Saskatchewan Health Authority

Roy Romanow Provincial Laboratory Newborn Screening for Inborn Errors of Metabolism in Saskatchewan.

In Saskatchewan all babies are screened for approximately 30 metabolic disorders. The newborn screen includes testing for several amino acid disorders, organic acid disorders, fatty acid disorders, endocrine disorders and a few other inherited metabolic conditions. Methods of detection include tandem mass spectrometry, immunoassays using fluorescent detection and spectrophotometric techniques. All methods will produce some results that fall into the "gray zone." This means that a repeat newborn screening sample may be needed, not that a baby has a specific disorder. Recollection of all requested samples is extremely important to determine the significance of "gray zone" results. Parents should not be alarmed by the request to have a sample recollected, as this will occur in approximately 1% of all births.

Until 2001 routine screening of newborns for inherited metabolic disorders was limited to three to five disorders. Now, with the new method using tandem mass spectrometry (MS/MS), more than 30 of these diseases or disorders can be easily detected from a drop of blood. Parents of children with these disorders rarely have any family history to suggest the possibility of having an affected child. This is because these conditions are "autosomal recessive," which means that each parent carries a gene for the disease but is not affected. Each new baby born to those parents has a 1 in 4 chance of inheriting the defective gene from each parent. Unless the family has already had a child affected with one of these disorders, there is no warning.

Inborn errors of metabolism can affect a child in a variety of ways: they can appear as illnesses with recurrent episodes of low blood sugar, which can produce coma or sudden death following simple infections; as severe muscle pain and cramping requiring repeated hospitalizations, and possible severe kidney damage; as weak muscles and developmental delay often associated with epilepsy; as heart enlargement to the point of heart failure and death at 2 to 5 months of age; as nerve and muscle involvement interfering with walking and vision; as seizures, hair loss, and developmental delay; or even combinations of several of these problems. Even though the same gene is affected, some of the disorders can manifest themselves in two or three different ways, or "phenotypes." Different phenotypes of the same disease usually do not occur in a single family, but different families can have the same defect while their children have different problems. A good example of this is Very Long Chain Acyl-CoA Dehydrogenase deficiency (VLCAD).

The children in some families may have only problems with blood sugar; children in other families may have mostly the muscle problems often associated with problems with blood sugar; while other families may lose children to sudden onset of severe heart disease before 6 months of age.

The time that symptoms appear is also very variable. The more severe forms of these conditions present in the first week of life and are often lethal. Other forms may not appear until the child has an ear infection or some other stress to his system or until a child is unable to eat for more than twelve hours. Some forms can first appear as an adult.
Often, when one child is finally diagnosed with a disorder, testing siblings will reveal that there is another affected child in the family who has not yet had an episode of illness.

Testing siblings of affected children is, therefore, urgent. It is also not unusual for a mother to be pregnant at the time one of her children is found to have one of these diseases.

Newborn screening using MS/MS is a single test that can detect more than 30 inherited metabolic disorders by measuring two groups of compounds in dried blood spots. One of these is amino acid, the building blocks of protein; elevated levels of specific amino acids can indicate the presence of inherited amino acid disorders and urea cycle disorders. The other group is acylcarnitines. These chemicals come from fatty acids and other organic acids and also from amino acids. High concentrations of individual acylcarnitines can indicate more than 20 inherited disorders.

In Saskatchewan all babies are screened for 30 plus metabolic disorders as part of their routine newborn medical evaluation and exam.

The combined incidence of the 30-plus metabolic disorders is estimated to be about 1 in 5,000 babies, not including phenylketonuria (PKU). Most of the time, therefore, the screening result is normal. In about 1 out of 100 screens, if a slight elevation of amino acids or acylcarnitines is detected, a repeat blood spot usually indicates that the initial elevation was only temporary. If the elevation is still present when repeated or the initial screening result was clearly abnormal, then a metabolic disorder is very likely. For a few of the disorders, such as Medium-Chain Acyl-CoA Dehydrogenase deficiency (MCAD), the screening pattern is very specific and diagnosis is simplified; while for others, the elevations may be caused by more than one metabolic disorder. Therefore, additional confirmatory testing must be done to diagnose the exact metabolic disorder and to allow proper clinical treatment.

