National Healthy Childhood Programme

National Newborn Bloodspot Screening Programme

&

National Newborn Bloodspot Screening Laboratory

A Practical Guide to Newborn Bloodspot Screening in Ireland

10th Edition

April 2026

mychild.ie

Sláinte Leanaí Éireann
CHI
Children's Health Ireland

Contents

Significant changes from the 9th edition

Key messages: Section 1, based on recurring queries and issues with sample quality and avoidable repeats.

Section 4.1: An explanation on why information on feeds at time of sample collection is so important.

Section 11: Information on the two conditions newly added the NNSBP in 2026 – severe combined immunodeficiency (SCID) & spinal muscular atrophy (SMA).

Biohazard labelling and use of biohazard bags is no longer required. Universal precautions are practised within the NNBSL on all newborn bloodspot screening cards received.

Relevant Contact Details

Laboratory : 01 878 4277 or 01 878 4610 CHI at Temple St., Dublin, DO1 YC67 The laboratory will in time move to the new paediatric hospital adjacent to St James Hospital, Dublin 8. **Email**: info.newbornscreening@childrenshealthireland.ie **Website**: https://www2.hse.ie/conditions/heel-prick-screening/
Clinical Liaison Nurses based in the NNBSL, CHI: 01 892 1804
National Centre for Inherited Metabolic Disorders (NCIMD): 01 878 4317 CHI at Temple St., Dublin, DO1 YC67 for advice on metabolic disorders
National Healthy Childhood Programme (NHCP) contact details: **Email:** healthy.childhood@hse.ie / child.screening@hse.ie **Website:** www.mychild.ie

National Newborn Bloodspot Screening Laboratory Opening Hours

Day	Opening hours	Services provided
Monday-Friday	09.00-17:00	All screens including Beutler tests, reporting of results and Clinical Liaison Nurse (CLN) service.
Saturday and Bank Holiday Monday Sunday-closed	09:00-12:30	**Beutler test -** high risk screen for Classical Galactosaemia Beutler samples must be in laboratory before 10 am. The test takes approx. 2.5hrs and all maternity units are phoned with results. To facilitate phoning of results, please note contact number on screening cards where results are to be phoned to.
NOTE: Christmas and New Year period opening hours will be circulated in advance.		

Abbreviations

ADA	Adenosine Deaminase deficiency
ADOM	Assistant Director of Midwifery
ADPHN	Assistant Director of Public Health Nursing
BCAA	Branch Chain Amino Acids
CHI	Children's Health Ireland
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	Director of Nursing
DON	Director of Nursing
GA1	Glutaric Aciduria type 1
GCDH	Glutaryl-CoA dehydrogenase
GP	General Practitioner
HCRN	Health Care Record Number
HCU	Homocystinuria
HSE	Health Service Executive
IHA	Integrated Healthcare Area
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 Bloodspot 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
RHA	Regional Health Area
SCID	Severe Combined Immunodeficiency
SECM	Self-employed community midwives
SMA	Spinal Muscular Atrophy
TPN	Total Parenteral Nutrition
TSH	Thyroid Stimulating Hormone
UPI	Unique parenteral identifier

Glossary of Terms

Sensitivity refers to a screening method's ability to designate an individual with a condition as screen positive. A highly sensitive method minimises the occurrence of false negatives.

Specificity is the ability of the screen to designate healthy people as screen negative. A highly specific screen minimises the occurrence of false positives.

Positive predictive value (PPV) is the likelihood that the screening participant has the condition screened for when the screen is positive.

Negative predictive value (NPV) is the likelihood that the screening participant does not have the condition screened for when the screen is negative.

A **false positive** is a positive screen in a person who does not have the condition being screened for.

A **false negative** is a negative screen in a person who has the condition being screened for.

Purpose and target audience:

This guide is produced by the National Newborn Bloodspot Screening Laboratory (NNBSL) and the HSE National Healthy Childhood Programme to provide practical advice and guidance for public health nursing and maternity/midwifery services on key aspects of sample taking for the National Newborn Bloodspot Screening Programme (NNBSP), including:

- Overview of the NNBSP
- Mode of inheritance
- Information on the conditions included in the NNBSP
- Timing of sample taking
- Obtaining informed consent for screening
- How to take a high quality bloodspot sample
- Indications for repeat sampling
- How screening results are reported by the NNBSL
- How screen positive results are followed up

The information contained in this guide is also relevant for:

- Laboratory personnel, including those providing second-tier/confirmatory testing for the NNBSP
- Designated Liaison Persons (DLPs) and Paediatricians/Neonatologists communicating screen positive results to parents and arranging further testing and clinical evaluation for infants who screen positive
- Other stakeholders with a role or interest in the delivery and quality assurance of newborn bloodspot screening in Ireland

Alongside this Practical Guide, the HSE NHCP has developed a PPPG - 'National p*rocedure for all staff providing the National Newborn Bloodspot Screening Programme'*. This national procedure is in place to ensure standardised, safe and effective delivery of the NNBSP across Ireland.

Section 1: Key Messages

As described above, this guide is intended to provide practical advice and guidance for PHN and maternity/midwifery services on key aspects of sample taking for the NNBSP. Key messages contained in this guide include:

1.1 General messaging to support understanding of screening and obtaining informed consent from parents

- **Definition of screening**
  Newborn screening aims to identify infants at increased risk of serious conditions before symptom onset, facilitating early diagnosis and intervention and improved clinical outcomes.
  The purpose of the NNBSP is to identify infants at risk of having one or more of the conditions screened for. These infants can then be offered further testing (diagnostic testing) to determine whether they have the condition or not.

- **Effectiveness of screening**
  No screening test is 100% accurate. As with all screening programmes both false negative and false positive screening results are possible (see glossary of terms). The NNBSP monitors the occurrence of false positives and false negatives and takes action to ensure they are kept to a minimum.

- **Conditions screened for**
  The NNBSP screens for 11 conditions. Of note, SCID and SMA were recently added to the screening programme in 2026. Further information on these conditions (and all other conditions screened for) is provided in section 11.

- **Provision of consent**
  The parent(s)/legal guardians are required to sign the newborn bloodspot screening card before the sample is taken to confirm their consent for their infant to be screened. Informed consent is critically important for any screening programme and for this parent(s)/legal guardian(s) need to be provided with the relevant parent information leaflet(s) and any questions that they may have be answered. More information on consent is available in Section 3.

  By signing the screening card, the parents are confirming that:
  - they are the legal guardian for the infant
  - they got and understood the information about the heel prick screen
  - the information about their infant on the screening card is correct
  - they consent to having their infant screened. This involves different laboratory tests
    - screening will include a genetic test to look for spinal muscular atrophy only
    - screening may include a genetic test to screen for cystic fibrosis

- they consent to how the screening programme uses and stores their personal information
- they consent to the screening card being stored for 10 years
- they consent to other uses of the screening card and data such as when adding new conditions to the screening programme, for national and international quality assurance, related screening programme evaluation (Information for these purposes are anonymised)

- **Terminology**
  When coordinating/undertaking bloodspot sampling, please use the term "newborn bloodspot screen". The term "PKU test" is outdated and inaccurate. PKU (or phenylketonuria) is only one of the conditions included in the NNBSP. When discussing screening with parents/ obtaining informed consent, the term “heel prick test” can also be used.

- **Use of personal data**
  Parent(s)/legal guardians must be made aware that:
  - the newborn bloodspot screening programme collects and securely stores the parent(s)/legal guardian(s) and their infant's personal information (name, address, phone number, date of birth etc.) This also includes the infant's newborn bloodspot screening results.
  - the information on the infant's screening card and their screening results are securely stored by the healthcare professionals who deliver the screening programme
  - these healthcare professionals may use this information to contact the parent(s). For example, if the infant needs a repeat bloodspot screening sample or a further screening test.
  - information from the Irish bloodspot screening programme may also be used for:
    - national and international quality assurance
    - related screening programme research

    This information is anonymised and cannot be linked back to the infant
  - it is the parent(s)/legal guardian(s) choice to take part in screening or not. The NNBSP will never use the parent(s)/legal guardian(s) or the infants name in any reports, when teaching or in any programme reviews.
  - the NNBSP will keep the parent(s)/legal guardian(s) and their infant's personal information safe, secure and confidential in line with current data protection regulations.
  - the parent(s)/legal guardian(s) will have access to their and their infant's personal information held by the National Newborn Bloodspot Screening Programme upon request.

- **Use of the NBS card after screening**
  Parent(s)/legal guardians must be made aware that after screening the NNBSL will store the results and the screening card securely as part of their infant's health record. The NNBSL will store the card for 10 years. After this time the card will be disposed of. The stored cards may be used:
    - to check their infant's screening result
    - for other tests that their doctor recommends for their infant (Note: they will be asked for their consent).

    - Expanding the screening programme
      In the future, the NNBSP may add new conditions to the screening programme. If a new condition is added, the laboratory will need to test bloodspot samples. This is to make sure that the new screening test works well. These tests may include genetic tests specific for the condition that the screening programme has been requested to add.

      All samples used for this reason are anonymised. This means names are removed. The sample cannot be traced back to an individual child.

      Samples are never used for commercial purposes.

1.2 Guidance to support high quality sample taking

- **Filling out the newborn bloodspot screening card**
  The NBS card must be completely filled out with all information clear and legible. Errors made while filling out the card can lead to avoidable repeat samples being taken and screening results reported to the incorrect location.

  The current location of the infant, i.e. where they are at time of sampling, must be clearly documented on the screening card. This is of particular importance when the infant has moved from their birth hospital to another hospital/clinical setting.

- **Noting the correct geographic area on the NBS card**
  It is important that the correct LHO/Community Care Area/IHA is recorded on the NBS card as the screening results are reported back to this area via eReports. The terminology to describe the relevant areas has changed over the years but it reflects the geographic area under the responsibility of the Director of Public Health Nursing.

- **Noting Meconium Ileus (MI) on the NBS card**
  Meconium Ileus (MI) is a blockage in the small intestine of a newborn infant and is associated with a possible diagnosis of cystic fibrosis (CF). If an infant has MI at the time of sample taking, it is **imperative to document MI on the NBS card. This is to be documented in the box labelled 'Comments/Family Hx/Beutler/Meconium Ileus' (see Appendix 3 for a**

copy of the NBS card). No other information regarding meconium needs to be documented on the card.

- **Sample taking technique**
  The gold standard technique for sample collection is the **hanging droplet** technique – see Section 6.5.1.

  There are several bloodspot quality issues that may require a repeat sample to be taken that could have been avoidable, e.g. sample contamination, serum rings.

  The most significant bloodspot quality issue is the volume of blood contained within the 3.2 mm punch taken from the circle of blood on the card. The volume of blood has a significant impact on the reliability of analyte measurements taken from it. Therefore, all sample takers must ensure that the blood collected completely fills each of the four 10mm circles on the NBS card and is soaked through to the other side of the card.

  An inadequate amount of blood or a poor quality sample will require the procedure to be repeated, causing discomfort to the infant, anxiety to the parent, inconvenience to the sample taker and potentially resulting in delayed diagnosis. Additionally, parents may refuse repeat sampling due to concerns around the discomfort caused to the infant, resulting in a missed opportunity for screening.

  Please make every effort to take a high quality sample at your first attempt that fully fills each of the four bloodspot circles on the NBS card with blood soaked through to the other side of the card.

1.3 Guidance regarding timing of sample taking and red weather alerts

- **Samples due to be taken on Thursdays:** to ensure samples reach the NNBSL in a timely manner and to minimise a delay in reporting, please take these samples early on the Thursday morning (provided that the newborn is 72 hours old), allow sample to dry fully, and post on Thursday afternoon to arrive in laboratory on Friday morning for analysis.

- **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 for either the PHN or the parent and infant against the risk of delayed newborn screening. Further advice on sample taking in the context of red weather alerts can be sought from NNBSL.

1.4 Guidance regarding sample taking in infants less than 36 weeks and in infants requiring admission to NICU/PICU

- These infants require specific protocols. Please see sections 4.3.1 and 4.3.2 for further information.

1.5 Newborn bloodspot screening test results

- Parent(s)/legal guardian(s) are not routinely notified of normal ('no condition suspected') bloodspot screening results. However, they are entitled to, and must be given a copy of their infant's results by their PHN if requested.

1.6 Incidents – National Incident Management System

All staff involved in the provision of the NNBSP must ensure that all risks and incidents relevant to the screening programme are monitored and actioned as required as per the HSE Incident Management Framework (2020) with completion of National Incident Report Forms (NIRF) as required and submission to the National Incident Management System (NIMS).

1.7 Regional Health Areas/Integrated Healthcare Areas

- As part of HSE reform processes, there are now six Regional Health Areas (RHAs) replacing the previous nine Community Healthcare Organisations (CHOs).

- Within the six RHAs there are 20 Integrated Healthcare Areas (IHAs), each comprising the geography of a number of the (now obsolete) Local Health Office (LHO) areas. The LHO areas no longer exist. Table 1 outlines the new geographic areas and the LHOs that have been captured in the new IHAs.

Table 1: New HSE Regional Health Areas and Integrated Healthcare Areas

Regional Health Area	Integrated Healthcare Area	Local Health Office (obsolete)
HSE Dublin and North East	Cavan/Monaghan	Cavan/Monaghan
	Louth/Meath	Louth
		Meath
	Dublin North City and West	Dublin North West
		Dublin North Central
	Dublin North County	Dublin North
HSE Dublin and Midlands	Dublin South City and West	Dublin South City
		Dublin West
	Dublin South West	Dublin South West
	Kildare/West Wicklow	Kildare/West Wicklow
	Midlands	Laois/Offaly
		Longford/Westmeath
HSE Dublin and South East	Carlow Kilkenny and Tipperary South	Carlow/Kilkenny
		Tipperary South
	Waterford Wexford	Waterford
		Wexford
	Dublin South and Wicklow	Dublin South East
		Dun Laoghaire
		Wicklow
HSE South West	Cork North and East	North Lee
		North Cork
	Kerry	Kerry
	Cork South and West	West Cork
		South Lee
HSE Midwest	Limerick City and Tipperary North	Tipperary North/East Limerick
	Clare and Limerick County	Clare
		Limerick
HSE West and North West	Donegal	Donegal
	Sligo Leitrim	Sligo/Leitrim/West Cavan
	Mayo	Mayo
	Galway Roscommon	Galway
		Roscommon

Section 2: Background – Overview of the National Newborn Bloodspot Screening Programme

The HSE National Healthy Childhood Programme (NHCP)[1] provides two population level screening programmes:

- the National Newborn Bloodspot Screening Programme (NNBSP) and
- the National Universal Newborn Hearing Screening Programme (UNHSP)

These programmes are delivered as integrated components of the NHCP, the universal programme of clinical care offered to all children in Ireland to support them and their families form birth.[2]

Newborn bloodspot screening has been embedded in universal health services for the children of Ireland since 1966, when the programme commenced with screening for phenylketonuria (PKU). The NNBSP now screens for a total of 11 conditions (Table 2) following the addition of Spinal Muscular Atrophy (SMA) and all forms of Severe Combined Immunodeficiency (SCID) in 2026.

Table 2: Conditions included in the National Newborn Bloodspot Screening Programme

Condition	Date Started	Irish Incidence (2017-2024)	Worldwide Incidence
Phenylketonuria (PKU)	1966	1:4,078	1:12,000
Homocystinuria (HCU)	1971	1:66,417	1:120,000
Classical Galactosaemia (CGAL)	1972	1:10,566	1:45,000
Maple Syrup Urine Disease (MSUD)	1972	1:464,916	1:225,000
Congenital Hypothyroidism (CHT)	1979	1:836	1:3,500
Cystic Fibrosis (CF)	2011	1:2,142	1:3,500
Glutaric Aciduria Type 1 (GA1)	2018	1:85,379	1:100,000
Medium Chain Acyl Co-A Dehydrogenase Deficiency (MCADD)	2018	1:17,076	1:14,600
Adenosine Deaminase Deficiency Severe Combined Immunodeficiency (ADA-SCID)	2022	1:137,072	1:200,000
Severe Combined Immunodeficiency (SCID)*	2026	1:40,000	1:50,000-1:85,000
Spinal Muscular Atrophy (SMA)*	2026	1:12,200	1:8,900

Screening for GA1 and MCADD commenced in December 2018. Irish incidence reflects six years of screening (2019-2024)
Screening for ADA-SCID commenced in May 2022. Irish incidence reflects 2.5 years of screening
*Screening commenced in 2026 – incidence estimates obtained from HIQA HTAs

[1] https://www.hse.ie/eng/health/child/newbornscreening/
[2] https://www.hse.ie/eng/about/who/healthwellbeing/our-priority-programmes/child-health-and-wellbeing/national-healthy-childhood-programmenew.html

The overall aim of the NNBSP is to reduce morbidity and mortality by screening newborn infants for rare but clinically serious conditions that benefit from early detection and intervention. Each year in Ireland, approximately 130 infants are diagnosed with a rare condition through the programme.

