Endo-Thal
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The Preventive Programs for Hemoglobinopathies in Italy, Spain and Turkey: The Equality Plus Project (2nd Part)

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Abstract

The consistent multi-ethnic migrations of the last decades have considerably changed the epidemiology of the hemoglobinopathies, bringing an urgent need for treatment and primary prevention in welfare countries. Prevention of affected births constitutes the mainstay of the armamentarium against hemoglobinopathies, taking into consideration that no radical cure is currently available for the vast majority of patients. Preventive programmes have been implemented in several countries, a summary of the experience gained in Italy, Spain and Turkey is presented.

Key words: Migrations, hemoglobinopathies, Italy, Spain. Turkey, Equality Plus project.

Background

Hemoglobinopathies are highly prevalent hereditary disorders of hemoglobin (Hb) characterized by the presence of an abnormal β-globin chain [hemoglobin variant as in sickle cell disease (SCD)] or a decrease or absence of α - or β -globin chains (thalassemias). They are the commonest group of autosomal recessively inherited monogenic disorders of Hb production. Fairly recent esti-

mates suggest that 7% of the world population are carriers and that 300,000–400,000 affected children are born every year. The majority of these (approximately 250,000) have sickle cell disease. The prevalence of these disorders is high in the Mediterranean Basin, some parts of Africa, the Middle East, India, Southeast Asia, Malaysia, and the Pacific Islands (1, 2).
A World Health Organization (WHO) report estimated that around 20 per 1,000 births in Nigeria were affected by SCD, giving a total of 150,000 affected children born every year in Nigeria alone. The carrier frequency ranges between 10% and 40% across equatorial Africa, decreasing to 1-2% on the north African coast and <1% in South Africa (3). Healthy carriers of these conditions are present today in many nonendemic parts of the world, and severely affected children are now born where these diseases were previously rare or unknown.
In 2006, the WHO recognized hemoglobinopathies, including SCD, as a global public health problem and urged national health systems worldwide to design and establish programs for the prevention and management of SCD (3).
Clinically, β-thalassemias can be classified as transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) according to the severity of the phenotype, which is caused by a wide spectrum of mutations in a homozygous or compound heterozygous state (4, 5).
Current treatment of TDT consists of regular transfusions that lead to iron overload, requiring iron chelation to prevent iron-related organ toxicity. Hematopoietic stem cell allogenic transplant is the only approved cure for patients with TDT (3, 5).
NTDT patients do not require transfusions or only occasionally require them; however, they develop iron overload as well because of increased intestinal iron absorption caused by chronic anemia (3,5).
In patients with SCD a wide range of manifestations including hemolytic anemia, vaso-occlusive crises and tissue infarctions, life threatening infections and end organ failure. Clinical manifestations usually appear after three months of age, when the concentration of fetal hemoglobin (Hb F) decreases. Existing therapies are only focused on symptom management and do not alter the natural history of the disease. Currently, available treatments are limited to transfusions and hydroxycarbamide, although stem cell transplantation might be a potentially curative therapy. Several new therapeutic options are in development, including gene therapy and gene editing (6, 7).
Although hemoglobinopathies were rare in industrialized Northern and Central European countries, recently they have become much more common in these areas through the immigration from endemic areas in the last 10-15 years (3, 8-10). Furthermore, the numbers are increasing because a large number of asylum seekers and refugees (ASR) flow toward Europe.
Thus, preventive and diagnostic programmes regarding hemoglobinopathies in immigrant populations have been implemented. The purpose of this paper it to report a summary of the experience gained in Italy, Spain and Turkey in migrants, asylum seekers and refugees. Their definition status is reported in the appendix.

Screening and genetic counseling

The main aim of screening is to reduce the number of affected births and, in the case of SCD, to reduce childhood morbidity and mortality (11, 12).
Genetic counseling should ideally be provided by a medical specialist who has been trained in counseling families with hemoglobinopathies. Counseling can also be given by a trained genetic counselor, a hematologist, or a pediatrician. People at-risk, especially those identified by population screening, represent a randomly selected sample of the population. All medical programmes, including genetic prevention programmes, must operate within existing legal and social frameworks (13). In particular:

- Information is the first step of prevention, and efforts should be made to reach each foreign groups, promoting healthy education programs. In order to communicate effectively the counsellor must take into account the educational, social, cultural and religious background of the individual/couple. The information have to provide knowledge, not anxiety or stigmatization, and needs to be adopted to the different cultures, paying attention to make clear that being a carrier is not a disease and that when a carrier is diagnosed family analysis is requested (11).
- Scholastic information to adolescent and educational pre-matrimonial courses should be offered. Before marriage and conception a screening is recommended. The main role of counsellors is to provide information in a

non-biased manner and support decisions that are morally right for the individual, couple or family (11, 13).

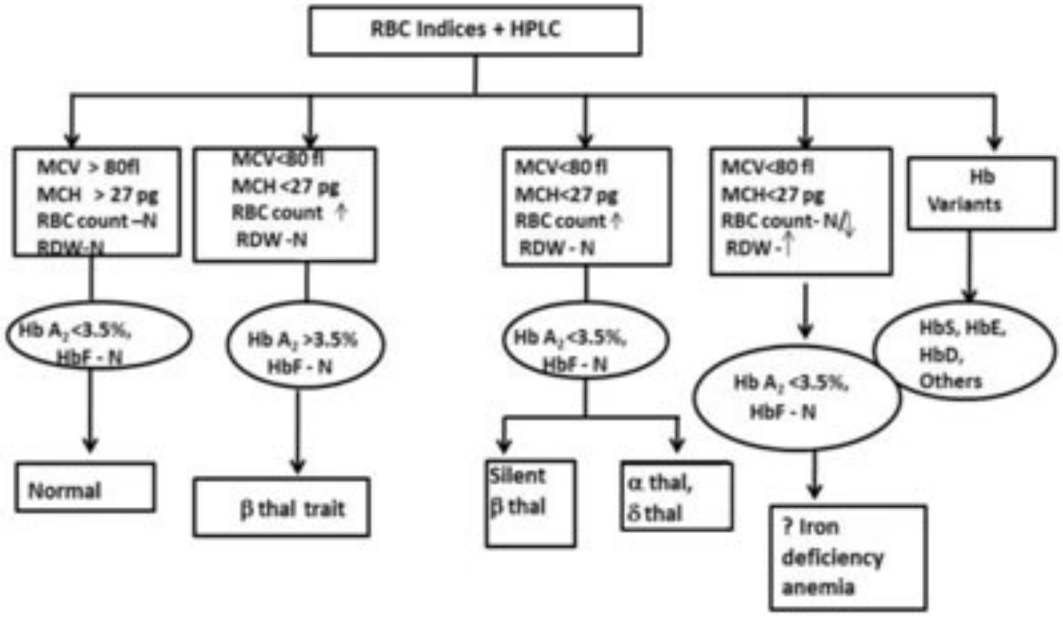
- Adequate dialogue with legal, ethical and religious leaders is recommended in early pregnancy in order to establish acceptability of the policy according to cultural environment of the country and the population. Respect of the wishes and choices of the couple should be a priority of these authorities. Several Muslim countries are also already offering prenatal diagnosis and selective abortion to at-risk couples, or are at various stages of developing these services. It is therefore important to comment on information so far available on the acceptability of such services in these countries (14).
- Newborn screening (NBS) should be offered to babies of foreign known carriers of hemoglobin variant, babies of immigrant parents from an ethnic risk group, and babies at-risk couples with a previous affected child ethical and multicultural-counseling problems taking in consideration ethical and multicultural-counseling problems (11, 12).

