

## Appendix 6: Questions & Answers about Newborn Screening in BC

### Disorders Screened and Test Accuracy

1. What disorders does the newborn screen detect?
  - BC's Newborn Screening Program screens for 22 disorders.

**Table 1: Disorders Screened**

Grouping	Metabolites Measured	Disorder	Abbrev.
Metabolic Disorders			
Amino Acid Disorders	Amino Acids	Phenylketonuria	PKU
		Maple Syrup Urine Disease	MSUD
		Citrullinemia	CIT
		Argininosuccinic Acidemia	ASA
		Homocystinuria	Hcy
		Tyrosinemia, Type I	Tyr I
Fatty Acid Oxidation Disorders	Acylcarnitines	Medium-chain Acyl-CoA Dehydrogenase Deficiency	MCAD
		Long-chain Hydroxyacyl-CoA Dehydrogenase Deficiency	LCHAD
		Trifunctional Protein Deficiency	TFP
		Very-long Chain AcylCoA Dehydrogenase Deficiency	VLCAD
Organic Acid Disorders	Acylcarnitines	Propionic Acidemia	PROP
		Methylmalonic Acidemia	MUT
		Cobalamin Disorders	Cbl A, B
		Glutaric Aciduria, Type I	GA I
		Isovaleric Acidemia	IVA
Galactosemia	GALT enzyme activity	Galactosemia	GALT
Endocrine Disorders	Thyroid stimulating hormone (TSH)	Congenital Hypothyroidism	CH
	17OH-progesterone (1 <sup>st</sup> tier) Steroid panel (2 <sup>nd</sup> tier)	Congenital Adrenal Hyperplasia	CAH
Hemoglobinopathies	Hemoglobin HPLC	Sickle Cell Disease	HbSS
		Sickle Cell/Hemoglobin C	HSC
		Sickle Cell/ $\beta$ -thalassemia	HbS/ $\beta$ -thal
Cystic Fibrosis	Immunoreactive trypsinogen (IRT) (1 <sup>st</sup> tier) CFTR mutation panel (2 <sup>nd</sup> tier)	Cystic Fibrosis	CF

## 2. Why screen for these disorders and not others?

- The disorders on the screening panel were selected by the Newborn Screening Advisory Committee of BC following an evidence-based review process.
- Factors considered in the decision process included: incidence and seriousness of the disorder, evidence of improved health outcomes with early detection, test performance (accuracy and reliability), availability of confirmatory testing and follow-up treatment.
- The Newborn Screening Advisory Committee will review the panel of screening tests periodically and recommend changes as new tests and/or information about disorders becomes available.

## 3. What are the possible results of a newborn screen?

- "Negative screen" for all disorders. The NBS Laboratory will send a "negative screen" report to the physician/midwife listed on the blood spot card and to the baby's birth hospital.
- "Repeat sample requested". The NBS Laboratory will send a report to the physician/midwife listed on the blood spot card to request a repeat sample. A copy of the report will be sent to the baby's birth hospital. Usual reasons are:
  - Baby was less than 24 hours old at the time of collection;
  - Baby was less than 1,500 grams at birth;
  - Baby had a blood transfusion prior to collection of the sample; or
  - Sample was unsatisfactory.
- "Positive screen" for one of the disorders. A positive screen does not mean that the baby has a disorder, but only that further testing is required. See question #4.
- Baby is a "CF carrier" or has a hemoglobinopathy "trait." See questions #5 and #6.

## 4. What is the process if a baby has a "positive screen" for one of these disorders?

- The NBS Laboratory will contact the baby's physician/midwife by phone to discuss the positive screen and coordinate the next steps.
- Generally, the physician/midwife will be asked to contact the family to assess the clinical state of the baby and organize the repeat testing. Contact information for an appropriate specialist on-call will also be provided in cases in which there are immediate clinical concerns.
- The NBS Laboratory will contact the baby's physician/midwife with the repeat testing results as soon as they are available and will coordinate referral to the appropriate clinical specialty if the repeat results are positive.

## 5. What is the process if a baby is identified as a cystic fibrosis (CF) carrier or as having a hemoglobinopathy trait?

- Screening for cystic fibrosis and hemoglobinopathies may identify a baby that is a CF carrier or has a hemoglobinopathy trait.
- It is important for the parents to know if the baby is a CF carrier or has a hemoglobinopathy trait so they can:
  - tell their child later in life. His or her future partner can choose to have testing to identify the couple's chances of having a baby with CF, or a clinically significant hemoglobinopathy.
  - decide whether they wish to be tested. If the baby is a CF carrier or has a hemoglobinopathy trait, one parent is almost certainly a carrier. There is a small risk that both parents are carriers which would have implications for future pregnancies.
- Resources are available to assist in counseling families with regards to these issues. Referral to the BC Medical Genetics program (see question #6) for genetic counseling may also be appropriate under some circumstances.

