Newborn screening for congenital metabolic diseases

Optional out-of-pocket tests

Information Sheet

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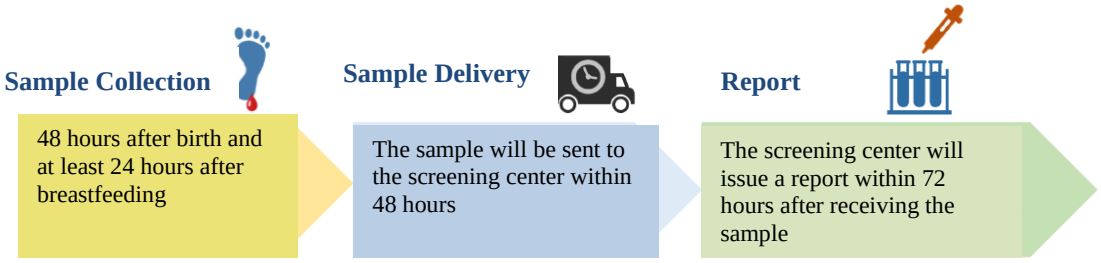
The Sample Collection Process and Schedule of the Neonatal Screening Programs



The handling and report of abnormal (with suspicions of positive results) neonatal screening results

Neonatal screening is the best approach for early detection. The neonatal screening aims to test whether or not the enzyme activities within the lysosomes of your baby's blood stream are below the normal limits (to detect lysosomal storage disease). No extra blood samples will be needed from your baby. If you have received the notification from the birth hospital, please return to the screening center for re-tests as soon as possible in accordance with the instructions of the medical staff. A simultaneous blood smear microscopic examination may also be performed to confirm the diagnosis if necessary. Or if the neonate develops related symptoms, please contact the neonatal screening center or local referral hospital immediately to seek proper medical assistance.

Search for the Neonatal Screening Reports

To comply with the administrative operation process in the birth hospital, the written neonatal screening report will be available within approximately 1-2 weeks after the birth. The parents are required to return to the neonatal clinic in the birth hospital with their babies for the screening results consultation (with the pediatrician). Or they can go to the website of the screening center at https://www.tipn.org.tw/INB/INB010.asp or scan the QR code on the right to self-log in to the report query webpage for the report results.

Report Query QR code

Reminder: The detection rate of the screening program is not 100%. The test results may vary or become false negative due to the interference of late onset or atypical disease nature, insufficient protein consumption or special diet. For any health-related queries, please consult your pediatrician.

Lysosomal Storage Disease, LSD

Lysosome contains abundant hydrolase, and is an important organelle for breaking down matter in cells. LSD is caused by the lack of a hydrolase in lysosome. LSD is a group of approximately 40 disorders that result from defects in lysosomal function caused by the deficiency of an enzyme. This leads to the accumulation of lipids, glycoproteins, mucopolysaccharides, and other metabolites in the lysosome. Consequently, cells and tissues lose their normal functions, causing severe organ damage, with severe progression leading to death in infancy or adolescence. The total incidence rate is approximately 1/5,000-10,000.

Extensive clinical heterogeneity is seen in most LSDs, but they are typically progressive (continue worsening), and may lead to generalized and irreversible damage and deterioration. The more severe form of the diseases can be fatal. Early detection, diagnosis, and treatment are critical for delaying disease progression and improve the prognosis of these patients. Based on the appropriate and effective treatment methods and testing techniques, an increasing number of LSDs are being included in the newborn screening tests. Currently, we provide screening for Pompe disease, Fabry disease, Gaucher disease, and Mucopolysaccharidoses type 1&2.

Pompe Disease

Pompe disease is also known as glycogen storage disease type 2

It is characterized by a deficiency of the lysosomal acid alpha-glucosidase enzyme, glycogen is therefore unable to be broken down and becomes accumulated, thus affecting cell function. Typical symptoms include: muscle weakness in the limbs, breathing difficulty, and heart failure. It can be fatal if left untreated. We currently provide screenings for infantile-onset Pompe disease.

Symptoms of Pompe disease

Babies with infantile Pompe disease may appear normal at birth, but begin to show symptoms in the first two to three months of life. They develop general muscle weakness to the limbs and poor head control. At three to four months, these patients may develop bronchitis, and an x-ray examination may reveal cardiomegaly. Muscle weakness and cardiomegaly tend to worsen progressively. Infantile-onset Pompe disease usually leads to death from cardiorespiratory failure before the age of one. Early detection through newborn screening is therefore crucial for subsequent treatment. Late-onset Pompe disease has slower disease progression. Symptoms may range from mild muscle weakness to requiring wheelchair and ventilator. In general, the earlier the onset, the more severe the symptoms and deterioration.

