Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

A Practical Guide to Newborn Bloodspot Screening In Ireland

National Newborn Bloodspot Screening Laboratory
Temple Street Children's University Hospital
Temple Street, Dublin D01 YC67

7th Edition – December 2018
Next review due December 2020

Contents

INTRODUCTION

The Newborn Screening Programme for phenylketonuria (PKU) was started in Ireland on behalf of the Department of Health by Drs Seamus Cahalane and Doreen Murphy at the Children's University Hospital, Temple Street in February 1966; approximately four years after the first newborns were screened in the States of Massachusetts and New York (USA). The Irish programme was one of the first programmes in the world. A number of other conditions have since been added. Some of these have been discontinued and others will be added in the future. All babies born on or after 1st July 2011 have now been offered screening for Cystic Fibrosis. In December 2018 screening for two additional metabolic disorders MCADD and GA1 will commence, see further details in this guide.

The screening programme involves many healthcare professionals, each with their own expertise and responsibilities. The programme is co-ordinated through the National Newborn Bloodspot Screening Laboratory (NNBSL) at Temple Street Children's University Hospital on behalf of the Health Service Executive (HSE) and the Directorate of Health and Wellbeing – Public Health and Child Health. The screening laboratory is fully integrated into the Hospital's Department of Paediatric and Laboratory Medicine in Temple St., thus ensuring rapid confirmatory testing of abnormal results and the biochemical monitoring of those diagnosed.

The worldwide screening community is small and we in Ireland are very cognisant of the differences between regional and national programmes and the Irish programme. The Irish programme has been tailored for the local population and the incidence of disorders occurring within the Irish population. The National Newborn Bloodspot Screening Programme (NNBSP) will continue to develop as new information and treatments become available for these rare disorders.

We would like to acknowledge the dedication and commitment that so many different healthcare professionals put into this programme for the benefit of the few babies born each year who are affected by one of these conditions.

This Guide should be read in conjunction with the HSE Standard Operating Procedure for Maternity Hospitals/Units and Primary Care Services delivering the National Newborn Bloodspot Screening Programme. We would welcome any comments and feedback that individuals may have on this edition. More information about the programme may be obtained at www.newbornscreening.ie and www.hse.ie/go/newbornscreening

Dr Kevin Kelleher
Assistant National Director
Strategic Planning and Transformation
Public Health and Child Health
Mt Kennett Pl. Henry St
Limerick
V94 KN3N

Dr Ingrid Borovickova
Director of the NNBSL
Children's University Hospital
Temple Street
Dublin
D01 YC67

Significant changes from 6th Edition

Some of the more significant changes which have been incorporated into this edition are highlighted below. However, users are advised to read the entire guide in order to familiarise themselves fully.

Section 3: Summary information on two additional disorders introduced to the Irish screening programme. **No additional blood spots will be required.**
The two disorders are:

- Medium chain Acyl CoA Dehydrogenase Deficiency (MCADD)
- Glutaric Aciduria type 1(GA1)

MCADD is a rare, but treatable inherited disorder where those affected are unable to break down fats from their food quickly enough to produce energy in times of illness (e. g vomiting). Treatment involves regular feeding and avoiding long periods of fasting. Medication may also be required. If early treatment is not commenced, the baby can become very unwell and may have serious complications, including seizures, coma or even premature death. If the diagnosis and treatment are commenced early, the baby can lead a healthy life and the serious; potentially life threatening complications of MCADD can be averted.

GA1 is a rare, but treatable inherited disorder, those affected are missing an essential enzyme needed to breakdown protein properly. This causes harmful substances to build up in the blood and urine and can make those affected very ill. If GA1 is left untreated, serious complications, for example seizures, coma and long term damage to the brain can occur. Premature death may also occur. The baby can have problems with muscle movement, sitting, walking and difficulty swallowing. They can also have a bleed around their brain. The treatment of GA1 is a special diet low in protein and medication. Babies with GA1 benefit significantly from early diagnosis and treatment and can lead healthy and active lives.

Section 3.2.3 and section 6.1.1 The sample should be collected between 72-120 hours in all babies including those who are breastfed. But in view of the new conditions included in the newborn screening programme (particularly MCADD); there is no longer an emphasis on taking the sample at the end of the 72-120 hour window in breast fed babies.

If protein intake is deemed suboptimal (poor feeding) a further sample should be taken on or around day 10 of life. This is to ensure that protein intake has been adequate to reveal a positive screen for the amino acid disorders, particularly for HCU. Breast milk contains less protein than formula feeds and a baby with poor protein intake may screen false negative for HCU.

Section 5: Clarification on consent issues.

Section 6: MCADD and GA1 high risk screening guidelines for sample collection.

Section 6: Procedure for infants who have missed the newborn screening window for CF.

Red weather alerts: In the event of a red weather alert due to adverse weather conditions, the sample taker in conjunction with the ADOM / ADPHN must assess the risk of travel of either the PHN or the parent and baby against the risk of delayed screening. Further advice can be sought from the laboratory on such occasions.

Parent(s)/legal guardian(s) are entitled to and can be given a copy of baby's results by their PHN.

N.B.: No screening test is 100% reliable

1 Contact Details and Laboratory Opening Times

1.1 Telephone Numbers

National Newborn Bloodspot Screening Laboratory (NNBSL)

Enquiries:		01 878 4277 or 4610
Email:		info.newbornscreening@cuh.ie
FAX		01 878 4596
Director	(Dr Ingrid Borovickova)	01 878 4277
Chief Medical Scientist	(Ms Loretta O'Grady)	01 878 4277
Clinical Liaison Officer	(Ms Olivia Walsh)	01 892 1804
National Centre for Inherited Metabolic Disorders (NCIMD) Temple St., Enquiries to		01 878 4317

Website: www.newbornscreening.ie

1.2 Laboratory Opening Times

Monday to Friday 09.00 to 17.00
Analysis including Beutler tests and reporting of results

Saturday Morning 09.00 to 12.00
Reporting of results and Beutler Assay
N.B. Beutler samples must be in the laboratory before 10.00am

Christmas and Easter: Opening hours will be circulated in advance and/or posted on website.

All samples received in the laboratory up to 12.00 will be analysed that day, samples received after that will be analysed the next working day. The 12.00 deadline may change on Christmas Eve or Good Friday, sample takers will be notified in advance.

2 Abbreviations

ADOM	Assistant Director of Midwifery
ADPHN	Assistant Director of Public Health Nursing
CHO	Community Healthcare Organisation
CHT	Congenital Hypothyroidism
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CGal	Classical Galactosaemia
CNS	Clinical nurse specialist
DBS	Dried Blood spot
DPHN	Department of Public Health Nursing
DNA	Deoxyribonucleic acid
DOB	Date of Birth
DON/M	Director of Nursing/Midwifery
GA1	Glutaric Aciduria type 1
GCDH	Glutaryl-CoA dehydrogenase
GP	General Practitioner
HCRN	Health Care Record Number
HCU	Homocystinuria
HSE	Health Service Executive
IHI	Individual Health Identifier
IV	Intravenous (fluids)
INAB	Irish National Accreditation Board
KPI	Key Performance Indicators
IRT	Immunoreactive Trypsinogen
LHO	Local Health Office
MCADD	Medium chain Acyl CoA dehydrogenase deficiency
MSUD	Maple Syrup Urine Disease
NBS	Newborn Screening
NBSC	Newborn Bloodspot Screening Card
NCIMD	National Centre for Inherited Metabolic Disorders
NNBSL	National Newborn Bloodspot Screening Laboratory
NNBSP	National Newborn Bloodspot Screening Programme
OLCHC	Our Lady's Children's Hospital, Crumlin
PHN	Public Health Nurse
PKU	Phenylketonuria
RPHN	Registered public health nurse
RBC	Red Blood Cell
SECM	Self-employed community midwives
TPN	Total Parenteral Nutrition
TSCUH	Temple Street Children's University Hospital
TSH	Thyroid Stimulating Hormone
UPI	Unique parenteral identifier
Hrs	Hours

3 Conditions Screened

All conditions which form part of the Newborn Bloodspot Screening Programme, have been selected because they all have a relatively high incidence within the Irish population and they fulfil, in part or in full, the criteria which have been set out Internationally for newborn screening. These include:

- the conditions screened are treatable;
- there is a test available which is easily applied to large population groups;
- there are few false positive and false negative results i.e. the test is reliable;
- the incidence of the conditions in the community is sufficiently high to warrant screening;
- the cost of screening makes the process cost-effective.

For all of the conditions, early diagnosis and treatment significantly improves the clinical outcome. Some of the conditions, for example, Congenital Hypothyroidism, Classical Galactosaemia, Maple Syrup Urine Disease, Medium Chain Acyl CoA Dehydrogenase deficiency and Glutaric Aciduria type 1 benefit from the earliest detection possible. Unfortunately, as with all screening programmes, not all individuals with a condition will be detected. This is particularly true for Homocystinuria and for Cystic Fibrosis where milder variants of the condition may not be detected.

N.B.: No screening test is 100% reliable

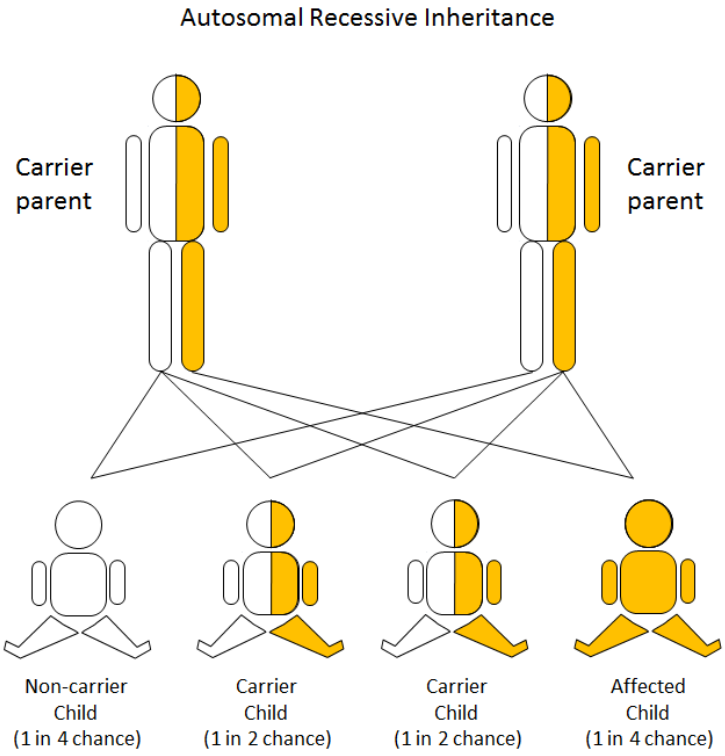
Table 1: Conditions included in the Irish Newborn Bloodspot Screening Programme

	Condition	Date started	Irish Incidence	Worldwide Incidence
1	Phenylketonuria (PKU)	1966	1:4,500	1:12,000
2	Homocystinuria (HCU	1971	1:69,400	1:120,000
3	Classical Galactosaemia (CGal)	1972	1:16,200	1:45,000
4	Maple Syrup Urine Disease (MSUD)	1972	1:155,200	1:225,000
5	Congenital Hypothyroidism (CHT)	1979	1:2,300	1:3,500
6	Cystic Fibrosis (CF)	2011	1:2,300	1:3,500
7	Glutaric Aciduria Type 1 (GA1)	2018	1:54,000	1:100,000
8	Medium Chain Acyl CoA Dehydrogenase deficiency (MCADD)	2018	1:66,000	1:14,600

3.1 Mode of Inheritance

The majority of the conditions screened for involve a defect in a metabolic process or pathway and are inherited as 'autosomal' conditions and can occur with equal frequency in both males and females.

Each step in a metabolic pathway is governed by an enzyme. An enzyme is a protein produced by a set (two) of genes on a pair of chromosomes. Each parent transfers to their off-spring one gene so that the off-spring has a set assembled from both parents. If one of these genes is defective (mutated), the metabolic pathway continues but at a reduced rate. These individuals, known as carriers, do not have symptoms of the condition but carry the defective gene. For autosomal recessively inherited conditions, both parents must be carriers of a defective gene and each of their off-spring has a one in four chance of having the condition and a one in two chance of being a carrier.



The clinical presentation and severity of the condition may vary between unrelated families. Different mutations may affect the same metabolic process differently; some individuals may present with a severe form of the condition and others with a very mild form.

Congenital hypothyroidism is slightly different in that for 90% of cases the condition just occurs, for reasons which are not fully understood; it is twice as common in girls as in boys. However, for one in 10 babies (10%) the condition is inherited as an autosomal recessive condition, as described above.

3 .2 Conditions included in the Irish Screening Programme

3.2.1 Phenylketonuria (PKU)

Screening case definition: to detect babies with Phenylketonuria (PKU). No distinction is made between those with PKU, hyperphenylalaninaemia and Dihydropteridine Reductase deficiency. Although it must be acknowledged that some babies with mild hyperphenylalaninaemia may not be detected by newborn screening as the blood level of the amino acid phenylalanine may be below the action cut-off level when screened.

Phenylketonuria is an autosomal recessive condition involving the breakdown of the amino acid phenylalanine. Approximately one in every 4,500 babies born in Ireland have PKU or a milder form called hyperphenylalaninaemia. When diagnosed within the newborn period and started on treatment, these babies grow up healthy and well. However, without treatment this condition may cause intellectual or physical disability.

In the majority of cases, the condition is caused by a lack of the enzyme phenylalanine hydroxylase, which normally converts phenylalanine, one of the building blocks in protein, into tyrosine. In the absence of the enzyme, phenylalanine accumulates and these high levels have a direct toxic effect on the brain.

Early treatment is very beneficial; it aims at giving a reduced intake of phenylalanine but a normal intake of all the other amino acids. This diet has to be continued for life. The screening test depends on detecting a high level of phenylalanine in the blood. If the test is carried out before 72 hours after birth, there is a possibility that the level of phenylalanine in blood may not be sufficiently elevated for the condition to be detected.

The treatment for PKU has been one of the major successes in medicine since it was first introduced in the early 1950s. There is substantial evidence to show that the earlier the treatment is started, the better the biochemical control throughout life and the better the outcome.

3.2.2 Maple Syrup Urine Disease (MSUD)

Screening case definition: to detect babies with the more severe neonatal onset form of Maple Syrup Urine Disease (MSUD). The programme may not detect those babies with the milder variants such as late onset or intermittent MSUD.

Maple Syrup Urine Disease is a life threatening condition if it is not detected and treated early. It too is an autosomal recessive condition caused by a defect in the metabolism of three amino acids, known as the branched chain amino acids because of their similar biochemical structure. Approximately one in every 155, 200 babies born in Ireland may have this condition or about one baby born every two to three years. The disorder is so called because the urine may have an odour similar to that of maple syrup.

Screening was originally justified on the basis that chronic handicap and even premature death had occurred in a number of families where this condition had gone undetected. The branched chain amino acids accumulate in blood following the establishment of feeding during the first few days of life, and may cause brain damage.

A diet similar to that for PKU but with low levels of the branched-chain amino acids is started as soon as the diagnosis is made. Normal brain development and good health result from early treatment; life-long adherence to the diet is essential. Urgent medical intervention may be required during illness, which may be precipitated by infection or stress.

3.2.3 Homocystinuria (HCU)

Screening case definition: to detect babies with Classical Homocystinuria (HCU).
The programme may not detect those babies with the milder variants such as those with pyridoxine (vitamin B_6) responsive HCU and babies with inadequate protein intake.