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. More than 50 SCD experts from 11 European countries supported development of NBS program

Screening for the identification of carriers of β thalassemia and other hemoglobinopathies, and laboratory methodology

Screening methods include full blood count and biochemical analysis including quantitative analysis of hemoglobin by HPLC or capillary electrophoresis. Molecular genetic confirmation by detecting pathogenic variants establishes the diagnosis. For neonatal and antenatal screening, identification of affected newborns or carriers is achieved by hematological tests. DNA analysis supports definitive diagnosis, and additionally facilitates prenatal diagnosis procedures (16).
A flow-chart for the for carrier screening. of thalassemias and Hb variants is reported in Figure 1.
The cut off value of HbA2 for diagnosis of β - thalassemia carriers is usually taken as 3.5% along with reduced MCV (<80fl) and MCH (<27pg) levels with a relatively high RBC count and normal RDW. However, borderline/normal HbA2 levels (3.0 e 3.5%) often lead to a diagnostic dilemma.
In subjects with iron deficiency apart from reduced MCV and MCH levels, the RBC count is also reduced in proportion to the hemoglobin value, and the HbA2 level is normal or reduced.
The RDW (red cell distribution width) measures the coefficient of variation about the MCV.

Figure 1. *Flow-chart for the diagnosis of hemoglobinopathies.*



It tends to be higher in iron deficiency but not in the thalassaemias. However, particularly during pregnancy, it is not unusual to find the presence of both.
It should be noted that the MCV can be raised by a number of conditions. In particular, vitamin B12 and folic acid deficiency Since the foetal to adult β globin switch is not usually complete until about 6 months of life, it is difficult detecting β -thalassaemia in the neonate based on the full blood count (16).
SCD is normally diagnosed by measuring the HbS content (% HbS) in blood of patients with high-performance liquid chromatography (HPLC), hemoglobin electrophoresis (HE) or isoelectric focusing (IEF). A simple, rapid and low-cost diagnostic test that could accurately identify normal individuals (HbAA), sickle trait carriers (HbAS) and individuals suffering from SCD (HbSS, Hb Sβ+-thalassemia) and, to a more limited extent, individuals with the HbSC in a population of adults and children over one year of age. This simple, rapid and low-cost diagnostic test represents a major step towards enabling universal screening of children and adults in countries with limited resources (17).
The racial heterogeneity of the immigrant population in a non-endemic country significantly increases the spectrum of haemoglobinopathy mutations and their combinations found in individuals, making the provision of a molecular diagnostic prenatal diagnosis service more challenging. The genetic subtypes among the different ethnic groups vary; this may pose challenges in prenatal diagnosis. DNA microarrays constitute an advanced DNA method for some mutation categories (16).

Italy

Around 5.1 million foreign citizens legally reside in the country (Table 1). That's nearly nine percent of the overall resident population. Italy is third, among European Union countries. That's according to an immigration report by Caritas and Migrantes. Germany and the UK are in first and second position, followed by Italy, France and Spain.
As of January 1, 2018, the foreign resident nationalities with the highest numbers in Italy were Romanian (1,190,091 people; 23 % of all migrants), Albanian (440,465 people; 8.6 %) and Moroccan (416,531 people; 8.1 %). The African and Asian population amount to approximately one million each, 20% and 19,5 % of the total respectively, while North and South Americans combined amount to 376,000 people (7,4 %) (18) (Table 2).
The migrant population is unequally distributed across the country. More than half (57.4 %), is located in the northern regions.
Over half of foreign residents in Italy live in the North (57.5 %), followed by Central Italy (25.4 %) and the South (roughly 12 %). Only some 5% legally reside on the Italian islands, although that figure is rising (18).

Table 1. *Estimates of different categories of foreign population in Italy in 2017. (Source: Caritas Italiana.Common Home Migration and Development in Italy. 2019.pp.1-30).*

Foreign residents (Istat 2018a)	5,144,440
Holder of a permit to stay (Istat 2018c)	5,359,000
Non-EU residence permit holders (Istat 2018c)	3,714,137
Refugees and people in fefugee-like situation (UNHCR 2018)	167,335
Migrants with no legal status (estimate) (ISMU 2018)	490,000
Asylum seekers lodging a claim in 2017 (Ministry of Interior 2018)	126,500
Total pending claims in 2017 (UNHCR 2018)	186,648
Total foreign population (Eurostat estimate 2018)	6,053,960
Number of immigrants naturalised in the last 10 years (Istat 2018c)	1,081,000

Table 2. *First 10 nationalities of immigrated people, as of 1st of January 2018, living in Italy. (Source: Caritas and Migrantes 2017/2018. Elaboration on ISTAT data).*

Nationality	Total	Females	Males
Romania	1,190,091	684,130	505,961
Albania	440,465	215,362	225,103
Morocco	416,531	194,599	221,932
China	290,681	144,231	146,450
Ukraine	237,047	184,780	52,267
Philippines	167,859	95,260	72,599
India	151,791	62,042	89,749
Bangladesh	131,967	35,543	96,424
Moldova	131,814	87,505	44,309
Egypt	119,513	39,119	80,394

The top five Italian regions for foreign residents are:
- Lombardy (1,181,772 foreign residents; 11.7 % of the total population)
- Lazio (683,409; 11.6 %)
- Emilia-Romagna (547,537;12.3 %)
- Veneto (501,085; 10.2 %)
- Piedmont (427,91; 9.8%)

and the top five provinces for foreign residents are:
- Milan (470,273, 14.5 % of the total population)
- Rome (556,826 foreign residents, 12.8 %)
- Brescia (157,463, 12.4%)
- Turin (221,842, 9.8 %)
- Naples (134,338, 4.4 %)

The majority are economic migrants and their effects in terms of genetic disease, are difficult to estimate in terms of numbers with accuracy, since many factors need to be considered. Such factors include the permanency of the migration, whether it is a migration of single people or of families, whether the migrant will marry locally or from the country of origin, whether consanguineous marriage will still be practiced in the host country, whether there will be free choice partner or an arranged marriage, whether birth rate of immigrant families will be that of the home or the host country and whether there is a second generation of migrants and the customs that they have adopted (19).

The Italian screening programs for hemoglobinopathies and their prevalence in immigrants

Screening programs started, in Italy, in the 1970s for thalassemias have increased public awareness and aided to prevention in target populations (20). In Ferrara (Italy), a voluntary screening programme for school children and young adults initiated in 1976-1977 has brought down the birth rate of those affected with thalassemia to almost zero. The preventative actions also include legislative action, a public awareness campaign, screening and carrier diagnostics, genetic counselling, and prenatal diagnosis (21).
In 1998, a questionnaire, requesting information about the cases of SCD was sent to all Italian centers of Pediatrics and determine the distribution and severity of SCD in Italy (22). A total of 696 cases were reported. The distribution of registered patients showed that, although the S gene originated mostly in Sicily. with an estimated mean frequency of 2% and a peak of 13% (23), and Southern Italy, 20% of patients with SCD lived in Central and Northern Italy. The types of SCD reported were as follows: compound heterozygotes HbS-beta thalassemia, (S-Th, 518 cases); homozygotes for HbS, (S-S, 149 cases); compound heterozygotes HbS and another abnormal hemoglobin (21 cases). Infections ranged between 0 and 6/year.
However, the prevalence of hemoglobinopathies throughout Italy is changing and the number of immigrants with SCD patients in Italian regions, with a historically low disease prevalence, is increasing, as documented by recent studies (24-29).

