Part Three
Newborn Screening

Newborn Screening - Introduction

The newborn screening test (often referred to as “neonatal screening” or the “Guthrie” test) is offered to all babies born in Scotland. The test utilises dried spots of capillary blood obtained by heel prick and collected on a special card when the infant is a few days old. Parents consent to testing (or very rarely may refuse) on behalf of their children. The objective is to identify, as soon after birth as possible and before the onset of recognisable clinical symptoms, specific disorders which can then be treated to ameliorate the consequences of untreated disease. At present, testing is targeted at three specific disorders with the imminent introduction of two more:

Current Screening Tests:
- Phenylketonuria (PKU)
- Congenital Hypothyroidism (CHT)
- Cystic Fibrosis (CF)

New Screening Tests:
- Sickle cell disorders
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)

Phenylketonuria (PKU)

Screening for elevated phenylalanine in blood (hyperphenylalaninaemia) using blood spot specimens began in Scotland in 1965. “Phenylketonuria” (PKU) is the name given to the severe form of hyperphenylalaninaemia in which there are very high phenylalanine values in blood. The name derives from the chemicals derived from phenylalanine (called “phenylketones”) which may also be present in urine. Severe hyperphenylalaninaemia is due to almost complete deficiency of a liver enzyme, phenylalanine hydroxylase, which converts the essential amino acid phenylalanine to tyrosine. Some people who have some residual enzyme activity may have “moderate” or “mild” forms of this condition. Several other disorders as well as transient metabolic disturbances can also cause hyperphenylalaninaemia.

In untreated PKU, phenylalanine accumulates in the body and impairs the growth and development of the brain, leading to failure of normal neurological progress. Babies with hyperphenylalaninaemia do not show any signs at birth but, without treatment, those with the severe form of the condition become severely and irreversibly mentally disabled. The condition may cause deficiency of tyrosine which is necessary for pigment production: untreated infants may have fair hair and blue eyes.

Phenylalanine is present in protein in foods including breast milk, infant formulas, cows’ milk, meat and eggs, but also in some vegetables and in foodstuffs derived from cereals. Treatment, which should begin as soon after birth as possible and be continued for life, involves restricting the intake of phenylalanine by means of a special diet.

PKU has an incidence of about 1 in 8000 births in Scotland. It is an autosomal recessive condition and about 1 in 45 people in the general population is a carrier. Usually parents of affected children are both asymptomatic carriers and there will be a 1 in 4 chance in any subsequent pregnancy that they will have another child with PKU. If a parent is already known to have hyperphenylalaninaemia, the risk of recurrence could be as high as 1 in 2.

It is rare, but possible, for the screening test to fail to pick up an affected baby. Occasionally however, a screening result may be suggestive of PKU but on follow-up testing it is shown to be falsely positive.

Congenital Hypothyroidism

Screening for Congenital Hypothyroidism (CHT) began in Scotland in 1979. The incidence of CHT in Scotland is approximately 1 in 3500 births. or about 25-35 cases a year. About 70 - 80% of CHT cases are not inherited but occur sporadically and have no known cause, with the remainder inherited in an autosomal recessive fashion so that there is a 1:4 risk of occurence in future pregnancies for the couple. CHT occurs when a baby is born with an absent or reduced amount of active thyroid tissue or a hormone synthesis enzyme defect. This leads to a deficiency of the hormone thyroxine which is produced by the thyroid gland. Babies with CHT may show prolonged jaundice, dry skin, coarse features, protruding tongue and slow feeding. Babies brains are growing at their fastest rate in the first 2-3 years after birth and brain growth and development is totally dependant on thyroxine. Thus, if left untreated, babies will have permanent mental impairment but will also suffer from linear growth impairment which is reversible.

The laboratory screening test for CHT measures the amount of thyroid stimulating hormone (TSH) in the blood spot sample. Affected babies have high levels of TSH. It is rare but possible for the screening test to fail to pick up an affected baby.

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False positive screening results are also rare. If the condition is left untreated, mental impairment and developmental delay will follow. Treatment, which is usually for life and takes the form of daily doses of oral thyroxine, is effective Optimal outcome is obtained when treatment is started as quickly as possible after birth.

