Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

Market Consultation

Newborn bloodspot screening

Consultation of the market on technical possibilities for the optimization of the Dutch newborn bloodspot screening program

Nx tendernumber not applicable

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1 General information

1.1 Organisation

RIVM
The National Institute for Public Health and the Environment (RIVM) is an agency of the Ministry of Health, Welfare and Sport (VWS) and carries out its duties for policy development and monitoring in the areas of public health, the environment and nature. The RIVM consists of thirty components, mainly laboratories, teams or centres with a specific research task. These components, all based in Bilthoven, have been placed in three knowledge domains: Infectious Diseases and Vaccinology, Environment and Safety and Public Health and Care.

The Centre for Population Screening (hereafter: RIVM-CvB) is placed under the Public Health and Care domain. RIVM-CvB has been commissioned by the Ministry of Health, Welfare and Sport and is responsible for overseeing the Dutch population screening programmes. The Newborn Bloodspot Screening is one of the screening programmes offered by the Dutch government and coordinated by RIVM-CvB. For more information about the Centre for Population Screening: https://www.rivm.nl/rivm/organisatie/centrum-voor-bevolkingsonderzoek.

1.2 The Dutch Newborn Bloodspot Screening (NBS) programme

Overview of the NBS programme
In the Netherlands, nearly all newborns (approximately 170,000 per year) are screened for 26 serious congenital diseases via the national NBS programme. These 26 diseases include 18 metabolic disorders, 2 hormonal disorders, 3 forms of hereditary anaemia, as well as spinal muscular atrophy, cystic fibrosis, and severe combined immunodeficiency. Children with these (rare) diseases benefit from early interventions such as medication or a diet, which can prevent or limit irreparable health problems.

As illustrated in figure 1, the executive process of the NBS can be described in 4 steps: First, a bloodspot sample from the newborn is obtained shortly after birth using heelprick blood, either at home or at the hospital. The blood is collected on a filter paper card, which is then sent to the laboratory for testing. The laboratory screens the dried bloodspots for the 26 diseases. An abnormal test result means there is an increased risk of one of the tested diseases and further diagnosis and treatment will be necessary. If the diagnosis is confirmed, further treatment and care will be provided to prevent the development of the disease or to minimize its effects. Each year, approximately 500 newborns are referred with an abnormal result, of which about 200 newborns are diagnosed with one of the 26 diseases.

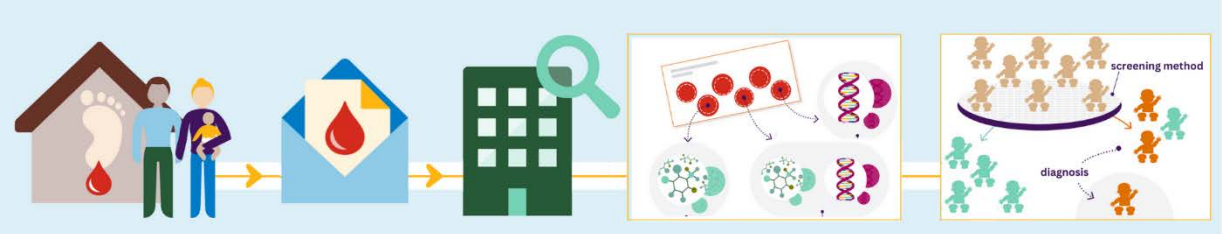

Fig. 1 – *Simplified overview of the NBS process. A dried bloodspot sample is collected from the newborn using heelprick blood. This sample is sent to the laboratory where it is tested using biochemical and/or genetic test methods. Newborns with an abnormal result are referred to a paediatrician and further tested to confirm diagnosis.*

Target group
The NBS is aimed at all newborn babies. The heel prick test to obtain the dried bloodspots should be taken between 72 and 168 hours after birth.

Screening laboratories

Analysis of the dried blood spots is carried out by five screening laboratories, of which the RIVM screening laboratory also serves as a reference laboratory. The laboratory screens the blood for the diseases according to agreed techniques and established cut-off values. These techniques include, among others, tandem mass spectrometry, immunochemical-, calorimetric-, and enzymatic assays, and qPCR.

The maximum amount of time that may elapse between an abnormal test result becoming known the screening laboratory and the moment the child is under responsibility of a paediatrician is known as the turnaround time. In the Dutch NBS, maximum turnaround times have been established: from ‘as soon as possible (within 24 hours) for certain metabolic diseases to ‘within 4 weeks’ for sickle cell carrier status.

