

SYNTHESIS

Inborn errors of metabolism: assessment of expanded newborn screening using tandem mass spectrometry in France (part 2)

March 22

Key messages

- Newborn screening is a public health intervention to detect certain rare but serious diseases at birth. The aim is to implement appropriate measures before symptoms appear in order to avoid or limit the negative consequences of these diseases on the health of children.
- In France, this screening is based on a national program. Six diseases are currently screened by biological tests carried out on a drop of blood collected on blotting paper (Guthrie): phenylketonuria, congenital hypothyroidism, sickle cell disease, congenital adrenal hyperplasia and cystic fibrosis, and since more recently, medium chain fatty acid acyl-CoA dehydrogenase (MCAD) deficiency.
- The arrival of tandem mass spectrometry (MS/MS) makes it possible to screen for many inborn errors of metabolism (IEM) at birth. In its work, the HAS has evaluated the opportunity to screen for 24 IEMs by MS/MS.

In France, a national NBS programme started in 1972 with the systematic screening of all newborns for one metabolic disease (phenylketonuria). Five other diseases have been progressively added to the programme: Congenital hypothyroidism, Congenital Adrenal Hyperplasia, Cystic Fibrosis, Sickle cell disease (targeted screening) and MCAD. In the last years, the responsibility of the programme has been transferred from an association to the Minister of Health.

Most inborn metabolic diseases are today detected by tandem mass spectrometry (MS/MS), a laboratory technique able to screen for multiple metabolic disorders simultaneously and rapidly, through the analysis of a single blood sample. This technique detects abnormal levels of a high number of metabolites and must be followed by confirmatory tests for final diagnosis. As the MS/MS technique allows to detect a high number of disorders, programmes must decide which disease should be screened for, aiming at an acceptable balance between benefits and risks. Possible benefits of screening for a disease are that early detection followed by effective intervention can prevent illness, sequelae and in

some diseases early death. The main risks are the impact of false negative and false positive results, involving false reassurance or unnecessary worry and costs respectively.

This technological improvement in the last decades, allow some countries to enlarge the list of diseases to be screened. As a result, there are large variations in the diseases screened for in European countries and no validated rules for decision making decisions on how to expand NBS programmes.

This leads the French Minister of Health to ask to the French National Authority from Health (Haute Autorité de Santé, HAS) in 2017 to conduct a study to explore methods to structure the health technology assessment surrounding the Newbron screening Program (NSP).

The scope of this study was to establish a method to prioritize diseases to be included in the French NSP using a Multi-Criteria Decision Analysis (MCDA) using a number of criteria that are weighed by a limited number of stakeholders (physicians, labs performing the tests, patient groups and ethical experts). This work was conducted between 2018 and 2019 and published by the French Authority from health in January 2020.

Inborn errors of metabolism: rare and serious diseases with no screening consensus

The term "inborn errors of metabolism" (IEM) does not characterize a disease but a group of metabolic diseases. These are rare, hereditary diseases, most often transmitted in an autosomal recessive mode. There is a large number of IEMs, but the scope of this referral is limited to diseases of intermediate metabolism (excluding phenylketonuria and medium-chain acyl-CoA dehydrogenase deficiency, MCAD): aminoacidopathies, organic acidurias and mitochondrial beta-oxidation anomalies. Although the individual prevalence of these diseases is low (1 out of 10,000 to 1,100,000), their collective prevalence and impact on morbidity and mortality make them a public health problem. In most cases, non-specific symptoms occur, and clinical diagnosis is usually made by exclusion. The most severe cases may lead to death within the first few weeks of life. In other cases, they manifest themselves by a metabolic decompensation, leading to irreversible sequelae (intellectual deficit, neurological disorders, growth retardation).

Early diagnosis, initiated before the onset of clinical symptoms, can avoid prolonged hospitalizations for diagnostic purposes; when intervention is decided, it can improve the prognosis. In the absence of early intervention, IEMs can lead to death. However, there is uncertainty about the clinical significance of some of these anomalies for which there are a large number of genetic variants with asymptomatic or pauci-symptomatic forms. Indeed, while some IEMs, such as phenylketonuria (PKU) have been known for several decades, others have been described only very recently and others will probably be discovered in the future.

The development of tandem mass spectrometry (MS/MS) has revolutionized the landscape of newborn screening programs (NSP) worldwide. The fundamental contribution of MS/MS is the ability to simultaneously identify multiple IEMs on small amounts of sample (such as a spot of blood on blotting paper, Guthrie). However, beyond PKU, there is no consensus on which diseases should be included in the programs, which are currently very heterogeneous. In Europe, despite harmonization efforts, the number and nature of metabolic diseases screened vary widely at both national and subnational levels.