Screening programmes in immigrants at risk for SCD

The implementation of screening programs for early detection of patients with SCD has become necessary in Italy as a result of the high rate of migration from areas with a high prevalence of the disease (Sub-Saharan Africa, Middle East and the Balkans).
Following a pilot study performed in the province of Modena, Italy in 2011-2013, an official screening program was established on May 31 2014 for all pregnant women, free-of-charge for the family according to the National Guidelines for Physiological Pregnancy. Hemoglobin (Hb) profiles of pregnant women within 10 weeks of pregnancy, of new mothers at delivery and of the newborns of mothers with variant Hb profiles (newborns at-risk), were evaluated by high performance liquid chromatography (HPLC). Samples from 17,077 new mothers were analyzed and 993 showed alteration of Hb patterns (5.8%) (1.0% Hb AS carriers); of the 1011 at-risk newborns, four (0.4%) carried sickle cell disease and 90 (8.9%) were Hb AS carriers. These data show that early diagnosis of SCD or carrier status can be obtained in high-risk newborns, providing valuable information on the frequency of these conditions in geographic areas in which the disease is historically rare (30).
De Franceschi et al. (31) reported the Italian experience on new cases of SCD and other hemoglobinopathies in refugees between 2014 and 2017 at 13 Italian reference centers for hemoglobinopathies. A total of 70 patients with hemoglobin disorders were identified (61 new patients with SCD, 6 with TDT, and 3 with other hemoglobi-

nopathies), the majority of whom were male. Half were adults with the median age of 21 years and the other half were children. Most came from West African countries Senegal and Nigeria, as well as Morocco, Egypt, and Tunisia in North Africa, and Syria in the Middle East. Approximately two-thirds of the 70 patients were diagnosed after an acute complication required emergency care and some of these complications were life-threatening and likely preventable with early diagnosis and treatment (31).
To expedite the identification of SCD – and mitigate complications – *De Franceschi et al.* (32) undertook a pilot study in which they performed point-of-care screening of refugees seen in a single refugee center during October 2017. More than 400 individuals were screened for using one of the new rapid point-of-care screening devices (*SickleSCAN® BioMedomics, Inc.*), the results of which were then validated using the gold standard laboratory test. Front-line health providers in refugee centers and emergency department personnel were trained to recognize the signs and symptoms of SCD and intervene to provide necessary care. Three percent were found to have SCD and 20% were found to have the heterozygous AS genotype. The majority of sickle hemoglobin (HbS) carriers were from West Africa, and the authors noted that "*none of the newly identified SCD patients were aware of their condition*".
These findings prompted the researchers to propose several initiatives to improve screening of SCD among migrants arriving to Italy. These include (32):

- Routine screening for SCD in refugees from countries endemic for SCD within 10-14 days from their arrival to identify potentially vulnerable patients
- A structured, collaborative national network
- Educating ED physicians to identify and treat acute SCD-related events (such as: SCD-related acute vaso-occlusive events)
- Rapid referrals of refugees with SCD or symptomatic HbS-carrier genotype to a comprehensive SCD reference center
- Earlier initiation of disease-modifying treatment (e.g., hydroxyurea).

Together, these data suggest that the increased number of patients with SCD in Italy has mostly resulted from migratory patterns of immigrants arriving, in recent years, from countries in which there is a high disease prevalence and that there are approximately 2,000 patients with SCD currently living in Italy. The main challenges for physicians are lack of awareness of the asylum seekers' specific health care problems, language and intercultural communication problems, as well as access and integration of asylum seekers into the health care system, Language barriers and poor multicultural competencies should be also considered.
It is generally recognized that registries are important tools for detecting demographic patterns, allocating resources, monitoring patient outcomes, and guiding decisions (33-35).

Spain

As in other Mediterranean countries, the main hemoglobin disorder in Spain is beta-thalassemia. Until 2003, however, the prevalence of hemoglobinopathies in Spain was unknown, and only the establishment of universal pilot screening programs of hemoglobinopathies allowed to identify an overall incidence of 0.33% (36, 37).
The first study of hemoglobinopathies in Spain was carried out in 1981, in Barcelona by *Baiget et al.* (38) that reported a global prevalence of hemoglobinopathies in Spain of 0.14%, a value significantly lower value than that reported by the WHO in 1995 (39).
Although after this first publication, many studies have been carried out to establish the prevalence of β-thalassemia in Spain, in only one, the individuals included were representative of almost all Spanish geographical regions (40). This study was undertaken under the auspices of the Spanish Society of Hematology and demonstrated that, in Spain, β-thalassemia distribution is very heterogeneous with a prevalence ranging from 0.1% to 5%, pointing out that most of the HbS, and also HbC and other hemoglobinopathies carriers, were from southern and western geographical regions of Spain. Moreover, control programs based on the screening of couples at risk for thalassemia and the offer of antenatal diagnosis have demonstrated to be beneficial for reducing the frequency of β-thalassemia major when properly performed (41).
Noteworthy, some of the Spanish regions exhibited a significantly higher prevalence of both β-thalassemia and structural hemoglobinopathies, most probably due to the well known genetic influence of Arab populations in the past (42).

In 1999, *Martìn Nùñez et al.* (43) performed the first detection campaign for hemoglobinopathies and thalassaemias among school children in northern Extremadura and from a total of 2,818 screened samples, the global prevalence of hemoglobinopathies was of 0.24% Notably 0.10% of the autochthonous population was found to be a carrier of HbS, a relatively high prevalence of HbS in this geographical area that may be explained by the influence of malaria infection in the past.

In 2006, screening for hemoglobinopathies and thalassemia was carried out among 2,436 pregnant women in Lanzarote (Canary Islands) by *Calvo-Villas et al.* (44), and a hemoglobin variant was found in 23 women (0.94%): HbS trait (13 cases), HbC trait (7 cases), and HbD-Punjab trait (3 cases). An additional heterozygote for unstable hemoglobin. In 82.6% of cases, the variant hemoglobins were found in immigrant populations from Africa and Central and South America. This value is three times higher than that recently reported by *Modell et al.* with an estimated percentage of pregnant woman carriers for hemoglobinopathy of 0.34% (45). The results of a very recent hemoglobinopathy study, also performed in the Canary Islands by *De Las Heras et al.* (46) reported that a total of 198 hemoglobinopathies were found in an adult population, with 125 of them corresponding to structural variants. In three cases SCD was identified, and in 70 cases AS was identified. It was noteworthy that 60% of the cases identified as AS was born in the Canary Islands.

