



May 31, 2007

Dear Doctor:

In January 1995, my partner at NeoGen Labs, Thomas Mookken, and his wife had a baby boy, Ayden. By all appearances Ayden was a normal, healthy child doing what babies do best; sleeping and crying when hungry. The hospital he was born in participated in a Newborn Screening Program and one of the screening tests detected G6PD, an Inborn Error of Metabolism (IEM). As you know this could be fatal in some cases but is very easily treatable; avoidance of Sulpha drugs and some foods. It is estimated there are about 360, 000 births every year in India that test positive for G6PD.

This incident made Thomas realize the power of Newborn Screening (NBS). A simple concept with very beneficial implications; detecting and treating conditions before symptoms appear, thereby saving numerous babies lives. He felt this would have a very big impact in India with over 24 Million babies born every year.

Thomas decided to move to India with his family and asked me to join him in his efforts to promote NBS and its benefits here. We invested a significant portion of our savings to form NeoGen Labs with the sole purpose of offering Newborn Screening for IEMs on par or better than what is currently offered in the West.

To help us in our goal, we entered into an exclusive Technology Licensing Agreement with Pediatrix Screening, Inc., Bridgeville, USA, the world's leading company for Newborn Screening. They pioneered the use of Tandem Mass Spectrometry (MS/MS) which currently screens for 42 metabolic disorders, from a single dried blood spot collected on a filter paper 24 to 72 hours after birth. Pediatrix Screening has screened over 3 million babies of all ethnicities, using MS/MS since 1994, and continues to screen over 300, 000 every year. We have replicated Pediatrix Screening's facilities at the NeoGen NBS lab in Bangalore.

The **First Step Newborn Screening Test** offered by NeoGen Labs has two major benefits: first, it identifies, as early as possible, the babies that need treatment and second, it provides peace of mind for the majority of parents whose newborns are healthy. In addition to screening for 42 conditions with MS/MS, **First Step** also includes 3 biochemical tests for metabolic disorders that cannot be detected by MS/MS.

We hope you find the enclosed information useful. Please contact me if you have any questions or need more information.

Sincerely,

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Giving babies the best start in life!

First Step Newborn Screening Panel

First Step will screen babies for over 42 Inborn Errors of Metabolism (IEM) by Tandem Mass Spectrometry and Biochemical Analysis.

DISORDERS DETECTED BY TANDEM MASS SPECTROMETRY

ACETYLCARNITINE PROFILE

Fatty Acid Oxidation Disorders

- Carnitine / Acylcarnitine Translocase Deficiency
- Carnitine Palmitoyl Transferase Deficiency Type I¹
- 3-Hydroxy Long Chain Acyl-CoA Dehydrogenase Deficiency
- 2,4-Dienoyl-CoA Reductase Deficiency¹
- Medium Chain Acyl-CoA Dehydrogenase Deficiency
- Multiple Acyl-CoA Dehydrogenase Deficiency
- Neonatal Carnitine Palmitoyl Transferase Deficiency Type II
- Short-chain Acyl-CoA Dehydrogenase Deficiency
- Short chain Hydroxy Acyl-CoA Dehydrogenase Deficiency
- Trifunctional Protein Deficiency
- Very Long Chain Acyl-CoA Dehydrogenase Deficiency

Organic Acid Disorders

- 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency
- Glutaric Acidemia Type I
- Isobutyryl-CoA Dehydrogenase Deficiency
- Isovaleric Acidemia
- 2-Methylbutyryl-CoA Dehydrogenase Deficiency
- 3-Methylcrotonyl-CoA Carboxylase Deficiency
- 3-Methylglutaconyl-CoA Hydratase Deficiency
- Methylmalonic Acidemias
- Methylmalonyl-CoA Mutase Deficiency
 - Some Adenosylcobalamin Synthesis Defects
 - Maternal Vitamin B12 Deficiency
 - Mitochondrial Acetoacetyl-CoA Thiolase Deficiency
- Propionic Acidemia
- Multiple CoA Carboxylase Deficiency
- Malonic Aciduria

