Newborn Screening for Sickle Cell Disease in Europe: recommendations from a Pan-European Consensus Conference

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ORIGINAL RESEARCH

Newborn Screening for Sickle Cell Disease in Europe: recommendations from a Pan-European Consensus Conference

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Running Title: Consensus on NBS for SCD in Europe

Abstract

Sickle Cell Disease (SCD) is an increasing global health problem and presents significant challenges to European health care systems. Newborn screening (NBS) for SCD enables early initiation of preventive measures and has contributed to a reduction in childhood mortality from SCD. Policies and methodologies for NBS vary in different countries, and this might have consequences for the quality of care and clinical outcomes for SCD across Europe. A two-day Pan-European consensus conference was held in Berlin in April 2017 in order to appraise the current status of NBS for SCD and to develop consensus-based statements on indications and methodology for NBS for SCD in Europe. More than 50 SCD experts from 13 European countries participated in the conference. The aim of this paper is to summarise the discussions and present consensus recommendations which can be used to support development of NBS programmes in European countries where they do not yet exist, and to review existing programmes.

Key Words

Sickle cell disease, sickle cell anaemia, haemoglobinopathies, newborn screening, prevention

Introduction

SCD is an autosomal recessive inherited blood condition. It has recently been reviewed elsewhere (Piel, *et al* 2017, Ware, *et al* 2017). Briefly, the sickle mutation causes a substitution of valine for glutamic acid at position 6 of the beta globin chain. This results in a defective haemoglobin molecule (HbS) which can aggregate and form polymers with adjacent haemoglobin molecules when in the deoxygenated state. As a consequence, red blood cells become damaged by polymerised HbS. Repeated cycles of polymerisation-depolymerisation damage the erythrocyte cytoskeleton and cell membrane, leading to a decrease in erythrocyte lifespan which is clinically apparent as haemolysis and its sequelae. There is also defective flow of red blood cells in the microcirculation resulting in occlusion of capillaries and postcapillary venules. Haemolytic and vaso-occlusive phenomena give rise to vascular remodelling and large vessel complications. Both, acute infarctions and large vessel disease cause progressive life-limiting organ damage.

Complications of vaso-occlusion include dactylitis (painful swelling to the hands and/or feet), acute pain episodes, acute chest syndrome and others. Children with SCD are particularly prone to Invasive Pneumococcal Disease (IPD) as a result of functional hypo-/asplenia (Overturf, *et al* 1977, Payne, *et al* 2013, Powars, *et al* 1983, Wong, *et al* 1992b). Other causes of morbidity and mortality include acute anaemia secondary to splenic sequestration, parvovirus B19 infection and malaria (in endemic regions) (Ballas, *et al* 2010). Complications of SCD result in frequent hospitalization for treatment, which is burdensome for health care systems (Bou-Maroun, *et al* 2018, Brozovic, *et al* 1987, Colombatti, *et al* 2008, Lanzkron, *et al* 2010, Raphael, *et al* 2013).

Globally, SCD is among the commonest inherited disorders. Every year, more than 300.000 babies are born with SCD, the majority in Sub-Saharan Africa and in India (Piel, *et al* 2016, Piel, *et al* 2013, Serjeant 2017, Ware, *et al* 2017). Although morbidity and mortality rates in affected children from these regions are very high (Grosse, *et al* 2011, Makani, *et al* 2011), outcomes have been dramatically improved in higher income countries by implementation of early preventive measures and improvements in comprehensive care (Couque, *et al* 2016, Gaston, *et al* 1986, Le, *et al* 2015, Quinn, *et al* 2010, Vichinsky, *et al* 1988). Life-threatening early complications of SCD can be reduced by parental education and preventive medical interventions (Couque, *et al* 2016, Quinn, *et al* 2010, Wang, *et al* 2011, Yawn, *et al* 2014). Pneumococcal prophylaxis with oral penicillin from three months of age, and pneumococcal

vaccination significantly reduce the risk of IPD (Falletta, *et al* 1995, Gaston, *et al* 1986, Overturf and Powars 1980, Rankine-Mullings and Owusu-Ofori 2017, Sobota, *et al* 2015, Wong, *et al* 1992a). Parents can be taught how to recognise signs and symptoms of anaemia, and how to examine for splenic enlargement so that they can bring the child to medical attention promptly and avoid adverse outcomes from acute splenic sequestration (Wang, *et al* 2011). These observations have helped to support inclusion of SCD in the NBS programmes of several European countries (Table 1).

There are two alternative approaches to NBS. "Targeted screening" takes the ethnic ancestry of every newborn into account. Testing is restricted to babies whose parental family origins are from 'at risk' ethnic groups. In contrast, "universal screening" is offered to the whole newborn population irrespective of family origins.

In its publication "A Roadmap for European Haematology Research" (Engert, *et al* 2016), the European Haematology Association (EHA) recommended undertaking detailed epidemiological studies in all countries, in particular in Western Europe, as a prerequisite for the implementation of effective prevention programmes. Previously there have been efforts to develop uniform standards for care of SCD across Europe (de Montalembert, *et al* 2011, Engert, *et al* 2016), but significant variation in practice persists. Two factors have recently highlighted the need for a more coordinated approach to diagnosis and management. Firstly, the globalization of migration flows has increased cultural diversity, bringing to Europe populations from areas with high prevalence of SCD and increasing the number of patients (Cortes-Castell, *et al* 2017, Inusa and Colombatti 2017, Kunz, *et al* 2017, Piel 2016, Roberts and de Montalembert 2007). Secondly, health policies and health systems across the European Union (EU) are becoming increasingly interconnected, because of patients getting healthcare across the EU, health professionals working in different EU countries, higher expectations for healthcare and new developments in health technologies (EU 2011). The "Pan-European Consensus Conference on Newborn Screening for Haemoglobinopathies" which took place in Berlin, Germany, on April 29 and 30, 2017, brought together more than 50 experts with both laboratory and clinical background from 13 European countries; it was endorsed by EuroBloodNet, the European Reference Network (ERN) in Rare Haematological Diseases (www.eurobloodnet.com).