Between 2003 and 2008, a pilot study for neonatal screening of hemoglobinopathies was performed in Catalonia by *Mañú et al.* with the help of a grant of the Spanish Ministry of Health (47, 48). The neonatal blood samples obtained by heel prick and/or umbilical cord sampling were analysed by HPLC. A total of 4696 newborns from at-risk ethnic groups were studied using two different targeted neonatal screening approaches. Neonates were classified into four different categories according to mother's birthplace: 1, North Africa; 2, sub-Saharan Africa; 3, Asia; and 4, Central and South America) and the prevalence of hemoglobinopathies and SCD was calculated for each category. The expected number of births in Catalonia for 2006 was 82 300, and there was an estimated prevalence of 0.021% for SCD and 0.37% for AS, with an overall prevalence of hemoglobinopathies of 0.5%. Using the SCD prevalence obtained for the different ethnic categories of high-risk immigrant populations in the targeted screening study of

Table 3. *Number of births from African origin immigrants (and indigenous residents of African ethnicity) and estimation of SCD prevalence in different Spanish regions (2006).*

Region	No. of births	Africa (%)	North Africa (%)	Sub-Saharan (%)	N° cases of SCD (prevalence in %)
Andalusia	95 304	2400 (2.5)	2085 (2.1)	315 (0.33)	4.8 (0.005)
Aragòn	12 280	807 (6.5)	518 (4.2)	289 (2.35)	3.7 (0.030)
Asturias	7596	51 (0.6)	51 (0.6)	16 (0.21)	0.2 (0.003)
The Balearic Islands	11 675	828 (7.0)	631 (5.4)	197 (1.69)	2.6 (0.023)
The Canary Islands	20 668	617 (2.9)	400 (1.9)	217 (1.05)	2.8 (0.013)
Cantabria	5229	35 (0.6)	22 (0.4)	13 (0.25)	0.2 (0.003)
Castilla y Leòn	19 775	441 (2.2)	405 (2.0)	36 (0.18)	0.6 (0.003)
Castilla-La Mancha	20 389	699 (3.4)	649 (3.1)	50 (0.25)	0.9 (0.004)
Catalonia	82 300	7207 (8.7)	5986 (7.2)	1221 (1.48)	17.4 (0.021)
Valencia	52 756	2453 (4.6)	2036 (3.8)	417 (0.79)	5.9 (0.011)
Extremadura	10 118	203 (2.01)	199 (1.9)	4 (0.04)	0.1 (0.001)
Galicia	21 392	161 (0.75)	115 (0.5)	46 (0.22)	0.6 (0.003)
Madrid	71 912	2690 (3.7)	1888 (2.6)	802 (1.12)	10.4 (0.014)
Murcia	18 091	1443 (7.9)	1358 (7.5)	85 (0.47)	1.7 (0.009)
Navarra	6551	384 (5.8)	310 (4.7)	74 (1.13)	1.0 (0.016)
Basque Country	20 026	388 (1.9)	259 (1.2)	129 (0.64)	1.7 (0.008)
La Rioja	3070	289 (9.4)	254 (8.2)	35 (1.14)	0.5 (0.018)
Ceuta	1041	140 (13.4)	138 (13.2)	2 (0.19)	0.1 (0.009)
Melilla	1122	383 (34.1)	372 (33.1)	11 (0.98)	0.3 (0.027)

Catalonia, the number of births from non-indigenous populations affected by SCD in each Spanish region has been also calculated (Table 3).

After 2003, the increasing immigration flows, especially from Africa (northern and sub-Saharan regions) led to the emergence of SCD as one of the most common hereditary disorders in Spain, with an impact on the burden of healthcare in several of its geographical regions. In these regions, the prevalence of SCD is directly related to the impact of immigrant populations, mainly from sub-Saharan Africa (49). The national consensus in Spain indicates that the number of African immigrants has doubled in only 5 years. Furthermore, the distribution of this immigrant African population is very heterogeneous and differs widely from one region to another (Table 4).

In conclusion, all the studies performed until 2008, demonstrate that in Spain the prevalence of hemoglobinopathies is lower when compared to other Mediterranean countries (50) or concerning the European median (0.5 cases for thalassemia and 15 for SCD per 100,000 inhabitants) (51). Moreover, the prevalence of SCD is heterogeneous and strongly influenced by the migratory flows.

After 2008, the most updated information on the current situation of Hemoglobinopathies in Spain has been recently published by the Spanish Society of Pediatric Hematology and Oncology (SEHOP) from a multicentric study with the participation of 51 hospitals all over Spain in which 75 thalassemias (62 Major Thalassemia) 826 Sickle Cell Disease (SCD) and 58 other hemoglobinopathies were registered (Table 5) (52).

Table 4. *Distribution of African immigrants and indigenous residents of African ethnicity in the different regions of Spain (2008).*

Region	Total population	Africa countries (%)	North Africa (%)	Sub-Saharan (%)
Andalusia	8 177 805	120 295 (1.47)	98 298 (1.20)	21 997 (0.27)
Aragòn	1 325 272	31 282 (2.36)	19 699 (1.49)	11 583 (0.87)
Asturias	1 079 215	3738 (0.35)	2022 (0.19)	1716 (0.16)
The Balearic Islands	1 071 221	30 027 (2.80)	21 634 (2.02)	8393 (0.78)
The Canary Islands	2 070 465	27 804 (1.34)	16 733 (0.81)	11 071 (0.53)
Cantabria	581 215	2523 (0.43)	1526 (0.26)	997 (0.17)
Castilla y Leòn	2 553 301	20 919 (0.82)	18 068 (0.71)	2851 (0.11)
Castilla-La Mancha	2 038 956	34 209 (1.68)	30 188 (1.48)	4021 (0.20)
Catalonia	7 354 441	275 746 (3.75)	216 180 (2.94)	59 566 (0.81)
Valencia	5 016 348	102 377 (2.04)	82 366 (1.64)	20 011 (0.40)
Extremadura	1 095 894	9847 (0.90)	9378 (0.86)	469 (0.40)
Galicia	2 783 100	8549 (0.31)	5146 (0.18)	3403 (0.12)
Madrid	6 251 876	112 860 (1.81)	78 817 (1.26)	34 043 (0.54)
Murcia	1 424 063	67 863 (4.77)	60 818 (4.27)	7045 (0.49)
Navarra	619 114	12 984 (2.10)	10 069 (1.63)	2915 (0.47)
Basque Country	2 155 546	20 089 (0.93)	13 344 (0.62)	6745 (0.31)
La Rioja	3 17 020	9532 (3.01)	8096 (2.55)	1436 (0.45)
Ceuta*	77 320	2620 (3.39)	2610 (3.38)	10 (0.01)
Melilla*	71 339	5225 (7.32)	5215 (7.31)	10 (0.01)

** Regions in the north of the African continent.*

Table 5. *Characteristics of the registered 959 patients with hemoglobinopathy in Spain (Medicina Clinica. 2020; 155:95-103).*

	Thalasemia	Sickle Cell Disease (SCD)	Other Hemoglobinopathies	Total
Number of patients (%)	75 (7.8)	826 (86.1)	58	959 (100)
	Major 62 (6.5) Minor 13 (1.3)	SS: 653 (68.1) SC: 100 (10.4)	HbH: 12 (1.2) HbCC: 8 (0.8)	
		S^{+}: 34 (3.5)	Other: 38 (4.0)	
		S^{0}: 33 (3.4)		
		S^{0}: 33 (3.4)		
		Unknown: 6 (0.6)		
Male/Female ratio	0.94	1.11	0.79	1.04
Alive (%)	43 (69.3)	521 (63.1)	40	604 (63.8)
Dead (%)	2 (3.2)	18 (2.2)	2	22 (2.3)
Failed follow-up (%)	17 (27.4)	286 (34.6)	17	320 (33.8)
Age at diagnosis (years)	0.7 (0-3.8)	2.7 (0-52.0)		
Current age (years)	10.9 (0.7-64.3)	10.2 (0.7-55.7)		
Time of follow-up (years)	11.0 (2.2-44.7)	8.4 (0-33.5)		

Characteristics of Thalassemia in Spain

The main reason for the diagnosis of beta-thalassemia is anemia and in some patients, acute cerebrovascular accident (AVA) with few post-stroke sequelae. In these patients, magnetic resonance imaging (MRI) of the brain has demonstrated the presence of lacunar infarcts that may explain the neurological alterations, mainly neurocognitive that appear after the AVA Treatment is based on antibiotic prophylaxis with penicillin, administered for a minimum of 5 years, and chelation therapy with deferasirox (79%), deferoxamine (58%) or deferiprone (17%) for an average duration of 9 years. A small percentage of patients are splenectomised with or without concomitant cholecystectomy. In almost 50% of children with severe thalassemia major (TM) an HLA-identical hematopoietic stem cell transplant (HSCT) can be prescribed with overall survival of 96.7%, and a mean follow-up of 13.7 years. The main complications of HSCT are chronic graft-versus-recipient disease (GVHD) and graft rejection. Very few patients die due to septicemia or cardiorespiratory failure.

