Saskatchewan Health Authority

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PILOT Study

NEWBORN SCREENING IN SASKATCHEWAN

INFORMATION AND GUIDELINES FOR HEALTH CARE PROVIDERS

2022

Newborn Screening
Roy Romanow Provincial Laboratory
Regina, Saskatchewan

Newborn Screening: a healthy start leads to a healthier life

Since the mid-1960s, health care providers have offered newborn screening for phenylketonuria (PKU) to all infants born in Saskatchewan. As of February 2022, Saskatchewan Newborn Screening will be expanded to screen for 32 conditions. Four new conditions will be phased in as a pilot until validations are complete. For the conditions under validation any positives will be acted on, however, there may be more false-negative results (i.e. missed cases) during the initial phase while the laboratory methods are quality controlled. Individually, these disorders are rare, but will, as a group, affect as many as 1 in 750 newborns in the province each year.

Roy Romanow Provincial Laboratory (RRPL) in Regina conducts all testing for these congenital disorders from the same blood spot card collection.

Pilot Study - Newborn Screen additions for validation – beginning February 2022

The following four conditions will be added in two phases. A real-time pilot where true positive cases may be missed but all cases identified confirmed external before acted on for appropriate clinical management. Once validated these will be permanent additions to the newborn screen panel. These additions will be performed using the same bloodspot.

Severe Combined Immunodeficiency (SCID) — SCID is the most profound form of primary immunodeficiency disease and is characterized by the lack of a functioning immunesystem. Infants born with SCID appear healthy at birth but invariably develop multiple severe infections, which often prove fatal within the first year of life if affected infants do not receive therapy to restore immune function (e.g. hematopoietic stem cell transplantation). The incidence of this disease in Canada is 1:70,000.

Spinal Muscular Atrophy (SMA) — SMA is characterized by the progressive loss of motor neurons causing muscle atrophy and weakness. Intelligence is unaffected, but infants with the most severe form of SMA may never achieve major developmental milestones such as sitting or rolling over. Fatal respiratory failure usually occurs by 2 years of age and often before 6 months. SMA carrier frequency is 1 in 50 resulting in a disease prevalence of approximately 1 in 10,000 live births, making SMA the most common genetic cause of childhood death. Treatment options are available to mitigate this disease.

Hemoglobinopathies — Hemoglobinopathy refers to a group of genetically determined abnormalities of hemoglobin (including Sickle Cell disease). These disorders are characterized by chronic hemolysis (premature destruction of red blood cells) and intermittent vascular occlusion causing episodes of severe pain and a variety of other disease manifestations. There is evidence that with the introduction of universal newborn screening and appropriate follow up, the mortality in the first 4 years of life from these conditions (historically as high as 20%) can virtually be eliminated.

Congenital Cytomegalovirus (cCMV) — Saskatchewan's universal hearing screening program will fail to identify up to 50% of children with hearing loss caused by cCMV because the infection frequently results in hearing loss that begins after the newborn period. cCMV infection is relatively common (6 to 7 cases per 1000 births) and it is the most common cause of acquired congenital hearing loss. Universal newborn screening for cCMV can improve outcomes if antiviral medications are started before one month of age.

Early detection. Early treatment. Big benefits.

Babies with these conditions appear healthy at birth and, unless they are screened, might otherwise not be identified to have one of these disorders until irreversible damage has occurred. If not treated, these conditions are associated with recurrent illnesses, developmental disabilities, or death. Early diagnosis and treatment can result in significantly improved outcomes. In some, preventive care can improve or maintain the quality of life of these babies. For babies who start to become ill soon after birth, newborn screening may save valuable time and resources in making a definite diagnosis.

Informed parents make smart choices

It's important that you, as a health care provider, emphasize to parents that newborn screening is part of their baby's routine care and could save their baby's life and/or prevent serious health problems. The vast majority of parents agree to have their baby screened.

Should a parent refuse newborn screening, the decision should be documented in the baby's medical records and the parents will be required to sign a refusal form.

What health care providers need to do

A newborn screening specimen card should be completed between day 1 (after 24 hours) and day 7 after birth; ideally, between 48 and 72 hours after birth. If tested before 24 hours of age, the baby's health care provider should repeat the test within five days, at the first postnatal check-up.

Blood spots from infants are collected using the heel-prick method, which is detailed on the back of the specimen card. If you are providing care for an infant who is premature (i.e. less than 37 weeks gestation), ill, has been transfused, or has been on total parenteral nutrition (TPN) or antibiotics, please refer to the Special Considerations section on the next page.