The conference had two major goals:

1) To provide an overview of current NBS policies and epidemiological data across Europe.

2) To identify key questions from both laboratory and clinical perspective which relate to implementing and sustaining NBS programmes in Europe, and to attempt to reach a consensus statement on each of these questions.

The purpose of this paper it to report a summary of the data discussed at the conference and to present the consensus statements.

Methodology

The idea of a European meeting to address priorities for SCD was first suggested at the Global Sickle Cell Disease Network (GSCDN) meeting in Rio de Janeiro, Brazil, 11-14 November 2014, and further developed at the 10th Annual Conference of the Academy of Sickle Cell and Thalassaemia (ASCAT) in London, 5-7 October 2016. NBS was suggested as the first issue to be addressed, being the first specific intervention after birth.

Four months before the conference, clinical and laboratory experts in the field of SCD were invited from European countries where SCD is considered a health care issue. Experts were selected on the basis of their publications and/or presentations at scientific meetings. They were joined by representatives from national scientific societies, national SCD reference centres and national NBS programmes.

The steering committee (RC, EC, JE, SL) prepared a standardized form for the presentation of each country's national data on NBS (available as online supplementary material 1) that was sent to the speakers one month in advance of the conference. The committee also drafted a list of questions for consensus discussion (available as online supplementary material 2). On the first day of the conference, key topics in epidemiology, screening and NBS techniques were reviewed. Representatives from 12 countries (Cyprus, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, Turkey, UK) then reported available data on NBS for haemoglobinopathies in their countries (agenda available as online supplementary material 3).

On the second day, consensus questions were discussed and experiences of NBS for SCD outside Europe were explored. The discussion was moderated by an independent non-European specialist (KOF) who was assisted by a patient representative (JJ).

Results

National Policies and Country Presentations

National screening policies were found to be quite heterogeneous across European countries, and data on the number of affected patients were not available for every country. Moreover, there was no standardized approach to defining the population to be screened, the screening methodology and the flow of samples and patient reports.

England, Wales, Scotland, Northern Ireland (Streetly, *et al* 2010, Streetly, *et al* 2017), France (Bardakdjian-Michau, *et al* 2009, Couque, *et al* 2016), Spain (Cela, *et al* 2017, Manu Pereira and Corrons 2009) and the Netherlands (Bouva, *et al* 2010, Jans, *et al* 2012) have established national NBS programmes for SCD. In Belgium, a regional screening programme has operated in Brussels and surrounding areas since 1994 and in Liège and surrounding areas since 2002 (Gulbis, *et al* 2009). In Germany (Frommel, *et al* 2014, Grosse, *et al* 2016, Kunz, *et al* 2016, Lobitz, *et al* 2014), Ireland (Gibbons, *et al* 2015) and Italy (Ballardini, *et al* 2013, Lodi, *et al* 2017, Martella, *et al* 2017, Rolla, *et al* 2014), there are completed pilot studies. Some countries have reported a reduction in mortality and SCD related complications (Le, *et al* 2017, Telfer, *et al* 2007, van der Plas, *et al* 2011) and economic benefits for their health care systems (Castilla-Rodríguez, *et al* 2016, Okpala, *et al* 2002, Streetly, *et al* 2017).

Haemoglobinopathy programmes in Turkey and Cyprus are aimed at prevention, and based on premarital screening and prenatal diagnosis (Angastiniotis and Hadjiminas 1981, Canatan 2014, Kountouris, *et al* 2016). A few countries with evidence of increasing number of patients have not yet considered planning national strategies. Table 1 provides an overview of the status quo of NBS for SCD in Europe. Detailed data presented by country representatives are summarized in Table 2.

Consensus Questions and Statements

1. Do you agree that the future burden of SCD in Europe will be increasing?

It was undisputed that the burden of SCD in Europe has been increasing and is likely to continue to increase in the foreseeable future (Piel 2016). This increase is due to three factors: (1) an increase in the number of newborns (Piel*, et al* 2013); (2) an increase in life expectancy of SCD (Gardner*, et al* 2016, Le*, et al* 2015, Quinn*, et al* 2010) and (3) an increase in the number of immigrants with SCD from areas of high prevalence (Inusa and Colombatti 2017, Kunz*, et al* 2017).

These three factors make a variable contribution to the burden of SCD in different European countries. For example, in Spain, the number of SCD patients increased significantly 10-15 years ago as a result of immigration from Africa, but appears to have stabilized in the past couple of years (Cela*, et al* 2017). In contrast, Italy, France and Germany have recently been accepting large numbers of refugees and have faced a dramatic increase in their patient numbers since 2014. In England, where there is a well-established linked newborn and antenatal screening programme for SCD and thalassaemia, a downward trend in reported screen positive results is discernible in some areas (NHS 2018). However, the total patient number continues to increase due to the improved life expectancy attributed to the success of the national disease management programme and awareness campaigns (Gardner*, et al* 2016).

