



EU Tender

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

**Short Executive Summary of 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**

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The opinions expressed in this document are those of the Contractor only and do not represent the official position of the Executive Agency for Health and Consumers.

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Abbreviations

3hmg	3-Hydroxy-3-methylglutaric aciduria
3mcc	3-Methylcrotonyl-CoA carboxylase deficiency/3-Methylglutacon aciduria/2-methyl-3-OH-butyric aciduria
AAD	Disorders of amino acid metabolism
arg	Argininemia
asa	Argininosuccinic aciduria
bio	Biotinidase deficiency
bkt	Beta-ketothiolase deficiency
btha	S, beta 0-thalassemia
cah	Congenital adrenal hyperplasia
cf	Cystic fibrosis
ch	Primary congenital hypothyroidism
citI	Citrullinemia type I
citII	Citrullinemia type II
cpt I	Carnitin palmitoyltransferase deficiency type I
cpt II	Carnitin palmitoyltransferase type II-/Carnitine acylcarnitine transporter deficiency
cud	Carnitine uptake defect
decr	2,4-Dienoyl-CoA reductase deficiency
EFTA	European Free Trade Association
ELISA	Enzyme Linked Immunosorbent Assay
Endo	Endocrinopathies
EQA(S)	External Quality Assessment (Scheme)
ERNDIM	European Research Network Diagnosis Inherited Disorders of Metabolism
EUNENBS	European Network of Experts on Newborn Screening
FAOD	Disorders of fatty acid metabolism
FYROM	Former Yugoslavian Republic of Macedonia
gal	Glutaric acidemia type I
gall	Glutaric acidemia type II
galt	Classical galactosemia
hci	Homocystinuria (CBS deficiency)
hcsd	Holocarboxylase synthetase deficiency
Hemo/ HpB	Hemoglobinopathies
hpa	Hyperphenylalaninemia
HPLC	High Performance Liquid Chromatography
hpt I, III	Hypermethionemia types I, III
ISO	International Standards Organization
iva	Isovaleric acidemia (IVA)/ 2-Methylbutyrylglycinuria
lchadd	Long-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency/Trifunctional protein deficiency
M	Miscellaneous disorders
mcadd	Medium-chain acyl-CoA dehydrogenase deficiency
mma	Malonic acidemia
mmacbl	Methylmalonic acidemia including Cbl A,B, C, D deficiencies
NBS	Neonatal (newborn) Screening
NEQAS	National External Quality Assessment Scheme (UK)
OA	Disorders of organic acid metabolism
pa	Propionic acidemia
QA/QC	Quality assurance/Quality control
RP-NBS	Report on the practices of newborn screening for rare disorders implemented in Member States of the European Union, Candidate, Potential Candidate and EFTA Countries
s_s	S,S disease (Sickle cell Anemia)
sc	S,C disease (Sickle – C disease)
scadd	Short-chain acyl-CoA dehydrogenase deficiency
schadd	Medium-Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
tyrI	Tyrosinemia type I
tyrII, III	Tyrosinemia types II, III
udp	UDP-galactose-4-epimerase deficiency
UK	United Kingdom
vlcadd	Very long-chain acyl-CoA dehydrogenase deficiency

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A. Introduction

The tender “Evaluation of population newborn screening practices for rare disorders in Member States of the European Union”, is one of the actions launched by the European Commission within the EU Program of Community Action in Public Health (work plan 2009). The EU Council Recommendation for an Action in the Field of Rare Diseases (9 June 2009)¹ foresees the adoption of national plans and strategies for rare diseases within 2013, and establishes the lines for the cooperation and coordination among Member States to better utilize national resources and expertise in this field and reduce inequalities in the access-to high quality care.

The tender delivers 4 results:

1. A Report on the practices (RP-NBS) of NBS for rare disorders implemented in all Member States
2. An Expert opinion document, including a decision-making matrix, on the development of European policies in the field of newborn screening for rare diseases
3. Establishment of a European Network of Experts on Newborn Screening (EUNENBS)
4. A European Expert Consensus Workshop on NBS (June 2011)

This short executive summary gives an overview of deliverable 1, 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 (RP-NBS)”. The numeration of the chapters of the summary corresponds to the RP-NBS document which should be consulted for detailed information. Tables and figures in the present document are numbered according to the sequence, however, references to numbers and pages of the extended document are given in brackets.

What is already known?

NBS is available in many European countries and has been extended after the introduction of tandem mass spectrometry technique. European countries have different panels of disorders screened for, also with great organisational variation in the different jurisdictions.

What this survey adds

The survey gives a first overview of screening panels, guidelines structuring the screening process from legal regulations, information of prospective parents, procedures of confirmation diagnostics, start of treatment and QA and QC of the whole NBS program.

Proximal steps of the programs (information of parents and laboratory procedures) are better regulated than distal steps (epidemiological evaluation by registries and evaluation of the outcome of treatment).

Cut offs of metabolites for screening the same disorder are different across countries and even between screening laboratories within countries.

Training of professional groups involved in NBS programs is poorly developed and offers opportunity for substantial improvement.

The development of systems coordinating the collection and exchange of data (e.g. registries) would be very important to allow the assessment of the procedural and clinical aspects as well as the cost-effectiveness of neonatal screening programs.

NBS programs should be understood as the complete process from legislation to the systematic evaluation of the outcome of treatment and not merely as the technical part in the NBS laboratory.

¹ European Commission. complete Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02). Official Journal of the European Communities C151, 3/7/2009, p. 7-10.

B. Methods of the survey

The process steps of a complete NBS program were organised in a set of 5 modules (A, B, C, D, and E) described in the legend to Figure 1. The survey has been conducted in a modular structure executed by three interacting scientific teams in cooperation with the project leaders.

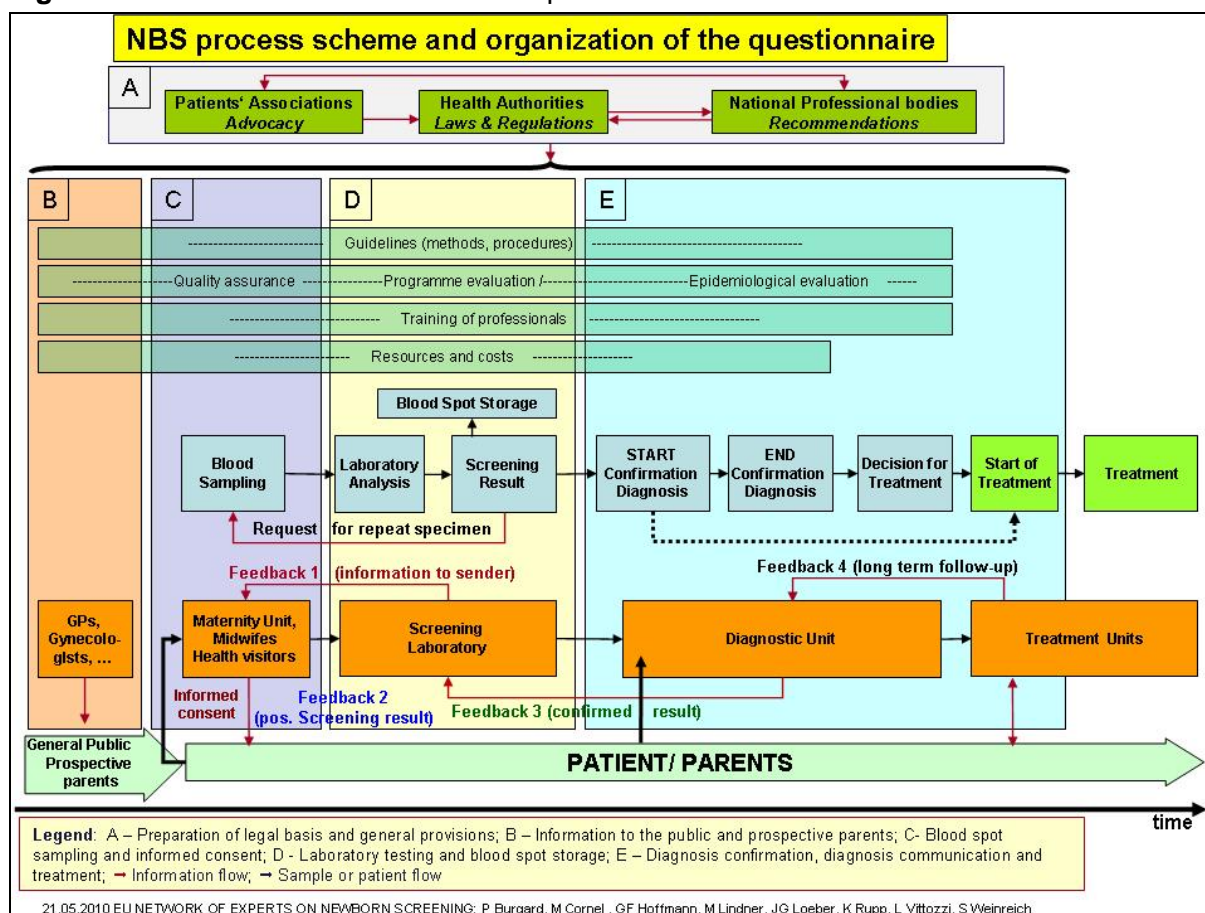
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Figure 1 Modular structure of the NBS process



Each team developed a set of questions covering the respective modules with regard to

- the current practices of the different steps within each module and
- the type of regulation of current practice by directives (i.e. legally binding standardization by state authorities and/or health system) and/or guidelines (i.e. information intended to advise people on how something should be done).

Questions were implemented in a web-based questionnaire and respondents were contacted via professional organisations and national health authorities. The survey started in August 2010 and was closed on January 14th, 2011, with all data referring to the situation on September 1st, 2010.

Table 1 Countries contacted for the survey, their screening panels and data sets received by the five modules

	Countries in the survey	Screening panel (n of disorders)				Received data sets for Module				
		Meta-bolic	Endocrino-logical	CF	Hemoglo-binopathies	A	B	C	D	E
EU	Austria	26	2	yes	-	x	x	x	x	x
EU	Belgium (Flemish)	9	2	-	-	x	x	x	x	x
EU	Belgium (French)	6	1	-	-	x	x	x	x	x
EU	Bulgaria	1	2	-	-	x	x	x	x	x
EU	Cyprus	1	1	-	-	x	x	x	x	x
EU	Czech Republic	9	2	yes	-	x	x	x	x	x
EU	Denmark	13	2	-	-	x	x	x	x	x
EU	Estonia	1	1	-	-	x	x	x	x	x
EU	Finland	-	1	-	-	x	x	x	x	x
EU	France	1	2	yes	1	x	x	x	x	x
EU	Germany	12	2	yes	-	x	x	x	x	x
EU	Greece	2	1	-	-	x	x	x	x	x
EU	Hungary	24	1	-	-	x	x	x	x	x
EU	Ireland	4	1	-	-	x	x	x	x	x
EU	Italy*	1	1	-	-	x	x	x	x	x
EU	Latvia	1	1	-	-	x	x	x	x	x
EU	Lithuania	1	1	-	-	x	x	x	x	x
EU	Luxembourg	2	2	-	-	x	x	x	x	x
EU	Malta	-	1	-	2	x	x	x	x	x
EU	Netherlands	14	2	yes	3	x	x	x	x	x
EU	Poland	1	1	yes	-	x	x	x	x	x
EU	Portugal	24	1	-	-	x	x	x	x	x
EU	Romania	1	1	-	-	x	x	x	x	x
EU	Slovakia	1	2	yes	-	x	x	x	x	x
EU	Slovenia	1	1	-	-	x	x	x	x	x
EU	Spain	23	2	yes	1	x	x	x	x	x
EU	Sweden	3	2	-	-	x	x	x	x	x
EU	United Kingdom	2	1	yes	3	x	x	x	x	x
EU cand*	Croatia	1	1	-	-	x	x	x	x	x
EU cand*	FYROM	-	1	-	-	x	x	x	x	x
EU cand*	Iceland	25	1	-	-	x	x	x	x	x
EU cand*	Montenegro	1	-	-	-			x	x	x
EU cand*	Turkey	2	1	-	-					x
EU pot cand**	Albania	-	-	-	-	x	x			
EU pot cand**	Bosnia-Herzegovina	1	2	-	-		x	x	x	x
EU pot cand**	Kosovo									
EU pot cand**	Serbia (Central)	1	1	-	-	x	x	x	x	x
EFTA	Norway	1	1	-	-	x	x	x	x	x
EFTA	Switzerland/ Liechtenstein	5	2	-	-	x	x	x	x	x

* national screening panel; * EU candidate; ** EU potential candidate, highlighted cells = no data

Respondents were supported during data entry by members of the teams. Where necessary, respondents were contacted for correction or completion of their data set. Final approval of the national data sets was achieved during a conference of the EUNENBS members held in Luxembourg on 20.-21.06.2011.