Fabry Disease

What is Fabry disease?

Fabry disease is caused by mutations in the gene responsible for making an enzyme called alpha-galactosidase (α-GLA). This prevents the breaking down of some types of fat, especially globotriaosylceramide (GL-3), resulting in the buildup of these fats in the lysosomes in the body's cells. The mutated gene that causes the disorder is located on the X chromosome hence has greater impact on male patients. Due to X-chromosomal inactivation, female patients with Fabry disease may demonstrate symptoms of the disease, but are typically milder.

Symptoms of Fabry disease

Accumulation of GL-3 in vascular endothelial cells can cause peripheral neuropathy, resulting in extreme pain in the extremities. This is more common during warmer weather or seasonal change. This pain is often described as a burning sensation. Other manifestations include renal, cardiac, and cerebrovascular pathology. Some patients remain asymptomatic until the development of renal failure.

Gaucher Disease

What is Gaucher disease

It is a genetic disorder affecting the glucocerebrosidase (GCsae) producing enzyme, resulting in the accumulation of glucosylceramide and other glycolipids in the lysosomes of various organs. This leads to the collection of considerable amount of substances that cannot be hydrolyzed in the liver, spleen, and bone marrow. Increased accumulation of glucosylceramide in the bone marrow cells and nervous system can cause enlarged liver and spleen, anemia, bleeding tendency, and impaired skeletal development.

Symptoms of Gaucher disease

There are 3 types of Gaucher disease:

Type 1: The most common form of the disease. Manifestations include enlarged liver and spleen, skeletal deformity and anemia. The central nervous system is unaffected.

Type 2: Also known as acute europathic type, typically begins in infancy. Symptoms include an enlarged liver and spleen, extensive brain damage. The disease progresses rapidly and is fatal.

Type 3: Also known as the chronic neuropathic type, with the severity of between type 1 and type 2. Major symptoms include an enlarged spleen, progressive intellectual decline, and loss of motor function. Sometimes patients are also presented with skeletal and lung involvement.

Mucopolysaccharidoses, MPS

What is MPS?

Glycosaminoglycans are the primary molecules that help build bone, blood vessels, skin, and hair. Mucopolysaccharidoses (MPS) are a group of inherited metabolic disorders caused by the absence of specialized enzymes needed to break glycosaminoglycans. Over time, these glycosaminoglycans collect in the cells and connective tissues. The result is progressive damage to organ functioning.

Symptoms of MPS

MPS patients typically appear normal at birth, but symptoms progress as storage of glycosaminoglycans increases. Patients gradually develop distinctive physical features and symptoms involving the skin, bones, joints, cornea, trachea, and brain. Symptoms to the appearance generally include thick eyebrows, flat nasal bridge, thick lips, excessive facial hair, enlarged skull, claw-like hands, short lower-extremity, genu valgum, and short stature. Other physical symptoms include joint deformity and stiffness, enlarged liver and spleen, umbilical or inguinal hernia, and cloudy cornea. These symptoms vary depending on the degree of enzyme inactivity, however the condition tend to deteriorate with age. Some types of MPS feature intellectual impairment or hyperactivity.

There are currently seven types of MPS, each caused by different pathogenic genes hence have varying severity and prognosis. It is an autosomal recessive disorder with the exception of type 2, which is a sex-linked recessive inherited disorder and is most common in Taiwan and around Asia.

Incidence rate in Taiwan

Infantile-onset Pompe disease: Approximately 1/50000; late-onset Pompe disease: Approximately 1/30000.
Classic Fabry disease: Approximately 1/40000; cardiac-type Fabry disease: Approximately 1/1500.
Gaucher Disease: Approximately 1/50000.
Various types of mucopolysaccharidoses: approximately between 1/50000- 1/100000.

Diagnostic methods for lysosomal storage disorder

1. Clinical symptom assessment
2. Family history and family analysis
3. Biochemistry analysis
4. Blood enzyme and metabolite analysis
5. Genetic analysis of infant and parents

Treatment of lysosomal storage disorder

1. Treatment of symptoms
2. Stem cell transplant
3. Enzyme Replacement Therapy，ERT

Please note: the screening sensitivity is not 100%. The results could be false negative for diseases that are late-onset or non-classic, or when the child has low protein intake or on special diet. Please consult your pediatrician for other health concerns.