Many epidemiologic questions on SCD remain unanswered due to the lack of standardized national data collection systems across Europe. A European Haemoglobinopathy Registry could enhance monitoring of changing demographics, service delivery, and patient outcomes, and improve patient access to care (Inusa and Colombatti 2017). Of the countries that participated in the conference, national registries for SCD exist in the Belgium, Cyprus, Germany, Greece, Spain and the UK (Cela*, et al* 2017, Kountouris*, et al* 2016, Kunz*, et al* 2017, Le*, et al* 2015, NHS 2017a, Voskaridou*, et al* 2012).

Consensus Statements

1a. In Europe the burden of SCD has increased and will continue to increase.

1b. It is desirable that all European patients with SCD are enrolled onto registries, with standardized data collection and coordinated follow-up.

2. What are the target diseases in a NBS programme for haemoglobinopathies?

The panel noted that there was good evidence for the benefit of detecting SCD at birth and was unanimous that SCD (all genotypes) should be the primary target disease of a NBS programme. Although there was insufficient evidence of a clinical benefit in diagnosing beta thalassaemia major in newborns, the panel supported the recommendation that a suspected diagnosis should be reported to the family. This consensus takes into account that beta thalassemia major will be detected as a "by-product" of most test methods ("F only pattern"). All panel members agreed that it is advantageous to detect thalassaemia major early in order to counsel and prepare the family for the care of a sick child.

Consensus Statements

2a. The target disease of a NBS programme for haemoglobinopathies is SCD, including all genotypes.

2b. Beta thalassaemia, whilst not a formal target disease of a NBS programme for haemoglobinopathies, should also be reported.

3. What are the benefits of an early detection of SCD?

The panel noted good evidence that early detection of SCD reduces morbidity and mortality. In particular, IPD can be reduced by pneumococcal vaccination and early initiation of prophylactic oral penicillin (Couque*, et al* 2016, Le*, et al* 2015, Quinn*, et al* 2010, Sobota*, et al* 2015). This benefit of early detection may have reduced in recent years because children in most European countries receive conjugate pneumococcal vaccinations as part of routine infant vaccination schedules. However, strains not included in the vaccine remain a problem, which may worsen in the future (Camilli*, et al* 2017, Latasa Zamalloa*, et al* 2017, Oligbu*, et al* 2018, Payne*, et al* 2013, Tin Tin Htar*, et al* 2015, Waight*, et al* 2015). Antibiotic prophylaxis therefore remains necessary. Morbidity and mortality due to infections, acute anaemic episodes, and vaso-occlusive events such as acute chest syndrome can be further reduced by parental education and clear pathways for accessing care and effective treatment protocols (Olney 1999, Serjeant*, et al* 2018). The incidence of childhood stroke can also be reduced by about 90% through transcranial Doppler (TCD) screening from two years of age and transfusion of children with confirmed abnormal transcranial Doppler velocities (Adams*, et al* 2005, Adams*, et al* 1998, Adams*, et al* 1992).

The panel agreed that a NBS programme must be accompanied by a comprehensive care programme for affected infants. This requires a sufficient number of centres to provide access to comprehensive care, together with awareness campaigns and patient involvement throughout the geographical region of screening. A treatment guideline adapted to national specifics is desirable. However, as several guidelines are available in Europe, including a European recommendation on comprehensive care for children with SCD (de Montalembert*, et al* 2011), the presence of a national guideline is not mandatory.

Consensus Statement

3. Early diagnosis by NBS, together with anti-pneumococcal penicillin prophylaxis and vaccination, coordinated follow-up and parental education, reduces morbidity and mortality from SCD in childhood.

4. Which countries should screen for SCD?

The panel agreed that it is not necessary to define a threshold of birth prevalence that would be required for implementation of NBS for SCD. Nevertheless, epidemiological data should be available to support the decision to implement NBS screening (e.g. pilot studies, registry) and cost-effectiveness should be evaluated (Castilla-Rodríguez*, et al* 2016, Davies*, et al* 2000, Grosse*, et al* 2005, Kuznik*, et al* 2016).

The panel acknowledged that it is not possible to detect SCD as a by-product of tests currently used in NBS for metabolic or endocrine target diseases. NBS for SCD requires the addition of a further testing methodology to the existing NBS programme.

In principle, any screening programme should be cost-effective. There is evidence from the literature that cost-effectiveness of NBS for SCD is reached if the birth prevalence is in the order of 1:6000 births (Castilla-Rodríguez*, et al* 2016). However, other factors such as organization of the screening programme (centralised vs. de-centralised infrastructure), screening method and effectiveness of health care measures (Grosse 2015) could also determine cost-effectiveness. Each screening programme should be periodically evaluated to ascertain its benefits

Consensus Statements

4a. The implementation of a national NBS programme for SCD should be informed by a review of national epidemiological data on SCD, but should not be based solely on a threshold birth prevalence. Where not available, these data should be collected.

4b. A NBS programme should be developed and implemented alongside a national disease management strategy.

5. Who should be screened?

This question aimed at a consensus on whether to screen all newborns ("universal NBS") or only newborns considered to be at risk on the basis of ethnic origin ("targeted NBS"). The panel agreed that NBS for SCD should be universal, i.e. all newborns should be screened independent of their putative ethnic origin.