Newborn screening aims to identify infants at increased risk of serious conditions before symptom onset, facilitating early diagnosis and intervention and improved clinical outcomes. Screening is a pathway, not a diagnostic test. No screening test is 100% accurate and no screening programme will identify all infants with the condition screened for.

Newborn bloodspot screening involves taking a small sample of blood from a newborn infant's heel, (also referred to as the 'heel-prick'), between 72 and 120 hours after birth and placing the blood on a screening card. The blood sample is taken by either a midwife or a public health nurse (PHN) as part of routine postnatal care for mothers and infants. The screening card is then sent to the National Newborn Bloodspot Laboratory (NNBSL) at Children's Health Ireland (CHI) Temple Street, where samples are analysed, results reported, and from where onward care is organised. This includes referral of screen detected infants to the appropriate paediatric service for further testing and treatment, if indicated.

Newborn bloodspot screening is available to all infants born in the Republic of Ireland and to any child (up to one year of age) who arrives in Ireland before any screening has been performed or if conditions that are screened for in Ireland are not screened for in their country of birth. The screening method for cystic fibrosis (CF) is not reliable in infants over six weeks of age – see section 8 for further information on CF screening, including recommendations for infants over six weeks of age.

Governance for the National Newborn Bloodspot Screening Programme

Overall programme ownership, clinical governance and quality assurance for the NNBSP lies with the National Public Health Function of the Chief Clinical Officer (CCO) of the HSE. As described above, the NHCP screening programmes are delivered as integrated components of the NHCP, which sits within the National Public Health function of the CCO. The HSE has also convened a Child Screening Oversight Group, chaired by the National Clinical Director HSE Quality and Patient Safety. The purpose of the Oversight Group is to provide strategic oversight and direction to the NNBSP through review and monitoring the performance and governance of the NNBSP.

Clinical governance (including quality assurance) for the NNBSP is provided through the NNBSP Clinical and Quality Assurance Group and the NNBSP Operational Group. These multidisciplinary groups, chaired by the National Clinical Lead Child Heath Public Health, include representation from key stakeholder groups including the NNBSL, paediatrics, public health nursing, midwifery, public health medicine and administrative staff.

Section 3: Consent for newborn bloodspot screening

3.1 Who can give consent?

Only an infant's legal guardian can provide informed consent for screening and sign the NBS card. Being clear who can give informed consent can be challenging.

The HSE has published the revised National Consent Policy (2022, revised 2024) and Part 2 specifically related to children and young People. Appendix 9 (page 107) of the National Consent Policy provides clarity as to who qualifies as a child's legal guardians and are therefore authorised to give consent.

The National Consent Policy (2022, revised 2024) notes that this is a complex legal position and the relevant provisions are set out in the *Guardianship of Infants Act 1964*, as amended by the *Child and Family Relationships Act 2015.*

If you have any cases of challenging informed consent, or where you are unclear who can consent, please contact National Healthy Childhood Programme (NHCP) by emailing child.screening@hse.ie or phone (086)1033771.

Given the tight timeframe for sample taking (72-120 hours) early contact is advisable. If unable to get advice to allow screening within the recommended timeframe ensure that a National Incident Report Form (NIRF) is completed and entered onto the National Incident Management System (NIMS).

3.2 Consent in non-complex cases

Mother and father are married: both are legal guardians and either can give consent for newborn bloodspot screening as per Section 6 of the *Guardianship of Infants Act 1964*.

Mother and father are not married: the birth mother is automatically the infant's legal guardian and can provide consent for screening and sign the NBS card. The father is not the legal guardian unless conditions in the bullet below are met and therefore, cannot provide consent for screening (see next bullet point for further info).

- If unmarried, the infant's father is an automatic legal guardian only if he has lived with the infant's mother for 12 consecutive months including at least 3 months with the mother and infant following the infant's birth. This may be relevant in situations where newborn bloodspot screening is offered to an infant older than 3 months and up to the age of one year.

Female same-sex couples: the infant's biological parent is the legal guardian. If the biological parent is not available, please contact NHCP by emailing child.screening@hse.ie or phone (086)1033771.

Where a same-sex couple has a baby through Donor Assisted Human Reproduction (not including surrogacy) and has complied with the provisions of Part 2 of the Children and

Family Relationships Act 2015 (i.e. they have used a recognised fertility clinic and have signed all the relevant consents and declarations), the spouse, civil partner or cohabitant of the mother will be the legal parent of the infant. In this situation, the spouse or civil partner of the biological parent will automatically be a legal guardian. If you are unclear whether a recognised fertility clinic was used and all the relevant consents and declarations were signed, please contact the NHCP by emailing child.screening@hse.ie or phone (086)1033771.

- A cohabitant will be a legal guardian if they fulfil the residence requirement stated above (i.e. have lived with the infant's mother for 12 consecutive months including at least 3 months with the mother and infant following the infant's birth).

Specific situations:

- If the father is unmarried to the birth mother and the birth mother is unavailable to provide informed consent and sign the NBS card, i.e. through illness or hospital transfer, the unmarried second parent cannot provide consent for screening.
  In these cases, the sample taker should make every effort to contact the birth mother to get verbal consent and should document this in the relevant clinical notes/child health record. Written consent from the birth mother must be obtained at the earliest opportunity and forwarded to the NNBSL.

- If the father is unmarried to the birth mother and the birth mother is not contactable, for example due to severe illness, then you should discuss with the NHCP by emailing child.screening@hse.ie or phone (086)1033771.
  Efforts should be made to ascertain what the birth mother's opinions/views are regarding newborn screening as well as a detailed family composition and medical history to support discussion with the NHCP programme.

- If the father is unmarried to the birthmother, if the birth mother is well but not available at the time of the midwife's bedside visit or the PHN home visit, alternative arrangements should be made to ensure the birthmother is present at the time of the test and can give informed consent. No other relative or friend can provide consent for screening

- Where an interim care order is in place only the parent(s)/legal guardian(s), or the birth mother if unmarried, can provide consent.

- If there is a full care order in place, consent can be provided by the relevant health or social care provider. HSE National Consent Policy (2022, revised 2024) notes that it is good practice to seek consent from parent(s)/legal guardian(s), but it is not mandatory.

- If the parent(s)/legal guardian(s) has literacy difficulties, they can be asked to make a mark on the NBS card to indicate that they have been fully informed about the benefits and risks of newborn bloodspot screening and that they consent to screening for their infant.

- Where married parents or legal guardians disagree about consent for newborn bloodspot screening, Section 4 (p.58) of the HSE National Consent Policy (2022, revised 2024) applies. A sample must not be taken against the wishes of a legal guardian (as per a 2001 Supreme Court ruling). The sample taker should confirm both parents are legally able to consent, assess any family history suggesting increased risk for screened conditions, and consult the NHCP by emailing child.screening@hse.ie or phone (086)1033771.

  If a high risk is identified, the NHCP may need to seek legal advice.

  If no increased risk is identified, screening should not proceed, and parents should be advised to seek to resolve the dispute, with support from the NHCP or the child's GP/PHN.

3.3 Obtaining consent in complex cases

There are other complex circumstances which may affect newborn screening and should be discussed with the NHCP by emailing child.screening@hse.ie or phone (086)1033771. A detailed family composition and medical history should be taken to support discussion with the programme.

Adoption

Where an infant has been jointly adopted, the adoptive parents are the infant's legal guardians and either adoptive parent can provide consent for screening. However, adoption is unlikely to have been completed at the time that newborn bloodspot screening is due to take place (72-120 hours after birth), and the birth mother would be the legal guardian at that time. Consent must be obtained from the birth mother.

Surrogacy

Surrogacy in Ireland

Where a child is born through surrogacy in Ireland, the surrogate mother is the legal guardian at birth, until the commissioning mother/father are appointed as legal guardians. The surrogate mother, as birth mother, has legal responsibility for the newborn until the infant is legally adopted. The commissioning parents cannot provide consent for screening until the adoption is completed.

For infants born to surrogates in Ireland it is permissible under the HSE National Consent Policy (2022, revised 2024) for consent to be obtained from the surrogate mother by the sample taker by telephone/electronic means (Part 2 Section 4.2.2) if deemed necessary.

If practicable, the surrogate mother may give consent prior to the infant being discharged from the maternity hospital/unit, but it must be made clear to the surrogate mother that she is consenting to newborn bloodspot screening for the infant. The discussion that has taken place and the consent agreement must be documented.

The commissioning mother, or a commissioning father, may apply to the Court for legal guardianship one they/she has fulfilled the relevant legal requirements (see National Consent Policy 2022, pages 140-141).

Surrogacy in another jurisdiction:
Under current Irish legislation, when an infant is born through surrogacy in another jurisdiction, only the birth mother has legal responsibility for the infant until the adoption is completed. Therefore, only the birthmother can provide consent for screening but may be resident in another jurisdiction. The commissioning parents cannot provide consent for screening until the adoption is completed.

The sample taker should discuss screening in these complex cases with the NHCP by emailing child.screening@hse.ie or phone (086)1033771.

Legal Father
To identify the legal father of the infant, the marital status of the surrogate mother must be determined:

- If the surrogate mother is married, under section 46 of the Status of Children Act 1987, the surrogate mother's husband is presumed by law to be the father of infant. The husband, will also, along with the surrogate mother, be the joint legal guardian of the infant.

- If the commissioning father is the genetic father, i.e. sperm donor, it is possible to overcome the presumption of paternity in favour of the surrogate mother's husband, so as to allow the commissioning father to be recognised as the legal parent of the infant. A guardianship order may also be sought by the commissioning father.

  Under domestic Irish law, this requires an application for a declaration of parentage to be made to the Circuit Court under Part VI of the Status of Children Act 1987. Application should also be made by the commissioning father for a guardianship order. The commissioning father will need to provide evidence of paternity in support of this application.

- If the surrogate mother is not married, and the commissioning father is the genetic father of the infant, their paternity of the infant may be recognised in Irish law on the receipt of reliable DNA evidence.

- As the genetic father is not married to the surrogate mother, they are not automatically a guardian of the infant under Irish law, even if granted a declaration of parentage. Under Irish law the commissioning father can obtain a guardianship order if they are the genetic father of the infant.

3.4 Consent - sample taker responsibility

The sample taker is responsible for ensuring that appropriate informed signed consent is obtained prior to any sample being taken, or that it has been discussed with the NHCP.

Sample takers must inform the parent(s)/legal guardian(s) that by signing the NBS card they are confirming that:

- they are the infant's legal/guardian
- they received and understood the information about the heel prick screen
- the information that is written on the screening card about their infant is corre
- they consent to having their infant screened and that this involves different laboratory tests
    - Screening will include a genetic test for spinal muscular atrophy only
    - Screening may include a genetic test for cystic fibrosis
- they consent to how the NNBSP use and store their personal information
- they consent to the screening card being stored for 10 years
    - they consent to other uses of the card and personal information and data such as when adding new conditions to the screening programme, for national and international quality assurance, related screening programme evaluation (Information for these purposes are anonymised)

The NNBSL has a duty of care to analyse all NBS samples received, irrespective of 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 informed consent is obtained when taking the sample.

3.5 Return or disposal of newborn bloodspot screening cards

Parent(s)/legal guardian(s) may request that the NBS card be returned to them or disposed of. It is 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 of CHI. 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.

Section 4: Preparing for taking the newborn bloodspot screening sample

Sample collection timeframe

Samples on all newborn infants must be collected **between 72-120 hours after birth**, irrespective of feed status, gestational age or clinical condition.

This sample must be collected by heel-prick, air dried and dispatched without delay to the NNBSL. If a screening sample is taken outside the 72-120 hrs window, it may adversely affect the result as follows:

- **If collected before 72 hours:** It is essential that all infants receive an adequate protein and lactose/galactose intake before the sample is taken, otherwise a false negative result may occur for several of the metabolic conditions. For this reason, the sample is taken after 72 hours.

  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 hours) some infants may have a false positive screen for CHT.

  If an NBS sample is taken before 72 hours, a repeat card will be requested.

- **If collected after 120 hours:** because the programme includes screening for time critical conditions, it is essential that samples are not collected too long after birth. If screening is delayed, some infants may die or present clinically with serious symptoms before the screening results are available. Refer to Section 8: Infants who are not screened within the 72-120 hour recommended timeframe.

4.1 Assessing feeding status

The NBS sample should be taken **not earlier than 72 hours and not later than 120 hours** after the infant's birth.

4.1.1 Feeds at time of sample collection

Infants should be established on **full protein and lactose containing feeds for at least 24 hours** before the screening sample is taken to minimise the risk of a false negative result.

Infants at high risk of CGAL should not be given lactose/galactose containing feeds until the result of the Beutler test is available (see section 4.2.1).

Feed type(s) must be clearly documented on the NBS card to ensure correct result interpretation and to ensure that a false negative is not reported.

Sample takers must determine feeding status by reviewing the infant's intake over the preceding 24 hours and applying professional, clinical judgment in their decision-making.

Sample takers should use their professional clinical judgement in decision making around the infant's feeding intake at the time of sampling.

- For breastfed infants in the community, the Breastfeeding Observation Assessment Tool (BOAT) should be used to guide assessment of feeding and support professional decision making.

- For breastfed infants in the maternity hospital/unit, local individual feeding records (i.e. LATCH score) are available to guide assessment of feeding and support professional decision making.

- For infants on expressed breast milk or formula, the sample taker can review the infant's intake over the previous 24 hours to aid assessment of feeding and support professional decision making.

Using professional clinical judgement, if an infant has not been feeding well, then:

- the sample taker should arrange to take the NBS sample the next day if it is still within the 72 to120 hour window and as close to 120 hours as possible

- if still not feeding well, take the initial sample within the 72 to 120 hour window, but arrange for an additional sample to be taken on or around Day 10 after birth.

Please contact the NNBSL (01 892 1804) for advice on feeds if unsure.

4.1.2 Soy feeds, total parenteral nutrition (TPN), IV fluids, glucose/dextrose

It is imperative that information on soy feeds/TPN/IV fluids/glucose/dextrose intake only within the last 24 hours is recorded on the NBS card.

Please ensure to tick the appropriate box(es) in the 'Type of feed' section of the NBS card (Appendix 3). For example do not tick TPN if the infant was previously on TPN but is no longer on TPN at time of sampling.

This is to ensure correct screening result interpretation.

A repeat screening sample should be collected when IV fluids have been discontinued and full feeds have been established for at least 24 hours.

See below for further clarifications and actions.

- Infants on IV fluids may not have adequate protein and galactose intake, which may result in a **false negative** screening result for some metabolic conditions, including CGAL.

- If an infant is on IV/Glucose or dextrose a **false negative** screening result may be reported for MCADD.

- TPN and soy feeds do not contain galactose. As a result, infants that are on TPN or soy may receive a **false negative** screening result for CGAL. A Beutler test can be performed on these infants to out-rule CGAL, provided the infant has not had a RBC transfusion.

- TPN is weaned very gradually in newborns, particularly preterm infants, with milk feeds increased as TPN is reduced. A repeat sample should be taken after full feeds have been established for at least 24 hours.

- CGAL cannot be out ruled on RBC transfused infants who have not had a pre-transfusion Beutler, until the infant is established on full lactose/galactose containing feeds for a period of time to allow for detection of a raised galactose level.

- In the event where an infant remains on TPN/IV fluids and a Beutler could not be performed due to RBC transfusion, the infant should be monitored for clinical and laboratory signs (prolonged clotting times and raised liver enzymes) of CGAL when being established on lactose/galactose containing feeds. If a conclusive diagnosis is required molecular genetic testing may be indicated and should be followed up with clinical team in Maternity/Paeds unit.

4.2 High risk infants

Some infants require additional samples before or after the 72 to 120 hour window.

4.2.1 Infants born to Irish Traveller parents

The incidence of CGAL amongst members of the Irish Traveller population is high. As a result, a specific screening test, the Beutler test, is required.

Sample takers should take a NBS sample as soon as possible on day 1 after birth on all infants of Irish Traveller parents.

This is in addition to the routine screening sample which still must be taken between 72 and 120 hours.

Parents/legal guardians are advised to keep the infant on a galactose free diet until the results of the Beutler test is available.

Beutler samples must be dried and sent to the NNBSL as soon as possible. Do not batch Beutler samples before sending.

For Traveller mothers who wish to breastfeed, they should discuss this with their midwife as they can express their milk and store it until the results of the Beutler test are available.

4.2.2 Infants at high risk due to family history

If there is a family history (parent or sibling) of the newborn infant with a known case of any of the conditions screened for by the NNBSP, the newborn is considered at high risk of having this condition. These infants require specific sample requirements as described below.

In these circumstances, the pregnancy will typically have been identified as high risk at an early stage and will be carefully monitored by the relevant clinical services.

Screening requirements for the infant will be determined by the clinical team. In addition to specific screening testing requirements for the condition suspected, the infant will also typically require a routine NBS card in the usual timeframe of 72-120 hours following birth.