Severe Combined Immunodeficiency (SCID)

Disease summary:

Severe Combined Immunodeficiency (SCID) is a disease characterized by a defective immune system resulting from insufficient T lymphocyte count or functional impairment. Newborns with this disease have compromised immune system hence are vulnerable to bacterial, viral, or fungal infection. Without proper treatment, these patients die within a year after birth. The patients must be isolated in a sterile chamber away from the outside world, thus SCID is also called the "bubble baby" disease. Early stage SCID is generally asymptomatic and is difficult to diagnose. Performing this screening test in newborn screening allows SCID to be detected and treated early, increasing the patient's chance of restoring health. The approximate incidence rate in Taiwan is 1/80000.

Screening method: T-cell count can be estimated by analyzing the T-cell receptor excision circles (TREC) number in the blood smear, therefore no additional sample is required from your child.

Symptoms: Due to a defective immune system, patients are susceptible to recurrent bacterial, viral or fungal infection to the respiratory tract or oral mucosa, diarrhea or develop generalized fungal infection. The symptoms are not easily differentiated from those of other diseases therefore treatment can be delayed.

Treatment:

1. Treatment of symptoms: Avoid active vaccine (e.g. BCG vaccination).
   Administer prophylactic antibiotics to treat infection
   Regular immunoglobulin administration
2. Bone marrow transplant or cord blood stem cell transplant:
   According to the literature, SCID patients transplanted under the age of 3 months have a likelihood of survival of 95%, the likelihood of long-term survival is only 70% for those transplanted after 3 months.
3. Enzyme replacement therapy: Enzyme replacement therapy can be used for individuals with adenosine deaminase (ADA) deficiency

Caution:

1. For those choosing to undergo this out-of-pocket screening, please avoid vaccination with live vaccine (including BCG, oral polio, and oral rotavirus) before receiving the screening results.
2. If the screening results indicate suspected positive for SCID or suggest referral, the parents should bring their child in for a repeated blood smear collection or report to the hospital as soon as possible for further diagnosis or treatment.
3. A confirmed diagnosis of SCID may affect your child's right to receive coverage by commercial insurance.

Biotinidase Deficiency / BD

What is biotinidase?

Biotinidase commonly exists in mammalian cells, with the function of decomposing the biocytin into biotin. Biotin is the co-enzyme of the carboxylase group *in vivo* to facilitate the functions of the enzymes. The carboxylase group contains four enzymes, including pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase and acetyl-CoA carboxylase. For example, the infant multiple carboxylase deficiency (MCD) is usually caused by BD.

Genetic patterns, disease classifications and symptoms:

Biotinidase deficiency is an autosomal recessive inheritance disorder. The chromosomal locus is at 3q25. It is known that over 100 genetic mutations have resulted in biotinidase insufficiency or deficiency. The disorder can be classified as a profound deficiency or a partial deficiency depending on the severity.

(1) Profound deficiency:

Profound biotinidase deficiency refers to situations where the enzyme activity is 10% or less. Symptoms of profound deficiency can appear one week to 10 years after birth, the average onset latency is 3~6 months. Some patients may develop a single symptom, but some may develop multivariate neurological and dermatological symptoms, including seizures, muscle hypotonia, ataxia and developmental delay. The optic atrophy and hearing loss caused by delayed treatment are irreversible, even the supplementation of biotin fails to reverse such sequelae. The immune dysfunction caused by BD may result in skin infections (*e.g.* viruses and fungi). However, the respiratory symptoms such as hyperventilation, wheezing or apnea are some of the causes of sudden infant death. A few late onset adolescent patients may display sudden vision loss in combination with optic atrophy and spastic lower limb paresis.

(2) Partial deficiency:

Individuals with partial biotinidase deficiency may have an enzyme activity of 10-30%. These patients are usually asymptomatic but neurological and dermatological symptoms may develop while facing physiological stresses, including illness, infection, hunger, etc. The above symptoms will disappear after the supplementation of biotin.

In summary: Through early detection, diagnosis and proper treatment, neonates with BD can be completely asymptomatic. However, without proper treatment, neonates with BD may have irreversible neurological sequelae.