Targeted screening is error-prone (Thuret*, et al* 2010) and could result in stigmatization of certain individuals from at risk ethnic groups. Missed cases (false negatives) result from incorrectly assigning a parent to a low-risk ethnic group, failure to take into account more distant ancestral origins, or to a range of administrative errors (Grosse 2015). In countries where SCD is rare, health care professionals may not be aware of the individual risk for a couple. Language barriers may be another source of error, particularly for parents from at-risk immigrant populations in Europe who may not be familiar with the language of the new country. Considering the disadvantages of targeted screening approaches, the panel urges health care teams involved with antenatal and neonatal care to evaluate newborns on a case-by-case basis (carefully considering the family history) if there is no NBS programme in place.

In countries where all pregnant women are offered carrier testing (antenatal screening), universal NBS may be considered unnecessary. However, in practice, linkage of antenatal screening and NBS is operationally challenging. Furthermore, deficiencies in the antenatal screening pathway, such as failure to notify and counsel the mother of a positive carrier screening result could impact the offer of NBS and result in failure to identify an affected infant.

Consensus Statements

5a. The panel recommends universal NBS screening for SCD in all countries participating in the conference.

5b. Targeted screening based on ethnic origins is not recommended because of the higher risk of failure to identify an affected newborn.

5c. In countries where national NBS screening for SCD is not implemented, an interim policy should be agreed for testing at-risk newborns on a case-by-case basis according to family origins.

6. Should carriers identified in NBS be informed about their result?

The carrier status (HbAS) is not completely harmless and is a risk factor for several complications, including heat-related rhabdomyolysis (Kotila 2016, Naik and Haywood 2015). These complications are nevertheless extremely rare and unlike SCD, the carrier status does not fulfil criteria required of a medical condition to justify newborn screening. However, it is reliably identified by the testing and can be considered as by-product of NBS screening. The identification of carriers is a potential instrument for future disease control (Jans*, et al* 2012, Piel 2016, Roberts and de Montalembert 2007). According to the patient representative (JJ), most carriers would like to know about their future risk of having an affected baby. Experiences from countries outside Europe show that parents are willing to receive this information (Ulph*, et al* 2014), and a variety of strategies have been adopted for informing parents of carrier results (Ontario 2015).

There was consensus that parents of carriers should be informed about these test results and that families should know that a disease-causing mutation is present as this information may affect reproductive choices in the future. The panel also considered the knowledge of carrier status an important means of increasing awareness about SCD within society. The panel agreed that reporting positive carrier results should be followed by the offer of counselling of affected families by trained staff in order to avoid confusion and anxiety. The delivery of the information should follow a well-defined standardized policy. Such counselling is time-consuming and expensive and may not be feasible within the framework of a NBS programme. Patient organizations should be involved in the national decision-making process to define and plan such programmes.

It is important to acknowledge that in some European countries, including Germany and Switzerland, currently there are legal restrictions on reporting carrier status. The panel urges the national authorities to re-think these policies.

Consensus Statement

6. SCD is a genetic condition. The knowledge of the carrier state in the family provides opportunities for prevention of affected births. The carrier status (all mutations that might cause SCD) should be reported and counselling offered to carriers.

The panel acknowledges that there is virtually no other evidence for this recommendation than solely "expert opinion" and encourages future research on this question. Any national decision-making process should take this into account.

7. Which methods are recommended and which methods are acceptable?

The panel agreed that the conventional biochemical methods to separate haemoglobin variants, i.e. high performance liquid chromatography (HPLC), capillary electrophoresis (CE) and isoelectric focusing (IEF), are all suitable for NBS. There was also consensus that tandem mass spectrometry (TMS) is an appropriate technology and it was noted that some countries are shifting to TMS as the first test. It was also acknowledged that other methods are emerging, e.g. MALDI-TOF MS, and DNA-based methods (Daniel and Henthorn 2015, Daniel and Henthorn 2016, Detemmerman*, et al* 2017, Hachani*, et al* 2011, Moat*, et al* 2017, Moat*, et al* 2014, Theberge*, et al* 2015). There was consensus that new methods should be demonstrated to be at least as sensitive and as specific as HPLC and CE before they be adopted for routine screening. Automated high-throughput methods are advisable for screening of large populations. The English NHS laboratory handbook can serve as a guide for other countries (NHS 2017b).

Consensus Statements

7a. HPLC, CE, IEF and MS/MS are appropriate methods for NBS for SCD.

7b. New methods currently being tested should prove to be as specific and sensitive as HPLC and CE before being implemented on a larger scale.

8. What is the recommended procedure after a positive screening result?

The approach to a first positive (presumptive SCD) screening result varies among the European countries and there were detailed discussions on the appropriate procedure after

a positive screening result. The panel agreed that there is a distinction between "best practice" and "acceptable practice" in different settings.

NBS for SCD from dried blood spot samples

After a first-tier screening test indicates presumptive SCD, the "best practice" is to re-test with a fresh punch using a different method on the same sample and to subsequently confirm the positive screening result with one of the two initial tests or with a third method on a second sample. Second-tier testing aims to ensure that the right sample was tested as errors may emerge from the automated punching procedure using dried blood spot cards. In addition, it aims to increase the probability that the variant haemoglobin identified by the first-tier method is HbS, since definitive identification of HbS in newborn samples can only be obtained by DNA or mass spectrometry based methods. Confirmatory testing aims to make a diagnosis as screening is, by definition, not diagnostic.

