ECFS Neonatal Screening Working Group

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UPCOMING EVENTS

39th ECFS Conference,
Basel, Switzerland
08-11 June 2016

# The Neonatal Screening Working Group Annual Meeting

**Brussels, Belgium**
**10th June 2015**

The Grand Place, Brussels

Newborn screening for CF was a hot topic at the European CF Conference in Brussels, with a dedicated symposium and workshop and mentions in many meetings including the Plenary sessions. In addition, the Working Group organised the sixth satellite meeting to be held on the Wednesday before the meeting. Attendance has increased year on year and in the Lecture Theatre in Brussels we had over 110 delegates. The presentations were excellent and summaries from selected presentations are presented below.

## Progress Report from Belgium, Marijke Proesmans, University of Leuven, Belgium

Professor Proesmans welcomed delegates to Brussels and provided a summary of the current status of newborn screening for CF in Belgium. Most neighboring European countries have national or regional screening programmes for CF. In Belgium a project was started in 2009 investigating the need and feasibility of neonatal screening for CF in Belgium. This project was initiated and coordinated through the national knowledge center (Federaal Kenniscentrum). A group of experts including CF clinicians, doctors involved in current newborn screening, geneticists and health economists participated in this project. The consensus of this project was that there is an indication for newborn screening to be started in Belgium. The median age of diagnosis in Belgium is around 7 months which can be improved with neonatal screening to about 2 months of age. BMI z-score is lower than the general population already from the age of 2 to 5 years and worsening after the age of 5 years. Different possible algorithms were investigated.

After this project was finalized, Belgium went through an unsettled political situation; not being able to form a government after the elections. An additional difficulty is that newborn screening programmes are not under the responsibility of the national government but regional governments. The Flemish and Walloon parts of the country have different screening programmes. In 2012 an application was made to 'the Flemish agency for population screening' after which a positive decision

was given. Since then we have been trying to lobby with the different regional governments for institution of screening but apparently this is not on the priority list of the government right now. We hope that hosting the ECFS conference in Brussels his year will put Cystic Fibrosis in the spotlight. This may help to bring newborn screening for CF on the political agenda. (Editorial note; this certainly was a common theme throughout the meeting and during a presentation to MEPs at the town hall).

## Newborn screening for CF at National Level in Spain

**Silvia Gartner, Hospital Universitari Vall d´Hebron, Barcelona, Spain**

Spain has settled into its present structure with 17 autonomous communities. Each community decides independently which diseases to include in its newborn screening (NBS) programme. In 1999, Cataluña and Castilla-León, started NBS programme for Cystic Fibrosis (CF). A few years later the Balearic islands and Galicia began NBS. In the last 5 years, implementation has spread more rapidly and from 2015 all 17 autonomous regions of Spain include CF in their NBS programmes.

The Clock Tower at the Square Meeting Centre, Brussels

Spain has a population of approximately 46 million people with nearly 450,000 births annually. Up to 2014, these programmes had screened almost 3,000,000 infants for CF and detected 470 affected babies. Because of the heterogeneous ethnic mix in the South compared to the North, there are many different NBS strategies across Spain. All regions use IRT measurement as the first step in the protocol, most often followed by DNA testing + sweat test. Some strategies measure the IRT level on a second blood spot from newborns with raised IRT at birth. Babies with persistently elevated IRT levels are tested for *CFTR* mutations. For other protocols a high IRT measurement triggers *CFTR* mutation analysis with a selected panel of mutations or *CFTR* scanning. Infants with one or two mutations are referred for sweat testing in the CF Units.

In Cataluña, during 17 years more than one million newborns were screened with an incidence of positive cases of 1/6631, lower than expected. Other examples of prevalence in Spain are: Castilla-León 1/4925, Madrid 1/ 6160, Pais Vasco 1/ 7.700 and Balearic islands 1/5853.

