EU Tender

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

Newborn screening in Europe
Expert Opinion document

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Abbreviations

BBMRI	Biobanking and Biomolecular Resources Research Infrastructure
CAH	congenital adrenal hyperplasia
CF	cystic fibrosis
CH	congenital hypothyroidism
CPT II/CACT	carnitine palmitoyltransferase II/carnitine-acylcarnitine translocase
EU	European Union
EUNENBS	European Union Network of Experts on Newborn Screening
HTA	health technology assessment
MCADD	medium chain acyl-CoA dehydrogenase deficiency
MSUD	maple syrup urine disease
NBS	neonatal screening
PKU	phenylketonuria
QALY	quality-adjusted life year
SCD	sickle cell disease
WHO	World Health Organisation
CoE	Council of Europe

Preface

The EU Council Recommendation on Rare Diseases (9 June 2009)[1], identified rare diseases (i.e.: a life-threatening or chronically debilitating condition affecting not more than 5 in 10.000 persons in the Community) as a public health concern and highlighted the need for public health actions promoting the development of research on rare disorders and the improvement of the health care of rare disease patients. Following this Recommendation, the European Commission launched a tender on neonatal screening in July 2009[2], to (1) report on the practices of neonatal screening (NBS) for rare disorders implemented in all the Member States including number of centres, estimate the number of infants screened and the number of disorders included in the NBS as well as reasons for the selection of these disorders, (2) to identify types of medical management and follow-up implemented in the Member States, (3) to establish a network of experts analysing the information and formulating a final opinion containing recommendations on best practices and recommending a core panel of NBS conditions that could be included in all MS practices and (4) to develop a decision-making matrix that could be used by Member States' programs to systematically expand (or contract) screening mandates.

A report on the practices on NBS, including medical management and follow-up, is provided in the Current Practices document. A network of experts (EUNENBS: European Network of Experts on Newborn Screening) has been established. Their assessment and evaluation of screening possibilities and recommendations how to further implement NBS in a responsible way are provided in this Expert Opinion document.

These documents have been developed within the EU Council Recommendation perspective that rare diseases are a public health priority and that health systems' measures devoted to the improvement of knowledge and care of rare disorders may result in a significant benefit for the health condition of the EU populations. However, the actual opportunity of developing a neonatal screening program is to be assessed taking into consideration the overall needs and priorities regarding health conditions and health system resources in a country as well as the feasibility of international cooperation. These documents intend to support efficaciously the discussion for the development of European policies in the field of NBS of rare disorders, including: the discussion of existing barriers; the proposals for solutions to be implemented, if feasible, at EU level; and the development of a decision-making matrix that could be used by Member States to support decision-making on NBS.

The goal of this Expert Opinion is to provide as far as possible a shared view of the factors that should be considered in the whole process of implementation of a neonatal screening, from the evaluation of its opportunity and definition of its benefit, to its actual implementation and the assessment of its efficacy and quality. Moreover, this document identifies the activities for which the mechanisms of Community cooperation can be exploited profitably. Therefore, this document intends to provide the expertise for an EU framework of national decision-making which balances the technological possibilities with ethical principles and local conditions. The principles outlined in this document apply to all parties offering tests, whether in or outside public health care. Cooperation between actors involved is needed.

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF

[2] http://ec.europa.eu/eahc/health/tenders_H09C2.html

This document does not intend to interfere in any aspect of the "domestic" organisation of the health system, which is established in a country; in principle the opinions presented in this document can be adapted to the health care organisation and to the distribution of responsibilities and competencies which are or will be developed at national and local level in each country. Consequently, the definition of lists of screened conditions as a common reference for the uniform operation of neonatal screening in the EU member states is outside the scope of this document. However, the EU member states should consider agreeing on a common and transparent framework for decision-making, which can contribute to reduce costs and time for the assessment of diseases that are candidates for neonatal screening; can reduce costs of screening and diagnostic confirmation; and can allow a better assessment and quality of the neonatal screening system.

1. Introduction

More than four decades ago many countries started up neonatal screening programs to identify infants with conditions for which early treatment would prevent serious irreparable health damage. Phenylketonuria (PKU) was in many countries the first disorder for which newborn screening (NBS) programs were started. In the decades thereafter the programs expanded gradually. Disorders included are individually rare conditions, that have a high impact for individuals affected. Since the turn of the century, high-throughput screening techniques as well as the increase of possibilities for treatment led to expansions of the screening programs in many countries. Intuitively it is felt that screening, leading to early diagnosis and treatment, will always be beneficial. However, the following quotation of Sir Muir Gray, former program director of the National Screening Committee in the United Kingdom, illustrates that this may be a rather naïve position:

> *"All screening programs do harm. Some do good as well and, of these, some do more good than harm at reasonable cost."*[3]

The benefit of screening programs is the improved health status in patients diagnosed early and treated optimally. Harms of screening programs include false positives (causing additional costs, parental stress and anxiety) and false negatives (potentially causing a delay in diagnosis in missed cases). Screening raises concerns about privacy and autonomy, highlighting the importance of the evaluation of ethical, legal and societal aspects. As most screened conditions are inherited disorders, consequences for family members often exist. Furthermore, health care expenses need to be balanced: if screening programs are funded, other activities may not be possible. Proposals for neonatal screening require careful scrutiny by decision makers because of the potential for harms and the need to demonstrate benefits commensurate with the opportunity cost of resources expended.[4]

Opportunities and threats for neonatal screening in the next decade

New forms of screening can help people to live longer and healthier lives, and avoid the symptoms and consequences of conditions. There are several developments both in the early detection of conditions and in treatments that make neonatal screening a topic of great importance. Enzyme replacement therapy and stem cell transplantation are examples of promising treatments. The recent sequencing of the human genome and major investments in genomics research have generated high expectations for translation of genetic and genomic knowledge from laboratory to population health gains. The fact that most conditions in NBS programs are genetic conditions raises specific issues. A major challenge when facing the possibilities to expand NBS programs is the balancing of pros and cons. All forms of screening raise certain social and ethical concerns.[5] For instance, tensions may exist between the aims of promoting effective health care and promoting individual choice. While on the one hand informed decision-making is increasingly promoted, in neonatal screening parents

[3] Raffle A, Gray M. Screening. Evidence and Practice. Oxford: Oxford University Press, 2007.

[4] Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ. Population Screening for Genetic Disorders in the 21st Century: Evidence, Economics, and Ethics. Public Health Genomics 2010;13:106–115.

[5] Andermann A, Blancquaert I, Dery V. A conceptual framework for genetic screening and policy-making. Journal of Health Services Research & Policy 2010;15: 90-97.

choose in the best interest of their child, and one might argue that it is the responsibility of the parents to have their child participate in NBS in its own interest.

The need for an overall framework for the assessment of neonatal screening

Rapid advances in genetics and genomics are outpacing the ability to adequately integrate new discoveries into health services and have led to a growing implementation gap between what is technologically possible, what exists in practice and what is acceptable and desirable or clearly justifiable. There is increasing pressure to introduce or expand genetic screening programs, although evidence of the clinical validity and utility of screening tests is often lagging behind.[6] Many existing programs, particularly opportunistic screening programs, have better designed and funded laboratory levels as compared to the clinical and program management strata. The reason for this is that proponents of new and expanded screening programs often focus on the availability of a valid and inexpensive test, without considering the additional costs and implications of the screening. As a result, programs which lack sufficient resources to develop important aspects such as education, counselling, treatment, follow-up and oversight may be unable to evaluate their intended objectives. As well, unless there is funding available from the outset to ensure appropriate evaluation, many programs may continue unaltered, missing important opportunities for continuous quality improvement.[7]

Several countries have expanded their NBS programs recently, as documented in the Current Practices (CP) of NBS document that is also a result of this EU project. Some programs screen for only one or two conditions, other for several up to a few dozens (Chapter 8 CP). The Health Technology Assessment (HTA) of screening possibilities has often been performed in national contexts, for instance in Denmark, Finland, the Netherlands, Spain and the UK.[8] HTA reports summarize evidence, ethics and economics and come to different conclusions, partly due to insufficient evidence and due to differences in the organisation of

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[6] Andermann A, Blancquaert I, Beauchamp S, Costea I. Guiding policy decisions for genetic screening: developing a systematic and transparent approach. Public Health Genomics. 2011;14(1):9-16

[7] Andermann A, Blancquaert I, Dery V. A conceptual framework for genetic screening and policy-making. Journal of Health Services Research & Policy 2010;15: 90-97.

[8] Danish National Board of Health. Biokemisk screening for medfødt sygdom hos nyfødte - Principper, erfaringer, anbefalinger. *Rapport fra en arbejdsgruppe nedsat af Sundhedsstyrelson* 2008. http://www.sst.dk/publ/publ2008/CFF/Screening/biokemisk_screening.pdf

Autti-Ramo I, Laajalahti L, Koskinen H, Sintonen H, Makela M. [Screening for rare metabolic disease in newborn infants] Vastasyntyneiden harvinaisten aineenvaihduntatautien seulonta FinOHTAn raportti 22. *STAKES / FinOHTA* 2004. http://finohta.stakes.fi/NR/rdonlyres/A328A3E7-8E06-459B-9837-57E30A9CD883/0/r022f.pdf

Health Council of the Netherlands. Neonatal Screening. *The Hague: Health Council of the Netherlands* 2005; publication no. 2005/11E. http://www.gezondheidsraad.nl/en/publications/neonatal-screening

Paz Valinas L, Atienza Merino G. Clinical effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry. Systematic Review. *Santiago de ComPostela: Galician Agency for Health Technology Assessment (AVALIA-T)* 2007. http://aunets.isciii.es/ficherosproductos/110/Informetandem.pdf

Burton H, Moorthie S. Expanded newborn screening. A review of the evidence. Cambridge, PHG Foundation, 2010. http://www.phgfoundation.org/reports/5504/

And: UK NSC policy database. Available from http://www.screening.nhs.uk/policydb.php

health care services. Systematic reviews as well as follow up studies to assess long-term effectiveness of strategies for diagnosis and treatment may not be feasible for most EU member states to undertake on their own. More evidence is required on the natural history of several conditions, the effectiveness of treatment and the costs of care, both when the infant is not diagnosed soon after birth as well as after NBS. Assessment of screening possibilities has to be repeated if techniques ant treatments improve. As some of the reports referenced above date from 2004 and 2005, these HTA reports do not include recent evidence. The UK NSC policy review proposes a three year cycle for revisions.[9]

The application of different criteria in the selection of conditions and in the decision for the implementation of new neonatal screening has progressively led to rather wide variation in the neonatal screening services offered in the EU member states, as documented in the Current Practices document, with potential implications for the equity of access to, and level of, health protection of EU citizens.