As the target questions of the different modules required differential expertise, each team contacted respondents via corresponding professional organisations (see Appendix 2 page 237, RP-NBS). Where necessary, also respondents for selected disorders were invited to contribute to the survey, i.e. in general the data set for a country is the result of data delivery by multiple respondents. Table 1 shows that national data sets are complete for almost all countries. In Albania there is no screening and it was not possible to contact Kosovo. Table 2 gives an overview of the screening panels of the countries targeted in the survey. The disorders listed for each country also include conditions not contained in the official screening panel but investigated in research programs. The last line of Table 2 gives the frequency distribution for the disorders screened for. The final data set has 3 basic dimensions: (1) countries, (2) disorders screened for, and (3) questions related to the screening program (subdivided by current practice and existence type of regulation).

C. Main Results

C.1 Provisions assuring the control of NBS programs

1 Governance

In Europe, each country is independently developing its own health care policy, including policy on newborn screening. National policies are mainly responding to national pressures and circumstances, which is also reflected in the governance of the neonatal screening programs. When countries or health regions face the decision to extend their neonatal screening program, important issues are how to take such a decision and whom to involve.

1.1 Is participation to NBS mandated by law?

About half the jurisdictions surveyed (17 of 35) reported to have laws or regulations mandating participation in newborn screening (see RP-NBS, Table 1.2), and several more jurisdictions (20 of 36) indicated to have laws dealing with at least some aspect of newborn screening (see RP-NBS, Table 19.2). Countries that clearly do not have legal regulation of newborn screening are Lithuania, Finland, Greece, and Switzerland. Some states have mandated the implementation of a screening program, without obliging parents to use it (e.g. Germany). Notably, screening is sometimes perceived as mandatory by parents even when it is not (reported from Austria, Norway). Most jurisdictions (26 of 36) allow for opting-out or dissent, but in 9 of them it is not or not clear whether this is legally regulated. Only a few countries seem to mandate parents to participate in the program (no consent is required), although, to the best of our knowledge, non-complying parents do not receive a penalty.

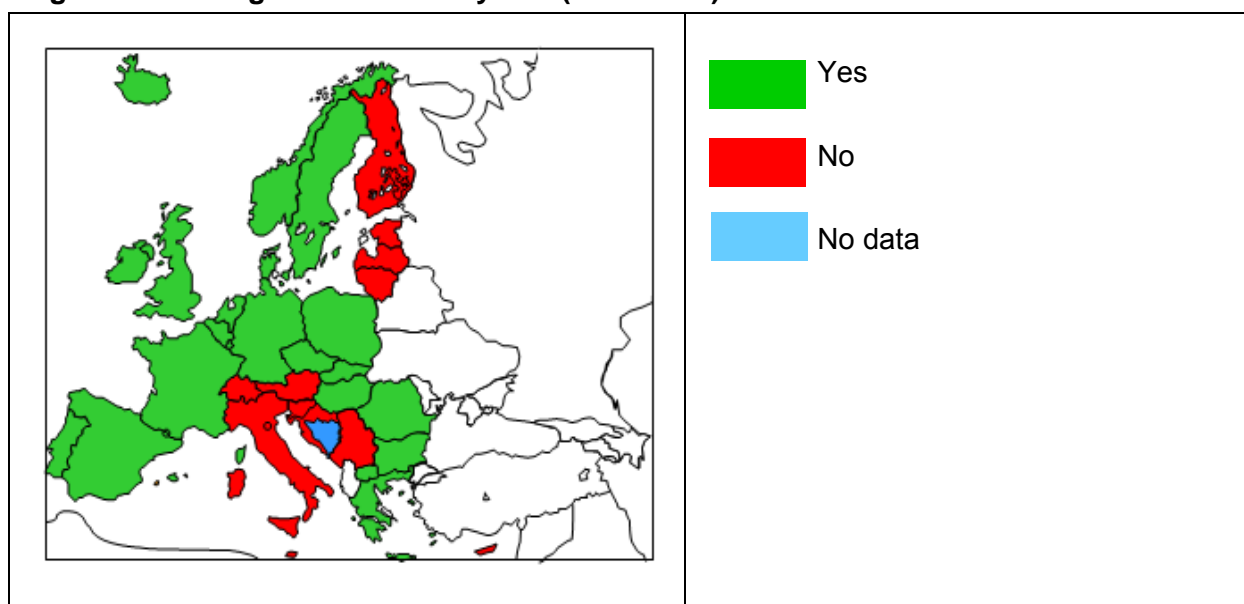
1.2 Oversight by steering committee

The majority of reporting EU countries (18 of 27) has a body which oversees newborn screening. Such bodies were described with a variety of terms, e.g. board, council, management unit etc. Some are devoted to newborn screening only, some have a broader task in health policy, public health, prevention, insurance and rare diseases. The non-EU countries participating in this survey, including (potential) candidate countries, did not report having oversight committees.

1.3 Changes last 5 years

Of the 34 responding countries 21 reported to have changed their newborn screening policy in the last five years (Figure 2; not including the reported changes made in Austria in 2002). Most of the changes in policies involved health authorities (20 of 22 reporting jurisdictions).

Figure 2 Changes in the last 5 years (2005-2010)



Usually they were national or federal health authorities (18), occasionally only regional authorities (2) and sometimes both (2). Varying involvement of health technology assessors

and patient organisations was reported. In the two countries where health authorities were not actors in expanding screening, involvement was noted of physicians specialized in paediatrics and clinical chemistry in one case (Sweden). In the other case (England/UK) a newborn screening committee made recommendations which were supported by families and members of parliament. Additional actors mentioned to be involved in expansion of screening were screening centres and health insurance companies.

1.4 Present/future evaluation of conditions for NBS

The survey requested a short description of how any new newborn screening test is currently being evaluated or how it would be evaluated in the near future. Informants provided various types of information, e.g. the parties who would initiate evaluation, the committee who would perform the evaluation, the methods they would use (e.g. literature survey), inclusion criteria, the organisation of pilot studies, the political authority which would make the decision and the service which finally would implement screening. In a few cases respondents conveyed steps in a chain, from evaluation through to a political decision.

1.5 Factors helping/challenging building the NBS programs

A variety of factors were indicated as helpful in building newborn screening programs, a selection of which will be mentioned here. Pre-existing, favourable conditions can be the high local prevalence of certain disorders, traditions in public health policy, a culture of compliance with regulations, or a high rate of hospital deliveries. Also beneficial can be pre-existing infrastructure (including qualified institutions and trained professionals). External factors helping build newborn screening programs can be successful examples or pilot studies in other (neighbouring) countries. The availability of evidence or guidelines was also indicated among the beneficial factors. Finally, positive factors at the policy level included a national plan for rare diseases, international collaboration with laboratories and centres of expertise, and political will. Costs of the programs and missing resources were often mentioned as obstacles in the maintenance or expansion of the programs. There is a need for evidence of efficacy of screening. Other obstacles can be related to infrastructure (e.g. provision of adequate care after a positive screening result) as well as practice (e.g. communication among relevant specialists). A special category of challenges relate to ethics and governance, e.g. how to deal with information on carrier status.

1.6 Written policies

The survey found variability among which areas of the screening process are covered by written policies (See RP-NBS, Table 1.3). A substantial proportion of jurisdictions reported having a written policy for who informs parents about the necessity for confirmatory procedures, in case of a positive screening test (25 of 36 responders, RP-NBS chapter 8.6). The retention of residual blood spots was reported to be governed by policy or laws by 18 of 32 responders, including 1 country with regional variation (RP-NBS chapter 7.1). Notably, written policy is uncommon for disclosure of carrier status (8 of 36 responders including 1 country with regional variation) and disclosure of mild forms of disease (7 of 35 responders including 1 country with regional variation, RP-NBS chapter 8.6). Only Germany, UK and some regions in Italy and Romania reported the existence of written policy on reporting unintentional findings (RP-NBS chapter 8.6).

1.7 Number of screening laboratories

The number of screening laboratories ranges reaches from 1 to 40 per country. Liechtenstein does not have its own screening laboratory and is assisted by Switzerland. Albania does not perform neonatal screening, Turkey and Kosovo did not respond to the questionnaire. The number of births per screening lab and year was averaged for each responding jurisdiction. It ranges from 2,050 (Malta) to 112,000 (Greece) (median 33,500). More information on this topic can be found in RP-NBS chapter 8.1.

2 Criteria for the selection of screened conditions

The increasing possibilities for neonatal screening need to be evaluated to weigh advantages and disadvantages. Already in 1968 Wilson and Jungner² developed a framework for the World Health Organisation to help decide when a screening program would have more advantages than disadvantages.

2.1 Deliberations used when deciding on the current set of screened conditions

The results from the survey show that Wilson and Jungner criteria are still being deliberated in most countries (23 out of 35 responding jurisdictions) when deciding on the set of conditions to screen for in newborns. In addition, most jurisdictions (22 out of 35) also take guidelines of scientific societies in consideration (which in turn might be based on Wilson and Jungner criteria as well, but this was not asked). Most responding countries (22 out of 35) based their current set of screened conditions also on literature surveys (22) and/or national scientific research (17). As one country stated, sometimes primarily the possibilities (e.g. costs and resources) of the country have to be considered.

2.2 Arguments used in expansion of the set of conditions

For inclusion of specific conditions in the national neonatal screening program most countries used epidemiological evidence or economics as the strongest arguments (both arguments were used in 18 of the 22 jurisdictions where they said to have had changes in their national program in the last five years). More than half of the jurisdictions (14 out of 22) also used ethical arguments in the decision on which conditions to include in the set of screened conditions.

2.3 Arguments used for exclusion of conditions

Arguments used to exclude conditions were mainly economic (in 10 out of 15 jurisdictions), but also (lack of) epidemiological evidence (9 out of 15) and/or ethics (7 out of 15).

3 Costs and resources

Since neonatal screening is a highly complex system, as outlined in Figure 1 on page 5, its costs need to be considered in components.

3.1 Costs and resources for the NBS programs

Most jurisdictions (26 of 33) reported that neonatal screening is financed through state or regional public funds. Screening was also reported to be supported wholly or supplementally from social insurances (6 of 33 cases) or funds of the hosting structure or hospital (7 of 33 cases). Annual costs reported for national neonatal screening programs range from € 70,000.- (FYROM; 24,000 annual births, screening for 1 condition) to € 15,000,000.- (the Netherlands; 185,000 annual births, screening for 17 conditions). In percentage of gross domestic product (GDP) based on purchasing-power-parity (PPP) this ranges from 0.00021% (Romania) to 0.00323% (the Netherlands).