Specific criteria to screen IEMs at birth

A review of the criteria used in European and North American screening programs was conducted. Most of the recommendations published by countries are based on the Wilson and Jungner principles.

They constitute a historical foundation that has become more complex over time, with adaptation to each national public health context. It is also in line with technological evolution, and with the evolution of public opinion on the various ethical issues related to NSP for rare diseases.

Although the evaluation methods are different, and NSP do not include exactly the same pathologies, the reflections are generally on the same aspects, leading to a convergence of the selected criteria: epidemiological data, test performance, ethical, economic, social and organizational issues.

This review concluded that the criteria defined in 2004 by the former French National Health Evaluation and Accreditation Agency (ANAES), and used by HAS, remains robust and still relevant. In the context of rare diseases, the notions of beneficiary and the reduction of diagnostic errancy must be considered. The state of the art of current NSP practices worldwide shows the need to clearly define the problems of each disease in France, according to its public health context.

A multi-criteria analysis method for disease screening

Given the difficulty to define the relevance of screening each disease on a sequential disease-by-disease evaluation, a generic evaluation approach was implemented, covering all the diseases included in the selected scope.

The aim of this work was to select the IEMs that could be included in the national NSP. The evaluation approach was both systematic (based on the usual screening criteria) and adapted to the number of diseases evaluated and expert-consulting methods.

A three-step multi-criteria decision analysis method was implemented.

The evaluation criteria determined in consultation with the working group (WG) were transcribed into a grid layout. Each IEM was evaluated by a panel of 35 different experts using an ad-hoc process flow chart, and then compared to one another.

- ➔ The first step of the process was to determine the specific criteria to evaluate IEMs. The WG distinguished two types of criteria:
 - major criteria (knowledge of the natural history, severity of the disease, effectiveness of the treatment, individual benefit of early intervention, and reliability of the screening test);
 - minor criteria (incidence of a rare disease and organizational impact).

The notions of beneficiary (child) and reduction of diagnostic wandering were considered. Other aspects were examined, such as relevance, non-redundancy, independence and discriminatory power (between diseases). Then, a list of permanent criteria was determined.

- ➔ The second step presented the state of knowledge and practice for the 24 diseases examined. For each of them, a summary sheet was produced in order to document all the criteria. These summary sheets were reviewed and validated by the members of the WG in subgroups (aminoacidopathies, organic acidurias and beta-oxidation deficiencies).

Simultaneously, an ad-hoc method was proposed to the WG members to evaluate the diseases that need to be screened. An evaluation grid was developed to prioritize/organize the criteria, according to a logical sequence. The application of this flowchart allowed the discernment of the relevant IEMs to the NSP.

- ➔ In a third step, the panel of 35 experts (clinicians and biochemists/biologists) scored each criterion for every IEM, using the evaluation grid and the bibliographic summaries produced for this purpose.

Diseases selected from the evaluation

Based on the review of the literature and the results of the expert panel, a proposal for IEMs to be included in the national NSP was finalized at the last WG meeting.

The WG analysed and discussed the results of the expert panel for each of the 24 IEMs evaluated. The analysis and discussion took into account the five major decision criteria, considering that there had to be more than 85% consensus for each criterion for the disease to be eligible.

Three categories of diseases were defined (Table 1):

- Proposed for inclusion in the NSP (primary target),
- Not proposed, to be re-evaluated within three years (based on expected new data),
- Not proposed to the national NSP, as the criteria have not been met to date.

Table 1. Outcome of the metabolic disease assessment: diseases proposed for inclusion in the national NSP, in addition to PKU and MCAD deficiency, and diseases not proposed.

Diseases	Aminoacidopathies	Organic aciduria	Deficits in beta-oxidation
Proposed	HCY Homocystinuria MSUD Leucinosis TYR1 Tyrosinémie type 1	GA-1 , Glutaric acidemia type 1 IVA , Isovaleric aciduria	LCHAD , Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency CUD , Carnitine uptake defect
Not proposed To be re-assessed	CIT1 , Citrullinémie type 1 OTC Ornithine transcarbamylase	PA , Propionic aciduria MMA , Methylmalonic acidemia	VLCAD , very-long chain acyl-CoA dehydrogenase deficiency
Not proposed	ASA Argininosuccinic Aciduria ARG Hyperargininemia	3MCC , 3-hydroxy-3-methylglutaric aciduria HLCS , Holocarboxylase synthetase deficiency BKT , β -ketothiolase deficiency	SCADD , short-chain acyl-CoA dehydrogenase deficiency CPT1 , carnitine palmitoyl transferase deficiency I deficiency CPT2 , carnitine palmitoyl transferase deficiency II deficiency CACT , carnitine-acylcarnitine translocase deficiency MTP mitochondrial trifunctional protein deficiency MADD , Multiple acyl-CoA dehydrogenase deficiency