AMINO ACID PROFILE

Amino Acid Disorders

- Argininemia
- Argininosuccinic Aciduria
- 5-Oxoprolinuria¹
- Carbamoylphosphate Synthetase Deficiency¹
- Citrullinemia
- Homocystinuria
- Hypermethioninemia
- Hyperammonemia, Hyperornithinemia, Homocitrullinuria Syndrome¹
- Hyperornithinemia with Gyral Atrophy¹
- Maple syrup disease
- Phenylketonuria
 - Classical / Hyperphenylalaninemia
 - Biopterin Cofactor Deficiencies
- Tyrosinemia
 - Transient Neonatal Tyrosinemia
 - Tyrosinemia Type I¹
 - Tyrosinemia Type II
 - Tyrosinemia Type III

Other

- Hyperalimentation
- Liver Disease
- Medium Chain Triglyceride Oil Administration
- Presence of EDTA coagulants in blood specimen
- Treatment with Benzoate, Pyvalic Acid, or Valproic Acid
- Carnitine Uptake Deficiency

¹ There is a lower probability of detection of this condition during the immediate newborn period.

DISORDERS DETECTED BY OTHER TECHNOLOGIES

- Galactosemia
- Congenital Hypothyroidism
- Congenital Adrenal Hyperplasia



Answers to Frequently Asked Questions

Q. What is the Newborn Screening (NBS) Test?

A. It tests babies for serious disorders and is usually performed when your baby is 24 - 72 hours old. Ideally, the specimen should be sent to the laboratory by the fastest way possible to prevent delay.

Q. Why is the test done?

A. The test is done to find out if your baby has a disease or condition for which early treatment can prevent death, mental retardation, or physical disability.

Q. How is the test performed?

A. The test is performed by pricking a baby's heel and putting a few drops of blood on a special filter paper. The paper is allowed to dry and then sent to the newborn screening laboratory where several different tests will be performed.

The heel prick feels no worse than being stuck by a pin. Problems from the prick, such as infection of the heel, are very rare.

Q. But we have no family history of these disorders . . .

A. Parents who have no family history of problems and/or who have already had healthy children can still have children with these disorders. In fact, most children with these disorders come from families with no previous history of the condition.

Genes for these diseases can be passed along through generations of healthy people without anyone ever knowing about them. These "carriers" are healthy because the normal gene in the pair (genes come in pairs—one from each parent) is working, making up for the flawed gene. But when two people who coincidentally carry the same flawed gene get together, their risk of having an affected child is 25% for each pregnancy. This pattern, called recessive inheritance,

explains how most metabolic diseases appear unexpectedly.

Q. But my baby looks healthy . . .

A. Most babies with disorders look and act normal and seem perfectly healthy. The newborn screening test helps your doctor catch a problem with your baby before it makes him or her sick. Most babies that are diagnosed and treated early do well. The earlier the disorder is detected, the higher the chance of having a good prognosis.

Q. What is a Retest?

A. If the result of your child's test is abnormal, a repeat test or a "retest" is usually required. A request for a retest does not necessarily mean your child has a disorder, but it is possible. If you are asked for a retest, it is important that you take your baby for the retest as soon as possible.

Q. How will I know the results of my baby's test?

A. Generally, parents and doctors are notified of the test results. However, it is a good idea to call your doctor or NeoGen Labs and request the results if you have not received it within 2 weeks of the test. This is important to ensure that your child's test results have not been lost or misplaced.

If your child's test shows an abnormal result, you will be notified immediately and given directions about what to do next. Follow the directions of your doctor very carefully. If your child's test is abnormal, additional tests are usually necessary to verify if your child has the disorder. It is important that you advise your doctor if you move or change phone numbers soon after your baby is born in case there is a problem with your baby's test.

Q. What does a positive result indicate?

A. Parents should not be alarmed by



positive results as the screening gives only preliminary information, albeit with a high degree of accuracy. It should be followed by a precise confirmatory test.

Q. What exactly are Inborn Errors of Metabolism (IEM)?

A. These are disorders caused by the accumulation of chemicals produced naturally in the body to abnormal levels. The symptoms manifest themselves in a variety of ways; slow physical development or mental retardation. In some cases, they could result in death. Unfortunately, most infants with these disorders show no signs of these conditions. If these conditions are detected at birth by NBS, the child can lead a normal, healthy life.