3.2 Costs of disseminating information about NBS

Costs of disseminating information reported ranged between € 0.013(Serbia) and € 0.541 (the Netherlands) per newborn in the population.

3.3 Costs of screening per newborn

Costs of the screening procedure reported range from € 0.46 per newborn (Serbia; screening for 2 conditions) to € 43.24 (the Netherlands; screening for 17 conditions).

3.4 Costs of confirmatory procedure

The direct health costs of confirming or rejecting a positive screening result depend on the type of condition. Briefly, costs were calculated to range between € 182,- (for UDP-galactose-4-epimerase deficiency) and € 2,439,- (for organic acidurias). Costs of the confirmatory procedure are shown in detail in RP-NBS (chapter 10, Table 10.6, page 81).

² Wilson JMG, Jungner G (1968). The principles and practice of screening for disease. Public Health Papers n. 34. Geneva: World Health Organization. (p 11)
(retrieved from http://whqlibdoc.who.int/php/WHO_PHP_34.pdf; 15. November 2010)

C.2 Operation of the newborn screening system

4 Information to prospective parents

In the majority of countries participation in the neonatal screening program is based on informed consent or dissent (see chapter 5). Therefore, prospective parents need to be informed about the program and its consequences for them and their child. Information to prospective parents and the public can be disseminated at different times and in different ways.

4.1 National NBS websites and when information is given to prospective parents

In more than half of the responding jurisdictions (19 out of 35) there is a website where anyone can get information about the neonatal screening program, while the other half does not have a website. About seventeen percent (6 out of 35) of the responding jurisdictions do not actively inform prospective parents, while 29 (of the 35) do. Almost half of the jurisdictions informing prospective parents (13 of the 29) do this only after birth at the time of blood sampling. No country specifically informs prospective parents in the first or second trimester of the pregnancy. Most others do this at any time during pregnancy and some specifically in the third trimester of the pregnancy. Prospective parents are informed at two or even three time points in about 40% (12 out of 29) of the programs informing parents.

4.2 Information material for communication to public and prospective parents

The minority of the responding countries (10 out of 34) disseminate information material to the general public. From the ten countries doing so, at least one was referring to the website that was in place for this (the Netherlands). It is not clear from this survey in what other ways the general public is informed about neonatal screening, but this could include e.g. television or radio broadcastings and publications in newspapers or magazines. Prospective parents receive information material about the neonatal screening program in 20 of the 35 responding jurisdictions. In most cases this material is prepared by the screening laboratories (in 15 countries) and/or health authorities (in 11 countries), but sometimes also by scientific societies (in 5 countries) and/or with participation of patient groups (in 3 countries).

4.3 Guidelines on how professionals should inform the public and/or prospective parents

Guidelines on how professionals should inform the public and/or prospective parents exist in 10 of the 25 responding jurisdictions. Some of them do not have official documents, but for example only have educational material for the professionals who are giving the information. In none of the answers was reference made to information from other countries or international sources.

5 Informed consent

Since most governments are convinced of the benefits of their neonatal screening program, countries strive for maximum uptake. As seen in the governance chapter (chapter 1), about half of the countries mandate participation in the program. Often however, parents are not obliged to use it, based on the ethical principle of autonomy. Different solutions have been chosen to let parents decide whether they want their baby to be screened. Some countries have an opt-out system, which entails that parents will have their child screened unless they specifically state that they do not want this to happen. Another solution is the opt-in procedure, where parents are specifically asked to agree to have their baby tested. Similar strategies can be chosen when asking parents' consent for storage of the blood sample and usage of the material for research purposes.

5.1 Informed consent and opt-out possibilities

Seventeen of the 37 responding jurisdictions report that they (or some of their sub-jurisdictions) do not ask for informed consent (or dissent) from parents before the blood sampling (see RP-NBS table 5.1). Some of them report that they do have the possibility to opt-out from screening (5 out of 17). Seven jurisdictions said neither to have informed consent nor to allow opting out. Twenty of the 37 responding jurisdictions report asking for informed consent (or dissent) (in at least some of their sub-jurisdictions). Seventeen of them also have the possibility to opt out. Spain reported to ask for informed consent, but nevertheless does not allow opting out. Mandatory participation is discussed in chapter 1.1.

5.2 Informed consent concerning storage of samples and research

In almost half of the responding jurisdictions (16 out of 33) parents are informed about the fact that bloodspots are retained (see RP-NBS table 5.2). Samples are stored for different periods of time, ranging from 1 year or less in France, Germany, Hungary, Poland and some regions in Italy to “1000” years in Denmark, Norway, Sweden and some regions in Spain. Ten of the regions where parents are said not to be informed about the retention of the bloodspots reported that they have the possibility to opt out of this procedure. Taken together, in 24 of the 27 responding jurisdictions parents have the option to refuse that their baby’s blood sample be stored. In addition in 25 out of the 27 responding jurisdictions parents can opt out of the residual materials being used for research purposes.

6 Blood spot sampling

Taking a blood sample from a newborn infant is not straightforward and easy. Almost all programs are using a heel prick procedure, some use hand dorsal vein puncture. The performing person has to have ample experience, some programs demanding a continued education certificate. The interval between birth and sampling may influence the screening results because of physiological variations of the selected markers in the blood. The dried blood spot specimen has to be transferred to the screening laboratory and it is essential that the conditions are chosen such as to prevent deterioration of the sample quality (short interval, medium temperature and humidity). Details about transport are given in RP-NBS, table 8.4 and discussed in chapter 8.

6.1 Guidelines for sampling procedure

In 31 out of 36 countries a formal guideline for the sampling procedure is available, however, not in Bosnia-Herzegovina and Italy (nor in Finland and Malta because of cord blood sampling) (see RP-NBS table 6.1). In Belgium French Community screening centres have their own guidelines. In about half the countries these guidelines have been developed by health authorities and in the other half by professional groups, either locally or nationally. A number of these guidelines are available on the internet.

6.2 Location of sampling and profession of sampler

In all countries (except Iceland where sampling is the responsibility of midwives) sampling can take place in the hospital and in private clinics if available, usually by a nurse or a laboratory technician. In certain countries sampling can also be done at home by either the family physician (9 countries) and/or midwives (21 countries) (see RP-NBS table 6.1). From this survey there is no evidence for a relationship between the time and the location of sampling.

6.3 Training of personnel concerning sampling

In 21 countries guidelines for the training of personnel concerning bloodspot sampling exist. These guidelines have been developed by health agencies (9 countries), professional societies (7 countries) and/or by the local director (9 countries) (see RP-NBS table 6.2). In 14 countries no such guidelines exist (including Finland and Malta because of cord blood sampling).

6.4 Interval between birth and sampling

Finland and Malta use cord blood samples, taken immediately after birth. In only three countries (Austria, Croatia, and Germany), samples may be taken before 48 h. In Croatia then a second sample is requested between 4 and 7 days after birth. However, in Croatia usually sampling takes place between 48 and 168 h and in Austria sampling is recommended between 36-72 h. Five countries recommend sampling before 72 h but none earlier than 48 h; 15 countries between 48 and 96 h, 1 country recommends between 48 and 168 h but the sooner the better, 7 countries between 72 and 120 h, 5 countries between 4-7 days (approximately between 96 and 168 h). One country recommends sampling between 72 and 96 h.

In 25 countries the blood sample is taken before the infant leaves the hospital, in 4 countries the recommended time of sampling is adhered to (see RP-NBS table 6.3). In some countries, e.g. the Netherlands and the UK, for economical reasons the heel blood sampling is combined with neonatal hearing screening or other screening tests. There is evidence to

indicate that hearing screening cannot be carried out earlier than 96 h after birth. That poses a problem for earlier blood sampling.

7 Blood spot storage

Blood spot storage nowadays is in the centre of public interest, mainly for legal and ethical reasons. Some countries have legislation or codes of practice. Most of the legal and ethical questions surrounding retention of residual neonatal screening specimens have been reviewed in depth elsewhere and will not be revisited in detail here³. An operationally important point is to discriminate between storage allowing repeating screening analyses and storage for research and other purposes. The potential interest for research and the possible use of residual NBS specimens has increased the need for regulation of certain aspects of specimen storage and access policies for both ethical and legal reasons. In the present survey we have collected data which may be relevant to the legal and ethical aspects associated with blood spot storage and, ultimately, to the development of NBS policies.

7.1 Purposes of storage

All countries retain the left over blood spots. The purpose is often indicated as quality control, later confirmation of a screening result, research studies, legal purposes or a combination. Most countries have developed a policy that for scientific research purposes an ethical approval is necessary (see RP-NBS table 7.1).

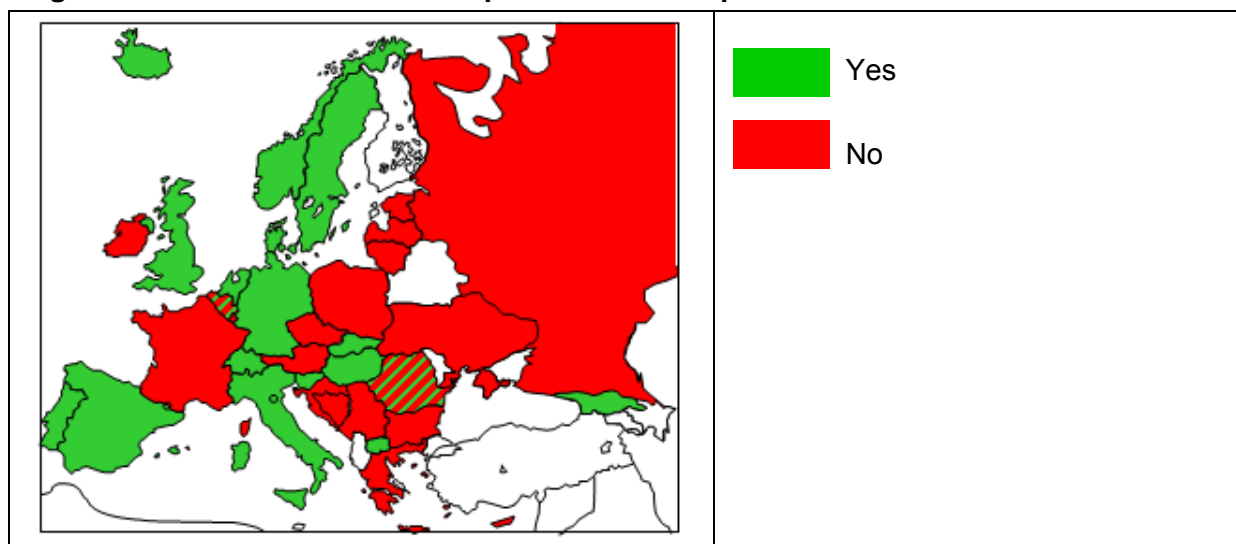
7.2 Informed consent and opting out

About half of the countries inform the parents about storage of the blood spots (Figure 3), but the majority provides an opt out possibility whether or not for the use for scientific research (see RP-NBS table 7.2).