Homocystinuria results from the accumulation in blood of the amino acid methionine and one of its metabolic products homocysteine. Homocysteine accumulates due to a deficiency of the enzyme cystathionine β-synthase. Homocysteine is toxic to the lining of blood vessels and predisposes the individual to thrombus formation, blood clots and a number of other complications including osteoporosis (thinning of the bones) and dislocation of the lens of the eye. Again the treatment is similar to that for PKU. For those individuals who adhere to the diet, the risk of developing any of the complications is greatly reduced. Approximately one in every 69,400 babies born in Ireland may have the condition or one baby every year.

The screening programme detects high blood levels of methionine. This is one of the more difficult conditions to detect, as the blood methionine level may not be raised initially. The methionine concentration is low in many baby foods, particularly in breast milk. The screening programme may not detect approximately one in every five babies born with this condition. There are a variety of reasons why this may occur. These include:

- Breast fed babies as there may be an inadequate intake of methionine in the feed to enable the blood methionine level to rise above the level for diagnosis.
- A milder vitamin B_6 responsive form of the condition. These patients usually have milder symptoms and disease progression is slower and they are unlikely to be detected by newborn screening.

Consequently, if protein intake is deemed to be suboptimal, a further sample should be taken on or about day 10 of life for Homocystinuria screening. All babies or children who present clinically in later life with signs and symptoms suggestive of Homocystinuria, such as dislocation of lenses, osteoporosis or inappropriate tall stature should have the disorder excluded formally by measuring plasma levels of methionine and total homocysteine using a standard amino acid analyser.

3.2.4 Classical Galactosaemia (CGAL)

Screening case definition: to detect babies with Classical Galactosaemia.
The programme tries to avoid diagnosing individuals with non-classical galactosaemia such as the Duarte/Galactosaemia variant as they usually remain asymptomatic throughout life.
The NNBSP does not screen for Epimerase or Galactose Kinase deficiency.

Classical Galactosaemia is an autosomal recessive condition caused by the deficiency of the enzyme galactose-1-phosphate uridyl transferase. This enzyme is important for the breakdown of galactose, one of the two sugars that make up lactose in human and cow's milk. Approximately 1 in every 16,200 babies born in Ireland each year may have this condition. However, it is particularly common among babies born to Irish Traveller parents in whom the incidence is approximately 1 in 450 births. Consequently, in the non-traveller Irish community the incidence is about one in every 36,000 births.

If not detected and treated during infancy, the disorder may cause damage to the liver or there may be an increased risk of infection, which may be life threatening. As a result of the condition, galactose and its metabolite galactose-1-phosphate accumulate in blood. Galactose-1-phosphate is extremely toxic. The baby may present with jaundice and there may be a bleeding disorder with a tendency to bleed spontaneously. The affected baby may also develop an *E coli* infection of the blood, septicaemia or present with cataracts in their eyes. Early detection and treatment with a lactose or galactose-free diet will prevent the early clinical complications of the disorder; some of the longer term complications, such a dyspraxia, ataxia or reduced fertility in women, may still occur in older children and adults despite dietary treatment.

Because the condition is more common in babies born to Irish Traveller parents and to siblings of known cases, a special screening test, the Beutler test, is offered to all these babies at birth (preferably Day 1 of life). Parents/legal guardians are advised to keep baby on a galactose free feed (Soya-based) until the result of the Beutler test is available. This protects the baby should he/she have the condition. For those mothers wishing to breast feed, they should discuss this with their midwife as they can express their milk until the result of the Beutler test is available.

Clinicians should never depend upon the general population screening for the diagnosis of Classical Galactosaemia, but should query this condition in any baby who presents early with jaundice and other symptoms suggestive of Galactosaemia e.g. vomiting, floppiness, hypoglycaemia, conjugated hyperbilirubinaemia or abnormal clotting of unknown cause.

3.2.5 Cystic Fibrosis (CF)

Screening case definition: to detect babies with Cystic Fibrosis (CF) who would have presented clinically with significant respiratory symptoms or fat malabsorption. The programme is not designed to detect individuals with minor respiratory symptoms or other symptoms, such as infertility in men due to congenital absence of the vas deferens.

Ireland has one of the highest incidences of CF in the World with approximately one in every 2,300 babies being affected. CF is also an autosomal recessive condition with both parents carrying an abnormal Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene.

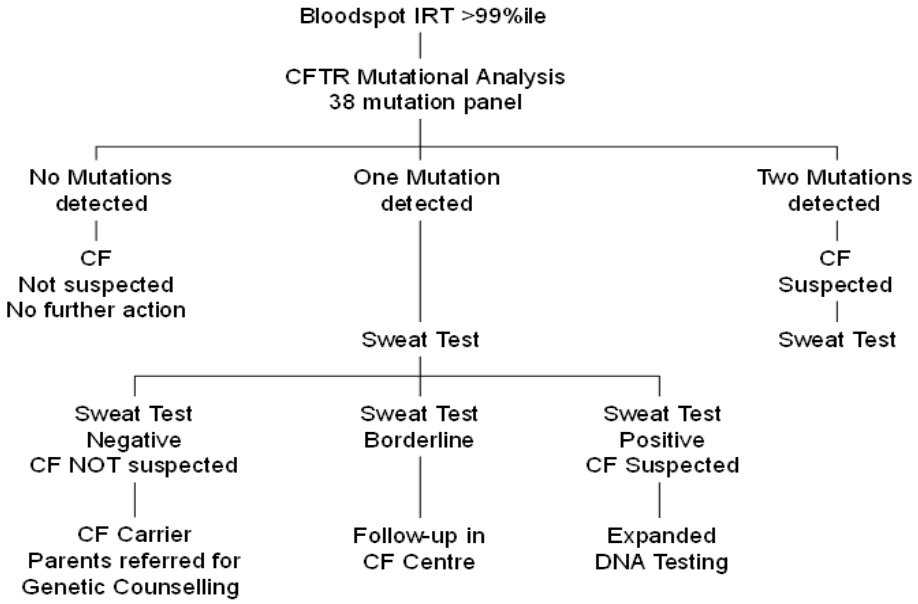
As a consequence of the condition, thick mucus secretions are produced by a number of organs including the lungs and pancreas; it is this thick mucus secretion which causes the problems. The thick secretions in the lungs may become infected, ultimately causing damage to the lungs. If the pancreas is involved this may cause diabetes mellitus, digestive problems and malabsorption of important vitamins. Consequently babies with CF may present with failure to thrive and frequent chest infections.

Newborn blood spot screening means that babies with CF are identified earlier; they can be treated with a high energy diet to improve weight gain and medicines and physiotherapy to improve lung function. Although a child with CF may still become ill, early treatment does improve their quality of life, significantly reducing the time that they have to spend in hospital; they can live healthier and longer lives. Specific treatment is now available for a significant number of persons with CF depending on the specific mutation affecting the CFTR gene.

The screening programme measures the blood level of immunoreactive trypsinogen (IRT). IRT is normally excreted by the pancreas into the intestinal tract, but in individuals with CF, it is regurgitated back into the blood due to the thick mucus secretions which block the pancreatic ducts. Levels of IRT may remain high in blood for about the first six weeks of life. If the blood IRT level is high the sample will be referred for CFTR mutational analysis. This DNA test screens for the presence of 38 possible mutations on the original bloodspot collected.

- If two CF mutations on the newborn screening sample are identified, then the baby probably has CF and this will be confirmed by a sweat test which will be organised and carried out by the babies local CF centre without delay.
- If one mutation is identified then a sweat test will be performed to determine whether the baby is a carrier of CF or has the condition. If the sweat test is positive, further DNA analysis will be undertaken to identify the second mutation.

Figure 1: Algorithm for Newborn Screening for Cystic Fibrosis



The 'sweat test' used to confirm or out-rule CF, measures the chloride concentration in sweat, and is usually performed before the fourth week of life in one of six designated HSE paediatric CF centres, based on the baby's address. The sweat test is considered the 'gold' standard for confirming the diagnosis of CF. As with some of the other conditions included in the screening programme, not all babies with CF will be detected by the newborn bloodspot screening programme. Milder variants of the condition may not be detected; some of these individuals may have a very benign clinical course which may not require treatment.

Note

- Newborn dried blood spot IRT screen for CF is not suitable for babies/children over six weeks of age.
- Babies with meconium ileus (MI) should be strongly suspected of having CF and followed up accordingly, including CF mutations at birth. These babies may have a normal CF screen (normal IRT). MI must be noted on the screening card.
- The Irish CF mutational genetic panel screens for 38 mutations chosen to reflect the Irish population, therefore babies of non-Irish ethnic origin are at increased risk of non-detection within the Irish programme, particularly if parents are consanguineous.

3.2.6 Congenital Hypothyroidism (CHT)

Screening case definition: to detect babies with congenital hypothyroidism, with either thyroid agenesis or dysgenesis or dyshormonogenesis, based on the results of a Technetium-99m pertechnetate thyroid scan. The programme is not designed to detect minor aberrations of thyroid function in the newborn.

Unlike the other conditions, CHT is a congenital rather than an inherited condition, in the majority of cases. This is an endocrine condition, which results from failure of the thyroid gland to produce the hormone thyroxine. There are a number of different forms of the condition. Some babies may have a very small thyroid gland or no gland at all while others may not be able to make thyroxine. It is important to identify the cause; this can be done by performing a thyroid scan soon after the diagnosis has been made and usually before treatment has been started. Approximately 1 in every 2,300 babies born in Ireland may have the condition; early detection allows for early treatment and the prevention of symptoms.

The diagnosis is made by measuring blood thyroid stimulating hormone (TSH), high levels of which are suggestive of the condition. However, TSH rises in blood immediately after birth and then falls to normal by about the second day of life. This is one of the reasons why the heel-prick sample should not be taken before 72 hours after birth, otherwise a false-positive result for congenital hypothyroidism may occur.

The majority of babies with congenital hypothyroidism require thyroid hormone replacement. Some babies will be reviewed between two and three years of age at which time a small number may be able to discontinue treatment under medical supervision. Otherwise treatment is for life and the dose of thyroxine adjusted as the baby grows.

Compared to some of the other conditions, the frequency of false positive results for CHT is relatively high. Consequently the number of requests for repeat blood samples is also high. Possible reasons include:

- A transiently raised TSH concentration, which returns to normal in time. These babies may require a number of repeat samples to be collected.
- Hypothyroidism is more common in babies and children with Down Syndrome, as a result a disproportionate number of repeat samples may be requested from these babies as they may have a transiently elevated plasma TSH level during the newborn period before developing hypothyroidism later.
- Babies, who have had surgery before having the screening sample taken, may have a transiently elevated plasma TSH level. This may occur as some antiseptic skin preparations contain iodine which may be absorbed through the skin and cause transient hypothyroidism. This occurs more commonly in premature babies.

3.2.7 Medium Chain Acyl CoA Dehydrogenase deficiency (MCADD)

Screening case definition: to detect babies with MCAD deficiency (MCADD).
Not all babies with MCADD will be detected by newborn screening, patients carrying c.199T>C mutation in combination with c.985A>G or another mutation have been shown to have significantly lower acylcarnitine markers compared to other genotypes and there is a potential for false negative screening result. Also older infants with MCADD (greater than approximately one month of age) may have C8 levels below the screening cut-off and there is a potential for false negative screening result. Babies with carnitine depletion and very low concentration of free carnitine might not be detected by the newborn screening programme.
If a baby is on IV/Glucose or dextrose a false negative screen may be reported for MCADD. It is imperative that this is noted on the screening card.
It must be noted that rarely, a baby may present clinically before results of a newborn screening are available.

MCADD is an autosomal recessive inherited defect of fatty acid oxidation due to deficiency of the enzyme medium-chain acyl-CoA dehydrogenase. This enzyme is required for the metabolism of medium-chain fatty acids and is necessary to enable the body to use its own fat reserves to produce energy in periods of fasting or stress.

Symptoms are not apparent at birth and about one third of cases of MCADD remain asymptomatic throughout life, however, symptoms can develop very quickly in affected infants who are not feeding well. Complications typically arise during periods of stress caused by an illness, fasting or vomiting, when the infant needs to break down fat quickly.

Episodes of metabolic decompensation can be prevented through avoidance of fasting, and monitoring of the infant to determine 'safe' time periods between meals and following a strict feeding schedule. MCADD mainly presents before the age of two years with a mean age of thirteen months, although neonatal presentations have also been reported.

Hypoglycaemia and a decompensated state develop which can result in serious life threatening symptoms including seizures and brain damage. When diagnosed within the newborn period and started on treatment, these babies grow up healthy and well. However, without treatment this condition may cause intellectual or physical disability or even death.

3.2.8 Glutaric Aciduria Type 1 (GA1)

Screening case definition: to detect babies with GA1. The programme may not detect all babies with GA1, particularly those who excrete a low concentration of glutaric acid (low excretors) and those with very low concentration of free carnitine.

Glutaric aciduria type 1 (GA1) is an autosomal recessive inherited condition caused by a deficiency of the enzyme glutaryl-CoA dehydrogenase (GCDH). With this condition the body is unable to break down certain proteins properly. It is an organic acid condition as it can lead to harmful amounts of organic acids and toxins in the body. If left untreated it can cause brain defects or even death, however if the condition is detected early in life and proper treatment begins children with GA1 can lead healthy lives.

The enzyme GCDH is involved in the decarboxylation of glutaryl-CoA, which is an intermediate in the breakdown of the amino acids lysine, hydroxylysine and tryptophan. Defective catabolism causes the toxic accumulation of glutaric acid, 3-hydroxyglutaric acid, glutaconic acid and glutaryl carnitine.

Over 150 disease causing mutations have been identified; of these the R402W mutation is the most prevalent among Caucasians. Most mutations, including the R402W mutation, are associated with undetectable GCDH activity and excretion of high amounts of glutaric acid. However, mutations that lead to varying levels of residual GCDH activity and low excretion of glutaric acid have also been reported. Consequently, patients with GA1 can be divided into two biochemically defined subgroups low or high excretors, based on the levels of glutaric acid present in the urine.
About 70% of patients (including both low and high excretors) have an encephalopathic crisis, which is most common at around nine months, with 90% by age two years. These are usually precipitated about 1–3 days after onset of a non-specific intercurrent illness, gastrointestinal infection or pneumonia and lead to dystonia and dyskinesia as permanent sequelae but with relative preservation of the intellect.

4 Responsibility for ensuring all babies are offered newborn bloodspot screening

Newborn bloodspot screening is an integral part of the health service provided to newborn babies. Screening involves the co-operation of many agencies involved in sample collection, sample transport, sample analysis and recording of results to the referral and management of those babies diagnosed with one of the conditions. It is a complex process ensuring that all babies born in hospital or in the community are offered screening and followed-up until the screening process has been completed.

Ref.: HSE Standard Operating Procedure for Maternity Hospitals/Units and Primary Care Services delivering the National Newborn Bloodspot Screening Programme.