There are situations e.g. after surgery or serious neonatal illness when a baby may have a raised or even high level of TSH. This transient level returns to normal after a period of time.

Cystic Fibrosis

Cystic fibrosis (CF) has an incidence in the UK population of about 1 in 2500 births. It is inherited as an autosomal recessive condition and there is a 1 in 4 chance of a recurrence in any future pregnancy. Parents of affected children are asymptomatic carriers, and 1 in 25 people in the UK population is a carrier of CF.

Patients with CF have a defect in the structure of a protein called CFTR (Cystic Fibrosis Transmembrane conductance Regulator) which controls the passage of chloride ions in and out of the cells of various tissues. The defect is a result of a mutation in the CF gene. Over 1000 different mutations have been identified and all but a few are exceedingly rare. The most common mutation (or allele) occurring in the UK is call “delta F508” which accounts for about 70% of the CF genes in the population. Other mutations are found at higher frequencies in other ethnic groups.

Possession of one mutation is associated with CF carrier status and such individuals do not have CF. Affected individuals have two mutations, either both the same e.g. delta F508/delta F508, or some other combination of rarer alleles. The type of mutations present may have an influence on the severity of the disease. The resulting faulty CFTR protein leads to abnormally thickened secretions from certain organs and excessively “salty” sweat. The main organs which are affected are the pancreas, where blockage of the pancreatic ducts leads to a failure to secrete enzymes required for digestion, and the lungs, where sticky mucous predisposes the individual to repeated bacterial infections and progressive damage and loss of lung function. Early diagnosis and treatment based on a regime of enzyme supplements, physiotherapy and antibiotics may improve morbidity and mortality.

The laboratory screening test operates in

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two stages. First, the level of immunoreactive trypsinogen (IRT) is measured in the dried blood spot. Normally, IRT is produced by the pancreas and secreted into the lumen of the gut, but in newborns with CF, the pancreatic ducts are blocked and excess IRT finds its way into the circulation, raising the levels above normal. If blood spot testing identifies a high level of IRT, another blood spot from the same card is sent to the molecular genetics laboratory for mutation analysis. In this second stage of testing, DNA extracted from the blood spot is analysed for the presence of any of the 32 most common mutations, including delta F508. If two mutations are found, a diagnosis of CF is confirmed. If no mutations are found, then there is only a very small chance that the baby has CF. If only one mutation is found there are two possibilities:

(i) The baby is a carrier of CF (just like one or both parents) or

(ii) The baby is affected as it is possible that there is another undetected rare CF allele.

In the latter case, another blood spot sample is obtained when the infant is 27 days old and retested for IRT levels. If IRT is still elevated, a sweat test is carried out to confirm or exclude a diagnosis of CF. If the second IRT test is negative, it is unlikely that the baby has CF.

Around 1 in 200 babies will be found to have an elevated IRT at the first stage of testing. Subsequent mutation analysis will show that the majority do not have CF, and these are therefore false positive results. Occasionally, a baby affected by CF will not have an elevated IRT and will therefore be missed by the screening test. These are false negative results.

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) is an autosomal recessive disorder, first identified in 1976.

Consequences of MCADD

MCADD is one of a group of disorders called the “fatty acid oxidation disorders”. Fatty acids are an important source of energy for the body during fasting, and particularly during infectious illnesses which interrupt the normal intake of food. The body “oxidises” fatty acids in a sequence of steps. “Medium-chain acyl-CoA dehydrogenase” is the name of one of the many enzymes which carry out this process.

Fatty acids cannot be used as “fuel”, so patients quickly use up glucose and may develop low blood sugar (hypoglycaemia). High levels of partially broken down fatty acids, with or without hypoglycaemia may cause affected people to to become drowsy, vomit, become comatose and eventually stop breathing.because of swelling of the brain.

it is imperative to know that a person has this disease so that crises can be prevented. If unrecognised, as many as 25% of affected individuals may die in their first crisis. Those who survive a severe crisis may have permanent developmental and behavioural disabilities.