Family history of the condition suspected should be noted on the NBS card(s) and clarified; for example, whether a parent or sibling has the condition and the name of the condition, e.g. MCADD.

This section provides further information on the actions to be taken when there is a family history of any of the conditions screened for under the NNBSP, Table 3 provides more detailed information on sampling requirements for these infants.

For clarifications, please contact the relevant clinical teams or the NNBSL – see details below.

	Contact Details
Clinical Liaison Nurses NNBSL	01 892 1804
NNBSL Laboratory	01 878 4277 info.newbornscreening@childrenshealthireland.ie
Metabolic Conditions (PKU, HCU, MSUD, MCADD, GA1 and CGAL) National Centre for Inherited Metabolic Disorders (NCIMD)	01 878 4317
Cystic fibrosis Department of Clinical Genetics, CHI, Crumlin	01 4096733 duty.scientist@childrenshealthireland.ie
ADA-SCID or SCID Clinical Immunology Team, CHI Crumlin	01 4096893 immunology@childrenshealthireland.ie
SMA Paediatric Neurology Team, CHI Temple Street	01 8784200

Specific considerations based on family history of condition

Maternal phenylketonuria (PKU)
Phenylalanine is actively transported across the placenta. As a result, the blood level in the foetus is about twice that of the mother. Pregnancy should be discussed with the metabolic clinical team in the National Centre for Inherited Metabolic Diseases (NCIMD), and women who have PKU should aim to ensure that their PKU is under optimal control at the time of conception. Regular and frequent monitoring of blood levels of phenylalanine and tyrosine is required throughout pregnancy in order to safeguard the wellbeing of the foetus.

If the 72 hours following birth falls on a Saturday, the required 2mls lithium heparin liquid sample can be taken and sent to metabolic laboratory in CHI Temple Street on the preceding Friday morning (i.e. at less than 72 hours of age) and the metabolic laboratory phoned in advance, in order to try to ensure that results are available on the Friday, thereby minimising parental anxiety over the weekend.

MCADD

Infants at high risk of MCADD should be screened at the earliest opportunity. Pregnancy should be discussed with the metabolic clinical team in the National Centre for Inherited Metabolic Diseases (NCIMD) to plan careful management at birth to minimise risk of decompensation. Management at birth may depend on the clinical presentation of previous sibling(s).

It is essential to ensure that an infant considered high risk for MCADD, such as a sibling of a confirmed case, maintains a good milk intake until their screening results are available. If the infant is well, they should be breast fed every 2-3 hours during day time and every 3 hours at night (at least 10 minutes on the breast). If bottle fed, then feeding every 3 hours is recommended.

Exclusively breastfed infants with undiagnosed MCADD/awaiting screening are particularly at risk of clinical decompensation in the first few days, as the initial supply of breast milk may be low. Top up feeds of expressed breast milk or formula may be necessary until a good milk supply is established. A feeding protocol can be provided by the NCIMD team.

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

Please seek advice from the metabolic clinical team in the National Centre for Inherited Metabolic Diseases (NCIMD 01 8784317) if needed.

Note: If an infant is on IV/glucose or dextrose, a false negative screen may be reported for MCADD. It is imperative that this is noted on the NBS card, and a repeat card collected when IV fluids discontinued.

Classical Galactosaemia

Advise lactose/galactose free feeds only (e.g. soy feeds) for infants at high risk of CGAL (i.e. infants with a parent/ sibling with CGAL and infants born to Irish Travellers) until results of Beutler test is available. The Beutler test is performed Monday to Saturday by the NNBSL.

Cystic fibrosis

For an infant born to a parent with CF, where no prior CF genetic testing has been carried out for the parents or the foetus, a blood sample from the infant and both parents should be sent, with parental consent, to the Department of Clinical Genetics, CHI Crumlin for genetic analysis against the 38 genetic variant panel currently included in the Irish newborn bloodspot screening programme for CF.

Table 3: Sampling requirements for high-risk infants

(ref: NNBSL: LI-NNS-0065 – High risk screening protocol for siblings or children of known cases)

Condition	Samples to be taken	When to take sample (time after birth)
PKU *Metabolic Lab* *01 878 4724*	**Lithium heparin** liquid sample for Phenylalanine and Tyrosine	72-120 hours
	NNBS Card	72-120 hours
	NNBS card *(if first card is not suspected*)	Day 10

Condition	Samples to be taken	When to take sample (time after birth)
HCU *Metabolic Lab* *01 878 4724*	**Lithium heparin** liquid sample for Methionine and Total Homocysteine (separate and freeze within 15 minutes)	72-120 hours
	NNBS Card	72-120 hours
	Lithium heparin liquid sample for Methionine and Total Homocysteine	Day 10

Condition	Samples to be taken	When to take sample (time after birth)
MSUD (Clinically urgent) *Metabolic Lab* *01 878 4724*	**Lithium Heparin** liquid sample for Branch Chain Amino Acids (BCAA) (separate and freeze within 15 minutes)	Day 1 after 2nd feed, then daily until established on full feeds
	Urine or blood for ketones tested	Daily
	NNBS card	72-120 hours
	NNBS card at Day 10 or Lithium heparin sample for BCAA	Day 10

Condition	Samples to be taken	When to take sample (time after birth)
CGAL (Clinically urgent)	NNBS Card (remain on soya feeds)	Day 1 Beutler
	NNBS Card	72-120 hours

Condition	Samples to be taken	When to take sample (time after birth)
CF	**EDTA** liquid sample sent directly from maternity hospital/unit to Genetics Lab, CHI Crumlin (if parents consent) *(Consent is the responsibility of the maternity unit)*	
	NNBS Card	72-120 hours
<u>Baby presenting with Meconium Ileus</u>	**EDTA liquid** sample sent directly from maternity hospital/ unit to Genetics Lab, CHI Crumlin for mutation analysis	
	NNBS card is sent for CFTR mutations regardless of IRT	72-120 hours

Condition	Samples to be taken	When to take sample (time after birth)
CHT	TFT sample (Lithium heparin liquid sample) Day 3, taken and analysed locally	
	NNBS Card	72-120 hours

Condition	Samples to be taken	When to take sample (time after birth)
MCADD (Clinically urgent) *Metabolic Lab* *01 8784458* *01 8785557*	DBS Acylcarnitine on **<u>Metabolic Screening Card.</u>** Write ‘’Family History of MCADD’; indicate if infant on IV fluids, glucose/dextrose *N.B. It is essential that the infant maintains a good milk intake*.	24-48 hours
	Urine for Organic acid – 5 mls fresh sample (frozen immediately at -20ºC) with no preservative	
	NNBS Card	72-120 hours
	DBS Acylcarnitine on **<u>Metabolic Screening Card</u>**	Day 10

Condition	Samples to be taken	When to take sample (time after birth)
GA1 Metabolic Lab 01 8784458 01 8785557	**DBS** Acylcarnitine on **Metabolic Screening Card**. Write ''Family History of GA1''; indicate if infant on IV fluids *N.B. It is essential that the infant maintains a good milk intake*	24-48 hours
	Urine for Organic acid – 5 mls fresh sample (frozen immediately at -20ºC) with no preservative	
	NNBS card	72 – 120 hours
	DBS Acylcarnitine on **Metabolic Screening Card**	Day 10

Condition	Samples to be taken	When to take sample (time after birth)
ADA-SCID **&** **All SCID** St James's Lab 01 4162925 01 4162927	**EDTA** liquid sample (2mls), sent unseparated at room temperature (marked *for 'Immunology' if SCID suspected and marked for 'ADA SCID' if ADA SCID suspected)* Send to: Immunology Laboratory, St James' Hospital, Dublin 8, D08 NHY1. *(Monday-Friday service only, cut-off for samples is 12pm Friday)* Sample is to be sent directly by Maternity unit and marked 'FHx SCID' detailing type of SCID condition Contact SJH Lab 01 4162925/ 01 4162927 and Clinical Immunology Team in advance 01 4096893 or email immunology@childrenshealthireland.ie	Day 1
	NNBS Card	72 – 120 hours

Condition	Samples to be taken	When to take sample (time after birth)
SMA	**NBS card** for SMA screening **1.2 ml EDTA** liquid sample sent unseparated at room temperature to Genetics Lab, CHI at Crumlin for MLPA	24 – 48 hours 24 – 48 hours
	NNBS Card	72 – 120 hours

Infants presenting with meconium ileus at birth
Meconium ileus (MI) is a common complication in infants with CF. Therefore, CF should be considered in all infants who present with meconium ileus and MI must be noted on the NBS card, plus the clinical team in the maternity hospital/unit should actively follow-up if MI is suspected.

Irish Travellers, consanguinity and endogamous populations
Twenty percent of the world's population practice consanguinity. This is a traditional practice in the Middle East, Pakistan, Bangladesh and North Africa. Couples in consanguineous marriages/unions and those who both come from the same endogamous community (e.g. Irish Travellers and Roma) have an increased risk of having a child with a rare inherited medical condition. There are certain autosomal recessive conditions that occur more commonly in different countries or endogamous populations. The Department of Clinical Genetics, CHI at Crumlin, can provide further advice on these conditions, the likely risk and genetic tests to consider in high-risk groups.

4.3 Special circumstances

There are a number of special circumstances that necessitate a different NBS protocol.

4.3.1 Bloodspot sampling in infants born at <36 weeks corrected gestational age who do not require NICU/PICU admission

Infants born at <36 weeks gestational age are at risk of false negative screening results for several conditions, including metabolic conditions, CHT and SCID.

For these infants:

- Take a routine screening sample at 72-120 hours
- Take further samples at weekly intervals for a maximum of 4 weeks (samples) and/or until they reach 36 weeks corrected gestational age
- If they have had 4 weekly samples but not yet reached 36 weeks, they will require a final sample at 36 weeks corrected gestational age
- Take a final sample when the infant reaches 36 weeks corrected gestational age.

The usual Beutler testing and pre-transfusion advice applies for preterm infants, i.e. if the infant is of Irish Traveller ethnicity, a day 1 Beutler is required (see section 4.2.1) and if the infant will receive a blood transfusion before the 72-120 hour time frame for routine sampling, a pre-transfusion sample should be taken (see section 4.3.3). Infants admitted to a NICU require an admission sample (see section 4.3.2)

4.3.2 Infants admitted to a Neonatal/Paediatric Intensive Care Unit (NICU/PICU

Sick infants who require admission to NICU also require additional consideration and protocols to ensure they are appropriately screened. Please see the protocol below for sampling in infants that are admitted to a NICU or a PICU.

NICU/PICU Admission Sample	Take a sample on all infants on admission to NICU/PICU, regardless of timing. This ensures all infants have had a sample taken before they receive any treatment such as RBC transfusion.
Routine Sample	Take a 72-120 hour sample on all infants, regardless of feeds or transfusion status
Weekly Samples	Following the routine 72-120 hour sample, take further samples at weekly intervals to a maximum of four samples. Less than 4 samples may be required if the infant has reached 36 weeks corrected gestational age (see info on final sample below) If infant has received RBC transfusion, take the sample 72 hours post the last transfusion otherwise a repeat sample will be required.
Final Samples	Take the final sample when the infant reaches 36 weeks corrected gestational age or If not on full feeds by 36 weeks, take the final sample when the infant is established on full feeds.

4.3.3 Infants receiving red blood cell (RBC) transfusions

- If a RBC transfusion is scheduled to be given before the routine 72 to 120 hour screening sample is taken, a pre-transfusion sample should be collected and marked clearly.

- This pre-transfusion sample is used to screen for CGAL by Beutler test and also assess acylcarnitine analytes (to screen for MCADD, GA1 and SCID) more accurately than a sample collected post transfusion.

- A routine screening sample must also be collected between 72 and 120 hours after birth regardless if the infant has had a transfusion. **The 72 to 120 hour sample should not be delayed due to transfusions**.

- For any further screening samples collected on transfused infants, please allow at least 72 hours to pass after any further transfusions before taking any additional screening samples, unless specifically requested by the NNBSL or relevant clinical team.

- If the infant received an **intrauterine transfusion**, this should be clearly noted on the NBS card, as this could give a **false negative CGAL** screening result.

- **The date and time of any RBC transfusions** should be clearly noted on the screening card.

- **Note:** A RBC transfusion invalidates the Beutler test for Classical Galactosaemia as the enzyme measured in the test is in the infant's red blood cells, and donor blood may cause a false negative screening result. For this reason a pre-transfusion sample is advised.

4.3.4 Infants on TPN or IV fluids

Infants who are on TPN or IV fluids may not be receiving galactose/lactose containing feed. TPN/IV fluids do not contain these sugars so the screening test could generate a false negative result.

Infants should have their 72-120 hour sample taken as well as a repeat screening sample when TPN/IV fluids are discontinued and full feeds have been established for at least 24 hours.

Information on TPN/IV fluids including glucose and dextrose intake at the time of screening must be recorded on the NBS card at the time of screening. For example, do not tick TPN if the infant was previously on TPN but is no longer on TPN at the time of screening.

Section 5: Recording of information on the newborn bloodspot screening card

Correct recording of information on the NBS card

- Ensure to check the expiry date on the NBS card – if it is out of date a repeat sample will be requested.

- Ensure that the NBS card has been completed in full and that all the information is correct and legible (parent/guardian to validate demographic details when NBS card is signed to indicate informed consent).

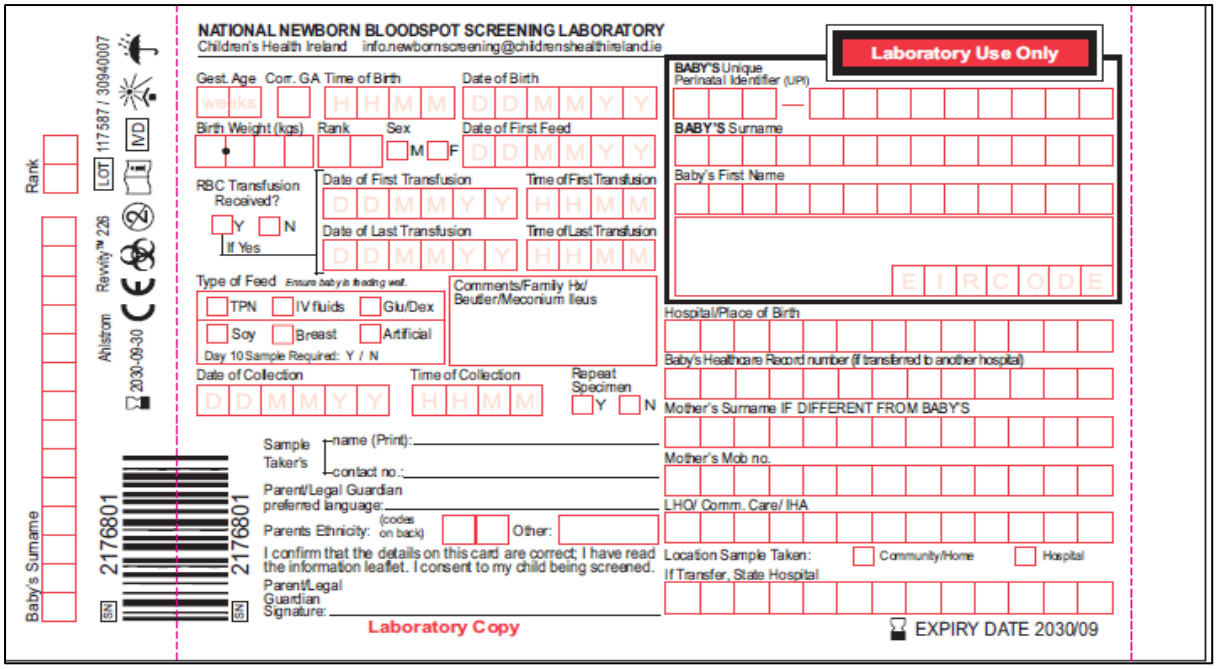
- A fully completed address, including Eircode, is required to ensure results are reported to the correct PHN/IHA area or maternity hospital/unit via the eReports electronic system.
    - Sample takers can use printed addressographs, if available, and if they can fit on the relevant section of the NBS card without obscuring other information/ fields – **please ensure addressograph is attached to <u>all copies</u> of the NBS card.**

- Particular care should be taken to distinguish twins, triplets etc, using the 'rank' field on the NBS card, as this is a recurring error and poses a risk of misidentification.

- The NBS card **must be signed by a parent(s)/legal guardian(s)** before the sample is collected to show evidence of informed consent and to confirm the details noted are correct.

- Ensure that there is no missing or incorrect information in the date/time of birth, date/time of collection, or date/time of blood transfusion(s) fields. This is a common recurring error that often requires clarification.

- Please complete all relevant fields on the NBS card. All the information requested is required to correctly identify the infant, aid in interpretation of results and ensure sample timing is correct, see further clarification below.