Figure 2: National Governance Structure for Child Health Screening and Surveillance Programmes

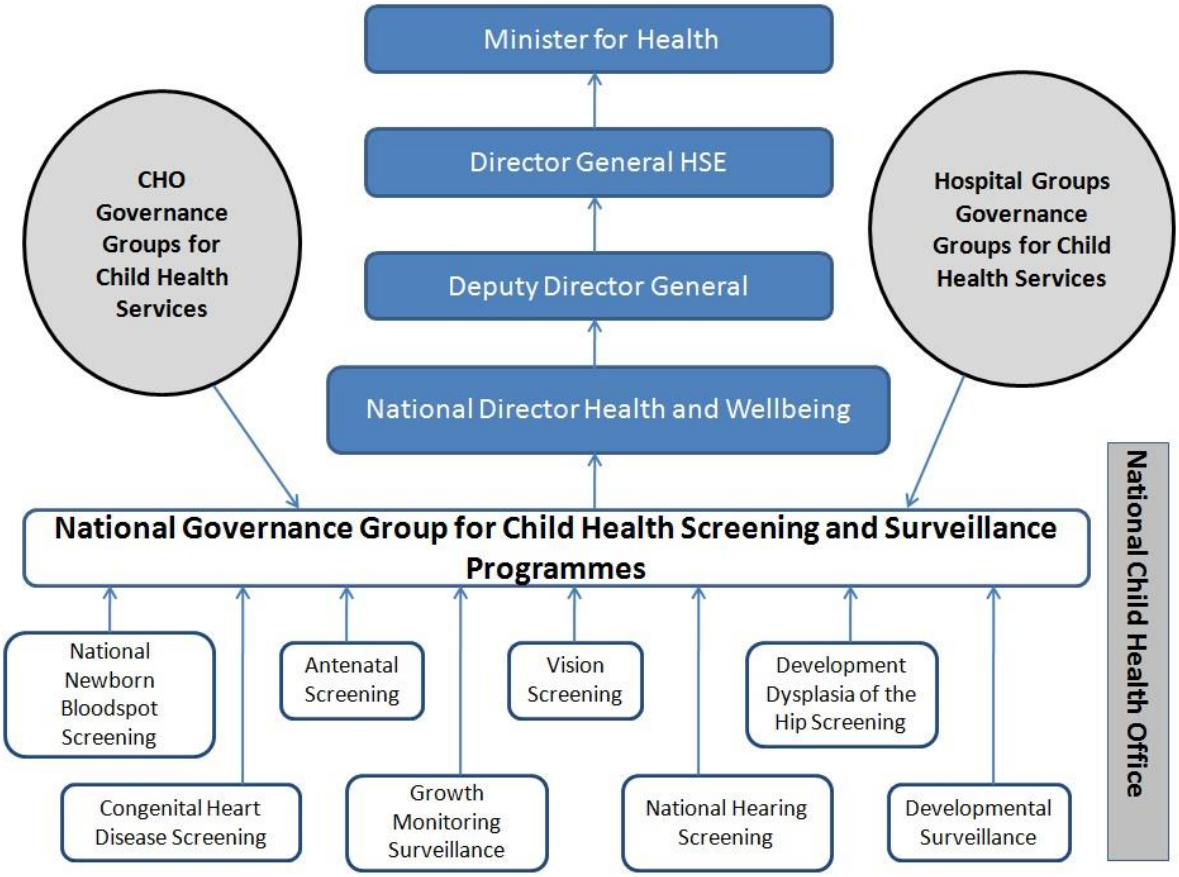
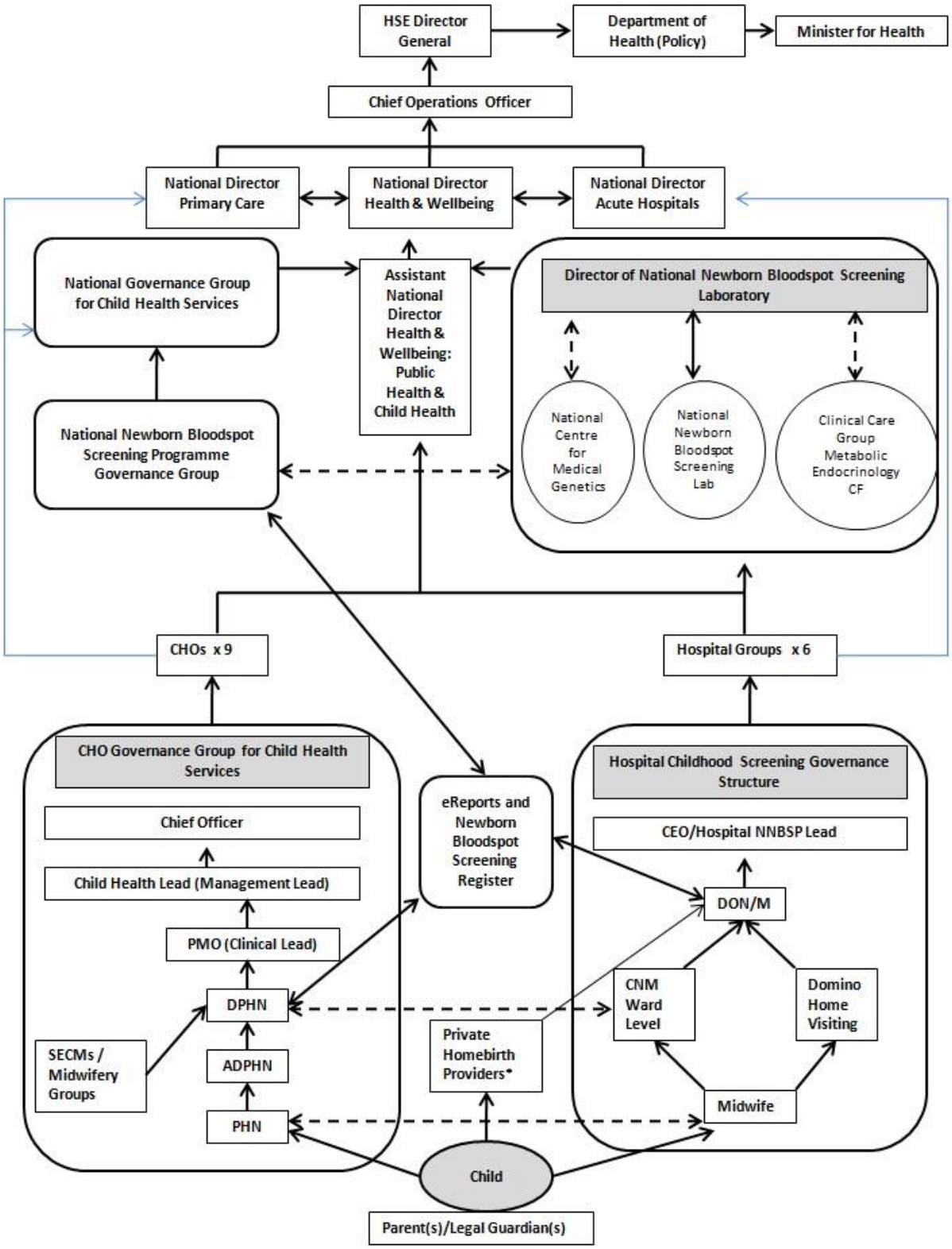


Figure 3: National Newborn Bloodspot Screening Governance Structure



4.1 Responsibility of the Health Service Executive

The ultimate responsibility for ensuring that all babies are offered screening in accordance with agreed protocols and procedures rests with the HSE and the Assistant National Director of Health and Wellbeing – Public Health and Child Health, who chairs the national newborn bloodspot screening programme (NNBSP) Governance group. The Director of the national newborn bloodspot screening laboratory (NNBSL) is responsible for the day to day coordination and management of the programme.

4.2 Responsibility and role of the NNBSP Governance Group

The NNBSP Governance Group is responsible for providing multidisciplinary advice to the HSE regarding technical and operational aspects of the programme and to the Director of Childhood Screening regarding strategic direction, policy and quality standards, funding objectives, legislation reviews and documentation relating to the programme, such as referral guidelines, manuals for practitioners, guidelines for storage, retention and use of residual bloodspots etc. The Governance Group is responsible for coordinating a quality assurance programme in partnership with health professionals and parents and monitors and facilitates improvements in the quality of the screening processes and their outcomes for parents and babies. The Governance Group is also responsible for supporting the development of information and training resources for health professionals and parents.

4.3 Responsibility of Community Healthcare Organisation (CHO) Child health leads

The CHO Child Health Leads are responsible for ensuring that all babies born and residing in their CHO are offered screening and that structures for the timely checking and recording of the test results are in place. The CHO Child Health Leads are also responsible for reporting newborn screening uptake and coverage to the NNBSP Governance Group.

4.4 Responsibility of maternity units and maternity hospitals

Directors of Nursing/Midwifery in maternity units/hospitals are responsible for ensuring that all babies born in hospital are offered screening. If the test is not performed in the maternity unit/hospital before discharge, hospital staff are responsible for ensuring that the baby is screened either by returning to the maternity unit/hospital or in the community, by informing public health nurses (PHNs). The maternity unit/hospital informs the PHN Nursing Service of the discharge and the requirement for newborn bloodspot screening.

Biohazard samples: The maternity unit/hospital must inform the PHN Nursing service if the newborn screening sample is to be flagged as biohazard due to maternal infection, the nature of the infection does not need to be disclosed. It is sufficient to enclose the sample 'fully dried' in a biohazard bag, the outer envelope for posting should not be labelled biohazard.

4.5 Responsibility of the public health nursing service in the CHO

Directors of Public Health Nursing (PHN) are responsible for ensuring that the screen is carried out in their Local Health Area (LHO) following notification from the maternity unit/hospital, on babies residing in their designated area. The Directors of PHN are also responsible for the timely recording of results in the newborn screening register including details of those babies who require follow-up, repeat sample or further investigation.
Babies born in Northern Ireland but with an address in the Republic should have a screening card taken and sent to the NNBSL, Temple St. Dublin.

N.B In the case where the maternity hospital/unit requests a repeat sample on a newborn and the NNBSL have already reported a 'Not suspected' result on that baby, the request from the maternity unit must be followed up. The NNBSL cannot override this request for a repeat from the maternity hospital/unit staff.

N.B. Parents can request and are entitled to a copy of results from their PHN

4.6 Responsibility of General Practitioner's, self-employed community midwives and private midwifery groups

General Practitioners (GP), self-employed community midwives (SECMs) and Private Midwifery groups are responsible for performing the NNBSP screen in accordance to agreed HSE protocols and procedures and for dispatching the newborn bloodspot screening card to the NNBSL as soon as possible after collection in accordance with packaging transport regulations (see sec 9.0). GPs rarely take heel prick samples and should contact the NNBSL for advice; they should also ensure they have an 'in date' newborn screening card if taking samples.

N.B.: The dispatching of the sample is the responsibility of the sample taker and should not be delegated to the parents.

4.7 Responsibility of parents/legal guardians

Parent(s)/legal guardian(s) are responsible for their baby and their participation in the NNBSP. In the case of parent(s)/legal guardian(s) opting out of the NNBSP and having been informed by healthcare practitioners of the potential consequences to their baby in so doing, the responsibility for any possible adverse consequences of their decision lies with the parent(s)/legal guardian(s). They must be requested to signify their decision to opt-out in writing by completing the Opt-out Form (see Appendix) A copy of the completed form must be retained by the parent(s)/legal guardian(s) and a copy forwarded to the Directors of Midwifery/Nursing and Public Health Nursing, the NNBSL and the baby's GP.
If parent(s)/legal guardian(s) change their mind in the future, it is their responsibility to bring this 'change of mind' to the attention of the PHN or their GP.

4.8 Responsibility of the national newborn bloodspot screening laboratory (NNBSL)

The NNBSL is responsible for managing the programme on a day to day basis within the parameters and standards laid down by the Director of Childhood Screening and the NNBSP Governance Group. The NNBSL is responsible for overseeing the quality management system and reporting activities of the screening programme and ensuring that all screen positive cases are referred to the appropriate clinical care team within agreed standards and procedures and that a definitive diagnosis is ultimately made.

The NNBSL is responsible for providing on-going training and education where possible for all staff involved with the programme within agreed standards as required. The NNBSL also liaises with the individual clinical care groups to ensure that appropriate clinical audits are performed, thus optimising screening outcomes.

5 Consent for Newborn Screening

5.1 General overview

The Irish newborn bloodspot screening programme screens for conditions that if not identified and treated promptly can have devastating consequences for the infant such as disability and possibly premature death. The newborn bloodspot screening or 'heel-prick' test should be offered to all infants through their parent(s)/legal guardian(s). All infants who are born in Ireland, or who enter the country before the screen would have been performed in their country of origin if they are under one year of age, are eligible.

As per current legislation and the 31st Amendment to the Constitution, the NNBSP Governance Group regards the best interest and welfare of the infant as the paramount consideration but is cognisant of the 2001 Supreme Court case of North Western Health Board v HW/CW. The 31st Amendment to the Constitution which involved the addition of Article 42A and governs the legal position around parental decision making has not yet been definitely tested by the Irish Courts.

The HSE National Consent Policy is also available for reference by staff and has recently been updated. Consent is also covered in the Nursing and Midwifery Board of Ireland Code of Professional Conduct and Ethics (2014).

5.2 Consent and responsibility for obtaining consent

Parent(s)/legal guardian(s) must be given the appropriate verbal and written information and sufficient time to make an informed decision. The HSE Parent Information Leaflets are available and should be given to parents during the third trimester of pregnancy by

midwives and again when the newborn bloodspot screening sample is being taken. Parent(s)/legal guardian(s) should also be given the top page of the newborn bloodspot screening card which contains information about the newborn bloodspot screening programme.

The sample taker is responsible for ensuring that appropriate consent is obtained and for informing the parent(s)/legal guardian(s) that by signing the newborn bloodspot screening card the parent/legal guardian is:

- confirming that they have read the parent information leaflet
- verifying that the details on the newborn bloodspot screening card are correct
- consenting to the screening blood sample being taken
- agreeing to the storage of the newborn bloodspot screening card as per current Department of Health recommendations

N.B. It is important to note that the National Newborn Bloodspot Screening Laboratory has a duty of care to analyse all newborn bloodspot screening samples they receive irrespective as to whether they are signed by a parent(s)/legal guardian(s) or not. It is the responsibility of the sample taker to ensure that signed consent is obtained when taking the sample.

5.3 Who can give consent

- **Married parents**

If the mother and father are married at the time of the birth then either can give consent to screening as they are joint guardians of the infant as per Section 6 of the *Guardianship of Infants Act 1964*.

- **Unmarried parents**

If the mother and father are unmarried at the time of the birth, only the mother can give consent as per Section 6 (4) of the *Guardianship of Infants Act 1964*.

If the mother is unavailable to sign the consent, i.e. through illness or hospital transfer, the unmarried father cannot sign the consent. In these cases, the sample taker should make every effort to contact the mother to get verbal consent and to document this in the relevant clinical notes/child health record. This may include liaising with the mother's medical team to obtain developments on her condition and position to provide consent for the newborn bloodspot screening sample to be taken.

If the mother is not contactable, for example due to severe inpatient medical illness, then the HSE must act in the best interest of the infant which would be to take the newborn bloodspot screening sample and inform the mother as soon as possible as to the decision taken and to record that in the child health record. If appropriate, this should ideally be in discussion with the father or primary care giver of the baby to ensure that they are aware of the need and benefit of newborn bloodspot screening.

If the infant has been discharged home to the care of the father and the mother is too unwell to be discharged, the father should be instructed to bring the infant back into the hospital to obtain consent from the mother and then proceed to take the newborn bloodspot screening sample. This is similar to bringing infants back into hospital in areas where there is no weekend public health nursing service.

Registered Public Health Nurses (RPHNs) arranging a house call to perform the newborn bloodspot screening must insist on the mother being present. Grandmothers or other relatives/friends cannot provide written consent.

If a Midwife is taking the newborn bloodspot screening sample in hospital and the mother is not present on the ward, they should return when the mother is present.