Q. How can these disorders be cured?

A. These conditions have no cures and are inherited. The symptoms and effects can be mitigated if they are detected and treated early, leading to a normal and healthy life.

Q. Can Newborn Screening be performed on older children or adults?

A. Yes. Older children or adults also can be screened.

Q. Will Newborn Screening by NeoGen Labs detect all conditions?

A. The analyses conducted produce results that can be used by qualified physicians in the diagnosis of IEMs. Evidence of these conditions will be detected in the vast majority of affected individuals; however, due to genetic variability, age of the patient at the time of specimen collection, quality of the specimen, health status of the patient, and other variables, such conditions may not be detected in all affected patients.

Q. When will NeoGen Labs start offering Newborn Screening?

A. NeoGen Labs expects to start screening commercially from July 1, 2007. From April 15, 2007 until June 30, 2007, NeoGen Labs will be conducting validation testing.

Q. What disorders can Newborn Screening identify?

NeoGen Labs tests babies for over 42 metabolic disorders from a dried blood spot. Some of these are described below. These disorders are present at birth, rare, and often serious. Some are passed on from parents while others are caused by a chemical imbalance. Some are life-threatening while others may slow down physical development or cause mental retardation or other problems. These disorders can affect a child early in life, often within the first few days or weeks of life. This is why it is important to identify babies with these disorders as early as possible.

- **Maple Syrup Urine Disease (MSUD)** results when the baby's body does not break down parts of a food protein causing the urine to smell like maple syrup. Treatment with a special diet can prevent mental retardation and other complications.
- **Galactosemia (ga-LAK-toe-see-me-a)** results when milk sugar (galactose) is not broken down due to the lack of a chemical in the body. A diet low in galactose can prevent irreversible damage and other complications.
- **Phenylketonuria (FEN-nil-KEE-tone u-ree-ah)** is also called PKU and results when a part of a food protein (phenylalanine) is not broken down by the baby's body. Brain damage that would normally result can be prevented by a special diet low in phenylalanine.
- **Tyrosinemia I (TY-ro-SIN-e-me-ah)** results when another part of a food protein (tyrosine) cannot be broken down and used properly in the baby's body. Some forms of this disorder can result in liver and brain damage, and may be life-threatening.
- **Homocystinuria (HO-mo-SIS-tin-u-ree-ah)** results from the absence of a

chemical in the liver. A special diet can help prevent mental retardation, body changes and life-threatening complications.

- **Hypothyroidism (HI pO-THI-royd-ism)** results when the baby's body does not produce enough of a hormone (substance) called thyroxin. Treatment with thyroxin tablets helps prevent mental and growth retardation.

- **Congenital Adrenal Hyperplasia (CAH) (con-GEN-I-tle ah-DRE-nal HY-per-PLA-se-a)** results when the baby's body does not produce enough of a substance (hormone) called cortisol. Treatment with hormone medications can prevent low blood sugar, salt loss, poor growth and abnormal body changes.

- **Fatty Acid Oxidation Disorders**
The body usually gets energy from sugars and fats. The sugar is used first but when the sugar is all used up, the body must use fats. In this group of disorders, the body cannot use fats because of the lack of one of several enzymes. The disorders in this group do not have common names. They are usually described by the length of the fatty acid that cannot be used. The most common of these is,

- **Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD).** Because they cannot use stored fat for energy, babies with these disorders may develop seizures, coma and life threatening complications when fasting (no food eaten for longer than 4 hours). Treatment includes making sure the baby eats regularly and avoiding fasting. A special diet and medications may also be used.

Other fatty oxidation disorders screened for are,

- **Long Chain Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD)**
- **Trifunctional Protein Deficiency (TFP Deficiency)**
- **Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD)**
- **Carnitine Uptake Defect (CUD)**

- **Organic Acidemias**

The body cannot use the branched chain amino acids from the protein in food properly because of the lack of one of several enzymes. The breakdown products of these amino acids are organic acids. The organic acids build up to dangerous levels in the blood damaging the nervous system. Babies with some of these disorders can become very sick very fast. Symptoms can sometimes be lessened with special diets (low in protein) and medications.