It is "acceptable" to use the same method on a re-punch of the same sample if no second-tier screening method is available and to confirm the screening result with a second method on a second sample to make a diagnosis. Diagnosis should be confirmed by the end of the second month of life to ensure that penicillin prophylaxis is started in a timely way.

NBS for SCD from cord blood and venous samples

After a first-tier screening test indicates presumptive SCD, it is necessary to confirm the positive screening result and the identity of HbS with another method on a second sample.

Carrier identification

"Best practice" after a first-tier screening test indicates HbS heterozygosity is to re-test with a fresh punch using another method on the same sample. "Acceptable practice" is to use the same method on a fresh punch of the same sample. Confirmatory testing from a second sample is not recommended in presumptive carriers.

Please note: one expert (MJB) found a single positive screening test sufficient to proceed to confirmatory testing from another sample with another method. It appeared that there are regional differences in terms of the variety of haemoglobin variants found in NBS. While some laboratories reported a significant prevalence of haemoglobins with biophysical

properties similar to HbS, other laboratories rarely or never observed haemoglobins migrating like HbS in HPLC, CE or IEF. This finding should be taken into account and included in risk assessment of protocols when the local decision on methods is made.

The appropriate communication of positive test results is of fundamental importance to reduce fear and anxiety in the families and to avoid stigmatization of the baby. Results should thus reflect the testing strategy and be communicated in a standardized way.

Consensus Statements

8a. A haemoglobin pattern that is in accordance with any genotype of SCD requires a re-test with a fresh punch from the same sample. If available, a different method from the first one should be used (second-tier screening). If a second alternative method is not available, a re-test with the same method is acceptable. If the re-test is positive, the newborn should be re-called for confirmatory testing.

8b. Screen-positive newborns should be referred to a paediatric haematologist for counselling and confirmatory testing by a certified laboratory. The confirmatory test result should be available by the end of the second month of life. If not available at that time, penicillin prophylaxis should be initiated and continued at least until the result is available.

In NBS programmes where carrier states are reported, any haemoglobin pattern in accordance with a carrier state requires a re-test with a fresh punch from the same sample, preferably using a different method.

8c. All children with SCD should be enrolled in a comprehensive care programme. The programme should ensure equal access to high-level clinical care.

Consensuses on specific issues raised during the conference

9. Which blood specimens are recommended/acceptable for screening?

All kinds of blood specimens from the baby are appropriate for newborn screening (Nennstiel-Ratzel*, et al* , 2017b).

10. Do we need additional guidelines for NBS for SCD?

The panel agreed that current NBS guidelines are appropriate to ensure reliable SCD screening results. Critical issues include prematurity, transfusions and maternal contamination in case of screening from cord blood. If a newborn should receive

transfusions, re-screening three months after the last transfusion is indicated (Nennstiel-Ratzel*, et al* 2011, NHS 2017b).

11. Which false-negative and which false-positive rates are acceptable?

The panel agreed that false-negative and false-positive rates should be as low as possible. The screening programme should thus be under constant review, e.g. by external quality assessment services, to constantly improve its quality.

Conclusions

SCD is becoming a priority for European Health Care Systems. Newborn Screening enables a child to be diagnosed before presenting with symptoms and provides an opportunity to ensure early entry into a comprehensive care programme. The increased burden of SCD in Europe and the growing interconnections among European Health Care Systems raise the need for a common approach to NBS. This panel recommends universal newborn screening in all countries participating in the conference, collection of data on clinical outcomes through setting up of registries and development of shared clinical protocols for comprehensive care of all affected newborns. Raising public awareness about SCD is recommended, as well as focused education about the condition for health care workers, allied professionals, managers and commissioners of health care systems.

Statement on Levels of Evidence

The authors would like to emphasize that the level of evidence for most of the following recommendations is “expert opinion”. Nevertheless, all questions have been discussed very carefully and all recommendations were made in all conscience.

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RC, EC, JE and SL organised the conference, SL hosted the conference in Berlin. RC and SL wrote the manuscript. PT edited the manuscript. All authors joined the conference and contributed to the discussions actively. All authors reviewed the manuscript and commented on it.

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Disclosures and competing interests statements

The authors have various disclosures and competing interests. All statements are available as online supplementary material 4.

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Table 1a. Newborn screening programmes for sickle cell disease in Europe

Country	Level	Coverage	Reference
Belgium	regional (Brussels)	universal	(Gulbis, *et al* 2009)
Belgium	regional (Liége)	universal	(Gulbis, *et al* 2009)
France	national	targeted in metropolitan France and universal in overseas territory	(Bardakdjian-Michau, *et al* 2009, Saint-Martin, *et al* 2013, Thuret, *et al* 2010)
Netherlands	national	universal	(Bouva, *et al* 2010)
Spain	national	universal	(Manu Pereira and Corrons 2009)
United Kingdom (England, Scotland, Wales, Northern Ireland)	national	universal	(Ryan, *et al* 2010, Streetly 2000, Streetly 2005, Streetly, *et al* 2008, Streetly, *et al* 2010, Streetly, *et al* 2018)

Please note: The UK has a linked antenatal and neonatal screening programme for haemoglobinopathies. Cyprus and Turkey have antenatal programmes only (Angastiniotis and Hadjiminas 1981, Canatan 2014, Kolnagou and Kontoghiorghes 2009, Kountouris, *et al* 2016).