The optimum time for collection of the dried blood spots is between 2 to 3 days of age, since many of the disorders will show maximum abnormality at this time. Early detection of an abnormality by screening before the baby has clinical symptoms should lead to earlier clinical management and a better clinical outcome. All babies should be collected in the time frame of 24 hours to 7 days of age. All babies should have a newborn screening sample collected before discharge from the hospital regardless of age, and a second sample, if necessary, collected before 7 days.

Which parents should consider screening their newborn baby? Everyone!

Parents with no family history of a metabolic disorder should also consider the screen, since most affected babies are born to parents who do not know they are carriers. Having already had healthy children does not rule out the possibility that the next child may be affected. The older children may be normal, carriers, or even affected with a metabolic disease that has not yet manifested itself.

If a family has a history of a particular metabolic disorder, MS/MS screening is appropriate, depending upon the particular disorder. This decision should involve the pediatrician or geneticist, who may also suggest more specific diagnostic testing.

Families with a history of SIDS (or unexplained childhood death) should consider the screening, since as many as 3 out of 100 cases of SIDS or unexplained death may have been due to a metabolic disorder.

When should parents consider having supplemental MS/MS newborn screening of their baby? This should be considered during pregnancy, well before delivery. This screening is relatively new but is now available in most Provinces in Canada or States in the USA. What if the baby or child is older and not ill or exhibiting symptoms of a disorder, but the parent has just heard about this screening? Testing can be done at any age. Although many of the disorders will cause clinical symptoms at an early age, some may not show symptoms for months or years. Therefore, it is important to screen all siblings, or to perform more specific diagnostic tests of siblings of any babies found to have one of these disorders. If testing of older siblings is important for your family, please contact your family doctor or pediatrician for further information.

What if a child has clinical symptoms? The MS/MS screen may or may not be appropriate, depending on what the symptoms are and what diagnostic tests have already been done. For example, if a plasma amino analysis, a plasma or dried blood spot acylcarnitine profile, and a urine organic acid analysis have been done, the MS/MS screen may not offer additional information. Parents should discuss with their pediatrician, genetics counselor, or other specialist whether the MS/MS screen for the 30- plus disorders could be helpful.

Metabolic Disorders Found Through Newborn Screening

Newborn screening can be performed after the neonatal period, although the accuracy will be somewhat reduced, as the child gets older. Other tests can be performed to pinpoint specific disorders; however, testing decisions should involve the child's pediatrician as well as any specialists who might have been consulted. Tandem mass spectrometry (MS/MS) can discern approximately thirty inborn errors of metabolism. Many of these conditions, especially the organic acidurias, are extremely rare; some have fewer than 100 known cases worldwide. A brief description of the more common ones follows, with treatment information where available.

AMINO ACID DISORDERS

Argininosuccinic Aciduria—The disorder is extremely rare, affecting fewer than 100 people in the US. Symptoms are hyperammonemia accompanied by lack of appetite, vomiting, listlessness, seizures, and coma. Onset is usually at birth, but symptoms may not be noticeable for days or weeks. Left untreated, brain damage, coma, and death may occur. Treatment includes a high-caloric, protein-restrictive diet, arginine supplementation, administration of sodium benzoate and sodium phenylacetate. Dialysis may be necessary.

Citrullinemia—Citrullinemia stems from a deficiency of argininosuccinic acid synthetase. Epidemiology, symptoms, and treatments are the same as those for argininosuccinic aciduria.

Homocystinuria—The most common cause of homocystinuria is a deficiency in the enzyme cystathionine-synthase. Incidence is 1 in 200,000, but prevalence is 1 in 82,000 in Great Britain, Ireland, and Australia. Among the symptoms are thromboembolism, optic lens dislocation (which may occur even with treatment), scoliosis, osteoporosis, mental retardation, seizures, and psychiatric disturbances. Approximately 50 percent of untreated individuals die before age 25. Treatment may include a methionine-restricted, cystine-supplemented diet, as well as large doses of Vitamin B6.

Maple syrup urine disease (MSUD)—MSUD is caused by abnormal metabolism of three branched-chain amino acids. Although the overall incidence of the disorder is 1 in 200,000, it is about 1 in 760 among Mennonites. Symptoms include an odor of maple syrup in the urine, poor feeding, lethargy, coma, and mental retardation. Death commonly occurs within three months of birth. Treatment requires dietary restriction of branched- chain amino acids, necessitating a complicated formula and intensive monitoring.