Characteristics of Sickle-Cell Disease in Spain

As mentioned before, the largest registered SCD population in Spain is concentrated in Catalonia and Madrid. The entire sample is diagnosed by universal newborn screening, anemia symptoms, and vaso-occlusive pain crisis, with a mean age at diagnosis of 3 years. As in beta-thalassemia, cerebrovascular accidents, with few sequelae can occur in about 3% of patients, which show a somewhat higher percentage of neurocognitive complications and lacunar infarcts. Treatment consists of antibiotic prophylaxis with penicillin at around 2 years, with a mean duration of 5 years and, when necessary chelating treatment with deferasirox in about 90% of cases and deferoxamine in the remaining 10% of cases. Hydroxyurea treatment can be started in, approximately, 40% of the patients and blood transfusions in about 8% with a mean age of onset at 7 years and a mean duration of 3 years A small percentage of patients had to undergo implantation of a central venous catheter (CVC), usually Port-a-cath®, and splenectomy, accompanied by cholecystectomy after 10 years of age. In severe cases of TM, the HSCT is an option with overall survival of 99% at 5 years of age, 98% at 15 years, and 96% after 20 years. As in beta-thalassemia, complications of HSCT that may decrease the survival rate are generally unrelated to GVHD and in general associated with prematurity, metabolic disorders, congenital heart disease, and neuroblastoma. The average age of death is around 7 years.

Newborn screening for hemoglobinopathies and SCD in Spain

The first Newborn Screening Program (NSP) in Spain was introduced in Granada in 1968 by the initiative of professors Federico Mayor-Zaragoza, Magdalena Ugarte, and Antonio Martínez Valverde. In 1978, the National Plan for mental retardation was established within the Real Patronato de Educación y Atención a Deficientes (Royal Council of Education and Care for Individuals with Disabilities), and several laboratories were established within its framework. Between 1982 and 1983, the authorities of each autonomous region in Spain took over the management of government-run programs for the early detection of congenital and metabolic disorders (53).
Between 2000 and 2015, there were significant differences in the NSP programs of the different Spanish autonomous communities, as many only included 2 or 3 diseases while others included more than 20. To establish the actual benefits of the early diagnosis of diseases susceptible to screening, the Spanish Federation of phenylketonuria and other Metabolic Disorders, along with a group of health professionals, agreed to review the existing NSP programs in Spain to develop the broadest possible consensus on aspects such as the criteria applied to select diseases for inclusion, the establishment of units for the diagnosis, treatment, and follow-up of the detected diseases, and the creation of a national register of affected patients. They developed the consensus document for Newborn Screening Programs (NSP) for endocrine and metabolic disorders that were approved in 2013 by the general assembly of the "*Consejo Interterritorial*" that encouraged the establishment of consensus-based protocols within the framework of the National Health Service (NHS) so that screening programs could be uniformly implemented, based on rigorous quality criteria.
The first neonatal screening of hemoglobinopathies started in Catalonia by *Baiget et al.* (41) in 1981. Also in Catalonia, *Cabot et al.* (54) performed, in 1998, a targeted screening study limited to newborns of sub-Saharan African

mothers, initiated because of the high and increasing delivery rate of black origin immigrants in this geographical area.
However, the first universal pilot screening of hemoglobinopathies was performed by *Dulìn et al.* (36) in the Community of Madrid. A total number of 29,253 specimens, obtained by heel prick and preserved as a dried blood spot on a filter paper (a "*Guthrie spot*"), were screened by high-performance liquid chromatography (HPLC), and 98 hemoglobinopathies were identified with an overall incidence of 0.33%. Seventy-one cases were AS with a prevalence of 0.24%, four cases were SCA, and one case was a compound heterozygote for HbS and beta-thalassemia with a prevalence of 0.017%. In 2007, *Cela et al.* (37) reported the results of the first 32 months of running this program, with the study of a total of 190,238 newborns blood samples (Guthrie spots) by HPLC and the identification of 1,060 hemoglobin variants, corresponding to a prevalence of 0.56%. Thirty-one of these cases were SCD, corresponding to a prevalence of 0.016%. In all of these cases, prevention measures consisting of antibiotic administration, vaccination, and comprehensive clinical care were initiated. The results from newborns identified as carriers of HbS, HbC, HbD or HbE were also reported to the family, and family studies were recommended for carriers and SCD patients. In subsequent pregnancies, prenatal diagnosis was performed in three families after a parental investigation.

The Catalan Network for Hemoglobinopathies and Thalassemia (CATGLOBIN)

In 2007, The Red Cell Pathology Unit from the Hospital Clinic of the University of Barcelona (HCB) led by Prof. Joan-Lluis Vives Corrons contacted with the Catalan Government "*Generalitat de Catalunya*" to implement a newborn screening program (NSP) for Sickle-Cell Disease (SCD) in Catalonia. This proposal arose as a need created by the large increase in the incidence of SCD in this Country as the result of the high migration impact during at least 30 years. The estimated prevalence of SCD in the neonatal population of Catalonia is 1 in 3,634 babies, and the sickle cell carrier condition is of 1 in 148 babies (47, 48).
In 2009, the TV3 Marathon, in its edition dedicated to "*Rare Diseases*" awarded the HCB in collaboration with the Hospital of Santa Creu and Sant Pau (HSCSP), also in Barcelona, with a Grant to create the Catalan Network for Diagnosis and Follow-up of severe hemoglobinopathies (CATGLOBIN). This allowed to implement the diagnostic procedures for hemoglobinopathies and to improve the clinical care of patients with chronic anemia and vaso-occlusive crises due to SCD. 15 hospitals from all over Catalonia take part in this network, and in 2012, within the framework of the Advisory Committee on Rare Diseases of the Public Health Agency of the Generalitat of Catalonia, presented the proposal to be included within the second phase expansion of the official Catalan NSP preceded by a one-year pilot study carried out in collaboration with CATGLOBIN. At the beginning of 2015, the Public Health Agency of the Catalan government approved the inclusion of the NSP of hemoglobinopathies and SCD within the Catalan NSP Organisation and the creation of a Diagnostic Confirmation Unit for SCD in Catalonia.