Incidence:

One in 137,400 for profound deficiency. One in 110,000 for partial deficiency
Carrier frequency with both deficiencies is approximately one in 61,000

Treatment:

The current treatment is oral biotin supplementation. Normally a dose of 5-20 mg/day is effective to eliminate or prevent the clinical manifestations, which is therefore considered a very economic and effective treatment. However, the hearing and vision impairment may not be cured or improved completely, the same goes for the spastic lower limb paresis.

Adrenoleukodystrophy / ALD

Adrenoleukodystrophy (ALD) is a genetic mutation disorder of abnormal intra-cellular peroxisomes (peroxisomal fatty acid beta oxidation), which results in the great accumulation of an unbreakable very long chain fatty acids (VLCFA) in the brain white matter and the adrenal cortex. This causes damages to the myelin sheathes of the cranial nerves and central nervous system (CNS) developmental delay, and eventually leads to neurotransmission dysfunction. The trace of VLCFA accumulation is also found in skin fibroblasts.

ALD is caused by mutations in the ATP-binding cassette, sub-family D, member 1 (also called X-ALD or ABCD1 gene), a gene located in the X chromosome. The clinical presentation of ALD can vary greatly based on different onset ages. The initial symptoms include inattention, memory loss, hyper activity, etc. Symptoms such as progressive hearing, vision, language and action abilities loss or even coma may develop following the progression of the disorder. Based on the onset age and clinical presentations, ALD can be generally classified as the following sub-types:

(1) Childhood Cerebral (also called CCER or CCALD, accounts for approximately 31-35% of all ALD): The disorder's onset is between 4~8 years old. The initial symptoms include learning disability or abnormal behavior, vision and hearing loss along with occasional diplopia and seizures. Normally, the neurological, autonomous and motor functions of the patients are gradually lost and rapidly degenerate 6 months to 2 years after the onset.

(2) Adrenomyeloneuropathy (also called AMN; accounts for approximately 40-46% of ALD): The primary symptoms consist of progressive leg stiffness, weakness, incontinent, CNS degeneration, etc. Approximately 10％~20％ of patients may have severe cognitive, behavioral and language impairments due to brain degeneration, and eventually leads to complete incapacitation or death.

(3) Adolescent cerebral ALD: Accounts for approximately 4~7% in ALD population, and the onset of this sub-type is between 11~21 years old. The symptoms of this sub-type are similar to the CCALD/CCER except the progression is milder.

(4) Female Symptomatic Heterozygote: ALD is an X-linked recessive inheritance disorder, thus female carriers usually do not present clinical symptoms. However, ALD symptoms (from mild to severe) can actually still be found in female symptomatic heterozygote carriers. Therefore, female carriers should also pay attention to their clinical presentations.

Incidence:

In the United States, the incidence of affected males is estimated at 1: 42,000. The overall incidence of hemizygous males and carrier females is estimated at 1:16,800. The average incidence in European and American countries is approximately at 1/45,000. The reported incidence recently is estimated at 1/17,000~1/25,000.

Treatment:

(1) Dietary supplementation (*e.g.* Lorenzo's Oil) is the most commonly accepted approach by the ALD patients without neurological symptoms due to its large content of monounsaturated fatty acids to postpone the onset of the neurological symptoms. However, the dietary supplement has limited effects on the improvement of the accumulation of VLCFA in brain tissues. The existing neurological lesions in adult patients cannot be reversed either.

(2) Bone marrow transplantation: CCALD/CCER could be cured by bone marrow transplantation but the success rate is limited to about 60%. It is not recommended to ALD patients with developed symptoms.

(3) Gene therapy in combination with blood stem cell therapy: It can be used to effectively postpone the damages to the brain caused by the ALD, reduce the risks of death and invasive damages caused by bone marrow transplantation and avoid the issues of finding suitable bone marrow donors.

Spinal Muscular Atrophy / SMA

Spinal Muscular Atrophy (also called SMA) is an autosomal recessive inheritance disorder caused by genetic defects and thus results in the death or degeneration of neuronal cells in the anterior horn of the spinal cord. The motor neuron in the anterior horn of the spinal cord is the transit station of neurotransmitters. The death of motor neurons may interrupt neurological signal transduction and thus result in gradual muscle weakness or paralysis along with muscular atrophy and myasthenia. The clinical presentations are usually symmetrical, more severe involvement in the lower extremities than the upper extremities, and in the proximal parts than the distal parts.