Most of these disorders do not have common names and are described by the name of the organic acid found in the urine. The organic acidemias screened for include,

- **Isovaleric Acidemia (IVA)**
- **Glutaric Acidemia Type I (GA-1)**
- **3-Hydroxy-3Methylglutaryl-CoA Lyase Deficiency (HMG)**
- **Multiple CoA Carboxylase Deficiency (MCD)**
- **Methylmalonyl-CoA Mutase Deficiency (MUT)**
- **Methylmalonyl Adenosyl-Cobalamine Synthesis Defects (Cbl A & B)**
- **3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)**
- **Propionic Acidemia (PROP)**
- **Beta-Ketothiolase Deficiency (BKT)**

- **Urea Cycle (Amino Acid) Disorders**

The body cannot dispose of nitrogen properly. The body usually disposes of nitrogen by changing it into a substance



called urea, which leaves the body in the urine. Because of the lack of one of several enzymes, the body cannot make urea effectively and the nitrogen builds up as ammonia in the blood. This makes the baby very sick very fast. These disorders cause seizures, poor muscle tone, breathing problems, and coma. Death will result if the baby is not treated. Symptoms can be lessened with special diet and medications that

help the baby to get rid of ammonia in other ways. Screening for this group of disorders is very new. The urea cycle disorders screened by NeoGen Labs include,

- Argininosuccinic Aciduria (ASA)
- Citrullinemia (CIT)

The FAQ was created from information from multiple sources that include **Pediatrix Screening, Inc.** (www.pediatrix.com), **Save Babies Through Screening Foundation** (www.savebabies.org) and **Virginia Dept. of Health** (www.vahealth.org).

Neonatal Screening

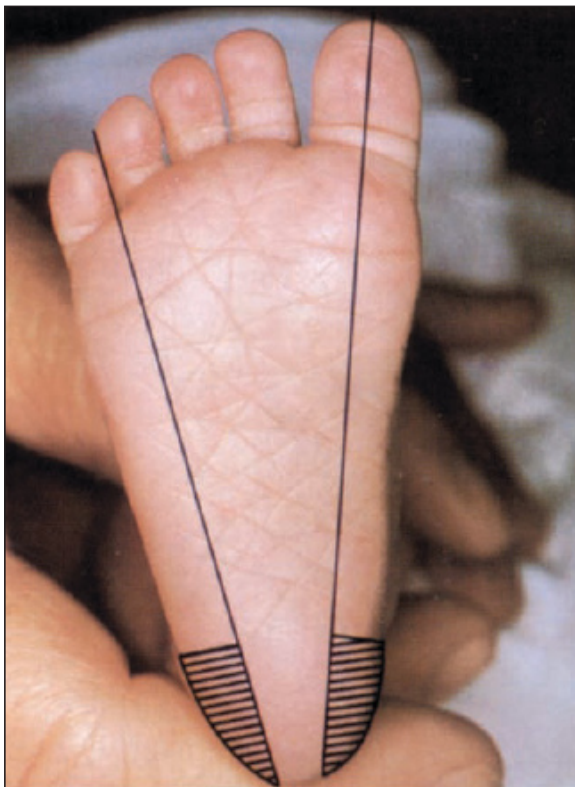
Steps for Blood Specimen Collection and Handling Procedure



1 Equipment: sterile lancet with tip approximately 2.0 mm – sterile alcohol prep, sterile gauze pads, soft cloth, blood collection form, gloves.



2 Complete ALL information. Do not contaminate filter paper circles by allowing the circles to come into contact with spillage or by touching before or after blood collection. Keep "SUBMITTER COPY" if applicable.



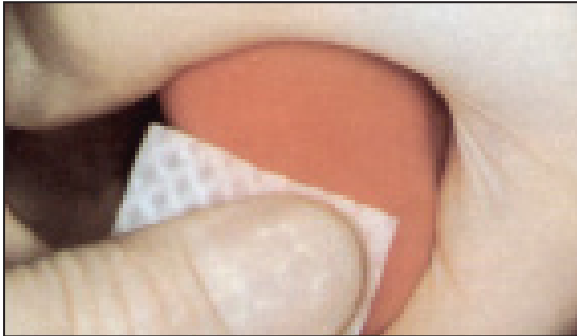
3 Hatched area (▨) indicates safe areas for puncture site.