Closing remarks

Throughout the last 5 years, thanks to the implementation of The Spanish Undiagnosed Rare Diseases Program (Spain UDP) a great push has been provided to the implementation of neonatal screening for hemoglobinopathies and especially for SCD. After the dissemination of neonatal screening to most of the autonomous communities and the inclusion of patients of all ages in the registry, a high number of cases have been registered to allow the follow-up of each one of them and to increase their survival by more than 95.5% at 20 years of age in SCD, and 96.7% in thalassemia major. The NSP has become the most widely used diagnostic method, which has made it possible to pave the way for future cohort studies and to be able to compare data with other European registries, as has been done during the first stage of the ENERCA project. This has greatly contributed to the awareness of doctors and the general population against this imported disease that affects a large number of European countries. It is also important to mention that with this new dimension adopted to face the health problem, a great advance has been made in the process of the transition of SCD patients from childhood to adulthood through communication between pediatric hematologists and their adult counterparts. Moreover, this has facilitated the possession of evolutionary data from the beginning, which may have an impact

on the creation of new protocols and updating of existing guidelines. and recommendations. The consolidation of the registry led by SEHOP will make it possible to propose the realization of new multicenter studies since just by keeping the registry up to date, the epidemiological studies that are deemed necessary can be promoted by the pertinent health authorities.

Turkey

Migrants in Turkey

Turkey is located in the intersection point of Asia, Europe and Africa and Turkey is a bridge between economically and politically underdeveloped states and rich Western countries.
Irregular migrants consider Turkey as a transit route. In addition, Turkey has rising power in its region and this makes Turkey a destination country instead of transit country for third country nationals. Besides, the turmoil which has continued for years in the Middle East, Caucasus and the Balkans has led to a mass influx to Turkey and Turkey has welcomed asylum seekers in a difficult situation as a consequence of its historical ties and its sense of obligation. After 1980s, Turkey has become not only immigrant sending country but also immigrant receiving country.
Conflict, violence and persecution worldwide force due to the number of people displaced by Turkey reached record levels, the highest number in the world continues to host refugees.
Turkey already serves to host 3.6 million registered Syrian refugees and about 370,000 people anxious from other nations (55).

The screening programs for hemoglobinopathies in Turkey

Hemoglobinopathies are a very important health problem in Turkey. In 1958, the first clinical and hematological studies were published by *Aksoy et al.* In 1971, Cavdar and Arcasoy reported that the overall incidence of β-thalassemia was 2.1% (56, 57).
Altay and Akar published abnormal hemoglobins in Turkey in different years . Forthy-two abnormal hemoglobins were identified in the Turkish population. The most frequently observed abnormal hemoglobins were: Hb S, Hb D, Hb C, HbE and Hb O Arab. HbS was the most common abnormal hemoglobin in Turkey (58).
In various surveys, the prevalence of HbS in Eti-Turks living in the Çukurova Region, that is an Arabic speaking closed population, was found to be between 3-47%. The overall frequency in Turkey is 0.3% and that in Thrace was 2.5% (59).
The Ministry of Health (MOH) established thalassemia centers in Antalya, Antakya, Mersin and Mugla, the southern provinces of Turkey, after the law named "*Fight Against Hereditary Blood Disease* (FAHBD)" was accepted in 1993.
The Turkish National Hemoglobinopathy Council (TNHC) was installed to combine all centers, foundations and associations into one organization together with the MOH in 2000.
The written regulations of FAHBD were published in 2002.
Thirty-three provinces situated in the Thrace, Marmara, Aegean, Mediterranean and South Eastern regions were selected for the Hemoglobinopathy Prevention Program. (HPP) by MOH and TNHC. The HPP was started in these provinces on May 8 2003. The HPP had the following goals: (a) to assess the present situation of thalassemias and hemoglobinopathies in Turkey, (b) to establish first level centers for prevention programs, (c) to educate the healthcare personnel about thalassemia, (d) to inform the community by using press and media, and (e) to provide premarital screening tests and genetic counseling to couples.
According to the written regulations, first level centers were responsible for diagnosis, public education, screening and genetic counseling. Second level centers were responsible for the diagnosis,therapy and follow-up of patients. Third level centers were for prenatal diagnosis, genetic analysis or stem cell transplantation (60).
A premarital hemoglobinopathy test is mandatory and free of charge in this program.
According to the Ministry of Health reports, 46 first level hemoglobinopathy diagnostic centers were established for premarital tests. While the percentage of premarital screening tests was 30.0% of all couples in 2003, it reached 86.0% in 2013. The number of newborn with thalassemia and hemoglobinopathies were 272 in 2002 and dropped to 25 in 2013. There has been a 90.0% reduction in affected newborns as the results of educational and prevention in the last 10 years. This program has been run as successfully run in 41 provinces by the MOH till to 2013 (61-63).
As of November 1, 2018, the Hemoglobinopathy Control Program has been implemented in 81 provinces covering whole country, under the name of "*Pre-Marriage Hemoglobinopathy Scree-*

ning Program". Counseling service is provided to spouse candidates who apply to family physicians to get a pre-marital report, and then blood samples are taken from the male spouse candidate for screening and screening tests are performed by sending blood samples to the Public Health Laboratory in the province or province. If the male partner is found to be a carrier or suspect in terms of hemoglobinopathy, a screening test is also performed for the female partner. Couples who are both carriers are directed to the centers to receive genetic counseling and when they think of having children, they are directed to have a healthy baby (64).

Migrant Health Centers

In order to provide preventive health services and basic health services to Syrians in our country more effectively and efficiently, to overcome the problems arising from the language and cultural barrier, and to increase access to health services, the immigrant health centers (GSM) are established.

Reinforced GSM is being established in temporary accommodation centers with a relatively high population and are far from a full-fledged public hospital and in settlements where the number of Syrians is over 20 thousand. The number of strengthened migrant health centers is 34.

Currently, 780 migrant health units have been established in 180 migrant health centers in 29 provinces and continue their activities.

"*Syrians Temporary Protected Health Status and Development of the Republic of Turkey presented by Related Services Project (Feelings)*" framework; Efforts are being made to support the currently operating GSM's, to create new GSM where needed, and to employ Syrian health workers to provide services in these centers.

The number of Syrian physicians employed in GSM is 694, the number of Syrian auxiliary health personnel is 954, the number of patient referral personnel is 1,121, the number of support services personnel is 399, the number of social workers is 11 and the number of psychologists is 12 (65). All health services to immigrations in Turkey between 2011 and 2019 are summarized in **Table 6**.

In places where there are no migrant health centers, Foreign Nationals Polyclinics (YUP) have been established to provide health services to foreigners.First of all, it has been planned to open at least one YUP in each province, and currently 98 polyclinics are in service in 80 provinces. YUPs are planned to be opened within the scope of Community Health Centers in every province, in the districts where these people are most concentrated (66).

Increasing the service capacity for migration health by training GSM personnel working in these centers on migration and migrant health is among the goals (**Table 7**).

Data of health service for immigrations in overall Turkey	2011-2018 years	2019 years	2011-2019 years
Number of out patients	48.795.278	17.509.194	66.301.472
Number of patients in the clinic	1.863.522	451.566	2.315.098
Number of patients with surgery	1.581.661	401.861	1.983.522
Number of birth	415.582	110.612	526.194
Number of casualties taken from the border	50.806	5.634	56.440

Table 6. *Health Service Provided to Refugees (HSGM, 2019).*

Number	Total 2018	Total 2019	Total
Application	65.416	93.079	158.855
Examination	49.525	72.934	122.459
Vaccine	44.464	53.225	97.689
Following up baby	5.759	7.263	13.022
Following up children	1.904	3.410	5.314
Following up pregnant	1.480	1.995	3.475

Table 7. *YUP data for immigration in Turkey (From: www.goc.gov.tr. Directorate General of Migration Management of Ministry of Interior of Republic of Turkey).*

Conclusions

Through mobility and migration flows, haemoglobinopathies have spread from the Mediterranean, Africa and Asia to the whole Europe, the Americas and Australia, and there is scientific evidence that they have become a global public health problem. Prevention and management of haemoglobin disorders is well established and managed in countries where these conditions were traditionally endemic or in countries that have a longstanding tradition of receiving migrants.

