	1/618000

Lamellar ichthyosis (TGM1)

The *TGM1* gene provides instructions for making an enzyme called transglutaminase 1. This enzyme is found in cells that make up cornified cell envelope in the outermost layer of the skin (the epidermis).

Deficient transglutaminase 1 prevents the formation of the cornified cell envelope, causing the skin abnormalities of lamellar ichthyosis.

Infants with lamellar ichthyosis are typically born with a tight, clear sheath covering their skin called a collodion membrane. This membrane usually dries and peels off during the first few weeks of life, and then it becomes obvious that affected babies have scaly skin, and eyelids and lips that are turned outward. People with lamellar ichthyosis typically have large, dark, plate-like scales covering their skin on most of their body. Infants with lamellar ichthyosis may develop infections, an excessive loss of fluids (dehydration), and respiratory problems. Affected individuals may also have hair loss (alopecia), abnormally formed fingernails and toenails (nail dystrophy), a decreased ability to sweat (hypohidrosis), an increased sensitivity to heat, and a thickening of the skin on the palms of the hands and soles of the feet (keratoderma). Less frequently, affected individuals have reddened skin (erythema) and joint deformities (contractures). Signs and symptoms of lamellar ichthyosis are usually limited to skin.

There is no available cure except local treatment by emollients and surgical procedures.

Birth prevalence of lamellar ichthyosis is 1/100000. Carrier frequency of the TGM1 gene mutations is 1/158. CarrierTest targets frequent mutations in *TGM1* gene.

More info: https://ghr.nlm.nih.gov/gene/TGM1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	50	1/320	1/409600

Neuronal Ceroid-Lipofuscinosis - CLN2 disease (TPP1)

The *TPP1* gene provides instructions for making an enzyme called tripeptidyl peptidase 1 found in lysosomes. Tripeptidyl peptidase 1 breaks down protein fragments, known as peptides, into amino acids. Tripeptidyl peptidase deficiency results in the incomplete breakdown of certain peptides and accumulation of pigmented substances in lysosomes (lipopigment). The accumulations can cause cell damage leading to cell death leading to the signs and symptoms Classic Late Infantile Neuronal Ceroid Lipofuscinosis (CLN2 disease).

CLN2 disease typically begin between ages 2 and 4. The initial features usually include recurrent seizures (epilepsy) and difficulty coordinating movements (ataxia). Affected children also develop muscle twitches (myoclonus) and vision loss. CLN2 disease affects motor skills, such as sitting and walking, and speech development. This condition also causes the loss of previously acquired skills (developmental regression), intellectual disability that gradually gets worse, and behavioural problems. Individuals with this condition often require the use of a wheelchair by late childhood and typically do not survive past their teens. CLN2 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs), which may also be collectively referred to as Batten disease.

There is no specific treatment of CLN2 disease. Stem cells transplantation or gene therapy is considered.

Birth prevalence of CLN2 disease is 1/100 000. CarrierTest targets frequent mutations in *TPP1* gene. More info: https://ghr.nlm.nih.gov/gene/TPP1

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/100000	1/158	35	1/240	1/230400

Syndromic hearing loss-Usher syndrome (USH1C)

USH1C gene is encoding anchoring/scaffolding protein that is a part of the functional network mediating mechanotransduction in cochlear cells. Mutations in the *USH1C* gene can cause Usher syndrome type 1.

Usher syndrome is a condition characterized by partial or total hearing loss and vision loss that worsens over time. The hearing loss is classified as sensorineural, which means that it is caused by abnormalities of the inner ear. Gradually deteriorating loss of vision is caused by an eye disease called retinitis pigmentosa (RP), which affects the layer of light-sensitive tissue at the back of the eye (the retina).

There are three major types of Usher syndrome, designated as types 1, 2, and 3. These types are distinguished by their severity and the age when signs and symptoms appear. The types are further divided into subtypes based on their genetic cause.

Most individuals with Usher syndrome type I are born with severe to profound hearing loss. Progressive vision loss caused by retinitis pigmentosa becomes apparent in childhood. This type of Usher syndrome also causes abnormalities of the vestibular system, which is the part of the inner ear that helps maintain the body's balance and orientation in space. As a result of the vestibular abnormalities, children with the condition have trouble with balance.

Usher syndrome type 2 is characterized by hearing loss from birth without difficulties with balance and progressive vision loss that begins in adolescence or adulthood. People with Usher syndrome type 3 experience hearing loss and vision loss beginning somewhat later in life.

All Usher's syndrome types prevalence is 1/23000 representing 3 to 6% of hereditary hearing loss, and about 50% deafblindness of adults.

CarrierTest targets frequent mutations in *USHC1* gene. More info: https://ghr.nlm.nih.gov/gene/USH1C

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/500000	1/354	50	1/710	1/2016400

Syndromic hearing loss-Usher syndrome (USH2A)

The *USH2A* gene provides instructions for making a protein called usherin present in the inner ear and the retinal cells. Usherin deficiency can cause Usher syndrome type 2.

Usher syndrome is a condition characterized by partial or total hearing loss and vision loss that worsens over time. The hearing loss is classified as sensorineural, which means that it is caused by abnormalities of the inner ear. Gradually deteriorating loss of vision is caused by an eye disease called retinitis pigmentosa (RP), which affects the layer of light-sensitive tissue at the back of the eye (the retina).

There are three major types of Usher syndrome, designated as types types 1, 2 and 3. These types are distinguished by their severity and the age when signs and symptoms appear. The types are further divided into subtypes based on their genetic cause.

Most individuals with Usher syndrome type 1 are born with severe to profound hearing loss. Progressive vision loss caused by retinitis pigmentosa becomes apparent in childhood. This type of Usher syndrome also causes abnormalities of the vestibular system with difficulties with balance.

Usher syndrome type 2 is characterized by hearing loss from birth and progressive vision loss that begins in adolescence or adulthood. The hearing loss associated with this form of Usher syndrome ranges from mild to severe and mainly affects the ability to hear high-frequency sounds. Unlike the other forms of Usher syndrome, type II is not associated with vestibular abnormalities that cause difficulties with balance.

People with Usher syndrome type 3 experience hearing loss and vision loss beginning somewhat later in life.

Usher's syndrome prevalence is 1/23000 representing 3 to 6% of hereditary hearing loss, and about 50% deafblindness of adults.

CarrierTest targets frequent mutations in *USH2A* gene. More info : https://ghr.nlm.nih.gov/gene/USH2A

Prevalence	Carrier frequency	Test coverage (%)	Residual carrier risk	Offspring risk (both parents test -ve)
1/73984	1/136	50	1/270	1/291600