5.1 Clarification as to why certain information is required on the newborn bloodspot screening card

Gestational Age:	Preterm infants require additional screening samples. Gestation age of the infant aids result interpretation.
Date and time of birth:	This informs the NNBSL how many hours old the infant is at time of sampling. This should be greater than 72 hours of age and less than 120 hours of age when the first sample is taken, unless an earlier sample is indicated, e.g. pre RBC transfusion or family history of a metabolic condition.
Date of first feed:	This is reviewed and if there are concerns that there may be inadequate protein intake, a repeat NBS card will be requested for when the infant is established on full feeds, to reduce the risk of false negative screening results for metabolic conditions.
RBC transfusions if given:	Date(s) and time(s) to be documented accurately as transfusions can impact screening results. Refer to section 4.3.3: Infants receiving RBC transfusions, for more information

All feed types:	The type of feed at time of sample taking needs to be clearly noted on the NBS card to ensure accurate interpretation of the screening results. For example, if an infant is receiving some breast feeds and formula top ups and is also on intravenous fluids and/or glucose/dextrose at the time of sample taking, then 'breast, artificial, IV and Glu/Dex' should all be ticked. If an infant is on glucose/dextrose fluids when the screening sample is taken, this could give a false negative screening result for MCADD. If an infant is on TPN this also must be recorded because if an infant is solely on TPN, this increases the risk of a false negative CGAL screening result.
Comment/Family Hx/Beutler/Meconium Ileus:	Only relevant family history pertaining to one of the conditions screened for through the NNBSP needs to be recorded on the NBS card. If a sample is being taken for a day 1 Beutler high risk screen for CGAL, this must be highlighted clearly on the NBS card. If the infant presented with, or is suspected of having meconium ileus (MI), this is important to highlight as CF risk is increased and appropriate action can be taken. If the NNBSL is not made aware of the presence of MI, a false negative screening result for CF may be reported. Enquire about family history of immunodeficiency and maternal history of taking medication during pregnancy (e.g. steroids, immunosuppressant medication). This is of particular importance as certain medications may cause low T-cells leading to false positive results for SCID.
Repeat specimen:	It is important to record whether this is a repeat sample. This allows the NNBSL to link two or more samples on an infant and often prevents requesting unnecessary repeat cards.

Parents Ethnicity:	Collecting the ethnicity of both parents of infants screened is important as: • different ethnic groups will have different prevalences of the conditions screened for • identifying infants of Irish Traveller ethnicity allows us to offer the Beutler test to those who need it • capturing ethnicity data helps the bloodspot screening programme to ensure provision of an equitable service that meets the needs of the population Sample takers are requested to record an ethnicity code on the screening card for each parent. The list of ethnicity codes has been updated to reflect recent changes implemented by the Central Statistics Office (CSO) when carrying out the national census. If the ethnicity is unknown please leave blank or record '*unknown*'. For any queries around ethnicity in complex situations, please contact child.screening@hse.ie or phone (086)103377 for advice.
Consent:	The NBS card must be signed by the parent(s)/legal guardian(s) before the sample is collected. This indicates that the parent(s)/guardian(s) consent for their infant to be screened.
Unique Perinatal Identifier (UPI):	The UPI, issued by the maternity hospitals/units and DPHN offices, **must** be used to track each infant through the newborn bloodspot screening process. The UPI consists of the three digit hospital inpatient enquiry (HIPE) code of the respective maternity hospital/unit of birth followed by the healthcare record number (HCRN) or medical record number (MRN) of the infant. Infants born via homebirth will be issued with a UPI by the DPHN in the area in which the birth occurs. Infants born outside of Ireland will be issued with a UPI by the DPHN in the area in which the infant resides. An infant must only have one UPI assigned and this must be used on all NBS samples sent to the NNBSL.

Receiving hospital:	If an infant is transferred from the hospital of birth to a different hospital, the birth hospital is responsible for ensuring that the infant's UPI is included on all referral correspondence. If the UPI is not provided, the receiving hospital must contact the birth hospital to obtain the UPI. They **must not** generate their own UPI.
Hospital Healthcare Record Number (HCRN) (if transferred to another hospital from birth hospital):	If an infant is transferred to another hospital, the HCRN or MRN of the receiving hospital must also be recorded on the NBS card.
Baby's address	This needs to be fully completed, including the full address and Eircode. This will help identify the DPHN/Community Care Area/Integrated Healthcare Area (IHA) that the screening result is to be reported to.
Mother's surname (if different from the baby's):	On occasion, the surname of the parent/legal guardian signing the consent can differ from the infant's surname and may require clarification, e.g. if the parent must be contacted because a repeat sample is required or a screen positive result reported. Recording the mother's surname on the NBS card can assist with these clarifications and provide reassurance around the identity of the infant.
LHO/Comm Care/IHA area:	All results are issued via the eReports electronic reporting system to the LHO/Community Care Area/IHA area that is recorded on the NBS card. This area is reflective of the geographic area of responsibility of the DPHN. They are also reported to the maternity hospital/unit of birth. If an incorrect area is recorded, the result will be reported to the incorrect area. This can lead to delays in follow up of infants who need a repeat sample taken and is problematic for liaison PHNs tracking results of infants notified to their area.

Section 6: Taking the newborn bloodspot sample

6.1 Provision of Parent Information Leaflet

Ensure that the parent(s)/legal guardian(s) are provided with the information leaflet '*What you need to know about newborn bloodspot screening – the heel prick test'*.

Review the information with them and answer any questions that they may have.

6.2 Assess feeding status

Refer to Section 4.1 on how to assess the feeding status of the infant prior to taking the NBS sample.

6.3 Obtain signed informed consent

Ensure that sample takers obtain signed informed consent from the parent(s)/legal guardian(s) – refer to Section 3 on Informed Consent.

6.4 Complete all data fields on the NBS card

Ensure that all data fields are completed on the NBS card – refer to section 5 and there are also instructions on the back of the NBS card.

Ask the parent to sign the card to confirm informed consent for screening and that the demographic details are correct.

Tear off the top information sheet from the NBS card and give this along with the <Parent Copy> to the parent(s)/legal guardian(s) along with the Parent Information Leaflet.

Retain the <Sample Taker Copy> for filing in the child health record or maternity chart.

Ensure the <Laboratory Copy> remains attached to the card.

6.5 Gather equipment for the procedure:

- Automated incision device (lancet) of penetrative depth of no more than 2.4 mm in depth and gauze. Smaller lancets should be used for premature infants (0.85mm lancets are available)
- Latex free gloves (latex can interfere with the test and may give a false result)
- NBS card (Check expiry date on NBS card and do not use if this date has passed)
- Gauze
- Cool, sterile water
- Envelope for dispatch to lab, water resistant and tear-proof (Tyvek or equivalent

envelope)
- Drying box if necessary
- Sharps box for safe disposal of automated incision devices.

6.6 Technique for sample collection

- Ask parent(s)/legal guardian to keep the infant's feet warm prior to taking the sample by applying two sets of socks approximately an hour in advance.

- Do not use any active heating mechanism such as warm water or a hair dryer to warm the infant's heel prior to undertaking screening as there is a risk of thermal burns from such practice.

- Wash hands and apply latex free gloves. DO NOT touch bloodspot rings on the NBS card with gloves before, during or after the sample is taken.

- Ensure the heel is visibly clean, dry and warm. Routine cleansing of the heel is not required but if the heel is visibly dirty or soiled, clean the foot and heel with gauze soaked in cool sterile water and dry.

- Do not use alcohol or baby wipes as they may interfere with sample results and can cause serum rings to form and contaminate samples.

- Do not use soft paraffin (e.g. Vaseline) or any cream at the puncture site as it can cause contamination or abnormal results.

- Ensure the infant's foot is below heart level to assist with blood flow.

- Discuss with the parent their preferred method of holding their infant during sample taking. Where possible, collect the sample while the parent cuddles the infant on their knee or on their shoulder in an upright position, ensuring the infant feels secure and comforted, with the heel gently supported and hanging below the level of their heart.

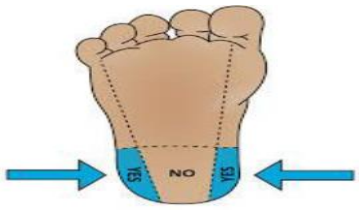
- Ensure the infant is warm and comfortable.

- Encourage safe skin to skin contact, breastfeeding or non-nutritive sucking to aid comfort during sample taking.

- Place a paper towel on the lap of the individual holding the infant.

- Select the puncture site on the heel. The preferred puncture site and least hazardous site are indicated by the shaded areas of the heel on the back of the NBS card and the image below; i.e. the lateral borders of the planter, avoiding the central area of the heel. The heel is the preferred site because it

has a good supply of capillaries close to the skin surface, making it easier to collect blood.



- If required, gently rub the heel for the heel for one to two minutes to increase blood supply.

- Encircle the heel with finger(s) and thumb and hold the foot downwards. Gently massage the heel to encourage blood flow. Squeeze gently until the skin looks taut and suffused/filled with blood.

- Place the automated incision device (lancet) firmly against the side of the ball of the infant's heel and activate the device.

- Wipe away the first drop of blood as this may be diluted, and allow another drop to form.

- Blood should only be applied to one side to the NBS card, from the back. All blood is to be dropped onto the NBS card from the back of the card using the 'hanging droplet technique' – see further details below.

- Allow the blood drop to fall freely from the heel onto the centre of the circle marked on the NBS card.

- Check that the blood has soaked through to the other side of the NBS card.

- Fill each of the four circles marked on the NBS card using the 'hanging droplet technique'.

- The hanging droplet technique is the recommended method for applying blood drops and uses the kinetics of blood spreading to soak blood evenly across the spot diameter, as opposed to touching the filter paper to the heel.

- To enhance blood flow, very gentle, intermittent pressure may be applied to the area surrounding the puncture site.

- DO NOT touch the NBS card to the heel.

- DO NOT press or squeeze the bloodspot to force it through the NBS card as this can compress the blood cells.

- DO NOT layer more than one drop of blood per circle.

- Ensure that the blood has soaked completely through the circle from the back to the front of the card for all four circles.

- When sample is turned over for final checks it will be obvious if blood has not fully soaked through and if the pre filled printed spot areas are fully filled or not.

- Wipe away any excess blood with sterile gauze. Apply gentle pressure with the sterile gauze to the infant's heel to stop bleeding.
  It is not recommended that a plaster is used as this may be a choking hazard if swallowed.

- Ensure the screening sample is completely dry by air drying the newborn screening card before putting it into the tear-proof, water resistant envelope. Do not use any type of heat (e.g. radiators) or place in direct sunlight as this may invalidate the test and could led to a false result. Failure to fully dry the sample may invalidate the screening sample result.

- Ensure not to contaminate the filter paper circles. Possible reasons for contamination include spillage of liquids or lotions or allowing the card to come in contact with gloves or placing the sample wet into the envelope.

- Drying bloodspots stabilises analytes, allowing longer time periods between taking the sample and sample analysis without compromising results. If the NBS sample is not dry when it is put in an envelope, blood will leach from the filter paper onto the envelope, altering the blood volume left in the filter paper and could generate an inaccurate result.

- Send the sample by using registered post or by courier to the NNBSL using the recommended water proof envelope and the yellow fluorescent address labels. If more than one NBS card is placed in an envelope, ensure they are placed at 180 degrees to each other to avoid blood touching blood. Indicate how many NBS cards have been placed in each envelope and provide a separate list of the names and UPIs of infants whose samples have been included in each envelope. A sample checklist is available to download from the www.newbornscreening.ie or Appendix 7.

- Do not store or batch samples.

- Dispose of lancets as per local guidelines; never enclose the lancet in the envelope with the NBS card.

6.6.1 Hanging droplet technique

The gold standard method for collecting the newborn bloodspot screening sample is the **hanging droplet technique**. This involves allowing capillary blood to flow from the puncture site until a large droplet forms on the infant's heel. The droplet is suspended from the heel until it reaches critical volume capacity and then it drops freely onto the filter paper.

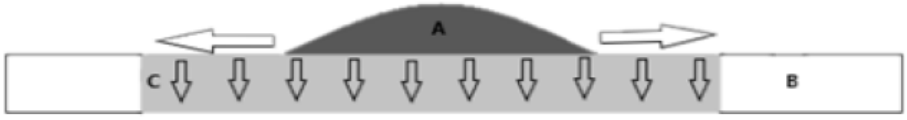
The filter paper used to manufacture NBS cards is a medical device, designed using certified graded filter paper to absorb blood, taking into account blood haematocrit of newborn infants and the kinetic properties of blood spreading.

When blood is applied to the porous filter paper, two processes occur in tandem. The blood penetrates from the droplet into the porous material, and at the same time the blood spreads across the saturated porous material (see figure below).

The blood should be dropped into the centre of the pre-printed circles to allow radial dispersion to the edges of the circle. The blood, when applied in this manner, rapidly spreads radially across the filter paper whilst simultaneously fully soaking the paper by penetrating the porous fibres. It is the effect from having the hanging droplet drop onto the filter paper that allows uniform spreading to happen.

When blood is applied in other ways, such as touching the heel to the NBS card, the spreading through the filter paper matrix will not happen in the same way and is likely less uniform.

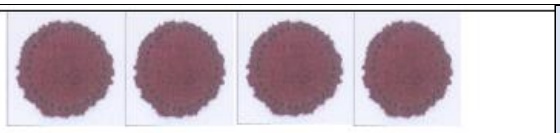
Kinetics of Blood Flow Through Filter Paper



Note. A – blood droplet, B – filter paper, C – area of spread (wetting area). The arrows indicate the flow of blood simultaneously through and across the filter paper

Each of the 4 circles on the NBS card is 10mm in diameter. In the NNBSL, a machine is used to take punches 3.2mm in diameter from the NBS card. All laboratory testing calculations are based on a completely filled, evenly saturated 3.2mm punch.

See the figure below demonstrating four perfect bloodspots, and Table 4 illustrating examples of poor samples, possible causes and guidelines on prevention.



Sufficient amount of blood to completely fill all 4 circles, 3.2 mm punches are taken from the card. All testing calculations are based on a completely filled punch, this is why a fully saturated spot is essential

Infants with severe haemophilia: Infants with haemophilia should have their NBS sample taken in the routine 72-120 hour window. A preterm infant lancet should be used, and direct pressure should be applied to the site for at least 5 minutes afterward until haemostasis is achieved (Chalmers et al., 2011)[3].

6.7 Quality of the newborn bloodspot screening sample

There are several bloodspot quality issues that can affect screening results, such as contamination and insufficient blood volume.

Anything that impacts the volume of blood in a 3.2 mm punch is considered a sample quality issue. This includes:

- overall bloodspot size
- application technique, such as layering or multi-spotting
- compression of the sample

For this reason, all samples identified as having an issue that could affect blood volume or sample quality must have a repeat sample taken.

Each blood spot is visually assessed for sample quality in the NNBSL to determine suitability for analysis and result accuracy.

[3] Chalmers et al (2011), Guideline on the management of haemophilia in the fetus and neonate, British Journal of Heamatology, Vol 154; Issue 2, 208-215 **https://doi.org/10.1111/j.1365-2141.2010.08545.x**

Poor quality screening samples which occur due to poor application technique can be categorised as follows:

- **Layering** blood over blood to fill a circle. Layering is likely due to the first drop being insufficient, but creates a barrier to the second droplet, preventing spreading and penetration.

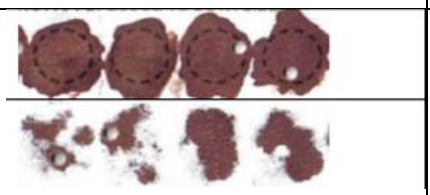
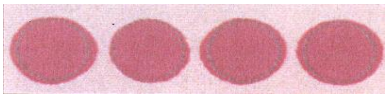
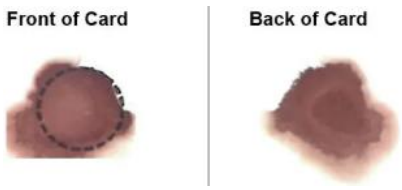
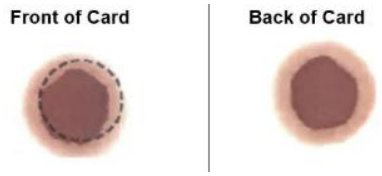
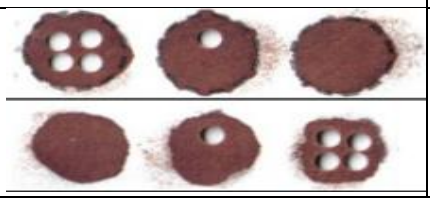
- **Multi-spotting** is when several small spots are applied to the NBS card which may all join together to create one big bloodspot. There will be patches of overlapping and patches where there is only a single layer or blood. Multi-spotting will significantly decrease homogeneity across the bloodspot.