Newborn screening allows aggressive treatment of the first isolation of *Pseudomonas aeruginosa*. Lower rates of chronic *Pseudomonas aeruginosa* infection were reported with an average of 8% (in a region with NBS for more than 5 years). However, higher rates of chronic *Staphylococcus aureus* are reported with an average of 24% (0-40%).

To achieve these benefits, early diagnosis must be followed by a high standard of CF care. If this care is not available, it is unlikely that screening will have a significant favourable effect on either the health or survival of affected children.

Finally, each strategy has different advantages in terms of CF prevalence, *CFTR* mutation distribution and financial aspects. Our current aim is to harmonize protocols in order to ensure that all babies born in Spain receive equitable access to an early diagnosis and appropriate management.

## Early experience from the Turkish Newborn Screening Programme
Refika Ersu and Bülent Karadağ, Marmara University, Istanbul, Turkey

The national Newborn Screening Programme started in Turkey at the beginning of 2015. Collaboration with patient organizations and effective media use made it easier to convince the decision makers. Turkey has a relatively low incidence of CF (approximately 2500 CF patients in a population of 80 million) and NBS was presented as a good opportunity to diagnose patients in a timely manner and increase the public awareness.

There are 1.3 million births each year in Turkey and the expected number of CF infants would be between 250-500. Given the geography and the population characteristics, a two stage IRT-IRT protocol was chosen with the first IRT sample taken between days 3-5 and the second between days 7-14.For infants with two raised IRT values (for the 1st and 2nd IRT measurements, 90 and 70 ng/ml, respectively), sweat testing was organised as a confirmative diagnostic test. Due to the wide distribution of CF causing mutations we did not use genetic testing. Educational leaflets for sweat testing and CF Screening Guideline were prepared.

In the first 5 months, 550,000 babies were screened. There have been some early challenges including collecting data on the exact number of infants diagnosed with CF. Efforts are underway to improve reporting pathways to the Ministry of Health. At the moment only 18 cases have been confirmed, though reports from CF centres suggest this should be nearer to 70. There appears to be a relatively low positive predictive value, with a large number of sweat tests being organised. The IRT cut-offs will be reassessed; however the main problem has been the challenge of organising sweat tests (with 30% of tests missing or not organised). The screening team are considering pragmatic solutions to this problem. In summary despite some early problems a national programme has been established in this large country with a low incidence of deltaF508.

## Moving towards a national newborn screening programme for CF in Germany
Olaf Sommerburg, University Children's Hospital III, Heidelberg, Germany


L-R. Kevin Southern, Milan Macek, Refika Ersu, Olaf Sommerburg, Danya Vears, Patrick Sosnay, & Bülent Karadağ

Concerns about DNA testing as part of CF newborn screening (CF NBS), including detection of heterozygotes, clinically equivocal forms, legislative and ethical issues, as well as limited coverage of ethnic diversity; has led to consideration of alternative purely biochemical protocols in Germany in favour over the well performing IRT/DNA protocols. In 2008, two regional NBS centers launched individual studies evaluating CF screening protocols with IRT as first and pancreatitis associated protein (PAP) as second tier analysis. The CF NBS center in Dresden (East-Saxony), which has experience with CF NBS since the 1980s, started using IRT/PAP according to the original protocol (Sarles et al. 2005). The NBS center Heidelberg (Southwest Germany) started with a modified IRT/PAP protocol (floating IRT cut-off and one single cut-off for PAP) which is since then compared internally to a standard IRT/DNA protocol (using the most common four mutations in Southwest Germany) run in parallel. In contrast to other NBS centers evaluating PAP based protocols both German NBS centers implemented an IRT-dependent safety net (SN) into the protocol. Accordingly, CF-NBS was also rated positive when IRT was 99.9th centile. Since 2013 a third German NBS center (Greifswald, Mecklenburg-Western Pomerania) offers CF screening as well using the IRT/PAP protocol with SN as done in Dresden.

