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Newborn screening programmes in Europe; arguments and efforts regarding harmonization. Part 1 - From blood spot to screening result

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Abstract In many European countries neonatal screening has been introduced over the last 50 years as an important public health programme. Depending on health care structure, available funds, local politics, input from professional groups, parent groups, and the general public this introduction has led to different approaches in the way the screening programmes have been set up, financed and governed. To get some insight about the current situation, in 2009 the European Union, via its EAHC agency, put out a call for a tender that was acquired by our project group. An online survey was compiled in which the whole screening programme was covered by a questionnaire. This survey covered the EU member states, (potential) candidate member states and EFTA countries, in total 40 countries. Results showed little consensus concerning 1. information of parents including informed consent; 2. which conditions are screened for, ranging from 1 to around 30 conditions; 3. sampling time post partum; 4. screening methodology including cut-offs values even between screening laboratories within countries.; 5. storage of residual specimens, varying from 3 months to 1000 years. In addition, confirmatory diagnostics and follow-up also show large discrepancies (Burgard et al. http://www.iss.it/cnmr/prog/cont.php?id=1621&lang=1&tipo=64 2011). In addition to the current practices report an expert opinion document has been produced with recommendations to the EU Commission for future improvements, e.g. in parallel to the way the USA has harmonized its practices based on recommendations by the American College of Medical Genetics (Watson et al., Pediatrics 117: S296-S307, 2006).

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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-thalassaemia
CAH	Congenital adrenal hyperplasia
CF	Cystic fibrosis
CH	Primary congenital hypothyroidism
CITI	Citrullinaemia type I
CITII	Citrullinaemia type II

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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
EAHC	Executive Agency for Health and Consumers
EQA(S)	External Quality Assessment (Scheme)
EUNENBS	European Network of Experts on Newborn Screening
FAOD	Disorders of fatty acid metabolism
FYROM	Former Yugoslavian Republic of Macedonia
GAI	Glutaric acidaemia type I
GAII	Glutaric acidaemia type II
GALT	Classical galactosaemia
HCI	Homocystinuria (CBS deficiency)
HCSD	Holocarboxylase synthetase deficiency
Hemo/ HpB	Haemoglobinopathies
HPLC	High performance liquid chromatography
HPT I III	Hypermethionaemia types I, III
ISO	International Standards Organization
IVA	Isovaleric acidaemia (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 acidaemia
MMACBL	Methylmalonic acidaemia including Cbl A,B C, D defects
MSUD	Maple Syrup Urine Disease
NBS	Neonatal (newborn) Screening
NEQAS	National External Quality Assessment Scheme (UK)
OA	Disorders of organic acid metabolism
PA	Propionic acidaemia
PKU/HPA	Phenylketonuria/Hyperphenylalaninaemia
QA/QC	Quality assurance/Quality control
S-S	S,S disease (Sickle cell anaemia)
SC	S,C disease (Sickle – C disease)
SCADD	Short-chain acyl-CoA dehydrogenase deficiency
SCHADD	Medium-short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
TYRI	Tyrosinaemia type I
TYRII_III	Tyrosinaemia types II III
UDP	UDP-galactose-4-epimerase deficiency
UK	United Kingdom
VLCADD	Very long-chain acyl-CoA dehydrogenase deficiency

Introduction

Neonatal or newborn screening (NBS) programmes using dried blood spots were first developed in the 1960s, inspired by the work of Dr Robert Guthrie. In the early days the whole system was focused on the detection of one or just a couple of disorders ("conditions"). Tremendous technological improvements made it gradually possible to screen for a multitude of conditions almost simultaneously. Increased methodological sensitivity made it possible to perform reliable screening after 48 hours post partum.

By these improved performance characteristics NBS has firmly established its place in the group of cost-efficient public health tools. It has risen above the level of small scale amateur-enthusiasm and in many countries moved into well organised nation-wide long term health care provisions.

In the European Union treaties health care has always been left to the individual member states ("principle of subsidiarity", see Maastricht Treaty Art 129 (1992)). Nevertheless in the last few years the EU has recognised the importance of close collaboration between member states especially in the detection and treatment of cases of rare diseases (less than 1 affected person per 2000 persons). Each member state by itself cannot cope with the multitude of rare diseases in a cost-effective way. This has been laid down in a number of relevant documents (e.g. Communication from the EU Commission (2008), Council Recommendation (2009), Aymé and Rodwell (2011)).

Based on these documents the European Agency for Health and Consumers in 2009 initiated a call for tender for a project aiming to make a survey of the current NBS practices in the EU member states and the (potential) candidate member states as well as to develop a set of recommendations for improvement and further expansion of NBS programmes. This and the subsequent paper (Burgard et al. 2012) highlight the most important survey results and recommendations.

Materials and methods

The project group viewed the NBS system as a process with five different aspects: a. preparation of the legal basis and general provisions; b. information to public and prospective parents; c. informed consent and blood sampling; d. laboratory screening procedures and blood spot storage; e. confirmatory diagnostics, communication of diagnosis, and treatment. See Fig. 1 in the accompanying paper by Burgard et al. (2012). For each aspect a series of questions were developed. All questions were converted into a web based survey to which respondents could log on with a given username and password. The

project group members were able to view the replies from each respondent and could ask for further clarification and elaboration if needed.

The project group member identified the participants of the survey in collaboration with the European Union Network of Experts on Newborn Screening (EUNENBS), the International Society for Neonatal Screening (ISNS), the European Board of Clinical Obstetricians and Gynaecologists (EBCOG), the Society for the Study of Inborn Errors of Metabolism (SSIEM), the European Society for Paediatric Endocrinology (ESPE), and the European Cystic Fibrosis Society (ECFS) for the recruitment of knowledgeable colleagues in each of the 40 countries and jurisdictions. This recruitment was not always an easy process. In some countries the NBS practice is very much fragmented into regions and provinces without coordination on a national level. In other countries it was difficult to identify the persons having a good overview of the situation in that country. In some instances this resulted in partially incorrect data from such a country and conclusions which subsequently had to be corrected.

The project group repeatedly consulted with an advisory group consisting of around 30-40 experts from various professional disciplines, closely related to NBS in practice. In total three face-to-face conferences were organised to discuss the process of the project and the results.

The final documents were approved by this group of experts prior to submission to EAHC (Burgard et al. 2011; Cornel et al. 2011).

Results

Countries

Table 1 shows the list of countries included in the survey. The colours of the country names indicate whether the country is a European Union member, a candidate member, a potential candidate member country, or a member of the European Free Trade Association (EFTA), respectively. In general the results are presented per whole country with a few exceptions. Belgium has been regarded as two separate jurisdictions (Flemish respectively French Community). The Liechtenstein infants are screened in Switzerland. Therefore, for the purpose of this project the Liechtenstein data are not mentioned separately. In some countries, notably Italy and Spain, there appeared to be large regional differences, making a result per country not meaningful. For Turkey only information concerning questions about confirmatory diagnostics and treatment could be obtained. For Albania and Kosovo no results were available. There was only a general statement that there is no screening at all in Albania.

Table 1 also includes the population size, and the approximate number of newborns.

Informed consent

Table 1 shows in which countries there is (written) information for the prospective parents and if they are asked for informed consent for participation in NBS as well as for storage of the dried blood spot sample after the screening has been completed. In addition the length of storage is indicated.

In most countries information is available and consent is asked for but there are countries, mainly in central Europe that do not yet have all such policies available. In Austria, Belgium-French Community, parts of Bulgaria, Czech Republic and Romania, consent is asked without such written information.

The length of storage varies considerably between 3 months (Germany) to more or less indefinite (Denmark, Norway, Sweden).

Sampling and transport

Table 1 shows per country the interval between birth and sampling and the interval between sampling and start of analysis. For most analytes sampling should not be done before 48 post partum in view of physiological variation leading to potential false positive or negative results, but in general the sooner the better after 48 hours. Finland and Malta both use cord blood but do not screen for phenylketonuria. The interval between sampling and analysis, i.e. the time needed for transportation of the sample should be as short as possible to avoid unnecessary and potentially harmful delay in diagnosis and treatment. It is, however, often several days.

Laboratory quality and workload

Table 1 shows per country the number of screening laboratories, the average annual number of samples per laboratory and whether the laboratories operate under an accredited quality system. The average annual number of samples varies from 2050 (Malta) to 121852 (Greece) but the range per individual laboratory in countries with multiple laboratories varies as well.

In 19 countries there is some form of accreditation. However, different systems are in use. In 17 countries there is none at all.