Organizational impact of expanded newborn screening by MS/MS

As a reminder, in part I of this recommendation, the HAS recommended a reduction of the number of laboratories performing NSP. A limited number of laboratories equipped with MS/MS is required to ensure the acquisition and maintenance of expertise, as well as the efficiency of the process. This reorganization was based on demographic criteria, existing expertise, and inter-regional collaboration networks. It also required the reduction of the number of the equipment of the 13 regional centers with dedicated mass spectrometry machines.

In addition to the material investments, the extension of the NSP requires special attention to various aspects:

- **Organizational aspects:** it is essential to insist on a deadline for results that is strictly less than 8 days after birth. Blood should be strictly collected between 48-72 hours of life. For the screening to be useful, the blotters must be sent to the center within 24 hours.
- The introduction and increase in the number of pathologies screened by MS/MS will impact the organization of the reference and competence centers for hereditary metabolic diseases, particularly in terms of workload and management of result controls. An impact on the articulation with clinical services is also expected to ensure optimal and rapid care of screened patients. The work processes will have to be clearly defined.
- Questions about the storage of MS/MS data, for a posteriori use for diagnostic purposes, and about the duration of their storage (infrastructure, data confidentiality, data protection) will have to be clearly resolved in accordance with the current standards.
- The importance of documenting family history, lifestyle, and exposures, especially of the mother at the time of birth (diets, deficiencies due to vegan diet, antibiotic intake) was highlighted.
- **Technical aspects:** a definition of biochemical markers and threshold values should be clearly communicated for each IEM, although this aspect is outside the scope of this recommendation. A reminder of the precautions has to be taken with regard to:
 - Premature babies (in particular carnitine uptake deficiency: CUD needs to be carried out at the time of discharge, at the same time as congenital hyperplasia),
 - Carnitine deficiency situations (need to repeat the analyses after supplementation).

The implementation of newborn screening for each metabolic inborn error, as well as for MCAD deficiency, requires the development and use of a screening algorithms. It aims to obtain a presumptive diagnosis with the highest possible degree of certainty from the first sample, and a confirmation (or refutation) of the diagnosis in the shortest possible time. Such screening also requires a standardised protocol for the management of screened and positive cases.

- **Professional aspects:** strengthening collaboration between biologists and clinicians is imperative. The introduction of IEMs into the NSP will lead to a better knowledge of diseases and a care organisation by clinicians, requiring the drafting of national care protocols (*Protocoles nationaux des soins*, PNDS) as a priority for each pathology selected during this evaluation. The Perinatal Network will have to anticipate the information that could be delivered at the prenatal stage; the scope of training will have to be extended.
- Training of personnel is imperative to use the machines, interpret the results and carry out the necessary investigations to confirm positive tests. The extension of the NSP implies that all professionals involved in its management have been trained.
- **Aspects regarding the information of the public:** it will be necessary to provide two distinct moments of information to families and health professionals involved in the birth process, on the nature of these new screened diseases.
 - The first concerns all families whose children will be screened. The expansion of screening to new diseases may increase the difficulty to provide information to parents in a limited time. According to the literature and the opinion of the working group, the days following birth are not the best time to pass on information to parents about recommended biological tests for rare disease screening. It should be given during the third trimester of pregnancy, to avoid refusals, and to reduce anxiety at the time of a possible recall. The importance of providing

information during pregnancy was also emphasised in part 1¹ and is mentioned in the ministerial decree of 28 February 2018².

- The second information moment concerns families whose children will be affected by these diseases. Information sheets for the public and health professionals will have to be produced to accompany the announcement process. The bibliographic sheets produced as part of this study will be used to update or create Orphanet disease summary sheets.

Program management and monitoring

A screening program should include a program management and monitoring plan as well as a set of quality assurance standards recognised by the medical community. In addition, the evaluation criteria and indicators should be validated, in a limited number, and chosen at the a priori evaluation stage, on an evidence basis.

In line with the decree of 28 February 2018², regular evaluations at national level and by territory, with well-defined indicators, will enable prospective monitoring of the diseases introduced into the NSP. The following list of indicators is not exhaustive, as other may be defined according to specific programme objectives:

- participation rate,
- recall rate for abnormal results,
- prevalence (and distribution) of the various mutations,
- positive predictive value,
- number of false positives,
- false negatives,
- number of confirmed cases,
- time of sampling in days after birth,
- time of the result returned to the paediatrician,
- time taken to meet the family,
- time taken for management,
- follow-up rate,
- clinical results (clinical evolution, complications, death),
- overall cost and per IEM.