Since 2008, the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) is responsible for the decision whether to include CF as part of the regular NBS programme in Germany. The G-BA is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany. It issues directives specifying which services in medical care are reimbursed by health insurances. In 2014, the G-BA published a first draft directive on CF NBS in Germany. It was recommended that CF NBS with

an IRT/PAP/DNA protocol should be implemented. The studies to date had shown that PAP may provide advantages in the German screening program which routinely collects samples between 36 and 72 hours of age. The inclusion of PAP shows sufficient sensitivity and specificity. However, the committee has realized that a lower positive predictive value (PPV) is obtained in screening protocols using IRT/PAP solely when compared to other existing CF screening protocols. Therefore, DNA analysis as third tier was included to improve PPV. The protocol finally chosen uses one single PAP cut-off (1.6 ng/ml) together with an IRT-dependent safety net (set at IRT > 99.9th centile). Third tier analysis will make use of a DNA panel with 31 *CFTR* mutations. The draft directive is currently discussed by a number of medical societies and commissions, including the German Gene Diagnostic Commission, which is able to advice corrections. The final decision on the implementation of CF NBS in Germany is now expected for late summer 2015.

## CFSPID from the Perspective of an Adult CF physician
## Nicholas Simmonds, Royal Brompton Hospital, London, UK

Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID) may be a new definition but it has long been recognised that patients within the spectrum of CF and CFTR-related disorders can have variable penetrance of the disease and thus present in adulthood with a variety of symptoms. Some of these patients would have fulfilled the criteria for a designation of CFSPID had newborn screening existed when they were born. When these patients present to adult services they can have established disease, such as bronchiectasis, and may have been misdiagnosed by many physicians over a protracted period (e.g. labelled as an 'asthmatic'). This can lead to poor health, psychological challenges and general disillusionment with the health service.

Dr Simmonds presented three cases all presenting to the adult clinic with significant morbidity and psychological issues. On receiving the diagnosis of CF, their health statuses improved significantly and many of the psychological issues were better controlled as the patients finally had an understanding of their disease and a coordinated health care system which could appropriately manage their needs. The key message from the presentation was that adult patients are frequently relieved and grateful to receive the diagnosis; speculating that much of their suffering may have been alleviated had they been through a neonatal screening programme and had an appropriate level of follow-up with the designation CFSPID.

## Plans to develop a coordinated international approach to diagnostic designation
## Patrick Sosnay, John Hopkins, Baltimore, USA (on behalf of Phil Farrell)

The US CF foundation will revisit the CF diagnostic criteria last published in 2008, with a consensus meeting planned for the North American CF Conference (October 2015). The key objectives, and the major revisions needed to the existing guidelines include:

- Now that there is greater newborn screening (universal in the US, much of Europe, Canada, Australia, and New Zealand; increasing in other parts of the world), there is a need to examine how different NBS methods lead to different diagnostic challenges.
- There is some disagreement over the utility and validity of sweat testing, especially in the USA where the need for and value of confirmatory sweat testing after NBS has been challenged.
- Assessment of advances in standardization of ancillary procedures such as nasal potential difference, fecal elastase measurement and intestinal current measurement.
- Increased screening has identified individuals who do not meet CF criteria, but have clinical features and/or genetics variant that may be associated with disease later in life. These individuals are labelled as CFTR related metabolic syndrome (CRMS) in the US and CF screen positive, inconclusive diagnosis (CFSPID) in Europe. The consensus will examine the utility of both terms, and provide guidance for ways to reconcile that diagnosis and determine optimal follow-up.
- Issues related to diagnoses in non-screened populations such as adults will also be reviewed and revisions in guidelines considered.

These objectives will be addressed by a team of experts from throughout the world. Diagnostic challenges in the screened as well as non-screened populations will be considered. These results will be published as an update of the CF diagnostic criteria.

## Impact of carrier identification in families

**Danya Vears, University of Melbourne, Melbourne, Australia**

Identification of children as carriers of cystic fibrosis can occur in a number of different ways. In some cases, testing might take place intentionally, when parents request for their other children to be tested following the diagnosis of a child with CF. However, the majority of international guidelines which address carrier testing in childhood recommend delaying testing until the child either reaches the age of majority or can be involved in the decision making process.