Why Screen for MCADD

Early identification of MCADD results in appropriate early preventative treatment and reduces the risk of acute, life-threatening episodes and death. With dietary management, individuals are expected to have a completely normal life.

Genetic Facts about MCADD

MCADD is most common in people of North European origin. MCADD affects about one in 10,000 babies born in the UK. It is estimated that screening should identify about 5 – 10 cases a year in Scotland.

- A child who has MCADD has inherited two altered genes, one from each parent, both of whom are usually asymptomatic carriers . (It is possible however for a parent to have MCADD , without ever having shown any manifestation of the condition).
- It is thought that between 1 in 40 and 1 in 80 healthy people are carriers and do not have any symptoms
- The MCADD gene is found on chromosome 1
- The most common mutation is 985A>G but over

25 other variants found. Two copies of the most common mutation are found in 85 – 90% of those with symptoms.
- For each pregnancy where both parents are carriers, there is:
- A 1 in 4 chance that the child will be born with MCADD
- A 1 in 2 chance the child will be a carrier of the defective gene
- A 1 in 4 chance that the child will not be a carrier.
- **If a parent has the condition (rare, but possible) the risk of recurrence will be 1 in 2.**

Diagnosing MCADD

The marker for the condition is the presence, in blood, of raised amounts of a chemical substance called octanoylcarnitine. This is an indirect test, and the abnormality may be caused by other conditions. The diagnosis must always be confirmed by a repeat blood test for octanoylcarnitine and other related substances, a test for associated substances in urine, and mutation analysis. More extensive tests for non-typical cases may be required. Carriers are not intentionally identified and within the English pilot very few were detected.

Older siblings born before newborn screening started will need to be tested and this will be arranged by the metabolic clinician. Some authorities also recommend testing of parents, who could be at risk.

Management of MCADD

At the time of the positive screening result, the baby requires assessment by a suitable professional to ensure that he or she is clinically well and feeding. Care will then be coordinated by the multidisciplinary metabolic specialist team. Affected children can tolerate the usual routine of most healthy babies and children including sleeping for normal periods at night. However special precautions have to be taken to avoid long periods of fasting, particularly during infectious illnesses.

Parents need to know to avoid a 'metabolic crisis' in the child, and need to closely monitor the child's 'safe' time periods between feeds or meals. The 'safe' time increases as the child grows older. If the child becomes unwell,and is not eating or drinking well, he or she needs to have regular supplements of sugary drinks or glucose Clear instructions will be given by the child's dietitian.

Additional management of babies
- Babies should complete a full immunisation programme
- Some children may require a supplement of a vitamin-like substance called carnitine to prevent carnitine deficiency.
- Influenza vaccine is recommended annually
- For events such as operations and anaesthetics which require fasting there is a need for an infusion of dextrose before, during and following the procedure, until the child is eating and drinking normally.

Summary

- MCADD may present acutely
- Acute presentation may result in death or serious morbidity
- Treatment is simple and effective in preventing crises
- Knowledge that a child is affected with MCADD is key in preventing future crises

Further information go to: www.climb.org.uk

CLIMB – Children Living with Inherited Metabolic Diseases, is a support group for parents and health professionals.

Reference
Leonard, JV Dezateux C. (2008) Newborn screening for medium chain acyl CoA dehydrogenase deficiency. *Arch. Dis. Child*. 94: 235 – 238

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Haemoglobinopathies

Haemoglobinopathies are common in people who have family origins from the malarial parts of the world and in the UK are seen particularly amongst minority ethnic groups from Africa, the Caribbean, the Mediterranean, South East Asia, the Middle East and the Far East but can be found (less frequently) in all ethnic groups.

Sickle cell disorders affect individuals who have inherited two HbS genes or a sickle cell gene together with an interacting gene.

Conditions screened for in newborns

- HbSS
- HbSC
- HbSD
- HbS/ß thalassaemia
- HbS OArab
- HbS/HPFH

Sickle Cell Disorder affects the normal oxygen carrying capacity of red blood cells due to a change in the biochemistry of haemoglobin. When deoxygenated, red blood cells are unable to pass freely through capillaries and instead form clusters, which block blood vessels. This blockage prevents oxygenation of the tissues in the affected areas resulting in tissue hypoxia and consequent intense pain (known as sickle cell crisis). The other symptoms of sickle cell disorders include severe anaemia, damage to major organs and infections.