Expected technical developments as well as increasing possibilities for early treatment make further expansions in the near future likely. A structured decision-making process should be established, which can be used to prospectively and systematically assess the utility, acceptability and feasibility of new or expanded genetic screening programs in a way that promotes accountability and permits policy-makers to revise decisions as new technologies emerge and as the knowledge base evolves.[10] Initiatives to offer NBS can come from public health agencies, but also from private health care institutions or commercial companies. Attunement between all parties involved is needed.

Because of recent expansions and increasing possibilities for further application of technical developments to improve the health of children, it is timely that a close examination of the practices of neonatal screening in the EU is carried out and that the feasibility of a common framework of screening criteria is explored within the context of the primary values and principles of the European Union treaty.

International collaboration in the field of neonatal screening is ongoing in professional organisations such as the International Society for Neonatal Screening (ISNS),[11] the Society for the Study of Inborn Errors of Metabolism (SSIEM),[12] European Society for Paediatric Endocrinology (ESPE),[13] and in patients' and parents' organisations such as EURORDIS. The Patients Network for Medical Research and Health (EGAN[14]) is an alliance of both National Genetic Alliances and European disease specific patient organisations with a special interest in genetics, genomics and biotechnology.[15] EPPOSI (European Platform for Patients' Organisations, Science and Industry) is an independent, not-for-profit, partnership-based multi-stakeholder think tank.[16] Furthermore, several research projects on rare diseases have

[9] http://www.screening.nhs.uk/policydb.php

[10] Andermann A, Blancquaert I, Dery V. A conceptual framework for genetic screening and policy-making. Journal of Health Services Research & Policy 2010;15: 90-97.

[11] http://www.isns-neoscreening.org/htm/home.htm

[12] http://www.ssiem.org/home/welcome.asp

[13] http://www.eurospe.org/

[14] European Genetic Alliances Network)

[15] http://www.egan.eu/

[16] http://www.epposi.org/web/Home/Home.aspx

been funded by the EU (ORPHANET, EUROCAT).[17] These stakeholders could be involved in exploring the potential for expanding NBS programs in a responsible way.

Neonatal screening vs genetic screening

Depending on the definitions used, neonatal screening can be seen as a form of genetic screening, as many of the conditions screened for are autosomal recessive inherited disorders. Sometimes a test is only considered "genetic" when "*DNA-based testing*" is referred to, however, usually "*any unambiguous genetic information*" is included in the definition of "genetic" testing.[18] The latter view implies that most neonatal screening is genetic screening, except for screening for congenital hypothyroidism, which is usually not genetic, and screening for congenital deafness, which is often but not always genetic.

Some authors distinguish "genetic testing" from "genetic screening", where "testing" may relate to requests in individual health care, for instance diagnostic or prenatal. Different definitions exist. We use a broad definition of genetic testing, that includes population screening.

Genetic screening may raise multiple concerns about eugenics, abortion, storage and future use of samples, population-based DNA banks, breach of privacy, labelling, stigmatisation, discrimination, fatalism, and many more.[19] Many of these concerns are not necessarily inherent to neonatal screening, but as for other forms of screening, they depend on how decisions are made with respect to introducing screening, how screening services are organised and what safeguards are in place. Genetic screening does bring with it certain aspects that are not common to other forms of screening, including the issue that genetic information may also have implications for other family members. For preconceptional and prenatal genetic screening the 'intervention' may not be a specific treatment, but rather nondirective counselling to better understand reproductive choices in light of the test results. Neonatal screening may lead to the identification of carriers, for instance if HPLC is used for screening for sickle cell disease, or DNA analysis is performed in cystic fibrosis screening. If the newborn is a carrier, at least one of the parents is a carrier, and the risk that the parents are a carrier couple is increased. It is thus relevant for the parents to be informed of carrier status as an incidental finding. There is growing international consensus that any abnormal results associated with clinical significant conditions, including the definitive identification of carrier status, should also be reported.[20] However, not all countries agree with this position. In Germany for instance the law protects the right not to know, and prohibits informing parents

[17] http://www.orpha.net/consor/cgi-bin/index.php; http://www.eurocat-network.eu/

[18] Pinto-Basto et al. Scope of definitions of genetic testing: evidence from a EuroGentest survey. J Community Genet (2010) 1:29–35 http://www.eurogentest.org/uploads/1273480884000/JCommGenet2010(1)29-35.pdf

[19] Andermann A, Blancquaert I, Dery V. A conceptual framework for genetic screening and policy-making. Journal of Health Services Research & Policy 2010;15: 90-97.

[20] European Society of Human Genetics. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2009;17:720-1.

Burton H, Moorthie S. Expanded newborn screening. A review of the evidence. Cambridge, PHG foundation, 2010.

Bombard Y, Miller FA, Hayeems RZ, Avard D, Knoppers BM, Cornel MC, Borry P. The expansion of newborn screening: is reproductive benefit an appropriate pursuit? Nat Rev Genet. 2009;10:666-7.

Borry P, Nys H, Dierickx K. Carrier testing in minors: conflicting views. Nat Rev Genet. 2007 Nov;8(11):828.

of carrier status of their infant.[21] NBS may furthermore cause a parent to feel guilty about transmitting a genetic condition to his/her children.[22]

Neonatal screening may raise questions on the recurrence risk in future pregnancies. In clinical genetic follow up investigations it may turn out that the partner was not the biological father (non-paternity). NBS in itself will not provide this information on non-paternity.

Rare diseases vs common late-onset diseases

Although genetics is an important determinant of what makes people healthy or unhealthy, it is only one factor among a long list of determinants of health. As science advances it becomes increasingly possible to screen for susceptibility to common disorders. Thus public health experts, policy-makers, and society more generally, will need to make difficult judgements regarding the added value of 'personalised medicine'. Based on genetic profiling of multiple low-penetrance genes, personalised health care would become possible, as compared to a more global approach to disease prevention centred on primary prevention and health promotion strategies which attempt to address the social, behavioural and environmental determinants of health. Thus, the decision to develop new genetic screening programs involves consideration of multiple ethical, social and legal implications, including whether alternative strategies to improve health may not be funded as a result.

Thus, although there are high expectations regarding the potential medical applications of genetic research on common late-onset diseases, rare disorders are increasingly viewed as a legitimate public health concern.[23] Screening for rare conditions, 80% of which are genetic in origin, may therefore be considered as part of a continuum of health improvement strategies ranging from prevention to early detection, treatment and rehabilitation, which can be offered to support individuals and families faced with rare and debilitating diseases.[24] There are some 7000 rare disorders. Between 6% and 8% of the population in Europe is affected by one of them. NBS is aiming at a small number of these, for which screening for early diagnosis, followed by suitable care, can decrease morbidity and mortality and improve quality of life and life expectancy.

Neonatal screening vs general healthcare strategies

Screening is known in public health terms as a secondary prevention strategy, which identifies conditions before symptoms develop, since early intervention may lead to improved health outcomes. Screening is thereby offered to members of a specified population, who do not necessarily perceive that they are at risk of a disease or its complications, to identify those individuals who are more likely to be helped than harmed by further tests or treatments. However, screening is not the only type of strategy that can be used in reducing the burden of genetic conditions. Indeed, screening forms part of a continuum of approaches for improving

[21] In Germany on February 1st, 2010 the "GendiagnostikGesetz" (Genetic testing law) came into force, protecting the right-not-to-know incidental findings. http://www.gesetze-im-internet.de/bundesrecht/gendg/gesamt.pdf

[22] Simopoulos AP. Genetic screening: programs, principles, and research--thirty years later. Reviewing the recommendations of the Committee for the Study of Inborn Errors of Metabolism (SIEM). Public Health Genomics 2009;12:105-111.

[23] http://ec.europa.eu/health-eu/health_problems/rare_diseases/index_en.htm

[24] Andermann A, Blancquaert I, Dery V. A conceptual framework for genetic screening and policy-making. Journal of Health Services Research & Policy 2010;15: 90-97.

population health, ranging from health promotion and disease prevention to treatment and rehabilitation.[22] Moreover, benefits tend to be defined more broadly now to include more intermediate outcomes, such as preparing parents prior to the onset of illness and reduction in the length of the diagnostic odyssey, even if life expectancy or quality of life of the patient may not be altered. As the definition of benefit evolves, this raises questions of what is socially acceptable. The potentially broadening goals of NBS (from identifying conditions where irreparable health damage can be avoided by early diagnosis to include reduction of diagnostic odyssey) should be subject to public debate.

Neonatal screening programs and related interventions should be defined in a way that they are consistent with the overall health care strategies, capacities and the culture of a country. Screening goals and benefits should be assessed versus goals and benefits established/accepted for other clinical and public health interventions and strategies adopted in the country. The opportunity offered by neonatal screening should also be assessed taking into consideration the possibility of screening at a later life stage, for those goals (reproductive choices?) and disorders where preventive intervention is still timely, so that participation in screening can be decided directly by the subject. Presymptomatic testing in minors shall generally be limited to conditions where there is direct benefit, because early treatment can prevent irreparable damage.

Relevant charters, declarations and principles recognised by EU member states

Besides the Wilson and Jungner criteria[25] for neonatal screening (Chapter 4), which have been followed with varying flexibility in many EU countries, other principles have been developed for different purposes, which, however, have bearing on the context of neonatal screening and on this document.

Article 168 of the Treaty on European Union[26] indicates that a high level of health protection is to be sought in the Union policies, with the European Union action being subsidiary to national policies.

In 2006 the EU EPSCO Council also signed a declaration[27] recognizing that universality, access to good quality care, equity and solidarity are common values of the EU health systems, although differences in approaches and the need for financial sustainability limit the uniform operation of the health care in EU. It is also recognised that EU citizens should find health systems anywhere in the EU that operate on principles such as quality; safety; care that is based on evidence and ethics; patient involvement; redress; privacy and confidentiality.

The charter of fundamental rights of the European Union[28], solemnly proclaimed by the EU Parliament, the Council and the Commission in 2007, recognises, among other fundamental rights:

- the free and informed consent of the person concerned
- the prohibition of eugenic practices

[25] http://whqlibdoc.who.int/php/WHO_PHP_34.pdf

[26] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:083:0047:0200:EN:PDF

[27] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2006:146:0001:0003:EN:PDF

[28] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2007:303:0001:0016:EN:PDF

- Non-discrimination (with reference to any discrimination based on any ground such as sex, race, colour, ethnic or social origin, genetic features, language, religion or belief, political or any other opinion, membership of a national minority, property, birth, disability, age or sexual orientation).
- Children shall have the right to such protection and care as is necessary for their well-being. They may express their views freely. Such views shall be taken into consideration on matters which concern them in accordance with their age and maturity.
- Health care: Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices.

A large number of EU countries have also signed the Council of Europe Convention on Human Rights and Biomedicine,[29] whose aim, as defined in Article 1, is to protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. This document underlines fundamental aspects with regard to consent, the protection of persons not able to consent, private life and right to information, non-discrimination, non-selection of sex, protection of persons undergoing research, research on embryos in vitro, and organ and tissue removal. With regard to consent, interventions in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. Where, according to law, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law, and may only be carried out for direct benefit of that person.