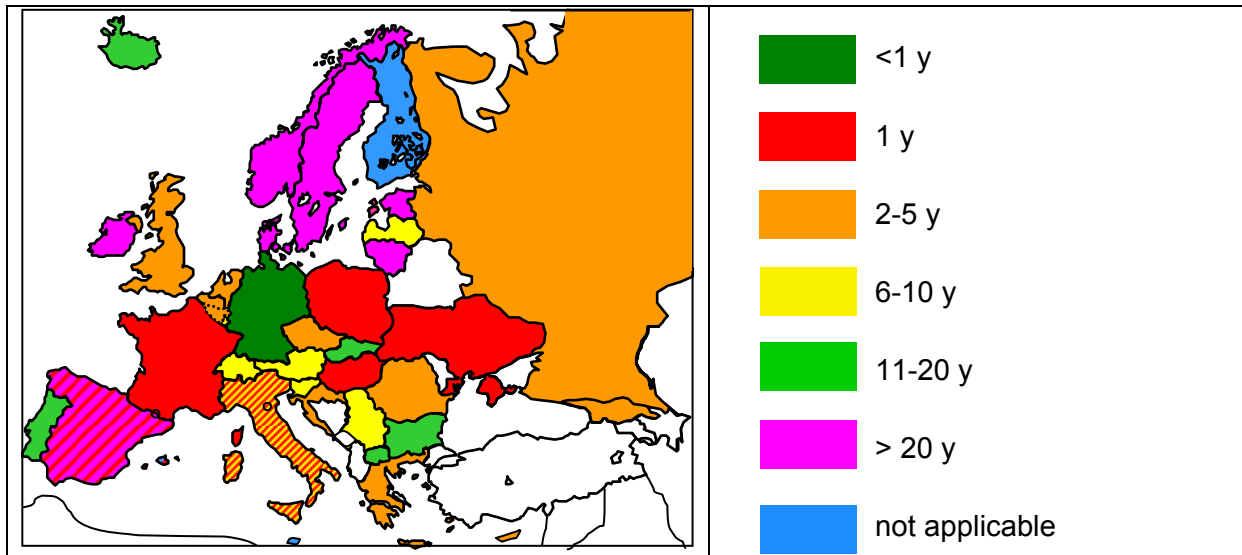
7.3 Length and conditions of storage

The indicated duration of the blood spot storage ranges from 3 months in Germany to “1000” years in Denmark and Sweden (Figure 4, and RP-NBS table 7.3). Irrespective of duration, most common practice is to store samples at room temperature; the use of a desiccant (or of environmental humidity control) is indicated only by few respondents.

Figure 3 Information on bloodspot-retention for parents



³ McEwen JE, Reilly PR. Stored Guthrie cards as DNA banks. *Am J Hum Genet*. 1994;55:196-200.

Figure 4 Length of storage

8 Laboratory procedures

The success of the NBS program is largely dependent on the quality of the screening laboratory and its procedures. Quality is assessed by a number of factors. Being accredited by some third party accreditation body provides a general notion of the quality of the laboratory procedures. The actual screening test performance is checked at least to a large extent by participation in one or more external quality assessment schemes. Other important factors are the turn over time of the sample processing (the shorter the better) and the number of specimens analysed per day/week/month/year (some minimum number per unit time is needed both to ensure sufficient experience and for economic reasons). It is common practice that the residual blood spots are stored for some time and for different purposes. They are indeed a precious material for evaluating and improving the screening test quality.

For each condition it is important to check whether the right marker(s) has/have been selected as well as the cut off limits of the measured concentrations which form the basis for referral for confirmatory diagnostics and possible follow up. With the current methodologies which allow measuring many markers with one assay, the possibility exists to observe findings which are not in the scope of the screening program. Therefore, the quality of the screening laboratory depends also on the way the results are logged and reported to the responsible person/body that is next in the sequence within the NBS program.

8.1 Number of screening laboratories and number of samples screened

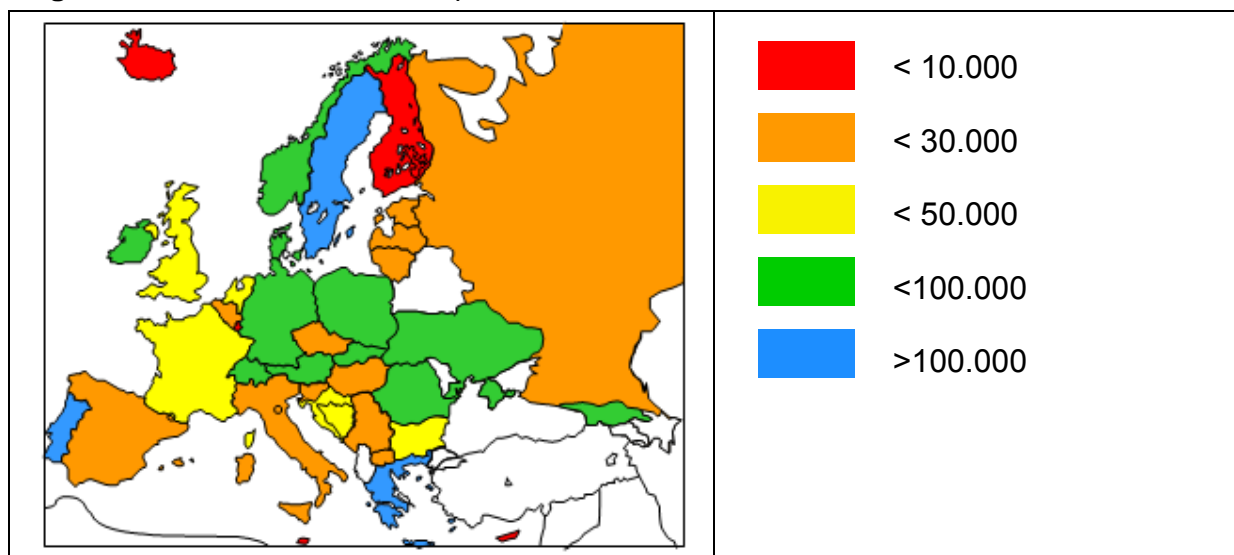
The number of laboratories per country varies tremendously both in absolute numbers as in relation to the number of screened infants (Figure 5 and RP-NBS table 8.1). In Europe each country, except Liechtenstein, has at least one laboratory even if the number of infants born in that country is very low. It is understandable that the larger countries have more laboratories, often because of historical reasons. Spain has decentralised its health care including neonatal screening to 20 autonomous regions, therefore 20 independent laboratories.

The situation in Italy is more complicated. Not only has each Italian region its own laboratory; some regions have more than one laboratory, each screening for just one or a handful of conditions. In the UK Scotland and Wales each has 1 laboratory whereas England has 14. In Germany in the last decade there has been a steady decrease in the number of laboratories. In France at present there are 22 labs, but the introduction of ms/ms technology will probably result in a decrease down to 10-15 labs in the near future. The actual number of samples screened per laboratory often varies within the country. The average annual number of screened samples per laboratory per country varies from 2050 (Malta) to 120852 (Greece).

In order to have high quality expanded screening, literature indicates that the laboratory workflow should be at least 30.000 samples/year. In some guidelines an average of around 40.000 to 50.000 screened infants per laboratory per year has been mentioned or even

mandated⁴. In this survey 21 countries have an average of less than 40.000, and 17 countries even less than 30.000 screened infants per lab. Some of these countries have more than 1 screening laboratory (i.e. Malta, Finland, Italy, Czech Republic, Spain, Belgium Flemish community, Belgium French community and Serbia). A reorganization of the analytical support to the neonatal screening system might be necessary before undertaking the expanded screening. Belgium Flemish community recently started a discussion to reduce the number to 1 or maximum 2 laboratories.

Figure 5 Number of newborns per lab



8.2 Accreditation/Certification

In 17 countries the laboratories have no form of accreditation or even certification (see RP-NBS table 8.2). In 10 countries the laboratories are accredited formally against the standard ISO 15189 or ISO 17025 (Denmark). In 6 countries, laboratories have an ISO 9001 certificate, but it is uncertain if all laboratories have been enrolled. In 3 countries another official form of recognition is in place.

8.3 External Quality Assessment (EQA)

According to the responses all programs, except in Bosnia-Herzegovina, participate in one or more EQA schemes or monitoring systems (see RP-NBS table 8.3). The way of organisation and the validity of these EQA schemes is not always clear. Ideally they should be organised according to ISO 17043, but this is rarely the case.

8.4 Interval between sampling and analysis

The responses indicate a variation between 1 and 15 days between the moment of sampling and the start of analysis in the screening laboratory (see RP-NBS table 8.4). For 35 reporting countries the median of the indicated maximum time is 3 days. Thirty countries perform the analysis within 7 days from sampling. In 10 countries sample cards are transported by normal mail (Ireland: registered mail), in 19 countries there is both transport by normal mail and courier service, in 4 countries only courier service. In 5 countries there are additional ways of transport, e.g. through parents or midwives. In Finland and Malta where cord blood samples are taken the way of transport is different altogether.

There seems to be no relationship between way of transport and its duration. Countries should consider taking measures to shorten this period as much as technically feasible, in

⁴ For example 50.000 samples are required in Germany; Richtlinien des Bundesausschusses der Ärzte und Krankenkassen über die Früherkennung von Krankheiten bei Kindern bis zur Vollendung des 6. Lebensjahres („Kinder-Richtlinien“), 2011; Bundesanzeiger 2011; Nr. 40: S. 1013

view of possible deterioration of the sample quality as well as the unfavourable length of obtaining a screening result.

8.5 Panel of screened conditions

There are a number of different observations to be made. All countries that responded to the survey screen for congenital hypothyroidism (Table 2, page 9 this summary and RP-NBS table 8.5). Albania did not reply because there is currently no screening at all. All countries screen for hyperphenylalaninemia/phenylketonuria, except Finland (because of a too low prevalence) and Malta. In addition, Finland and Malta screen by using cord blood. If there would be an extension to their programs with metabolic conditions they would have to change to heel prick samples because cord blood is then not suitable.

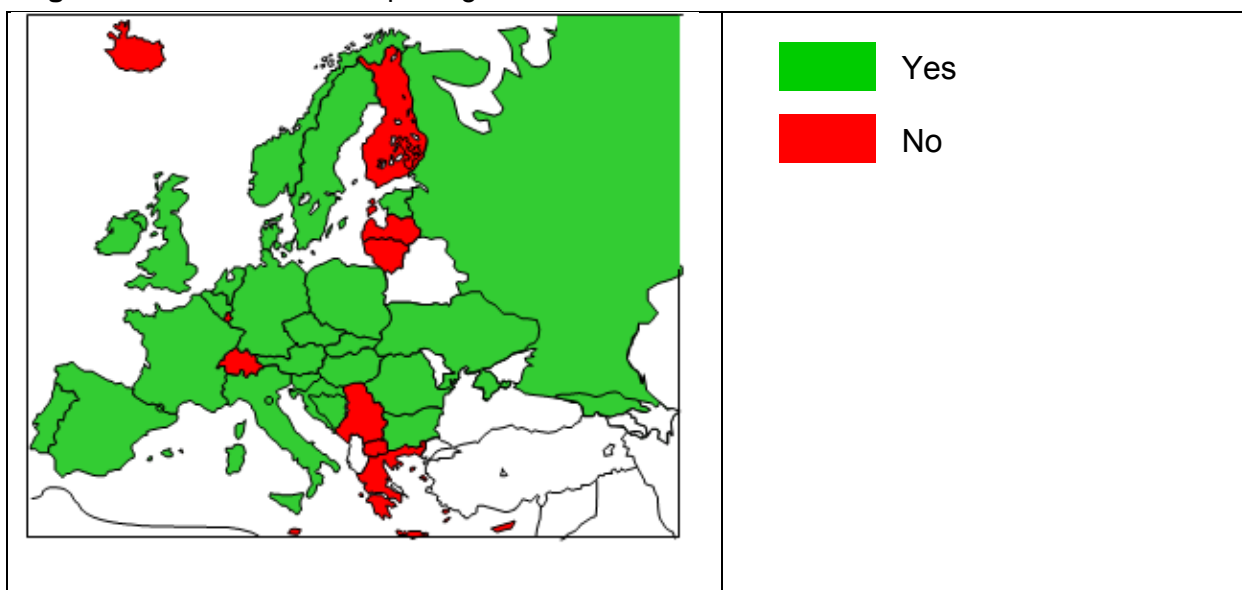
A small number of countries use the ms/ms technology to screen for virtually all conditions possible (Austria, Iceland, (parts of) Italy, Hungary, Portugal, and Spain). Overall there seems to be no consensus among the countries what to screen for or not, every country has made a selection more or less on its own weighing of literature evidence. For some conditions, literature indicates a North-South or East-West gradient in prevalence but that is not reflected in the different screening panels of the countries.