Table 1b. Pilot studies on newborn screening for sickle cell disease in Europe

Country	Level	Coverage	Reference
Germany	regional (Berlin)	universal	(Frommel, *et al* 2014, Lobitz, *et al* 2014)
Germany	regional (Hamburg)	universal	(Grosse, *et al* 2016)
Germany	regional (Southwest Germany)	universal	(Kunz, *et al* 2016)
Germany	regional (Berlin + Brandenburg)	universal	submitted
Ireland	national	targeted	(Gibbons, *et al* 2015)
Italy	regional (Friuli Venezia Giulia)	targeted	personal communication
Italy	regional (Modena)	targeted	(Lodi, *et al* 2017)
Italy	regional (Ferrara)	targeted	(Ballardini, *et al* 2013)
Italy	regional (Novara)	targeted	(Rolla, *et al* 2014)
Italy	interregional (Padova-Monza)	universal	(Martella, *et al* 2017)

Table 1a. Newborn screening programmes for sickle cell disease in Europe

Country	Level	Coverage	Reference
Belgium	regional (Brussels)	universal	(Gulbis, *et al* 2009)
Belgium	regional (Liége)	universal	(Gulbis, *et al* 2009)
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Netherlands	national	universal	(Bouva, *et al* 2010)
Spain	national	universal	(Manu Pereira and Corrons 2009)
United Kingdom (England, Scotland, Wales, Northern Ireland)	national	universal	(Ryan, *et al* 2010, Streetly 2000, Streetly 2005, Streetly, *et al* 2008, Streetly, *et al* 2010, Streetly, *et al* 2018)

Please note: The UK has a linked antenatal and neonatal screening programme for haemoglobinopathies. Cyprus and Turkey have antenatal programmes only (Angastiniotis and Hadjiminas 1981, Canatan 2014, Kolnagou and Kontoghiorghes 2009, Kountouris, *et al* 2016).

Table 1b. Pilot studies on newborn screening for sickle cell disease in Europe

Country	Level	Coverage	Reference
Germany	regional (Berlin)	universal	(Frommel, *et al* 2014, Lobitz, *et al* 2014)
Germany	regional (Hamburg)	universal	(Grosse, *et al* 2016)
Germany	regional (Southwest Germany)	universal	(Kunz, *et al* 2016)
Germany	regional (Berlin + Brandenburg)	universal	submitted
Ireland	national	targeted	(Gibbons, *et al* 2015)
Italy	regional (Friuli Venezia Giulia)	targeted	personal communication
Italy	regional (Modena)	targeted	(Lodi, *et al* 2017)
Italy	regional (Ferrara)	targeted	(Ballardini, *et al* 2013)
Italy	regional (Novara)	targeted	(Rolla, *et al* 2014)
Italy	interregional (Padova-Monza)	universal	(Martella, *et al* 2017)

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Table 2. Summary of presentations given by the country representatives during the conference

Country	Population [million]	Annual births *(year)*	National NBS program for endocrine/ metabolic diseases	Voluntary or mandatory participation*	National NBS programme for HGP	Start year HGP screening	SCD positive babies *(year)*	Estimated number of SCD patients *(source)*	Estimated number of thalassaemia patients *(source)*	References
Cyprus	1,2	9.341 *(2013)*	yes	voluntary	no	N/A	N/A	49 *(registry)*	592 *(registry)*	(Angastiniotis and Hadjiminas 1981, Kolnagou and Kontoghiorghes 2009, Kountouris, *et al* 2016)
England	54,3	661.496 *(2014)*	yes	voluntary	for SCD	2006	278 *(2014)*	11.000 *(registry)*	1.000 *(registry)*	(Ryan, *et al* 2010, Streetly 2000, Streetly 2005, Streetly, *et al* 2008, Streetly, *et al* 2010, Streetly, *et al* 2018)
France	67,0	828.856 *(2014)*	yes	voluntary	for SCD	1995	466 *(2015)*	15.000 *(expert opinion)*	600 *(registry)*	(Bardakdjian-Michau, *et al* 2009, Saint-Martin, *et al* 2013, Thuret, *et al* 2010)
Germany	82,2	714.927 *(2014)*	yes	voluntary	no (but several pilots)	N/A	N/A	3.000-5.000 *(expert opinion)*	400 *(expert opinion)*	(Frommel, *et al* 2014, Grosse, *et al* 2016, Kunz, *et al* 2016, Lobitz, *et al* 2014)
Ireland	4,8	67.558 *(2014)*	yes	voluntary	no (but opt-in for both, pilot)	2003	16 *(2016)*	550 *(screening data)*	20 *(screening data)*	(Gibbons, *et al* 2015)
Italy	60,6	502.596 *(2014)*	yes	mandatory	no (but several pilots)	N/A	N/A	2.000 *(expert opinion)*	7.000 *(expert opinion)*	(Ballardini, *et al* 2013, Lodi, *et al* 2017, Martella, *et al* 2017, Rolla, *et al* 2014)
Netherlands	17,0	176.952 *(2014)*	yes	voluntary	for both	2007/2017 *(SCD/Thal)*	35 *(2014)*	1.500-2.000 *(expert opinion)*	100 *(expert opinion)*	(Bouva, *et al* 2010, Jans, *et al* 2012)
Portugal	10,3	82.367	yes	voluntary	no	N/A	N/A	800-900	30-35	

Table 2. Summary of presentations given by the country representatives during the conference