5.4 Other circumstances

If there is social work involvement at the time of birth, the social worker should link with the Midwife or Public Health Nurse and the mother to ensure that informed consent is obtained to perform the newborn bloodspot screening. However, in the absence of a full care order, only the parent(s)/legal guardian(s), or the mother if unmarried, can provide consent. An interim care order is not sufficient.

Other circumstances which more than likely will not apply to newborn screening due to the timing but are worth noting include:

- Surrogacy: The surrogate mother has legal responsibility for the newborn until the infant is legally adopted
- Same sex parents: Male or female (not the birth parents) - the birth mother has legal responsibility until the infant is legally adopted by the same sex parents who then become the legal guardians.

5.5 Literacy difficulties

If the parent(s)/legal guardian(s) has literacy difficulties they can be asked to make a mark on the newborn bloodspot screening card to indicate that they have been fully informed about the benefits and risks of newborn bloodspot screening. The same applies if parent(s)/legal guardian(s) decide to sign the opt-out form.

If parent(s)/legal guardian(s), in this case married parents, disagree as to the provision of consent for newborn bloodspot screening the HSE National Consent Policy provides guidance on this.
Parent(s)/legal guardian(s) should be advised that they have a responsibility to discuss the matter and reach an agreement between themselves as quickly as possible with the assistance of HSE advocacy services and a third party mediator if required. If agreement is not possible then the services should generally not be provided to the infant unless it is deemed by the health and social care professional to be necessary to safeguard the infants

best interests – in the case of newborn bloodspot screening it is clearly in the infants best interest to take the newborn screening sample.

5.6 Right to opt-out of newborn screening

Parent(s)/legal guardian(s) do have the right to opt-out from the newborn bloodspot screening programme on behalf of their infant. If married, either parent can decide to opt out. If unmarried, only the mother can decide to opt out. However, they should be clearly counselled and fully informed about acting in the best interest of their infant's health. If parent(s)/legal guardian(s) do decide to opt-out, it is essential that they are fully informed of the potential clinical consequences to their infant. Parent(s)/legal guardian(s) must sign the National Newborn Bloodspot Screening Programme Opt-Out form (available on www.newbornscreening.ie).

Parent(s)/legal guardian(s) must be informed that they may change their mind in the future but that it is their responsibility to make their change of mind known to either the PHN or their GP. They must also be aware, that depending on the age of the infant at this point, it may alter how and for what conditions can be screened for.

5.7 Informing parent(s)/legal guardian(s) about the programme

Parent(s)/legal guardian(s) should be told:

- About the nature of the conditions included in the screening programme.
- They must be reassured that, with early detection and treatment of most of the conditions, their baby will develop essentially normally providing that they and then the child/adolescent adheres to the medical advice and treatment given.
- If these conditions are detected soon after birth, treatment can be started early and significant handicap and possibly premature death can be prevented. Treatment is essentially by modification of the diet under careful medical supervision or by drugs, as for congenital hypothyroidism or treatment for the prevention of complications as for CF.
- That a further sample may be required, either to check the first result or because of an equivocal result or a technical problem in the first analysis, such as a borderline result, an insufficient quantity of blood collected, a contaminated sample or assay interference.
- A further sample may be requested if the identity of the baby is unclear; this can occur if the screening card is not filled in accurately – this is particularly important for twins, triplets etc. It is important to record on the card the rank of the baby, twin 2 of 2, recorded as 2/2.
- That parent(s)/legal guardian(s) of babies with a positive result will be contacted directly, usually by the maternity unit/hospital; clear instructions on how to proceed will be given.
- The screening card will be retained at a secure site by the HSE for the benefit of their child and the screening programme.

Depending on the condition, parent(s)/legal guardian(s) may be asked to bring their baby immediately to hospital, usually to Temple Street Children's University Hospital, Dublin where the baby may be admitted for a period of time while treatment is commenced.

If the baby is suspected of having CF, they will be contacted by a CF Nurse Specialist from one of the six HSE designated paediatric CF Centres and asked to bring their baby in the following day for further tests.

5.8 Retention of the Newborn Bloodspot Screening Card

After screening, the NBSC is stored at a secure site by Temple St. on behalf of the HSE as part of the baby's health record, after which time it may be disposed of (pending decision from the Minister for Health). After screening the sample may be used to:

- Check the results of the screening test or to perform other investigations recommended by the child's doctor, for which parent(s)/legal guardian(s) will be asked to give their signed consent.
- In the event of sudden unexpected death, consent may be obtained from the State Coroner.
- For quality assurance purposes and to help improve the screening programme as approved by the HSE. In such circumstances, all samples will be completely anonymised and it will not be possible to trace any result back to an individual baby.

N.B. Newborn screening cards are never used for commercial purposes.

5.9 Data protection legislation and newborn bloodspot screening

Under a Service Level Agreement between the NNBSP Governance Group and Temple Street Children's University Hospital (TSCUH) the NNBSL manages the programme on behalf of the Governance Group on a day to day basis. TSCUH acts as the Data Controller under the terms of the Data protection legislation on behalf of the NNBSP Governance Group, retaining baby demographic details and a copy of the results as part of the baby's record.

5.9.1 Access to the database

Access to the database is password protected and restricted to scientific and secretarial staff working in the NNBSL and to a third party who supplied and maintains the software. Maternity units/hospitals and local health offices have limited password protected access to data and results, only on babies born in their maternity unit/hospital or residing within their local health office through an electronic report handling system (eReports).

5.10 Return or disposal of newborn bloodspot screening cards

Parent(s)/legal guardian(s) may request that the newborn screening card be returned or disposed of. It is the NNBSL policy to retain all samples for a minimum of six months before any return or disposal. Such requests must be made in writing to the; Risk management department, Temple Street Children's University Hospital, Dublin D01 YC67. Requestors will be asked to provide proof of identity, e.g. a copy of their passport or driving license and a recent utility bill and a copy of the baby's birth certificate.

Consent References

- Guardianship of Infants Act 1964
- Child Care Act 1991
- Thirty-first amendment of the Constitution (Children) Act 2012 – enacted April 2015
- Children and Family Relationships Act 2015
- North Western Health Board v HW/CW (2001) 3 IR 622 http://www.bailii.org/ie/cases/IESC/2001/90.html
- Paper of Emily Egan SC delivered to the Citizens Assembly 4th March 2017 (page 15 (https://www.citizensassembly.ie/en/Meetings/Emily-Egan-s-Paper.pdf)
- HSE(2016) National Consent Policy http://www.hse.ie/eng/about/Who/QID/Other-Quality-Improvement-Programmes/Consent/National-Consent-Policy-August-2017.pdf
- Nursing and Midwifery Board of Ireland (2014). Code of Professional Conduct and Ethics. Available at https://www.nmbi.ie/nmbi/media/NMBI/Publications/Code-of-professional-Conduct-and-Ethics.pdf?ext=.pdf

6 Sample Collection

General

Samples on all newborns must be collected by heel-prick irrespective of feed status, prematurity or clinical condition **between 72 hours and 120 hours after birth**, air dried and dispatched immediately to the NNBS Laboratory.

If the sample is collected outside this window (72-120 hours) it may adversely affect the result as follows:

- **Collected before 72 hours** – it is essential that all babies should receive an adequate protein and galactose intake before the sample is taken, otherwise a false negative result may occur, for this reason, the sample is taken after 72 hours.
- Also the TSH level (test used to screen for congenital hypothyroidism) may be transiently elevated immediately after birth; as a result, if the sample is taken too early (before 72 hrs.), some babies may have a false positive screen for congenital hypothyroidism.

- **Collected after 120 hours** – because the programme includes screening for Classical Galactosaemia, MCADD and MSUD, it is essential that samples are not collected too long after birth, otherwise some babies may present clinically before the results of the screening test are available.

Exceptions to 72-120 hours window are pre-transfusion samples and high risk screens

- For babies at high risk of Classical Galactosaemia (Irish Travellers or a family history of Classical Galactosaemia) take a sample on day 1 for 'BEUTLER' test, then a routine card at 72-120 hours
- Take a pre-transfusion sample on any baby that is due to have a red blood cell (RBC) transfusion especially premature/low birth weight / sick babies and pre-surgery, then take the routine card at 72-120 hrs.
- If there is a family history of a metabolic condition seek advice from the NCIMD on these occasions (phone 01 878 4317), and also take a routine card at 72-120 hours.

6.1 Feeds at time of sample collection

Babies should be established on full lactose and protein containing feeds for at least 24 hours before the heel-prick sample is collected, unless as specified above they are in the high risk group. Please contact the NNBSL (01 892 1804) for advice on feeds if unsure.

6.1.1 Breast fed babies

The sample should be collected between 72-120 hours in all babies including those who are breastfed. In view of the new conditions included in the newborn screening programme (particularly MCADD); there is no longer an emphasis on taking the sample at the end of the 72-120 hour window in breast fed babies.

If protein intake is deemed suboptimal (poor feeding) a further sample should be taken on or around day 10 of life. This is to ensure that protein intake has been adequate to reveal a positive screen for the amino acid disorders, particularly for HCU. Breast milk contains less protein than formula feeds and a baby with poor protein intake may screen false negative for HCU.

6.1.2 Babies on total parenteral nutrition (TPN), intravenous (IV) fluids and soya feeds

This should be clearly indicated on the screening card. These babies may not be on any galactose/lactose or adequate protein containing feed and the screen could give a false negative result.
TPN and soya feeds do not contain galactose, as a result babies on TPN or soya may produce a false negative result for Classical Galactosaemia (CGAL). A Beutler test can

be performed on these babies to out-rule CGal provided baby has not had a RBC transfusion, as a RBC transfusion will invalidate the test.
Babies on IV fluids may not have adequate protein and galactose intake and may result in a false negative for amino acid disorders as well as CGal.
CGal cannot be out ruled on transfused babies who have not had a pre-transfusion sample collected for the Beutler test, until the baby is established on full lactose/galactose containing feeds for a period of time to indicate a possible raised galactose level.
In the event where a baby remains on TPN/IV fluids and a Beutler could not be performed due to RBC transfusion, the baby should be monitored for clinical and laboratory signs (prolonged clotting times and raised liver enzymes) of galactosaemia when being established on lactose/galactose containing feeds.
If a baby is on IV/Glucose or dextrose a false negative screen may be reported for MCADD. It is imperative that this is noted on the screening card.

N.B: Feeds protocol for high risk (sibling) MCADD screens

It is essential to ensure that the baby maintains a good milk intake until results are available. If baby is well it should be bottle fed every 3 hours or if breast fed every 2-3 hours during day time and every 3 hours at night (at least 10 minutes on the breast).
Exclusively breast fed babies are particularly at risk in the first few days when the supply of breast milk is poor; top up feeds of expressed breast or formula milk may be necessary until a good milk supply is established. Seek advice from the metabolic clinical team in Temple St.

If oral feeds are not tolerated, or if the baby is unwell in any way, urgent referral should be made to a Metabolic Paediatrician for review and consideration of IV glucose.

6.2 Babies receiving red blood cell (RBC) transfusions

If a RBC transfusion is scheduled to be given before the routine 72-120 hr. screen is taken, a pre-transfusion sample should be collected to perform a Beutler test to out-rule CGal. A newborn screening sample should also be collected between 72-120 hrs. after birth regardless if the child has had a further transfusion.
Do not delay this 72-120 hr. sample due to transfusions.

For any further cards collected on these transfused babies, please allow 72 hrs. to pass post any further transfusions before taking any more cards.

If the baby received an intrauterine transfusion, this should be clearly stated on the screening card, as this will invalidate the result of the Beutler test and could give a false negative screen result.

NB. A RBC transfusion invalidates the Beutler test for Classical Galactosaemia as the enzyme measured is in the red cells.

6.3 Preterm and low birth weight babies

All premature babies (< 36 weeks gestation) should have a pre-transfusion sample taken if a RBC transfusion is planned or likely, to out-rule Classical Galactosaemia. These babies may not be established on full feeds for some time (may be on TPN and/or IV fluids) and a false negative may be reported. A routine sample should be taken between 72-120 hours after birth.

Further samples should be collected at regular intervals, usually to a maximum of four samples. Ensure final card is taken when baby is established on full feeds for a least 24 hours.
It is recommended to take a final card before discharge or when baby reaches 36 weeks gestational age. Please call the laboratory for advice if unsure (01 892 1804).
On some occasions additional samples may be requested by the NNBSL or Clinical team.

6.4 High Risk Screening

N.B. Note relevant family history on screening card and inform metabolic laboratory Temple St 01 8784670/4727

6.4.1 Siblings of a known confirmed positive case

Phenylketonuria (PKU)

A newborn screening sample (NBS) and a lithium heparin blood sample should be taken between 72-120 hrs. following birth AND another NBS sample on day 10.
If the 72 hrs. following birth is due to fall on a Saturday, then we recommend that the liquid sample is taken and sent to the Metabolic laboratory in Temple St on the Friday morning and laboratory phoned in advance, in order to avoid parental anxiety over the weekend.

Homocystinuria (HCU)

A NBS should be taken between 72 -120 hrs. following birth AND a lithium heparin blood sample taken at the same time for plasma methionine, total homocysteine and free homocysteine and be immediately deproteinised. A further lithium heparin blood sample should be taken on day 10 of life and again deproteinised immediately.
N.B. *For advice on sample deproteinisation, contact the Metabolic Laboratory in Temple St.*

Maple Syrup Urine Disease (MSUD)

A lithium heparin blood sample should be taken on **Day 1** after the second feed and then **DAILY** until established on full feeds. Urine should be tested daily for ketones. A routine NBS sample should be taken between 72-120 hrs. to test for the other conditions.
Then a further NBS card or lithium heparin sample at day 10. Staff at the NNBSL and the National Centre for Inherited Metabolic Disorders, Temple Street must be informed, prior to the delivery of the baby.

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)

It is very important that any baby at risk of having MCADD due to a relevant family history is tested at the earliest opportunity. The pregnancy should be discussed with the metabolic team in the National Centre for Inherited Metabolic Disorders, Temple St., early in the pregnancy for careful management of birth to minimise the risk of decompensation. Management at birth may depend on the presentation of the previous sibling.

A dried blood spot sample should be collected on a metabolic card at 24–48 hours for dried blood spot Acylcarnitine profile, indicate if baby is on IV fluids, glucose or dextrose and also collect a sample for urinary organic acids (5mls fresh urine, frozen, with no preservative added). Then take a routine sample, between 72-120 hours to test for all the other conditions and a repeat screening card at day 10.

It is extremely important that any baby at risk of having MCADD due to a relevant family history is tested at the earliest opportunity. The pregnancy should be discussed with the Metabolic Clinical Team for careful management of birth to minimise decompensating risk. Management at birth may depend on the presentation of previous sibling.

N.B.: Feeds protocol for high risk (sibling) MCADD screens
It is essential to ensure that the baby maintains a good milk intake until results are available. If baby is well it should be bottle fed every 3 hours or if breast fed every 2-3 hours during day time and every 3 hours at night (at least 10 minutes on the breast).
Exclusively breast fed babies are particularly at risk in the first few days when the supply of breast milk is poor; top up feeds of expressed breast or formula milk may be necessary until a good milk supply is established. Seek advice from the Metabolic clinical team in Temple St.

If oral feeds are not tolerated, or if the baby is unwell in any way, urgent referral should be made to a Metabolic Paediatrician for review and consideration of IV glucose.

