

## ***Spotlight on...Newborn screening for rare diseases in Spain***

### ***Evolving technology for newborn screening challenges existing programmes and policies***

*The advent of now technologies such as electrospray ionization tandem mass spectrometry (MS/MS) means that newborn screening can now capture many more diseases, including the inherited disorders of intermediary metabolism. However, placing greater importance on the capability of a technology than on the diseases themselves makes it more likely for a now-detectable disorder to be included in a testing panel - regardless of whether treatment exists or not.*

*These developments, coupled with Spain's organisation into seventeen autonomous communities, present a challenge when it comes to organising, implementing, regulating, and gathering data for newborn screening programmes in order to ensure that all babies born in Spain receive equitable access to life-saving diagnostics. Dr. Teresa Pampols is a member of the board of directors of AECNE, the Spanish Society for Newborn Screening, in addition to working with the Institut de Bioquímica Clínica's Servei de Bioquímica y Genètica Molecular at the Hospital Clínic de Barcelona and CIBER de Enfermedades Raras (CIBERER). Here, she has graciously accepted to describe for OrphaNews Europe how newborn screening is organised and implemented in Spain and how the country is addressing the challenges brought about by evolving technology:*



## ***Historical Background***

Blood spot newborn screening (NBS) in Spain dates from 1968–1969, at which time Pr. Federico Mayor-Zaragoza at Granada University and Dr. Joan Sabater at the Institut de Bioquímica Clínica in Barcelona began offering NBS for phenylketonuria (PKU) and other amino acid disorders using existing paper chromatography and thin layer chromatography methods. Other centres soon followed this initiative and in 1977 the National Council of the “Real Patronato de Educación y Atención a Deficientes”, under the presidency of Her Majesty Queen Sofia, launched the *Plan Nacional Prevención Subnormalidad*, which included newborn screening amongst other actions. After several organisational changes, the *Plan Nacional Prevención Subnormalidad* was assumed and financed by the Ministry of Health and by 1980 there were 10 centres covering 25% of Spanish newborns. In 1983, after large political upheavals, the Spanish State settled into its present structure with 17 Autonomous Communities. Many competences, including Health, transferred to the corresponding Autonomous Governments. This fact is relevant for NBS, because it means that each Community has the authority to take its own decision of which diseases to include in its newborn screening programme. This organisation contributes to understanding the present situation.

## ***Current Scenario***

Spain has a population of approximately 46 million people, with nearly 500,000 births annually. NBS has never been mandatory, but in the 17 Autonomous Communities it is developed as a Public Health Programme that is universally and fairly offered to all the target population and has a compliance of practically 100%.

The newborn screening sample is taken in the maternity centres prior to discharge, most often after 48 hours of life. Early discharge is not frequent, but could increase; thus there is a field in the NBS cards for the registration of the number of hours of life, in order to interpret results and request a new sample when necessary. There is an exception in this procedure: six centres take two samples - from cord blood at birth or by heel prick at 48 hours – to screen for congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH) and sickle cell disease (SC) where they are included in the programme- as well as a second sample after 5 days of life for PKU. There are 21 centres/screening laboratories in Spain, all of which are public. This means that some Communities have more than one laboratory. Four laboratories analyse between 50,000-100,000 newborns per year; another four analyse between 20,000 and 50,000; and the rest analyse less than 20,000; six of these analyse less than 10,000 per year.

Screening for PKU and CH is universal. According to data from 2007, CAH is included in five programmes, representing a coverage of 25% of Spanish newborns; cystic fibrosis (CF) is included in seven programmes, covering 35% of the newborn population; SC is present in two programmes covering 17.5% of newborns; biotinidase deficiency and galactosaemia are available in one programme covering 4.4% of newborns and medium chain acyl-CoA dehydrogenase deficiency (MCAD) is offered in three programmes, covering 11.2% of newborns.

There are still some centres that historically continue looking for amino acid disorders in blood (six laboratories) and in urine (three laboratories), in an open manner using thin layer chromatography or other qualitative methods. It deserves to be mentioned that interest for the introduction of CF and SC is clearly growing; there is less enthusiasm for CAH, biotinidase deficiency and galactosemia. Indeed, in the case of the latter, Spanish paediatricians in general hold the opinion that the classic form is recognisable in time through clinical signs and that NSC is therefore not necessary. The expansion of newborn screening to the group of disorders of intermediary metabolism detectable by MS/MS merits specific mention and will be commented on later in this article.

The methodology used in the laboratories also illustrates disparity. Of the 20 laboratories testing for CH by measuring TSH, twenty use DELFIA® and one uses ELISA; some centres measure T4 in the same sample when TSH exceeds the cut-off value, while two centres systematically measure TSH and T4 in all the newborns. Hiperphenilalaninemas are detected via fluorimetry in 16 laboratories, MS/MS in three, enzymatically in one, and by thin layer chromatography in one. CAH is detected measuring 17-OH-P with DELFIA®. CF detection is also heterogeneous due to the adoption of different algorithms; basically the first test measures IRT via DELFIA® or ELISA, followed by DNA (30 mutations) and/or a second IRT at 20-30 days of life and posterior DNA.