		(2014)						*(expert opinion)*	*(expert opinion)*	
Spain	47,6	427.595 *(2014)*	yes	voluntary	for SCD	2015	28 *(2014)*	800 *(registry)*	100 *(registry)*	(Cela, *et al* 2017, Manu Pereira and Corrons 2009)
Sweden	9,9	114.907 *(2014)*	yes	voluntary	no	N/A	N/A	unknown	unknown	
Switzerland	8,4	88.333 *(2014)*	yes	voluntary	no	N/A	N/A	200 *(survey)*	30 *(survey)*	
Turkey	81,6	1.337.504 *(2014)*	yes	mandatory	no	N/A	N/A	1.265 *(registry)*	3.135 *(registry)*	(Canatan 2014)

* Please note: In all participating countries virtually 100% of newborns are tested for endocrine and metabolic diseases. However, the target diseases are variable from country to country.
HGP = haemoglobinopathy

Table 2. Summary of presentations given by the country representatives during the conference

Country	Registries for haemoglobin disorders	Coverage of NBS programme	First-tier screening method	Confirmation of positive results	Test quality data	Beneficial effects of NBS for haemoglobinopathies	Special features
Cyprus	for both	N/A	N/A	N/A	N/A	N/A	no NBS, but very effective premarital screening programme
England	for both	universal	HPLC, CE, MS/MS	screening or specialist referral lab with same sample, but different method	specificity 95-100%, sensitivity 100%	paper submitted	linked antenatal and neonatal screening programme, thalassemia is no formal target disease in NBS, but reported
France	for thalassaemia only	universal in overseas territory, targeted in metropolitan France	HPLC, CE, IEF, MS MALDI-TOF	screening lab with same sample, but different method	N/A	N/A	decision for targeted screening based on an oral questionnaire
Germany	for SCD only	N/A	N/A	N/A	N/A	N/A	several pilot studies, application to introduce NBS for SCD submitted in May 2018
Ireland	for both	targeted, based on a questionnaire	HPLC, CE	HPLC, IEF at reference center	specificity 99%, sensitivity 100%	no death < 1 year since NBS commenced	very far developed pilot screening programme available to every newborn in the country
Italy	approved for both, not yet implemented	N/A	N/A	N/A	N/A	N/A	several NBS pilot studies, few regional registries, antenatal screening offered to all pregnant women
Netherlands	no	universal	HPLC	no 2nd-tier method	specificity 100%, sensitivity 100%	N/A	
Portugal	no	N/A	N/A	N/A	N/A	N/A	local registries available; pilot study in planning
Spain	for both	universal	HPLC, CE	variable, same method on same sample or same method on different sample	specificity 100%, sensitivity 100%	N/A	thalassemia is no target disease, but reported if detected as a by-product

Table 2. Summary of presentations given by the country representatives during the conference

Sweden	no	N/A	N/A	N/A	N/A	N/A	antenatal anaemia screening of all pregnant women
Switzerland	no	N/A	N/A	N/A	N/A	N/A	
Turkey	for both	N/A	N/A	N/A	N/A	N/A	no NBS, but very effective premarital screening program has reduced the number of affected birth by 90%

Online supplementary material 1: Template for the presentation of national data

Slide 1: History of newborn screening in your country How long has the NBS programme been running for? Which conditions are part of the NBS programme? Is participation voluntary of mandatory?
Slide 2: Numbers for your country I How many babies were born in 2010-2014? How many babies did you screen in 2010-2014? How many babies were tested positive for any target disease in 2010-2014?
Slide 3: Numbers for your country II Please provide an estimate of the number of SCD patients? What is this estimate based on? Please provide an estimate of the number of beta thalassaemia major patients? What is this estimate based on? Do you have registries for haemoglobin disorders?
Slide 4: NBS for haemoglobinopathies in your country I Do you already screen for SCD and/or thalassaemia at a national level? If no: do you have official regional NBS programmes for SCD and/or thalassaemia? If no: do you or did you conduct any pilot study now or in the past? If no: do you plan to do any pilot study within the next two years?
Slide 5: NBS for haemoglobinopathies in your country II Is your screening universal or targeted? If targeted: how do you determine who is screened? Which method(s) do you use as first-tier-method? How do you confirm positive results and who does it? If available: please provide your test quality data! (True positives, false positives, true negatives, false negatives)
Slide 6: Effects of NBS for disorders of haemoglobin Do you have any data on beneficial effects of NBS for haemoglobinopathies (e.g. data on improved survival)?
Slide 7: Anything else you would like to tell us about haemoglobinopathies and/or NBS in your country?

Online supplementary material 2: Questions to guide the consensus-finding process

1. Do you agree that the number of children born with SCD is currently increasing?
2. What are the target diseases in a newborn screening programme for haemoglobinopathies? What is the significance of thalassaemia?
3. What is the justification of a newborn screening for SCD (and thalassaemia)?
    a. What do these programmes aim at?
    b. What are the beneficial effects?
    (E.g. early initiation of penicillin prophylaxis)
4. Which countries/regions/cities should screen?
    a. Is there a threshold for the prevalence?
    b. If yes, what is this threshold?
    c. What are the minimal infrastructural and medical requirements to start NBS?
    (E.g. NBS for other disease(s) already in place, tracking system, treatment guideline, patient registry etc.)
5. Who should be screened? (Basically: universal or targeted screening or selected?)
    a. In case targeted screening is considered acceptable: Which methods are recommended to identify individuals at risk?
6. How to handle carriers? (This will probably not result in a recommendation, but in an objective description of different scenarios.)
    a. Does carrier screening increase awareness?
    b. What about costs and resources of counselling?
    c. Do we need more involvement of patient organisations?
    d. Are there concerns about stigmatization of carriers how to handle them?
7. Which methods are recommended/acceptable?
8. What is the recommended procedure after a positive screening result?
    a. Re-screening from the same sample? Same method? Second-tier screening?
    b. When should the family be informed?
    c. Where and when should the family be referred to for confirmatory testing and which methods are recommended?
    d. What about carriers?
9. Which blood samples are recommended/acceptable for screening?