Table 1 Country data

Country	Approximate population 2011 (millions)[1]	Approximate number screened infants 2011	Number of screening laboratories	Average number of samples per laboratory	Accreditation system in place	Information /material for prospective parents	Informed consent for participation in programme	Informed consent fordried blood spot storage	Length storage of dried blood spots (y)	Interval birth-sampling (h)	Interval sampling-analysis (d)
Albania	3.0	n.d.[3]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Austria	8.2	83649	1	83649	ISO 9001	No	Yes	No	10	36-72	1-2
Belgium-Flemish	6.0	62000	3	20666	ISO 15189	Yes	Yes	Yes	5	48-96	2
Belgium-French	4.3	43472	3	14490	ISO 9001/15189	No	Yes	Yes	5	72-120	2
Bosnia-Herzegovina	4.6	45000	1	45000	none	n.d.	No	No	n.d.	72-120	n.d.
Bulgaria	7.1	74510	2	37255	Nat.Standards	No	Yes/No[4]	No	20	72-120	5-10
Croatia	4.5	45146	1	45146	DAC-IS-004-06-00	No	No	No	5	24-96[5]	10
Cyprus	1.1	9749	1	9749	ISO 15189	Yes	No	No	5	96-168	5
Czech Republic	10.2	118348	6	19725	varies per lab	No	Yes	No	5	48-72	2
Denmark	5.5	65000	1	65000	ISO 17025	n.d.	Yes	Yes	1000	48-72	2
Estonia	1.3	15730	1	15730	ISO 9001	Yes	No	No	100	48-72	7
Finland	5.3	60794	18	3377	ISO 15189	No	No	n.a.[3]	n.a.	n.a.	2
France	65.1	841931	22	38269	none	Yes	Yes	No	1	48-96	2
FYROM	2.1	22845	1	22845	none	No	No	Yes	10	48-96	3
Germany	81.4	675000	11	61364	ISO 15189	Yes	Yes	Yes	0.25	48-96	1
Greece	10.7	120852	1	120852	none	No	No	No	3	96-168	4
Hungary	10.0	95000	2	47500	ISO 9001	No	No	Yes	1	48-72	3
Iceland	0.31	4925	1	4925	none	Yes	Yes	Yes	20	48-72	3
Ireland	4.6	74278	1	74278	ISO 15189	Yes	Yes	No	26	72-120	1
Italy	61.0	576000	40	14400	ISO 9001	Yes	Yes	Yes/No[4]	1-10[4]	48-96	1-15
Kosovo	1.8	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Latvia	2.2	21655	1	21655	none	No	No	No	7	72-120	5
Liechtenstein[2]	0.036	400	0	n.a.[3]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Lithuania	3.5	32456	1	32456	none	No	No	No	25	48-96	7
Luxembourg	0.50	6159	1	6159	none	Yes	Yes	No	8	96-168	2
Malta	0.41	4100	2	2050	none	Yes	No	n.a.	n.a.	n.a.	1
Montenegro	0.66	8618	1	8618	none	n.d.	No	No	n.d.	48-96	4
Netherlands	16.6	185743	5	37149	ISO 15189	Yes	Yes	Yes	5	72-168	1
Norway	4.7	61581	1	61581	none	Yes	Yes	Yes	1000	48-96	2-3
Poland	38.4	421000	8	52625	Nat.Standards	Yes	Yes	No	1	48-96	3
Portugal	10.8	99809	1	99809	none	Yes	No	Yes	12	48-96	2
Romania	21.9	226000	4	56500	none	No	Yes	Yes/No[4]	2-5[4]	48-96	7-14
Serbia	7.3	55000	2	27500	none	Yes	No	No	10	48-96	10
Slovakia	5.5	56475	1	56475	none	Yes	Yes	Yes	20	72-96	2
Slovenia	2.0	20268	1	20268	none	Yes	No	n.d.	10	72-120	3
Spain	46.7	498711	20	24935	ISO 15189	Yes	Yes	Yes	1-1000[4]	48-168	4
Sweden	9.1	110523	1	110523	ISO 15189	Yes	Yes	Yes	1000	48-96	2-3
Switzerland	7.6	81259	1	81259	none	Yes	Yes	Yes	10	72-120	2
Turkey	78.8	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
United Kingdom	62.7	797214	16	49825	ISO 15189	Yes	Yes	Yes	5	120-192[6]	2-3

EU member, candidate EU member, potential candidate EU member, EFTA member

[1] http://www.census.gov/population/international/data/idb/rank.php (visited Aug 17, 2011)

[2] Liechtenstein screening carried out in Switzerland

[3] n.d. = no data; n.a. = not applicable

[4] depending on region

[5] Croatia: if <48 h, 2nd sample between 96-168 h

[6] UK: preferably at 120 h

The laboratories in all countries take part in some form of external quality assessment; in this respect there are no data for Bosnia-Hercegovina.

Panel of screened conditions

Table 2 provides an overview of the screening panels in the various countries. The number of conditions per country varies from 1 in Montenegro to 29 in Austria. The conditions most screened are congenital hypothyroidism (37 countries) followed by phenylketonuria/hyperphenylalaninaemia (33 countries). Congenital adrenal hyperplasia is in third place (15 countries). Where ms/ms technology has become available, MCADD is the condition that has first priority (13 countries), but many other amino acidaemias, organic acidurias and fatty acid oxidation defects are also screened for, be it to a different degree.

Cut off limits (not shown) for each condition appear to differ to a certain extent. Long tem evaluation should provide evidence to better attune these limits.

Haemoglobinopathies are screened for in France, Malta and Spain, because of relatively high prevalences as well as number of immigrants, and in addition in The Netherlands and United Kingdom because of a large number of immigrants. Surprisingly, haemoglobinopathies are not screened for in the other Mediterranean countries.

Discussion

Countries

Although the original call for tender referred to a survey in the European Union member states only, the project group decided to extend the survey also to the candidate and potential candidate member states, in the expectation that in due time these countries will join the EU. Likewise, because of the close interrelationship between EU and EFTA countries, also Norway and Switzerland were included. The situation concerning newborn screening in Kosovo is somewhat unclear. At any rate, no contact person could be found to provide information on the NBS status. Likewise, contacts with Turkey were difficult. Only some limited information concerning confirmatory diagnostics and treatment was obtained. Furthermore, it became clear that in Albania there is no NBS at all yet. Out of the 39 countries data on only 36 could be obtained by the survey, although some additional data was obtained through other routes.

Informed consent

Participation in the NBS programme preferably is based on informed consent (or dissent). To achieve this, (prospective) parents must be informed about the aims of the programme. The optimal period to provide information seems to be during the last trimester of pregnancy, separated from all information on prenatal screening. It is obvious that the postpartum period should be avoided because the magnitude of events and emotions new parents have to face. Before delivery prospective parents have more time to read and understand the information, at least if that information is available to them. In order to provide such information it is imperative that the professionals concerned have themselves access to such information.

Informed consent for storage of the dried blood spot sample after the screening has been completed and for further (scientific) use of the blood sample is lacking in 16 countries while in another eight this information could not be obtained. Nevertheless, all countries store dried blood spot samples. It is not clear if storage without consent is legal. The storage period varies from only 3 months to 1000 years or actually “indefinitely”. Three months is obviously too short to use the cards for analytical checking in case of a possible missed case and has little practical value. It must be noted that over time (> 3 years) the biochemical parameters are difficult to analyse because they will degrade or not elute from the filter paper anymore, unless the cards are kept at -20^{o} C with dessicant. This may be too costly for the programme organisations. However, for DNA-analysis cards can be used for a very long time, even if kept at room temperature without special conditions. It is unclear whether such biobanks are governed by regulations concerning physical access to prevent misuse.

Sampling and transport

In the first 48 h post partum blood concentrations of any analytes are subject to large variations. Analysis of a sample taken during that interval may lead to false positive or false negative screening results. However, many results obtained in this period are already reliable, and it is better to have at least a sample rather than no sample at all. In health care systems where it may be cumbersome to retrieve the newborns after 48 hours, early sampling is justified. Later sampling (> 96 h) may lead to an unwanted delay in screening, diagnostic and treatment process or even no screening with possible negative health effects.

Once the sample is available it should be analysed as quickly as possible, again in view of an unwanted delay if further steps should be needed. In addition, the quality of the dried blood spot sample may deteriorate over time. In most countries the collected samples are sent to the screening laboratory by normal mail or courier which should not last longer than 2 days.