Submitting cards: time is critical

It is critical that RRPL receives the newborn screening specimen card as soon as possible after the blood spots are collected. The cards should be sent no later than 24 hours after collection and, ideally, as soon as the blood spots are dry (four to six hours after collection). Babies with some of the conditions screened will start to become ill and may suffer irreversible damage soon after birth. Rapid diagnosis and treatment can prevent this damage.

Screening test results: positive and negative

Once RRPL has received and analyzed the specimen card, one of the following will be reported:

Negative

The infant under your care "screens negative" for all conditions. A report is issued to both the referring health care provider and hospital and should be filed in the baby's medical records.

Repeat Sample

If the initial sample is insufficient or unacceptable, or if the results are equivocal, the caregiver will be contacted and asked to obtain another sample from the newborn as soon as possible and repeat the submission procedure.

Positive

The infant under your care "screens positive" for a disorder. A screen positive **does not necessarily mean that the baby has a disorder, but that it needs further investigation.** The Provincial Laboratory will initiate a referral according to the table below so the infant can be assessed and arrangements made for care and additional testing. In all cases, the patient's caregiver and family physician will be contacted directly. Arrangements will be made for confirmatory testing. If a diagnosis of a disorder is confirmed, health-care providers will provide management, counselling and follow-up. A report is also issued to the referring health care provider and hospital, and should be filed in the baby's medical records.

Table: Positive Screen follow-up actions

Screening Test	**First contacts for screen positives**
SMA	Medical Genetics to then contact pediatric neurology
SCID	Medical Genetics to then contact pediatric hematology and immunology
cCMV	Me3Genetics to then contact pediatric infectious disease and audiology services
Hemoglobinopathy (sickle cell)	Pediatric Hematology
Congenital Adrenal Hyperplasia	Pediatric Endocrinology
Amino Acid Disorder	Metabolic Program
Fatty Acid Disorder	Metabolic Program
Organic Acid Disorder	Metabolic Program
Biotinidase Deficiency	Metabolic Program
Galactosemia	Metabolic Program
Cystic Fibrosis	Cystic Fibrosis clinic

The screening test: there are limitations

It's important to remember that, as with all screening tests, there will be false positive and false negative results. False positives will increase parental anxiety, while false negatives will give a misleading sense of reassurance. If a baby in your care exhibits symptoms of a particular disorder, but the newborn screen was negative, the child should be investigated and managed appropriately and the relevant consultant specialist should be contacted immediately for further advice (see table above).

There is wide clinical variation in some of the disorders that the newborn screen detects. Therefore, there will be so-called "affected" individuals — babies who are confirmed by diagnostic testing to have a particular disorder — who will remain asymptomatic even without treatment or will only have very mild symptoms.

Special considerations

Prematurity or illness

Infants who are premature (i.e. less than 37 weeks gestation) or who are sick should have their first specimen collected for newborn screening when they are 24 to 72 hours old. For infants born at 32 weeks or less, a second card should be collected after TPN has been discontinued for 7 days or prior to discharge home. Premature infants will often have a high thyroid-stimulating hormone (TSH) levels and may screen positive for congenital hypothyroidism. However, on repeat specimens, results can be differentiated into false and true positives. Prematurity or illness in an infant being screened should be clearly indicated on the newborn screening specimen card.

Total Parenteral Nutrition (TPN) and antibiotics

RRPL can analyze heel-prick blood spots from infants who have had TPN (hyperalimentation) or antibiotics. However, levels of certain amino acids and organic acids can be elevated in these infants. In order to ensure the most accurate analysis, the administration of these therapies should be clearly indicated on the newborn screening specimen card.

Transfusions

Infants who are affected with one of the disorders screened for by RRPL may be missed if they have had a recent blood transfusion. Normal levels of newborn screening analytes may be found in these cases because of the donor blood. Ideally, a specimen card should be completed before transfusion or repeated X# days after their last transfusion.

Disorders screened

Organic acid disorders

Organic Acidemias (OA) are a class of inherited metabolic disorders that occur when the body cannot metabolize certain amino acids and fats. This leads to an accumulation of organic acids in the blood and urine, which can cause serious health problems. Clinical symptoms of OA may include acute encephalopathy, vomiting, metabolic acidosis, ketosis, dehydration or coma, hyperammonemia, lactic acidosis, hypoglycemia, failure to thrive, hypotonia, global developmental delay, sepsis, hematological disorders, and death. Newborns with OAs are perfectly healthy at birth, but may become quite ill within the first few days of life, even before the results of the newborn screening are known. Treatment often involves a low-protein diet and/or a diet low in specific amino acids and/or dietary supplements (such as carnitine, biotin, riboflavin), medical foods or other medications. It is very important for affected individuals to avoid fasting. Included in the OAs for which Saskatchewan screens are isovaleric academia (IVA), glutaric acidemia type 1 (GA1), HMG-CoA lyase deficiency (HMG), multiple carboxylase deficiency (MCD), methylmalonic acidemia, 3-Methylcrotonyl¬CoA carboxylase (MCC) deficiency, propionic acidemia (PROP), B-Ketothiolase (BKT) deficiency, and dienoyl CoA reductase deficiency.