- **Compressed** screening samples will inherently contain lower volumes of blood than non-compressed samples, in some cases causing analyte levels to drop by up to 44%. Compressed samples but will look visually similar to non-compressed samples, but may produce a false negative screening result. This is why it is important that the screening sample is dry and not touched at any point.

- **If blood is applied to the front and back of the card**, the size and shape on each side of the card is different and there are areas where the samples do not meet, and therefore the blood volume is reduced.

Table 4 provides examples of poor quality screening samples, the causes and some tips for prevention.

Table 4: Examples of poor quality screening samples

Problem	Examples	Causes	Prevention
Insufficient size Bloodspot diameter less than the 10 mm pre-printed circle		Unable to obtain adequate drops of blood from heel to fill circles and soak evenly through	Use hanging droplet technique, ensure infant is warm, hydrated and heel is lower than heart
Insufficient quantity As blood not saturated on both sides, blood did not permeate through from back to front		Blood applied to each circle did not soak through evenly	Apply one large drop per circle and check reverse for soak through. Use hanging droplet technique
Wet sample Received in the laboratory wet		Sample packaged before completely air dried. Wet samples can give a false result and pose a health and safety risk to staff	Allow samples to fully air dry before packaging
Filter paper damage: Creases and tears		Wet filter paper is easily damaged	Do not overload card or touch the wet sample, do not crease
Layered & oversaturated sample		Sample taker layered blood over blood, or put blood on both sides of card	Apply one large drop per circle, never add to a partially dry spot, or apply to both sides
Contamination or dilution		Possible reasons include: Spillage of liquid or lotions on sample or allowing card to come in contact with gloves, or placing wet sample into envelope	Keep samples away from liquids, only package when dry. Do not compress or touch bloodspots
Serum Rings Serum or tissue fluid separates from red blood cells on card		Sample in contact with liquids. Drying specimen incorrectly, dispatching to lab when still wet, squeezing area around heel puncture site, exposing spots to direct heat	Dry sample fully at ambient room temperature, do not allow contact with liquids or gloves, do not use excessive squeezing of heel during sampling.
Clotted Specimen		Delayed application of blood to card, or layering blood over blood	One drop of blood per spot (if possible), no anticoagulant
Blood applied to both sides (smearing front and back of same card)		Smeared blood on both sides suggests blood applied to both sides of card	Apply blood to one side of the card only and allow to soak through to the other side of the card

6.8 Why repeat newborn bloodspot screening samples may be requested

It is the responsibility of the sample taker to tell the parents the correct reason as to why a repeat NBS screening sample is required.

There are a number of reasons why a repeat sample may be requested including:

Avoidable repeat samples:

- Insufficient bloodspots for all or some of the screens to be performed
- Unsatisfactory sample quality due to a compressed or diluted sample, serum rings formation or contamination of the sample
- Sample received wet
- Unlabelled or inadequately labelled samples
- Samples collected before 72 hours after birth
- There is a query about the identification of the infant or infants if multiple births
- The sample was taken on an expired card
- The card was delayed, greater than 14 days and is too old for reliable analysis
- The name on the bloodspot portion does not match that on the demographic part of the card; the identity of the infant may need clarification or a repeat sample
- The screening sample is unsuitable for analysis if taken within 72 hours of a red blood cell transfusion
- the bloodspot portion of the NBS card and demographic portion were re-attached but NBS card barcodes do not match up

All above are classed as avoidable repeats and the most common errors noted – these need to be kept to an absolute minimum

Repeats that are required for valid reasons:

- For borderline or equivocal results, a repeat NBS screening sample is required to ensure an accurate screening result.

6.9 Packing and transporting NBS cards

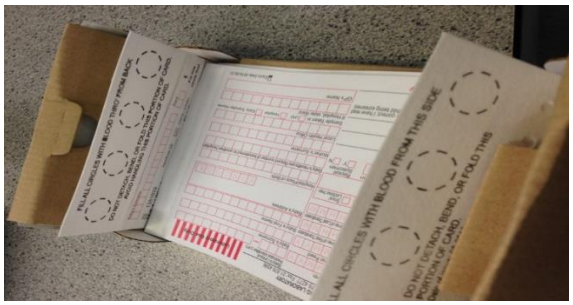
- Do not put screening samples in the post knowing that there may be a delay in transit to the NNBSL due to either a postal dispute or over the Christmas period when the post may be delayed. Monitoring timely sample dispatch is a key performance and quality measure for the NNBSP. Alternative arrangements should be made by the sample taker to ensure screening samples are dispatched without delay. Parents should never be asked to post or deliver screening samples to the NNBSL. This is the responsibility of the sample taker.

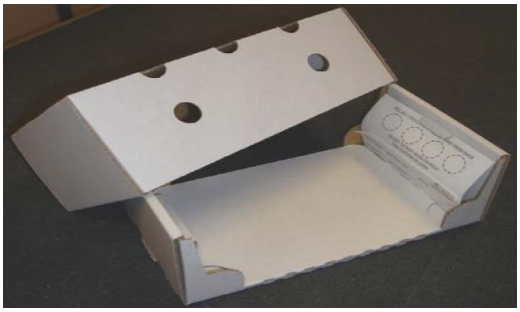
- The sender of screening samples by registered post/courier is responsible for ensuring the packaging and transportation of the samples complies with transport regulations regarding Health and Safety as laid down in the European Directive (ADR 2015) Packaging Regulations P650. Once the screening sample has dried, it should be inserted into a water resistant, tear proof Tyvek® envelope or equivalent.

- Pre addressed printed registered envelopes may be purchased directly by DPHN from An Post by emailing customer care using a locally generated HSE purchase order number.

Drying/transport boxes are available form Mega-Pak Ltd to facilitate the drying and transport of screening samples in a safe manner, see example below. These boxes can contain two cards and are reusable. However, if they become contaminated with blood they should be disposed of as biological waste.

They can be ordered directly from Mega-Pak Ltd. 16 Highfield Green, Swords, Co. Dublin, Ph. (0) 1 840 2063, e-mail vhalhedmoran@mega-pak.com; order reference TEMPLE03C.





Section 7: Reporting newborn bloodspot screening results

7.1 Procedure for reporting newborn bloodspot screening results

Screening results for each infant are reported electronically to the maternity hospital/unit of birth and to the relevant LHO/Community Care Area/IHA area where the infant resides via eReports™, which is a secure, password protected electronic reporting system. Only those authorised with access to eReports™ can view screening results for infants.

Each maternity hospital/unit and LHO/Community Care Area/IHA, through the DPHN, nominates two authorised users who are provided with a username, password and the weblink to access eReports™ by the NNBSL.

Authorised users can:

- verify that a NBS sample has been received by the NNBSL
- check screening results are available once they have been authorised by the NNBSL, usually within 2 days of receipt of the NBS sample
- use the search facility to find or link results
    - this search facility includes infants or mother's surname, infant's UPI and date of birth or a range of dates within the previous 60 days
- print individual screening reports for filing in the infants healthcare record and/or to provide a copy to the parent(s)/guardian(s) when requested

Authorised users must review eReports™ daily and notify colleagues if a repeat NBS sample has been requested. The reason for requesting a repeat sample will be indicated on the report and must be communicated to the parent/legal guardian by the sample taker at the time when the repeat sample is taken.

If screening results are reported to an LHO/Community Care Area/IHA area that an infant does not reside in, an 'incorrect location form' can be completed and the location changed. The results report will then be resent to the correct LHO/IHA/DPHN area (Appendix 1).

The reports are available for 60 days from the date of birth and are then archived due to limited storage space on the server, but are available from the NNBSL if required.

Refer to Appendix 5 for user instructions for accessing results on eReports™.

Section 8: Infants who are not screened within the 72-120 hour recommended timeframe

Infants who are not screened within the 72-120 hour recommended timeframe for logistical reasons or programme failure (e.g. lost screening card, mix up in identification etc.), can have their newborn bloodspot screening completed without delay once the error is identified.

8.1 Infants over six weeks of age who missed CF screening due to non-compliance with NNBSP processes

Immunoreactive trypsinogen (IRT), the screen for CF, is not suitable if the infant is over six weeks of age. Therefore, for infants greater than six weeks of age who were missed or if there was a problem with the sample, or the testing, such that no result for CF newborn bloodspot screening is available, a sweat test should be performed to out rule CF.

If required, the sweat test should be performed in one of the six specialist CF centres based on the infant's home address.

The following steps should be taken:

- The individual aware or concerned that an infant has not been screened should contact the NNBSL to confirm that no screening sample was received and then proceed to take a screening sample without delay to screen for the other conditions.
- The NNBSL will contact the relevant specialist CF centre, schedule a sweat test to out rule CF and follow-up until results are recorded with other screen results on the LIMS.
- The NNBSL will inform the individual who highlighted the case that the infant has been assessed and record as a non-conformance on laboratory system. Full screen results will be issued on eReports™, including CF when sweat performed.
- The NNBSP must be informed of these instances through the Programme Manager (child.screening@hse.ie)

Note: arranging a sweat testing to out rule CF only applies when there was an issue with the NNBSP. This process does not apply to infants who had newborn bloodspot screening performed in another country which did not include CF, and then moved to Ireland at a later date, or infants/children who moved into Ireland after six week of age. The CF screen on these infants/children will be reported as '*screen for CF is invalid*' as the infant is aged greater than six weeks.

If there is a clinical suspicion of CF or a strong family history this should be followed up by the infant's GP and/ or paediatric team.

8.2 Infants born outside Ireland and who may not have been screened in their country of birth

All infants up to one year of age, who arrive in Ireland and may not have been screened in their country of birth, should be offered screening for all the conditions on the Irish panel (excluding CF if the infant is over six weeks of age). This may occur following international adoption, surrogacy, immigration, or where people are refugees or seeking asylum.

A UPI number can be obtained from the local DPHN. Some considerations include:

- Screening for CF by measuring blood IRT is not reliable for any infants over six weeks of age.

- Sample takers should be aware that many countries including Northern Ireland's newborn bloodspot screening programme, do not include screening for Classical Galactosaemia, SMA or SCID. Therefore, there is a likelihood that while newborn bloodspot screening may have been performed in the country of origin, not all conditions included in Ireland's NNBSP were screened for.

- While heel-prick is the recommended method, if it is not possible to take a heel-prick sample a venous sample can be taken and spotted onto the card. 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.).

Section 9: Procedure for contacting parent(s)/legal guardian(s) following a screen positive result

Parent(s)/legal guardian(s) of an infant with a screen positive result are contacted directly by telephone by the maternity hospital/unit for follow up. The procedure varies depending on the condition suspected. Some infants will be admitted to CHI, while in other instances follow up may be arranged via a local maternity or paediatric unit.

The NNBSP Clinical and Quality Assurance Group has set out key performance indicators (KPIs) to ensure that infants detected with a condition are referred to the relevant clinical service within a specific time interval. This is to ensure prompt diagnosis and establishment on appropriate treatment as soon as possible.

The general procedure for contacting parent(s)/legal guardian(s) is set out below with more specific details depending on the condition.

The Clinical Liaison Nurse in the NNBSL contacts a designated liaison person (DLP) or paediatric registrar/ team in the maternity hospital/unit of birth by telephone and the following information is given:

- infant's name
- UPI
- date of birth
- address
- the condition suspected
- the result of the screening

The team in the maternity hospital/ unit will be asked to contact the parent(s)/legal guardian(s) and explain to them:

- the screening result and the condition suspected
- why the infant has to be referred to hospital (typically for further testing to confirm/ refute the diagnosis)
- what further tests are needed, e.g.
    - a blood test
    - a further NBS sample
    - a thyroid scan if CHT is suspected
    - a urine sample

Arrangements will be made for the infant to be brought directly to CHI or to the local paediatric unit depending on the condition suspected.

Parent(s)/legal guardian(s) should be advised that their infant might be kept in hospital for a few days, depending on the result of the repeat investigation(s). Therefore, they should bring change of clothes for the infant and themselves.

The DLP or registrar in the maternity hospital/unit may contact the CLN or the Director of the NNBSL if further information is required. They can also give the contact number of the NNBSL CLN to the parent(s)/legal guardian(s), and invite them to make contact for more information, if they wish to do so.

The person contacting the parent(s)/legal guardian(s) must impart the information in a calm and professional manner and must aim to minimise parental anxiety. They must be fully informed of all the facts and explain to the parent(s)/guardian(s) what condition the infant is suspected of having.

See Appendix 8 for an overview of actions based on the relevant condition. Note that this may change depending on clinical advice from the clinical specialist team.

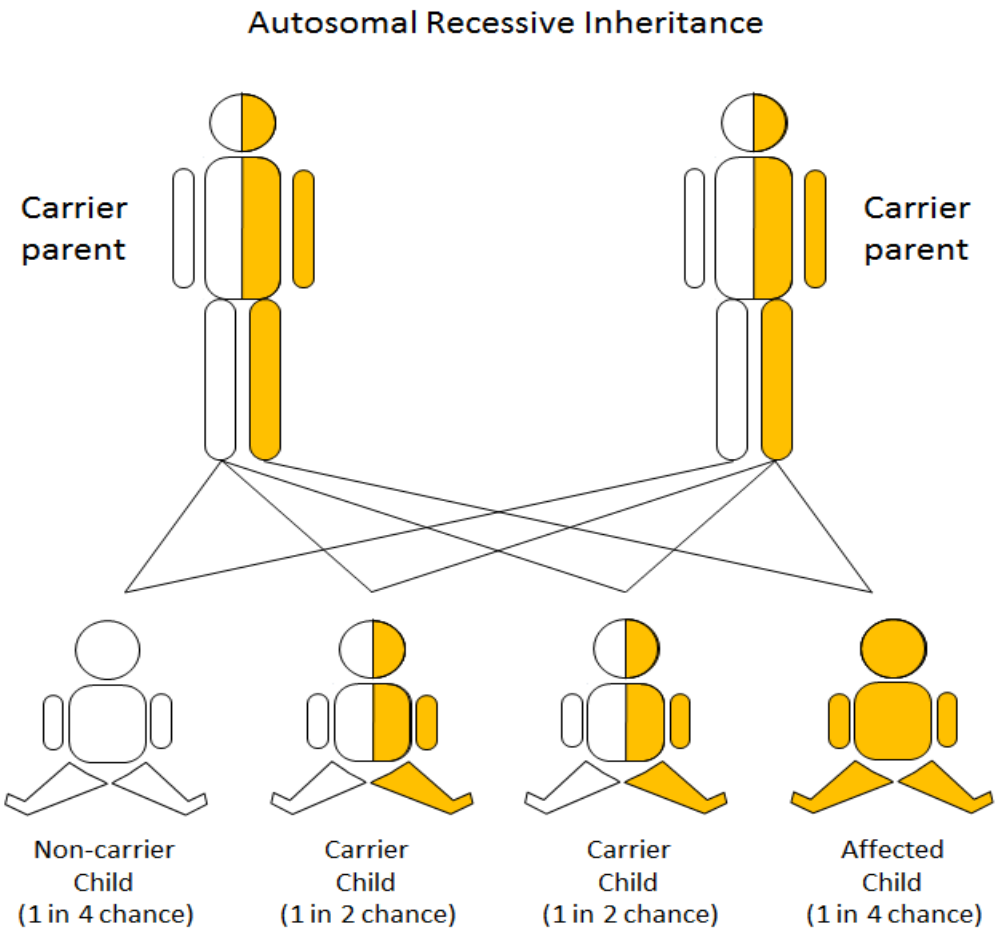
Section 10: Mode of inheritance

All of the 11 conditions screened for through the NNBSP are autosomal recessive genetic conditions, with the exception of CHT, which is genetic in a minority (15-20%) of cases. In autosomal recessive inherited conditions, both parents must be carriers of a pathogenic gene variant, resulting in each of their off-spring having a one in four chance of having the condition and a one in two chance of being a carrier (Figure 1). Conditions occur with equal frequency in both males and females.

Carriers have a copy of the pathogenic gene variant, but do not have any symptoms of the condition. The NNBSP **does not** aim to identify carriers of pathogenic gene variants.

As described above, CHT is inherited as an autosomal recessive genetic condition in approximately 15-20% of cases. The majority of cases (80-85%) occur sporadically for reasons that are not fully understood – sporadic cases are twice as common in females compared to males.

Figure 1: Mode of autosomal recessive inheritance



As described previously, the NNBSP screens for 11 conditions. These comprise:

- **Six metabolic conditions,** (PKU, MSUD, HCU, CGAL, MCADD, GA1), where the body cannot metabolise macronutrients properly. Each step in a metabolic pathway is governed by an enzyme. In the metabolic conditions, affected infants inherit two copies of a pathogenic gene variant, one from each parent, resulting in absent or insufficient enzyme activity. This impacts the normal breakdown of macronutrients and results in a build-up of toxic substances in the body, with potentially devastating health consequences in the absence of early detection and treatment.