6. **If parents wish to have carrier testing for CF or hemoglobinopathy, what is the process?**
- Pre-test counselling and testing can be done or arranged by the physician.
  - If parents wish additional genetic counselling, the physician may refer them to the Provincial Medical Genetics Program in Vancouver (604-875-2157) or Vancouver Island Medical Genetics in Victoria (250-727-4461).
  - Questions from physicians and nurses about carrier testing and the interpretation of results may be directed to a genetic counsellor in one of the Medical Genetics clinics listed above.
7. **Will the newborn screening test identify disorders other than the 22 targeted disorders?**
- Nine secondary disorders that are not primary targets of the screening program may be identified as “by-products” of the screening process:
    - a. Amino Acid Disorders
      - i. Hypermethioninemia (MET)
      - ii. Citrin Deficiency (CIT II)
      - iii. Mild Hyperphenylalaninemia (H-Phe)
      - iv. Biopterin Biosynthesis Defects (BIOPT BS)
      - v. Biopterin Recycling Defects (BIOPT REC)
    - b. Organic Acid Disorders
      - i. Cobalamin C/D (Cbl C/D)
      - ii. 2-methylbutyrylglycinuria (2MBG)
    - c. Fatty Acid Oxidation Disorders
      - i. Multiple Acyl-CoA Dehydrogenase Deficiency (MAD)
    - d. Hemoglobinopathies
      - i. Variant Hemoglobinopathies (Var Hb)
8. **How accurate are the newborn screening tests?**
- The testing accuracy varies between disorders but the testing protocols have been designed to maximize sensitivity (proportion of cases detected) and positive predictive value (PPV: percentage of babies with a positive screen that truly have the disorder.)
  - Some tests have multiple “tiers” of testing where a rapid first tier is completed on all samples to identify those at greatest risk for a disorder, and a more complicated second tier test is then performed to identify those with a false positive result on the first test.

**Table 2: Sensitivity and Positive Predictive Value of Newborn Screens for Each Disorder<sup>1</sup>**

Disorder	Abbrev	# Tiers	Sensitivity	Positive Predictive Value (PPV)
Metabolic Disorders				
Amino Acid Disorders				
Phenylketonuria	PKU	1	99%	~100%
Maple Syrup Urine Disease	MSUD	2	95%	95%
Citrullinemia	CIT	1	99%	~50%
Argininosuccinic Acidemia	ASA	1	99%	~50%
Homocystinuria	Hcy	2	99%	95%
Tyrosinemia, Type I	Tyr I	1	99%	~100%
Fatty Acid Oxidation Disorders				
Medium-chain Acyl-CoA Dehydrogenase Deficiency	MCAD	1	99%	100%
Long-chain Hydroxyacyl-CoA Dehydrogenase	LCHAD	1	~95%	30%
Trifunctional Protein Deficiency	TFP	1	~95%	30%
Very-long Chain AcylCoA Dehydrogenase Deficiency	VLCAD	1	98%	~80%
Organic Acid Disorders				
Propionic Acidemia	PROP	2	97%	30%
Methylmalonic Acidemia	MUT	2	95%	30%
Cobalamin Disorders	Cbl A, B	2	95%	30%
Glutaric Aciduria, Type I	GA I	1	99%	39%
Isovaleric Acidemia	IVA	1	98%	50%
Galactosemia	GALT	1	99%	20%
Endocrine Disorders				
Congenital Hypothyroidism	CH	1	~90%	26%
Congenital Adrenal Hyperplasia	CAH	2	99%	~90%
Hemoglobinopathies				
Sickle Cell Disease	HbSS	1	~99%	~85%
Sickle Cell/Hemoglobin C	HbSC	1	~99%	~85%
Sickle Cell/ $\beta$ -thalassemia	HbS/ $\beta$ -thal	1	~99%	~85%
Cystic Fibrosis	CF	1	95%	15%

<sup>1</sup> Sensitivity and positive predictive values estimated from BC empirical data (where available) or literature values for equivalent methods.