Table 2 Screening panels of countries (including research programs) and frequency distribution of disorders screened for (for explanations see abbreviation list)

Country	ch (Endo)	cah (Endo)	cf (Cys F.)	pku/hp (AAD)a	msud (AAD)	hci (AAD)	tyrI (AAD)	asa (AAD)	citI (AAD)	arg (AAD)	hptI_III (AAD)	tyrII_III (AAD)	citII (AAD)	gaI (OA)	iva (OA)	mmacbl (OA)	pa (OA)	3mcc (OA)	gaII (OA)	hcsd (OA)
Albania																				
Austria	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X
Belgium (Flemish)	X	X		X	X									X	X	X	X		X	
Belgium (French)	X	X[2]		X	X	X	X					X								
Bosnia-Herzegovina	X	X		X																
Bulgaria	X	X		X																
Croatia	X			X																
Cyprus	X			X																
Czech Republic	X	X	X	X	X									X	X					
Denmark	X	X		X	X		X	X						X		X	X			X
Estonia	X			X																
Finland	X																			
France	X	X	X	X																
FYROM	X																			
Germany	X	X	X	X	X									X	X					
Greece	X			X																
Hungary	X			X	X	X	X	X	X			X		X	X	X	X	X	X	
Iceland	X			X	X			X	X	X	X		X	X	X	X	X	X	X	X
Ireland	X			X	X	X														
Italy	X		X[2]	X																
Kosovo																				
Latvia	X			X																
Lithuania	X			X																
Luxembourg	X	X		X																
Malta	X																			
Montenegro	X																			
Netherlands	X	X	X	X	X	X	X							X	X			X		X
Norway	X			X																
Poland	X		X	X																
Portugal	X			X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Romania	X			X																
Serbia	X			X																
Slovakia	X	X	X	X																
Slovenia	X			X																
Spain	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X
Sweden	X	X		X																
Switzerland[1]	X	X		X																
Turkey	X			X																
United Kingdom	X		X	X																
Frequency	37	15	10	33	12	7	7	6	5	4	3	3	2	10	9	7	7	6	6	6

Table 2 (continued)

Country	3hmg (OA)	bkt (OA)	mma (OA)	mcadd (FAOD)	vlcadd (FAOD)	lchadd (FAOD)	cptI (FAOD)	cptII (FAOD)	cud (FAOD)	scadd (FAOD)	schadd (FAOD)	decr (FAOD)	s-s (Hemo)	btha (Hemo)	sc (Hemo)	bio (M)	galt (M)	udp (M)	N disorders screened for
Albania																			0
Austria		X		X	X	X	X	X	X	X						X	X	X	29
Belgium (Flemish)				X												X			11
Belgium (French)																	X		8
Bosnia-Herzegovina																			3
Bulgaria																			3
Croatia																			2
Cyprus																			2
Czech Republic				X	X	X	X	X											12
Denmark				X	X	X			X							X			15
Estonia																			2
Finland																			1
France													X						5
FYROM																			1
Germany				X	X	X	X	X								X	X	X	15
Greece																	X		3
Hungary	X	X		X	X	X	X	X	X	X						X	X		25
Iceland	X	X	X	X	X	X	X	X	X	X	X								26
Ireland																	X		5
Italy																			3
Kosovo																			0
Latvia																			2
Lithuania																			2
Luxembourg				X															4
Malta														X	X				3
Montenegro																			1
Netherlands	X			X	X	X							X	X	X	X	X		20
Norway																			2
Poland																			3
Portugal	X			X	X	X	X	X	X		X								25
Romania																			2
Serbia																			2
Slovakia																			4
Slovenia																			2
Spain	X			X	X		X	X	X				X			X	X		27
Sweden																X	X		5
Switzerland[1]				X												X	X	X	7
Turkey																X			3
United Kingdom				X									X	X	X				7
Frequency	5	3	1	13	9	8	7	7	6	3	2	0	4	3	3	10	10	3	

[1] including Liechtenstein

[2] Belgium (French) screens for CAH not nationwide; likewise Italy screens for CF but not nationwide

Laboratory quality and workload

The quality of the screening laboratory depends on several factors.

1. The screening laboratory, as all medical laboratories, should operate under a quality system that preferably is accredited or certified by an external body. For the development and implementation of such quality systems several documents have become available. The most appropriate is ISO15189 (2007), specifically oriented towards medical laboratories. A more general document is the ISO9001 (2008) standard. In several countries screening laboratories can apply for accreditation or certification by an independent body. In other countries there may be national or local regulations or guidelines that are mandatory for the laboratories to follow. In several countries NBS is performed in laboratories that are not accredited, according to our respondents (Table 1). This may endanger the quality of the results.
2. The laboratory should participate in one or more external quality assessment schemes EQAS) to monitor the quality of the measurement of the screening parameters. An EQAS typically sends out a number of quality samples, several times per year, and asks the participants to analyse them as if they were routine samples and report back the results to the organiser. Reviewing the results of all participants provides insight about the performance of their own laboratory. The results of the survey show that the laboratories in all countries (no data for Bosnia-Herzegovina) participate in one or more EQA schemes.
3. The laboratory should analyse a minimum number of samples per year, not so much to attain a constant quality level, but more to obtain and keep a sufficient level of experience on what to do with a result that is outside the normal range, e.g. to inform the screening organising body or the medical professionals involved. The conditions screened for are usually rare, which means that aberrant results occur just occasionally. For many screened conditions time is critical in diagnostic confirmation and treatment, so all laboratory personnel must know what to do in such rare situations. It is not easy to state what should be the minimum number of samples per year, but a number of 30,000-50,000 is a good approximation. If a laboratory does not receive this minimum it should consider sending the samples to a neighbouring laboratory or it could be the responsibility of the screening organisation in a country to come to terms with all participating laboratories to reduce their number. In certain countries the number of births is less than 30,000. In that case the screening organisation can accept this or make a deal with a laboratory in a neighbouring country.

Panel of screened conditions

Policy making concerning which conditions to screen for varies per country. It may depend on national health care politics, local medical professional interests and habits, input from parent advocacy groups, etc. In many countries the criteria of Wilson and Jungner (1968), sometimes in a modified form, are the backbone of the screening policy. However, these criteria provide a number of questions to be answered and deliberations to be made, often with financial consequences. It was to be expected that countries with a lower socio-economic status have a smaller screening panel. On the other hand, preventive medicine through screening can be considered to be cost effective and even some countries with a relatively high socio-economic status still have a relatively small screening panel, so there must be other reasons as well, such as the structure of the health care system, national or local politics, requirements for scientific evidence, ethical considerations (e.g. detecting of carriers, uncertainty about treatability, etc). Unfortunately, not all conditions can be screened with a single methodology. Some require immunochemical techniques (CH, CAH, CF), some colorimetric techniques (GAL, BIO), some tandem mass spectrometry (MCADD and other fatty acid oxidation disorders, amino acidaemias, organic acidurias), high pressure liquid chromatography (SCD/thal), sometimes in combination with molecular biological techniques. For this broad spectrum of techniques extensive knowledge and experience both in the laboratory and of the medical professionals are necessary. Nonetheless, although several countries have all of this available, other countries slow reluctance to ask for assistance to reach the same goals. On the contrary, in some countries policy makers tend to want to obtain all experimental evidence in their own country before extending their own programme, which could take decades.

In comparison to previous surveys (Zabransky 2002; Bodamer et al. 2007; Loeber 2007) it is noted that there has been a large increase in the number of conditions screened for in at least 11 countries. The major impetus has been the introduction of the tandem mass spectrometry technique making multiplex screening for fatty acid oxidation disorders, amino acidaemias, and organic acidurias possible.

Conclusion

The results as outlined in this and the subsequent paper (Burgard et al. 2012) indicate that there are large variations in the design of the newborn screening programmes in the European countries and the day-to-day practices. To a large extent the programmes themselves run smoothly. However,

efficiency can be improved by studying the details and learning from the experiences in other countries.

The recommendations of the project group (Cornel et al. 2011) include the use of a decision-making matrix. This should be stimulated by the European Commission and its subordinate governing bodies. The ultimate goal is to have a uniform screening panel as has been achieved in the USA (Watson et al. 2006; NNSGRC 2011) resulting in equal screening opportunities for all European newborn infants.

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SSIEM SYMPOSIUM 2011

Newborn screening programmes in Europe; arguments and efforts regarding harmonization. Part 2 – From screening laboratory results to treatment, follow-up and quality assurance

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Abstract In a survey conducted in 2010/2011 data from the 28 EU member states, four EU candidate states (Croatia, FYROM, Iceland, Turkey), three potential EU candidate states (Bosnia Herzegovina, Montenegro, Serbia), and two EFTA states (Norway and Switzerland) were collected. The status and function of newborn screening (NBS) programmes were investigated from the information to prospective parents and the public via confirmation of a positive screening result up to decisions on treatment. This article summarises the results from screening laboratory findings to start of treatment. In addition we asked about the existence of feedback loops reporting the conclusions of confirmation of screening results to the screening laboratory and communication of long-term outcome to diagnostic units and possibly existing central registries. Parallel to the description of actual practices of where, how and by whom the different steps of the programmes are executed, we also asked for the existence of guidelines or directives regulating the screening programmes, material to support information of parents about diagnoses and treatment and training facilities for professionals involved in the programmes. This survey gives a first comprehensive overview of the steps following a positive screening result in European NBS programmes. The 37 data sets reveal substantial variation of national screening panels, but also a lot of similarities. Analysis across all countries revealed that actual practice is often organised but not regulated by guidelines. Material to inform patients is available more often for explaining treatment (69 %) than explaining the necessity of confirmatory diagnostics (41 %). Training of professionals is rarely regulated by a guideline (2 %), but is offered for paediatricians (40 %) and dieticians (29 %) and only rarely for other professions (e.g. geneticists, clinical nurse specialists, psychologists). Registry-based evaluation of long-term outcome is as yet almost nonexistent (3 %).

