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**EU Tender**

**"Evaluation of population newborn screening practices for rare disorders in Member States of the European Union"**

# Executive Report to the European Commission on newborn screening in the European Union

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# A. Existing barriers to the development of EU policies in the field of neonatal screening

## 1. Disease selection

Decisions for screened conditions are based on criteria largely derived from those formulated by Wilson and Jungner and from guidelines of scientific societies. Also literature surveys and national scientific research are commonly considered in the deliberations made when deciding on the set of conditions screened for. Cost seems to be the most important reason not to screen a disorder while epidemiological evidence and cost-effectiveness are the main reasons to implement screening for a certain disorder.

It is possible that the heterogeneity in the sets of disorders screened for in the various countries is not due to large differences in criteria applied but to different interpretation of the same criteria, pre-existing regional differences, differences in (strength of) initiatives and unequal availability of technical means and expertise. Moreover, protocols for diagnoses and treatments have been developed fast in the last years for a number of rare conditions. Therefore it is challenging for each country to perform prompt assessments of new technological possibilities, ensure economic sustainability and making decisions.

While it is likely that disease selection criteria and mechanisms can be brought to a common framework, the different financial, infrastructural and human resources of the EU Member States prevent the adoption of a uniform panel of screened conditions.

## 2. Attitude to regulate by written policy

Wide variation exists among countries on which aspects of neonatal screening are covered by written policy. Moreover, there are countries that have regulated NBS processes rather extensively by guidelines (legally non-binding prescriptions) or directives (legally binding prescriptions), while other countries have not. Therefore, EU policies in NBS, which do not take into account these differences, will develop with difficulty.

## 3. Mandatory nature of the offer of neonatal screening

The offer of neonatal screening by health care services usually is supported by a legal basis or is an implicit public health measure if it is financed with public funds. It seems that a common agreement on the mandatory nature of the service can be achieved, although there might be difficulties regarding the possibility of opting-out, discussed in the next paragraph.

## 4. Mandatory participation of the newborn

Usually, in countries where the offer of screening has a legal basis, parents can opt out of screening; this is, however, not allowed in a very small number of countries. Opting-out balances the right of the child to health promotion with the parents' responsibility to make choices for their child. If the mandatory participation, as implemented in a few countries, is based on a firm and motivated position, it can impact on the possibility to have an easy

common agreement on combining the mandatory nature of the service with the possibility of opting out.

## 5. Consent

Obtaining informed consent should be a normal procedure accompanied by the possibility of opting out. However it appears that the association of this procedure with a choice to opt out is not always the case. In many countries, the procedure of providing information to the parents is not regulated and wide variations exist, likely resulting from local arrangements. Proper information to parents may result in additional workload of the staff and increased costs. However, the development of educational material, possibly taking advantage of that already available in some countries, may facilitate the development of a common position.

## 6. Eligible benefits and communication of findings

The Wilson and Jungner criterion "There should be an accepted treatment for patients with recognized disease"[1] has been broadened in many discussions on genetic screening to include other advantages to parents, especially (a) avoiding a diagnostic odyssey and (b) informed reproductive choice for future pregnancy(ies). Both these benefits are shared among parents and the child. The information on a child's carrier status may be of benefit, although not immediately, to the child itself. The concept of treatment includes not only a medical meaning, but rather can be extended to other interventions, which may reduce the burden of the disease and improve the quality of life. Also the detection of any abnormal finding (and its communication to the individuals who may benefit from this information) is being considered as a possible benefit in current debates regarding genetic testing and is as well applicable to neonatal screening.

Assessment of the benefit to the child should be distinguished from benefit to the parents or other subjects. The primary aim of a NBS programme is to improve the health status of infants with treatable conditions. However, the possibilities offered by new technologies should be exploited as far as a balance between the benefits to other subjects and the right of the child to protect its own health data is to be found with the involvement of patients' and parents' advocacy groups.

Different national positions in this area have been found in the survey and in the debates during the meetings; they may likely be based on overall different ethical and pragmatic approaches to health prevention and care. In some countries, communication of information for benefits other than those to the child is regulated by law.

Defining a single position in this area is very unlikely because of the difficulties intrinsic to the question and in the different histories and cultures of the EU communities. Within the development of EU policies, it might be explored whether a common set of eligible benefits (a kind of pick list) can be defined as part of the assessment leading to the adoption of a neonatal screening programme; however, it seems rather clear that the final decisions on the benefits to be recognised are to remain at country level.