2 Market consultation

2.1 Introduction to the market consultation

The expanded Dutch NBS

The NBS programme in the Netherlands started in 1974 with testing for phenylketonuria (PKU). Over the years, innovations in both treatments and screening test methods has enabled the expansion of the Dutch NBS with many additional diseases. The final decision to expand the Dutch NBS is made by the Ministry of Health, Welfare and Sport (VWS). The minister of VWS makes the decision based on advice from the Dutch Health Council, an independent national scientific advisory board. The Health Council has advised the Ministry of VWS on NBS expansions in 2005 (advice to add 14 diseases), 2011 (advice to add cystic fibrosis), 2015 (advice to add 14 diseases) and 2019 (advice to add SMA). After a decision of the Ministry of VWS to expand the NBS, RIVM-CvB is responsible for the implementation and execution. The Dutch NBS is internationally regarded as a leading example of a highly advanced programme screening for many important diseases.

Tandem mass spectrometry

In the past decade, tandem mass spectrometry (hereafter: tandem MS) has become a powerful tool for disease screening; enhancing sensitivity, specificity, and turnaround time. Within the dried bloodspot analysis techniques in the Dutch NBS, tandem MS is the most used method, with 15 of the 26 diseases being screened for using tandem MS. At the moment, the Dutch screening laboratories use two tandem MS techniques, namely flow-injection analysis (FIA)- and liquid chromatography (LC)- tandem MS. These techniques are used in two different screening algorithms: (A) One-tier test using only FIA-MSMS, or (B) a two tier test where the first tier uses FIA-MSMS, and the second tier uses LC-MSMS. Appendix 1 gives an overview of the 15 diseases in the Dutch NBS currently screened for using tandem MS, as well as with which the screening algorithm. Because of its extensive use in the programme, advancements in the field of tandem MS have the potential to further optimize the Dutch NBS.

Screening for homocystinuria in the Netherlands

Homocystinuria (hereafter: HCY) is a metabolic disease that can be caused by different errors in the homocysteine metabolism pathway. One error in the homocysteine metabolism is caused by a defect of the CBS enzyme (known as CBS deficiency), which leads to both elevated homocysteine and methionine concentrations in dried blood spots of newborns. Another error in the homocysteine metabolism that can cause HCY is because of defects in the remethylation pathway of homocysteine. This form of HCY leads to elevated homocysteine, but different from CBS deficiency, remethylation deficiency leads to lowered methionine concentrations.

Both of these forms of HCY are generally regarded as treatable, which is why HCY has been marked as a candidate disease by the Dutch Health Council for the NBS programme. HCY caused by CBS deficiency was screened for in the Dutch NBS between 2005 and 2010, by testing for elevated methionine concentrations in dried bloodspots using tandem MS. This method has been used in the NBS programmes of several other countries as well. However, this test method turned out to be insufficient for the Dutch situation, because HCY caused by CBS deficiency is not as frequent as the HCY caused by remethylation deficiency in the Dutch population. As remethylation deficiency is characterized by lowered methionine, the screening method used did not detect this form of HCY. Due to the fact that a large portion of the HCY-patients would be missed, while at the same time a considerable number of false positives was found, it was decided to stop screening for HCY using methionine in 2010.

The current advice of the Health Council is that HCY could be considered for reimplementation in the Dutch NBS if an adequate test method becomes available that detects HCY caused by both CBS- as

well as remethylation- deficiency. One option would be to determine the concentration of total homocysteine in dried bloodspots using tandem MS techniques.

In vitro diagnostics medical device regulations

On April the 5th 2017, the European Parliament adopted a new regulation for medical devices and a regulation for in vitro diagnostics: the Medical Device Regulations (MDR) and the In Vitro Diagnostic Medical Device Regulations (IVDR). Existing IVD certificates are still valid until may 2025. The new legislation imposes more rigorous standards for the market approval of medical devices and in vitro diagnostics. This includes heightened requirements for Notified Bodies, more stringent demands for clinical evidence, and stricter pre-market scrutiny for high-risk products.

For the Dutch NBS programme, RIVM-CvB prefers the use of commercial tests that fall within the regulations of CE-IVD(R) marking.

2.2 Reason for the market consultation

Tandem MS is an important test method used extensively in the Dutch NBS. Developments in tandem MS equipment and/or assay kits can further improve the NBS programme, either by providing new opportunities for using tandem MS in the current screening algorithms, or by enabling the addition of new diseases such as HCY. Therefore, RIVM-CvB attaches great importance to the knowledge of market parties and wants to consult them about the technical possibilities for optimization that are or will become available. An open market consultation is therefore held for additional information to determine future scenarios and strategies.