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Introduction

The survey for the evaluation of regulations and practices of population newborn (neonatal) screening (NBS) for rare disorders in Member States of the European Union, as well as candidate, potential candidate and EFTA countries, originates from the actions launched by the European Commission within the EU Programme of Community Action in Public Health. The EU Council Recommendation for an Action in the Field of Rare Diseases (European Commission 2009) 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 in order to better utilise national resources and expertise as well as reducing inequalities in the access to high quality care. The aim of the survey was to describe current practices and existing regulations (guidelines and directives) of NBS in all European States.

In a first step, a model for a complete NBS programme was developed based on pertinent literature (e.g. Wilson and Jungner 1968; Raffle and Gray 2007; see Fig. 1). This model has five structural modules: (A) the legal basis and general provisions, (B) information to the public and prospective parents, (C) blood sampling and informed consent; (D) laboratory testing and blood spot storage, and (E) confirmation and communication of diagnosis, and treatment. Across all modules, guidelines, programme evaluation and epidemiology, training of professionals and resources and costs were investigated. The modules are functionally interconnected by flow of information, samples and people.

Although the modules are arranged in a logical sequence, this does not necessarily represent the factual establishment and development of a programme, for example screening can start even before legislation or guidelines come into practice.

Results of module B to D are reported in a separate publication (Loeber et. al. this issue). In this article we focus on the results of module E, covering the domains information and communication of the laboratory screening to parents, practices of confirmation of diagnosis, treatment and monitoring of long-term outcome, epidemiological evaluation, quality assurance, empowerment of patients and training of professionals.

Material and methods

For a more comprehensive description of the survey procedures the reader is referred to the accompanying paper by Loeber et al. (this issue). For module E a questionnaire was developed covering current practice and its regulation by directives (defined as legally binding standardization by state and/or health authorities) and/or by guidelines (defined as information intended to advise how something should be done).

The questionnaire was cross-reviewed within the project and by external reviewers suggested by the Society of the

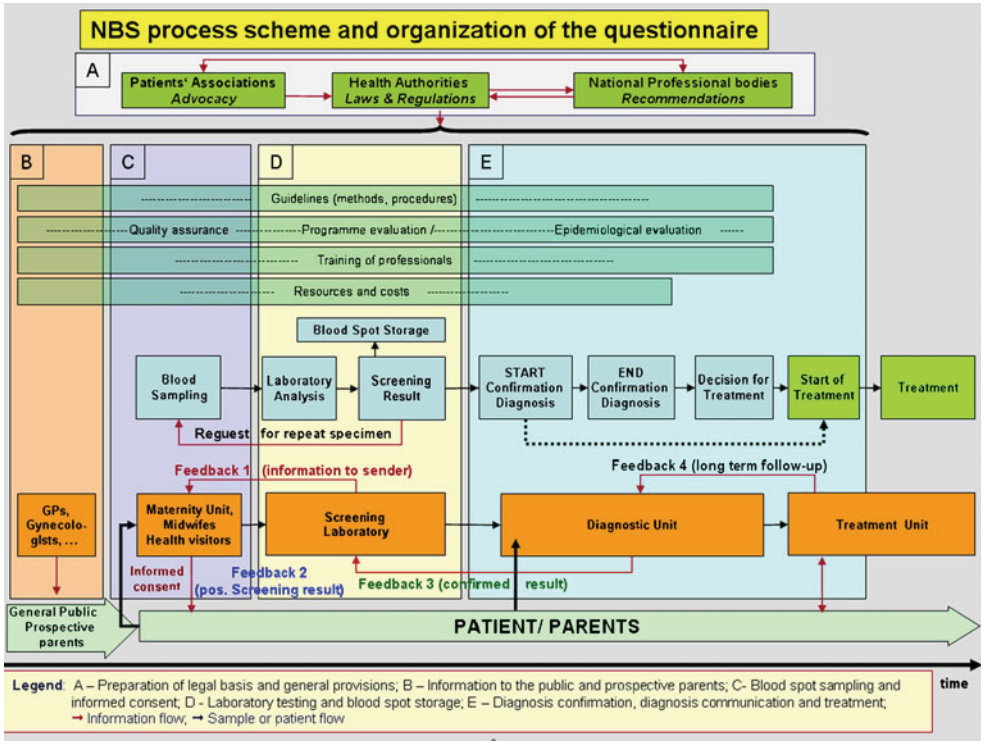

Fig. 1 Five modules of a NBS programme

Study for Inborn Errors of Metabolism (SSIEM; Jim Bonham, Philip Mayne), and converted to a web-based instrument. In each country respondents nominated by different European professional societies (Society for the Study of Inborn Errors of Metabolism (SSIEM), European Society for Paediatric Endocrinology (ESPE), and European Cystic Fibrosis Society (ECFS)) were asked to report national data by remote data entry for all disorders (metabolic, endocrinologic, and cystic fibrosis) screened for in their country. Respondents for haematological disorders were recommended by colleagues contacted for other disorders. The survey started in August 2010 and was closed on January 14th, 2011, with all data referring to the situation on September 1st, 2010. Extensive reports of the project can be downloaded at http://www.iss.it/cnmr/prog/cont.php?id=1621&lang=1&tipo=64.

Results

Description of the data set

The data set for module E has three dimensions: (1) countries, (2) disorders screened for, and (3) questions related to the screening programme (subdivided by current practice and mode of regulation). Supplementary Table 1 (identical with Table 2 in Loeber et al. this issue) gives an overview of the 40 target countries/regions of the survey, as well as the countries' screening panels (including conditions investigated in research programmes). In Belgium NBS is organised per legislation, and therefore data were collected separately for the Flemish and the French speaking communities. As there is reportedly no screening in Albania and no response was received from Kosovo (both potential candidate countries for the European Union), these countries were excluded from further analysis. Newborn screening for Liechtenstein is done in Switzerland, resulting in a total number of 37 data sets.

The number of disorders included in national screening panels ranges from one (Finland, FYROM, Montenegro) to 29 (Austria), with congenital hypothyroidism being the only condition screened in all 37 countries and malonic aciduria (MMA) only screened for in Iceland.

Most of the data presented in this article are based on an analysis by disorder. In a first step answers related to single disorders were averaged across all countries screening for this disorder, and in a second step data have been aggregated across disorders. For example MSUD is screened for in 12 countries, 11 countries have answered the question about the method of confirmation of a positive screening result, five out of 12 countries (42 %) reporting mutation analysis to confirm a positive screening result. HPA is screened for in 33 countries, 32 countries have answered the question about the method of confirmation of a positive screening result, with 17 out of 33 countries (52 %) reporting mutation analysis to confirm a positive screening result. Combining the results for these two disorders would allow the conclusion that on average mutation analysis is used for confirmation of diagnoses in 47 % of the cases MSUD or HPA is screened for.

Confirmation of screening results

As screening does not result in a diagnosis, positive screening results have to be confirmed or rejected by additional investigations. Seven questions have been asked in the domain of confirmative diagnostics (Table 1).

The questions aim at four aspects related to the structure, process and outcome of the confirmation of diagnoses: institutions (confirmatory investigations can be executed in specialised centres, local hospitals, GP/Paediatricians, or other institutions), methods (results are confirmed by quantitative analyses of metabolites/hormones, enzyme activity, mutation analysis, and other methods), time (age at start and end of confirmational procedures), and costs (for inpatient and outpatient care and laboratory analysis).

Feedback of confirmed screening results to the screening laboratory is particularly important, as it is necessary to improve screening algorithms and cut-off values in the screening laboratory. Costs and economic efficiency as well as quality of care and timely management are essential parameters of NBS programmes (Pandor et al. 2004). As soon after birth as possible access to specialised clinical diagnostic and treatment services will be particularly necessary when disorders with a risk for neonatal decompensation are screened for.