Children may also be identified as carriers incidentally, where carrier status is a by-product rather than the goal the test. This may occur through prenatal testing, excluding affected status in an older sibling following the diagnosis of another children, or most commonly, through newborn screening. Interestingly, there are considerable differences with how these incidental carrier results are managed and recommendations vary regarding whether these results should be disclosed to parents.

A small number of studies have assessed how parents cope with receiving carrier information about their children following newborn screening, with mixed results. Some studies have shown that parents may experience confusion after receiving these results (Ciske et al. 2001; Kai et al. 2009) and some parents may have residual anxiety about their child's health or future reproduction (Lewis at al. 2006). However, a recent study showed that in most cases this anxiety is transient and that distress is often due to the way the information is conveyed, rather than the information itself (Ulph et al. 2014). In addition, parents often receive this information at the same time they are told their child is not affected with CF so carrier status is less of an issue for them (Vears, 2015).

Little is known about how children found to be carriers through newborn screening programs fare after learning their carrier status. Yet a few studies have assessed psychosocial outcomes in adolescents following deliberate carrier testing in childhood in the context of an affected child (McConkie-Rosell at al. 2008; Jarvinen et al. 1999; Jarvinen et al. 2000). These studies do not show any negative outcomes from this testing, although more research is needed. In particular, although parents seem to have good intentions to communicate carrier information to their children when they have an affected child (Vears, 2014), more information is required to determine whether parents do tell their children who are found to be carriers through newborn screening about their status.

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## Milan Macek - Department of Biology and Medical Genetics, Charles University Prague – 2. Faculty of Medicine and University Hospital in Motol, Prague, Czech Republic

There are increasing disparities in terms of the rapid production of biomedical data, by e.g. next generation sequencing technologies (NGS) in genetics / genomics and lagging clinical validity and utility of such data within the domain of health care. The falling price of DNA sequencing which now exceeds Moore´s law for semiconductors and the relative rapid increase in genetic testing outside of the traditional "germ line" diagnostic domain, e.g. tendency to use DNA sequencing in neonatal screening within second line "post-IRT" tiers creates strong pressures on a) finite resources in all solidarity principle-based European health care systems and b) on proper interpretation of detected variants (i.e. detection of variants of unknown significance).

A view from above the conference centre, Brussels

It should be noted that the CFTR2.org database has established "disease liability" of *CFTR* gene mutations in a small fraction of the overall allelic variation in the *CFTR* gene. Moreover, data on intragenic rearrangements, larger indels are mostly missing, majority of which could be identified by "deep sequencing". Utilisation of DNA sequencing in neonatal screening, be it classical (Sanger sequencing) or NGS leads to a substantial increase in costs and also increases the overall number of cases with CFSPID. Moreover, NGS enables sequencing of not only the *CFTR* gene itself, but also of the remainder of the human coding sequence (hence "exome"), which creates additional problems in terms of detection of unsolicited secondary findings (eg. in breast cancer genes *BRCA1/BRCA2*). Due to the aforementioned reasons and if possible DNA sequencing within the context of CF neonatal screening should be avoided at this stage of knowledge. Sequencing could be justified if the screened population is very heterogeneous (eg. due to sizeable non-European admixture). On the other hand specific panels of CF-causing mutations, accounting for at least 85 % of population specific alleles, provide maximum diagnostic utility and least "headache" in terms of uninterpretable results. Overall, CF newborn screening programs should carefully examine the pro/cons related to the use of DNA sequencing within secondary screening tiers.

## Aims of the NSWG

1. To support the implementation of newborn screening for CF
2. To monitor performance and compare protocols to optimise effectiveness, whilst reducing negative impact
3. To encourage enrolment of all infants identified through NBS in clinical trials
4. To determine the optimal management of infants with CF Screen Positive, Inconclusive Diagnosis (CFSPID)
5. To improve the processing of positive newborn screening results

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If you have anything you wish to add to the next ECFS NSWG Newsletter please email:
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