Laboratory participation in quality assurance programs and in international collaborations is essential to optimise the sensitivity and specificity of the test and the screening algorithm. It is important that a quality assurance system is also in place for the other components of the screening program (information, diagnosis, follow-up and management, evaluation). A monitoring and evaluation system includes routine monitoring and the various forms of evaluation, namely structural, process, outcome, and impact evaluation. Routine statistical data collection is mainly used to evaluate structure and processes and, to a lesser extent, outcomes. The collection of routine statistical data should be extended to information relevant to the screening of deficits detected by MS/MS and integrated into the

¹ Evaluation of the extension of newborn screening to one or more inborn errors of metabolism by tandem mass spectrometry. Part 1: MCAD deficiency. [Haute Autorité de Santé - Évaluation de l'extension du dépistage néonatal à une ou plusieurs erreurs innées du métabolisme par spectrométrie de masse en tandem. 1er volet: déficit en MCAD \(has-sante.fr\)](#)

² Ministerial decree of 22 February 2018 on the organisation of the national newborn screening program using medical biology tests. [Arrêté du 22 février 2018 relatif à l'organisation du programme national de dépistage néonatal recourant à des examens de biologie médicale - Légifrance \(legifrance.gouv.fr\)](#)

computerised information system. It is important to have a policy for archiving and possible future use of samples (blotters) under conditions that ensure the privacy of individuals and their family.

It is also very important to evaluate the long-term impact of the NSP and to measure the positive and negative effects of the program. This implies the comparison of the clinical course of screened children with that of children diagnosed based on clinical symptoms. The evaluation of the impact of screening will require observational studies. This requires the establishment of registries containing follow-up information on patients diagnosed by screening and based on clinical symptoms. The establishment of international rare disease studies is important to increase the statistical power of the studies. The evaluation of specific aspects, such as the impact of false positives, requires the setting up of ad hoc studies.

Active scientific monitoring, as well as the follow-up and evaluation of the NSP will make it possible to evaluate the opportunity to extend this screening to new diseases. To this aim, the WG proposed the re-evaluation of five diseases (CIT1, OTC, PA, MMA and VLCAD) within three years, if new data occur.

Recommendations

Inborn errors of metabolism to be screened by MS/MS

1. The HAS recommends extending NSP in French general population to TYR-1, HCY, MSUD, GA-1, IVA, LCHAD, and CUD deficiencies. This screening necessarily involves the use of MS/MS technology.

Methods of implementation

2. The HAS recommends the use of validated screening algorithms for each recommended IEM, as well as a standardised management scheme for the cases of "TYR-1, HCY, MSUD, GA-1, IVA, LCHAD and CUD" detected deficiencies.
3. The HAS recommends the use of succinylacetone as a marker of TYR-1 screening to reduce the number of false positives.
4. The HAS recommends the use of tHCy as a second-line test for HCY screening to reduce the number of false positives.
5. The HAS recommends that maternity units send blood sample cards to the regional neonatal screening centers (*Centres régionaux de dépistage neonatal*, CRDN) within 24 hours (including weekends and public holidays), to optimise the delivery of results.
6. The HAS recommends that the proposal to extend the NSP be accompanied by training for all health professionals involved in the NSP. This training should cover both technical and relational aspects, in particular the provision of information.
7. The HAS recommends providing the initial information on NSP for parents during the third trimester prenatal consultations.
8. The HAS recommends either the development of information material adapted to different audiences, including parents and future parents, healthcare professionals involved in NSP, and the management of screened patients, their family and the general public.
9. The HAS recommends that sufficient human and financial resources be dedicated to the implementation and follow-up of this screening.

Monitoring and evaluation

10. The HAS recalls the importance of the indicators reported in Annex I of the ministerial decree of 28 February 2018² ; these will make it possible to assess the time taken to obtain the sample, the time taken to deliver it, its quality, the time taken to carry out the biological screening tests, the time taken to deliver the result, the results of the NSP, the prevalence of the new diseases

screened here recommended, the performance of the test (false positives, positive predictive value, false negatives), etc.

11. The HAS encourages implementing clinical and epidemiological research projects based both on collected data and their evaluation importance. In this particular context, the HAS insists on the central role of the epidemiology commission of the National Coordination Center for Neonatal Screening (*Commission d'épidémiologie du Centre National de Coordination du Dépistage Néonatal*, CNCDNN).

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