On 7 May 2008 the Committee of Ministers of the Council of Europe adopted the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes.[30] Although this document is not a binding document at this moment, it has underlined various crucial elements in the provision of genetic services. In particular, it underlines the non-discrimination and non-stigmatisation, the quality of genetic services, the importance of clinical utility, individualised medical supervision, information, genetic counselling and consent, protection of persons not able to consent, respect for private life and right to information, genetic screening programs.

Article 19 states that "A health screening program involving the use of genetic tests may only be implemented if it has been approved by the competent body. This approval may only be given after independent evaluation of its ethical acceptability and fulfillment of the following specific conditions:

a) the program is recognised for its health relevance for the whole population or section of population concerned;

b) the scientific validity and effectiveness of the program have been established;

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[29] http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=&DF=&CL=ENG

In total 28 countries have signed and ratified this text. But important countries such as U.K., the Netherlands, France, Belgium, Poland, Germany did not ratify it yet.

[30] http://conventions.coe.int/Treaty/en/Treaties/html/203.htm

c) appropriate preventive or treatment measures in respect of the disease or disorder which is the subject of the screening, are available to the persons concerned;

d) appropriate measures are provided to ensure equitable access to the program;

e) the program provides measures to adequately inform the population or section of population concerned of the existence, purposes and means of accessing the screening program as well as the voluntary nature of participation in it."

Other reference frameworks that are to be taken into consideration are the UN Convention on the Rights of the Child[31] and the Unesco declaration on Bioethics and Human Rights[32].

2. Work methodology

As part of the activity and work methodology requested by the tender specifications, a European Union Network of Experts on Newborn Screening (EUNENBS) was constituted with experts from national competent institutions of all the EU member states and experts from European professional and scientific organizations involved in neonatal screening. The task of EUNENBS was to supervise the work of the tender and participate in the revision of the tender deliverables, including this Expert Opinion document The EUNENBS members have provided informally their input and advice without implying any obligation or commitment of their national authorities or Organizations. In its meeting on 06-07 December 2010 the EUNENBS discussed the future of neonatal screening in a workshop. The conclusions have been integrated in this document. A draft of this expert opinion document was prepared and circulated by email on 9 March 2011 to the membership of EUNENBS and to EUCERD members from the Candidate and EEA/EFTA countries (Appendix 1). to invite comments. This consultation ended on 6 April 2011. The preparation of the second draft, integrating the suggestions received, took place until 6 May 2011. Before the consensus meeting the document was circulated for a second consultation, which took place from 11 to 27 May 2011, and amended considering the comments received.

Working documents were prepared reviewing most relevant scientific literature on the development of NBS policy and submitted to EUNENBS to stimulate the discussion during its meeting held on 06-07 December 2010. The meeting conclusions have been integrated in this document. Experiences from other countries have served as useful sources, although their applicability may need to be checked against information from EU countries and agreement needs to be sought with EUNENBS. Some of the survey results have also been incorporated.

This expert opinion document reports the results of the debate among the EUNENBS members with respect to the elements that are part of a system to evaluate the quality and ethical aspects of neonatal screening in the light of available literature.

After this general introduction on background and methodology, chapters 3, 4 and 5 will discuss the further development of NBS:

[31] http://www2.ohchr.org/english/law/crc.htm

[32] http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html

Chapter 3: Who: Governance of neonatal screening

Chapter 4: What: Criteria to evaluate whether a screening program should be performed (desirability)

Chapter 5: How: Criteria on how a screening program should be performed (feasibility, quality)

Chapter 6 will discuss how implementation could be performed.

Finally chapter 7 consists of a proposal for a decision-making matrix.

3. Governance of neonatal screening

If a new technical possibility for a screening test would become available, the discussion on adding this to the NBS program would in most countries be initiated by health care professionals. Parent- or patient groups as well as industry might play a role as well. The EUNENBS recognizes the potential for overoptimistic expectations as well as premature decisions based on partial evidence.

In the CP document 21 out of 34 responding countries reported to have changed their newborn screening policy in the last five years. Usually national or federal health authorities decided, occasionally regional health authorities or medical professionals. Parent- and patient groups were not always existing. However, when existing, they were involved in the changes only in about half of countries (Table 20.2 CP).

As many different aspects underlie the decision whether or not to implement a new screening possibility, a standing screening committee with multidisciplinary expertise would be needed to review the scientific evidence including all pros and cons. As many similar decisions on new screening possibilities are foreseen in the near future, an EU-centralised standing screening committee for scientific evaluation, horizon scanning, prioritisation, health technology assessment, evaluation of cost-effectiveness and ethics is needed. The expertise needed in assessments includes laboratory expertise, paediatricians, ethicists, health economists and health technology assessment experts (Table 1). The Health Technology Assessment may be more efficient if general aspects are summarized at international EU level, instead of in different countries (p. 10).

Screening committees within the EU countries may be necessary to assess the feasibility of a screening program depending on country-specific factors. In the CP document the majority of EU countries (18 of 27) report to already have a body which oversees newborn screening. Some are devoted to newborn screening only, some have a broader task in health policy, public health, prevention, insurance and rare diseases.

About half of the jurisdictions reported to have laws or regulations, that regulate a diversity of aspects related to newborn screening, from mandating the implementation of a screening program, without obliging parents to use it; informed consent or dissent; to the obligation for parents to have their baby screened (§1.1 and Section D of CP).

Health care policy makers (ministers or departments of health; national or regional health authorities) would have to make a decision (not) to implement a new screening, on the basis of the assessment as prepared by the screening committee in the country. In the end this is a political decision, based on the possibilities of (national or regional) health care systems. There is room for synergy between EU countries as screening committees in different countries will have to evaluate similar issues. It would be desirable to have a mechanism to share evaluations.

Table 1: Issues to be addressed and network of actors involved in the attunement of new NBS possibilities (modified from Achterberg 2007, Andermann 2010)[33].

Issues to be addressed	Actors involved
Technology	Scientists in laboratories and clinics Industry (biotechnology, pharmaceutical, biomedical) HTA experts/committees
Organisation	Physicians and other professionals in (public) health care Units for confirmation of the screening result and for treatment Scientific and professional societies Governmental agencies in health sector
Demand	General public Patients and families Patient (support) advocacy groups Community groups
Acceptability, including economics and ethics	Regulatory, advisory and governmental agencies in health sector and other sectors Scientific and professional societies (including ethicists) General public Patients and families Patient (support) advocacy groups Community groups Politicians
Decision	Politicians Governmental agencies (national and regional)
Implementation	Physicians and other professionals in (public) health care Scientists

The European Network for Health Technology Assessment (EUnetHTA) has developed and continues to develop tools and methods that will facilitate a transparent and efficient high quality health technology assessment (HTA).34 Collaboration with this network is needed. NBS is related to rare conditions, which demands special methodology. If evidence from randomised controlled studies would be waited for, optimal health gain will not be achieved. Furthermore, knowledge of the fast developing high throughput technologies in genomics, proteomics and metabolomics is needed. EUnetHTA provides a mechanism to share evaluations.

[33] Achterbergh R, Lakeman P, Stemerding D, Moors EHM, Cornel MC. Implementation of preconceptional carrier screening for cystic fibrosis and haemoglobinopathies: A sociotechnical analysis. Health Policy 2007; 83: 277-286.

Andermann A, Blancquaert I, Dery V. A conceptual framework for genetic screening and policy-making. Journal of Health Services Research & Policy 2010;15: 90-97.

[34] Kristensen FB, Mäkelä M, Neikter SA, Rehnqvist N, Håheim LL, Mørland B, Milne R, Nielsen CP, Busse R, Lee-Robin SH, Wild C, Espallargues M, Chamova J; European network for Health Technology Assessment (EUnetHTA). European network for health technology assessment, EUnetHTA: planning, development, and implementation of a sustainable European network for health technology assessment. *Int J Technol Assess Health Care*. 2009;25(Suppl 2):107-16.

Besides the actors mentioned earlier to be represented in such a central standing NBS committee, (organisations of) parents and patients should have the possibility to share their points of view with the standing NBS committee. Industry, commercial parties or industrial researchers should have a possibility to inform the central committee, however, their role should be limited to consultation.

A formalised decision process is needed to start the screening. The fast developments require also re-evaluation of the pros and cons of screening on a regular basis, for instance every two years, or if another actor raises the issue (e.g. a charity).

Should NBS be mandated for public health authorities or parents?

Public health authorities have a responsibility to offer NBS to their citizens[35]. A legal obligation to offer NBS can help to ensure quality and improve accessibility. On the other hand, participation in the program should be voluntary[36]. One of the questions in the survey on current practices of NBS was "Is participation to NBS mandated by law?". This turned out to be an ambiguous question: some replied about legislation that would oblige health authorities to implement neonatal screening, others replied about parents (not) being free to participate to the program. The latter is the interpretation often found in American publications on the topic. Referring to this interpretation, eight countries described in the current practices of NBS document have mandatory screening, including 3 EU countries (Greece, Hungary, Malta). The CoE Additional Protocol clearly specifies that participation should always be voluntary, although it must be recognised that parents have the obligation to act to the benefit of their child.

[35] Charter of fundamental rights of the European Union, Art 24.

CoE additional protocol, art 11, item 2, par 2

Comment: A law mandating NBS ensures also the long-term sustainability and quality of a program: Wilson and Jungner, criterion 10; plus Common values and principles in European Union Health Systems.

EU policies take responsibility for health protection of individuals and in particular of children, rather than leaving the responsibility to individual parents. EU policies must take also responsibility for providing quality information in view of the request for informed consent by parents.