It is known that the pathogenic gene SMN is located on chromosome 5q111.2-13.3, which includes two very similar SMN sequences: SMN1 and SMN2. The SMN proteins encoded by the SMN1 gene are mostly functionally intact, but only few SMN proteins encoded by the SMN2 gene are functionally intact. Because the two gene sequences are very much alike, the occurrence of genetic deletion or conversion between SMN1 and SMN2 genes is extremely frequent. Approximately 95% of patients with SMA (including SMA1, 2, 3) have SMN1 gene deletion or conversion, and the rest of the 5% have SMN1 intra-genic mutation. If the allele SMN1 genes are both deleted, the copies of the SMN2 gene will be the determining factor of the severity of SMA.

(1) SMA 1: Severe SMA, which is also called Werdnig-Hoffmann Disease. The clinical manifestations are developed within 6 months after birth, including four limbs and trunk weakness due to severe muscle hypotonia (floppy baby syndrome). The baby has difficulties in controlling the neck muscles, swallowing and breathing as well as weak crying and loss of deep tendon reflex. Normally, the baby will die due to respiratory failure before 2 years old.

(2) SMA 2: Moderate SMA, which is also called Dubowitz disease. The clinical manifestations are developed within 6 months to 1.5 years old, it includes symmetrical lower limbs weakness, where the proximal parts are more severely affected than the distal parts. Patients with SMA2 usually are unable to stand and walk independently, they have lost or weak deep tendon reflex, but have normal facial expressions. Most of the SMA2 patients may survive until adulthood through the assistance of physical therapy and respiratory care, but a few may die from respiratory tract infection in childhood.

(3) SMA 3: Mild SMA, which is also called Kugelberg-Welander Disease. The age of onset is from 1.5 years old to adulthood. The clinical manifestations include mild, symmetrical and proximal musculature weakness in the four limbs, particularly the lower limbs. Although patients with SMA3 may feel slightly inconvenienced when jogging, jumping and climbing stairs along with a decreased deep tendon reflex, their long-term survival rate is relatively high.

Incidence: Approximately 1/10,000~1/25,000.

Treatment:

Currently, the treatment for SMA in clinical practice is mainly based on supportive therapies to ameliorate the occurrence of complications. By 2015/12/16, a total of 18 medications have been in the developmental pipelines for SMA treatment in the world, of which 7 medications are under clinical trial investigations. Through the combined medical care, including the neonatal screening program and the early diagnosis of SMA, the mortality rate as well as the morbidity rate of SMA can be.

Late infantile neuronal ceroid lipofuscinosis type 2/CLN2

CLN2 disease is an inherited disorder that primarily affects the nervous system. The signs and symptoms of this condition 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 behavioral problems. Individuals with this condition often require the use of a wheelchair by late childhood and typically do not survive past their teens.

Some children with CLN2 disease do not develop symptoms until later in childhood, typically after age 4. These individuals tend to have milder features overall compared to those diagnosed earlier, but with more severe ataxia. They have a shortened life expectancy, although they tend to survive into adulthood.

Incidence: 1.3~7/1,000,000

Treatment:

In 2017, the U.S. Food and Drug Administration (FDA) approved an enzyme replacement therapy indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with CLN2 disease.

Duchenne muscular dystrophy (DMD)

Duchenne muscular dystrophy (DMD) is an X-linked rare disease. DMD occurs as a result of mutations in the dystrophin gene. It leads to an absence of or defects in the protein dystrophin and is manifested by progressive muscle degradation.

Typically the disorder is diagnosed only around 4-5 years of age. Duchenne patients are often wheelchair bound between the ages of seven and 13 years old. Eventually, increasing difficulty in breathing due to respiratory muscle dysfunction requires ventilation support, and cardiac dysfunction can lead to heart failure. The condition is universally fatal, and without intervention the mean age at death is around 19 years.

Although DMD is an X-linked recessive disease and females are typically asymptomatic carriers of mutations, some female carriers may manifest symptoms varying from mild muscle weakness to a more severe clinical course and are classified as manifesting or symptomatic carriers. The manifesting phenotype is based on inactivation of the normal X chromosome or on translocation between X chromosome and an autosome. Female carriers having elevated CK-MM concentrations due to muscle degeneration at birth may result as screen positive (depending on the cut-off used) in newborn screening for DMD. The incidence of DMD is 1 in 3000-6000 live male births worldwide.

Treatment

Although no cure exists for the progressive muscle weakness of DMD, corticosteroid treatment improves muscle strength and function, and in combination with supportive medical care is associated with delayed loss of ambulation and markedly improved survival. In addition, novel molecular therapies are under development and therefore interest towards newborn screening is increasing.