(E.g. Heel prick, cord blood, venous sampling)

10. What are the pitfalls? (E.g. preterm newborns, transfusions etc.)
11. Which false-negative and which false-positive rate are acceptable?
12. Are these recommendations valid for all high-resource countries or is there any dependency on specific local characteristics?
13. How to deliver the consensus? (e.g. publication, involvement of political bodies like WHO, national institutes/ministries of health)

Online supplementary material 3: Agenda of the Pan-European Consensus Conference on Newborn Screening for Haemoglobinopathies (speakers in brackets)

1. **The changing epidemiology of sickle cell disease (SCD) in Europe: past, present and future** (Frédéric Piel, London)
2. **Newborn screening (NBS) in Europe - where are we in 2017?** (Béatrice Gulbis, Brussels)
3. **NBS - much more than just testing newborns** (Paul Telfer, London)
4. **Classical screening methods (IEF/HPLC/CE)** (Claudia Frömmel, Berlin)
5. **Point-of-care diagnostics** (Raffaella Colombatti, Padova)
6. **MALDI-TOF MS** (Patrick Ducoroy, Dijon)
7. **Tandem-MS** (Yvonne Daniel, London)
8. **Targeted versus universal NBS? Information of carriers?** (Catherine Badens, Marseille)
9. **The central African REDAC network and NBS in Africa** (Leon Tshilolo, Kinshasa)
10. **Setting up the English program - key elements and challenges** (Allison Streetly, London)
11. **NBS in France** (Bichr Allaf, Paris)
12. **The French comprehensive care program** (Mariane de Montalembert, Paris)
13. **NBS in The Netherlands** (Marelle Bouva, Bilthoven)
14. **NBS in Spain** (Elena Cela, Madrid)
15. **NBS in Cyprus** (Michael Angastiniotis, Strovolos)
16. **NBS in Germany** (Stephan Lobitz, Berlin/Cologne)
17. **NBS in Ireland** (Corrina McMahon, Dublin)
18. **NBS in Italy** (Giovanna Russo, Catania)
19. **NBS in Portugal** (Celeste Bento, Coimbra)
20. **NBS in Sweden** (Carolina Backman Johansson, Stockholm)
21. **NBS in Switzerland** (Ralph Fingerhut, Zurich)
22. **NBS in Turkey** (Duran Canatan, Antalya)
23. **The role of patients organisations** (John James, London)
24. **North-South collaboration on SCD: a global view** (Jacques Elion, Paris)
25. **ITHANET** (Marina Kleanthous, Nicosia)
26. **Setting up a newborn screening in Africa - The Ghanaian experience** (Kwaku

Ohene-Frempong, Philadelphia/Ghana)

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S Lobitz: received grants and honoraria from Novartis, Nordic Pharma, Bluebird, Celgene, Pfizer, Jazz Pharma and BioRad

Telfer P: none

E Cela: participated in an advisory board of Novartis (Eltrombopag) and her group received an educational grant from Novartis to support the Spanish Hemoglobinopathy Registry

B Allaf: none

M Angastiniotis: none

C Backman Johansson: none

C Badens: none

C Bento: none

MJ Bouva: none

D Canatan: none

M Charlton: none

C Coppinger: none

Y Daniel: none

M de Montalembert: received grants and honoraria from Novartis and Addmedica

P Ducoroy: created the Biomaneo company and is today the CEO

E Dulin: none

R Fingerhut: none

C Frömmel: none

M García-Morin: participated in an advisory board of Novartis (Eltrombopag)

B Gulbis: member of the Belgian Novartis scientific board for SCD

U Holtkamp: none

B Inusa: received research funding support form Novartis and educational grants from AstraZeneca, Apopharma, Addmedica, Pfizer and Bluebird.

J James: none

M Kleanthous: none

J Klein: none

JB Kunz: none

L Langabeer: none

C Lapouméroulie: none

A Marcao: none

JL Marin Soria: advisor to the Catalan Health Service for SCD

C McMahon: none

K Ohene-Frempong: none

JM Périni: none

FB Piel: none

G Russo: received honoraria for participation in Advisory Boards from Novartis

L Sainati: none

M Schmugge: received remunerations for talks and chairs at conferences in 2015-17 from Novartis

A Streetly: medical advisor to the English sickle cell society

L Tshilolo: none

C Turner: Director of SpOtOn Clinical Diagnostics, a company that supplies kits for newborn screening of haemoglobinopathies

D Venturelli: none

L Vilarinho: none

R Yahyaoui: none

J Elion: member of the Follow up Committee of Assay HGB-205: gene therapy of the hemoglobinopathies, BlueBird Bio, Inc.

R Colombatti: received honoraria for participation in Advisory Board from Novartis, Global Blood Therapeutics, Bluebird Bio and Addmedica