## Consent for Newborn Screening

### 9. Is newborn screening mandatory?

- Newborn screening is considered “standard of care” and is recommended for all babies born in BC.
- Newborn screening is not mandatory. Parents or the legal guardian may decline screening after having received information on the purpose and benefits of the screening (see “Informed Refusal” process outlined in this guideline).
- Note: A surrogate mother will not likely have completed the papers to be the legal guardian by the time blood is collected for the newborn screening tests. Consult your health authority policy and/or risk management department as to the acceptability of a surrogate mother signing the refusal form if legal documentation is not in place.
- Information about newborn screening is available in several languages on the website: [www.newbornscreeningbc.ca](http://www.newbornscreeningbc.ca).

## Timing of Blood Spot Card Collection

### 10. What is the best time to collect blood spot cards for newborn screening?

- Blood spot cards are best collected prior to discharge and between 24 and 48 hours of age (pre-term and term babies). If collection is not completed during this time, collection should be done no later than 7 days of age in order to ensure early detection of these treatable disorders.
- If a baby is discharged from hospital prior to 24 hours of age, an initial card is collected before discharge. A second card is collected by 2 weeks (14 days) of age.

### 11. Is it too late to collect a specimen if the baby is older than 7 days old?

- No, newborn screening can still be done, but the sensitivity of some of the screening tests will be reduced if the sample is collected at greater than 4 weeks of age.

### 12. Must the baby have started feeding before collecting the specimen?

- No, as long as the specimen was collected after 24 hours, the screen will detect the conditions regardless of whether the baby has started feeding (breast/bottle) or is on Total Parenteral Nutrition (TPN) or intravenous fluids.

### 13. What if the baby has had a blood transfusion?

- Blood transfusions are known to affect the results of hemoglobinopathy and galactosemia screens and may affect other screens as well (Reed, 2000; Korson, 1990).
- If a blood transfusion is anticipated, whenever possible, collect a blood spot card prior to the transfusion regardless of the baby’s age.
- If the baby is less than 24 hours old when the card is collected, the NBS Laboratory will request, through the baby’s physician/midwife, that a repeat card be collected by two weeks (14 days) of age.
- If a blood spot card is not collected prior to the transfusion, collect at 24 – 48 hours of age. The NBS Laboratory will request, through the baby’s physician/midwife, that two repeat cards be collected, one at three weeks (21 days) and one at four months (120 days) after the date of the transfusion.

### 14. What if the baby is less than 1,500 grams at birth?

- Very low birth weight babies who have congenital hypothyroidism (CH) may have a delayed rise in thyroid stimulating hormone (TSH). The first screen (done at 24 – 48 hours) may miss the identification of CH in some of these babies (Tylek-Lemariska D, 2005; Grufeiro-Papendieck L., 2005).
- For this reason, the NBS Laboratory will request, through the baby’s physician/midwife, that a repeat card be collected at day 21 or on discharge from hospital, whichever is sooner.
- For babies where blood is difficult to draw (e.g., premature infants), it is acceptable to fill 2 out of the 4 available spots on the card.

15. Does the baby have to return to the hospital of birth to have a repeat specimen collected?
  - No, the baby can go to any birthing hospital laboratory in British Columbia.
  
16. For babies discharged from hospital at less than 24 hours of age, what is the benefit of collecting the blood spot card in hospital if a second card is required anyway?
  - The first blood screen will identify over 80% of disorders and will help to prevent life threatening events such as severe or potentially fatal bacterial infections in babies with galactosemia or significant metabolic crises in babies with medium-chain acyl-CoA dehydrogenase deficiency (MCAD), very-long chain acylCoA dehydrogenase deficiency (VLCAD) or maple syrup urine disease (MSUD).
  - The 2nd screen optimizes detection of phenylketonuria (PKU), cystic fibrosis (CF) and homocystinuria (Hcy) which are time sensitive and cannot be reliably detected until 24 hours or more after birth.
  
17. Why not defer testing and have the parent(s)/guardian return to the hospital lab to have the blood spot card collected later?
  - A pilot study at BC Women’s Hospital to trial deferral of testing revealed that up to 8 percent of parents did not return with their baby to the hospital for blood collection. Many parents find it difficult to return to the lab shortly after discharge with their baby, despite their best intentions. If a second sample is never collected, at least the baby will have received most of the benefits of screening.
  
18. What if parents do not wish to have their baby tested prior to discharge from hospital?
  - Provide the parent(s)/guardian information about the rationale for collecting blood prior to discharge and the risks if newborn screening is not done.
  - If they still decline collection of the card prior to discharge from hospital, have them sign the “Informed Deferral: Newborn Screening” Form (see Appendix 4) and make arrangements for them to have a blood card collected after discharge.
  - Exceptions to collection of two blood spot cards may apply if a health authority/hospital has a standard process in place to follow-up after discharge to ensure a blood spot card is collected or if the baby is under the care of a registered midwife. See Appendix 5 in this guideline for information about setting up a deferral process.