Glutaric aciduria type 1 (GA1)

A dried blood spot sample, taken at 24–48 hours on a metabolic screening card for dried blood spot Acylcarnitine profile and urinary organic acids (5mls fresh urine, frozen with no preservative added). A routine NBS sample should be taken between 72 -120 hours to test for all the other conditions and a repeat screening card at day 10. Feeding routine needs to be established and the baby should continue with oral feeds.

Cystic Fibrosis (CF)

Soon after birth, an EDTA blood sample should be sent directly by the maternity unit/hospital (if parent(s)/legal guardian(s) request/consent), to the Department of Medical Genetics in OLCH, Crumlin, clearly stating the name and DOB of the affected sibling. Take a routine NBS screening sample at 72-120 hrs.
N.B. Blood IRT measurement is unsuitable for CF screen in infants older than six weeks of age.

Congenital Hypothyroidism (CHT)

Thyroid function tests should be performed on day three of life on a lithium heparin/serum blood sample (check local guidelines). The risks are dependent on the type of CHT. For those with dyshormonogenesis the risk is one in four, while those with a family history of thyroid agenesis or dysgenesis the risk is about one in 2,000, depending on the gender of the baby; thyroid agenesis/dysgenesis CHT is more common in girls than in boys.

Classical Galactosaemia (CGAL)

Sibling testing, known family history and Irish Traveller babies including settled travellers

The incidence of Classical Galactosaemia among members of the Irish Travelling community is high at one in 450 births.
To screen for Classical Galactosaemia, a NBS sample should be taken immediately after birth and before any blood transfusion has been given. A cord blood sample is not suitable.

The sample should be sent to the NNBSL for a 'Beutler Test'. This test measures the enzyme activity in red blood cells (this is why a RBC transfusion invalidates the test) and is NOT dependent of feeds. The sample should be clearly marked "FOR BEUTLER TEST". The Beutler assay is not performed as an emergency on-call investigation, unless clinically indicated. However, they are performed on Saturday mornings providing that the sample is received in the NNBSL by 10.00am. Special provision is made for Bank Holidays and long weekends. Two fully saturated circles are required.

N.B.: All *at-risk* babies should be fed with lactose/galactose free feeds (e.g. SOYA feeds) until the result of the Beutler test are known. The routine NBS sample should be taken between 72-120 hours following birth to test for the other conditions.

6.4.2 Baby born to a parent diagnosed with a disorder on newborn screening panel

Babies born to a parent with a condition included on the newborn screening panel are at high risk of having the condition, the risk being approximately twice the carrier incidence for the disorder within the Irish population. Irrespective of the condition, these babies should be screened as outlined above as if they were a sibling of a confirmed case for the specific condition.

6.4.3 Family history of a metabolic disorder in extended family

If there is a history of a metabolic disorder within the extended family other than a sibling, this should be clearly stated on the screening card to include the name of the disorder, in such circumstances please contact the NNBSL or NCIMD Temple Street for advice.

6.4.4 Cousin marriages within the Irish Traveller community

Some members of the Irish Traveller community might wish to seek genetic counselling advice; this can be arranged through the Department of Medical Genetics, OLCH, Crumlin.

6.5 Maternal phenylketonuria

Phenylalanine is actively transported across the placenta; the blood level in the foetus is about twice that of the mother. Therefore, women who themselves have PKU, should plan conception so that their condition is under optimal control at the time of conception. Regular and frequent monitoring of blood levels of phenylalanine and tyrosine are required throughout pregnancy in order to safe-guard the well-being of their foetus. Following the birth of the baby a liquid sample should be taken from the baby at the same time as the newborn screening sample (72-120 hrs.) and a repeat screening sample on day 10 of life.

6.6 Babies born to immigrant parents or refugees

6.6.1 Arriving before NBS has been performed in country of birth

All babies and infants of immigrant parent(s)/legal guardians, up to one year of age, who arrive in Ireland before any newborn screening test has been performed, should be screened for all the conditions on the Irish panel. Screening for CF by measuring blood IRT is not reliable for any infants over six weeks of age.

6.6.2 Arriving after NBS screen has been performed in country of birth

The sample taker should be aware that many countries including Northern Irelands newborn screening programme does not include screening for Classical Galactosaemia. If there is clinical concern of Classical Galactosaemia, then the Beutler test should be requested on a dried bloodspot. The full screening panel (excluding CF if baby over six weeks of age) can be performed on babies under one year of age.

Decision to screen is a local clinical decision, dependent on family history and country of origin of parents. Often a venous sample is taken and spotted onto the card as it may not be possible to take a heel prick sample, it is imperative that this sample is whole blood and has not been collected in a tube with any preservative (such as EDTA, lithium heparin etc.). For children greater than one year, screening can be performed (excluding CF screen) if there is concern raised by the Paediatrician.

If there is no documented evidence in the child's medical records that screening was performed please contact the NNBSL who may have a record and can advise.

The NNBSL on occasion performs TSH analysis on dried blood spot samples from Down Syndrome patients, as it is often less traumatic than a venous sample.

6.7 Babies presenting with meconium ileus at birth

Meconium ileus is a common complication in babies with CF, occurring in about 18% of all CF babies born in Ireland. Not all these infants present with a raised blood IRT (i.e. a positive CF screen) from the NBS screen. Therefore, CF should be considered in all babies who present with meconium ileus within the first days of life. An ETDA sample should be collected and sent directly by the maternity unit/hospital to the Department of Medical Genetics, OLCH, Crumlin for CF mutation analysis, giving full clinical information.
The routine NBS sample should be taken at 72- 120 hours to screen for the other conditions.

6.8 Procedure for infants over six weeks who have missed newborn screening for CF

Children who have missed the 72-120 hours window for newborn bloodspot screening (NBS) for logistical reasons, (clinical condition, lost screening card, delay in receipt in laboratory, etc.) can have their screen completed without delay when issues identified.

Immunoreactive trypsinogen (IRT) the screen for cystic fibrosis (CF) is not suitable if the infant is over six weeks of age. This applies to premature infants as well as term infants. Beyond six weeks of age the IRT value is not interpretable and a bloodspot sample is invalid for the purpose of CF screening.

Therefore, for children greater than six weeks of age who were missed or there was a problem with the sample, or the testing, such that no result for CF NBS is available, a sweat test should be performed to out rule CF.

The sweat test should be performed in one of the six specialist CF centres involved in accepting children for assessment as per the CF NBS programme. The following steps should be undertaken;

1. The individual aware of, or concerned that, a child has not been screened for CF as part of the CF NBS programme should inform the National Newborn Bloodspot Screening laboratory (NNBSL) in the Children's University Hospital, Temple St, Dublin.
2. The NNBSL should collect the relevant details of the infant involved, and the details of why screening was missed, and then contact the specialist CF centre nearest the baby's geographic catchment area to request a sweat test.
3. Contact with the specialist CF Centre should use the existing lines of communication for the CF NBS programme; i.e. a telephone call to the CF clinical nurse specialist (CNS) followed by faxed written details. This will be carried out by the NNBS laboratory.
4. The CF CNS will organise a sweat test and review by a CF Consultant as per the usual procedure for the CF NBS programme.
5. The specialist CF centre will provide the results to the parents/legal guardians and NNBSL as soon as they are available.
6. The NNBSL will inform the individual who highlighted the case that the infant has been assessed and will inform the maternity unit and the Director of Public Health Nursing in that area.

The procedure as described above does not apply to infants who had newborn bloodspot screening performed in another country which did not include CF NBS, and then moved to Ireland at a later date. These children should not be screened for CF, but should have a sweat test performed only if clinically indicated, such as if they develop clinical features, or have a strong family history of CF.
If unable to perform a sweat test, for example if skin condition deems it unsuitable, genetic analysis to be offered following parental consent.

7 Recording of Information

7.1 UPI and hospital codes and use of Eircodes

Until the HSE's Individual Health Identifier (IHI) is introduced nationally, the Unique Perinatal Identifier (UPI), issued by the maternity units/hospitals must be used to track each baby through the NBS process. The UPI consists of the three digit hospital inpatient inquiry (HIPE) code of the maternity unit/hospital of birth (see Table 2.) followed by the Healthcare Record Number (HCRN) of the baby. Babies born either at home or in a maternity hospital outside Ireland will be issued with a UPI by the Director of Public Health Nursing in the area in which the birth is registered following notification of the birth.

The same UPI must be used on all samples sent to the NNBSL, even when the baby is transferred to a paediatric hospital or another maternity unit. The HCRN of the paediatric hospital should also be included in the appropriate space on the NBSC.

N.B. Eircode: the Eircode should now be recorded in the appropriate boxes on the screening cards. This will in time be linked to the Local Health Office (LHO) to verify that the LHO on the sample is correct.

Table 2 HIPE Code Numbers for 19 Maternity Units/Hospitals

HIPE Code	Maternity Hospital / Unit	HIPE Code	Maternity Hospital / Unit
201	Midland Regional Hospital Portlaoise	724	Cork University Maternity Hospital
202	Midland Regional Hospital Mullingar	726	Kerry University Hospital, Tralee
301	University Maternity Hospital Limerick	800	University Hospital Galway
402	Cavan General Hospital, Cavan	802	Mayo University Hospital
500	Letterkenny University Hospital	919	Portiuncula Hospital, Ballinasloe
501	Sligo University Hospital	922	Our Lady of Lourdes Hospital, Drogheda
600	Waterford University Hospital	930	Coombe Women's Hospital, Dublin
601	St. Luke's General Hospital Kilkenny	931	National Maternity Hospital, Holles St, Dublin
605	Wexford General Hospital	932	Rotunda Hospital, Dublin
607	South Tipperary General Hospital, Clonmel		

7.2 Recording of results of newborn blood spot screen

The following steps must be adhered to, to ensure that adequate records are maintained in the hospital of birth in order to identify any baby who has not been screened before discharge:

a) A person should be nominated by the hospital to take responsibility for checking records
b) Details of each baby should be recorded in a single register
c) The register must indicate whether or not the test was performed and if there is follow up required
d) When the results of the test are returned from the NNBSL, the entry should be ticked in a different colour pen (if a manual procedure is used) or entered into the electronic register – therefore, any case where there is no report received from the NNBSL is noticeable at a glance and can be followed up
e) The person who checks the register to identify possible omissions should initial the entries to indicate that he/she has undertaken the exercise

N.B. Parents can request and are entitled to a copy of results from their PHN

7.3 Early discharges from hospital

The nurse/midwife discharging a baby from hospital before the screen has been carried out must ensure that the mother understands the importance of the screen and when the screen should be done.
If it is not appropriate to carry out the screen before discharge from hospital, the nurse/midwife should ensure that the baby is screened either:

- By returning to the hospital
- Or in the community. The nurse/midwife should notify the DPHN that the baby has been discharged prior to the screen being carried out to enable the PHN to take the NBS sample on those babies

The DPHN in the LHO/CHO in which the parent(s)/legal guardian(s) live is responsible for ensuring that babies, discharged from hospital prior to having the screen performed, have the screen carried out.

Weekend sampling varies across the country as not all areas provide a weekend PHN service and babies may have to return to the hospital for the sample to be taken.

7.3.1 Newborn bloodspot screening to be performed by PHN

If the screen is to be performed by a PHN, the following procedures should be followed:

(a) The ward manager should ensure that the appropriate DPHN has been notified that the screen is to be carried out. The Director should be provided with the full details of the baby, including the UPI. They should also be informed if either the baby or mother is being investigated for an infectious disease.

(b) The Director of Public Health Nursing should:

- Keep a register of requests from hospital/s;
- Request the appropriate PHN to perform the screen and to send the sample by registered post (and obtain a receipt of postage) to the NNBSL, Temple Street Children's University Hospital, Dublin D01 YC67.
- Notify the maternity unit/hospital where the birth took place that the screen has been carried out.

The NNBSL send a copy of all results both to the maternity unit/hospital and to the LHOs. For this reason, it is essential to ensure the LHO is correct.

If results are received back to an LHO that a baby does not reside in, an 'incorrect location form', can be completed and location changed, forms are available on the website or see appendix. The report will then be resent to correct area.

7.3.2 Newborn bloodspot screening to be performed by GP or independent midwife

If the screen is to be performed by a GP or an independent midwife, the following procedures should be followed:

(a) The DPHN must contact the GP or the independent midwife to ensure that the screen will be performed and sample sent by courier/registered post (retain proof of postage) to the NNBS Laboratory. It is the responsibility of the GP/independent midwife to arrange the transport of the sample; this should NOT be delegated to the parents.

(b) The NNBSL will send a copy of results to the maternity unit/hospital, the DPHN and to the GP / independent midwife if noted on the NBS sample.

(c) The GP/ midwife must contact the DPHN in cases of non-attendance by the parent(s)/legal guardian(s).

In the situation where a family have moved out of the area before the screen was performed, the DPHN must be informed of the circumstances as early as possible so that alternative arrangements may be made.

NB. It is not normal practice for GPs to take NBS samples and they do not hold a supply of cards. GPs should contact the laboratory for advice if performing newborn blood spot screening.

7.4 Transfer from maternity unit/hospital to tertiary referral paediatric hospital

The nurse/midwife responsible for the transfer of a baby from a maternity unit/hospital to a tertiary referral paediatric unit for continuing medical or surgical treatment before the NBS sample has been taken MUST inform the receiving unit and give them the baby's UPI.

The paediatric unit must have written procedures for:

- Performing the screen between 72-120 hrs. after birth
- Documenting that the sample has been collected
- Have a valid, in date card to collect sample on
- Be aware of necessity for signed consent
- Be informed about taking pre-transfusion samples
- Sending the sample to the NNBSL
- Recording the results in the baby's medical records
- Informing the maternity unit/hospital of the results of the screen and any request for repeat sampling or follow-up action

8 Procedure for taking the routine blood sample

The blood sample should be taken between 72 hours and 120 hours after birth

8.1 Equipment required

- Sterile lancet (metered tip no more than 2.5 mm in depth)
- Latex free gloves
- Gauze
- Newborn bloodspot screening card (NBSC) – card must be in date
- Envelope for dispatch to lab, water resistant and tear-proof (Tyvek or equivalent envelope)

8.2 Completion of the newborn bloodspot screening card (NBSC)

Ensure that the NBSC has been completed in full and that all the information is correct and legible, including the name of the baby. Particular care should be taken to distinguish twin, triplets etc. The NBSC must be signed by a parent(s)/legal guardian(s) before the sample is collected to show evidence of consent.