In Europe screening results are almost always confirmed in specialised centres. However, significant exceptions among the more frequently screened disorders are biotinidase deficiency, galactosaemia, congenital hypothyroidism, congenital adrenal hyperplasia and MCADD. These disorders are screened in more than ten countries and are confirmed and treated in at least 15 % of the cases in local hospitals. However, it should be noticed that "specialised centre" is not a well-defined concept. Furthermore, as confirmation, follow-up and treatment is different for most

Table 1 Questions of the domain "Confirmative diagnostics"

1. Is there a directive/guideline **where** to confirm diagnosis?
2. **Where** are positive screening results predominantly confirmed?
3. Is there a directive/guideline **how** to confirm diagnosis?
4. **How** are positive screening diagnoses actually confirmed?
5. What are the average **direct health costs** of the different national screening panels?
6. Is there a guideline concerning the **age** to confirm a suspected diagnosis?
7. At what **ages** is confirmation actually started and terminated?

conditions more specification would be necessary for a detailed evaluation.

Methods of confirmation show a complex pattern across the different disorders, possibly also depending on the aims of confirmation. For example, in the case of hyperphenylalaninaemia (HPA) mutation analysis might be regarded as necessary to establish the severity of phenylalanine hydroxylase (PAH) deficiency and possible tetrahydrobiopterin (BH_4) responsiveness whereas others may rely on pterine analysis and/or a loading test with BH_4. Local availability of tests will determine the set of analyses applied. In disorders where genetic counselling and prenatal diagnosis in further pregnancies is needed, genetic analysis will be mandatory. On average in 61 % of the cases where a disorder is screened for, mutation analysis is included as a method to confirm screening results.

Process times

Twenty-six countries inform prospective parents about NBS after birth at time of blood sampling, four of them also provide information during the 3rd trimester of pregnancy, 11 countries reported informing parents any time during pregnancy. Across all countries blood sampling is performed at a median age of 2.8 days (min=2.5, max=3.5). Laboratory screening analysis starts at a median age of 5.3 days (min=4.1, max=7.1). Confirmatory diagnostics started at a median of 8.5 days (Q25=8.3, Q75=8.9). Median age at end of confirmation was 16.2 days (Q25=15.2 Q75=20.1) and treatment starts at a median age of 14.9 days (Q25=13, Q75=16.7). Median age at start of treatment is earlier than median age at end of confirmation because treatment sometimes is initiated immediately after a positive screening lab result in order to avoid early decompensation following a risk-minimizing strategy. Overall for 75 % of all screened disorders positive screening results are confirmed within the first 20 days of life.

Costs

Table 2 shows costs for confirmation of a single screening result. Sum of costs 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 mentioned that in a strict sense the figures represent **prices**, i.e. amounts of money realised by the provider and not the cost of the provider's activities.

In order to make data from nations with different gross domestic products and/or purchasing power comparable, raw data from each respondent were converted to percent of Gross Domestic Product (GDP) based on purchasing-power-parity (PPP) per capita. Results show that total costs show a large variation between disorders as well as between countries screening for the same disorder. On average confirmation of a screening result costs between 182 € (UDP) and 3.077 € (GA II).

The large variability within disorders only can be compared against the background of more detailed information, for example the methods used to confirm a screening result. 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 and medical practises of a country.

One of the pillars of economic analysis of health care programmes is costs (Drummond et al. 2005). Although respondents predominantly reported that figures have been estimated, and source of data often has not been specified, data could be interpreted as educated guesses and serve as a basis for more in depth analysis.

Information and communication to parents

Legal and ethical norms require informed consent and some confirmatory investigations necessitate practical cooperation of parents (e.g. observation of the child or providing parental blood samples for molecular biological analysis). This domain was investigated by six questions, four dealing with regulations and two with actual practice (Table 3).

The predominant first informant of parents about a positive NBS result is the GP or a paediatrician (80 %), but on average, in 24 % of the cases a disorder is screened for, the screening laboratory informs parents. The preponderant mode of information is a phone call (87 %), but also in 50 % of the cases information is given in person. Parents mostly already get detailed information during the first contact (83 %). Paediatricians (97 %), dieticians (69 %) and geneticists (65 %) are the key persons in teaching parents about diagnosis and treatment.

Treatment

Presymptomatic start of treatment is the ultimate goal of screening (Wilson and Jungner 1968). In those cases where disorders with a substantial risk for acute neonatal decompensation are included in a screening panel, age and clinical status (asymptomatic vs. symptomatic) at start of treatment become central outcome parameters of a NBS programme. Structural features of NBS programmes are the type of treatment units (specialised centres, local hospital or paediatricians/GPs) and professionals involved (paediatricians specialised in cystic fibrosis, metabolic, endocrinologic or haematologic disorders, dieticians, psychologists, social workers, clinical nurse specialists, geneticists).

In Europe 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 %).

Table 2 Average direct health costs to confirm or reject a positive screening result

Disorder[1]	No. of countries screening	No. of replies	% Replies	Sum of costs €		% GDP PPP 2009[2]		% countries reporting calculated costs	% countries reporting estimated costs
				Mean	SD	Mean	SD		
PKU/HPA	33	25	76	1,746	1,947	9.0	6.7	15	52
BIO	10	10	100	832	399	3.9	1.9	20	40
GALT	10	7	70	1,760	1,406	7.6	5.4	10	60
UDP	3	1	33	182	-	0.7	-	33	0
CH	37	29	78	601	670	3.5	3.7	19	54
CAH	14	11	79	1,555	1,249	8.5	5.2	21	57
CF	9	8	89	764	571	4.2	3.0	22	56
ARG	4	2	50	2,165	555	8.8	1.2	0	25
ASA	6	4	67	1,855	630	9.0	1.0	17	33
CIT I	5	3	60	1,855	630	9.0	1.0	20	20
CIT II	2	2	100	2,165	555	8.8	1.2	0	50
HCI	7	4	57	1,675	1,288	8.0	5.0	14	43
HPT I_III	3	1	33	2,720	-	10.1	-	0	0
MSUD	12	9	75	3,030	1,517	13.2	4.9	8	58
TYR I	7	4	57	2,583	1,648	12.1	5.2	14	43
TYR II-III	3	2	67	3,070	1,835	14.4	5.0	33	33
CUD	6	4	67	1,855	630	9.0	1.0	17	33
CPT I	7	5	71	1,894	553	9.1	0.8	14	43
CPT II	7	5	71	1,888	548	9.1	0.8	14	43
LCHADD	8	5	63	1,648	637	8.0	1.7	13	38
MCADD	13	8	62	1,351	677	6.5	2.8	8	38
SCHADD	2	1	50	2,720	-	10.1	-	0	0
SCADDD	3	2	67	1,977	742	9.7	0.4	33	0
VLCADD	9	6	67	1,570	652	7.8	2.5	11	44
DECR	0	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3HMG	5	3	60	1,838	647	8.9	1.00	20	20
3MCC	6	3	50	1,838	647	8.9	1.00	17	17
GA I	10	7	70	2,890	1,471	13.0	4.8	10	50
GA II	6	4	67	3,077	2,218	13.36	7.8	17	33
HCSD	6	3	50	2,165	555	8.84	1.2	0	33
IVA	9	6	67	2,528	996	11.51	2.9	11	44
MMA	1	1	100	2,720	-	10.07	-	0	0
MMACBL	7	5	71	2,327	1,015	10.40	2.8	14	43
PA	7	5	71	2,327	1,015	8.88	1.0	14	43
BKT	3	2	67	1,952	767	9.52	0.6	33	0
BTHA	3	3	100	529	395	2.02	1.2	33	33
SC	3	3	100	529	395	2.02	1.2	33	33
S-S	4	4	100	881	614	3.77	3.0	0	75

[1] 3HMG 3-Hydroxy-3-methylglutaric aciduria; 3MCC 3-Methylcrotonyl-CoA carboxylase deficiency/3-Methylglutacon aciduria/2-methyl-3-OH-butyric aciduria; 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; GAI Glutaric acidaemia type I; GAII Glutaric acidaemia type II; GALT Classical galactosaemia; HCI Homocystinuria (CBS deficiency); HCSD Holocarboxylase synthetase deficiency; HPT I_III Hypermethionemia types I, III; IVA Isovaleric acidemia (IVA)/ 2-Methylbutyrylglycinuria; LCHADD Long-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency/Trifunctional protein deficiency; MCADD Medium-chain acyl-CoA dehydrogenase deficiency; MMA Malonic acid-aemia; MMACBL Methylmalonic acidaemia including Cbl A,B, C, D defects; MSUD Maple sirup urine disease; PA Propionic acidaemia; PKU/HPA Phenylketonuria/Hyperphenylalaninaemia; S-S S,S disease (Sickle cell anaemia); SC S,C disease (Sickle – C disease); SCADD Short-chain acyl-CoA dehydrogenase deficiency; SCHADD Medium-short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; TYRI Tyrosinaemia type I; TYRII-III Tyrosinaemia types II, III; UDP UDP-galactose-4-epimerase deficiency; VLCADD Very long-chain acyl-CoA dehydrogenase deficiency

[2] GDP PPP 2009 = Per capita Gross Domestic Product based on purchasing-power-parity (PPP) in International Dollar converted to Euro at the currency exchange rate of 01.01.2009; Source: World Economic and Financial Surveys: World Economic Outlook Database. International Monetary Fund. http://www.imf.org/external/pubs/ft/weo/2010/02/weodata/index.aspx. Retrieved on 04.04.2011 n.d. no data

Table 3 Questions of the domain "Information and communication to parents"

1. Is there a guideline **how** professionals should inform parents about positive NBS?
2. Is there a directive/guideline **who** should inform parents about the necessity of confirmatory procedures?
3. **Who** actually informs parents on the necessity of confirmatory procedures?
4. Is there a guideline **how** professionals should explain the confirmed diagnosis and its overall implications?
5. Is there a guideline concerning the participation of **professions to be involved** in teaching parents about diagnosis and treatment?
6. Which **professional groups** actually participate in teaching parents?