[1] Wilson JMG, Jungner G (1968). The principples and practice of screening for disease. Public Health Papers n. 34. Geneva: World Health Organization. (page 26). (retrieved from http://whqlibdoc.who.int/php/WHO_PHP_34.pdf; 15. November 2010)

## 7. Organisational arrangements

There is huge variation among countries concerning blood sampling organisation and timing and sample transport logistics, partly related to the time when mother and infant are discharged from the hospital or maternity clinic, to the occurrence of home delivery and to the way of birth notification and the signal to the organisation that is responsible for sampling. A specific case is the sampling of cord blood at delivery, instead of a heel prick at a later time, as performed in Finland and Malta; this is suitable for screening for congenital hypothyroidism and haemoglobinopathies, but not for many other diseases.

EU policies usually do not deal with the modalities in which national services are delivered. These operative differences therefore should not represent a barrier to the adoption of EU level policies; however, these differences may have important consequences in the national (regional) decision-making process for the extension of the neonatal screening.

## 8. Disease specialists and treatment centres

Information on the range of specialists and centres of expertise available has not been requested in the survey. The WHO-HFA[2] database can give some information on the availability of paediatricians in different countries. Other information on centres of expertise for each disease can be retrieved in the ORPHANET[3] database. Some answers, however, suggest that, beside infrastructure (e.g. provision of adequate care after a positive screening result) other obstacles can result from practice (e.g. communication among relevant specialists).

Comparing data of countries screening for 2 disorders (phenylketonuria and congenital hypothyroidism), it appears that confirmation of the screening results operates rather differently across countries: with these two traditionally screened disorders, lengths of in-patient stays range from 2 days in Latvia to 12 days in Norway.

At least some of the disorders with a longer average inpatient stay have a risk for early decompensation (e.g IVA, proprionic aciduria, methylmalonic aciduria, MSUD). Therefore the efficiency of the system for diagnosis confirmation is an important prerequisite for an effective intervention and may have important consequences in the performance of a neonatal screening programme.

The national (regional) availability of infrastructure, medical professionals with expertise in screened diseases' diagnosis and treatment and the organisation of the entire chain of health care is to be part of the assessment of the national (regional) situation during the decision-making process.

## 9. Costs and sustainability of the screening programme

Cost of screening may be a problem in some countries and is among the most frequently cited factors limiting the panel of screened diseases. Moreover, the implementation costs associated with the first period after introduction of a new screening programme, before the beneficial effects become apparent, may represent another obstacle even if screening itself is cost-saving.

The costs of the whole screening process, from the information on NBS programmes to prospective parents and the general public to the start of treatment, have been investigated in

[2] http://data.euro.who.int/hfadb/

[3] http://www.orpha.net/consor/cgi-bin/Clinics.php?lng=EN

the survey. However, the uncertainties underlying the replies prevent a reliable analysis of costs of most steps of this process. Although a more detailed and comprehensive analysis of economic issues is warranted to include direct and indirect costs of treatment and of non-treatment, the results collected here suggest that the costs for running the service for screening and diagnosing are limited to a very minor fraction of the gross domestic product(GDP), as well as of the part of the GDP spent for health by the general government (including social security funds), even in case of extended screening and adoption of more sophisticated techniques. .

## 10. Political advantages and disadvantages

For some lower or middle income countries, cost of screening is an important variable. Even if a programme will be cost effective (or even cost-saving) in the long run, the initial phase implies higher costs for the health system. In some countries this might be a political problem, especially since the party that is charged with fund raising is not always the party that can show the benefits for health and will receive political advantage.

## 11. Lack of evidence for the development of agreed common quality operation and standards

Differences in practical aspects of the operations (sampling times; delays between sampling and screening analysis; storage times; protocols for confirmation of screening results) are the consequence of organisational arrangements which may be traced to previous and current lack of clear evidence for best procedures.

Analytical screening methods for the same disorder often differ among countries. Although evidence and consensus exists on the most reliable methods and techniques, the variety in analytical methods can be due partly to economic and organisational reasons. Different cut-off values are used by different laboratories; although the methods for their determination have not been investigated with the tender survey, ideally they are set with the intent to minimise the false positive and false negative results on the basis of the actual screening data. Statistical uncertainties due to low frequencies of cases and the ethnic patterns of the screened autochthonous and immigrant population may have an influence on these values.

Confirmatory diagnostic investigations are very well regulated in all screening countries. It is likely that these prescriptions are based on updated scientific knowledge. However, the practices show a complex pattern of confirmatory techniques, the basis of which has not been investigated and is not clear. Although protocols may be well developed and up to date, the relative efficiency of different diagnostic strategies is not known.

Although in some cases there might now be sufficient knowledge to establish the best practices, the expected advantages may not outweigh the consideration of increased costs and inherent risks of changes for the overall organisation of the screening system.

The adoption of common reference practices for the operation of the screening system in different countries seems rather premature at present.