Phenylketonuria (PKU)—This metabolic condition results from the lack of an enzyme in the liver that converts phenylalanine to tyrosine. Incidence is 1 in 12,000 and is most prevalent among people of Irish or Scottish descent. Symptoms include severe mental retardation, seizures, autistic-like disorders, and a peculiar odor; lifespan is reduced. Treatment consists of lifelong dietary management and counseling.

FATTY ACID DISORDERS

These are rare autosomal recessive conditions in which the body cannot oxidize fatty acids because an enzyme is either missing or not functioning correctly. Many of the effects are attributed to secondary carnitine depletion.

Carnitine Palmitoyltransferase Deficiency Type II (CPT II)*—CPT II affects males more than females and is more apparent in people with diabetes or malnutrition. Fasting may trigger symptoms. It usually becomes apparent in adults, but a more serious form affects children. Major symptoms are myalgia, fatigue, and reddish-brown urine. Treatment includes a diet low in

proteins and fats and high in carbohydrates, adequate hydration, avoidance of fasting, and keeping warm. Carnitine supplementation may be effective.

Glutaric Acidemia Type II--Multiple Acyl-CoA Dehydrogenase Deficiency—This disorder manifests in three forms; the neonatal is most serious and often fatal within a few weeks. Symptoms of neonatal GA II in infants with congenital anomalies may include severe hypoglycemia, metabolic acidosis, hypotonia, hepatomegaly, and, often, an odor of "sweaty feet." It can be fatal within the first week. When congenital anomalies are absent, symptoms may be milder and untreated infants may survive for a longer period. Treatment includes a high-carbohydrate, low-protein, low-fat diet, and frequent feeds; supplementation with riboflavin and carnitine may be helpful.

Trifunctional Protein Deficiency (TFP)—TFP in infants is characterized by failure to thrive, enlarged liver, enlarged heart, metabolic encephalopathy, and hypotonia. Unless treated immediately it is generally fatal. Treatment includes a high-carbohydrate, low-fat diet; administration of medium-chain triglyceride oil (MCT oil), supplementation with carnitine and/or riboflavin, and avoidance of fasting.

LCHAD--3-Hydroxy Long Chain Acyl-CoA Dehydrogenase Deficiency—Typical symptoms of LCHAD are hypoglycemia, lethargy, failure to thrive, and developmental delay, often accompanied by hypotonia and cardiomyopathy. Some SIDS events are likely caused by LCHAD. Early identification and treatment can prevent life-threatening episodes. Fasting should be avoided and a high-carbohydrate diet followed.

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)—MCAD is characterized by recurrent episodes of metabolic acidosis, and by hypoglycemia, lethargy, and coma. Symptoms typically begin in infancy or early childhood. MCAD occurs mostly among Caucasians of northern European background. Initial episodes are often triggered by fasting and may lead to death in 20 to 25 percent of those affected. About one in 100 SIDS deaths are probably a result of MCAD. Avoidance of fasting is imperative; use of glucose IV is required when food cannot be tolerated. High intake of medium- and long- chain fatty acids should be avoided. Supplemental carnitine is recommended for children.

Short Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)—Presenting symptoms of SCAD are failure to thrive and hypoglycemia; over time, development is delayed. As with the other fatty acid disorders, fasting can be a precipitating event and must be avoided. Diet must be monitored and supplemental carnitine should be administered.

Very long Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)—VLCAD's initial manifestations may include hypoketotic hypoglycemia, hepatocellular disease, and cardiomyopathy; fatal infantile encephalopathy may be the only indication of the condition. Attention to diet, avoidance of fasting, and supplemental carnitine comprise the treatment.

ORGANIC ACID DISORDERS

This is a group of autosomal recessive conditions with exceedingly limited incidences.

2,4-Dienoyl-CoA Reductase Deficiency*—This is a deficiency in an auxiliary enzyme of beta-oxidation. Primary symptoms are neonatal hypotonia and respiratory acidosis. Treatment calls for dietary restrictions and carnitine supplementation.

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency*—If this disorder is untreated, it is likely to result in death during childhood. Symptoms may include metabolic acidosis, hypoglycemia, sensitivity to dietary leucine, carnitine deficiency, hepatomegaly, fever, somnolence, and coma. Treatment involves restriction of leucine, supplementary glucose to prevent hypoglycemia, and carnitine supplementation.