8.3 Technique for Sample Collection

a) Ask the parents to keep the baby's feet warm prior to sampling, by applying two sets of socks or placing a set of socks beneath the babygrow.
b) Read the instructions printed on the back of the NBSC.
c) Explain to the parent(s)/legal guardian(s) the reason for the screen and its importance to the baby's well-being.
d) Obtain consent (See Section. 5) if not already obtained.
e) Tear off the top information sheet and the <Parent Copy> from the NBSC and give them, along with the Parent Information leaflet, to the parent(s)/legal guardian(s); retain the <Nurse Copy> for filing in the child health record.
f) Ensure <Laboratory Copy> remains attached to the card.
g) Assemble the equipment and put on gloves. Do NOT touch the printed rings on the NBSC with gloves, as latex interferes with the Beutler Test and may cause a false positive result.
h) Preferably take the sample from the baby while the mother cuddles the baby on her knee or on her shoulder; this not only assists you but also comforts the baby. It also allows the mother the opportunity to ask questions about the screen.
i) Place a paper towel on the lap of the individual holding the baby.
j) Ensure that the heel is warm. Warm water, tested by the elbow of the sample taker, may be used.

k) Cleanse the heel thoroughly with warm (to touch) soapy water. Air dry the heel or wipe dry with gauze. Avoid using alcohol wipes to clean the skin as this may interfere with the formation of a blood drop.

l) Rub the skin for 1-2 minutes to increase blood supply.

m) Encircle the heel with finger(s) and thumb and squeeze gently until the skin looks taut and suffused with blood.

n) Press the lancet firmly against the side of the ball of the heel and trigger the sterile lancet.

o) Hold the foot downwards and gently massage the heel to encourage blood flow.

p) Touch the circles marked on the NBSC gently to the hanging drop of blood so that the blood soaks through from the back of the NBSC to the front:
   - blood drops must soak through from the back to the front of the card, filling all circles completely;
   - check that the blood has soaked completely through the circle on the front as well as the rear of the card;
   - do not press/squeeze the bloodspot to 'force' it through the NBSC as this can compress the blood cells and may require repeat.

q) Wipe away excess blood with gauze. Press clean gauze firmly onto the wound until bleeding stops.
   N.B. It is not recommended that a plaster is used as this may be a choking hazard if swallowed.

r) Ensure that the NBSC is air-dried before putting it into the envelope. Do not use excessive heating as this may invalidate the test. Failure to fully dry the bloodspot before placing it in the envelope may result in serum rings, invalidating the sample and thus requiring a repeat sample to be taken.

s) If a repeat sample is required for <u>one</u> test only, then <u>two well-saturated</u> bloodspots are sufficient, ensure sample is saturated through from back to front.

t)

N.B. The blood spots collected do not need to be the outside spots; they can be any of the four spots outlined on the card.

8.4 Sample collection from central line in sick babies

On occasion the blood sample may be collected from a central line. Ensure that sufficient blood is discarded prior to placing drops of blood on the NBSC. Failure to do this may result in a dilute sample and give false negative results.

8.5 Packing and dispatching the newborn bloodspot screening cards

a) Send the NBSC by registered post or by courier to the NNBSL using the yellow fluorescent address labels, to reach the laboratory as soon as possible after collection. Do NOT store or batch the completed NBSCs.
b) If more than one NBSC is placed in an envelope, they should be placed at 180^{O} to each other so that blood does not touch blood.
c) The sender MUST indicate how many NBSCs have been placed in each envelope and provide a separate list of the names of the babies and UPIs whose specimens have been included in each envelope.
d) Keep a record of all samples sent in each envelope; a sample checklist is available for downloading from the newbornscreening.ie website.
e) Dispose of lancets as per local guidelines; never enclose the lancet in the envelope with the NBSC. Please read Section. 9 on the transport of samples.

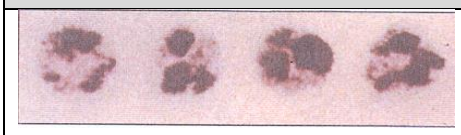
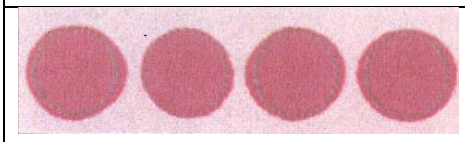
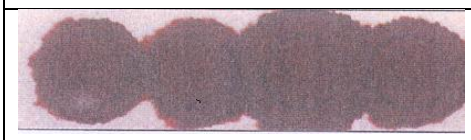
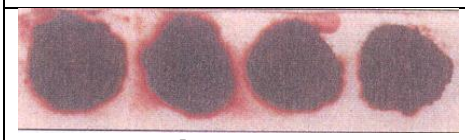
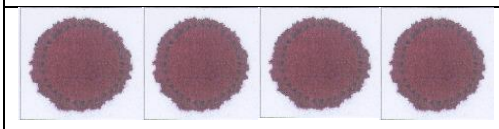
8.6 General tips on blood collection

- Alcohol wipes are not recommended – clean baby's foot with water.
- The heel must be clean prior to skin puncture to prevent skin infection and avoid contamination of sample, this is particularly relevant for CF testing as a false positive may result.
- Blood will flow more easily if the limb is lowered and warm.
- Alternative releasing of pressure for several seconds between squeezes should maintain blood flow.
- If blood flow stops, release pressure, lower the limb, wipe the puncture site firmly with gauze, wait ten seconds and then squeeze again gently.
- Do not use plasters over the puncture site – babies may swallow them; if they are used the mother must be warned of the potential risk.

8.7 Quality of the bloodspot sample

Please ensure that there is an adequate amount of blood on the NBSC that completely fills each circle. An inadequate amount of blood or a poor quality dried bloodspot will require the procedure to be repeated causing potential trauma to the baby, anxiety to the parent(s)/legal guardian(s) and inconvenience to the sample taker and may result in delay in making a diagnosis.

Figure 4: Quality of suitable and unsuitable dried bloodspots

Quality of Dried Bloodspot	Possible Causes/Comments
 **Insufficient sample**	Insufficient blood collected Blood should be soaked through from back to front to provide sufficient sample for analysis
 **Sample received wet**	Sample sent to laboratory before completely dry Wet samples can give a false result and pose a health and safety risk to staff
 **Sample over saturated/layered**	Applying layers of blood to card Applying blood to both sides of card
 **Sample appears contaminated**	Squeezing area surrounding puncture site Allowing card to come in contact with gloved hands or substances such as milk, hand lotion etc. Blood spot sample being compressed, causing cells to separate resulting in a diluted sample in the centre of spot
 **Sample shows serum rings**	Allowing card to come in contact with liquids e.g. hand lotion, water, milk. Drying specimen incorrectly, or dispatching to laboratory when still wet
 **Good quality blood sample with enough blood should a test need to be repeated**	**Sufficient amount of blood to soak through to completely fill all circles** **N.B**.: 3.2 mm punches are taken from the card, all assay parameters are based on a completely filled punch , this is why a fully saturated spot is essential

8.8 Why repeat blood samples may be requested

1. Insufficient blood on card for all or some of the screens to be performed.
2. Unsatisfactory sample quality – compressed/diluted sample, serum rings or contaminated
3. Abnormal, borderline or equivocal test result.
4. Baby too young when blood sample was collected, sample collected too early before 72 hrs. after birth.
5. Blood on the card not dried properly before being put into a plastic coated Tyvek® envelope, thus causing serum rings or a diluted sample.
6. There is a query about the identification of the baby or babies if multiple births.
7. The sample was taken on an expired card.
8. The card was delayed, greater than 14 days getting to the NNBSL and is too old for analysis.
9. The bloodspot portion of the NBSC and demographic portion were re-attached but NBSC barcodes do not match up.
10. The name on the bloodspot portion does not match that on the demographic portion of the card; the identity of the baby may need clarification or a repeat sample.
11. Sample is unsuitable for analysis if taken within 72hrs of a RBC transfusion.

N.B. It is the responsibility of the sample taker to tell the parents the correct reason why the repeat sample is required.

8.9 Problems with sample collection

Unlabelled or inadequately labelled specimens cannot be accepted for analysis. Red blood cell transfusions may invalidate the screen. Sample collection should be delayed for 72 hours if it is a repeat sample, but if it is the first card and it is in the 72-120hrs window, take sample and repeat 72 hrs. post any further transfusions.
All samples for the Beutler assay MUST be taken before a RBC transfusion is given, if possible; transfusion status must be clearly stated on the NBSC.

8.10 Bio-hazard samples

Newborns, whose mothers are known or suspected of being infected with an infectious disease e.g. HIV or Hepatitis B, MUST have the screen performed in the 72-120 hr. window.
The word ‘Biohazard’ may be noted on the card, but nature of biohazard should not be noted as it is not relevant to screens being performed.

The sample should be placed in a biohazard bag (or ‘Biohazard’ noted on bag/envelope) once completely air dry. The outer envelope does not require the UN3373 sticker, and ‘Biohazard’ does not need to be noted on the outer envelope.

NB: All samples received 'wet' pose a health and safety risk to staff and may give a false result, due to possible sample contamination or separation, please allow cards to fully air-dry.

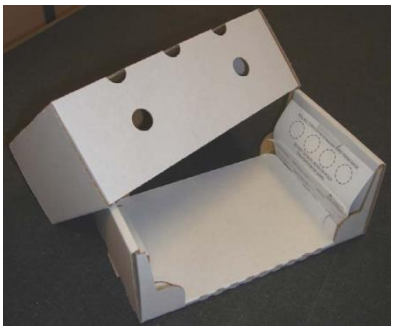
8.11 Completion of newborn bloodspot screening card at time of discharge

It is the practice of some maternity units/hospitals to give the NBSC to the parent(s)/legal guardian(s) either completed or blank at the time of discharge from hospital. It is the responsibility of the sample taker to check that ALL the details are correct, including the date and time of collection. In addition, the name of the baby, both surname and first name may have changed since discharge and these corrections MUST also be made.

9 Transport / drying boxes and pre-printed plastic envelopes

The NNBSL has designed drying/transport boxes in conjunction with Mega-Pak Ltd, to facilitate the transport of samples from the baby's home to the PHN's car in a safe manner. Once the bloodspot has dried, the sample should be removed from the box and packaged according to the regulations. These boxes can contain two cards and are reusable. However, if they become contaminated with blood they should be disposed of either by incineration or through the accepted procedure for disposal of hazardous waste.

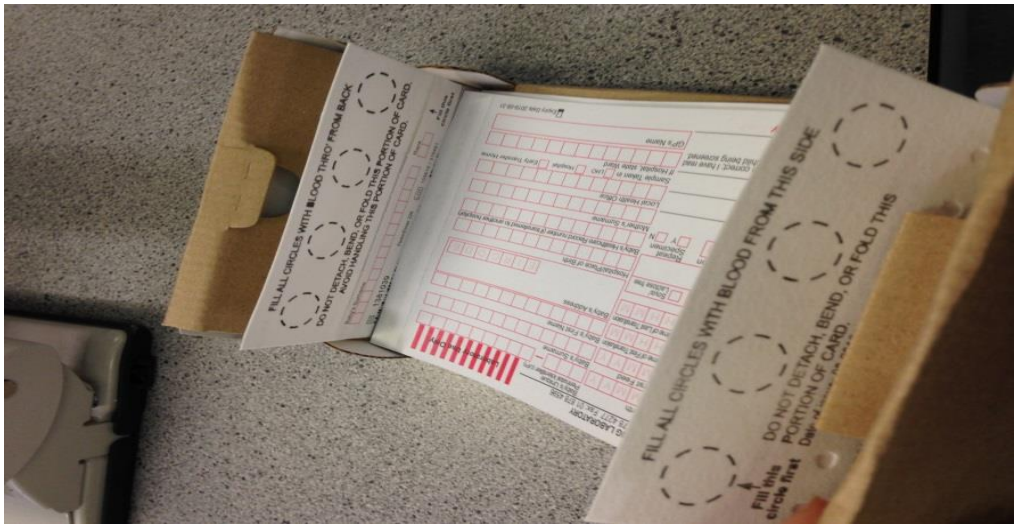
These boxes can be ordered directly from Mega-Pak Ltd – the minimum order is 150 boxes, flat packed in batches of 50.



Mega-Pak Ltd (Irish Office)
16 Highfield Green
Swords, Co. Dublin

Tel: +353 (0) 1 840 2063
Fax: +353 (0) 1 840 2063
e-mail: megapakireland@eircom.net
Website:www.mega-pak.com

Figure(s) 5: Transport/Drying Box



9.1 Procedure for transporting samples

The sender of samples by registered post or by courier is responsible for ensuring that the packaging and transportation of the sample complies with current transport regulations regarding Health and Safety as laid down in the European Directive (ADR 2015) Packaging Regulations P650. Dried bloodspots must be packaged appropriately. NNBSL recommends that once the blood has dried, the sample should be inserted into a water resistant, tear proof Tyvek® envelope or equivalent. The yellow fluorescent address label should be fixed to the outer envelope.

9.2 Pre-printed registered envelopes

Pre-printed plastic envelopes may be purchased directly from An Post by e-mailing customer care at An Post.

Please send an email for the envelopes to customer care, stating the amount of envelopes required and quoting a HSE purchase order number.
A Pro Forma invoice, with the HSE purchase order number as reference, will then be returned to enable payment by EFT. Once the EFT payment has reached An Post's bank account the Philatelic Section will despatch the order.

9.3 Responsibility of sender

If more than one screening card is put in an envelope, they should be placed at 180^{o} to each other (i.e. the bloodspots should not overlap and therefore not touch). The sender should state in writing how many cards are in each envelope and include a list of the names of the babies; a sample checklist is available to download from www.newbornscreening.ie

Screening cards, appropriately packaged, should be sent daily and not batched. It is the responsibility of the sender to dispatch the sample as soon as possible after collection, either by registered post or by courier. It is not appropriate to put the package into the post knowing that there may be a delay in it arriving at the NNBSL due to either a postal dispute (local or national) or over the Christmas period when the post is delayed. Alternative arrangements should be made by maternity units/ hospitals and CHO/LHOs to ensure samples are despatched to NNBSL without delay. Parents should never be asked to post or deliver samples to the NNBSL. This is the responsibility of the sample taker.

9.4 Red weather alerts

In the event of a red weather alert due to adverse weather conditions, the sample taker in conjunction with the ADOM / ADPHN must assess the risk of travel of either the PHN or the parent and baby against the risk of delayed screening. Further advice can be sought from the laboratory on such occasions.

10 Procedure for reporting results

All Newborn Screening reports are transmitted electronically via eReporting™ to

- The maternity unit/hospital of birth
- To the baby's LHO
- And to the referral or tertiary hospital if baby has been transferred and this is noted on the card

Therefore, it is essential that the correct LHO is recorded on the sample, and the parent(s)/legal guardian(s) residence Eircode.

eReporting™ is a secure data protected means of transmitting newborn screening reports. No paper copies of reports are now issued by the NNBSL. eReporting is password protected; only those with access to eReports can view results. It allows designated staff in the respective maternity unit/hospital and LHOs to review the reports in pdf format. The reports are available to view for 60 days from the date of issuing. They are then archived in the NNBSL.

10.1 Setting up authorised users for eReports

Each maternity unit/hospital and LHO nominates two authorised users; each will require access to the internet. Staff from the NNBSL will provide them with a User Name and User ID. They will also be provided with the internet link in order to access eReports.

10.2 Benefits of eReporting

- Authorised users can verify that a NBS sample has been received by the NNBSL.
- Results are available as soon as they have been authorised by laboratory staff, usually within 2 to 3 days of receipt of the sample.
- As requests for repeat samples are sent electronically, these repeat samples can be taken sooner.
- A search facility can be used to find or link results; this includes baby's or mother's surname, baby's UPI and DOB or range of dates within the previous 60 days.
- Individual baby newborn bloodspot reports can be printed locally and then filed in the healthcare record and/or a copy given to the parent(s)/legal guardian(s).

10.3 Requests for repeat sampling and responsibility for checking eReports

Authorised users must review eReports daily and notify colleagues if a repeat sample has been requested. The reason for requesting a repeat sample will be indicated on the individual report.

If results are sent to a LHO that a baby does not reside in, an 'incorrect location form' can be completed and the location changed; forms are available on the website or see appendix. The report will then be resent to the correct LHO.

Parent(s)/legal guardian(s) are entitled to and can be given a copy of baby's results by their PHN.

11 Procedure for contacting parent(s)/legal guardian(s) with a screen positive result

Parent(s)/legal guardian(s) of a baby with a suspected positive screen are contacted directly by telephone by the maternity unit/hospital. The procedure varies slightly depending on the condition suspected. The NNBSP Governance Group has set out Key Performance Indicators to ensure that babies detected with a condition are diagnosed and established on treatment within a specific time interval. The general procedure for contacting parent(s)/legal guardian(s) is set out below with more specific details depending on the condition.