Early detection in newborn babies and appropriate management can improve quality of life, especially when parents and users learn to recognize and avoid the risk factors that can trigger painful 'crisis' attacks and take antibiotics to prevent infections.

The objective of the newborn screening programme is to detect infants at risk of sickle cell disorders within the neonatal period in order to allow early treatment and care.

It is not reliable or necessary to undertake screening for carriers of thalassaemia disorders at birth, partly due to the limited expression of the ß-globin genes at birth and partly due to the limitations of the analytical procedures available for the thalassaemias.

Newborn sickle cell screening will be offered to all babies in Scotland as part of the newborn bloodspot screening test at day 5 of age. Although this is for the early identification of children affected with this disorder, many babies who are healthy carriers will also be identified.

Sickle cell disorders affects 1 in 2,500 babies in UK

Sickle cell disorders affects 1 in 2,500 babies in UK (ie about 240 born each year) and causes pain, tissue damage, infection and even death. Early treatment as well as parent education, improves health and prevents deaths.

Affected babies are treated with penicillin and the pneumococcal vaccine and treatment should be started by 3 months of age. Children with a sickle cell disorder are 600 times more likely to get pneumococcal infection than other children. This is because their spleen does not work properly and in young children the spleen is plays an important part in fighting infection. It is strongly recommended that penicillin is given throughout childhood and carried on into adulthood.

It is vital for the newborn screening laboratory to know parents carrier status – therefore this **must be** recorded on the bloodspot card.

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Transfused babies

The presence of transfused blood in the neonate will interfere with the interpretation of the results from haemoglobin analysis of the bloodspot and possibly invalidate the results. It is therefore recommended that all neonatal units take a bloodspot specimen for sickle cell screening prior to giving a transfusion whenever possible. This sample should be marked as pre-transfusion and sent to the laboratory with the 5 day sample if the baby receives a transfusion in the interim.

In Scotland, all newborn blood spot testing is carried out in the National Newborn Screening Laboratory in the Institute of Medical Genetics at Yorkhill, Glasgow.

Key contact telephone numbers are:
Laboratory: 0141 202 0809
Office: 0141 201 0870

Parental Consent and Refusal

Parents should be counselled regarding the newborn screening programme available in Scotland and its benefits. A copy of “A Parents’ Guide to Newborn Screening...” should be given prior to collection of the blood spot specimen. Parents should also receive a consent form and it is important that their signature is obtained consenting to or refusing testing and future anonymised research. The form must be countersigned by the midwife taking the blood spot sample who should also ensure that if permission is withheld to include details for anonymised research that ‘No Research’ is recorded on the bloodspot card. Completed forms are filed in the Child Health Record.

If parents refuse testing for religious or other reasons it is important to complete a Blood Spot card with all the relevant details and post the card to the laboratory stating that the parents have refused.

Newborn Bloodspot Sampling – Best Practice

Every section of the bloodspot card is important. The information supplied is entered into the Newborn screening computer and used for:

- The identification of the infant – to ensure that the correct result is issued to the correct baby.
- The determination of results - certain parameters have to be fulfilled before results are valid and issued.
- The correct protocol is followed – certain information will lead to different protocols for particular situations e.g. ethnic groups.

New Bloodspot Cards

New blue card **MUST** be used from implementation date for MCADD and sickle cell disorders

All old cards (pink) **MUST** be destroyed or preferably returned to the laboratory

Key Points

Date of Birth- Important for all tests.

The baby should be at least 96 hours of age before the specimen is taken.

Date of specimen is important for IRT. After 42 days the IRT test result is unreliable and false negative results may occur.

Delays can also make the sample unsatisfactory for analysis for sickle cell screening (excessive oxidation may occur if kept in unsuitable conditions)

Cards without dates will not be issued with a result until the dates have been established. Lack of information may result in the request for a second specimen.