In this market consultation, parties are asked for information that can help optimize the tandem MS based screening methods, in particular in relation to possibilities to screen for HCY. We encourage both current providers of tandem MS products for dried bloodspots and/or HCY test providers, and those who have yet to enter the market to share their perspective.

2.3 Objective of the market consultation

The goal of this market consultation is to gain a better understanding of market developments and also to obtain answers to specific questions. In this way, RIVM-CvB wants to get a realistic picture of the possibilities to optimize the newborn bloodspot screening programme in relation to tandem MS.

With this market consultation, the project team aims to:

a. reach, interest and stimulate as many parties as possible to think along
b. gain insight into possible solutions and the way in which parties can contribute to this
c. gain insight into potential market parties

3 Questionnaire

This consultation aims to give parties the opportunity to comment on the needs of RIVM-CvB to optimize the newborn bloodspot screening programme. The market consultation consists of a questionnaire with questions to the market, as shown below. The questions presented in this chapter are asked in the context of the preceding sections with regard to the background information and the expected developments within the programme.

You are kindly requested to answer the questions below in writing, by using the word-format answer form separately uploaded to TenderNed. The completed questionnaire can be sent directly to marit.swierstra@rivm.nl. Any business-sensitive information is not disclosed.

Participants in this market consultation can choose to which questions they want to formulate a response, it is not mandatory to answer all questions. RIVM-CvB does ask participants to provide sufficient substantiation for the questions answered. There is no restriction to the length and content of the answers. RIVM-CvB prefers concise and to the point answers.

The questions are asked in a direct sense, which does not exclude you from answering these in general (when you are not a supplier of the product in question). If your product only covers part of the laboratory procedure(s), please indicate this explicitly.

Number	Question
1	RIVM-CvB is interested in gathering perspectives and expertise from a wide range of MS related market parties. **Questions:** **a.** Does your company currently supply tandem MS products for high-throughput dried bloodspot analysis? ☐ Yes (continue to question 2) ☐ No (continue to question 3)
2	RIVM-CvB is interested in the contents of your company's in-vitro diagnostics MS product portfolio, both hardware and/or assay kits. **Questions** **a.** Does the product portfolio of your company include IVD/IDVR tandem MS hardware? If yes, could you provide a description of types of the equipment? **b.** If your company provides IVD/IVDR tandem MS assay kits, please provide a short description (e.g. what analytes does it detect?)
3	RIVM-CvB is interested in all tandem MS related market parties in the field and whether they would be interested to expand their portfolio for newborn screening / dried bloodspot analysis. **Questions** **a.** If your tandem MS equipment currently is not suited for high-throughput bloodspot analysis, would your company be interested to expand its portfolio for this purpose? If so, what opportunities do you see? **b.** If your company currently does not carry assay kits for dried bloodspot analysis, would your company be interested to expand its portfolio and for which analytes? **c.** If portfolio expansion is currently not feasible from your perspective, could you provide an explanation?

Number	Question
4	Currently, 15 of the 26 diseases in the Dutch NBS are screened for with tandem MS, using two screening algorithms: FIA-MS/MS with commercial assay kits as a 1st tier test, or LC-MS/MS with an in-house assay for 2nd tier tests (see also appendix 1). Developments in tandem MS equipment and/or assay kits can provide new opportunities for using tandem MS in the current screening algorithms, or enable the addition of new diseases. **Questions:** **a.** What possibilities do you see (have available) that could improve the current FIA- or LC- screening algorithms used in the Dutch NBS? **b.** What possibilities do you see (have available) for expanding the current number of 15 disorders in the Dutch NBS programme?
5	The RIVM-CvB is exploring methods to screen for both forms of HCY (CBS- and remethylation- deficiency) on dried bloodspots. **Questions** **a.** Does your company currently provide any analytical test to detect both forms of HCY using dried bloodspots as sample material? ☐ Yes, see question b ☐ No, see question c **b.** If yes, could you provide a description of the characteristics of the analytical test for HCY that your company provides (e.g. what biomarker does it measure? Which analytical method does it require?). **c.** If no, would your company be interested to expand its portfolio for this purpose?
6	Besides tandem MS, the Dutch NBS uses analytical methods such as fluorometric assays, PCR-based assays, immunoassays, and HPLC. The most important prerequisite is that the analysis can use dried bloodspots as sample material. **Question** **a.** What analytical method would you recommend for the Dutch NBS programme, for detecting both the CBS and remethylation deficiency forms of HCY?
7	The RIVM-CvB would preferably screen for both forms of HCY using tandem MS. **Question** **a.** What possibilities do you see (have available) to screen for both the CBS and remethylation deficiency forms of HCY using tandem MS?
8	The RIVM-CvB is aware of scientific studies reporting validated methods for screening total homocysteine using FIA-MSMS and LC-MSMS techniques, respectively. **Questions** **a.** Is your company aware of these developments? ☐ Yes ☐ No **b.** Does your company see opportunities to integrate these developments in its portfolio and in what way?