The median of patients presenting asymptomatically at the start of treatment is equal to 84 %. Disorders reported to have relatively high rates of patients presenting symptomatically at start of treatment are classical galactosaemia (50 % symptomatic cases), β-ketothiolase deficiency (45 %), glutaric aciduria type II (40 %), long-chain L-3-hydroxyacyl-CoA dehydrogenase/trifunctional protein deficiency (33 %), and congenital adrenal hyperplasia (32 %) (Fig. 2). It should be noted that 67 % of the data are estimated and not calculated.

Epidemiological evaluation

Feedback of confirmed or rejected diagnoses and parameters measured in the process of confirmation to the screening laboratory helps to adjust screening algorithms, and feedback of results of confirmation to a central registry will allow calculation of prevalence data. On average feedback of diagnoses is regulated by guidelines in 88 % and by a directive in 27 % of cases where a disorder is screened for. Guidelines are applied on a national level in 68 % of the cases a disorder is screened for whereas only 38 % of the directives have a national application. Confirmed diagnoses are mostly (87 %) fed back to the screening laboratory and less often to a registry (19 %). Organisation of feedback is reported to be predominantly "push", i.e. the clinical unit of confirmation actively delivers the results to the screening laboratory. If feedback is given, predominantly not only the diagnosis but also detailed results are transmitted.

Monitoring long-term outcome

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

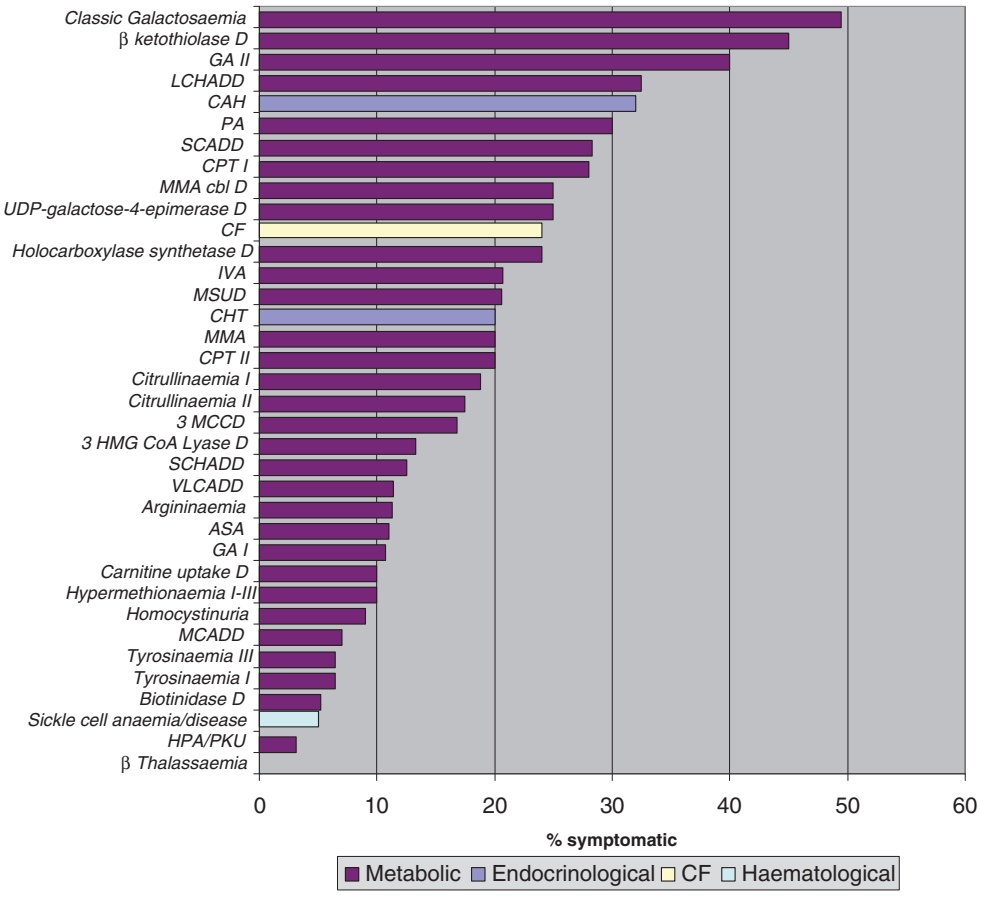

Fig. 2 Clinical presentation at the start of treatment. For abbreviations see Table 2

Averaged over all disorders data on long-term outcome are evaluated in 80 % of the cases. However, the evaluation is predominantly done on the level of treatment units and not combined with the emphasis of evaluation of screening practises. Data are reported in about 40 % of the cases to the diagnostic unit but only in 3 % to a registry. A noteworthy exception is cystic fibrosis where three out of nine (33 %) countries screening for the disorder report having a registry.

Quality control and quality assurance

Quality control (QC) is defined as a system of routine checks to assure that predefined requirements of the programme are fulfilled, whereas quality assurance (QA) activities include a planned system of review procedures conducted by personnel not directly involved in the programme. Actual practice of quality control and assurance was investigated regarding seven steps of a screening programme (see Fig. 3).

Quality measures were reported more often for QC than for QA. Overall activities for systematic assurance of quality are lacking in 60 to 90 % of the cases where a disorder is screened for. Laboratory diagnostic procedures are nearly always quality approved (either by QC of QA alone or by both); process steps dealing with information of parents show low levels for QC and/or QA.

Training of professionals

Across all four groups of disorders, systematic training is most often offered to paediatricians (40 %) and dieticians (29 %), followed by geneticists (16 %) and clinical nurse specialists (14 %). Training for psychologists (8 %) and social workers (4 %) is rarely offered. Analysis by groups of disorders revealed that training is most often offered for cystic fibrosis screening programmes (25 %), followed by metabolic (20 %) and endocrine disorders (17 %). For haemoglobinopathies, training is offered only for the clinical nurse specialist and the geneticist. Figure 4 summarises the results regarding the different professional groups involved in the confirmation of diagnosis and treatment.

Awareness and support

Political support for NBS

Political support for NBS has been reported by all responding countries. In most countries political support is represented by public funding of NBS or by a service of the public health system. In none of the answers was reference made to international political support. Reference was made to the national plan for rare diseases by Bulgaria, which has been 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.

Professional societies

National professional societies dealing with disorders screened for (societies for human or medical genetics, general paediatric societies, societies for endocrinology or metabolic disorders or working groups for newborn screening) have been reported for 24 of 35 jurisdictions.

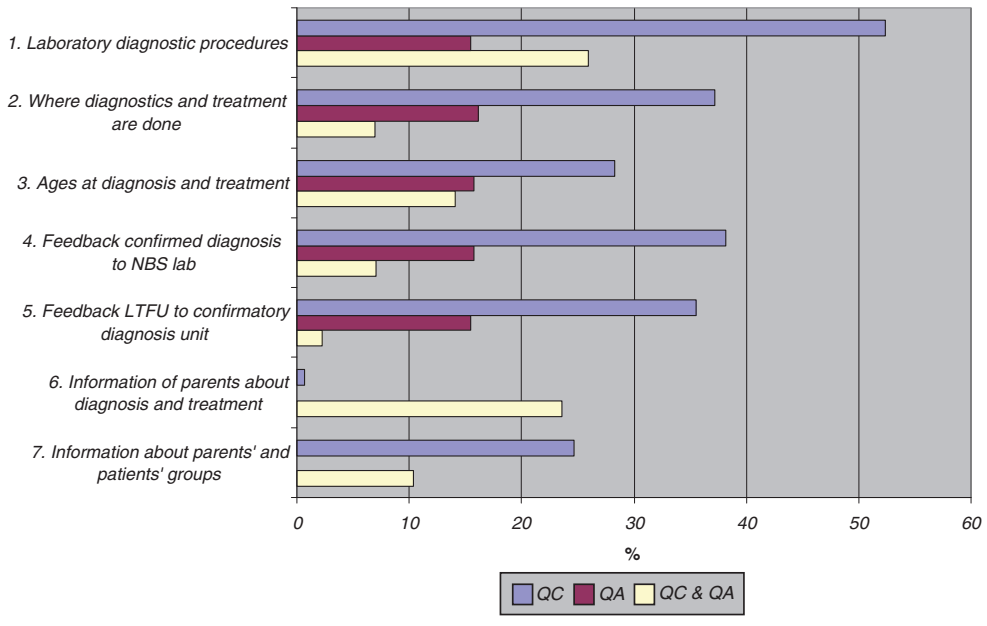

Fig. 3 Mean percentages of quality control (QC) and quality assurance (QA) in seven steps of the process of confirmation of a positive screening result. (FTFU = long-term follow up)