8.6 Reporting of screening laboratory results

A written guideline or policy how to report screening results to the program manager, steering committee or whatever other administrative body is responsible is available in 25 countries, and not available in 10 countries (Figure 6 and RP-NBS table 8.6). A guideline is not strictly needed but to prevent misunderstandings, possible leading to missed infants, it is advisable to have one. Only Germany, The Netherlands, and the UK reported a policy how to deal with unintentional findings, e.g. conditions that are not part of the screening program. This is striking because in certain cases it will occur, e.g. MADD (multiple acyl CoA dehydrogenase deficiency) sometimes is picked up in the screening for MCADD. Unintentional findings are difficult to pin down in definitions and, therefore, it is difficult to develop a clear cut policy. However, unintentional findings are a source of discussions and unrest with the parents because they are confronted with something unexpected.

A policy for reporting carrier status is established in 6 countries, not in 27 other countries, whereas there are regional differences in 2 countries (Italy, Romania). A policy for reporting mild forms of disease is available in 8 countries, not in 25 other countries, whereas there are regional differences in Italy and Romania.

Figure 6 Guidelines for reporting results



9 Test methodology

Screening panels vary very much among countries (see table 2). If the prevalence of a condition is very low it may not be considered to be part of the screening panel. On the other hand some countries have included conditions with a very low prevalence. For certain conditions there is general agreement as to methodology and related aspects, e.g. immunochemical assays for CH, CAH and CF, ms/ms technology for amino acidemias, fatty acid oxidation disorders and organic acidurias. However, the panel of conditions or cost considerations may cause that other techniques are still in use, e.g. the bacterial inhibition assay or enzymatic/fluorimetric assay for HPA/PKU (see RP-NBS table 8.5).

Cut off limits using the same methodology vary (see RP-NBS table 9.1). It is not clear how these have been selected. Ideally these are based on minimizing the number of false-positive and false-negative cases. It is essential that the clinical outcome is fed back to the screening laboratory and that regular evaluation of the appropriateness of cut off values and, if necessary, their correction is carried out. Prevalences of screen-positive results are not discussed in the summary, but can be found in RP-NBS table 9.2.

9.1. Hyperphenylalaninemia-Phenylketonuria

General

Hyperphenylalaninemia (HPA) or actually its more severe form phenylketonuria (PKU) is screened for in 32 countries; not in Finland, FYROM, Malta and Montenegro (see table 2). Neonatal screening started in the '60s with this disorder in view of its long-term consequences for mental development. The screening paradigm is based on the measurement of the concentration of phenylalanine, sometimes combined with that of tyrosine.

Methodology

The first developed method for HPA-PKU screening was the bacterial inhibition assay, which is still in use in 2 programs. This method is cheap but not very sensitive. Next generation methods were based on either colorimetric or fluorimetric endpoints, reported to be in use in 13 programs. Since the 1990's HPA-PKU is screened for more and more using ms/ms technology with the advantage of simultaneous measurement of a large number of markers for a series of metabolic conditions. In this survey, 19 programs were reported to screen for this disorder using ms/ms.

Cut off limits

The reported cut off limits vary largely between 103 and 250 $\mu\text{mol/L}$. This range can be explained by the fact that the time of blood sampling and the methodology has changed over time (see above) and has become more sensitive, but without the corresponding changes in cut off limits, which may result in a number of missed cases. Nine programs still use the old-fashioned unit of measurement of mg% instead of SI units. For reasons of comparability these have been converted to SI units.

9.2. (Primary) Congenital hypothyroidism

General

Primary congenital hypothyroidism (CH) is the only condition that is screened for in all 36 countries (see table 2). The primary marker is the pituitary hormone thyrotropin (TSH). As a secondary marker in the screening phase sometimes thyroxine (T4) is measured. Only in the Netherlands the reverse is true: T4 is used as the primary marker, followed by TSH in the samples with the 20% lowest T4-concentrations. This is to be able to detect cases of central (or secondary) CH.

Methodology

In 25 countries TSH is measured by either radioimmunoassay or nowadays more often the (auto)delfia methodology. In 5 countries an ELISA method is used and in 6 countries another, not specified method.

Cut off limits

There is a large variation in the cut off limits in the various countries, ranging from 6 up to 35 mIU/L blood. In most countries one cut off limit is used, but not in Italy and Romania. A lower cut off limit often leads to more screen positive results and a larger number of referred children. The benefit of detecting more and often milder cases has to be weighed against the higher cost of the diagnostic confirmatory process.

9.3. Congenital adrenal hyperplasia

General

Congenital adrenal hyperplasia (CAH) is screened for in 15 countries (see table 2). In view of the short asymptomatic period after birth it is essential to keep the interval between birth and screening (birth-sampling, sampling-analysis) as short as possible. Countries considering including CAH in their screening panel should be aware of this. Screening for CAH is based on the measurement of the steroid 17-hydroxyprogesterone (17-OHP).

Methodology

In 13 countries 17-OHP is measured by either radioimmunoassay or nowadays more often the (auto)delfia methodology. In 2 countries an ELISA method is used.

Cut off limits

The reported cut off limits vary between 15 and 60 nmol/L blood. It is well known that blood concentrations of 17-OHP vary with the gestational age. To optimise the screening system for CAH in preterm newborns, gestational age-related cut off limits are advised.

9.4. Cystic fibrosis

General

Cystic fibrosis is screened for in 8 countries. The primary marker is immunoreactive trypsinogen (IRT). In most current programs the second step is DNA mutation analysis using a panel of the 36 most abundant mutations. However, in the last few years attention has shifted to a second biochemical marker, pancreatitis-associated protein (PAP). It is expected that in the next decade the CF-screening will be based on a combination of these markers.

Methodology

In 6 countries IRT is measured by either radioimmunoassay or nowadays more often the (auto)delfia methodology. In 2 countries an ELISA method is used. As second step DNA mutation analysis is customary.

Cut off limits

Seven of the 8 programs carried out in EU reported their cut off limits, varying from 50-100 mg/L and in the UK the 99,5 percentile of normal IRT.

9.5. Biotinidase deficiency

General

Biotinidase deficiency is screened for in 10 countries (see table 2). The primary marker is the enzymatic activity itself. A problem with this condition is the fact that a large number of detected cases suffer from partial enzyme deficiency. It is not yet clear at what residual enzyme activity clinical treatment and follow-up is necessary.

Methodology

In all 10 countries biotinidase deficiency is measured by a relatively simple enzymatic reaction with a colorimetric endpoint. Instead of concentrations the results usually are expressed as a percentage of the daily mean of all samples.

Cut off limits

Six of the 10 programs reported their cut off limits, varying from 2.7-50%.

9.6. Galactosemia

General

Galactosemia is screened for in 10 countries (see table 2). In view of the short period after birth without clinical symptoms it is essential to keep the interval between birth and screening (birth-sampling, sampling-analysis) as short as possible. Countries considering to include galactosemia in their screening panel should be aware of this. Most screenings paradigms are based either on the measurement of the concentration of total galactose (TGAL) or on the activity of the enzyme galactose-1-phosphate uridyltransferase (GALT); sometimes a combination of these two is applied.

Methodology

Total galactose can be determined either by an enzymatic-colorimetric method or, traditionally, by the bacterial inhibition assay. GALT can be measured by its own activity with a colorimetric endpoint.

Cut off limits

Reported cut off limits are difficult to interpret because it is not clear if they refer to the measurement of TGAL or GALT.

9.7. Medium chain acyl CoA dehydrogenase deficiency (MCADD)

General

MCADD is screened for in 13 countries (see table 2). Historically, MCADD provided the impetus to implement ms/ms technology in the neonatal screening field since there was no suitable alternative method. The screening paradigm is based on the measurement of the concentration of octanoylcarnitine (C8), sometimes combined with that of decanoylcarnitine (C10).

Methodology

Tandem mass spectrometry is the only method available for the measurement of acylcarnitines, like MCADD. However, simultaneously a series of other acylcarnitines can be measured (LCHADD, VLCADD, CPT I, CPT II, etc.).

Cut off limits

The reported cut off limits vary largely between 0.35 and 0.5 $\mu\text{mol/L}$. Some programs use the ratio C8/C10 as an additional marker.

9.8. Amino acidemias

General

Besides Hyperphenylalaninemia/Phenylketonuria a range of other amino acidemias are screened for using ms/ms technology, such as Argininemia, Argininosuccinic aciduria, Citrullinemia, type I and type II, Homocystinuria, Hypermethionemias type I, III, Maple syrup urine disease and Tyrosinemias type I-III. Although every condition has its own merits to be included in the screening panel, usually the prevalence is too low to set up a screening system for that individual condition. The availability of a common technology has simplified the matter.

Methodology

Ms/ms technology.

Cut off limits

The reported cut off limits vary for all conditions per country, usually as a choice of the individual program manager. In view of the low number of positive cases it is difficult to establish appropriate cut off limits. International collaboration within the US Region 4 ms/ms data project may prove to provide a solution for this problem.

9.9. Fatty acid oxidation disorders

General

Besides Medium chain acyl CoA dehydrogenase deficiency a range of other fatty acid oxidation disorders are screened for using ms/ms technology, such as Very long chain acyl CoA dehydrogenase deficiency (VLCADD), Long chain hydroxyl acyl CoA dehydrogenase deficiency (LCHADD), Short chain acyl CoA dehydrogenase deficiency (SCADD), Carnitinpalmityltransferase type I and II deficiencies and Carnitine uptake defect (CUD). Although every condition has its own merits to be included in the screening panel, usually the prevalence is too low to set up a screening system for that individual condition. The availability of a common technology has simplified the matter.

Methodology

Ms/ms technology.

Cut off limits

The reported cut off limits vary for all conditions per country, usually as a choice of the individual program manager. In view of the low number of positive cases it is difficult to establish appropriate cut off limits. International collaboration within the US Region 4 ms/ms data project may prove to provide a solution for this problem.

9.10. Organic acid oxidation disorders

General

This group consists of 3-Hydroxy-3-methylglutaric aciduria (3-HMG), 3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC), Glutaric acidemia types I and II (GA I, II), Holocarboxylase synthetase deficiency (HCSD), Isovaleric acidemia (IVA), Methylmalonic acidemia (MMA),

Propionic acidemia (PA). Although every condition has its own merits to be included in the screening panel, usually the prevalence is too low to set up a screening system for a single condition. The availability of a common technology has simplified the matter.

Methodology

Ms/ms technology.

Cut off limits

The reported cut off limits vary for all conditions per country, usually as a choice of the individual program manager. In view of the low number of positive cases it is difficult to establish appropriate cut off limits. International collaboration within the US Region 4 ms/ms data project may prove to provide a solution for this problem.

9.11. Hemoglobinopathies (HbPs)

General

This group of haematological disorders consists of Sickle Cell Disease (S/S and S/C) and betathalassemia. In Europe, HbPs are prevalent mainly in the Mediterranean countries and elsewhere in some African and Asian countries. Immigration in e.g. the Netherlands and the UK has caused an increase of the prevalence in these countries, making neonatal screening worthwhile. HbP-screening takes place in selected populations and/or parts of France, Malta, Netherlands, Spain and UK, but not in Greece and Italy.

Methodology

As a first step usually HPLC is applied, sometimes followed by DNA-mutation analysis. HPLC separates the different hemoglobine molecules. Retention time is an indicator of the identity of the various hemoglobine types. The relative quantity of each type indicates the phenotype. A drawback of the HPLC method is that also carriers are detected in large numbers.