- **Five other conditions** impact key systems and processes in the body, including:
    - CHT – a disorder affecting the endocrine system
    - CF – a multisystem disorder primarily affecting the functioning of the lungs and pancreas
    - SCID (and ADA-SCID) – a group of disorders affecting the immune system
    - SMA – a disorder affecting the neuromuscular system

Section 11: Conditions included in the Irish NNBSP

These are listed in the order of when the screening for each condition was introduced.

11.1 Phenylketonuria (PKU)

Screening case definition: To detect infants with Phenylketonuria (PKU). No distinction is made between those with PKU, Hyperphenylalaninaemia and Dihydropteridine Reductase Deficiency.

Some infants 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.

Approximately 1 in every 4,100 infant born in Ireland has PKU or the milder form called hyperphenylalaninaemia.

PKU is an autosomal recessive condition caused by a pathogenic variant in the PKU gene. This results in a lack of the enzyme phenylalanine hydroxylase, which normally converts the amino acid phenylalanine into tyrosine. In the absence of this enzyme, phenylalanine accumulates and this can have a direct toxic effect on the brain. Without treatment, PKU can result in permanent intellectual and/ or physical disability.

When diagnosed and treated in the newborn period, infants with PKU grow up healthy and well. Treatment involves lifelong adherence to a low protein diet with restricted intake of phenylalanine, but a normal intake of all the other amino acids.

The screening test for PKU 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 phenylalanine level in the blood may not be sufficiently elevated for PKU to be detected.

Please see link below for further information about PKU and real patient stories:
https://metabolic.ie/patient-family-information/metabolic-conditions/phenylketonuria/

11.2 Homocystinuria (HCU)

Screening case definition: To detect infants with Classical Homocystinuria (HCU).

The programme may not detect those infants with the milder variants such as those with pyridoxine (vitamin B6) responsive HCU and infants with inadequate protein intake.

Approximately 1 in every 66,400 infants born in Ireland has HCU.

HCU is an autosomal recessive genetic condition caused by a pathogenic variant in the cystathionine β-synthase gene. This results in a deficiency of the enzyme cystathionine β-synthase, causing impaired metabolism of the amino acid methionine. This causes methionine, and one of its metabolic products homocysteine, to accumulate to harmful levels. Homocysteine is toxic to the lining of blood vessels and predisposes the individual to blood clots, stroke, learning and behavioural problems, and other complications including osteoporosis and dislocation of the lens of the eye.

The treatment is similar to that of PKU and MSUD, involving life-long adherence to a low protein diet.

The screening test for HCU aims to detect high level of methionine in the blood. HCU is one of the more challenging conditions to detect, as the blood methionine level may not be raised during the screening timeframe of 72-120 hours after birth. This is because the concentration of methionine is low in many baby foods, particularly in breast milk, so by the time an infant with HCU is screened they may not have had sufficient intake of methionine for it to accumulate in the blood. **Consequently, if protein intake is deemed to be suboptimal at the time of sample taking, a further sample should be taken on or about day 10 of life for HCU screening**.

Additionally, the screening test may not detect a milder vitamin B6 responsive form of HCU. Patients with this form of the condition typically have milder symptoms and disease progression is slower.

As a result of these limitation of the screening test, the screening programme may not detect approximately one in every five infants born with HCU. All infants or children who present clinically in later life with signs and symptoms suggestive of HCU, such as dislocation of lenses, osteoporosis or inappropriate tall stature should have the condition excluded formally by measuring plasma levels of methionine and total homocysteine.

Please see link below for further information about HCU and real patient stories:
https://metabolic.ie/patient-family-information/metabolic-conditions/homocystinuria-hcu/

11.3 Maple Syrup Urine Disease (MSUD)

Screening case definition: To detect infants with the more severe neonatal onset form of Maple Syrup Urine Disease (MSUD).

This programme may not detect those infants with the milder variants such as late onset or intermittent MSUD.

Approximately 1 in every 460,000 infants born in Ireland has MSUD.

MSUD is an autosomal recessive condition caused by a pathogenic variant in the MSUD gene. This results in impaired metabolism of three amino acids known as the branched chain amino acids (BCAA). The BCAA accumulate to harmful levels in the blood following the establishment of feeding in the first few days of life, and may cause brain damage and long-term brain impairment if not diagnosed and treated immediately. Infants can present with irritability, vomiting and seizures and have a sweet scent to their urine akin to Maple Syrup. MSUD is life-threatening in the absence of timely diagnosis and treatment.

Early diagnosis and intervention allows for normal brain development and good health. Treatment involves lifelong adherence to a protein restricted diet, similar to that required for PKU but with low levels of BCAAs. Urgent medical intervention may be required during illness, which may be precipitated by infection or stress.

Please see link below for further information about MSUD and real patient stories:
https://metabolic.ie/patient-family-information/metabolic-conditions/maple-syrup-urine-disease-msud/

11.4 Classical Galactosaemia (CGAL)

Screening case definition: To detect infants with Classical Galactosaemia (CGAL).

The programme tries to avoid diagnosing individuals with non-classical galactosaemia such as the Duarte/Galactosaemia variant as they usually remain asymptomatic throughout life and do not require treatment. The NNBSP does not screen for Epimerase or Galactose Kinase deficiency.

Approximately 1 in every 10,600 infants born in Ireland has CGAL.

However, it is more common among infants 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 approximately 1 in every 36,000 births.

CGAL is an autosomal recessive condition caused by a pathogenic variant in the GALT gene, resulting in a deficiency of the enzyme galactose-1-phosphate uridyl transferase. This enzyme is essential for the normal metabolism of galactose, one of the two sugars that make up lactose in human and cow's milk.

If not detected and treated during early infancy, CGAL may cause damage to the liver and there may be an increased risk of infection, which can be life-threatening. The infant may present with jaundice, cataracts or a bleeding condition. Affected infants can also develop *E coli* septicaemia.

Early detection and treatment with a lactose or galactose-free diet will prevent the early clinical complications of the condition. Some of the longer term complications, such as dyspraxia, ataxia or reduced fertility in women, may still occur in older children and adults despite dietary treatment.

11.4.1 Beutler test

Because CGAL is more common in infants born to Irish Traveller parents and in siblings of known cases, a special screening test, the Beutler test, is offered to all these infants at birth. The blood sample for the Beutler test should be taken and dispatched to the NNBSL on **Day 1 of life**, as soon as possible following birth.

Sample dispatch should not be delayed, e.g. by batching samples – all samples for Beutler testing should be dispatched to the lab **immediately** after the sample is taken and air dried.

The urgent timeline for Beutler testing (**Day 1 of life**) is required to:

- support rapid identification of infants with CGAL so that they can be managed appropriately as soon as possible. The variant of CGAL seen in

Ireland is very clinically serious/significant and infants are at risk of rapid decompensation if not identified and managed as early as possible.

- support breastfeeding optimisation among members of the Irish Traveller population. If the CGAL screen is negative/normal, the mother can be reassured and can commence breastfeeding if she wishes to. Beutler testing on day 1 minimises the time period where breastfeeding should be avoided.

The Beutler test measures levels of the GALT enzyme. Parent(s)/legal guardian(s) are advised not to breastfeed and to keep the infant on a galactose-free (soy-based) feed until the Beutler test result is available. This protects the infant should they have the condition. Mothers wishing to breastfeed should be supported to express and store breast milk until the Beutler result is available.

As with all population based screening, false negatives can occur, and a negative screening test result does not preclude a diagnosis of CGAL. Clinicians should query this condition in any infant who presents early with jaundice and other symptoms suggestive of CGAL e.g. vomiting, hypotonia, hypoglycaemia, conjugated hyperbilirubinemia or abnormal clotting of unknown cause.

It should be noted that Beutler testing cannot be undertaken within three months of a red blood cell transfusion. This is because the Beutler test measures the GALT enzyme in red blood cells. In infants with CGAL, donor blood may cause a false negative screening test result. If CGAL testing is required within 3 months of a red blood cell transfusion, molecular testing for pathogenic variants in the GALT gene is warranted.

Please see link below for further information about CGAL and real patient stories:
https://metabolic.ie/patient-family-information/metabolic-conditions/galactosaemia/

11.5 Congenital Hypothyroidism (CHT)

Screening case definition: to detect infants with congenital hypothyroidism (CHT), with either thyroid agenesis, dysgenesis or dyshormonogenesis, based on the results of a Technetium-99m percentage thyroid scan.

The programme is not designed to detect minor aberrations of thyroid function in the newborn.

Most cases of CHT (80-85%) occur by chance because the thyroid gland fails to develop properly, or is entirely absent in the newborn, for reasons that are not well understood. CHT is genetic/ inherited condition in the minority of cases (10-15%). CHT is an endocrine condition resulting from failure of the thyroid gland to produce the hormone thyroxine. There are several different forms of the condition. Some infants have a very small thyroid gland or no gland at all while others have a normal sized gland but are unable to produce thyroxine.

The screening test for CHT measures thyroid stimulating hormone (TSH) in the blood, high levels of which are suggestive of the condition. If the NBS sample is taken too early (before 72 hours), this may result in a false positive CHT screen. This is because TSH levels can be elevated following birth and may not return to normal for a few days.

Compared to 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 for false positive CHT screening results include:

- **Transiently raised TSH** – a phenomenon in which infants have raised TSH levels which return to normal in time without treatment. These infants require a number of repeat NBS samples to be taken to monitor TSH levels.
- **Down Syndrome/Trisomy 21** – hypothyroidism is more common in infants with Down Syndrome/Trisomy 21. As a result, repeat samples may be requested from these infants to monitor TSH levels.
- **Surgery** – infants who have had surgery before having the NBS sample taken may have a transiently elevated TSH level. This may occur as some antiseptic skin preparations contain iodine, which can be absorbed through the skin causing transient hypothyroidism. This occurs more commonly in premature infants.

Note: Preterm infants can have a delayed thyrotropin increase, most likely due to immaturity of the hypothalamic-pituitary thyroid axis and are at an increased risk of being undetected in the screening process as TSH levels may not have risen.

Please refer to Section 4.3.1 for more details.

CHT is treated with thyroid hormone replacement (thyroxine). In some cases, this can be discontinued between two to three years of age under the supervision of the endocrinology team. Otherwise, treatment is for life, and the dose of thyroxine adjusted accordingly.

11.6 Cystic Fibrosis (CF)

Screening case definition: to detect infants 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 the congenital absence of the vas deferens.

1 in every 2,100 infants born in Ireland has CF. Ireland has one of the highest incidences of CF in the world.

CF is an autosomal recessive condition caused by a pathogenic variant in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. As a consequence, thick mucus secretions are produced by a number of organs including the lungs and pancreas. This may cause repeated respiratory infections, ultimately resulting in lung damage. If the pancreas is involved, this may cause diabetes mellitus, digestive problems and malabsorption of important vitamins. Consequently, infants with CF may present with failure to thrive and frequent chest infections.

Treated includes a high energy diet to support weight gain, and medicines and physiotherapy to improve lung function. Although a child with CF may still become ill, early treatment improves their clinical outcomes and quality of life. Specific treatment is now available for a significant number of persons with CF, depending on the specific pathogenic variant affecting the CFTR gene.

The screening test measures the level of immunoreactive trypsinogen (IRT) in the blood. IRT is normally excreted by the pancreas into the gastrointestinal tract, but in individuals with CF, it is regurgitated back into the blood due to the thick mucus secretions which block the pancreatic ducts. In infants with CF, IRT levels may remain high in blood for approximately the first six weeks of life. If the blood IRT level is high, the original DBS sample will be sent for CFTR genetic variant analysis. This test screens for the presence of 38 possible pathogenic genetic variants.

- If two CF genetic variants are identified, then the infant is likely to have a diagnosis of CF. The infant will be referred to their local CF centre for a sweat test without delay. If the sweat test is positive, this confirms the diagnosis of CF.
- If one genetic variant is identified, the infant may have CF or may be a carrier of a CF-causing pathogenic gene variant. The infant will be referred to their local CF centre for a sweat test. If the sweat test is positive, the infant has a diagnosis of CF and further DNA analysis will be undertaken to identify the second pathogenic gene variant.

The ‘sweat test’ is a diagnostic test used to confirm or out-rule CF. The sweat test 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 infant’s address. The sweat test is considered the ‘gold’ standard for confirming the diagnosis of CF.

Not all infants with CF will be detected though the NNBSP. 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:

- The IRT screening test for CF is not suitable for infants/children over six weeks of age.
- Meconium ileus (MI) is a blockage in the small intestine of a newborn infant and is associated with a possible diagnosis of cystic fibrosis (CF). Infants with MI should be strongly suspected of having CF and followed up accordingly, including having CF pathogenic gene variants tested for at birth. These infants may have a normal CF screen (normal IRT). If an infant has MI at the time of sample taking, it is **imperative to document MI on the NBS card - document this in the box labelled ‘Comments/Family Hx/Beutler/Meconium Ileus’ (see Appendix 3 for a copy of the NBS card)**. No other information regarding meconium needs to be documented on the card.
- The Irish CF genetic variant panel screens for 38 pathogenic genetic variants chosen to reflect the most common variant in the Irish population. Therefore, infants of non-Irish ethnic origin are at increased risk of non-detection of CF within the Irish programme, particularly if parents are consanguineous.

11.7 Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD)

Screening case definition: to detect infants with medium chain Acyl CoA dehydrogenase deficiency (MCADD).

Not all infants 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 greater potential for false negative screening results. Older infants (greater than approximately one month of age) with MCADD may have C8 levels (marker for MCADD) below the screening cut-off causing them to also be at risk for a false negative screening result. Infants with carnitine depletion and very low concentration of free carnitine might not be detected by newborn bloodspot screening. It must be noted that rarely, an infant may present clinically before results of newborn bloodspot screening are available.

1 in every 17,000 infants born in Ireland has MCADD.

MCADD is an autosomal recessive condition caused by a pathogenic variant in the MCADD gene. This results in impaired fatty acid oxidation due to a 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. MCADD typically presents before the age of two years, at a mean age of thirteen months, although neonatal presentations have also been reported.

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 metabolise stored fat quickly to produce energy. Hypoglycaemia and a decompensated state develop, which can result in serious symptoms including seizures and brain damage. Untreated, MCADD can result in sever intellectual and physical disabilities, and can be life-threatening.

When diagnosed in the newborn period and started on treatment, infants with MCADD grow up healthy and well. Episodes of metabolic decompensation can be prevented through avoidance of fasting, monitoring of the infant to determine ‘safe’ time periods between meals and following a strict feeding schedule.

Note: If an infant is on IV fluids, Glucose or Dextrose a false negative screen may be reported for MCADD. **It is imperative that IV fluids, Glucose/Dextrose is noted on the screening card (tick the relevant box under the ‘Type of feed’ section of the NBS card), and that a repeat NBS sample is taken when IV fluids are discontinued.**
Please see link below for further information about MCADD and real patient stories.
https://metabolic.ie/patient-family-information/metabolic-conditions/mcadd/

11.8 Glutaric Aciduria Type 1 (GA1)

Screening case definition: to detect infants with Glutaric Aciduria Type 1 (GA1).

The programme may not detect all infants with GA1, particularly those who excrete a low concentration of glutaric acid (low excretors) and those with a very low concentration of free carnitine.

1 in every 85,300 infants born in Ireland has GA-1.

GA1 is an autosomal recessive inherited condition caused by a pathogenic variant in the GCDH gene. This results in a deficiency of the enzyme glutaryl-CoA dehydrogenase (GCDH), disrupting the metabolism of organic acids and leading to a harmful accumulation of these and other toxins in the body.

Over 150 pathogenic gene variants that can cause GA-1 have been identified. Of these, the R402W pathogenic variant is the most prevalent among people of Caucasian ethnicity. Most pathogenic variants, including the R402W variant, are associated with undetectable GCDH activity and excretion of high amounts of glutaric acid. However, variants 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.

Untreated, GA-1 can cause brain impairment and can be life threatening.
About 70% of patients (including both low and high excretors) have an encephalopathic crisis, which is most common at around nine months of age, with 90% by age two years. These are by a non-specific intercurrent illness, gastrointestinal infection or pneumonia, occurring 1-3 days after the onset of illness and resulting in dystonia and dyskinesia as permanent sequelae, but with relative preservation of the intellect.

Treatment is through lifelong adherence to a low protein diet.

Please see link below for further information about GA1 and real patient stories.
https://metabolic.ie/patient-family-information/metabolic-conditions/glutaric-aciduria-type-1/

11.9 Adenosine Deaminase Deficiency Severe Combined Immunodeficiency (ADA-SCID)

Screening case definition: To detect infants with ADA-SCID.

Infants with the delayed or late onset forms of ADA deficiency may also be detected, but are not the target of the screening programme.

Approximately 1 in every 137,000 infants born in Ireland has ADA-SCID. However, it is more common among infants born to Irish Traveller parents, in whom the incidence is approximately 1 in every 1,200 births.