Contact number for parents has been added - important in order to contact parents if immediate action is required

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Date of First Milk Feed is no longer required as tests can be performed regardless of whether baby is taking milk feeds or not

Ancestry code - important in CF screening as the laboratory processes the specimen according to this.

Also important in screening for Sickle Cell Disorders – this information is valuable in case the baby needs to be followed up and to help interpret the results.

Note Expiry date on card

Specimens that have been collected using expired cards are **UNSUITABLE** and will need to be **REPEATED**

CHI number is essential for identification

Currently cards are received without a CHI number. Also, the same CHI number has been used on more than one baby's card therefore care must be taken when entering the CHI number from a computer screen or a sheet of paper.

Be aware that as of April 1st 2010 there will be mandatory use of NHS number (English equivalent of CHI) on blood spot cards in England – although this does not currently apply to Scotland it may become necessary if there is poor compliance with CHI.

Bloodspot cards are in two parts - Surname and Date of Birth are required on the blood spot portion since blood spot portion will be separated from demographics

Transfusion date is essential

- Important to know this for current tests as a repeat specimen is required at **72 hours post transfusion**. For Sickle Cell screening a repeat will be required at **4 months post transfusion**. This also includes intrauterine transfusions.
- It is therefore recommended that all neonatal units collect a **pre-transfusion blood spot specimen** for SCD screening from all babies on admission.

Comments Box

Use this box to make any relevant comments such as meconium Ileus, family history, or mother on thyroxine, assisted conception, intrauterine transfusions.

Also make comment here if parents do not wish storage or research, If the parents refuse to allow one of the tests to be done then this should be marked in the box e.g. Parent refused CF testing.

Please note that the number of spots required is **NOT** related to No Storage or No Research written in the Comments Box.

All 5 spots are required for testing. This will be even more important with the introduction of testing for MCADD and SCD.

Specimens that are more than 14 days in transit will be UNSUITABLE for testing and will need to be REPEATED.

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Please note:
- Use FREEPOST ENVELOPES (SCO7580)
- Air dry
- Post Immediately to avoid harmful delays in diagnosis and treatment for babies with MCADD, CHT and PKU
- Be aware of postal strikes and local procedures for this.
- DO NOT include lancets in the envelopes
- Place one bloodspot card only in each glassine sleeve (opaque envelope)

The collection of blood samples

The routine Blood Spot specimen should be collected when the baby is at least 96 hours old irrespective of milk feeding or prematurity. The specimen should also be taken before the baby is 7 days old in order to confirm and initiate early treatment in cases detected through the screening programme therefore day 5 is the recommended age.

General tips about blood collection

The heel must be clean prior to skin puncture to prevent infection, but the use of alcohol is not necessary. Blood will flow more easily if the limb is lowered and warm. Puncture the heel and wait up to 15 seconds to allow the blood to flow naturally. Wipe away the first drop of blood. Allow one large drop of blood to fill each circle completely and seep through to the back of the card. Avoid layering of the blood. Squeezing the heel for too long may stop the blood flow therefore remember to release pressure for several seconds between squeezes. If blood flow slows or stops, release pressure, lower the limb, wipe puncture site firmly with cotton wool, wait 10 seconds, and then squeeze again.

Blood collection

Equipment required:
Examination gloves.
Skin puncturing device ("Tenderfoot" device preferred. If other device is used the blade must be no longer than 2.4mm.)
Sterile Cotton Wool
Blue blood spot card.

The routine Blood Spot specimen should be collected when the baby is at least 96 hours old