Fatty Acid Oxidation Defects (FAODs)

The breakdown of fatty acids in the mitochondria is an essential part of the body's ability to produce energy, especially if an infant has nothing to eat for more than a few hours, for instance, during illness.

Fatty acids are transported into the cell and then into the mitochondria. Once in the mitochondria, the carbon chains or fatty acids are metabolized two at a time, using specific enzymes. If the transporter molecule(s) or any of the enzymes used to reduce the number of carbons in the chain are missing, an accumulation of fatty acids in the body occurs and causes hypoketotic hypoglycemia and tissue damage, especially liver, muscle, and heart disease. Lethargy, seizures, coma, and sudden death are also signs of FAODs. An undiagnosed FAOD can present as sudden infant death syndrome (SIDS). Dietary supplementation with carnitine and/or cornstarch may also be part of the treatment for FAODs. It is very important for affected individuals to avoid fasting.

Included in the FAODs for which Saskatchewan screens are medium chain acyl-CoA dehydrogenase (MCAD) and short chain acyl-CoA dehydrogenase (SCAD) deficiency, very long chain acyl-CoA dehydrogenase (VLCAD) deficiency, long chain 3-Hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, trifunctional protein (TFP) deficiency, and carnitine uptake defect (CUD).

Amino acid disorders

These disorders occur when the body cannot either metabolize or produce certain amino acids, resulting in the toxic accumulation of some substances and the deficiency of other substances. Amino acids are derived from protein. Treatment often involves a low-protein diet and/or a diet low in specific amino acids. Specific medications and/or vitamins may also be prescribed, depending on the disorder. It is very important for affected individuals to avoid fasting.

Examples:

Phenylketonuria (PKU) is a condition in which individuals cannot use phenylalanine properly so it builds up in the blood (hyperphenylalaninemia).

Without treatment, phenylalanine accumulation will cause severe and irreversible developmental disabilities, eczema, and other problems. Saskatchewan has screened for PKU since 1965.

Tyrosinemia (TYR) occurs when tyrosine cannot be properly metabolized, leading to an accumulation of this amino acid and its metabolites in the liver, kidneys, and the central nervous system, causing liver disease and other problems.

Homocystinuria (HCY) occurs when homocystine accumulates in the urine. It is caused most commonly by a deficiency in an enzyme called cystathionine beta-synthase (CBS). Affected babies can have developmental disabilities and failure to thrive. They may also develop eye problems, skeletal problems, and a high chance of developing blood clots.

Citrullinemia (CIT) and argininosuccinic acidemia (ASA) are urea cycle defects. The urea cycle is the body's system for excreting waste nitrogen and ammonia, and for synthesizing arginine and urea. Hyperammonemia results when one of the enzymes in the urea cycle functions improperly. Symptoms can include lethargy, vomiting, coma, seizures, liver disease, failure to thrive, and death.

Maple syrup urine disease (MSUD) occurs when the amino acids, leucine, isoleucine, and valine cannot be metabolized. Symptoms include poor feeding, lethargy, convulsions, and even death. The urine of an affected child can have the odour of burnt sugar or maple syrup, giving the disorder its name.

Other disorders:

Congenital hypothyroidism (CH) can cause developmental disabilities and failure to thrive if not recognized and treated. It is a relatively common condition and is the result of a thyroid hormone deficiency. Saskatchewan has screened for CH by measuring thyroid stimulating hormone (TSH) levels in blood since 1978. Thyroid hormone replacement is a very effective treatment.

Congenital adrenal hyperplasia (CAH) is an inherited defect in which the adrenal gland cannot make cortisol and overproduces male hormones. Without cortisol, infants may be unable to regulate salt and fluids, and can die. Some newborns with CAH can be symptomatic at birth with virilization of females. Replacement of deficient hormones is an effective means of preventing a salt-wasting crisis and preventing long-term complications.

Biotinidase deficiency (BIOT) - Biotinidase is essential for the recycling of the vitamin biotin, which, in turn, is an enzyme cofactor. These enzymes, the carboxylases, are important in the production of certain fats and carbohydrates and for the breakdown of proteins. Features of this disorder include neurological symptoms, such as developmental disabilities and seizures, and cutaneous symptoms, such as hair loss and skin rash, which can be effectively treated with biotin supplementation.