[36] CoE additional Protocol, art 10

Expert opinion on governance:

1. Screening is different from diagnostics. Screening is offered to people who either do not have or have not recognized the symptoms of the disease(s) that the screening relates to. A screening test is not intended to be diagnostic. Screening aims to identify people at sufficient risk to benefit from referral for diagnostics.
2. Haven taken notice of the fact that a European body for the health technology assessment (HTA) will be developed (*EUnetHTA*[37]), the EUNENBS recommends a committee for neonatal screening.
3. This EU NBS committee should summarize the scientific developments (evidence, economics, ethics)[38] and advice transparently. It should update relevant information at national and European level. In addition, because it will gather the widest expertise on NBS at the EU level, it should act as a central point for any stakeholder (e.g. learned societies, industry and patient groups) to propose and discuss new NBS procedures.
4. The EU NBS body should promote synergies and best practice guidelines on policies concerning consent, storage of samples, pre-test information for parents, etc. (benchmarking, reviewing, updating etc.)
5. The body should have a clear governance structure and accountability. It should have a role in offering advice to (national) policy makers.
6. In each country national bodies should assess the country-specific factors, including epidemiological, economical, ethical and legal issues, and perform the monitoring and evaluation of the program.
7. A formalised decision process is needed to start the HTA of a screening and to re-evaluate the evidence for screening either periodically or on demand.
8. Actors to be involved in NBS decision-making include patients- and parents organisations, laboratory scientists, health care workers and professional organisations, ethical, legal and economic experts, governmental and non-governmental agencies and health care providers.
9. The role of industry, commercial parties or industrial researchers should be limited to consultation.
10. Existing examples of written policies should be translated and published, so that they could serve as examples for countries which do not have such policies yet but which are considering their development. The criteria used by national committees when considering new screening programs should be published. The examples of policies should cover both national and European practices in a way which could allow the assessment of trans-borders issues (e.g. equipment related issues, access to relevant new technologies, appropriate screening for people moving from one country to another).
11. Systems should be in place within the EU to learn from potential generic adverse incidents that may cross national boundaries e.g. equipment related issues.
12. Once the EU NBS body is in place and examples of good practices are available, it should be discussed to what extent harmonization of newborn screening in Europe is possible.

[37] http://www.eunethta.eu/Public/Home/

[38] Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ. Population Screening for Genetic Disorders in the 21st Century: Evidence, Economics, and Ethics. Public Health Genomics 2010;13:106–115.

1

4. Criteria to evaluate whether a screening program should be performed (desirability)

Early detection of disease can result in considerable health benefits. However, inevitably it also always implies negative effects. In the terms of Wilson and Jungner (1968):

"The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement (on the one hand, bringing to treatment those with previously undetected disease, and, on the other, avoiding harm to those persons not in need of treatment) is far from simple though sometimes it may appear deceptively easy." (p.26)

In 1968 Wilson and Jungner developed a set of screening criteria to balance pros and cons for the WHO, that have become a classic in the domain of screening:[39]

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

These criteria have been built on by many authors. The EUNENBS considers them still valid, though not sufficient. The Wilson and Jungner criteria were considering one disease at a time, while high throughput technologies (genomics, metabolomics) have made screening for several diseases at a low price possible (pages 9 and 10). Some of these technologies will provide more certainty that older screening tests did, thus blurring distinctions between screening and diagnostics. Furthermore, technology might drive decisions on what to screen for, while Wilson and Jungner put the benefit for the infant at the centre of deliberations. Several schemes of assessment have increased the number of criteria,[40] where others have tried to reduce them.[41]

Several frameworks of criteria have built on Wilson and Jungner and further specified elements. The UK National Screening Committee screening criteria[39] for instance also mention that "all the cost-effective primary prevention interventions should have been

[39] Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO; 1968. Available from: http://whqlibdoc.who.int/php/WHO_PHP_34.pdf

[40] UK National Screening Committee. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. Available from: http://www.screening.nhs.uk/criteria

Health Council of the Netherlands: Committee Genetic Screening. Genetic Screening. The Hague: Health Council, 1994; publication no. 1994/22E. ISBN 90-5549-073-3

Available from: http://www.gezondheidsraad.nl/sites/default/files/94@22E.pdf

[41] Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ. Population Screening for Genetic Disorders in the 21st Century: Evidence, Economics, and Ethics. Public Health Genomics 2010;13:106–115.

implemented as far as practicable" and "there should be evidence from high quality Randomised Controlled Trials that the screening program is effective in reducing mortality or morbidity". Further discussion in Europe is needed to attune these sets of criteria. As for primary prevention in the context of NBS, few examples exist. Clearly iodide deficiency must be dealt with to prevent hypothyroidism,[42] but otherwise this is less relevant for NBS. As for RCTs, the fact that NBS is aiming at rare disorders makes it almost impossible to satisfy the criterion of high quality level of evidence.[43] Disorders with a relatively high birth prevalence, such as cystic fibrosis, may be studied in RCTs, but observational evidence will often be the only evidence available at the moment of the (decision whether or not to) start NBS. Monitoring and follow-up must provide the evidence in the first years thereafter.

We will use the Wilson and Jungner criteria to structure the discussion on the *desirability*: criteria whether or not to screen. The ten Wilson and Jungner criteria have been grouped under the headings: Disease (#1,4,7), treatment (#2,3), test (#5,6,8), cost (#9). In this chapter we will discuss the desirability of screening. The last Wilson and Jungner principle (#10) is discussed in chapter 5, as it relates to *how* a screening program should be performed.

Expert opinion can seldom be based on one or two criteria only, but will usually be based on a combination of a serious health problem, for which treatment exists and a good test is available at reasonable cost. Therefore in this chapter the Expert opinion is formulated at the end of the chapter.

Pros and cons also relate to the performance of all steps in the chain of events relating to the screening program. Elaborated sets of criteria tend to specify much more than Wilson and Jungner the conditions *under which* a screening program could be executed.[44] These *quality* criteria will be discussed in chapter 4.

Disease

1) The condition sought should be an *important health problem*. 4) There should be a recognizable latent or early symptomatic stage and 7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.

The primary aim of NBS programs is to improve the health status of infants with treatable conditions. A case definition of the specific "treatable condition" or "important health problem" is needed for the assessment of the evidence on a specific test and treatment.

Phenylketonuria (PKU) was mentioned in the original publication to illustrate "important health problem" as a combination of frequency and severity. While it is "extremely uncommon", it "warrants screening on account of the very serious consequences if not

[42] Maberly GF, et al. Iodine deficiency: consequences and progress toward elimination. Food Nutr Bull. 2003 Dec;24(4 Suppl):S91-8

UNICEF. Sustainable elimination of iodide deficiency. Available from: http://www.unicef.org/media/files/IDD.pdf

[43] Wilcken B. Newborn screening: how are we travelling, and where should we be going? J Inherit Metab Dis 2011; DOI 10.1007/s10545-011-9326-4

[44] Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ. Population Screening for Genetic Disorders in the 21st Century: Evidence, Economics, and Ethics. Public Health Genomics 2010;13:106–115.

discovered and treated very early in life".[45] "If the defect is detected very early in life mental retardation can be prevented". Also galactosaemia is mentioned here, "but, unlike PKU, if untreated it leads to early death."

The health burden should be evaluated based on birth prevalence and severity.[46] This first Wilson and Jungner criterium is basically an efficiency question. It is most likely that screening is worthwhile, when there is a good intervention for a severe and relatively frequent disease. Once a neonatal screening program is in place, one could well imagine that screening for a rare and/or not so severe condition could still be cost-effective.

EU countries have included a diversity of disorders in their NBS programs. Congenital hypothyroidism (CH), PKU, congenital adrenal hyperplasia (CAH), medium chain acyl-CoA dehydrogenase deficiency (MCADD) and maple syrup urine disease (MSUD) have in many countries been included in the program as it is clear that these are important health problems where an early diagnosis prevents irreparable damage. The same is true for sickle cell disease (SCD)/β thalassemia in Mediterrean countries or countries with migrant populations.

The frequency of the disorder played a role in recent screening debates in Finland, where PKU does not occur in the indigenous population. Migration is changing the prevalence. Therefore targeted PKU screening is now offered by most of the maternity hospitals in Finland to people of non-Finnish ancestry. Also the frequency of sickle cell diseases (SCD) has changed in some populations due to migration (from Africa and Asia), raising the question of targeted screening of an ethnic group and the perception of inequality for those excluded or discrimination of those targeted. Finding the group at risk is not always straightforward. A population-wide approach minimizes these problems. There appears to be a growing consensus that ethnically targeted neonatal screening is not an acceptable public health strategy.[47]

In the current age of high throughput technology, a relevant question is whether each of the conditions in a NBS program needs to fulfil the criterion "important health problem". Alternatively, a technological development could define a group of disorders to be identified by one technology (such as tandem mass spectrometry: ms/ms). The EUNENBS considered that the pros of technology-driven combinations of disorders could be summarised, but cons count per disorder. There may be reasons to group conditions, especially cost-effectiveness, but this does not detract from any requirement for each individual condition to adhere to the prerequisites that there must be effective interventions as well as good test performance, few adverse effects on the unaffected population and adequate services to look after the children.[48] A responsible evaluation per disease is thus needed. Screening should only occur when it is clinically relevant. It was acknowledged by EUNENBS however that it is difficult to define the threshold for whether screening of a disorder is clinically relevant.

Performing a screening program will help to better understand all aspects of a disorder. The evaluation of the Wilson & Jungner criterium #7 may thus change after the start of a screening program as new information becomes available.

[45] http://whqlibdoc.who.int/php/WHO_PHP_34.pdf (page 27).

[46] Charter of fundamental rights of the European Union, art 35. Amsterdam Treaty of the EU, Art 168

[47] Grosse SC, Olney RS, Baily MA. The cost effectiveness of universal versus selective newborn screening for sickle cell disease in the US and the UK. Appl Health Econ Health Policy 2005;4:239-247.

[48] Burton H, Moorthie S. Expanded newborn screening. A review of the evidence. Cambridge, PHG Foundation, 2010.

For countries that have to start NBS programs, congenital hypothyroidism might be the first condition to screen for. Otherwise, NBS might be considered for disorders with a relatively high prevalence, for which the test is not too difficult and health gain is proven, such as PKU,[49] CH,[50] CAH,[51] CF[52] and MCADD[53] in most EU countries, and SCD/βthal[54] in Mediterranean countries and countries with migrant populations. As nearly all EU countries now have migrants, this is increasingly relevant.

Treatment

2) There should be an *accepted treatment for patients with recognized disease* and 3) *Facilities* for diagnosis and treatment should be available.

Already in the Wilson and Jungner (1968) publication several aspects of the management of the child and the underlying condition are mentioned. By treatment we mean medication (such as thyroxine in CH), diet (in PKU), lifestyle advice (frequent feeding in MCADD), avoiding complications (vaccination in SCD) and any measures to improve the health status and quality of life of the child. Treatment is thus used in a broad sense to include management and care.

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[49] Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet. 2010 Oct 23;376(9750):1417-27

Van Spronsen FJ. Phenylketonuria: a 21st century perspective. Nat Rev Endocrinol. 2010 Sep;6(9):509-14.

[50] Grosse SD, Van Vliet G. Prevention of intellectual disability through screening for congenital hypothyroidism: how much and at what level? Arch Dis Child. 2011 Apr;96(4):374-9.

LaFranchi SH. Newborn screening strategies for congenital hypothyroidism: an update. J Inherit Metab Dis. 2010 Oct;33(Suppl 2):S225-33.

The UK NSC policy on Congenital hypothyroidism screening in newborns

Available from: www.screening.nhs.uk/congenitalhypothyroidism

[51] Pass KA, Neto EC. Update: newborn screening for endocrinopathies. Endocrinol Metab Clin North Am. 2009 Dec;38(4):827-37.