**Note: If an initial blood spot card is collected, the NBS Laboratory will track that a follow-up card(s) is collected (if required). If an initial card is never collected, the NBS Laboratory is unable to identify or track babies for screening.**

### Refusal of Newborn Screening

19. What if parents do not wish to have their baby screened at all?
  - Ask the parent(s)/guardian to read the brochure “A simple blood test could save your baby’s life” (available in multiple languages at [www.newbornscreeningbc.ca](http://www.newbornscreeningbc.ca)).
  - Discuss the benefits of newborn screening and answer questions/address concerns. Often, their reservations are due to lack of understanding and can be easily resolved.
  - If they still decline screening, have them sign the “Informed Refusal: Newborn Screening” form.
  - Place a copy of the signed form in the baby’s health record and send a copy to the baby’s physician/midwife.

### Storage, Use, Retention, and Disposal of Blood Spot Cards

20. What happens to the blood spot card after the newborn screening tests are done?
  - After the tests are done, a very small amount of dried blood is left on the card. The amount left depends on how much blood was collected and whether more tests were needed to make sure the results were accurate. The amount left is usually smaller than a dime.
  - The BC Newborn Screening Program stores the cards with the leftover blood sample for 10 years in one of two secure locations: BC Children’s Hospital NBS laboratory storage or off-site storage. Blood spot cards may only be requested from storage by the Director of the NBS Program and senior staff designated by the Director. All staff that access stored cards have received training in data privacy. After 10 years and upon direction provided by the Director of the BC NBS Program, the cards are disposed of by incineration according to standard operating procedure for biohazardous materials.

## 21. Why keep blood spot cards after the newborn screening tests are done?

Blood spot cards are kept for clinical purposes such as:

1. Re-running a test in the event the first test result was not clear. This means the test can be repeated without having to get another blood sample from the baby.
2. Trying to find the reason for a health problem that has developed later in a child's life or trying to find the cause of an unexplained illness or death of a baby/child. Sometimes testing the leftover blood spot sample will help to find the cause.
3. Checking the quality of testing done by the laboratory to make sure that results are accurate.
4. Developing better tests for the disorders currently screened or for developing new tests to screen for other treatable disorders.

## 22. Are blood spot cards ever used for health research?

- Yes, a few studies have been conducted on stored blood spots. In all cases, stored blood spot samples were anonymized, meaning that all the information that identifies the baby (e.g., name, PHN and date of birth) was removed to protect privacy in accordance with the Freedom of Information and Protection of Privacy Act (FOIPPA). All research projects have been approved by a Clinical Research Ethics Board (CREB) to ensure high ethical standards.
- There is great potential to advance science and clinical care for newborns and children utilizing stored blood spots for health research. Public health research contributes to the public good through increased scientific knowledge.

## 23. Are baby's blood spot cards ever released to third parties?

- Blood spot cards are treated the same as hospital records or medical files held by doctors and hospitals in relation to the powers of the Court. On rare occasions the Court or other legislative authority (e.g., Coroner's Act) may order access to a blood spot card or related information. Without legislated authority, blood spot cards are not released to third parties.

## 24. Can a baby have the newborn screening tests done but not have the leftover blood card stored with the BC Newborn Screening Program?

- Yes. Parents/legal guardians who do not wish their baby's blood spot card to be stored with the BC Newborn Screening Program may request to have the card destroyed.
- Parents/legal guardians who wish to have their baby's blood spot card destroyed must sign a form called a Directive to Destroy Leftover Newborn Screening Blood Samples. The signed form is sent to the BC Children's Laboratory with proof of identity.
- Once a directive to destroy a card is received, the NBS laboratory separates the filter paper containing the blood spots from the blood spot card. The filter paper and blood spots are destroyed. A letter is sent to the parents/legal guardians to tell them the blood spots have been destroyed. Destroying the card means that the card will no longer be available for any purpose, including further tests if the baby or child develops an illness later in life.
- Both parents/legal guardians must sign the request to destroy their baby's card. If the baby has only one parent/legal guardian, that parent/legal guardian must sign the form to say they are the only parent/legal guardian.
- Occasionally, parents/legal guardians may request to have their baby's blood spot card returned. This may be possible in exceptional circumstances but would require the parents/legal guardians to come to the BC Children's Laboratory with proof of identity to pick up the blood spot card. The card itself will be heat treated (autoclaved) before returning in order to remove any potential biohazard associated with the dried blood. This means the card will no longer be usable for any type of biological testing.