Cystic fibrosis (CF) is an inherited disease that affects the lungs and digestive system. The body produces thick mucus that may interfere with lung function and/or digestion. Approximately one in 3600 children born in Canada has CF.

Galactosemia (GALT) — Lactose is the main sugar in breast milk, cow's milk, and many infant formulas. This sugar is metabolized into glucose and galactose in the intestine. Individuals with galactosemia are not able to break down galactose. This can result in life-threatening complications including feeding problems, failure to thrive, liver damage, bleeding, and sepsis in untreated infants. A diet restricted in lactose is very effective in preventing these complications. Even with early treatment, however, children with galactosemia are at increased risk for developmental disabilities, speech problems, abnormalities of motor functions and, in females, premature ovarian failure.

Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome (HHH) — HHH syndrome is a disorder of the urea cycle and ornithine degradation pathway, which is overrepresented in northwest Saskatchewan. If HHH syndrome is found early, babies can be treated by a metabolic specialist with established protocols to rapidly control hyperammonemic episodes. HHH syndrome can result in nerve, muscle and liver problems, tiredness, vomiting, slow mental development with seizures, and sudden infant death. Babies will automatically get the test in the Keewatin Yatthé Health Region, all Meadow Lake Tribal Council communities and all babies born at the Meadow Lake Hospital. For babies born in other areas of the province, this test can be done by special request.

Discussion guide

This discussion guide will help you to counsel your patients and answer their questions about newborn screening. The brochure Newborn Screening: A healthy start leads to a healthier life is also available to provide to your patient. https://rrpl-testviewer.ehealthsask.ca/SCI/Requisitions/Screening%20Programs%20-%20Newborn%20Screening/Newborn%20Screening%20-%20Information%20for%20Parents.pdf

Newborn screening is a strongly recommended part of neonatal care since babies affected with these disorders usually appear healthy at birth. Unless they undergo screening, they may not be identified as having a disorder until irreversible damage has occurred.

In many cases, preventive care can improve or maintain the quality of life of these babies and their families. For babies who start to become ill soon after birth, newborn screening may save valuable time and resources in making a definite diagnosis. These conditions, if not treated, are associated with recurrent illnesses and/or developmental disabilities and/or death. Early diagnosis and treatment can result in a normal outcome. That's why it's so important to discuss newborn screening with your patients.

Points to discuss with expectant parents

· Offer newborn screening

Newborn screening is strongly recommended for all babies born in Saskatchewan as part of routine neonatal care. Results are very accurate and cover more than 30 different conditions. These include disorders of metabolism and the endocrine system.

· Discuss the benefits of testing

Identifying a baby with one of the disorders is beneficial because early diagnosis and treatment can prevent consequences such as recurrent illnesses and/or developmental disabilities and/or death.

· Discuss how testing is done

The blood sample is obtained by pricking the baby's heel. The blood is transferred to a special paper card and sent to RRPL.

· Testing must be timely

Optimal collection of the baby's blood sample is when they are between one and three days old (between 24 and 72 hours after birth). If a baby is tested before one day (<24 hours) of age, the test should be repeated within five days, at the first postnatal check-up.

Babies with some of the disorders screened will start to become ill and may suffer irreversible damage right from birth. Rapid diagnosis and treatment can prevent this damage.

· A repeat sample is sometimes required

It may be that the first sample was not taken properly, the amount of blood taken was not enough to complete the testing, or there was some other problem with the sample. If requested, a repeat blood sample should be taken as soon as possible.

· Discuss the difference between a screening test and a diagnostic test

A screening test determines if there is a high or low risk that a baby has a particular condition. Only a subsequent diagnostic test will determine with certainty if the baby is affected with a condition or not.

· Discuss possible results of screening

The baby screens negative for all disorders. A report is issued by mail to the referring health care provider and hospital. Over 99 per cent of babies who have the newborn screen will have a negative result.

The baby screens positive for one of the disorders. A positive screening result does not necessarily mean that the baby has the condition, but only that further investigation is required.

Resources

For more information on Saskatchewan's newborn screening and the conditions screened for by the test, please visit https://www.saskhealthauthority.ca/facilities-locations/roy-romanow-provincial-laboratory-rrpl or contact RRPL at (306) 787-3131.

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Other resources:

- American Academy of Pediatrics: https://healthychildren.org/english/ages-stages/baby/Pages/default.aspx
- OrphaNet (information about rare disorders): www.orpha.net
- National Organization for Rare Disorders (NORD): www.rarediseases.org

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