Speiser PW. Prenatal and neonatal diagnosis and treatment of congenital adrenal hyperplasia. Pediatr Endocrinol Rev. 2007 Oct;5 Suppl 1:578-83.

[52] Health Council of the Netherlands. Neonatal screening for cystic fibrosis. The Hague: Health Council of the Netherlands, 2010; publication no. 2010/01E. Available from: www.gezondheidsraad.nl/sites/default/files/201001E.pdf

Castellani C, Massie J. Emerging issues in cystic fibrosis newborn screening. Curr Opin Pulm Med. 2010 Nov;16(6):584-90.

Sermet-Gaudelus I, Mayell SJ, Southern KW; European Cystic Fibrosis Society (ECFS), Neonatal Screening Working Group. Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening. J Cyst Fibros. 2010 Sep;9(5):323-9.

[53] Leonard JV, Dezateux C. Newborn screening for medium chain acyl CoA dehydrogenase deficiency.Arch Dis Child. 2009 Mar;94(3):235-8.

The UK NSC policy on Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD) screening in newborns Available from: www.screening.nhs.uk/mcadd

[54] Serjeant GR. One hundred years of sickle cell disease. Br J Haematol. 2010 Dec;151(5):425-9.

Benson JM, Therrell BL Jr. History and current status of newborn screening for hemoglobinopathies. Semin Perinatol. 2010 Apr;34(2):134-44.

The discussion by the EUNENBS on these criteria focussed on the availability of treatment, that may differ between EU countries due to economic differences. What is accepted and available in one country, may not be affordable everywhere.

Furthermore, the criterion "treatment available" 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 the next pregnancy(ies) including genetic counseling. The primary aim of NBS programs is to improve the health status of infants with treatable conditions. The broader benefit and the management of the family need to be taken into account when assessing the Wilson and Jungner criteria on "treatment".

Test

5) There should be a *suitable test* or examination 6) The test should be acceptable to the population and 8) There should be an agreed policy on *whom to treat as patients*.

Screening tests may be based on the concentration and/or activity of metabolites and/or enzymes. If the result is outside the normal range, it is considered "test-positive". The cut off chosen is a compromise between sensitivity and specificity. A cut off with very high specificity may lead to false negatives. A cut off with a very high sensitivity may lead to many false positives. Missing cases should be avoided because they reflect evidence of failure of a program, fail to prevent a serious harm to the patient, elicit doubts on the quality of the screening and may cause legal consequences; false positive results generate temporary distress in the involved individual/family and an unnecessary (unsustainable?) burden for the health system.

Also information on mild phenotypes, late-onset disorders or carrier status may be derived from neonatal screening tests. Examples of mild phenotypes are cases of cystic fibrosis or Pompe disease that might not develop symptoms for decades. The EUNENBS considers that NBS programs should avoid as much as possible these unintended findings. This may require adaptation of test and automatic data processing, for instance by using filters that limit the reporting of results to certain specific metabolites, values outside certain thresholds, or specific gene mutations. As a general rule, good information provision is a prerequisite. If unintended results are found (such as carrier status), people need to be informed adequately, both before screening about the possibility of unintended results, as well as after communication of the results. Legal issues are to be resolved if identifiable information/samples are stored in the NBS database that is not known to parents/patients.

As to information of carrier status, the ethics of recording and communicating this information should be assessed also in comparison with other common practices regarding reproduction (which may differ among countries), such as sexually transmitted diseases; prenatal investigations; interruption of pregnancy; assisted reproduction technologies; but also other health fields, such as infectious diseases; occupational and environmental exposures statistically associated with chronic diseases; other preventive screening programs in the normal population or in population groups at higher risk.

Cost

9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be *economically balanced* in relation to possible expenditure on medical care as a whole (Wilson and Jungner 1968).

All conditions screened for in NBS are rare disorders. Although individually rare, collectively their burden is large, both in terms of prevalence and in terms of morbidity and mortality. Rare diseases are a serious public health concern and a priority in the EU health and research programs.[55] Balancing the right to care of all patients needs to be done on the basis of the severity and of the burden of disease, taking both common and rare diseases into account.

For NBS programs, in some cases averted costs of care may exceed the screening cost. In other cases NBS may be "good value for money" in terms of cost per deaths prevented, life years gained or costs per QALY.[56] Neonatal screening for PKU, congenital hypothyroidism, CF and several other disorders may be cost saving or are cost-effective.[57] Cost-effectiveness analyses may give different results for different populations, since prevalence and cost of treatment may differ. Furthermore it may differ in time, as some screening techniques are getting cheaper and/or new treatments become available.[58] Among new possibilities for neonatal screening some require expensive treatment (enzyme replacement therapy) while for others the cost of treating a patient that was not identified during the first weeks of life may be extremely high (severe combined immuno- deficiency).[59] Policy makers and clinicians are often reluctant to consider cost-effectiveness in health care prioritisation.[60] Although in transparent policy making economic aspects have to be taken into account, considerations regarding the patient's social and disease burden and solidarity should have a recognized role in the decisions. Thus EUNENBS considered that cost-effectiveness is not the primary issue when deciding whether to screen or not. However, for some lower or middle income countries cost is an important variable. The number of studies on cost-effectiveness of NBS is limited, and may differ between countries. For small countries it may not be feasible to do a cost-effectiveness analysis on their own, so it would be desirable to have a mechanism to share evaluations. Even if a program will be cost effective in the long run, the initial phase implies higher costs for the health system. In some countries this might be a problem, especially since the party that should raise the funds is not always the party that receives the direct benefits.

10) Case-finding should be a continuing process and not a "once and for all" project.

This last Wilson and Jungner screening criterion relates to the organisation and quality of the program, and thus automatically leads to the discussion in the chapter 5.

[55] http://ec.europa.eu/health-eu/health_problems/rare_diseases/index_en.htm

[56] Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ. Population Screening for Genetic Disorders in the 21st Century: Evidence, Economics, and Ethics. Public Health Genomics 2010;13:106–115.

[57] Levy HL. Newborn screening conditions: What we know, what we do not know, and how we will know it. Genet Med. 2010 Dec;12(12 Suppl):S213-4.

Pollitt RJ et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. Health Technology Assessment 1997; Vol. 1: No. 7 http://www.hta.ac.uk/fullmono/mon107.pdf

Health Council of the Netherlands. Neonatal screening for cystic fibrosis. The Hague: Health Council of the Netherlands, 2010; publication no. 2010/01E. ISBN 978-90-5549-817-8

[58] Wilcken B. Newborn screening: how are we travelling, and where should we be going? J Inherit Metab Dis. 2011 Apr 16. [Epub ahead of print]

[59] Lipstein EA, Vorono S, Browning MF, Green NS, Kemper AR, Knapp AA, Prosser LA, Perrin JM. Systematic evidence review of neonatal screening and treatment of severe combined immunodeficiency. Pediatrics 2010;125:e1226-35.

[60] Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ. Population Screening for Genetic Disorders in the 21st Century: Evidence, Economics, and Ethics. Public Health Genomics 2010;13:106–115.

Expert opinion to evaluate whether a screening program should be performed (Chapter 4)

13. There is a clear need to develop and publish agreed case definitions for all disorders screened. There should be an attempt made to achieve agreement on these case definitions within the EU to facilitate assessment and international outcome studies.
14. The decision whether a screening program should be performed can be based on a framework of screening criteria updated from the traditional Wilson and Jungner criteria, relating to disease, treatment, test and cost.
15. The interest of the child should be central in the assessment of pros and cons.
16. The European NBS body (or the national NBS bodies) should further elaborate the specifications and the operative application of the screening criteria through discussion and agreement with the EU national authorities.
17. Health Technology Assessment to evaluate the evidence on the effectiveness of early detection through neonatal screening and treatment should be achievable in practice. For rare conditions, best level evidence should be used. Methods need to be developed to both optimize health benefit and careful evaluation.
18. Universal screening is generally preferable to ethnical targeted screening. If there are sound reasons (e.g. health gain) for targeted screening it is important to avoid stigmatisation.
19. The health system should ensure treatment to all confirmed cases diagnosed by screening. In case of suboptimal availability of treatment, it should plan to make treatment available for all confirmed cases.[61]
20. Systems should be developed in order to support universal screening in countries where it would be beneficial but not affordable for economic and/or social reasons.
21. Systems should be put in place by the EU for helping the countries where treatment is not available yet for all confirmed cases. The target of treatment for all confirmed cases should be achieved without reducing the quality of treatment.
22. The European NBS body (or the national NBS bodies) should consider other potential advantages, especially (a) avoiding a diagnostic odyssey and (b) informed reproductive choice for the next pregnancy(ies) of the parents, and later for the child, and the provision of genetic counselling to the family.
23. Screening methodology should aim to avoid unintended findings, such as cases with mild forms of the disorder screened for and information on carrier status, as much as possible.
24. If unintended results are found (such as carrier status), member states need to consider carefully how results are communicated. Parents need to be informed adequately in a way which is consistent with the individual data protection rights and the right to privacy as well as patient rights. (Pre-test information is discussed in Chapter 5).
25. Economic evaluations of NBS programs are needed. Balancing the right to care of all patients needs to take rare disorders into account.

[61] Based on common values and principles in European Union Health Systems (*universality, access to good quality care*)

26. Even if a program may be cost effective in the long run, the initial costs may represent a barrier to start. Raising specific initial funding should be considered.

27. Systems should be in place at EU level in order to support countries which for reasons of economic development might have difficulties in covering those initial costs.

5. Criteria on how a screening program should be performed

Screening criteria relate to the question whether a screening is desirable (previous chapter) as well as the conditions needed to perform a good program.[62] Facilities should be available for adequate surveillance, prevention, treatment, education, counselling, and social support. Screening should be a continual process, including pilot programs, evaluation of laboratory quality and health services, evaluation of the effect of screening, and provisions for changes on the basis of new evidence. The quality of a screening program depends on the quality of each step in the chain of events, in which the involvement of several health care providers is essential. The pitfalls are numerous and success depends on the attunement among a variety of actors under the public health leadership of a NBS coordinator. Quality management is needed at all levels: program management level, clinical services level, laboratory testing level.[63] In this chapter we will discuss the steps in the chain following the sequence of events. While often technology has driven the development of NBS, we prefer to start earlier: with the training of health care workers and information to parents and public.

Often a neonatal screening program will be coordinated by a public health institute. However, when private health care institutions or commercial parties offer neonatal screening, the same quality criteria apply. It should be remembered that NBS is a program, not a test. It would be wrong to offer neonatal screening tests, when paediatricians can not provide adequate care in case of positive results.

Training of relevant health care providers

Before NBS can start, all health care professionals involved need adequate training. Actors may include obstetricians, laboratory workers, paediatricians, primary care providers, etc. Information to prospective parents can be provided in obstetric care. Soon after birth health care providers will draw blood, often after discussing informed consent with parents. Laboratory workers have to report abnormal findings to physicians (often paediatricians), who in turn inform parents. Primary care physicians will be confronted with questions afterwards. Training needs to be organised at program management level, while also professional organisations have responsibility for adequate postgraduate training.