ADA-SCID is a specific form of severe combined immunodeficiency and is the most common cause of SCID in Ireland. It is an autosomal recessive condition caused be a pathogenic variant in the ADA gene, which causes a deficiency of the enzyme adenosine deaminase (ADA), required for the breakdown of adenosine and deoxyadenosine. In the absence of ADA, adenosine and deoxyadenosine can accumulate to toxic levels in the body. Lymphocytes are particularly sensitive to the toxic levels of deoxyadenosine, causing a marked depletion of T, B, and NK cells, resulting in SCID.

If not detected and treated early, ADA-SCID can be life-threatening. Patients typically present with frequent and severe infections such as pneumonia, often caused by an organism (pneumocystis jirovecii) that does not cause illness in healthy individuals.

The ADA enzyme is active in other cells of the body, so patients with ADA-SCID can also have non-immune symptoms. There can be an impact on nervous, auditory, skeletal, pulmonary, hepatic, cardiac and renal systems.

Definitive treatment is haematopoietic stem cell transplantation (HSCT), which results in immune reconstitution for the patient. Additional treatment options for ADA-SCID include gene therapy and enzyme replacement therapy.

Long-term follow-up is important even for those who have undergone HSCT, as infants with ADA-SCID have symptoms beyond the immune system such as developmental, behavioural and psychological symptoms.

11.10 Severe Combined Immunodeficiency (SCID)

Screening case definition: To detect all infants with severe combined immunodeficiency

Approximately 1 in 40,000 infants born in Ireland has SCID.

Some SCID phenotypes, including atypical ('leaky') SCID where the patient may have a population of poorly functional T-cells, and Omenn syndrome (OS), characterized by clinical features including rash, fever, and lymphadenopathy caused by clones of auto-reactive T-cells, may present with TREC values above the screening cut-off and may not be detected through the screening programme. This is an accepted limitation of TREC based SCID screening. Cases of atypical SCID or Omenn syndrome presenting with TREC values above the screening cut off will not be considered false negatives for programme performance metrics.

While TREC based screening will identify cases of non-SCID t-cell lymphopenias (TCLs), including those caused by clinically significant inborn errors of immunity, these conditions are not the target of the screening programme and will be considered false positives. Additional exclusions from the screening case definition include late and delayed onset ADA-SCID.

SCID is an inherited inborn error of immunity characterized by an intrinsic defect in the patient's hematopoietic stem cells (HSCs) that prevents their differentiation into phenotypically and functionally mature T cells. SCID may also have defects in B-cell differentiation and/or function and/or natural killer (NK)-cell differentiation. It is called a "combined" immunodeficiency, since patients have a combined impairment of both their T-cell mediated cellular immunity and their B-cell antibody mediated humoral immunity. It is termed "severe" since, without treatment, patients with this condition typically do not survive longer than one year, succumbing either to severe recalcitrant infection (including from live vaccination), malignancy, and/or complications from immune dysregulation. Patients are typically asymptomatic at birth, and most patients do not have a positive family history of the condition. SCID can be caused by a pathogenic variant in one of at least twenty different genes which impedes normal T-cell development. It is one of the most severe forms of primary immunodeficiency. SCID is typically characterised by T-cell lymphopenia (TCL), that is, lower than normal T-cell counts, with varying impact on B-cells and natural killer cells, depending on the gene affected.

SCID is considered a paediatric emergency that is almost uniformly fatal in the first year of life without appropriate treatment. It presents with features such as, the infant experiencing recurrent, opportunistic, and often severe infections, failure to thrive, persistent diarrhoea, and oral thrush.

SCID is treated with haematopoietic stem cell transplant (HSCT) or, in certain subtypes, gene therapy.

Early identification of SCID is also important given the implications for childhood immunisation. Children with SCID should not receive live vaccines (for example, vaccination against rotavirus infection), given the potential for severe illness and mortality.

11.11 Spinal Muscular Atrophy

Screening case definition: To detect infants with 5q spinal muscular atrophy (SMA) caused by a homozygous deletion of exon 7 of the SMN1 gene.

Approximately 1 in 9,000 infants born in Ireland has SMA.

The screening programme does not aim to detect SMA cases caused by compound heterozygous variants of SMN1, cases of non-5q SMA or carriers of pathogenic gene variants associated with SMA.

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular condition caused by a pathogenic variant in the survival motor neuron 1 (SMN1) gene and is associated with irreversible motor neuron loss and disease progression. In the absence of disease-modifying treatment, the natural history of SMA is broadly characterised by progressive motor and respiratory muscle wasting and weakness of varying severity. In most cases, this results in motor milestones not being reached, problems with breathing or swallowing (requiring mechanical ventilation in severe cases) and frequent respiratory infections.

The loss of the functional SMN1 gene can be partially compensated for by the presence of another gene, the survival motor neuron 2 (SMN2) gene. SMN2 can be considered a disease-modifying gene, since, typically, as SMN2 copy number increases, the severity of the disease course decreases. However, this correlation is not absolute, and all forms of SMA are degenerative and associated with progressive and severe motor disability.

In recent years, the availability of disease-modifying therapies has significantly improved prognosis, particularly when initiated early in the disease course, leading to rapid expansion in newborn bloodspot screening (NBS) for SMA internationally.

While there is currently no known cure for SMA, treatments including gene therapy, are available to increase production of functional SMN protein. Evidence suggests that earlier treatment with disease-modifying drugs may result in better clinical outcomes by preventing or reducing irreversible motor neuron loss and disease progression.

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 infants 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:
https://www.hse.ie/newbornbloodspotscreening

Appendices
Appendix 1: Incorrect Location Form

Children's Health Ireland, Temple Street, Department of Paediatric Laboratory Medicine
LF-NNS-0110 Incorrect Location Report Form EDITION 2

Direct Line: Ph. (01) 8784277 or 01 8784610 ● Email: info.newbornscreening@childrenshealthireland.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).

Location (LHO):	**Date:**
Reported By:	**Position:**

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

Comment:

Page 1 of 1

Author: Sophie Murphy Ref: LP-NNS-0001 Date of issue: 27/05/2025
Authoriser: Loretta O'Grady

Appendix 2: Opt-Out Form
(Revised December 2024)

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 (If Yes) 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/legal guardian of Baby _____ does not consent to allow the Newborn Bloodspot Screen (Heel-Prick) to be carried out on my baby.
- I have read the Newborn Bloodspot Screening information leaflet and the importance of screening 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 screened.
- I understand that not detecting or treating one of the conditions, should my baby have one, may result in severe intellectual or physical disability which could require long term care or result in premature death.
- Reason for opt-out: _____

Signed (Parent/Legal Guardian): _____

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

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

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

Ensure copies of opt-out form are sent to all locations below

Six copies of this completed form, signed by parent/legal guardian and sample taker should be made.
A copy to be given to the parent/legal guardian and a copy kept by the sample taker, plus a copy posted/emailed 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 D01 YC67	
Date Sent				

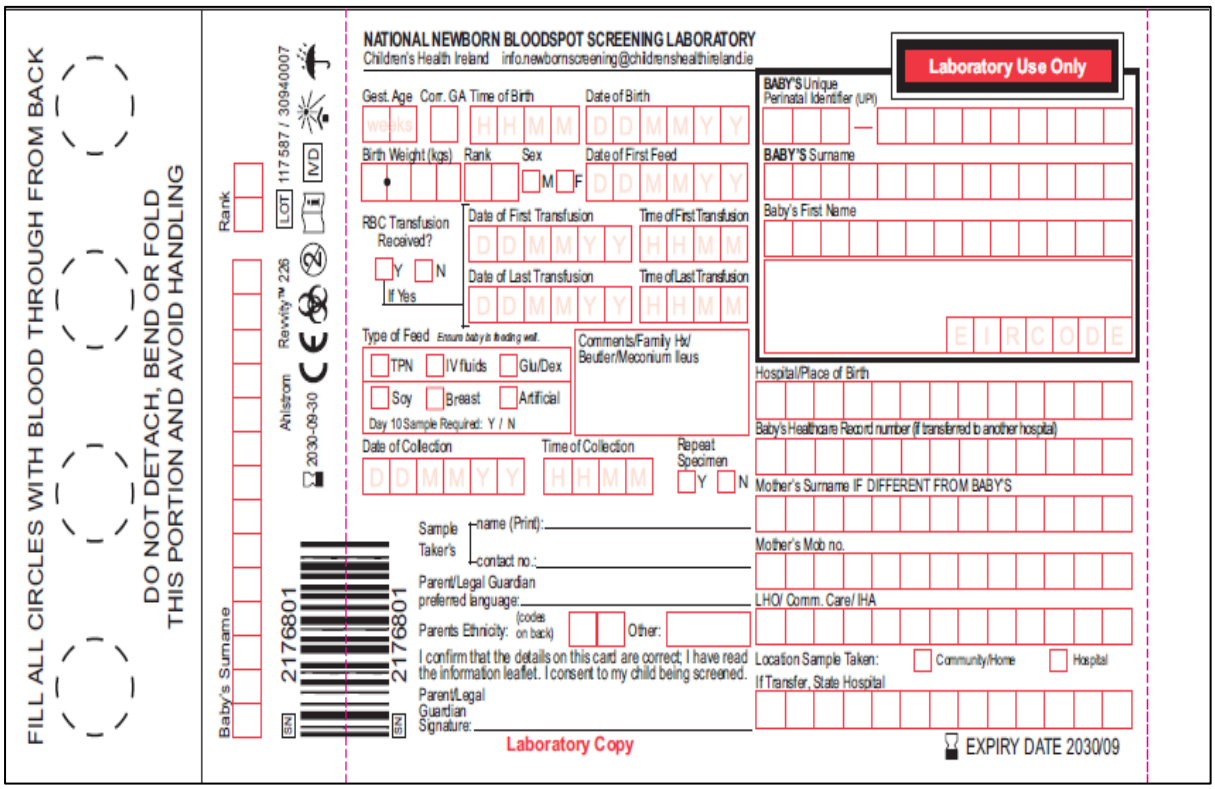
Signed *(Potential Sample taker)*: _____ Date: _____

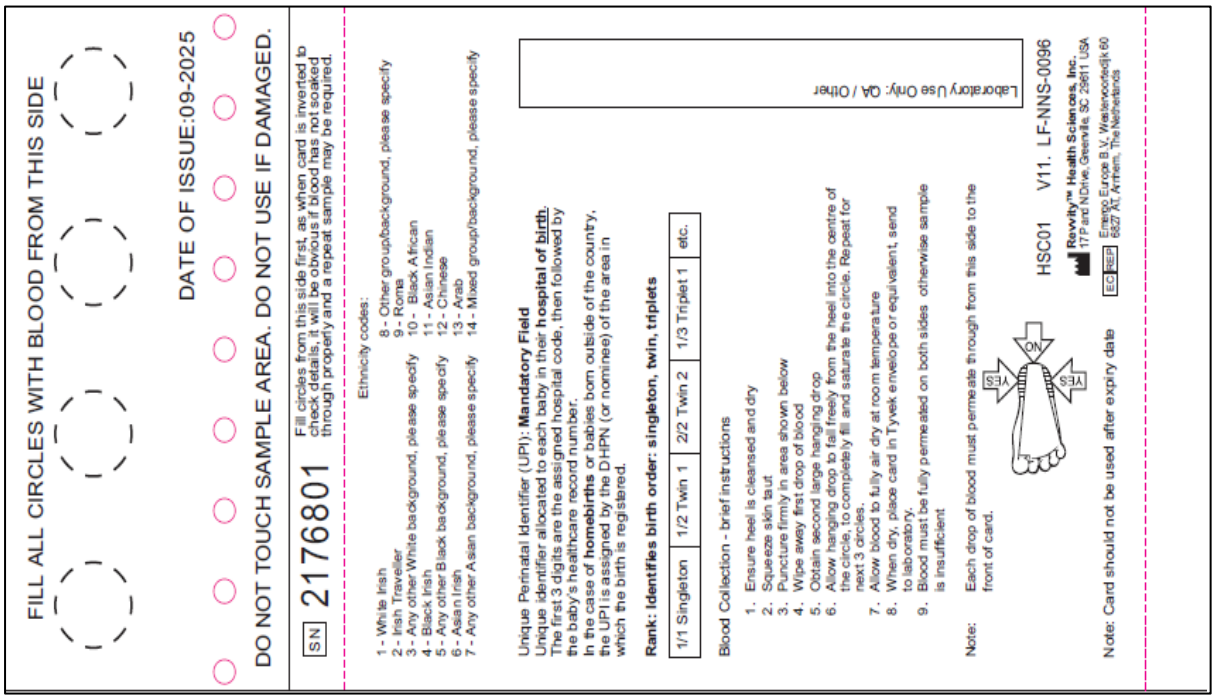
Name *(Block Capitals)*: _____

Parents/Legal Guardians may change their mind and 'opt back in' to have their baby screened, until their baby reaches one year of age, but it is their responsibility to inform their GP or Public Health Nurse. The Cystic Fibrosis newborn screen is not suitable if a baby is over six weeks of age and a different screen is necessary.

LF-NNS-0116 ver.3 *www.newbornscreening.ie*

Appendix 3: Scan of Newborn Bloodspot Screening Card





Appendix 4: Copy Result Request Form

N.B.: Forms only accepted from head office locations. Email to info.newbornscreening@childrenshealthireland.ie

****ALL RESULTS REQUESTED BY THE COMMUNITY SHOULD BE DONE SO THROUGH THEIR LIAISON HEAD OFFICE & WILL BE RETURNED TO THE SAME, WE CANNOT SEND RESULTS DIRECTLY TO INDIVIDUAL PHNs OR HEALTH CENTRES.****

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

Ensure **e-reports have been checked** prior to sending this form.

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

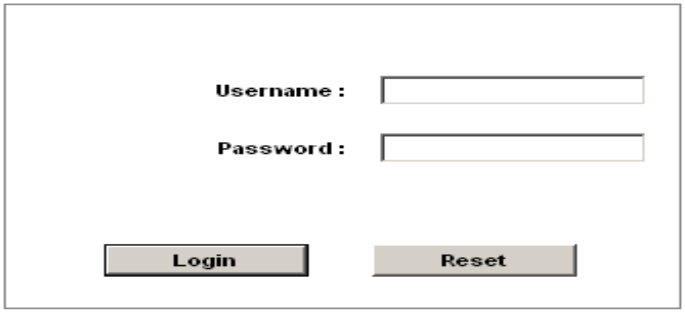
Issued by (NNBSL use only): _____ **Date** (NNBSL use only): _____

Author: Sophie Murphy Ref: LP-NNS-0047 Date of issue: 27/05/2025
Authoriser: Loretta O'Grady

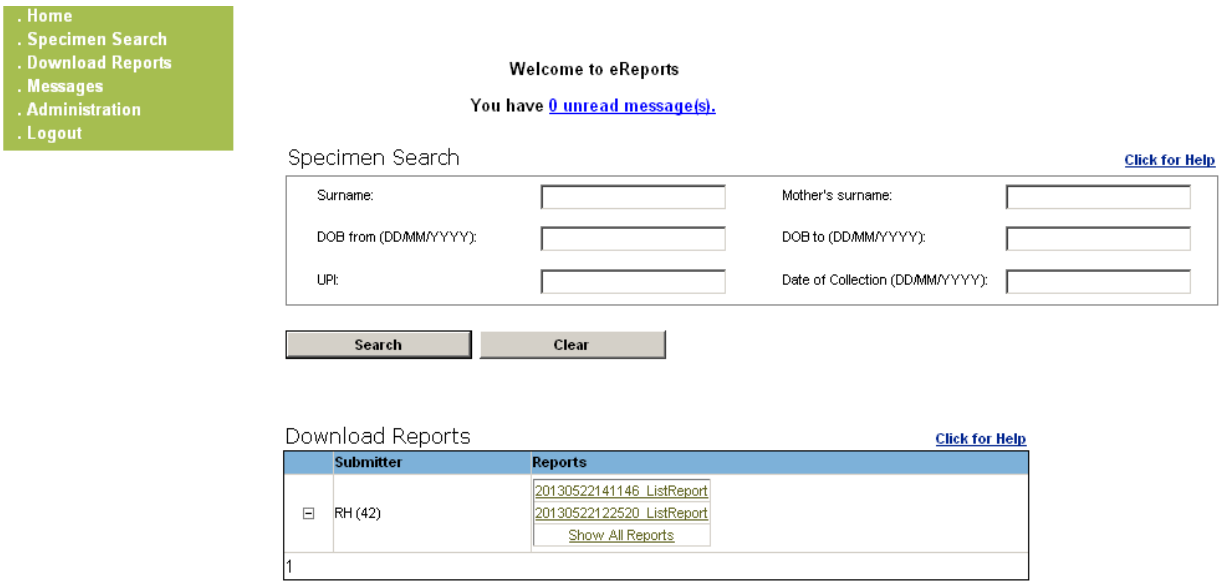
Appendix 5: eReports User Instructions

To access e-reports: In your internet browser type or copy the following URL and save to favourites.
https://nnbs.childrenshealthireland.ie/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.