1. (a) Complete ALL sections of blood spot card in clear printing using a ball point pen.
   (b) Please ensure all demographic details and all dates are correct.
2. Assemble equipment and put on gloves.
3. Ask the mother to cuddle the baby on her knee to assist you and comfort the baby.
4. Place a paper towel on the lap of the person holding the baby to protect from any blood drips.
5. Ensure that the heel is warm - hold in warm hands for 3 minutes
6. Cleanse the heel thoroughly with soap and water.
7. Air dry heel or wipe dry with cotton wool.
8. Encircle the heel with finger(s) and thumb and squeeze gently until skin looks taut and suffused with blood.
9. Puncture the heel with a firm deliberate stab only in the area shown in the diagram overleaf. The whole heel planter surface may be used in term and pre-term infants who have repeated heel punctures to a penetrative depth of no more than 1.0 mm. Avoid posterior curvature of the heel.
10. If a second puncture is necessary, make this a few millimeters away from the first or in the other foot.
11. Hold the foot downwards. Alternately squeeze the foot gently and then release pressure.
12. Just touch the circle marked on the card gently to the hanging drop so that the blood soaks through to the other side.
13. Repeat 12 until all **five** circles have been completely filled.
    DO NOT press the card on to the skin or apply multiple drops to fill each circle.
14. Press clean cotton wool firmly on to wound until bleeding stops.
15. Air dry Blood Spot card and insert into the glassine sleeve before placing in an envelope addressed to the laboratory. Avoid excessive heating as this will fix the blood to the card and invalidate some results. Unlabelled or inadequately labelled specimens should not be sent to the laboratory.

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Sending the cards to the Laboratory

Send card directly to the laboratory by **FIRST CLASS POST IN THE PREPAID, PREPRINTED ENVELOPE PROVIDED** or immediate transport delivery. More than one card can be placed in an envelope as the glassine sleeve will keep the specimens apart. However, do not delay posting in order to do this. Do not put more than eight cards in a single envelope as this will exceed the contracted postal weight and delay delivery of the specimens.

Biohazards

Babies whose mothers are known or suspected to be infected with HIV or Hepatitis B should have neonatal screening tests taken as usual. Please positively identify the Blood Spot card as a Biohazard. The envelope in which the card is placed must not be marked as Biohazard to avoid breach of confidentiality.

EDTA

All contact with EDTA should be avoided as this will have a detrimental effect on the IRT levels possibly leading to false negative results.

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Quality of Spots

Always fill blood through to the back of the card The blood specimen on the front of the card looks adequate **BUT** when the reverse side of the card is examined it can clearly be seen that the blood has not soaked through to the back. When the 3mm disc is punched there are white margins on the disc. This will lead to unreliable levels and could lead to a false negative report. A repeat specimen has to be submitted for analysis before a reliable screening result can be issued.

Don't layer blood spots as this will give a false reading

Why Repeat Blood Spot Specimens Are Requested

Occasionally it is necessary to collect a second blood specimen.

The reason may be:

1. There was insufficient blood available to perform all tests.
2. The Blood Spot card was damaged or did not reach the laboratory.
3. Equivocal or borderline test results.

   This means that means that the test result is not abnormal enough for the baby to be seen by a paediatrician but not completely within normal ranges. There are several reasons why tests give an unclear level and often the repeat specimen is completely normal.
   If a result remains unclear then arrangements will be made to have the baby seen by a paediatrician.
4. There were insufficient details on the card to make the result meaningful.
5. The baby was too young when the specimen was collected (less than 96 hours old).
6. The card was not dried properly prior to being posted.
7. The analysis was unsatisfactory due to specimen contamination or deterioration.

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Babies who have been missed

If the Blood Spot specimen has not been taken for any reason, the specimen should be taken as soon as possible, as it is better to be taken late than not at all. However, late specimens may affect the result for CF testing and will delay diagnosis and treatment of PKU, CHT, SCD and MCADD. Late specimens should therefore be avoided.

What happens to the Blood Spot Cards after testing is complete?

The Blood Spot cards are stored in the laboratory for a period of 12 months, so that, if necessary, one or more of the above screening tests can be repeated to check a particular result. The stored Blood Spot specimen can also be used to test for some other disorders which are not part of the standard screening programme. This may be useful if a child becomes ill and the doctor requests further tests, but this would always be discussed with the child's parents first.

Left-over Blood Spot specimens can also be used anonymously for other laboratory purposes such as comparing different screening methods and developing new tests. Occasionally it is necessary to use identifiable specimens in which case the parents' permission would always be sought. If a parent does not want the stored Blood Spot card to be used for further research, please write "No Research" in the comments box on the Blood Spot card.