[62] Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ. Population Screening for Genetic Disorders in the 21st Century: Evidence, Economics, and Ethics. Public Health Genomics 2010;13:106–115.

Simopoulos AP. Genetic screening: programs, principles, and research--thirty years later. Reviewing the recommendations of the Committee for the Study of Inborn Errors of Metabolism (SIEM). Public Health Genomics 2009;12:105-111.

Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva. WHO; 1968. Available from: http://whqlibdoc.who.int/php/WHO_PHP_34.pdf

[63] Andermann A, Blancquaert I, Dery V. A conceptual framework for genetic screening and policy-making. Journal of Health Services Research & Policy 2010;15: 90-97.

Expert opinion:

28. Before the start of a neonatal screening program, all health care professionals involved must be offered adequate training, and sufficient participation achieved.

Information to prospective parents

It is mandatory that public health authorities provide information to prospective parents.[64] Information should include a clear description of the aims within and outside of the scope of the screening. All prospective parents should receive timely information on general aspects of NBS. This information should start preferably during pregnancy, at the latest during third trimester of pregnancy if earlier is not possible, and be repeated before blood sampling at the moment informed consent is sought. The third trimester of pregnancy might be appropriate, because earlier people are not thinking about their infant but more about the pregnancy itself. The information communicated initially may be rather general, provided that detailed information is available on the internet or on request. If the program involves many disorders for which early treatment leads to a better prognosis, these disorders need not be explained in detail to all parents, but instead information can be provided according to parental needs. The provision of information needs to be organised at program management level and attuned with clinical services.

Expert opinion:

29. The provision of information needs to be organised at program management level by public health authorities and is the responsibility of the NBS program management. This should be developed in collaboration with the relevant users.

30. The information contents and communication guidelines should be defined at program management level; it may take advantage from sharing existing examples and experiences.

31. Sufficient general information on NBS should be given to prospective parents, starting during pregnancy. This could also come up in preconceptional care. Detailed information should be available upon request. On a program level the responsibility for this pre-test information needs to be clarified: public health authorities could mandate obstetric care providers.

32. Evidence based patient information on NBS in appropriate language should be made available on websites of the institutions responsible for the screening.

Informed consent

The EUNENBS considers that participation in NBS programs should be voluntary, although refusal should remain exceptional. Parents can usually be convinced of the advantages of NBS for their infants, and are responsible for their health. International debates on the ethics of mandating neonatal screening have on the one hand mentioned the child's best interest, however, even if a failure to consent is morally problematic, overriding parental authority is

[64] Council of Europe. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes. Available from: http://conventions.coe.int/Treaty/en/Treaties/html/203.htm

very difficult to justify when the likelihood of a bad outcome is quite remote.[65] Given that the likelihood of a true positive screen is quite low, parental refusal can not be described as abusive or neglectful.

In a few EU countries NBS is mandatory, but without penalty for non-compliance by parents. If participation to NBS is mandatory by law for parents, (leaving the possibility of refusal) this reduces the burden of seeking informed consent by the program staff, although informing parents is still needed. Written consent is needed only in a few countries (Ireland, Germany, and France for DNA testing), without negative effect on coverage. Separate informed consent is needed for reporting unintended findings such as carrier status, for the storage of blood spots and the use of blood spots for research. The legal protection of sensitive health information, whether DNA or other, needs attention. In some countries the legislation for genetic information is different from other sensitive health information (genetic exceptionalism). This may complicate the execution of NBS programs.

Expert opinion:

33. Neonatal screening must be offered to all infants in the EU.
34. It should be offered as a service governed by appropriate legal provisions, which also ensures compliance with quality requirements of other legislation (such as patient rights, personal data protection, biobanks, research approval by ethics committee, genetic testing, genetic counselling). The health care system should cover the costs.
35. The importance of NBS in the best interest of their child should be clarified to parents. Participation should be voluntary.
36. A specific consent should be sought for activities not strictly related to the benefit of the newborn, such as the use for research purposes.
37. The informed consent protocols should be defined at jurisdictional level, in consultation with the appropriate stakeholders; it may take advantage from sharing existing examples and experiences.

Blood spot sampling

In most countries NBS programs use heelprick blood or blood from the hand. A few programs use umbilical cord blood. The latter is available immediately after birth, and does not require extra blood sampling. It is suitable for hypothyroidism and haemoglobinopathy testing, but does not allow for screening of inborn errors of metabolism. The earlier the sampling takes place, the sooner the diagnosis can be made and the treatment can start. However, some metabolites, specific for certain conditions in the screening panel, fluctuate significantly during the first 48 hours after birth, making this time window less suitable. For most disorders screening between 48 and 72 hours is preferable (Current Practices Document, chapter 6). The diversity in the current situation of blood spot sampling in EU member states is described in the Current Practices document.

An important parameter for the quality of the program is the completeness of blood sampling, preferably very close to 100%. It should be possible for parents to refuse participation of their

[65] Ross L. Mandatory versus Voluntary Consent for Newborn Screening? Kennedy Institute of Ethics Journal 2010;. 20,: 299–328

child to NBS programs, therefore the uptake will never be 100%. Parents may have good reasons not to participate, such as having participated in NBS in another country or because of a lethal anomaly in the infant. If informed consent is taken seriously, opt-out will sometimes, though rarely, occur.

If blood spots are retained for scientific research, central storage may have the advantage of easy accessibility and optimal protection. Storage by "the central government" has in some countries undermined the trust of parents and politicians.

Expert opinion:

38. Blood spot sampling between 48 and 72 hours is preferable for most disorders in NBS programs.
39. Uptake needs to be monitored, an uptake of 100% is pursued. If informed consent is taken seriously, this value may not be reached.
40. Systems should be in place to maximise uptake and ensure that babies are not missed
41. Systems should be in place to deal with families moving into the area and crossing national boundaries to ensure that appropriate screening has been carried out or is offered.

Laboratory Procedures

Laboratory protocols should be ready to define "positive result", including cut offs, and the courses of action to be taken for each result.

Both at program management level and laboratory testing level procedures have to be available to perform NBS in daily practice and to facilitate quality control. In countries where several laboratories analyse NBS bloodspots, attunement among these laboratories is needed, at program level.

Expert opinion:

42. The target values and benchmarks ensuring the quality and efficacy of laboratory procedures should be defined at program management level;
43. The development of laboratory procedures should take advantage from sharing existing examples and experiences.
44. Defined screening protocols should be published by each member state and reviewed every 1-5 years or on demand in case of recognised developments.
45. Test turnaround time within the laboratory should be kept short: e.g. a maximum of 48 hours is recommended.

Blood spot storage

Blood samples need to be stored for quality control in individual cases, for a relatively limited period of time at laboratory level, but also for evaluation on a population level, for instance to determine the distribution of results and derive cut offs. The availability of stored samples for long time periods is important for research aiming at the improvement of the screening program. For some research questions that may be raised in the future, storage for decades

may even be needed (has the birth prevalence of a genetic variant or congenital infection changed over time?). The current situation of storage in EU countries is very diverse, with France not allowing storage for more than one year. Danish samples have been stored for more than 25 years, and were used for several research projects.[66] The collection of heelprick cards may be organised in collaboration with the BBMRI initiative (Biobanking and Biomolecular Resources Research Infrastructure; www.bbmri.eu). For research and long-term follow up, governance at the program management level is needed. Legal provisions are required especially for long term storage.

Expert opinion:

46. Blood spots need to be stored for quality control in the NBS screening laboratory for at least five years.
47. Blood spot storage should ensure appropriate protection of sensitive personal information and of biological samples (e.g.: compliance with the relevant regulations).
48. Informed consent should be asked, at least for activities not strictly related to the benefit of the newborn, such as storage for quality control and research. For use of the bloodspot after 18 years the child should have the possibility to consent or dissent.
49. Use of blood spots for research purposes is subject to national specific ethical regulations (e.g.: definition of research objectives and timing, informed consent, approval by the ethical committee). The potential interest for research and the possible misuse of residual NBS specimens has increased the need for regulation of specimen storage and access policies at the European level for both ethical and legal reasons. At the European level major differences in regulations should be avoided in view of trans-border health care and international research.

Communication of positive result

It is an enormous challenge to give parents adequate information in case of a positive NBS result. As health care professionals communicating this message may not be experts (often primary care physicians), letters must be provided summarizing the most important information. Appointments with expert health professionals (e.g. metabolic paediatrician, clinical geneticist) should be made preferably on the same day that the positive result is communicated. Webportals may be used to inform families and health professionals such as GPs.

Expert opinion:

50. Communication of the need for additional clinical investigations should be preferably carried out by specialists. In case good information has been provided to parents before the sampling/birth, this communication may be carried out also by non-experts, if clearly instructed what to communicate.

[66] Nørgaard-Pedersen B, Hougaard DM. Storage policies and use of the Danish Newborn Screening Biobank. J Inherit Metab Dis 2007;30:530–536

51. The information contents and communication guidelines, for the communication of the need for additional clinical investigations to parents, should be defined at program management level and published; there may be advantages to sharing existing examples and experiences.

52. For every positive NBS result a diagnostic confirmation test, performed by established laboratory methods according to predefined standards, must take place, for most disorders within 24 hours or the next working day after communicating a positive screening result.

53. Communication means should ensure timely delivery to parents, with check on receipt and understanding. Communication of any result, including negative results, may contribute to quality control and parental wellbeing.

Confirmation of diagnosis and treatment

Protocols for confirmation and diagnosis are needed at program management level, and need to be attuned at clinical services level. In small countries there is often not enough clinical expertise. As in the treatment of all rare disorders, expertise in other EU countries needs to be made available for the well-being of all EU patients. The EUNENBS considers that centralisation of care is not always needed, but that there should be (inter)national guidelines for the care. Whether centralisation is needed is dependent on the disorder, its prevalence and the difficulty of the treatment.

Once the diagnosis has been confirmed in the diagnostic unit by expert health professionals, parents need information on the diagnosis in their child. Common practice in EU is that a confirmed diagnosis is communicated by paediatricians. While some parents prefer to be informed only by physicians in person, physicians especially may be served by webportals containing high quality information to add to the information provided. ORPHANET-associated websites are present in almost all EU countries, mostly in the local language, and provide quality information of use for physicians and health professionals as well as for family carers and the patients. This could be a good possibility for validated and homogeneous information. Parents organisations also can support individual parents with information and peer contact. Help lines also may be useful, but their presence in the EU countries is less extended than ORPHANET websites. Existing national NBS websites can serve as examples for other countries. Protocols on whom to treat as patient and how to treat them, must be available at program management level.