The laboratories are deeply concerned by quality assurance issues; all participate in the External Quality Assessment (proficiency testing) programme for CH and PKU organised by [AECNE](#), the Spanish Society for Newborn Screening. The majority also participate in international controls based in Germany, the UK and via the Centers for Disease Control in the USA, that control for specific parameters. Nevertheless, very few laboratories are certificated under the Norm UNE-EN ISO 9001 and only one has the accreditation under the Norm UNE-EN-ISO 15.189.

***The expansion of newborn screening to the group of inherited disorders of intermediary metabolism detectable by means of electrospray ionization tandem mass spectrometry (MS/MS)***

MS/MS technology is used in Spain, along with a broad number of techniques, in certain Biochemical Genetics Laboratories, for the diagnosis of inherited metabolic disorders in symptomatic patients. Two of these laboratories have attained the criteria of excellence to be partners with [CIBERER](#), the Biomedical Network Research Centre for Rare Diseases. The differential diagnosis and study of positive cases proceeding from NBS, including gene studies, can therefore be validated. The use of ESI-MS/MS for newborn screening began in Galicia in 2001. Following a few years of dormancy, its use is now rapidly spreading. In 2007 three Autonomous Communities reported data (Galicia, Murcia and the Basque Country), in 2008 there will be four, with the addition of Andalucía, Zaragoza, Extremadura and probably some other Autonomous Communities will soon follow.

With MS/MS, Spanish screening centres began for the first time to use the name of the technology instead of the names of the diseases, breaking an important principle that must be restored. Evolving technology will scientifically and economically challenge existing programmes. The focus must be firmly on the diseases and it is indispensable that the criteria for inclusion in the NBS panel is based on sound principles and medicine-based evidence of the benefits for affected individuals, cost balanced, and with absolute control of incidental collateral damage, such as false positives.

Placing more weight on the capability of a technology than on the diseases makes it more likely for a disease to be included in a testing panel if it can be detected by the technology, regardless of whether the natural history of the disease is understood or whether treatment is limited or even non-existent. MS/MS technology is very attractive, and in some media it has been presented as the most powerful technology for the diagnosis of inborn errors of metabolism, introducing a dangerous bias. While it is true that MS/MS is a highly effective tool, it must be used in combination with other high performing technologies in patient diagnostics. Taking into account the small size of some laboratories together with the very low prevalence of the inherited disorders of intermediary metabolisms detectable by MS/MS, it is easy to be tempted to begin open screenings in order to try and justify the very low number of cases detected. However, this can be very dangerous; it is the antithesis of a newborn screening programme and would likely produce a high number of false positives. While it could be acceptable as a research project with an informed consent signed by parents or legal custodians, it is not acceptable as a public health intervention presenting succinct information.

In this context, the decision of the Basque Country is interesting. MS/MS was introduced uniquely for PKU and MCADD, because for these disorders studies exist demonstrating the cost-efficiency of NBS. Upon evaluation, the Basque Country health authority will consider adding other diseases.

Two studies deserving mention have been published on this subject in Spain. The first (see Reference 1) is a systematic review of the clinical effectiveness of NBS by means of MS/MS. This study concludes that while the heterogeneity of the studies makes it difficult to reach categorical conclusions, the best candidates for screening are PKU and MCADD; there are doubts for AGAI and Tyrosinemia Type I screening; and there is no evidence to support other diseases. The second article (Reference 2) is a cost/effectiveness study, which concludes that combined screening of PKU and MCADD shows a positive ratio; when the effectiveness of the screening of other inborn errors of metabolism becomes evident, it will improve the cost/effectiveness of the technology. The ratio is more positive when the number of samples is higher, being constant from 30,000-40,000 newborns/year. The results of this report support combined screening of PKU and MCADD in the Autonomous Communities that exceed 5,000 newborns/year.

In any case; it would be difficult in Spain to organise the screening in a few laboratories concentrating a number of samples to yield more efficient results, given the organisation of the country into Autonomous Communities.

Finally, another peculiarity could be mentioned – though it is perhaps not exclusive to Spain. Some professionals tend to misuse or to confuse the concepts of newborn screening and selective screening in symptomatic patients. This can be very dangerous for patients, because the clinical presentation of the inherited disorders of intermediary metabolism is stereotypic. There are more than one hundred diseases in this group and the Biochemical Genetics Laboratory must undertake a broad search in a sick newborn as prescribed by the clinician. The technology of MS/MS as applied to NBS is very limited and can delay reaching a diagnosis that is often urgent. It is absolutely necessary to keep generalist paediatricians educated about these facts and the diseases included in the panel must be clearly specified.