3-Ketothiolase Deficiency*—The main symptom of this disorder is recurrent, severe metabolic acidosis. Sodium bicarbonate and intravenous fluids are the usual treatment for acidosis; dialysis may be needed. Carnitine supplementation has been helpful in some cases.

3-Methylcrotonyl-CoA Carboxylase Deficiency—Symptoms may include hypotonia, muscle atrophy, seizures, and dermatological changes. Dietary restrictions are the primary treatment; supplementation with carnitine and/or biotin may be valuable.

3-Methylglutaconyl-CoA Hydratase Deficiency*—Fewer than 50 cases of this disorder have been identified. It is characterized by delayed motor development, short attention span, and delayed development of speech. Other symptoms may include dementia and optic atrophy. There is a dearth of information concerning this disorder, particularly concerning treatment options.

Glutaric Acidemia Type I—This enzyme deficiency disorder is characterized by hypoglycemia, dystonia, and dyskinesia. After a period of apparently normal development, the disorder may appear suddenly and present as vomiting, metabolic acidosis, hypotonia, and central nervous system degeneration. Fewer than 100 cases are known in the US. Intravenous fluids and bicarbonate are used to treat acidosis; dialysis may be necessary. Dietary restrictions have had inconsistent outcomes. Carnitine supplementation may be needed.

Isovaleric Acidemia—With onset between birth and 1 year, IVA occurs in both acute and chronic forms. Symptoms of acute IVA are attacks of vomiting, lack of appetite, and listlessness; lethargy, neuromuscular irritability, and hypothermia are other characteristics. Episodes can be triggered by upper respiratory infections or by excessive consumption of high-protein foods. Treatment involves a protein-restrictive diet and carnitine supplementation. Oral administration of glycine is lifesaving and may permit normal growth and development.

Methylmalonic Acidemias [Adenosyl- cobalamin Synthesis Defects (CblA and CblB) and Methylmalonyl-CoA Mutase Deficiencies (mut- and mut+)]—An enzymatic defect in the oxidation of amino acids is the cause of these conditions, with an incidence of 1 in 50,000 to 1 in 100,000 live births. Symptoms usually begin in the first few months of life, and include lethargy, failure to thrive, vomiting, dehydration, respiratory distress, hypotonia, and hepatomegaly. Acute episodes may include drowsiness, coma, and seizures, with subsequent developmental delays. Treatment includes a carefully controlled diet including a low-protein regimen and/or restriction of isoleucine, valine, and threonine. Medical food supplementation may be needed, as may carnitine.

Multiple CoA Carboxylase Deficiency*—A deficiency of biotin, part of the Vitamin B complex, leading to multiple carboxylase deficiency. Incidence is 1 in 87,000. Symptoms include seizures, hypotonia, immune system impairment, skin rashes, hair loss, hearing loss and mental retardation. Treatment is oral biotin supplementation, which should be begun immediately upon diagnosis.

Propionic Acidemia—This disorder usually results in catastrophic illness beginning in the newborn period. Incidence is 1 in 100,000 live births. Primary symptoms include protein intolerance, vomiting, failure to thrive, lethargy, and profound metabolic acidosis. Brain damage, including coma and generalized seizures, and death result if not treated. Treatment includes protein restriction and often calls for supplementation by medical foods. Fluids and electrolyte therapy may be needed. Acidosis is resolved by sodium bicarbonate, or by dialysis. Secondary carnitine deficiency is likely to occur, requiring supplementation.

ENDOCRINE DISORDERS

Congenital hypothyroidism—This disorder is caused by inadequate production of thyroxine, a thyroid hormone. Incidence is approximately 1 in 4,000. Symptoms include mental retardation, growth failure, deafness, neurologic abnormalities, and hypometabolic activities. Treatment is levothyroxine, thyroid hormone replacement therapy, given orally. The screen for this disorder is measurement of TSH. Borderline elevations will result in a repeat screening card request. Significant elevations will result in the primary care physician being contacted and a serum sample for Free T4 and TSH being requested. Immediate action is required. Dr. T. Best in Saskatoon is available for consultation in treatment of a diagnosed infant.