Expert opinion:

54. Defined "diagnostic protocols" should be developed which relate directly to the case definition. Protocols on whom to treat as patient, including referral to clinical services, should be available at program level.

55. Protocols for confirmation of diagnosis and guidelines for treatment should be defined at program management level; there may be advantages to sharing existing examples and experiences.

56. Communication after a confirmed diagnosis is extremely important. Personal communication by physicians can be supported by information from accredited webportals.

Communication of unintended findings

NBS will generate intended and unintended findings. Sometimes other conditions are diagnosed, such as thalassemias when looking for sickle cell disease with HPLC. The benefits of early diagnosis are less clear. As thalassemia is a treatable childhood condition, this is not a serious problem. On some occasions infants may have metabolic symptoms due to a maternal metabolic condition. Parents should be given the possibility to be informed of any relevant unintended finding in their infant, including carrier status,[67] unless forbidden by law.[68] If the infant is a carrier, at least one of the parents is a carrier too, and the risk of having a child with a serious condition is increased. Therefore the information on carrier status of the child is relevant to the parents. The EUNENBS considers that unintended findings that could be relevant to the parents always should be communicated. It acknowledges however that it might not always be straightforward to define whether a result is relevant. Communication plans on positive results must be developed at program management level for consistency reasons. Findings for which the assessment concluded for an unfavourable balance of risks and benefits, should not be communicated.[69] Information which is not necessary with reference to timely and effective benefit, should not be communicated and should be destroyed.

Expert opinion:

57. Parents should be given the possibility to be informed of any unintended finding that could be relevant, to the extent this is consistent with laws, individual data protection rights and the right to privacy.

58. Different positions have been taken in the debate on unintended findings. Discussion is needed in countries to develop policy, and legislation if appropriate. This should be published.

59. As far as unintended but relevant information for the health of the child or mother is concerned, parents should be given the possibility to be informed. For the return of information on carrier status a separate decision, consistent with other relevant national health regulations, is needed in each country. This is because carrier information is mainly important for reproductive choice of the parents and not directly for the health of the screened newborn. The content of the information and guidelines for its communication to parents should be defined at program management level; it may take advantage from sharing existing examples and experiences.

[67] European Society of Human Genetics. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2009;17:720-1.

Burton H, Moorthie S. Expanded newborn screening. A review of the evidence. Cambridge, PHG foundation, 2010.

Bombard Y, Miller FA, Hayeems RZ, Avard D, Knoppers BM, Cornel MC, Borry P. The expansion of newborn screening: is reproductive benefit an appropriate pursuit? Nat Rev Genet. 2009;10:666-7.

Borry P, Nys H, Dierickx K. Carrier testing in minors: conflicting views. Nat Rev Genet. 2007;8(11):828.

[68] In Germany on February 1st, 2010 the "GendiagnostikGesetz" (Genetic testing law) came into force, protecting the right-not-to-know incidental findings. http://www.gesetze-im-internet.de/bundesrecht/gendg/gesamt.pdf

[69] Council of Europe Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes , art 16, items 2, 3, 4

Quality assurance of laboratory results

Both at program management level and laboratory testing level the competence of personnel should be guaranteed. The presence of highly fragmented services in some countries is probably the single most important barrier to the successful organisation of neonatal screening to a consistent standard within the EU. The performance of laboratories may depend on number of samples handled and the successful participation in quality schemes. Smaller countries may consider collaboration with other countries. In countries where several smaller laboratories perform NBS reduction and/or centralisation may be needed. This should not endanger the quality of the existent system.

Expert opinion:

60. NBS laboratories should be certified and participate in external quality assurance/control programs. The EU NBS committee should advise on EQA, poor performance and offereducational support to poorly performing laboratories.
61. Within a jurisdiction the number of laboratories should be limited. Optimal quality performance and cost effectiveness requires a minimum number of samples handled, such as 30000-50000 samples per year.

Screening program evaluation

Databases are needed of all neonates, samples received, conclusion communicated, and positive results. Periodic (possibly annual) reports on the screening process should show uptake, time to receive sample and report result, time to start treatment, time to diagnosis. A communication plan should mention who should be informed of what information in the evaluation. If the results of NBS programs are not satisfactory, a decision to stop should be considered.

The quality of the program needs to be monitored in all relevant aspects, from the provision of information to parents-to-be till the storage of samples for future research. Monitoring and information collection should allow identification of the steps which may require corrective measures.

Expert opinion:

62. The quality of the process of the program needs to be monitored regularly (possibly annually) to allow the identification of steps requiring improvement and the adoption of appropriate corrective measures. Results should be made available by open access.
63. Evaluation of specific aspects of NBS programs must be considered for aspects other than those regularly monitored, such as recently changed information policies.
64. Databases are needed to monitor and evaluate the program. As all NBS conditions are rare, international collaboration may help to facilitate evaluation.
65. Systems should be in place to ensure that feedback of confirmed diagnosis and long term outcomes are available for program evaluation, also in case of screened children moving abroad.

Epidemiological evaluation

The goal of NBS is to reach better health outcomes of the patients. Databases on infants screened and patient population registries are needed for long term follow-up. The evaluation of the prevalence of the disorder and of the effectiveness of the early treatment of rare conditions is a challenge for many member states due to statistical power. Due to the rarity of the disorders, sufficient statistical power often cannot be achieved on an individual country basis. Therefore there is a need for collaborative international research projects.

Expert opinion:

66. Collaborative international projects are needed to assess the long term follow-up of the patients with rare conditions identified in NBS programs. Both evaluation of programs (expert opinion #65) and the success of screening and treatment for patients and families is needed. The EU should take a pro-active approach to organize long term follow-up.

6. Strategies for implementation

Strategies for implementation at international level

Many of the key issues that are relevant at all stages and in every type of screening program in any country, and are closely interrelated.[70] Genetic screening is an area that has developed very rapidly in recent years with the mapping of the human genome. Many see it as opening up a new era in the prevention, early diagnosis and identification of disease. However, caution is essential. Information needs to be more than a leaflet and possibly offering a brief discussion with a health professional, but should include benefits and harms based on a summary of scientific results. Economical and ethical issues must be studied and clarified in a transparent way. The importance of maintaining the quality of screening programs should never be underestimated. Evaluation, audit and quality control should be an integral part of any screening program to ensure that it is achieving what it has set out to do in a way that is acceptable to those involved. Developing and exchanging the knowledge for many of these aspects can profit from international implementation.[71]

Collaboration between member states would be useful to further elaborate methods for the assessment of screening criteria-associated parameters (evidence: prevalence, potential for health gain, sensitivity, specificity, predictive value; economics: cost effectiveness; ethics: informed consent, reporting unintended findings).[72] EUnetHTA is already building expertise on health technology assessment.[73]

Strategies for implementation at national level

Between countries there are differences in the structure of the health care system, health care insurance and the funding of national screening and prevention programs, legal issues and liability. These need to be taken into account in implementation in each member state. General principles, according to the EU Council Recommendation on rare diseases, are:

- Identification of centres of expertise for diagnosis and definition of treatment, where patients are streamlined: limited number of centres in order to ensure appropriate concentration of expertise.
- Participation of centres of expertise in EU reference networks and in registries for exchange of expertise and consultation.
- Centres executing treatments distributed in the territory in proximity of patients.

When implementing NBS programs, countries can profit from evidence and experiences developed elsewhere, and should try to avoid duplication. Countries should carry out a pilot study to find evidence of national or local system gaps and apply corrective measures, before making the final decision on starting a NBS program.

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[70] Holland WW, Stewart S, Masseria C. Policy Brief. Screening in Europe. World Health Organisation 2006 on behalf of the European Observatory on Health Systems and Policies.

[71] Hoffmann GF, Cornejo V, Pollitt RJ. Newborn screening-progress and challenges. J Inherit Metab Dis. 2010;33(Suppl 2):S199-200.

[72] Hoffmann GF, Pollitt R, Torresani T, Yamaguchi S. Focus on neonatal screening. J Inherit Metab Dis 2007;30:417;

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

The NBS program should include the periodic evaluation and revision of the program.

Activities which can benefit from gathering of expertise at EU level

- In Europe, standing NBS committees are needed both on a national and supranational level for scientific evaluation, horizon scanning, prioritisation, health technology assessment, evaluation of cost-effectiveness and ethics of potential screening possibilities.
- There is room for synergy between EU countries as screening committees in different countries will have to evaluate similar issues. EUnetHTA could contribute to this.
- A transparent governance procedure should allow input from medical professionals and parents/patients. As for industry and commercial parties, it should be possible for them to provide information. An open procedure should be set for the assessment of new tests. The final decision has to be made by relevant health authority (e.g. Minister or Department of Health) based on evidence provided.
- The survey of Current Practices collected data on many aspects. Some may change within a few years, some turned out not to be valid or precise as questions were interpreted differently than intended or data were not available. A repeated survey in a few years time should be considered. More detailed categorisation of costs could be addressed by interviewing experts.

Features of disorders which might be considered in the gradual expansion of NBS in EU

Several countries have evaluated screening possibilities according to criteria mentioned in chapters 4 and 5, and reached similar conclusions for some conditions. Congenital hypothyroidism is screened for in 37 European countries, including all 27 EU countries, as described in the Current Practices Document, and hyperphenylalaninemia/phenylketonuria in 33 countries. Disorders with a relatively high prevalence, for which the test is not too difficult and health gain is proven, besides PKU and CH that are already screened in all EU countries (but for PKU in Finland and Malta),[74] are CAH, CF and MCADD, and in addition SCD[75]/βthal in Mediterranean countries and countries with migrant populations.[76] Apart from these relatively frequent conditions, others should be considered as well, e.g. MSUD, GA-I and galactosaemia. Besides the common colorimetric and fluorimetric assays, PKU can be screened for with ms/ms technology, which is needed for MCADD and can be used for MSUD as well; CH, CAH and CF require the use of immunoassay, usually followed, for CF, by DNA mutation analysis; SCD/βthal require HPLC analysis, sometimes followed by DNA mutation analysis.

A second group of disorders, which appear promising candidates for screening, but for which evaluation according to the criteria mentioned in chapters 4 and 5 is more challenging,

[74] Current Practices Document, Chapter 8

[75] Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376:2018-31

Benson JM, Therrell BL Jr. History and current status of newborn screening for hemoglobinopathies. Semin Perinatol. 2010;34:134-44.