Cut off limits

In contrast to the other conditions in the neonatal screening panels for HbP's there are no quantitative cut off levels, but a pattern of peaks in HPLC instead.

10 Confirmative diagnostics

A positive result of neonatal screening by definition is not a diagnosis⁵, but it has to be confirmed or rejected by independent methods.

This domain contains 7 questions, 3 dealing with regulations and 4 dealing with actual practice.

The questions aim at 4 aspects related to the structure, process and outcome of the confirmation of diagnoses.

Institutions: confirmation can be executed in specialised centres, local hospitals, GP/Paediatricians, other institutions.

Methods: results are confirmed by metabolites/hormones, enzyme activity, mutation analysis, other methods.

Time: age at start and end of confirmation.

Costs: for inpatient and outpatient care and laboratory analysis

Organisation of data flow is particularly important as it is necessary to improve screening algorithms and cut-off values in the screening lab. Institutions and methods are related to costs and economic efficiency but also to quality of care and timely management. Whereas methods and data flow can be standardised even for all institutions involved, specialised clinical diagnostic services will be particularly necessary when disorders with a risk for neonatal decompensation are screened for.

Screening results are almost always confirmed in specialised centres. Exceptions among the more frequently screened disorders are biotinidase deficiency, galactosemia, congenital hypothyroidism, congenital adrenal hyperplasia and MCADD. These disorders are screened

⁵ Wilson JMG, Jungner G (1968). The principles and practice of screening for disease. Public Health Papers n. 34. Geneva: World Health Organization. (p 11)
(retrieved from http://whqlibdoc.who.int/php/WHO_PHP_34.pdf; 15. November 2010)

in more than 10 countries and are confirmed in at least 15% of the cases in local hospitals.

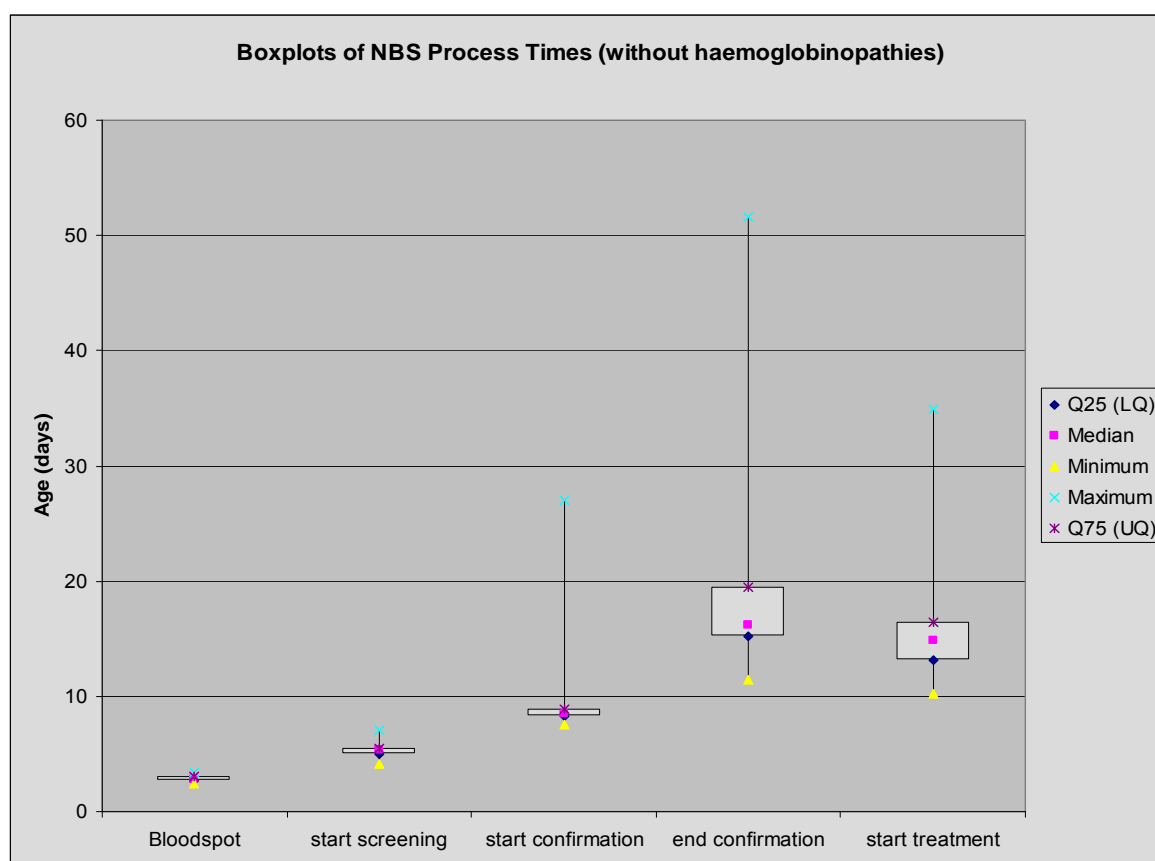
It should be noticed that “specialized centres” is not a well defined concept. Furthermore, as different conditions show quite different profiles of requirements, specification would be necessary for a more accurate evaluation.

Methods of confirmation reported show a complex pattern across the different disorders, possibly also depending on the respondents’ aims of confirmation. For example, in the case of hyperphenylalaninemia mutation analysis might be regarded as necessary to confirm the type of PKU, or residual enzyme activity might be estimated from the results of standardized loading tests with protein or BH₄. What has to be done mainly depends on the ultimate goal of confirmation, e.g. should only the positive screening result be confirmed or should also genetic counselling of the family be prepared? On the average in 61% of the cases mutation analysis is included as a method to confirm screening results.

It would be promising to investigate in a further study which approaches are necessary and sufficient to confirm the different disorders, and to demonstrate whether there would be equifinal strategies.

Figure 7 shows the time sequence of the different steps of the process of confirmation of screening results. Hemoglobinopathies are not included as these disorders do not require intervention in the neonatal period and infancy. On the average 75 % of all positive screened cases are confirmed within 20 days of life.

Figure 7 Boxplots of times of five process steps of neonatal screening programs without haemoglobinopathies (Figure 21.2, page 149 RP-NBS)



Costs for confirmation of a single screening result was calculated as (number of days in hospital * cost per hospital day) + (number of outpatient visits * cost per visit) + laboratory costs + other costs. It should be noted that in a strict meaning the figures represent prices, i.e. amounts of money realised by the provider and not the cost of the provider’s activities. Furthermore, data predominantly have been estimated, and source of data often has not been specified. In order to make data from nations with different gross domestic products and/or purchasing power comparable, raw data from each respondent were expressed as

percent of Gross Domestic Product (GDP) based on purchasing-power-parity (PPP) per capita. Results show that partial and total costs show a large variation between disorders as well between countries screening for the same disorder. On the average confirmation of one screening result costs between 200 € (udp) and 3.000 € (ga II).

Differences between countries only can be compared before the background of more detailed information, for example the screening panel and the number of replies. Whether confirmation of a diagnosis is done on an inpatient or an outpatient basis might depend on the disorder but also on the geographical situation of a country.

Overall the different aspects of confirmation of screening results are most often and predominantly regulated by guidelines (where to confirm: 83% guidelines, 35% directives; how to confirm: 81% guidelines, 23% directives; age when to confirm: 63% guidelines, directives have not been asked for). Regulation of time of start of the confirmatory process is difficult, as this depends on many other factors in previous steps of the screening program.

11 Information and communication to parents

There are several reasons why effective, efficient and successful information and communication are necessary after a positive screening result. Legal and ethical norms require informed consent and some investigations in the course of confirmation require the technical cooperation of parents (from the simple observation of their child to providing parental blood samples for molecular biological analysis).

The domain has 6 questions, 4 dealing with regulations and 2 dealing with actual practice.

The predominant informant of the parents about a positive NBS result is the GP or a paediatrician (80%). For a quarter (24%) of the cases the screening laboratory informs parents first. The preponderant mode of information is a phone call (87%), but also in 50% of the cases information is given in person.

Parents get detailed information already during the first contact (83%). Giving information in a physical setting can be regarded as an important mode, because a personal meeting with a specialist will offer the opportunity for parents to ask specific questions possibly reducing insecurity and anxiety.

Paediatricians (97%), dieticians (69%) and geneticists (65%) are the key persons in teaching parents about diagnosis and treatment. Absence of dieticians in the teaching team for biotinidase deficiency and haemoglobinopathies is reasonable, since these disorders are not treated by a diet.

On the average guidelines how to inform patients are available only in 50% of the cases. This is also true for the more frequently screened disorders (congenital hypothyroidism, hyperphenylalaninemia, congenital adrenal hyperplasia, classic galactosemia, glutaric acidemia type I, MSUD or MCADD).

If there is a guideline, the area of application is national. Material describing how to inform parents, associated with guidelines, is available digitally and in print. Most often material seems to be produced locally, but then applied on a national basis. Across countries at least one (and often multiple) guideline and at least one material for first communication are available for each screened disorder in Europe.

Overall the different aspects of information and communication to parents are less often regulated than laboratory parts, but if they are regulated this is predominantly done by guidelines (how to inform about NBS results: 54% guidelines, directives have not been asked for; who informs about necessity of confirmation: 76% guidelines, 62% directives; how to explain diagnosis: 37% guidelines, directives have not been asked for; professions to be involved in teaching: 34% guidelines, 12% directives). Regulation of time of start of the confirmatory process is difficult, as this depends on many other factors in previous steps of the screening program.

As already has been pointed out by Wilson and Jungner (1968)⁶ in their paragraph "groups to

⁶ Wilson JMG, Jungner G (1968). The principles and practice of screening for disease. Public Health

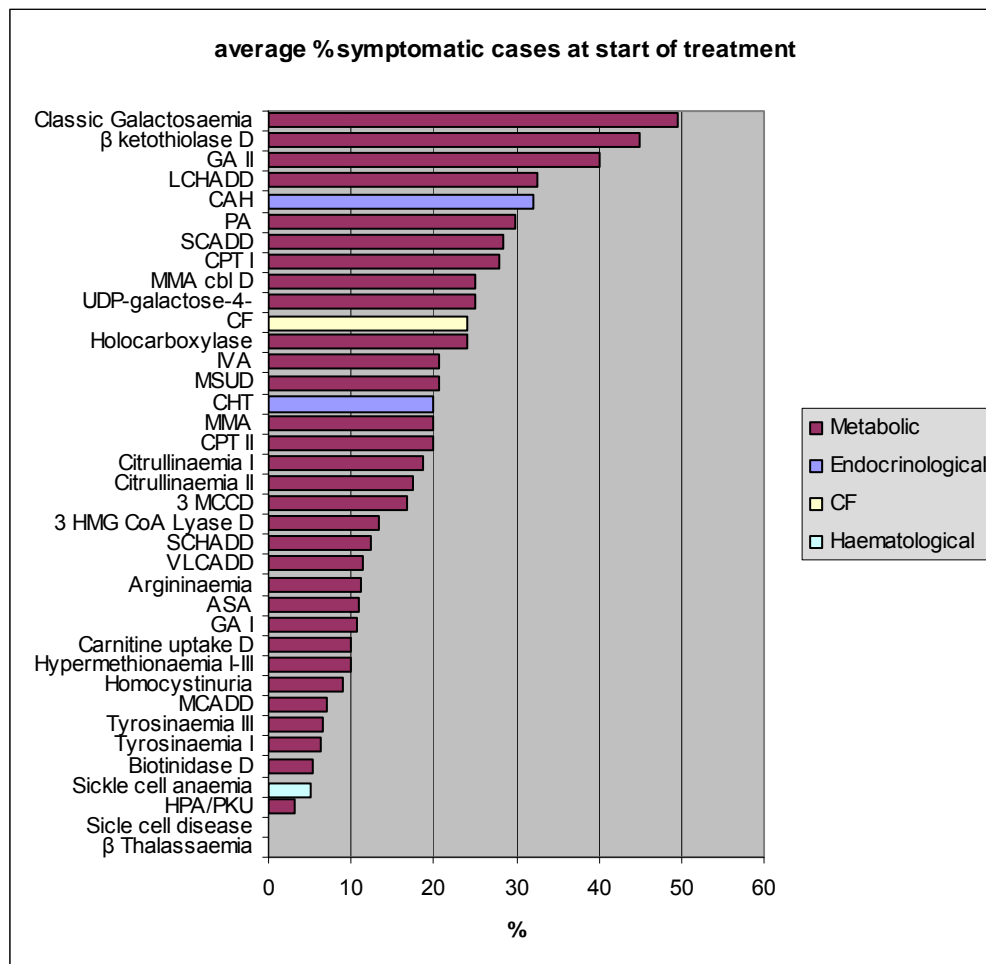
be treated in case-finding” (pp. 34), as there will be many people involved in screening programs there should be clear policies to avoid confusion of those who are screened. Particularly, it would not be appropriate, if professionals who are not directly involved in the procedure would be involved in communication.