### ***Professional issues: The Spanish Society for Newborn Screening (AECNE)***

In 1985 a group of professionals involved in NBS created a study group for “Inborn Errors of Metabolism” within the Scientific Committee of the Spanish Society for Clinical Chemistry and Molecular Pathology (SEQC). Amongst scientific activities, including courses, external quality control and the elaboration of guidelines, the group also succeeded in the 1995 organisation of an annual meeting between the screening centres, with the financial support of the “*Real Patronato sobre Discapacidad* (<http://www.rpd.es>)”. Nevertheless there was a growing awareness that laboratories are only one partner in the

complex system that constitutes newborn screening programmes, and that improving the laboratories alone was not enough. Screening programmes must be an integral and integrated process, including all concerned professionals and partners. With this purpose in mind, we closed this study group in 2006 and founded [AECNE](#), the Spanish Society for Newborn Screening.

Our aim is to group into a multidisciplinary forum all the different professionals involved from the heel prick, through the diagnosis, the treatment and the follow-up of positive cases: nurses, midwives, biochemists, laboratory technicians, paediatricians, geneticists, endocrinologists, public health professionals, epidemiologists, bioethicists, researchers, and any professionals manifesting interest in the field of NBS .

AECNE organises the External Quality Control for PKU and CH, and with the support of the “*Real Patronato sobre Discapacidad*”, the annual meeting of the newborn screening laboratories. AECNE also produces an electronic journal and collects data on the activity of the screening centres. Thus the information concerning screening statistics presented earlier in this paper comes from the AECNE website, where additional information concerning other indicators of the programmes, as well as the results and incidence of the diseases included since its beginning can be found. This is made possible by a joint contribution of all screening laboratory directors who permit the collection of data and offer this valuable information publicly. The willingness to communicate and discuss results amongst the Spanish centres must also be mentioned.

### ***Ethical, legal and social issues***

It has already been mentioned that newborn screening in Spain is not mandatory by law. However, our society places a great value on this programme and refusal, if any, is anecdotic.

Traditionally, there is not a document of informed consent to be signed by parents; rather they receive an informative leaflet at the maternal centre in order to guarantee their informed participation in the programme. In many centres, pregnant women receive information concerning NBS in the process of education preparative for labour, which implies that midwives and obstetricians are also partners in the NBS programme.

New issues have arisen recently with the introduction of screening for disorders such as cystic fibrosis, for which treatment is not as effective as for PKU or CH. Moreover, IRT assay generates a high number of false positives, detects some heterozygotes, and includes DNA technology in the screening algorithm. This example, together with the growing complexity of the programmes, the awareness of ethical issues, and the approval of the Biomedical Research Act (see below), has generated a process of reflection in

the screening centres concerning the benefits and inconveniences of the introduction of informed consent.

In 2006, the Ethical Committee of the IIER (*Instituto de Investigación de Enfermedades Raras. Instituto de Salud Carlos III. Ministerio de Ciencia e Innovación*) published a document with recommendations on the ethical aspects of screening population programmes for rare disease with the aim to promote a public debate and in the hope to contribute to responsible guidance (3). This document contains 14 main subjects and 17 recommendations. Amongst these are the evaluation of the appropriateness of the programme by an independent scientific committee; the establishment of specific and integrated programmes; the need to distinguish clearly between investigation and intervention in public health; the constitution of a multidisciplinary group with a general director of the programme for the design of a detailed protocol, the creation of quality indicators, and checkpoints for the follow up of the whole programme; the need for informed consent for non-treatable diseases and screening for research purposes; the destiny of the samples after NBS; and the evaluation of the programme by an Ethical Committee, especially in the process of communication to the targeted population.

In 2007 a new Biomedical Research Act (*Ley 14/2007 de Investigación biomédica*) was approved whose main aim is to encourage biomedical research while ensuring the highest possible level of health, ethical and legal guarantees to protect the general population. This law, among other important functions, regulates genetic testing as well as genetic screening in biomedical research, and also in its healthcare applications. Amongst other dispositions, it establishes that access to the screening programme should be voluntary; applies the same rules established for genetic testing to the screening tests, and stresses the importance of psycho-social aspects of the programmes and the integration into the health system, as well as the evaluation of the programme by an ethical committee.

There are other two Spanish laws not specific to but relevant in the context of NBS. The personal data protection act (Organic law 15/1999) and Royal decree 944/199 and the act 41/2002, delineates basic regulation concerning the autonomy of the patient and the rights and duties concerning providing information and clinical documentation.

### ***The future of the NBS in Spain***

The undertaking of a process of study and discussion are urgent in order to reach a consensus concerning the diseases to be included in the newborn screening panels. The establishment of a minimum programme of treatable diseases to be implemented in all the Autonomous Communities in order to satisfy the principle of equity for all newborns in Spain is indispensable. As professionals, we can not face this challenge alone. Recently, the President of AECNE (Pr. Ernesto Cortés) and a representative from its board of directors were received by

the Minister of Health, who took the commitment to set the pace to reach this objective. The “Inter-territorial Council” – the organ that joins representatives from all the Autonomous Governments and has the faculty to harmonise decisions in matter of health – will assume this responsibility. AECNE representatives have been invited as experts to work in this process. Probably, as has been seen in other countries, it will not be easy, but we think that we are on the right path and that we will see positive changes in the near future.

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(This can be accessed in Spanish and English at <http://www.isciii.es>)

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