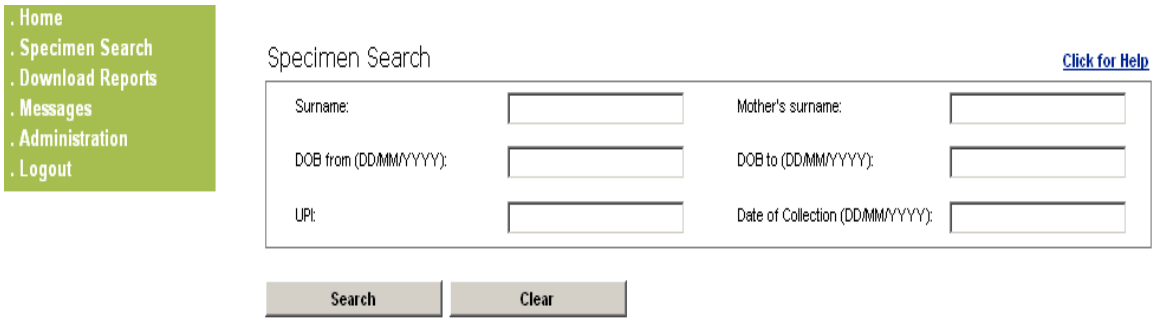


To Download Reports

- Select '**Download Reports'** (left hand side menu) – the most recent reports (list and single) for your location 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.
- Select '**Show all Reports'** to view / print all reports for the previous 60 days.

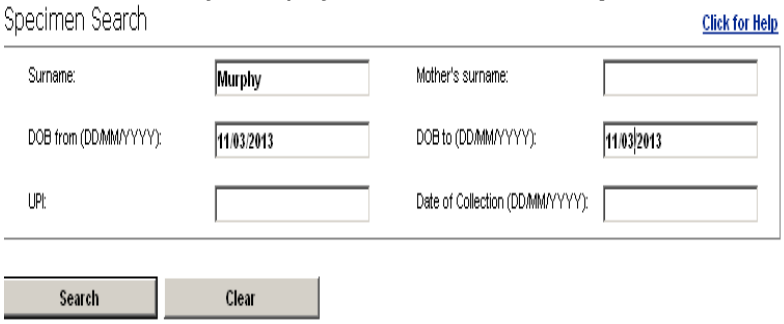
  Note: If reports have been archived after 60 days they will need to be individually regenerated. If reports are greater than 18 months they cannot be regenerated.

To do a search for a Specific Sample or group of samples select '**Specimen Search'** (left hand menu). Use below criteria, use DOB either for 1 day or a range.

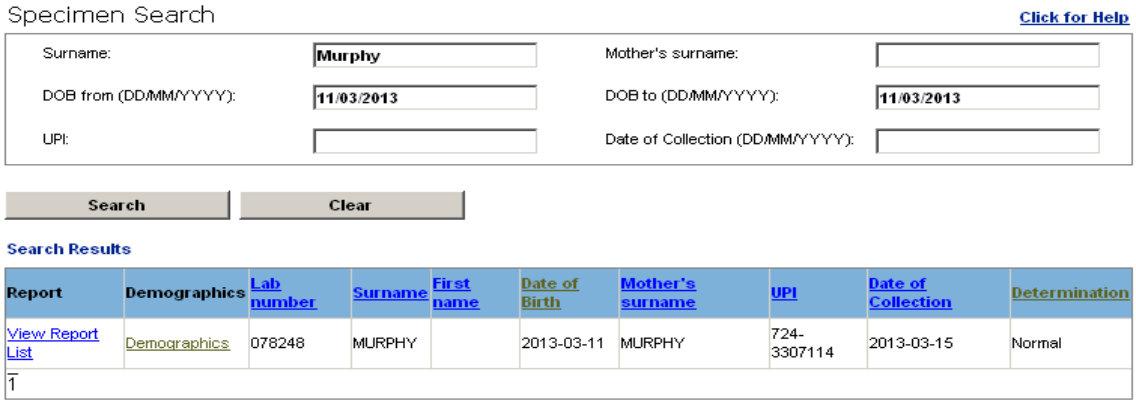


A

Example: To search for a Baby Murphy DOB 11/03/2013 **(MUST be 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.

To search for all samples from your location for a particular **DOB** enter range only: all infants with DOB of 14/05/2013 enter from 14/05/2013 to 14/05/2013.
To **search by UPI**, dash (-) must be placed after the three digit HIPE Code and ensure that the letter (if any) is included e.g. Coombe 930-B12345678.

Appendix 6: Patient Details Amendment Form

Children's Health Ireland at Temple Street, Department of Paediatric Laboratory Medicine

LF-NNS-0137 PATIENT DETAILS AMENDMENT FORM EDITION 4

This form is to amend incorrect details recorded by the laboratory or supplied by sample taker and/or to confirm information to complete babies' newborn screen details and comply with GDPR regulations gathering only minimum required demographics and sampling details

Lab sample no:

Baby's surname:

DOB:

Baby's Unique Perinatal Identifier:

Address:

Hospital of birth:

Dear NNBSL please amend the following details on baby noted above:

Signed by: **PRINT NAME:**

Position: Phone no:

Please forward to secure email
info.newbornscreening@childrenshealthireland.ie

NOTE: If attaching additional documentation please ensure it only contains required information on baby, not on parent(s) e.g. birth notification as not appropriate to share outside Maternity unit. All documents received will be attached to patient record and stored permanently.

Lab use only

Source of change: Lab/LHO/Maternity unit (please circle)
Details checked on LIMS: Disclaimer added:
Sample quality checked: Results reviewed:
Amended by: PC action complete:
Sign:

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Author: Sophie Murphy Ref: LP-NNS-0047 & 0057 Date of Issue: 27/05/2025
Authoriser: Loretta O'Grady

Appendix 7: NNBSL Screening Card Checklist

IMPORTANT – Ensure Samples are Dry, Envelopes Sealed and No Lancets Enclosed

Location:		**Contact No.:**
Total number of cards:	**Date Posted:**	**Checked by:**

Baby's Surname (as on card)	Baby's UPI (as on card)	Additional Comment *if relevant*
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
12.		
13.		
14.		
15.		
16.		
17.		
18.		
19.		
20.		
21.		
22.		

This form should be included in all envelopes containing more than one screening card
National Newborn Bloodspot Screening Laboratory, CHI, Temple Street, Dublin 1, D01 YC67
Ph: 01 8784610 /01 878 4277

For office use only - checked by: _____

Appendix 8: Follow up procedure for screen positives

Follow up of a screen positive case of PKU

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit directly and arrange for the infant to attend CHI under the care of the on-call Metabolic Consultant. The CLN in the NNBSL will book the bed for admission to CHI and liaise with the on-call metabolic team.

The contact number of the CLN can be given to the parent(s)/legal guardian(s) to make contact for more information, if they wish to do so.

Infants with a confirmed diagnosis of PKU are given a trial of the drug Kuvan, to test for responsiveness. This requires admission to hospital. The infant will also be started on lifelong dietary treatment and the parents will receive instruction on the monitoring and dietary management of their infant.

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

Follow up of a screen positive case of MSUD

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit directly and arrange for the infant to be admitted as a matter of urgency, either to the local SCBU or directly to CHI. The Clinical Director of the NNBSL/Deputy will discuss the case with the on-call Metabolic Consultant.

The contact number of the CLN can be given to the parent(s)/legal guardian(s) to make contact for more information, if they wish to do so.

If the infant is to be admitted to the local SCBU, the team will examine the infant in detail and check the urine/blood for the presence of ketones.

They will arrange for 2mls of whole blood to be collected into a lithium heparin tube for plasma branch chain amino acids to be sent immediately to the Metabolic Laboratory, in CHI.

Parent(s)/legal guardian(s) must be informed that the infant will be admitted to hospital until the results of these tests are known.

If the diagnosis is confirmed, the infant will remain in hospital until the Metabolic Paediatricians are satisfied that the infant's condition is under control and that the parents will be able to manage at home.

Follow up of a screen positive case of HCU

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit who will be asked to locate the infant and parent(s)/legal guardian(s) and explain to them why a blood sample is required and that the infant is suspected of having HCU.

The contact number of the CLN can be given to the parent(s)/legal guardian(s) to make contact for more information, if they wish to do so.

The local maternity hospital/unit will arrange for the infant to have 2mls of whole blood collected into a lithium heparin tube for total homocysteine and liver functions tests.

If the plasma total homocysteine is elevated this supports a HCU diagnosis.

Arrangements will then be made for the parent(s)/legal guardian(s) to attend the metabolic outpatients department at CHI for further follow up.

Follow up of a screen positive case of GGAL

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit who will be asked to urgently locate the infant and the parent(s)/legal guardian(s) to arrange immediate admission to the maternity hospital/unit or the local Paediatric hospital/unit. They must explain the nature of the condition to the parent(s)/legal guardian(s) and ask them to bring their infant directly into the maternity hospital/unit or the local paediatric hospital/unit where the infant will be admitted to hospital for assessment and further investigations.

The contact number of the CLN can be given to the parent(s)/legal guardian(s) to make contact for more information, if they wish to do so.

On admission, all lactose and galactose containing feeds including breast milk should be replaced by soy-based feeds, but this will depend on Metabolic Consultant advice. The infant should be examined and the following investigations are usually performed, liver function tests, coagulation screen, repeat NBS screen and blood cultures (to exclude, for example, *E coli* septicaemia), but advice may change depending on Metabolic Consultant advice.

Follow up of a screen positive case of MCADD

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit who will be asked to urgently locate the infant and the parent(s)/legal guardian(s) to arrange for them to urgently attend the maternity hospital/unit or the local Paediatric hospital/unit. They must explain the nature of the condition to the parent(s)/legal guardian(s) and ask them to bring their infant directly into the maternity hospital/unit or the local paediatric hospital/unit where the infant will be admitted to hospital for assessment and further investigations.

The contact number of the CLN can be given to the parent(s)/legal guardian(s) to make contact for more information, if they wish to do so.

All infants with an MCADD suspected screening result should be referred to the Metabolic Unit, CHI on the same day the screening result is available. The following tests are performed, urine organic acids and DBS acylcarnitines and the following may be considered: blood glucose, liver function tests, ammonia and CK. This information will all be clearly communicated.

Feeds protocol for MCADD screen positives or infants at high risk
It is essential to ensure that the infant maintains a good milk intake until results are available. If infant 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 infants 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 CHI Temple Street if oral feeds are not tolerated. If the infant is unwell in any way, urgent referral should be made to a Metabolic Consultant for review and consideration of IV glucose.

Follow up of a screen positive case of GA1

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit who will be asked to urgently locate the infant and the parent(s)/legal guardian(s) to arrange for them to urgently attend the maternity hospital/unit, or the local Paediatric hospital/unit or CHI for assessment. They must explain the nature of the condition to the parent(s)/legal guardian(s) and ask them to bring their infant directly into the maternity hospital/unit or the local paediatric hospital/unit or CHI for assessment and further investigations.

The contact number of the CLN can be given to the parent(s)/legal guardian(s) to make contact for more information, if they wish to do so.

If advised by the Metabolic Consultant, the infant may be admitted to hospital following further investigations. The following will be performed, urine organic acids and DBS acylcarnitine profile, but will depend on clinical advice.

Feeds protocol for GA1 screen positives
Feeding routine needs to be established and the infant must continue with regular feeding. If oral feeds are not tolerated, or if the infant is unwell in any way, urgent referral should be made to a Metabolic Consultant for review and consideration of IV glucose.

Follow up of a screen positive case of CF

The initial results of the CF screen will be available by approximately the third week of life. The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will collect the parent(s)/legal guardian(s) contact details, relevant clinical information and contact the appropriate HSE designated paediatric CF centre to notify them of the screen positive infant.

The CF Clinical Nurse Specialist (CNS) will book a sweat test appointment to confirm or out rule CF. They will contact the family to arrange for the infant to attend the following day.

The six HSE Designated Paediatric CF Centres are; CHI at Temple St., Crumlin and Tallaght**,** Cork University Hospital, University Hospital Limerick and University College Hospital, Galway. Infants are referred to a CF centre local to them and onward care is managed from that centre if CF is confirmed positive following a sweat test.

On arrival for the sweat test, the parent(s)/legal guardian(s) will be fully informed as to what will happen. The infant will have the 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 infant has CF or is a carrier of the condition. If the infant is considered to be a CF carrier and is therefore unlikely to have CF the parents will be referred for genetic counselling.

Follow up of a screen positive case of CHT

The follow up procedure for screen positive cases of CHT may vary slightly depending on the age of the infant, the degree of elevation of the blood thyroid stimulating hormone (TSH) level and clinical condition.

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit who will be asked to locate the infant and the parent(s)/legal guardian(s) to arrange for them to attend the maternity hospital/unit, or the local Paediatric hospital/unit for assessment. They must explain the nature of the condition to the parent(s)/legal guardian(s) and ask them to bring their infant into the maternity hospital/unit or the local paediatric hospital/unit where the infant will have tests to assess thyroid function and possibly a thyroid scan.

The contact number of the CLN can be given to the parent(s)/legal guardian(s), to make contact for more information, if they wish to do so.

Further actions will depend on thyroid function test result, following which the infant may be started on thyroid hormone replacement or be monitored for a period of time.

Follow up of a screen positive case of ADA-SCID

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit who will be asked to urgently locate the infant and the parent(s)/legal guardian(s) to arrange for them to attend the maternity hospital/unit, or the local Paediatric hospital/unit for assessment and further investigations. They must explain the nature of the condition to the parent(s)/legal guardian(s) and ask them to bring their infant into the maternity hospital/unit or the local paediatric hospital/unit for assessment and further investigation.

The contact number of the CLN can be given to the parent(s)/legal guardian(s) to make contact for more information, if they wish to do so.

Upon attendance at the maternity hospital/unit, or the local Paediatric hospital/unit, a sample of 2mls of EDTA (fresh, whole blood, ambient temperature, do not freeze) is taken and sent immediately to the Immunology laboratory in St. James's Hospital for flow cytometry and ADA enzyme analysis.

A clinical examination of the infant is required but this must be discussed with the Paediatric Immunology Team, CHI to determine whether the infant needs hospital admission or can be discharged home to await the flow cytometry results.

The NNBSL will provide specific instruction to the local paediatric team on the above requirements at the time of the identification of a screen positive.

If the flow cytometry confirms a diagnosis of ADA-SCID a plan will be agreed between the Paediatric Immunology Team, CHI and the local paediatric team for early transfer of the infant to CHI.

Follow up for a suspected case of Severe Combined Immunodeficiency

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit and request relevant clinical information. They will also contact the Paediatric Immunology team in CHI Crumlin and the Clinical Immunology team in St James's Hospital.

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) will contact the designated liaison nurse or paediatric registrar in the maternity hospital/unit who will be asked to locate the infant and the parent(s)/legal guardian(s) and to arrange for them to attend an urgent review in the local paediatric hospital. They must explain the nature of the condition to the parent(s)/legal guardian(s) and an information leaflet will be provided to the parents. The local paediatrics team will be provided with a suite of documents (maternity pack) to aid with this process and they can liaise with the Paediatric Immunology Team, CHI for advice regarding this review. This review should held in an isolation room and not in the Emergency Department or Outpatients Department. A weekend service is not required for review of screen positive cases and the cut-off for receipt of flow cytometry samples in St James Immunology Laboratory is 12 noon on a Friday. Any reviews to be carried out on an infant on a Friday should be sufficiently early so that the blood sample for flow cytometry can be received by the Immunology Laboratory in St James by 12 noon.

Upon attendance for the review, a blood sample of 1mls of EDTA (fresh, whole blood, ambient temperature, do not freeze) is taken and sent immediately to the Immunology laboratory in St. James's Hospital for flow cytometry. A blood sample for full blood count (FBC) is also taken and can be analysed in the local laboratory.

A clinical examination of the infant is required but this must be discussed with the Paediatric Immunology Team, CHI Crumlin to determine whether the infant needs hospital admission or can be discharged home to await the flow cytometry results.

If the flow cytometry confirms a diagnosis of SCID a plan will be agreed between the Paediatric Immunology Team, CHI and the local paediatric team for early transfer of the infant to CHI for ongoing management.

Follow up for a suspected case of SMA

The Clinical Director or Deputy, or Clinical Liaison Nurse (CLN) in the NNBSL will contact the Paediatric Neurology Team, CHI Temple Street and request that they contact the parent(s)/guardian(s) urgently to inform them of the screening result and to request them to attend an urgent appointment at CHI. An information leaflet will be provided to the parents.

The appointment will include a physical examination of the infant and the taking of blood samples for diagnostic testing (MPLA and AAV9 titres). Consideration of treatment with Risdiplam may also be discussed at this appointment pending the result of the MLPA.

If the MLPA confirms a diagnosis of SMA, the Paediatric Neurology Team, CHI will inform that parent(s)/guardian(s) and discuss next steps including treatment options.