The International Organization for Migration (IOM) estimates that in 2020, 1,046,600 migrants arrived in Europe by land and sea. These increased numbers have significant repercussions for European governments and the European Union (EU), which were somewhat unprepared to address such issues. Preventive strategies of the public health authorities that today are lacking, should be include three different types of actions:

a) information for foreign populations and caregivers;
b) healthy carriers detection among immigrants (screening programs); and
c) counseling and prenatal diagnosis for healthy carriers and at-risk immigrant couples (15).

Many questions remain unanswered due to the lack of standardized national data collection systems across Europe. Coordinated efforts should be made to develop diagnostic pathways for hemoglobinopathies, in order to plan interventions, including prenatal diagnosis and cure. The absence of national registries makes essential to identify ways and tools to better describe the extent of the problem in terms of numbers and distribution across each country (67, 68).

Furthermore, understanding the degree of patient-perceived health impairment is essential to determine the burden of illness. Language barriers and poor multicultural competencies of healthcare staff and support teams were also considered critical factors leading to under or misdiagnosis, poor disease management and patient adherence with treatment, lower patient safety and patient awareness.

Mediterranean Blood Diseases Foundation (AKHAV), the European Network for Rare and Congenital Anaemias (ENERCA) and the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) through the Equality Plus project of the EU have planned a common response to the rising number of SCD patients in Italy, Spain and Turkey with the objectives to create a national working group focused on subjects with hemoglobinopathies and to develop tailored guidelines and algorithms for the management of SCD that could be accessed and practiced by those involved in the care of these patients in order to improve their specific knowledge and their ability of communication with different cultures and to deal with the medical needs of patients with hemoglobinopathies, considering the insufficient level of knowledge of medical teams who are now having to take care of these patients.

References

1. *Weatherall DJ. The inherited diseases of haemoglobin are an emerging global health burden. Blood. 2010; 115:4331-4336.*
2. *Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ. 2008; 86:480-487.*
3. *Modell B, Darlison M, Birgens H, et al. Epidemiology of haemoglobin disorders in Europe: an overview. Scand J Clin Lab Invest. 2007; 67:39-70.*
4. *McGann PT, Nero AC, Ware RE. Clinical Features of β-Thalassemia and Sickle Cell Disease. Adv Exp Med Biol. 2017; 1013:1-26.*
5. *Viprakasit V, Ekwattanakit S. Clinical Classification, Screening and Diagnosis for Thalassemia. Hematol Oncol Clin North Am. 2018; 32:193-211.*
6. *Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet. 2017; 390:311-323.*
7. *Hoppe C, Neumayr L. Sickle Cell Disease. Monitoring, Current Treatment, and Therapeutics Under Development. Hematol Oncol Clin North Am. 2019; 33:355-371.*
8. *Aguilar Martinez P, Angastiniotis M, Eleftheriou A, et al. Haemoglobinopathies in Europe: health & migration policy perspectives. Orphanet J Rare Dis. 2014; 9:97.*
9. *Gulbis B, Eleftheriou A, Angastiniotis M, et al. Epidemiology of rare anaemias in Europe. Adv Exp Med Biol. 2010; 686:375-396.*
10. *Haemoglobinopathies on the Move: Is Europe ready? Health and Migration Policy Perspectives; http://www.enerca.org and http://www.thalassaemia.org.cy.*
11. *Giordano PC. Prospective and retrospective primary prevention of hemoglobinopathies in multiethnic societies. Clin Biochem. 2009; 42:1757-1766.*
12. *Cataldo F. Immigration and changes in the epidemiology of hemoglobin disorders in Italy: an emerging public health burden. Ital J Pediatr. 2012; 38:32.*
13. *Angastiniotis M, Eleftheriou A, Galanello R, et al. Prevention of Thalassaemias and Other Haemoglobin Disorders: Volume 1: Principles [Internet]. 2nd edition.Old J, editor. Nicosia (Cyprus): Thalassaemia International Federation; 2013.*