Congenital adrenal hyperplasia (CAH)—The most common form (more than 90 percent of all recognized cases) results from 21-hydroxylase deficiency. Incidence is 1 in 12,000, but may be as high as 1 in 5,000 among those of Italian background. CAH causes increased androgen production, resulting in ambiguous genitalia and virilization in girls and early virilization in boys. Other symptoms are accelerated skeletal maturation and ultimate short stature.

The initial screen is measurement of 17-OH progesterone. Elevated samples are tested by LC/MS/MS to confirm elevations. A serum sample for 17 OH progesterone, cortisol and androstenedione is requested from the primary care physician to confirm the diagnosis of CAH. In the future the LC/MS/MS method will be able to perform a steroid profile on the initial blood spot card, but a serum sample will still be recommended for confirmation of the correct baby. Dr. T. Best in Saskatoon is available for consultation in treatment of a diagnosed infant.

OTHER DISORDERS

Biotinidase deficiency—See Multiple CoA Carboxylase Deficiency, above. Many jurisdictions screen for biotinidase deficiency by a specific enzyme assay to measure the activity of biotinidase. Our laboratory uses the measurement of biotinidase by a colorimetric method to detect a possible deficiency. Repeat blood spot samples may be requested to confirm borderline results. Increased heat and humidity can cause false decreases in biotinidase enzyme in the summer months resulting in an increase in the number of repeat samples requested. Biotinidase deficiency is treated with oral biotin (Vitamin B).

Galactosemia—This is an inherited disorder of metabolism of galactose, the major sugar found in milk. Incidence is 1 in 50,000. Symptoms include severe mental retardation, overwhelming systemic infections, failure to thrive, vomiting, liver disease, and cataracts. Untreated galactosemia is generally fatal. Treatment requires elimination of milk and milk products (all products containing lactose) from the diet. RRPL uses a fluorometric method for the detection of Galactose-1-phosphate uridyltransferase (GALT) deficiency as the screening method. A method for the elevation of galactose-1-phosphate is used to confirm the GALT deficiency. Currently a moderately deficient GALT will result in a repeat newborn screening card being requested. Increased heat and humidity can cause false decreases in GALT activity, which may result in an increase in the number of repeat samples requested during the summer months. If the decrease in GALT activity is significant, the primary care physician will be contacted by telephone to determine the health of the baby, its feeding status at initial sample collection. A repeat newborn screening sample needs to be collected ASAP and shipped quickly to prevent deterioration due to heat.

Cystic Fibrosis -- Tests for newborn screening for CF are readily available, and involve measurement of Immunoreactive Trypsinogen. Those that have high levels of this enzyme need to be further tested by DNA analysis (PCR) for a panel of mutations in the CFTR gene, usually around 35-44 of the most common ones. Those that are shown to have disease-causing mutations will be advised to have a sweat chloride test at the Regina or Saskatoon CF Clinic. If their sweat chloride test is abnormal, it is considered presumptive evidence for the presence of CF. These patients are then advised to undergo further clinical evaluation and follow up to determine if treatment needs to be initiated. Since Alberta began testing for CF in 2006, they have identified 7 cases out of 16,000 babies screened, or ~1/2300. The Saskatchewan prevalence of CF is expected to be similar to Alberta. Cystic Fibrosis testing at RRPL will follow the following protocol: All samples received will be tested for IRT (immunoreactive trypsinogen).

Elevations will generate a request for a repeat blood spot card. If the repeat sample confirms the elevation, a portion of the blood spot will be sent to the Edmonton newborn screening program for DNA mutation analysis. Results of the test will be returned to RRPL. If the DNA test indicates 1 or 2 mutations, the results will be referred to the CF clinic in either Regina or Saskatoon based on the patient's home address. The CF clinic will arrange for sweat chloride testing. Based on the IRT, DNA and sweat chloride results, the CF clinic physicians will determine what if any further treatment or follow up is required. Results of the sweat chloride will be returned to RRPL only for the purpose of program evaluation. Extremely high IRT results will result in a portion of the original screening sample being sent for DNA analysis. The results of the DNA testing and the IRT result will be referred to the CF clinic in either Regina or Saskatoon based on the patient's home address. The CF clinic will arrange for sweat chloride testing, regardless of the DNA results.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency—(Neonatal screening in Saskatchewan does not include a test for G6PD Deficiency).