4 Warm site with soft cloth, moistened with warm water up to 41°C, for three to five minutes.

Neonatal Screening

Steps for Blood Specimen Collection and Handling Procedure



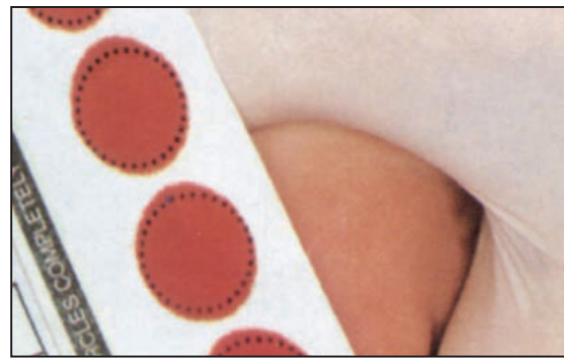
- 5** Cleanse site with alcohol prep.
Wipe DRY with sterile gauze pad.



- 6** Puncture heel. Wipe away first blood drop with sterile gauze pad. Allow another LARGE blood drop to form.



- 7** Lightly touch filter paper to LARGE blood drop. Allow blood to soak through and completely fill circle with SINGLE application of LARGE blood drop. (To enhance blood flow, VERY GENTLE intermittent pressure may be applied to the area surrounding the puncture site). Apply blood to one side of filter paper only.



- 8** Fill remaining circles in the same manner as step 7, with successive blood drops. If blood flow is diminished, repeat steps 5 through 7. Care of skin puncture site should be consistent with your institution's procedures.

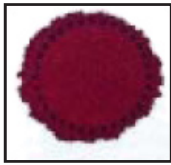
- 9** Dry blood spots on a dry, clean, flat, nonabsorbent surface for a minimum of four hours.



- 10** Mail completed form to testing laboratory within 24 hours of collection.

Information provided by: The New York State Department of Health.

Sample Spot Check



Valid specimen:

Allow a sufficient quantity of blood to soak through to completely fill the preprinted circle on the filter paper. Fill all required circles with blood. Do not layer successive drops of blood or apply blood more than once in the same collection circle. Avoid touching or smearing spots.

Invalid specimen:



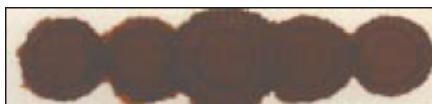
1. Specimen quantity insufficient for testing.



2. Specimen appears scratched or abraded.



3. Specimen not dry before mailing.



4. Specimen appears supersaturated.



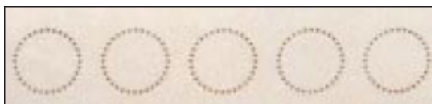
5. Specimen appears diluted, discolored or contaminated.



6. Specimen exhibits serum rings.



7. Specimen appears clotted or layered.



8. No blood.

Possible causes:

- Removing filter paper before blood has completely filled circle or before blood has soaked through to second side.
- Applying blood to filter paper with a capillary tube.
- Touching filter paper before or after blood specimen collection with gloved or ungloved hands, hand lotion, etc.
- Allowing filter paper to come in contact with gloved or ungloved hands or substances such as hand lotion or powder, either before or after blood specimen collection.
- Applying blood with a capillary tube or other device.
- Mailing specimen before drying for a minimum of four hours.
- Applying excess blood to filter paper, usually with a device.
- Applying blood to both sides of filter paper.
- Squeezing or “milking” of area surrounding the puncture site.
- Allowing filter paper to come in contact with gloved or ungloved hands or substances such as alcohol, formula, antiseptic solutions, water, hand lotion or powder, etc., either before or after blood specimen collection.
- Exposing blood spots to direct heat.
- Not wiping alcohol from puncture site before making skin puncture.
- Allowing filter paper to come in contact with alcohol, hand lotion, etc.
- Squeezing area surrounding puncture site excessively.
- Drying specimen improperly.
- Applying blood to filter paper with a capillary tube.
- Touching the same circle on filter paper to blood drop several times.
- Filling circle on both sides of filter paper.
- Failure to obtain blood specimen.

The FAQ was created from information from multiple sources that include Save Babies Through Screening Foundation (www.savebabies.org)