# B. Areas that could benefit from the development of an EU policy on NBS

Neonatal screening encompasses the whole system from information to prospective parents to treatment of those infants who have been identified as having one of the screened conditions. Neonatal screening in most countries is offered under the responsibility of the public health system. Yet in many countries the health system does not care for the collection and exchange of information between the confirmatory diagnostic, treatment and follow-up phases, which may prove invaluable for the quality of NBS.

There are a number of areas and steps of the whole neonatal screening system which show room for a feasible improvement by means of a dedicated EU policy, especially if it can benefit from synergies deriving from a coordinated action of the EU.

## 1. Decision-making framework

A structured framework, representing in a balanced way the views and needs of the patients and other citizens, the national health systems and other institutional stakeholders, such as social insurances and governmental scientific experts, could be defined at EU level consisting of three steps:

### *a. EU-level technology assessment*

The Community level technology assessment deals with the general and intrinsic features of a disease candidate for screening; it could receive and assess dossiers, submitted by interested parties, supporting disease candidates for neonatal screening. It might also assess spontaneously new technological developments (horizon scanning). This activity could be carried out in association or collaboration with existing European countries collaborative mechanisms, such as EUNetTHA[4].

### *b. National (regional) technology assessment*

The national (regional) technology assessment is performed within institutional processes with the participation of independent experts and takes into consideration the feasibility of the NBS programme with respect to local conditions, assessed according to criteria defined at EU level within the overall framework. More technical definitions might be provided by the EU-level technology assessment.

### *c. National decision-making*

The decision-making step remains at the national/regional level and is separate from the national technology assessment process. The decisions made and the ways in which the technology assessments have been taken into consideration are to be documented and made public.

This structured framework could result, at national level, in a decision making process centred on the improvement of health, reduced burden of the preliminary scientific assessment, and in increased trust in the health systems for patients, their advocates and citizens in general, while considering the health system sustainability and the health priorities of a country.

From an EU perspective, it will provide better consistency in the services offered by different countries and a flexible process, able to take into account the technological progress.

[4] http://www.eunethta.eu/

## 2. Legal basis and informed consent

A national legal basis for the operation of neonatal screening programmes, which can be tailored to local conditions within a common framework, would be important to ensure the necessary quality to the system. It would ensure the rights of infants to healthcare with an offer of NBS, which is defined through a shared procedure and transparent assessment.

Legal bases mandating participation in neonatal screening programmes might limit the burden of asking and archiving the informed consent; however the mandatory nature of NBS should be accompanied with provisions for adequate and transparent information to parents and public, as well as with an opt-out system, allowing parents to refuse the service.

The national legal basis might furthermore regulate consistently the following issues:

- the storage and the delayed use of samples and the associated consent;
- the identification of eligible benefits;
- the communication of results to parents and/or patients, including unintended findings;
- the collection and communication of data for the assessment of the programme and for improving the knowledge on disease and treatment;
- ensure quality control and and quality assurance
- sustain funding.

An EU action can help promote the extension of quality control and assurance processes, and define criteria of quality and of the operation of quality assessment, thus ensuring the achievement of health care quality targets, without dictating practical and technical arrangements of the national neonatal screening systems. Exchange of expertise might be key. Indeed, at present, the performance of the screening laboratory procedures in EU can hardly be assessed since studies are occasional and data are rarely known. Accreditation and certification procedures take place in about half of the countries, with a variety of standards. It is true, however, that most, if not all, screening laboratories participate in External Quality Assessment programmes. Other steps of the NBS system participate less frequently in quality control procedures. Use of guidelines and application of quality control and quality assurance programmes have to be more extensively used in a number of steps of the NBS process.

## 3. Training of professionals

While any assessment of the skills of laboratory screening professionals and of medical professionals is outside the scope of this work and is not addressed here, the survey indicated that professional training needs to be improved and extended on specific aspects especially relevant for NBS, such as communication with parents at all steps of the NBS process, from the pre-natal steps to the education of parents confronted with positive screening result.

Appropriate training may effectively contribute to improvements necessary in specific steps of the process, which are highlighted separately.

## 4. Networking of specialists, screening laboratories and centres of expertise

Already part of the recommendations for an action in the field of rare diseases, networking of centres of expertise and of specialists, may speed up consultation and confirmation of individual diagnosis, as well as facilitate debate and consensus on the best strategies for confirmatory investigations and treatment, and allow easier access to quality care in countries

with less expertise on selected diseases. Cooperation may help smaller jurisdictions to perform laboratory screening and confirmatory diagnosis at a reasonable cost. Good practices may serve to improve expertise in teams elsewhere.

## 5. Communication of screening results to parents

Availability of written material, at the time of first communication to parents of the meaning and the consequences of the positive outcome of NBS, can be regarded as particularly important, since it can support parents' understanding of and coping with the diagnosis of the chronic disorder in their children. However, printed and/or digital material is available in more than 50% screening countries for few diseases only.