11.1 General procedure of contacting parent(s)/legal guardian(s) with screen positive results

- The Clinical Liaison Officer in the NNBSL contacts a designated liaison nurse in the maternity unit/hospital by telephone – the following information is given:
- The baby's name, UPI, DOB and address
- The disorder suspected and the result of the screening test
- The designated liaison nurse in the maternity unit/hospital will be asked to locate the baby and parent(s)/legal guardian(s) and explain to them.
- Why the baby has to be referred to hospital.
- What disorder is suspected.
- Why a further card or blood sample is required, or thyroid scan if CHT suspected.
- Arrange for the baby to be brought directly to Temple Street Children's University Hospital or to the local Paediatric Unit as requested by the NNBSL.
- Parent(s)/legal guardian(s) should be advised that their baby might be kept in hospital for a few days, depending on the result of the repeat investigation. Therefore, they should bring a change of clothes for the baby and themselves.

- The designated liaison nurse will be given the number of the Director of the NNBSL or deputy. This number can be given to the parents, if they wish to make contact for more information before they arrive in the hospital.

At all times the designated liaison nurse must not instil any degree of anxiety when communicating with the parent(s)/legal guardian(s) but must impart the information in a calm and professional manner, being fully informed of all the facts.

Referral procedures for specific conditions are set out below

11.2 Follow up for suspected positive cases of PKU

The Clinical Liaison Officer in the NNBSL will book a bed for admission to Temple Street Children's University Hospital and liaise with the on-call metabolic team. The designated liaison nurse in the maternity unit/hospital will be contacted and asked to:

- Arrange for the baby to attend Temple Street Children's University Hospital under the care of the on-call Metabolic Paediatrician;
- Give the contact number of the Director of the NNBSL (or deputy) to the parent(s)/legal guardian(s), and invite them to make contact for more information, if they wish to do so.

If the initial blood phenylalanine level is high then it is likely that the baby will be kept in hospital for a number of days until the level has fallen. During this time the baby will be started on lifelong dietary treatment and the parents will receive instruction on the monitoring and dietary management of their baby. This should be the only time that the baby will be admitted to hospital for the specific management of PKU.

Babies with a milder variant of the condition may be referred to the outpatient clinic. This information will be clearly given to the designated liaison nurse at the time of the initial contact.

11.3 Follow up for suspected positive cases of MSUD

The Director of the NNBSL or deputy will discuss the case with the on-call Metabolic Paediatrician. He/She will then either contact the designated liaison nurse or the Paediatric Registrar in the maternity unit/hospital directly, and arrange for the baby to be admitted as a matter of urgency, either to the local Special Care Baby Unit or directly to Temple Street Children's University Hospital.

If the baby is to be admitted to:

- ***the local SCBU***
  - Explain to the parents what disorder the baby is suspected of having
  - On admission, examine the baby in detail and check the urine for the presence of ketones;
  - Arrange for 1.3mL of whole blood collected into a lithium heparin tube for plasma branch chain amino acids to be sent immediately to the Metabolic Laboratory, Temple Street.

Contact the on-call Metabolic Paediatrician at Temple Street for further advice on management.

- ***Temple Street Children's University Hospital***
  - Parent(s)/legal guardian(s) must be informed that the baby will be admitted to hospital until the results of tests are known. If the test is positive, the baby will remain in hospital until the Metabolic Paediatricians are satisfied that the baby's condition is under control and that the parents will be able to cope at home.

11.4 Follow up for suspected positive cases of HCU

The designated liaison nurse will be asked to:

- Locate the baby and parent(s)/legal guardian(s) and explain to them why a blood sample is required and what disorder the baby is suspected of having
- Arrange for the baby to have a blood sample taken (1.3 mL of whole blood collected into a lithium heparin tube) for methionine, total and free homocysteine and liver functions tests.

  NB. The sample for free homocysteine must be de-proteinised immediately by the local laboratory staff; instructions will be given over the telephone.

- If the plasma total and free homocysteine are raised and support the diagnosis, arrangements will be made for the parent(s)/legal guardian(s) to attend the metabolic outpatient at Temple Street Children's University Hospital.
- If the plasma methionine remains elevated but the total and free homocysteine are not raised and the baby is clinically well, further advice will be given to repeat the test. The baby will be followed up in the metabolic outpatient at Temple Street Children's University Hospital.

11.5 Follow up for suspected positive cases of Classical Galactosaemia

The Director, Clinical Liaison officer or deputy will contact the Paediatric Registrar in the maternity unit/hospital to arrange immediate admission to the local Paediatric unit. They will be asked to:

- Locate the baby and parent(s)/legal guardian(s) as a matter of urgency;
- Explain to the parents the nature of the condition and to bring their baby directly into the local paediatric unit where the baby will be admitted to hospital for further investigations.

On admission, all lactose and galactose containing feeds including breast milk should be replaced by soya-based feeds (e.g. wysoy). The baby should be examined and the following investigations performed:

- Liver function tests
- Coagulation screen
- Blood cultures (to exclude, for example, *E coli* septicaemia)
- Repeat screening card

As soon as the results of the investigations are available the local clinicians should either contact the Director of the NNBSL or the on-call Metabolic Paediatrician at Temple Street Children's University Hospital to discuss further action.

11.6 Follow up for suspected positive cases of MCADD

The Director, Clinical Liaison officer or deputy will contact the Paediatric Registrar in the maternity unit/hospital. They will be asked to:

- Locate the baby and parent(s)/legal guardian(s) as a matter of urgency;
- Explain the nature of the condition suspected and to bring their baby directly into the local paediatric unit for assessment and further investigations.

All babies with an MCADD suspected screening result should be referred to the Metabolic Unit Temple St. on the same day the screening result is available. The following tests should be performed: urine organic acids and DBS acylcarnitines and the following may be considered: blood glucose, liver function tests, ammonia and CK.

N.B.: Feeds protocol for MCADD screen positives

It is essential to ensure that the baby maintains a good milk intake until results are available. If baby is well it should be bottle fed every 3 hours or if breast fed every 2-3 hours during day time and every 3 hours at night (at least 10 minutes on the breast). Exclusively breast fed babies are particularly at risk in the first few days when the supply of breast milk is poor; top up feeds of expressed breast or formula milk may be necessary until a good milk supply is established. Seek advice from the Metabolic clinical team in Temple St.

If oral feeds are not tolerated, or if the baby is unwell in any way, urgent referral should be made to a Metabolic Paediatrician for review and consideration of IV glucose.

11.7 Follow up for suspected positive cases of GA1

The Director, Clinical Liaison officer or deputy will contact the Paediatric Registrar in the maternity unit/hospital. They will be asked to:

- Locate the baby and parent(s)/legal guardian(s)
- Explain the nature of the condition suspected and to bring their baby directly into the local paediatric unit or Temple St. for assessment.
  If advised by Metabolic Consultant the baby may be admitted to hospital following further investigations.

All babies with a GA1 suspected screening result should be referred to the Metabolic unit Temple St. on the same day the screening result is available. The following tests should be performed: urine organic acids and DBS Acylcarnitine profile. Renal and liver profile may be considered.

N.B.: Feeds protocol for GA1 screen positives

Feeding routine needs to be established and the baby must continue with regular feeding. If oral feeds are not tolerated, or if the baby is unwell in any way, urgent referral should be made to a Metabolic Paediatrician for review and consideration of IV glucose.

11.8 Follow up for suspected positive cases of Cystic Fibrosis

The results of the screening test will be available by approximately the third week of life:

- The Clinical Liaison Officer will contact the designated liaison nurse in the maternity unit/hospital to obtain the parent(s)/legal Guardian(s) contact details and any relevant clinical information. She/he will then contact the CF Nurse Specialists in the appropriate HSE designated paediatric CF Centres, to give them the full contact details, relevant clinical information and the results of the mutational screen.
- The CF nurse specialist will book a sweat test appointment, and then contact the parent(s)/legal guardian(s) to arrange for the baby to attend the nearest CF centre the following day.

On arrival, the parents will be fully informed as to what will happen; the baby will have a sweat test, the results of which should be available by early afternoon on the same day if sufficient sweat is collected. Depending on the results of the sweat test, the parents will be informed that their baby has CF or is a carrier of the condition. If the baby is considered to be a carrier, and therefore unlikely to have CF, the parents will be referred for genetic counselling.

HSE Designated Paediatric CF Centres

- Dublin North: Temple Street Children's University Hospital
- Dublin South two locations:
  Our Lady's Children's Hospital, Crumlin
  National Children's Hospital (AMNCH), Tallaght
- Cork: Cork University Hospital
- Limerick: University Hospital Limerick
- Galway: University College Hospital, Galway

11.9 Follow up for suspected positive cases of Congenital Hypothyroidism

The procedure may vary slightly depending on the age of the baby, the degree of elevation of the blood Thyroid Stimulating Hormone (TSH) level and referral hospital. However, clear instructions will be given. The designated liaison nurse will be asked to:

- Locate the baby and parent(s)/legal guardian(s)
- Explain to the parent(s)/legal guardian(s) what disorder is suspected
- Arrange for the baby to attend the designated hospital to be examined, have blood tests performed, and a thyroid scan; depending on thyroid function test result, following which the baby will usually be started on thyroid hormone replacement.

If the blood TSH level is confirmed as being very high, and if the baby is approaching ten days of age, thyroid hormone replacement may be started before they attend the hospital for a thyroid scan.

Acknowledgements
We would like to acknowledge the dedication and commitment that so many different healthcare professionals put into this programme for the benefit of the few babies born each year who are affected by one of these conditions.

We would welcome any comments and feedback that individuals may have on this edition. More information about the programme may be obtained at: www.newbornscreening.ie and www.hse.ie/go/newbornscreening

12 Appendix's

Appendix No. 1: Incorrect Location Form
Appendix No. 2: Opt-Out Form
Appendix No. 3: Scan of Newborn Bloodspot Screening Card
Appendix No. 4: Copy Result Request Form
Appendix No. 5: eReporting User Information
Appendix No. 6: Guide for Sample Takers

Appendix No. 1 Incorrect Location Form

National Newborn Bloodspot Screening Laboratory

An INAB accredited testing Laboratory Reg. No.224MT
Temple Street Children's University Hospital, Dublin 1
Direct Line: Ph. (01) 8784277 ● Fax: (01) 8784596 ● www.newbornscreening.ie ● Email: info.newbornscreening@cuh.ie

Please complete details below on babies on whom you have received reports which do not belong to your Area and return to NNBSL. Please indicate correct LHO (only if known).

Please FAX or email to NNBSL as soon as possible.

Location (LHO):	**Date:**

Reported By:	**Position:**

UPI	Lab Number	Date of Birth	Correct LHO (if known)

Comment:

Appendix No. 2 Opt Out Form

NATIONAL NEWBORN BLOODSPOT SCREENING PROGRAMME

OPT-OUT FORM

Baby's Unique Perinatal Identifier (UPI): ___ - _____ Gender: (Please circle) M F

Baby's Surname: _____ Gest Age: (weeks) ___

Baby's First Name: _____ Rank: ___

Baby's Address: _____ Hospital/Birth Place _____

Mother's Surname: _____

Time of Birth: H H M M Date of Birth: D D M M Y Y Birth Weight (kgs): ___ - ___

RBC Transfusion Received? Y / N Date of First Transfusion: D D M M Y Y

Time of First Transfusion: H H M M

Date of First Feed: D D M M Y Y Local Health Office: _____

- I _____ being the parent/guardian of Baby _____ do not consent to allow the Newborn Bloodspot Screening Test (Heel-Prick) to be carried out on my baby.
- I have read the information leaflet on Newborn Bloodspot Screening and the test has also been explained to me.
- I fully understand the importance of the decision that I am taking by not allowing my baby to be tested.
- I understand that not detecting or treating one of the conditions, should baby have one, may result in severe intellectual or physical disability which could require long term care or result in premature death.

Signed (Parent/Guardian): _____

Full Name (PRINT): _____ **Date:** _____

Signed by potential sample taker: _____ **Date:** _____

Position/Job Title: _____ **Health Area Office:** _____

OFFICIAL USE ONLY

6 copies of the completed form, signed by parent/guardian and sample taker should be made. A copy to be given to the parent/guardian and a copy kept by the sample taker.

Copies are to be posted to each of the following:- • The Director of Nursing/Midwifery • Director of Public Health Nursing • National Newborn Bloodspot Screening Laboratory • The baby's General Practitioner

	Director of Nursing/Midwifery	Director of Public Health Nursing	National Newborn Bloodspot Screening Laboratory (NNBSL)	General Practitioner
Name				
Address			NNBSL, Children's University Hospital, Temple Street, Dublin 1	
Date Sent				

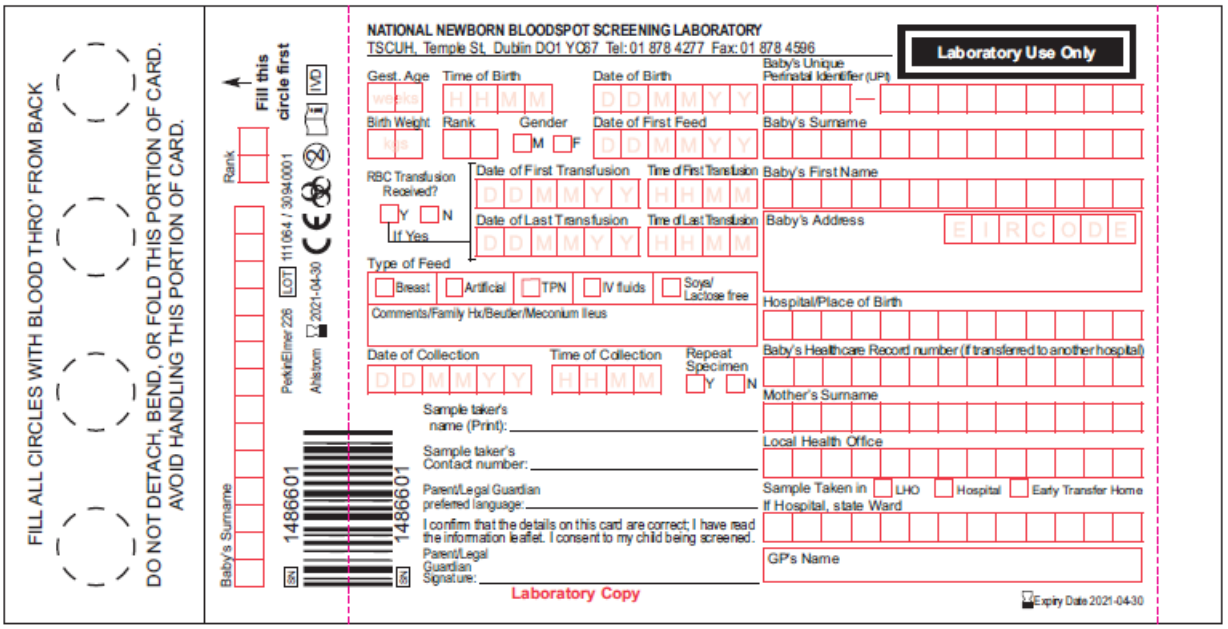
Signed *(Sample taker)*: _____ Date: _____