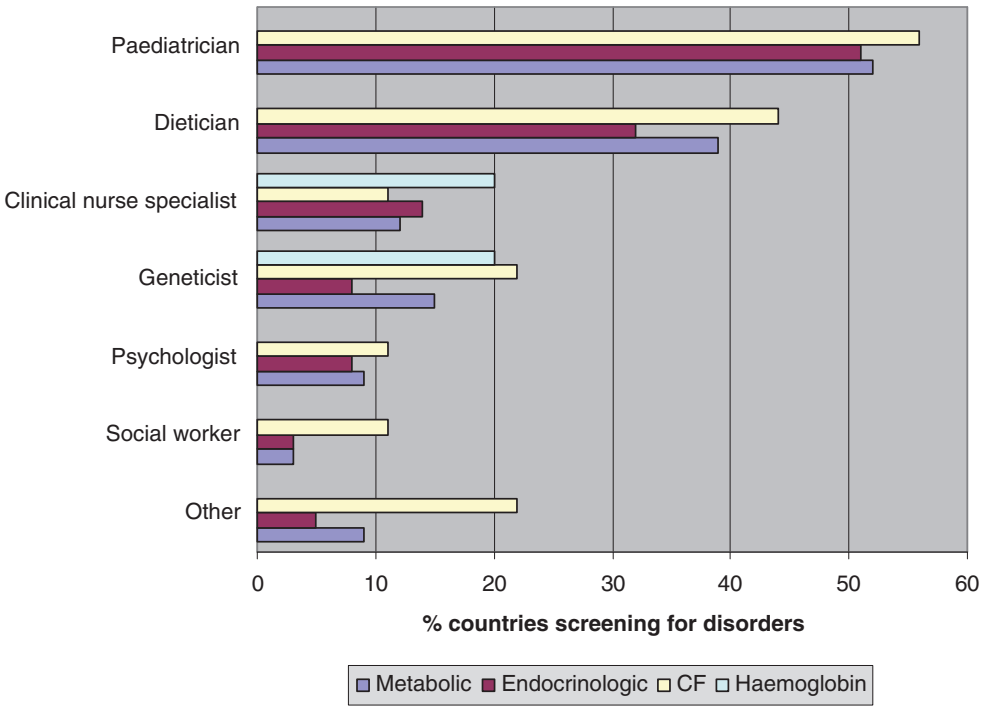

Fig. 4 Training offered to professionals

Patient'/parents' groups for disorders screened

Twenty-eight 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 (http://www.espku.org/), societies of patients and/or parents with cystic fibrosis (http://www.cfww.org/cfe/) and organisations for rare diseases (http://www.eurordis.org/).

Involvement of patient organisations in changes of screening programmes

Eighteen jurisdictions, which have expanded NBS during the last five years, have patient advocacy groups specific to screened disorders while two have not. In ten out of the 18 cases patient groups were reported to have been involved in the decision to expand NBS. While it is not clear whether these were disease-specific advocacy groups, it is noteworthy that in eight cases 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 only after NBS was expanded.

Empowerment

Most screened disorders are not only rare, but also do not fit with common concepts of disease and illness. In general, elaborated preventive treatment protocols have to be followed by patients who have never had or will have any symptoms. Providing parents/caretakers with instructive material supplementing and supporting communication aims to improve transmission of information, the understanding of the child's problem, compliance with recommendations, and thus the outcome. Treatment of disorders screened for in NBS programmes is mainly executed by parents, making empowerment of parents regarding understanding and execution of preventive medicine a central issue. Material to support the first communication of the meaning and consequences of a positive NBS result was reported to be available less often (41 %) than material explaining treatment (69 %). Quality of these materials has not been investigated during the survey, but there is evidence that parent educational material often does not meet standards regarding completeness or readability (Fant et al. 2005).

Guidelines and directives

Figure 5 gives an overview on the regulation (by a guideline or a directive) of different domains. Early steps proximal to the positive laboratory screening result appear to be better regulated than later or more distal steps

Overall confirmation of screening results (where, how, when) is predominantly regulated by guidelines (75 %) and less often by directives (29 %). The same was found for information and communication to parents (50 % guidelines and 37 % directives). 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) guidelines and at least one material for first communication are available for each disorder screened for somewhere in Europe.

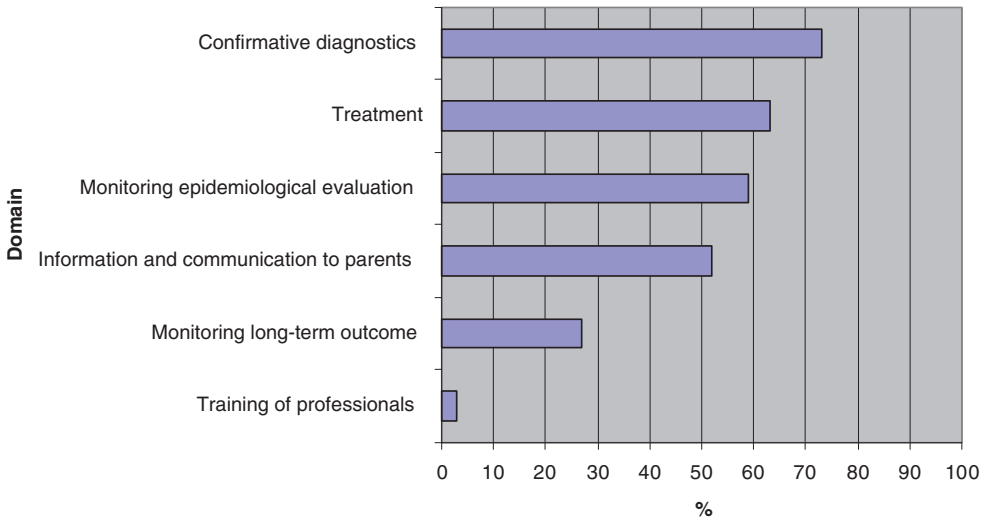

Fig. 5 Regulation (by guidelines and/or directives) of domains of European NBS programmes

Issues related to treatment (age at start of treatment, where to treat, professions to be involved in treatment,) are regulated on average in 60 % of the cases a disorder is screened for. Epidemiological evaluation is rarely regulated by guidelines (15 %) or directives (18 %). However, in practice on average evaluation was reported for 84 % of the cases a disorder is screened for. The 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 databases (50 %). In 8 % data have not been reported. Long-term outcome is scarcely monitored on the basis of a guideline (21 %) or directive (2 %). Feedback of long-term outcome to a registry or units for confirmation is scarcely regulated by guidelines (31 %) and never by a directive.

Correspondence between regulation (guidelines and directives) and current practice

For many facets of NBS programmes current practice has been reported to be organised, however, without being regulated by a guideline or directive. Therefore, the relationship between current practice and its regulation was analysed for the four domains of feedback of diagnoses to the screening laboratory or registry, monitoring of long-term outcome, feedback of long-term outcome to the diagnostic unit, and epidemiological evaluation of the screening programme. For each disorder and country four different results were possible in each domain: (1) there could be a practice and a regulation (guideline or directive), (2) there could be a practice without a regulation, (3) there could be a regulation without a practice, and (4) there could be neither a practice nor a regulation. Data were first averaged for each disorder across countries and then across disorders. Table 4 reports the results of the analysis.

Results show that the most proximal process of communicating the results of confirmatory investigations to the NBS laboratory seems to be very well regulated and organised. In a substantial number of cases, data collection and evaluation of long-term outcome and other epidemiological information is in place on a local level only without being regulated by a guideline. Feedback of long-term outcome to the diagnostic unit or to a registry was reported even less frequently but mostly in association with the existence of a guideline. The limited practice of this transmission of information 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 exchange of information across different steps of a NBS programme often is locally organised even if there is no regulation by a guideline or a directive.