Communication of a positive screening result and confirmed diagnosis could be better regulated with the aim of ensuring information which is more suitable to parents and families as well as reducing their anxiety.

## 6. Parents' and patients' empowerment after diagnosis

Only half of the respondents (49%) reported to have a guideline or directive regulating the involvement of professions in the treatment of patients with disorders they screen for. Written and/or digital material explaining treatment to parents is not always available. Better parents' and patients' empowerment may improve the management of care, reduce the burden of care for the public health system and improve the patients' and familys' quality of life. Patients' and parents' organisations may play a role in assuring optimal quality of care for their infants' disorder and in providing respite initiatives for the family carer.

Along the lines of the EU Recommendation for an action on rare diseases and the EUROPLAN documents, an EU policy may facilitate sharing documents and experiences for the benefit of countries which have not the material available yet, as well as to promote the involvement of parents' and patients' associations.

## 7. NBS programme assessment and epidemiological evaluation

Communication of long-term clinical outcomes to the different actors in the NBS system (including screening laboratory) and to a central registry will make the evaluation of the screening programmes and research on optimal treatment of the screened diseases possible.

Although treatments are, overall, started within the recommended age in practically all countries, there are some diseases where a rather high number of patients are already symptomatic at the start of treatment. At the same time there is wide variability among countries in the timing of each step of the NBS process preceding the start of treatment. Registries could help to evaluate the consequences of different approaches.

Important synergies may result if the initiatives of data collection at local levels would be harmonised and cross-linked to allow the establishment of national and international networks and registries for the NBS programme assessment and for clinical and epidemiological purposes.

## 8. Economic evaluation

Epidemiological evidence of effective prevention and cost-effectiveness are the main reasons to implement a screening programme for a certain disorder. Moreover, information on the cost-effectiveness of a program is of main importance for countries to plan and evaluate

public health services. However, systematic and economic analysis is very rare and is extremely difficult, especially for small population countries.

Therefore, there is a need for an action, which, in association with the initiatives devoted to the assessment of economic dimensions of NBS programmes, allows the recording and comparability of key data on NBS costs and outcomes.

# C. Actions proposed to facilitate the development of EU policies in the field of neonatal screening

## *Raising awareness and consensus among appropriate stakeholders*

- Submit to EUCERD members a proposal for the establishment of a working group on NBS based on EUNENBS core members and expert directory;
- Disseminate the Expert Opinion Document among the professional societies involved in neonatal screening programmes (including treatment units) and ask them for a formal opinion on it, including the feasibility of actions supporting European and national policies (e.g.: in the area of training of professionals);
- Disseminate the Expert Opinion Document among rare disease advocacy groups and associations in order to raise awareness.

## *Promotion of Member States' coordination and cooperation, EU collaborative research and knowledge improvement*

- Establish a specific HTA committee, taking into consideration the initiatives on-going at EU level for country cooperation in HTA (EUNetHTA). This committee will have a subsidiary role and shall not override national decisions. The scope of the committee will deal with the assessment of elements that are common to all countries (e.g. efficacy of treatments, reliability of screening tests) and not related to national specificities. It may begin the process of evaluation of new proposals for new disorders to be screened and may perform the evaluation and re-evaluation of screening programmes.
- Test the practical applicability of the proposed decision-making matrix in countries with different human, infrastructural and financial resources.
- Facilitate the gradual expansion of NBS with interdisciplinary projects networking countries with differently developed NBS systems.
- Prioritise EU Public Health projects on the assessment of critical control points in the NBS process
- Define an EU scheme for the quality assurance system of NBS, which promotes the implementation of national quality assurance programmes based on common principles, guidelines and criteria.
- Assist in cross-border and inter-country service cooperation, including sharing of information material, protocols and expertise and cooperation at laboratory and diagnostic level.
- Facilitate health insurance coverage in case of cross-border follow-up and treatment.

- Establish a platform for longitudinal registries for rare diseases including NBS screening results for long-term follow-up and NBS programme evaluation building on existing initiatives in the field of rare diseases.
- Prioritise EU collaborative research projects for the development of methods for the early detection, confirmative diagnostics and treatment of disorders amenable for NBS.
- Prioritise EU collaborative research projects on long-term follow-up of rare NBS conditions.

## *Promotion of national capacities*

- Provide seed money and/or targeted co-funding, including through the existing schemes of structural development funds, in order to reduce the financial burden to the national health care system and to promote the establishment and networking of multidisciplinary centres of expertise for diagnosis confirmation and definition of treatment.
- Promote the development of programmes and courses on training of professionals for the need of all steps of NBS and in particular regarding the communication to parents of the diagnostic suspicion and of positive confirmed diagnoses.

Fund the activities by NGOs and patients'/parents' alliances with regard to patients'/parents' empowerment.