Bain BJ. Neonatal/newborn haemoglobinopathy screening in Europe and Africa *J Clin Pathol* 2009;62:53-56

[76] See also chapter 4, paragraph "disease", references at page 25.

consists of biotinidase deficiency, CMV infection,[77] CPT II/CACT deficiency,[78] glutaric acidemia type II,[79] HMG-CoA lyase deficiency, holocarboxylase synthase deficiency, homocystinuria, isovaleric acidemia, ketothiolase deficiency, long-chain hydroxyacyl CoA dehydrogenase deficiency, lysosomal storage disorders, 3-methylcrotonyl-CoA carboxylase deficiency, SCIDD,[80] tyrosinemia type I and II, very-long-chain acyl-CoA dehydrogenase deficiency and vitamin B12 deficiency.[81] For these disorders HTA at EU level could inform the decision-making in individual EU countries. Due to fast technological changes in high throughput technology (genomics, proteomics, metabolomics) and treatment, this list is not extensive and needs revision when the assessment starts. As described in the Current Practices Document, changes occurred in the majority of countries in the last five years (CP 1.3), and panels included range from one or two to a few dozens of conditions.

Finally, although the tender work has focused on blood-detectable conditions due to the special implications associated with multiplex screening tests, it should be mentioned that also congenital hearing impairment shares the features of the first group of conditions. Testing for congenital dysplasia of hips, vision, congenital cardiac defects etc. can be considered by the EU NBS committee as well.

Expert opinion:

67. Training on all aspects of improving NBS programs should be facilitated at EU level.
68. EU countries should consider the assessment of the first group of disorders on the basis of local/national conditions in case that they intend to expand their NBS. This process and conclusions should be published.
69. The EU NBS body, charged with the assessment of the evidence and possibilities for neonatal screening,[82] might consider initiating its activity with reviewing the evidence for disorders to be screened. For the first group of disorders several countries have assessed the evidence already. Especially the conditions in the second group where limited evidence is available or different conclusions were reached need to be prioritized.
70. There is an opportunity to use the moment of bloodspot screening for other screening programs concerning e.g. hearing loss, hips, eyes, heart.

[77] Dollard SC, Schleiss MR, Grosse SD. Public health and laboratory considerations regarding newborn screening for congenital cytomegalovirus. J Inherit Metab Dis. 2010 Oct;33(Suppl 2):S249-54.

[78] Wilcken B. Disorders of the carnitine cycle and detection by newborn screening. Ann Acad Med Singapore. 2008 Dec;37(12 Suppl):71-3.

[79] Kölker S et al. Diagnosis and management of glutaric aciduria type I - revised recommendations. J Inherit Metab Dis. 2011 Mar 23. [Epub ahead of print]

[80] Lipstein EA, Vorono S, Browning MF, Green NS, Kemper AR, Knapp AA, Prosser LA, Perrin JM. Systematic evidence review of newborn screening and treatment of severe combined immunodeficiency. Pediatrics. 2010 May;125(5):e1226-35.

[81] Sarafoglou K, Rodgers J, Hietala A, Matern D, Bentler K. Expanded newborn screening for detection of vitamin B12 deficiency. JAMA. 2011 Mar 23;305(12):1198-200.

[82] Calonge N et al. Committee report: Method for evaluating conditions nominated for population-based screening of newborns and children. Genet Med 2010;12:153-9.

7. Proposal for a model of decision-making matrix

The tender specifications require the definition of a decision-making matrix, in view of preparing discussion for the development of EU policies in neonatal screening. To this aim, a model decision-making matrix has been defined making reference to: the original Wilson and Jungner criteria, which are still used by many countries as a "compass" for their decisions in NBS; the documents on principles, values or rights elaborated after the publication of the Wilson and Jungner criteria and have relevance for neonatal screening and the EU member states, candidate, potential candidate and EFTA countries; the observations raised by the EUNENBS members during the meetings and the consultations carried out for the rolling out of this tender; and the results and discussion of the European survey on neonatal screening presented in the other deliverable of this tender, the "Report on the practices of newborn screening for rare disorders implemented in Member States of the European Union, Candidate, Potential Candidate and EFTA Countries". Moreover, we have attempted to elaborate a model which can be suitable for the national/Community distribution of competences on health in the EU.

The actual definition and adoption of an operative algorithm to be used in EU, involves the balance of the many aspects regarding the national prerogatives and EU competences in health; the way in which the governance of neonatal screening is actually implemented and interconnected between the national and the Community level; and agreements, which may require long technical discussions and may differ case by case. All these aspects are far beyond the scope and powers of the tender.

Proposed model of decision-making matrix

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1) Does your country or health-care jurisdiction have a neonatal screening program?

a) If no: start neonatal screening for congenital hypothyroidism.[83]

2) If YES, consider disorders for which a neonatal screening program exists elsewhere, or for which research shows promising results.[84] For each disorder:

a) Can, according to international experience, considerable, irreparable damage be prevented by neonatal screening or other benefits for the patient and the family be achieved? Assessment includes:

i) The condition sought should be an important health problem (W&J1)

ii) There should be an accepted benefit for patients with recognized disease (W&J2)

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[83] The reason for the choice of congenital hypothyroidism is twofold: 1. CH is (one of) the most prevalent congenital disorders, the prevalence being largely independent of ethnicity; 2. The screening and confirmatory methodology is relatively simple. All European countries that contributed to the current Practices Document screen for CH.

[84] As specified in chapter 4

iii) There should be a recognizable latent or early symptomatic stage (W&J4)

iv) The natural history of the condition, including development from latent to declared disease, should be adequately understood (W&J7)

b) Is, according to international experience, a good test available? (Sensitivity, specificity, positive predictive value, acceptability) Assessment includes:

i) There should be a suitable test or examination (W&J5)

ii) The test should be acceptable to the population (W&J6)

iii) There should be an agreed policy on whom to treat as patients (W&J8)

3) If both questions YES, consider desirability in your country/region:

a) Is the disorder an important health problem *in your country*?

b) Is the test acceptable for the population from cultural/ethical perspective (Unintentional findings; carrier status; mild forms, late-onset forms)

4) If the previous questions are answered YES, consider the feasibility[85]:

a) Compare the burden of the disorders for the health system to the cost of screening, with a view to ensuring equity of access to health care and considering other feasible options.

i) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole (W&J9)

ii) What is the birth prevalence of the disorder(s)?

b) Can facilities be made available for adequate surveillance, prevention, treatment, education, counselling, and social support? Assessment includes:

i) Facilities for diagnosis and treatment should be available (W&J3)

ii) Case-finding should be a continuing process and not a "once and for all" project (W&J10).

iii) Is a good test available in your country?

iv) Are sufficient diagnostic specialists available?

v) Is treatment available in your country?

vi) Are sufficient treatment specialists available?

[85] As specified in chapter 5 and 6.

vii) Are there patients associations which may provide support to the patient and/or the family

5) If NBS is considered desirable and feasible, take care of adequate quality of the program,[86] including:

a) Training of relevant health care providers

b) Information to prospective parents,

c) Informed consent, both general and specific on communication of carrier status information and sample storage for research use

d) Procedures for blood spot sampling, laboratory handling, storage of cards

e) Protocols for communication of health care providers in case of positive results.

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[86] As specified in chapter 5 and 6.

Appendix 1: Experts asked to comment during the preparation of the Expert Opinion Document.

CoreMembers of EUNENBS nominated at 31 May 2011

	FAMILY NAME	FIRST NAME	AFFILIATION
EU Member States			
Austria	Kasper	David, C.	Medical University of Vienna Department of Pediatrics and Adolescent Medicine
Austria	Hintner	Helmut	Department of Dermatology, Paracelsus Medical University (PMU) Salzburg
Belgium (Flemish community)	Vandenbulcke	Pieter	Flemish Agency for Care and Health Flemish Ministry of Welfare, Public Health and Family
Belgium (French community)	Goyens	Philippe	Nutrition and Metabolism Unit & Laboratory of Pediatrics, Université Libre de Bruxelles
Belgium (French community)	Meulemans	Ann	Nutrition and Metabolism Unit & Laboratory of Pediatrics, Université Libre de Bruxelles
Bulgaria	Stoeva	Iva	Specialised Hospital for Active Treatment of Children's Diseases
Cyprus	Christophidou Anastasiadou	Violetta	Clinical Genetics Clinic, Archbishop Makarios III Medical Centre, Medical and Public Health Services, Ministry of Health
Czech Republic	Kožich	Viktor	Institute of Inherited Metabolic Disorders University Hospital Královské Vinohrady
Czech Republic	Macek	Milan	2nd Faculty of Medicine, Charles University Prague and University Hospital Motol
Czech Republic	Votava	Felix	Institute of Inherited Metabolic Disorders University Hospital Královské Vinohrady
Denmark	Jespersen	Marianne	National Board of Health
Estonia	Uudelepp	Mari-Liis	Tartu University Hospital (Center for Genetics)
Finland	Leipälä	Jaana	National Institute for Health and Welfare Finnish Office for Health Technology Assessment

France	Sarles	Jacques	French association of screening and prevention of childhood disability (AFDPHE)
Germany	Kulig	Michael	Abteilung Fachberatung Medizin - Joint Federal Committee
Greece	Mengreli	Chryssanthi	Department of Biochemical Laboratories of the Institute of Child Health
Hungary	Szonyi	Laszlo	1st Department of Paediatrics, Semmelweis University - Budapest
Ireland (and Advisory Board)	Mayne	Philip	Newborn Bloodspot Screening Laboratory The Children's University Hospital
Italy	Dallapiccola	Bruno	Paediatric Hospital "Bambino Gesù" - IRCCS
Italy	Cerone	Roberto	Dept. of Pediatric Sciences "Giovanni de Toni", G. Gaslini Institute - Genova
Latvia	Kreicberga	Ilze	Riga Maternity Hospital
Lithuania	Algirdas	Utkus	Genetics Center, Vilnius University
Luxembourg	Wagener	Yolande	Ministry of Health
Malta	Scerri	Christian A.	Specialties Clinic, Outpatients Block, Mater Dei Hospital, Neo-natal Paediatric Intensive Care Unit, Mater Dei Hospital
Malta	Attard Montalto	Simon	Specialties Clinic, Outpatients Block, Mater Dei Hospital, Neo-natal Paediatric Intensive Care Unit, Mater Dei Hospital
Netherlands	Groeneveld	Pepita	Ministry of Health, Welfare and Sports of the Netherlands, Public Health Department
Poland	Ołtarzewski	Mariusz	Institute of Mother and Child
Portugal	Vilarinho	Laura	Newborn Screening Unit, Medical Genetics Institute
Romania	Vlădăreanu	Ana Maria	Bucharest Emergency University Hospital
Slovakia	Dluholucky	Svetozar	Department of National Screening Centre of newborns Children University Hospital Namestie
Slovakia	Knapkova	Maria	Department of National Screening Centre of newborns Children University Hospital Namestie
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Iceland	Magnússon	Sveinn	Ministry of Wellfare
Iceland	Briem	Haraldur	Directorate of Health
Croazia	Baric	Ivo	Division for Metabolic Diseases, University Hospital Center
Croazia	Bajramovic	Dubravko	Ministry of Health and Social Welfare, Directorate of Medical Affairs, Hospital Health Care Department
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