G6PD deficiency is the most common genetic enzyme deficiency, occurring most often in tropical and subtropical Asia, tropical Africa, areas of the Mediterranean, the Middle East, and New Guinea. It can cause premature destruction of red blood cells (hemolytic anemia) when an affected individual is exposed to certain medications, chemicals, foods, or pollen. Severity of the condition is extremely variable. Treatment involves restricting exposure to pathogens that cause a reaction.

SICKLING HEMOGLOBINOPATHIES (these diseases are not tested for at this time in Saskatchewan)

These are a group of disorders characterized by abnormal hemoglobin-chains: sickle-cell disease and thalassemia are two. Overall incidence of hemoglobinopathies in the US is 1 in 58,000. Sickle cell is most commonly found in African-Americans and has an incidence of about 1 in 600. Thalassemia is most likely to affect people with eastern Mediterranean (Greek, Arabic, Italian) or East Indian ancestry. Symptoms are lifelong hemolytic anemia, abnormally shaped blood cells leading to acute and chronic tissue damage, episodic vaso-occlusive crises, splenic sequestration, and sepsis. Ongoing therapy is penicillin prophylaxis and vigilant treatment of infections. Aggressive pain management, management of dehydration and acidosis, blood transfusions, and oxygen are all utilized for acute episodes.

*Theoretically detectable in the newborn period.

List of diseases detected by newborn screening in Saskatchewan

Amino Acid Disorders (using tandem mass spectrometry):

Phenylketonuria

Maple Syrup Urine Disease Citrullinemias Argininosuccinic Aciduria Tyrosinemia Homocystinuria
Acylcarnitine Disorders (using tandem mass spectrometry):

Organic Acid Disorders:

Methylmalonic Acidemias:

Methylmalonyl-CoA Mutase Deficiencies (mut0 and mut+)

*Adenosylcobalamin Synthesis Defects (CblA and CblB) Propionic Acidemia (Acute and Late Onset)
Isovaleric Acidemia (Acute and Late Onset) Glutaric Acidemia-Type I
3-Methylcrotonyl-CoA Carboxylase Deficiency

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

Multiple CoA Carboxylase Deficiency

3-Ketothiolase Deficiency

3-Methylglutaconyl-CoA Hydratase Deficiency

2,4-Dienoyl-CoA Reductase Deficiency

Malonic Acidemia

Fatty Acid Oxidation Disorders:

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD) Short Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)
Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)

3-Hydroxy Long Chain Acyl-CoA Dehydrogenase Deficiency Carnitine Palmitoyl Transferase Deficiency-Type I and II Carnitine Acylcarnitine Translocase Deficiency
Multiple Acyl-CoA Dehydrogenase Deficiency (Glutaric Acidemia-Type II) Trifunctional Protein Deficiency

Sample Requirements

Blood specimens for newborn screening should be collected on filter paper by heel stick according to standard protocols in newborn screening laboratories.

Benefits of neonatal screening

1. Early detection of genetic diseases will result in early management and treatment with an improved outcome for most diseases screened for in the Saskatchewan Newborn Screening Program. This can result in lower long-term health care costs and can decrease the frequency of sudden unexplained deaths or hospitalizations.

2. False positive rate is lower due to our modern, accurate analytical techniques. This means fewer requested repeat specimens resulting in a decrease in stress on families concerned about a possible positive result. Prompt return of all requested repeat samples will also decrease family stress.

3. Newborn screening is good medicine and it helps everyone, especially our children.
   Web sites with additional information about screening for inborn errors of metabolism
   http://www.newbornscreening.info/
   www.newbornscreening.on.ca/
   www.bcwomens.ca/Services/PregnancyBirthNewborns/NewbornCare/NewbornScreeningProgram/
   http://en.wikipedia.org/wiki/Newborn_screening www.cysticfibrosis.ca/page.asp?id=292
   www.cord.ca/index.php/site/resources/newborn_screening
   http://www.mountsinai.on.ca/care/family-medicine-genetics-program/paediatric
   http://www.fodsupport.org/ http://www.savebabies.org/ http://genes-r-us.uthscsa.edu/
   http://www.nergg.org/nbsbrochures.php
   http://www.mayomedicallaboratories.com/articles/newborn/index.html

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