Summary and discussion

The 37 data sets reveal substantial variation across national screening panels, but also many similarities. Confirmation is done almost always in specialised centres, and in about 75 % of the cases screening results are confirmed within the first 20 days of life. However, the definition of a specialised centre has not been elucidated. Although reported costs for confirmation are predominantly based on respondents' estimations, the figures can be taken as educated guesses showing a large variation between disorders as well as for the same disorder between countries.

The person informing about a positive NBS result is most often the GP or a paediatrician, but also screening laboratories can be the first to inform parents. The preponderant mode of information is a phone call. Parents already get detailed information during the first contact, and paediatricians, dieticians

Table 4 Correspondence of guidelines and actual practice

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

and geneticists are the key persons in teaching parents about diagnosis and treatment. Material to support the first communication of the meaning and consequences of a positive NBS result was reported to be available less often than material explaining treatment.

For most disorders patients present asymptomatically at start of treatment, but for some disorders substantial numbers are confirmed at a symptomatic stage (classical galactosaemia, β-ketothiolase deficiency, glutaric aciduria type II, LCHADD, and CAH). Confirmed diagnoses are mostly fed back to the screening laboratory and less often to a registry. Long-term outcome is usually evaluated, however, the evaluation is predominantly done at the level of treatment units and outcomes are rarely reported to a registry.

Training of professionals involved in confirmation is most often offered to paediatricians, but less often to dieticians, geneticists, clinical nurse specialists, psychologists, and social workers.

Political support for newborn screening by public funding of newborn screening or by a service of the public health system seems to be present in all countries. Professional societies for screened disorders have been reported to exist in two thirds of the jurisdictions. Most countries have patient and/or parent associations for at least some of the screened conditions. Patient advocacy groups exist in about half of the countries where newborn screening was recently expanded, but these groups were rarely involved in the decision to expand newborn screening.

Guidelines are nearly always available for laboratory diagnostic procedures, often for confirmation of screening results, but information to parents showed low levels for regulation and quality control. Epidemiological evaluation is rarely regulated by guidelines or directives, but practiced in most of the cases. Long-term outcome is scarcely monitored on the basis of a regulation.

Based on the results of the survey, scientific evidence and clinical practice, the European Network of Experts on Newborn Screening (EUNENBS), which was set up with experts of health authorities of EU member states, relevant European learned societies and European parents'/patients' associations to prepare a consensus document to support discussion for a future policy initiative has formulated 70 recommendations on how to develop NBS in Europe (Cornel et al. 2011). In the following we summarise the most important recommendations, but the reader is referred to the original document for more detailed information (http://www.iss.it/cnmr/prog/cont.php?id=1621&lang=1&tipo=64).

1. There is a clear need to develop case definitions for all disorders screened for, including an attempt to achieve agreement on these case definitions within the EU to facilitate assessment and international outcome studies.
2. The decision whether a screening programme should be performed can be based on a framework of screening criteria updated from the traditional Wilson and Jungner (1968) criteria, relating to disease, treatment, test and cost.
3. The interest of the child should be central in the assessment of pros and cons.
4. A 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.
5. 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.
6. Health Technology Assessment to evaluate the evidence on the effectiveness of early detection through newborn screening and treatment should be achievable in practice. For rare conditions, best level evidence should be used. Methods need to be developed to both optimise health benefit and careful evaluation.
7. Universal screening is generally preferable to ethnically targeted screening. If there are sound reasons (e.g. health gain) for targeted screening it is important to avoid stigmatisation.
8. The health system should ensure treatment to all confirmed cases diagnosed by screening.
9. Systems should be developed in order to support screening in countries where it would be beneficial but not affordable for economic and/or social reasons.

10. The EU should put in place systems for helping those countries where treatment is not yet available for all confirmed cases. The target of treatment for all confirmed cases should be achieved without reducing the quality of treatment.
11. Screening methodology should aim to avoid unintended findings, such as cases with mild forms and information on carrier status, as much as possible.
12. 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.
13. Economic evaluations of NBS programmes are needed. Balancing the right to care of all patients needs to take rare disorders into account.

Following an extensive discussion of the results of the survey as well as current scientific evidence and clinical experience the EUNENBS approved a list of disorders to be considered in the gradual expansion of NBS in the European Union (Table 5).

Over 50 disorders can be detected by NBS based on blood samples with varying methods, but also with varying certainty. It should be stressed that NBS is a comprehensive programme: it can not be focussed or even reduced to the part of the screening laboratory. Screening includes confirmation of the positive screening result, decision for or against treatment, choice of appropriate treatment options (e.g. diet, drugs, behavioural measures or mere observation) as well as long-term follow-up of patients and evaluation of outcome (Rembold 1998; Wilcken et al. 2012, see also Fig. 1). This expanded concept of NBS is not really new, as it can already be found in the seminal work by Wilson and Jungner (1968) on principles and practice of screening for disease.

An important framework to put principles into practice has recently been published by the US Secretary for Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children (Hinton et al. 2011). A two axes model of long-term follow-up (LTFU) for newborn screening has been formulated. Axis one comprises four components of LTFU (care coordination, evidence-based treatment, continuous quality improvement, and research), axis two deals with stakeholders after NBS (children and families, primary care providers, specialists and clinical researchers, and national state entities). There are four central tasks to be done in effective and efficient NBS follow-up. First, coordination of the different disciplines and

Table 5 Disorders[1] suggested by the EUNENBS to be considered in the expansion of NBS in the European Union

Group 1a Disorders with a relatively high prevalence, the test is not too difficult and health gain is proven	N of countries screening	Group 1b Disorders with lower prevalence, the test is not too difficult and health gain is proven	N of countries screening	Group 2 Candidates disorders where screening is more challenging according to the criteria by Wilson and Jungner 1968; cost-effectiveness, RCTs	N of countries screening
HPA	33	MSUD	12	BIO	10
CH	37	GAI	10	CMV infection	not surveyed
CAH	14	GALT	10	CPTII	7
CF	9			CACT	not surveyed
MCAD	13			GAII	6
S_S/SC/BTHA[2]	3-4			3HMG	5
				HCSD	6
				HCI	7
				IVA	9
				BKT	3
				LCHAD	8
				lysosomal storage disorders	not surveyed
				3MCC	6
				SCIDD	not surveyed
				TYRI & TYRII_III	7-3
				VLCAD	9
				Vitamin B12 DEFICIENCY	not surveyed

[1] For abbreviations see Table 2

[2] in Mediterranean countries and countries with migrant populations

individuals involved in treatment and care. Second, coordination of all stakeholders in new knowledge discovery and translational research. The third task is information flow between professionals and from professionals to patients and vice versa. Finally, there should be a structured process of quality improvement of care, knowledge and information. The suggested solution for these tasks is the concept of a medical home for the patient, a focal point for collaboration and coordination (van Dyck and Edwards 2006). Basically the medical home is a concrete physical entity where the patient can address all his/her questions and problems, linked with all specialists needed for information, treatment and care, i.e. a physical but also a virtual centre for diagnosis, treatment and care.

These requirements can at least implicitly already be identified in an article published by Blumberg more than half a century ago (Blumberg 1957) defining the objectives of screening programmes by obtaining epidemiological data on the nature of the disease, perfecting the screening procedures for future use, increasing the likelihood of future acceptance of other screening programmes, and improving the health of those in the screened community. The author also formulated four questions to be answered in a screening programme: 1. What is the outlook for a person with the disease?, 2. Who is going to do the diagnostic follow-up?, 3. What facilities exist for treating cases found?, and last but not least 4. What mental status accompanies knowledge or suspicion of the disease?

Our survey revealed that there are positive examples of NBS programmes that can be used as templates for further research and practice. In Europe for each disorder screened for there exists at least one guideline for each step of a screening programme. Furthermore, detailed outcome studies have been published for the Australian (Wilcken et al. 2009) and German (Lindner et al. 2011) screening panels, but also for single disorders (e.g. glutaric aciduria type I; Kölker et al. 2006; Heringer et al. 2010). Evidence-based guidelines are available for cystic fibrosis (Castellani et al. 2009), congenital adrenal hyperplasia (Auchus et al. 2010), and glutaric aciduria type I (Kölker et al. 2011), and the German Working Group for inborn errors of metabolism has approved a guideline on how to confirm positive screening results (Lindner 2010).

There is an ongoing discussion about guiding criteria for inclusion of single disorders into a screening panel (e.g. Petros 2011) and professionals will have to face the questions (not only for research purposes but also as they are asked by parents) “why are we all doing different things” (Pollitt 2007) and “how are we travelling, and where should we be going” (Wilcken 2011). We hope that the EU Council Recommendation for an Action in the Field of Rare Diseases (European Commission 2009) will lead to the establishment of lines for the cooperation and coordination among Member States in order to better utilise national resources and expertise as well as reducing inequalities in the access to high quality care. Continued support of research and other activities to tackle these challenges will be required.

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Conflict of interest None.

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Parents and patient organisations

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