12 Treatment

Early start of treatment is an important goal of screening. Structural aspects are type of treatment units (specialised centres, local hospital or paediatricians/GPs) and professionals involved (paediatricians specialised in metabolic, endocrinologic or hematologic disorders, dieticians, psychologists, social workers, clinical nurse specialists, geneticists). In those cases where disorders with a substantial risk for acute neonatal metabolic decompensation are included in a screening panel, age at start of treatment and clinical status at start of treatment (asymptomatic vs. symptomatic) become central parameters of a neonatal screening program. The domain contains 7 questions, 3 dealing with regulations and 4 dealing with actual practice.

Patients are treated almost exclusively (mean=95%; median=98) in specialised centres. Professions involved in the treatment are paediatricians (99%), dieticians (80%), psychologists (46%), clinical nurse specialists (19%), geneticists (17%), and social workers (15%).

Figure 8 Clinical presentation at the start of treatment (data Table 12.8, page 115 RP-NBS)



Overall it is reported that 81% (mean; median=84%) of patients present asymptomatic at the start of treatment. Disorders reported to have relatively high rates of patients presenting

symptomatically at start of treatment are classical galactosemia (galt; 50% symptomatic cases), beta-ketothiolase deficiency (bkt; 45%), glutaric aciduria type II (gall; 40%), Long-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency/Trifunctional protein deficiency (lchadd; 33%), and congenital adrenal hyperplasia (cah; 32%) (Figure 8). It should be noted that 67% of the data are estimated.

Average degree of regulation by guidelines and/or directives of this domain ranks lower than in domain 10 (confirmative diagnosis) but higher than the one of domain 11 (information and communication). This might be due to the fact that more technical steps of the process are better regulated than non-technical steps.

Where to treat is only regulated by guidelines (77%), professions to be involved in treatment is regulated by guidelines in 49% and by directives in 18%. Age at start of treatment is only regulated by guidelines (18%).

C.3 Quality and Quality assurance

13 Monitoring epidemiological evaluation

Epidemiological evaluation is important for NBS programs. Feedback of confirmed diagnoses (and parameters measured in the process of confirmation) to the screening laboratory helps to adjust the screening algorithms, and feedback of results of confirmation to a central registry will allow calculation of prevalence data.⁷

Domain 13 contains 4 questions, 2 dealing with regulations and 2 dealing with actual practice.

On the average feedback of diagnoses is regulated by guidelines in 88% of the disorders and by a directive in 27%. Guidelines are applied on a national level in 68% whereas only 38% of the directives have a national application. Confirmed diagnoses actually are mostly (87%) fed back to the screening laboratory and less often to a registry (19%). Organisation of feedback is predominantly “push”, i.e. the clinical unit of confirmation actively delivers the results to the screening laboratory. If feedback is given, predominantly detailed results are transmitted.

Epidemiological evaluation is relatively seldom regulated by guidelines (15%) or directives (18%). However, in practice on the average data are evaluated for 84% of the cases a disorder is screened for. Main parameters evaluated are prevalence (79%), subtypes of severity (39%) and ethnic origin (28%). If evaluation is done, it is performed in national registries (42%) or on the level of local data bases (50%).

Ranking of the mean regulation of epidemiological evaluation corroborates the interpretation that non-clinical aspects of screening programs are less regulated than the most important clinical process steps of confirmation of positive screening results and treatment.

The high feedback rate of the data of the process of confirmation probably is due to the close temporal and procedural association of laboratories performing neonatal screening and units performing the confirmation. As will be shown in domains 14 (monitoring epidemiology) and 15 (monitoring of outcome) feedback of more distal steps of screening programs was observed to a much lesser extend.

14 Monitoring long- term outcome

Good long-term outcome is the ultimate goal of NBS and its monitoring is necessary evaluate the whole program.⁸

The domain contains 4 questions, 2 dealing with regulations and 2 dealing with actual practice.

⁷ Wilson JMG, Jungner G (1968) *Principles and Practice of Screening for Disease*. Geneva, World Health Organization. Available at http://whqlibdoc.who.int/php/WHO_PHP_34.pdf

⁸ Wilcken B (2011) Newborn screening: how are we travelling, and where should we be going. *J Inherit Metab Dis*. DOI 10.1007/s10545-011-9326-4

Averaged over all disorders data on long-term outcome is evaluated in 80% of the cases a disorder is screened for. Data are reported in 40% of the cases to the diagnostic unit but only in 3% to a registry. A noteworthy exception is cystic fibrosis where 3 out of nine countries (33%) report to have a registry.

Long-term outcome is scarcely monitored on the basis of a guideline (21%) or directive (2%). Feedback of long-term outcome is scarcely regulated by guidelines (31%) and never by a directive.

Calculation of the number needed to screen⁹ measured by the frequency of the prevention of adverse outcomes will be not possible for most actual screening programs. However, data for the long term evaluation of the outcome are actually collected on the local level and exchanged at least partly within local circuits. The development of systems coordinating the collection and exchange of data would be very important to allow the assessment of the procedural¹⁰ and clinical aspects as well as the cost-effectiveness¹¹ of neonatal screening programs.

15 Quality assurance in the confirmative diagnostics stage

Quality Control (QC) is defined by a system of routine checks to assure that predefined requirements of the program are fulfilled. Quality assurance (QA) activities include a planned system of review procedures conducted by personnel not directly involved in the program. The domain has been evaluated regarding the actual practice of AC and QA by 7 items.

1. Laboratory diagnostic procedures for confirmation of NBS result
2. Where diagnostics and treatment is done
3. Documentation of ages at diagnosis and start of treatment
4. Feedback of confirmed NBS result to NBS lab
5. Feedback of confirmed outcome to unit of confirmatory diagnostics
6. Information to parents about diagnosis and treatment

Information to parents about parents & patients groups

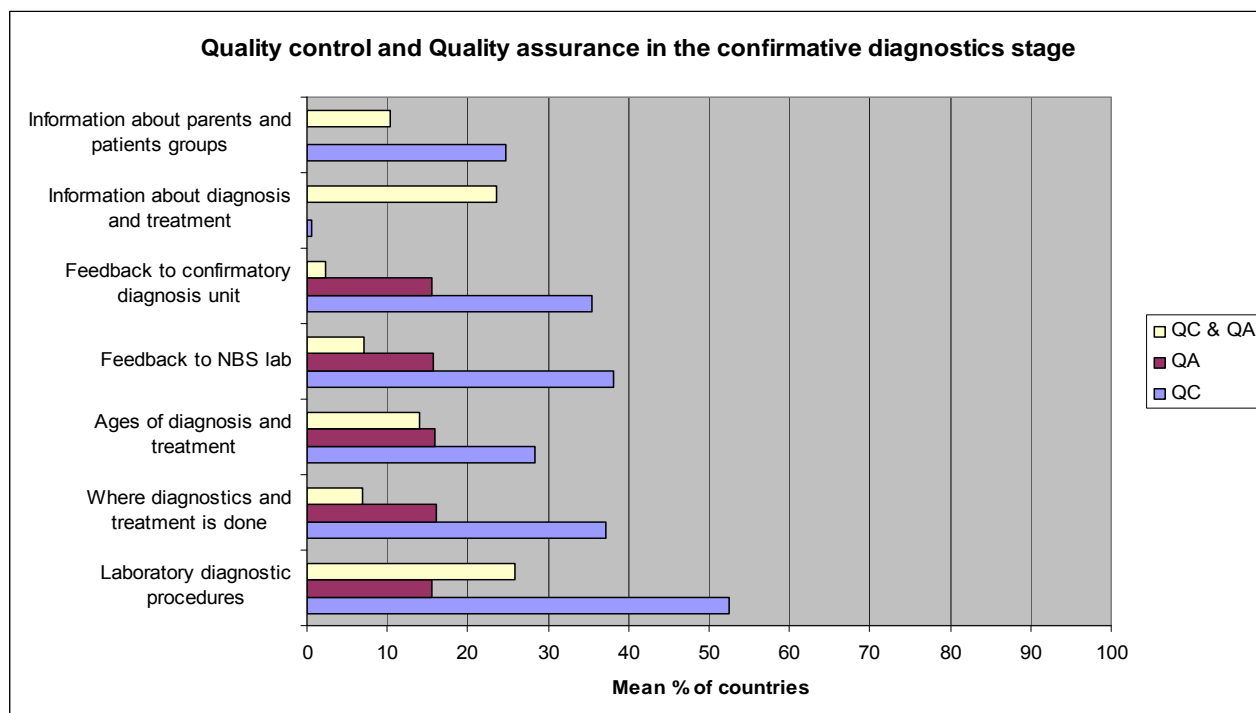
On the average for a screened disorder, activities for systematic assurance of quality are lacking in 40-75% of the countries. In particular, process steps dealing with information show low levels for QC and QA. (Figure 9)

⁹ Rembold CM. Number needed to screen: development of a statistic for disease screening. *BMJ*. 1998; 317: 307-12.