Number	Question
9	The RIVM-CvB prefers the use of commercial tests that fall within the regulations of CE-IVDR marking, and is interested in learning more about the trajectory of gaining IVDR certification. **Questions** **a.** If you have indicated in the previous questions that your company has any analytical tests/equipment in its portfolio, are these IVDR certified? If so, could you indicate which ones? **b.** Could you provide insight into the process and requirements involved in submitting an IVDR certification or switching from IVD to IVDR? **c.** If you have indicated that your company would like to include tests in its portfolio or is already working on developing them, could you please indicate how long the IVDR process will approximately take to get the certification?

4 Process, terms and conditions

4.1 Process

This market consultation starts by publishing this market consultation document in TenderNed. Interested market parties can answer the questions from the questionnaire that are included in chapter 3 of this market consultation document using the answer form separately uploaded to TenderNed. The results of the market consultation will be treated confidentially. Any business-sensitive information is not disclosed.

Completed questionnaires can be sent directly to marit.swierstra@rivm.nl.
The closing date for answering the questions is Thursday 1st of June, 2023.

Depending on the responses, it may be considered by RIVM-CvB to invite a number of market parties to deepen the relevant topics in an interview.

In case of any questions, please do not hesitate to email us at marit.swierstra@rivm.nl.

4.2 Terms and conditions

Through this market consultation, parties are given the opportunity to respond to RIVM-CvB's question regarding the technical options for optimizing the Dutch Newborn Bloodspot Screening programme.

Below are the general terms and conditions that apply to participation in this market consultation. Participants in the market consultation unconditionally agree to these conditions. It concerns the following conditions:

a. This market consultation will be conducted in the English language only.
b. This market consultation is carried out through TenderNed. The participants cannot derive any rights with regard to this market consultation from verbal statements made by or on behalf of RIVM-CvB.
c. The information made available by RIVM-CvB in the context of this market consultation should only be used for the purpose for which it was provided. It is not permitted to make this information available to third parties or to multiply it for a purpose other than that for which it was provided.
d. Parties cannot derive any rights from the information provided during the market consultation.
e. Participation is free. No costs will be reimbursed for your participation by RIVM-CvB.
f. The results of the market consultation may be shared in general and anonymously, at the discretion of RIVM-CvB and taking into account any business-sensitive nature of the information.
g. The project team may use the information obtained from the market consultation at its own discretion in policy advices and in documents for future tenders.
h. Information provided during the market consultation may differ from information to be provided in future procurement procedures.

Appendix 1

Overview of diseases screened for using tandem MS

Disease	Tier	Marker(s)	Method
Carnitine palmitoyltransferase deficiency (CPT1)	1	C0, C0/C16+C18	FIA-MS/MS
Glutaric acideamia type I (GA-1)	1	C5DC	FIA-MS/MS
Isovalerian acidity (IVA)	1	C5, C2/C5	FIA-MS/MS
Long-chain-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD)	1	C16OH	FIA-MS/MS
Maple syrup urine disease (MSUD)	1	Leu, Val, Phe/Val	FIA-MS/MS
Medium-chain acyl CoA dehydrogenase deficiency (MCADD)	1	C8, C8/C10	FIA-MS/MS
Methylmalonic acidemia (MMA)	1	C3, C3/C2, C3/C16	FIA-MS/MS
	2	MMA^MB	LC-MS/MS
Mucopolysaccharidosis type I (MPS I)	1	IDUA activity	FIA-MS/MS
	2	GAGs (DS, HS)	HPLC MS
3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC)	1	C5OH	FIA-MS/MS
HMG-CoA-lyase deficiency (HMG)	1	C5OH	FIA-MS/MS
Multiple CoA carboxylase deficiency (MCD)	1	C5OH	FIA-MS/MS
Phenylkeetonuria (PKU)	1	Phe, Phe/Tyr	FIA-MS/MS
Propionic acidemia (PA)	1	C3, C3/C2, C3/C16	FIA-MS/MS
	2	MCA	LC-MS/MS
Tyrosineama type 1 (TYR-I)	1	SA	FIA-MS/MS
Very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD)	1	C14:1, C14:1/C2	FIA-MS/MS