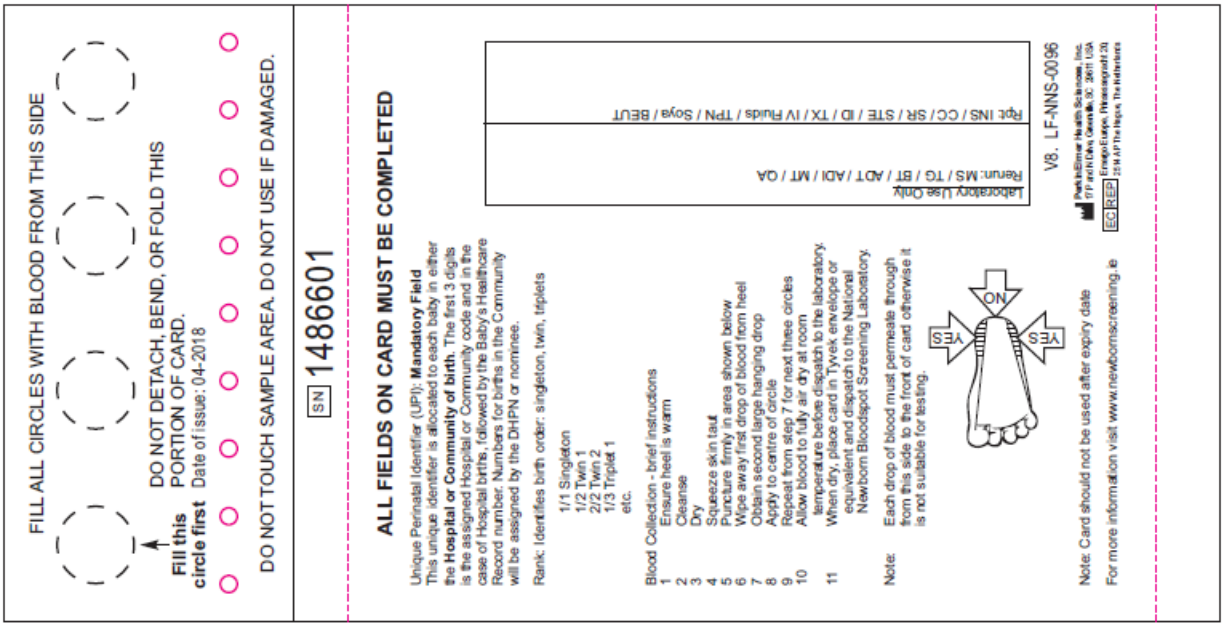
Name *(Block Capitals)*: _____

N.B.: The cystic fibrosis screen is not suitable if baby is over six weeks of age.

Parents/Guardians may change their mind but it is their responsibility to inform the GP or Public Health Nurse.

Appendix No. 3 Scan of Newborn Screening card (front and back)





Appendix No. 4 Copy result request form

Temple Street Children's University Hospital, Department of Paediatric Laboratory Medicine
LF-NNS-0046 COPY RESULT REQUEST FORM EDITION 3

No.	Baby Surname	Mother Surname	DOB	Baby Forename	Mother Forename	Address	Hospital of Birth	Unique Identifier (UPI)	NNBSL Office Use/Comments
1									
2									
3									
4									
5									
6									

N.B.: Please ensure e-reports have been checked prior to sending this form requesting copy reports.

Requested by: _____ **Address:** _____ **Tel No.:** _____

Issued by (NNBSL use only): _____ **Date** (NNBSL use only): _____

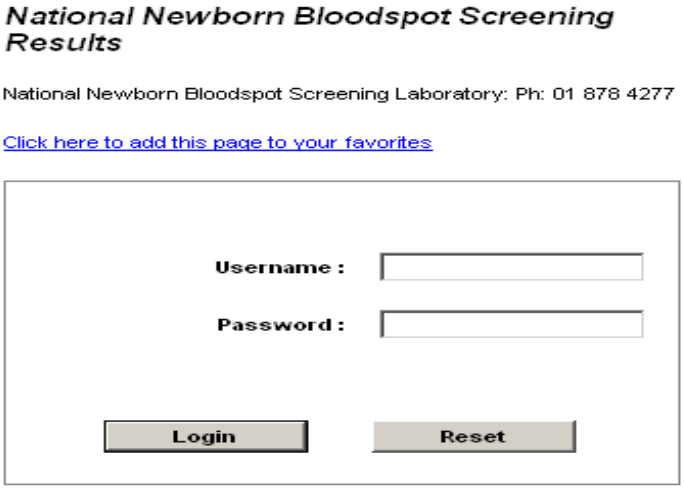
Page 1 of 1

Appendix No. 5 Specimen Gate eReports™ instructions

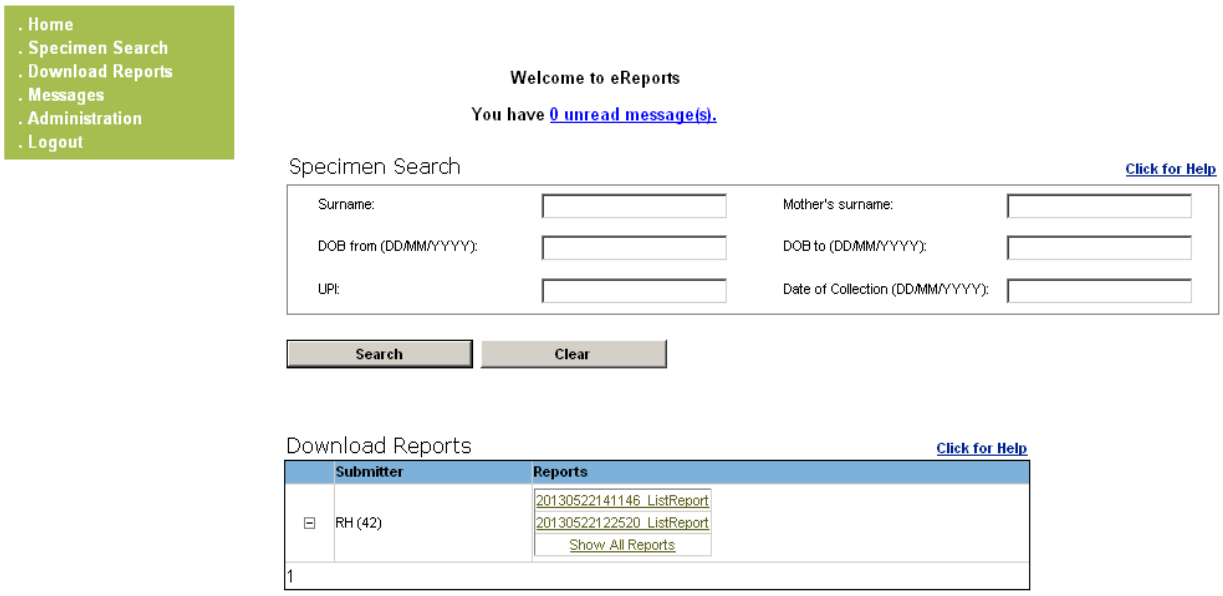
Specimen Gate eReports™ allows authorised users with appropriate access rights in Hospitals and Public Health to view NBS reports via the internet and to view 'pending' samples that have been received but not yet reported. Each centre has two accounts only, one named and one generic. User names and passwords are only assigned to authorised users specific to their organisation / location following completion of a 'User Authorisation Form', available from NNBSL.

To access e-reports: In your internet browser type or copy the following URL and save to favourites. **http://sgateweblive.healthirl.net/ereports** or **http://10.0.37.81/ereports**

Each user, logins using their own 'user name' and 'password' assigned by the NNBSL, *see below*



From here it is possible to search for a specific sample or download list or single reports.

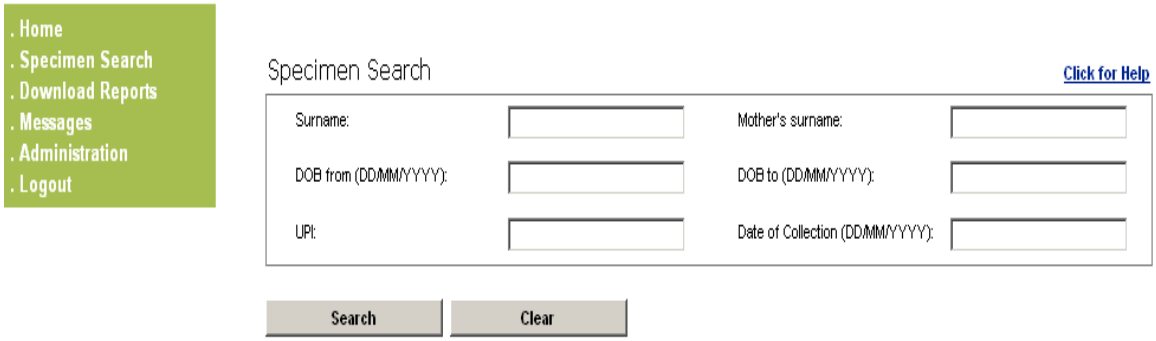


To Download Reports

- Select '**Download Reports'** from menu on left hand side – the most recent reports (list and single) for your location made available by the NNBSL will be visible to each user in pdf format.
- In this view, select '**List Report'** to open the latest List Report of normal results or select '**Single Report'** to open separately in pdf viewer each of the single reports.
- Select '**Show all Reports'** and all reports for the previous 60 days will be available to view / print which will enable users to print off their own copy reports if required.
  Note: Those reports previously viewed will appear in a different colour. If reports have been archived after 60 days they will need to be individually regenerated. If reports are greater than 18 months they cannot be regenerated.

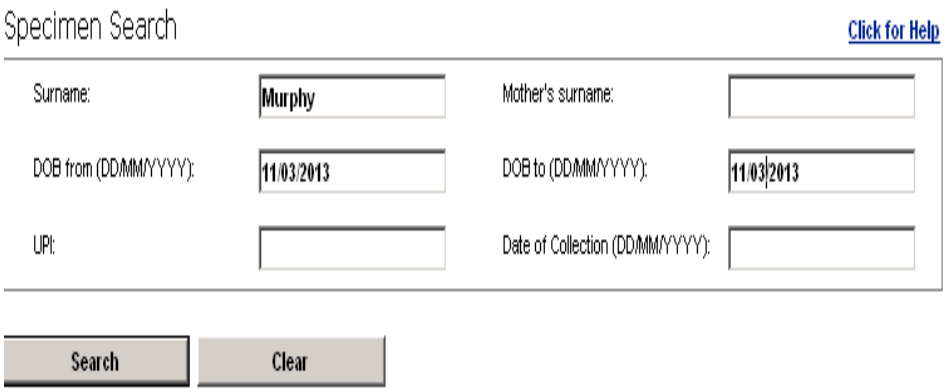
To do a search for a Specific Sample

To search for a particular sample or group of samples select '**Specimen Search'** from the left hand side menu using the criteria in the screen below.

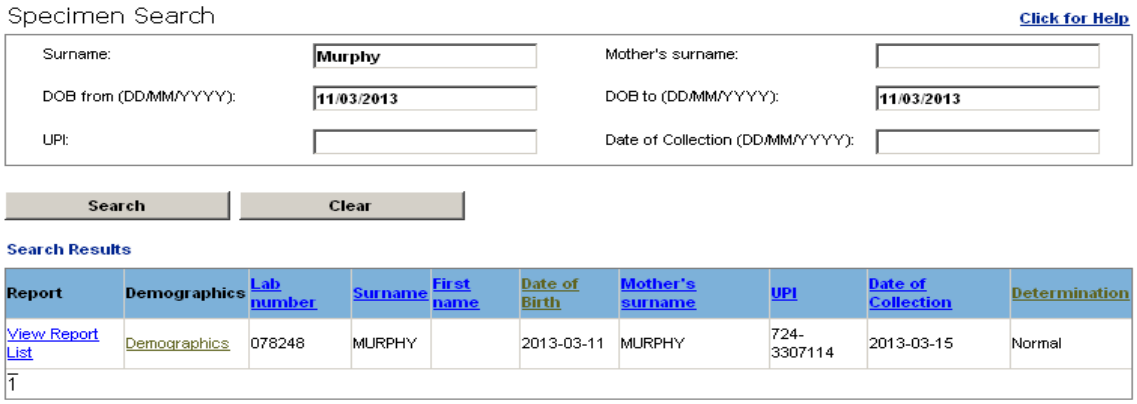


A specific sample can be searched for using the above criteria or a group of samples can be searched for using DOB either for one day or a range of days

Example: To search for a Baby Murphy DOB 11/03/2013, enter the details as follows:
Note: DOB MUST be in the format dd/mm/yyyy.



Select 'search' for the following screen:



Report: To view the report select 'View Report List' from left hand side 'Report' column to open. If the sample has been received in the laboratory but the results are not yet available then this will be viewed as 'Results Pending'.

Determination: The 'Determination' column will display 'Normal' if all the requested tests have a result of 'Not Suspected'. This column will display 'other' if a result for any condition is abnormal and/ or a repeat card is required.

Note:

1. To search for all samples from your location for a particular **DOB** enter the DOB range only i.e. for all babies in your location with DOB of 14/05/2013 enter from 14/05/2013 to 14/05/2013.
2. To search by UPI, please ensure a dash (-) is placed after the three digit HIPE Code and ensure that the letter (if any) is also provided e.g. Coombe 930-B12345678.

Appendix No. 6 Guide for Sample Takers

NEWBORN BLOODSPOT SCREENING TEST
10 STEP GUIDE FOR SAMPLE TAKERS

1

Equipment: Metered sterile lancet with tip no more than 2.5mm in depth, latex free gloves, cotton wool, newborn screening card, envelope, sharps bucket, paper towel, bowl of warm water and soap or cleansing heel.

2

Explain to the parents the reason for the test and its importance. Obtain written consent. Complete all sections of the newborn screening card in clear print using a black ballpoint pen. Do not contaminate filter paper circles by allowing circles to come in contact with spillage or by touching before or after blood collection.

3

Instruct parents to keep baby's feet warm prior to test by applying two sets of socks or placing a set of socks beneath babygrow.

4

Select the puncture site on the heel. The preferred puncture and least hazardous site are indicated by the shaded areas. Warm the site prior to sampling by rubbing the skin for 1-2 minutes to increase blood supply. Preferably take the sample from the infant while the parent cuddles the baby, the test may be taken while the baby is breastfeeding. Breastfeeding during a painful procedure effectively reduces the response to pain in the newborn infants. Non-nurtive sucking e.g. pacifier and skin-to-skin contact reduce procedural pain in newborn infants. Current pharmacological treatments are not appropriate for pain relief during minor procedures like the heel prick in newborn infants.

5

Cleanse the heel with warm soapy water. Pat dry.

6

Puncture heel. Wipe away first drop of blood with cotton wool. Allow another large blood drop to form.

7

Touch the circle marked on the card gently to the hanging drop of blood so that the blood soaks through from back of the card to the other side.

8

Fill the two outer circles first; blood drops must be soaked through from the rear to the front of the card, filling all circles completely. Check that the blood has soaked completely through completing the circle on the front as well as the rear of the card.
To enhance blood flow, very gentle intermittent pressure may be applied to area surrounding puncture site.

9

Wipe away any excess blood with cotton wool. Press cotton wool firmly onto wound until bleeding stops. Do not use plaster over puncture sites as babies may swallow them. Air dry the newborn screening card before putting into the envelope. This may take up to two hours. Do not use excessive heating as this may invalidate the test.

10

Send the card by Registered post or by Courier to the newborn Screening Laboratory using the yellow fluorescent address labels to reach the Laboratory as soon as possible after collection. Keep a record of all samples sent in each envelope.