¹⁰ Wilson JMG, Jungner G (1968). The principles and practice of screening for disease. *Public Health Papers* n. 34. Geneva: World Health Organization. (p 11) (retrieved from http://whqlibdoc.who.int/php/WHO_PHP_34.pdf; 15. November 2010), page 26

¹¹ Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S (2004) Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review. *Health Technol Assess* 8(12): iii, 1-121

Figure 9 Mean percentages of countries (averaged over all disorders) with activities of quality control and quality assurance in 7 steps of the process of confirmation of a positive screening result. (RP-NBS, page 130, Figure 15.1)

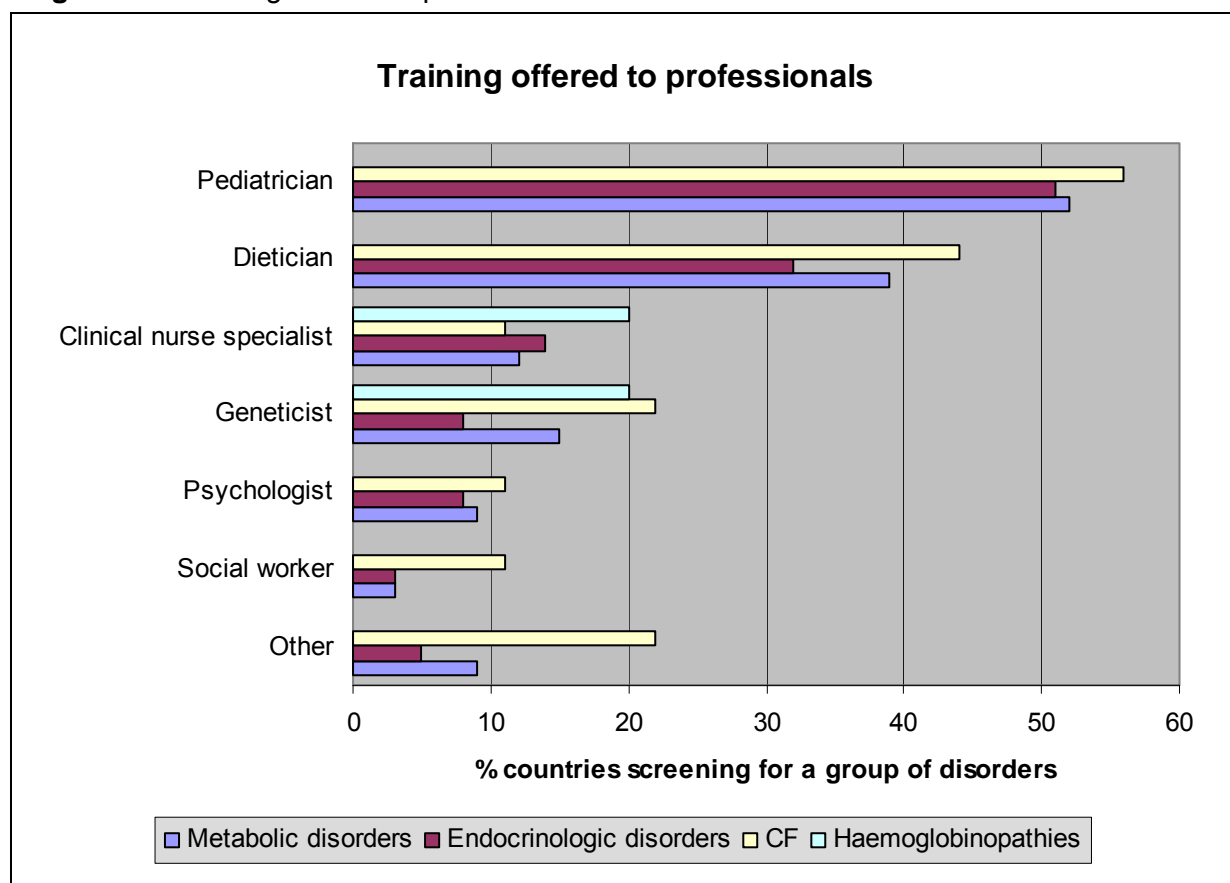


16 Training of professionals

A newborn screening program is high performance medicine, and in each step of a screening program all professionals involved should be well trained. The domain contains 2 questions, 1 dealing with regulations and 1 dealing with actual practice.

Training of professionals is regulated by a guideline in 2% and by a directive in 1% of the cases (RP-NBS Table 16.4). It is most often offered to paediatricians (40%) and dieticians (29%), followed by the geneticist and clinical nurse specialist (16%/14%). Training for psychologists and social workers are rare (8%/4%). Averaging the data for groups of disorders, training is most often offered for cystic fibrosis (25%), followed by metabolic (20%) and endocrinological disorders (17%). For haemoglobinopathies, training is offered only for the clinical nurse specialist and the geneticist.

Figure 10 summarizes the results regarding the different professional groups involved in the confirmation of diagnosis and treatment.

Figure 10 Training offered to professionals

Regulation of training of professionals by guidelines and/or directives is nearly absent in all screening programs, and current practice is relatively low for the most important professions, i.e. paediatricians and dieticians. Education of medical professions has already been a central subject by Wilson and Jungner (1968)¹², who suggested that in the transmission from disease-oriented education to preventive medicine..“ a number of new and special subjects are needed in training for preventive medical services, of which the epidemiological method takes first place, and which should include medical statistics, social sciences, genetics and the organization of health and welfare services.“, and they continue, that “It is important to remember that, in addition to physicians, there are other workers in the practice of medicine in whom more positive attitudes to the early detection and treatment of illness need to be inculcated - for example, nurses, health visitors, chiropodists and pharmacists” (p. 76). Finally, it is not surprising, that the authors of the seminal book had suggested that education should be the task of post-graduate institutes and departments of social medicine (p.146).

C.4 Awareness, support and empowerment

17 Awareness and support

17.1 Political support for NBS

There seems to be political support for neonatal screening in almost all responding countries (except for Lithuania) (RP-NBS, Table 17.2). In most countries political support is represented by public funding of neonatal screening or by a service of the public health system. In none of the answers reference is made to international political support, although reference is made to the national plan for rare diseases by Bulgaria, which is being

¹² Wilson JMG, Jungner G (1968). The principles and practice of screening for disease. Public Health Papers n. 34. Geneva: World Health Organization. (p 11)
(retrieved from http://whqlibdoc.who.int/php/WHO_PHP_34.pdf; 15. November 2010), page 26

stimulated by the EU. It is possible that the role of the EU was overlooked because the present survey was focused on collection of national information.

17.2 Professional societies

There are professional societies for the disorders screened in 24 of the 35 jurisdictions. Some of the mentioned societies are professional societies for metabolic disorders, societies for human or medical genetics, paediatric societies, societies for endocrinology and working groups for neonatal screening. Only one jurisdiction (the Flemish community) refers to international guidance.

17.3 Patient/parents' groups for disorders screened

At least 28 of the 35 responding jurisdictions have patient and/or parent associations for at least some of the screened conditions. Examples of these groups are national PKU-societies, societies of patients and/or parents with cystic fibrosis and organisations for rare diseases.

17.4 Support networks or other resources for genetic or metabolic disorders

More than half of the responding countries (20 out of 34) report having at least one family- or patient support network or other resource for assistance and care of those diagnosed with a genetic or metabolic disorder. The networks reported range from associations for rare disorders in general to societies for metabolic disorders or more specific conditions (e.g. sickle cell anemia, cystic fibrosis and phenylketonuria). Three other countries (Czech Republic, Portugal and Slovakia) reported having specialized medical centres for this purpose.

17.5 To what extent were patient organisations involved in changes in screening programs?

Eighteen jurisdictions which expanded neonatal screening in the last 5 years had advocacy groups specific to screened disorders while 2 did not. Of the 18 which had such advocacy groups, in 10 cases patient groups were involved in the decision to expand neonatal screening. While it is not clear whether these were the disease-specific advocacy groups, it is striking that in 8 cases specific, relevant advocacy groups were not involved in the expansion of screening. However, it may be the case that the disease-specific advocacy groups became active after neonatal screening was expanded.

18 Empowerment

Most screened disorders are not only rare, but also do not fit common concepts of disease and illness. Sometimes rather complicated preventive treatment protocols have to be followed. Providing parents/caretakers with instructive material supplementing and supporting communication aims to improve the effective transmission of information, the understanding of the child's problem, compliance with recommendations, and thereby to improve the outcome. As treatment of disorders screened for in NBS programs has to be executed by parents and not by medical professionals, empowerment of parents regarding understanding and execution of the preventive medicine is a central issue. The domain contains 2 questions aiming at the existence of (print or digital) material which is used in the screening program.

Regulation by guidelines and/or directives has not been asked for regarding the domain. Material to support the first communication of the meaning of consequences of a positive NBS result is less often available (41%) than material explaining treatment (69%).

D. Results across domains

19 Correspondence of guidelines and actual practice

Mean percentages were often higher for actual practice than for the existence of guidelines regulating the practice. In order to investigate the relationship between guidelines and practice we compared the data of four different domains.

1. Regulation (Question E8.1) and practice (Question E8.2) of **feedback of final diagnoses to screening labs or a central registry.**
2. Regulation (Question E17.1) and practice (Question E17.2) to **monitor the long-term outcome of patients identified by NBS.**

3. Regulation (Question E18.1) and practice (Question E18.2) for **feedback of long term outcome to the diagnostic unit.**
4. Regulation (Question E20.1) and practice (Question E20.2) of **epidemiological evaluation of screening programs.**

For each disorder and country 4 different results were possible: (1) the domain could be regulated and have a practice, (2) it could not be regulated but have a practice, (3) it could be regulated without having a practice, and (4) it could neither be regulated nor have a practice. For each disorder the number of countries screening this disorder was counted. In the four columns of table 16 the average percentages across disorders were calculated.

Table 3 Correspondence of guidelines and actual practice (RP-NBS Tables 23.1 to 23.4, pp. 155-158)

	Guideline & practice	No guideline & practice	Guideline & no practice	No guideline & no practice
1. Feedback final diagnoses to screening labs/registry	94%	6%	0%	0%
2. Monitoring long-term outcome	22%	60%	0%	18%
3. Feedback long term outcome to diagnostic unit	27%	16%	4%	53%
4. Epidemiological evaluation of screening programs	25%	60%	1%	14%

Results show that the most proximal process of communication of the confirmatory service with the NBS laboratory is very well regulated and organized. In a substantial number of cases, collection and evaluation of long term outcome and other epidemiological information is in place without being regulated by a guideline. Feedback of long-term outcome to the diagnostic unit or to the screening laboratory was reported less frequently and mostly in association with the existence of a guideline. The limited practice of this communication may be attributed to the number of intervening steps and to the usually long time interval between the two events, but may also be due to data protection regulations, as in general it is not allowed to transmit patient data from treatment units to screening laboratories. Overall the different steps of a NBS program appear to be organised even if there is no regulation by a guideline or a directive.

E. Results across countries

Screening panels across countries are very different regarding the number and the set of disorders screened for. Therefore, comparison between countries will only be meaningful if they are done on the basis of a single disorder. However, screening panels of countries can be compared regarding the degree of regulation of the process steps of the program. Table 17 summarizes the data of all questions aiming at the regulation of different steps in national screening programs. For a more detailed description see tables 10.2, 10.4, 11.2, 11.3, 11.5, 11.6, 12.2, 12.4, 12.6, 13.2, 13.4, 14.2, 14.4, 16.2, in the RP-NBS.

For each disorder 15 questions regarding a regulation (guideline or directive) had been asked. Multiplying the number of disorders screened for by 15 gives the maximum of possible regulation. The reader should be aware that the percentage given in the last column of table 17 is just a rough estimate, as we suppose that each of the 15 regulations is of equal importance. Furthermore a percentage of 50 could express that half of the disorders screened for are completely regulated but also that each disorder is only half regulated. Last not least the questions of the survey have been imposed post hoc to existing screening programs and there might be regulations not covered by the survey.

Table 4 Degree of regulation from confirmation of screening result to start of treatment of national screening panels (maximum of possible regulation is equal to number of disorders screened for multiplied by 15 regulations (guideline or directive) asked for each disorder.

Country	n disorder screened for	% of max possible regulation
Poland	3	91
France	5	85
Croatia	2	80
United Kingdom	7	77
Ireland	5	76
Slovakia	4	75
Bulgaria	3	73
Iceland	26	73
Netherlands	20	70
Sweden	5	69
Hungary	25	67
Romania	2	67
Turkey	3	60
Serbia (Central)	2	60
Denmark	15	53
Montenegro	1	53
Portugal	25	52
Belgium (Flanders)	11	51
Slovenia	2	50
Czech Republic	12	47
Greece	3	47
Lithuania	2	47
Belgium (French)	7	44
Estonia	2	43
Norway	2	43
Malta	3	40
FYROM	1	40
Germany	15	36
Austria	29	35
Cyprus	2	33
Finland	1	33
Italy	2	33
Luxembourg	4	28
Spain	27	24
Bosnia-Herzegovina	3	20
Latvia	2	13
Switzerland/ Liechtenstein	7	1
Albania	0	-
Kosovo	0	-