14. *Serour GI, Aboulghar MA, Mansour RT. Bioethics in medically assisted conception in the Muslim world. J Assist Reprod Genet. 1995; 12:559-565.*
15. *Lobitz S, Telfer P, Cela E, et.al. Newborn screening for sickle cell disease in Europe: recommendations from a Pan-European Consensus Conference. Br J Haematol. 2018; 183:648-660.*
16. *Clarke GM, Higgins TN. Laboratory investigation of hemoglobinopathies and thalassemias: review and update. Clin Chem. 2000; 46:1284-1290.*
17. *Piety NZ, Yang X, Kanter J, et al. Validation of a Low-Cost Paper-Based Screening Test for Sickle Cell Anemia. PLoS One. 2016; 11(1):e0144901.*
18. *Caritas Italiana.COMMON HOME MIGRATION AND DEVELOPMENT IN ITALY. 2019.pp.1-30.*
19. *Bittles AH, Black ML. Consanguinity, human evolution and complex diseases. Proc Nat Acad Sci. 2010; 107:1779-1786.*
20. *Cao A, Galanello R, Rosatelli MC, et al. Clinical experience of management of thalassemia: the Sardinian experience. Semin Hematol. 1996; 33:66-75.*
21. *Lodi M, Bigi E, Palazzi G, et al. Universal Screening Program in Pregnant Women and Newborns at-Risk for Sickle Cell Disease: First Report from Northern Italy. Hemoglobin. 2017; 41:230-233.*
22. *Russo-Mancuso G, Romeo MA, Guardabasso V, Schiliro G. Survey of sickle cell disease in Italy. Haematologica. 1998; 83:875-881.*
23. *Schilirò G. Sicily: the world reservoir for thalassemias and haemoglobinopathies. Nature.1978; 276:761.*
24. *Colombatti R, Perrotta S, Samperi P, et al. Organizing national responses for rare blood disorders: the Italian experience with sickle cell disease in childhood. Orphanet J Rare Dis. 2013; 8:169.*
25. *Po C, Colombatti R, Cirigliano A, et al. The management of sickle cell pain in the emergency department: a priority for health systems. Clin J Pain. 2013; 29:60-63.*
26. *Ballardini E, Tarocco A, Marsella M, et al. Universal neonatal screening for sickle cell disease and other haemoglobinopathies in Ferrara. Italy. Blood Transfus. 2013; 11:245-249.*
27. *Rolla R, Castagno M, Zaffaroni M, et al. Neonatal screening for sickle cell disease and other hemoglobinopathies in "the changing Europe". Clin Lab. 2014; 60:2089-2093.*
28. *Venturelli D, Lodi M, Palazzi G, et al. Sickle cell disease in areas of immigration of high-risk populations: a low cost and reproducible method of screening in northern Italy. Blood Transfus. 2014; 12:346-351.*
29. *Lodi M, Bigi E, Palazzi G, et al. Universal Screening Program in Pregnant Women and Newborns at-Risk for Sickle Cell Disease: First Report from Northern Italy. Hemoglobin. 2017; 41:230-233.*
30. *Lodi M, Bigi E, Palazzi G, et al. Universal Screening Program in Pregnant Women and Newborns at-Risk for Sickle Cell Disease: First Report from Northern Italy. Hemoglobin. 2017; 41:230-233.*
31. *De Franceschi L, Lux C, Piel FB, et al. Access to emergency departments for acute events and identification of sickle cell disease in refugees. Blood. 2019; 133:2100-2103.*
32. *De Franceschi L. Routine Sickle Cell Disease Screening Among Migrants May Help Fast-Track Treatment, Save Lives, and Reduce Health Care Costs. www.hematology.org. 9th may, 2019.*
33. *Inusa BPD, Colombatti R. European migration crises: The role of national hemoglobinopathy registries in improving patient access to care. Pediatr Blood Cancer. 2017; 64(7):e26515.*
34. *Hulihan MM, Feuchtbaum L, Jordan L, et al. State-based surveillance for selected hemoglobinopathies. Genet Med. 2015; 17(2):125-30.*
35. *Modell B, Khan M, Darlison M, et al. A national register for surveillance of inherited disorders: beta thalassaemia in the United Kingdom. Bull World Health Organ. 2001; 79:1006-1013.*
36. *Dulin Iñiugueza E, Cantalejo López MA, Cela de Julián ME, Garci G. Early detection of sickle cell anemia and other hemoglobinopathies in neonates in the autonomous community of Madrid. A pilot study. An Pediatr (Barc). 2003; 58:146-155.*
37. *Cela de Julian E, Dulin Iñiguez E, Guerrero Soler M, et al. Evaluation of systematic neonatal screening for sickle cell diseases in Madrid three years after its introduction An Pediatr (Barc). 2007; 66:382-386.*
38. *Baiget M, del Rìo E, Doménech M, et al. Escrutinio de hemoglobinopatías en sangre de cordon umbilical. Biolog´ıa Cl´ın Hematol. 1981; 3:251-256.*
39. *Angastiniotis M, Modell B, Englezos P, et al. Prevention and control of hemoglobinopathies. Bull World Health Org. 1995; 73:375-386.*
40. *Study Group for Hemoglobinopathies and Thalassemias. Thalassemia syndromes in Spain. Preliminary epidemiologic data. Sangre (Barc). 1986; 122:609-613.*
41. *Baiget M. Hemoglobinas estructurales en España. Sangre (Barc). 1985; 30:899-904.*
42. *Oliva Berini E, Cladera Serra A, Torrent Quetglas M. Campaign for the detection of minor beta-thalassemia and prevention of major beta-thalassemia in the isle of Menorca. 10-year experience. Med Clin (Barc) 1998; 110:361-4.*
43. *Martìn Nùñez GA. Incidencia de hemoglobinopat´ıas estructurales en la alta Extremadura. Estudio neonatal. Madrid: Universidad Complutense, 1989.*
44. *Calvo-Villas JM, Zapata Ramos MF, Cuesta Tovar J, et al. Prevalence of hemoglobinopathies in pregnant women in the Lanzarote health sanitary area. An Med Interna. 2006; 23:206-212.*
45. *Modell B, Darlison M, Birgens H, et al. Epidemiology of haemoglobin disorders in Europe: an overview. Scand J Clin Lab Invest. 2007; 67:39-70.*
46. *De las Heras Flo´rez S, P´erez Hern´andez LM. Hemoglobinopat´ıas diagnosticadas en el ´area sanitaria del Hospital Universitario Nuestra Señora de Candelaria de Santa Cruz de Tenerife durante un a˜no. An Med Interna (Madrid). 2008; 25:61-66.*
47. *Mañú-Pereira M, Maya A, Cararach V, et al. Neonatal screening of hemoglobinopathies and glucose-6-phosphate dehydrogenase in Catalonia. The pilot study in an anonymous, not related population. Med Clin (Barc). 2006; 126:281-285.*
48. *Mañú Pereira M, Cabot A, Martìnez Gonzàlez A, et al. Neonatal screening of haemoglobinopathies and G6PD deficiency in Catalonia (Spain). Molecular study of sickle cell disease associated with alpha thalassaemia and G6PD deficiency. Med Clin (Barc). 2007; 129:161-164.*
49. *Las Heras Manso G, Juncà Piera J, Feliu Frasnedo E, et al. Haemoglobinopathies and glucose-6-phosphate dehydroge-*

nase deficiency in the sub-Saharan immigrant population of the Center and South Maresme region, Catalonia, Spain. Med Clin (Barc). 2008; 131:5-9.

50. *Daniel Y, Elion J, Allaf B, et al. Newborn Screening for Sickle Cell Disease in Europe. Int. J. Neonatal Screen. 2019, 5:15.*
51. *Orphanet. Prevalence of rare diseases. Orphanet report series 2018 http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence of rare diseases by alphabetical list.pdf.*
52. *Bardón Cancho EJ, García-Morín M, Beléndez C, et al. Update of the Spanish registry of haemoglobinopathies in children and adults. Med Clin.2030; 155: 95-103.*
53. *Couce ML. Fifty years of neonatal screening for congenital diseases in Spain An Pediatr (Barc).2019; 90:205-206.*
54. *Cabot Dalmau A, Casado Toda M, Barberàn Pèrez J, et al. Screening neonatal de drepanocitosis en el Consorci Sanitari de Mataro. Justificaci´on y primeros resultados. An Esp Pediatr 1998; 49:157-160.*
55. *UNHCR - The UN Refugee Agency. www.unhcr.org.*
56. *Aksoy M, Lekin EW, Maurant AE, Lehmann H. Blood groups,hemoglobins, and thalassemia in Southern Turkey and Eti Turks.Br Med J. 1958; 2:937-939.*
57. *Cavdar AO, Arcasoy A. The incidence of β -thalassemia andabnormal hemoglobins in Turkey. Acta Hematol. 1971; 45:313-318.*
58. *Altay Ç. Abnormal hemoglobins in Turkey. Turk J Hematol 2002; 19:63-74.*
59. *Akar E, Akar N. A review of abnormal hemoglobins in Turkey. Turk J Hematol. 2007; 24:143-145.*
61. *Canatan D, Kose MR, Ustundag˘ M, et al. Hemoglobinopathy control program in Turkey. Community Genet. 2006; 9:124-126.*
62. *Ministry of Health of Turkey. Hemoglobinopathy Control Program. Canatan D, Ed. Tu˘rkiye Klinikleri J Hem Onc Special Topics. 2010; 3:5-8.*
63. *Canatan D. Thalassemias and Hemoglobinopathies in Turkey. Hemoglobin. 2014; 38:305-307.*
64. *Canatan D, Delibas S. Report on Ten Years' Experience of Premarital Hemoglobinopathy Screening at a Center in Antalya, Southern Turkey.Hemoglobin. 2016; 40:273-276.*
65. *Republic of Turkey Ministry of Health, General Directorate of Public Health, Child and Adolescent Health Department. www.goc.gov.tr.*
66. *www. Republic of Turkey Ministry of Health, General Directorate of Public Health January The report of activity of 2019 year. January - 2020. www.goc.gov.tr.*
67. *Telfer P, Coen PG, Christou S, et al. Survival of medically treated thalassaemia major patients in Cyprus. Trends and risk factors over the period 1980-2004. Haematologica. 2006; 91:1187-1192.*
68. *Angastiniotis M, Vives Corrons JL, Soteriades ES, Eleftheriou A. The impact of migrations on the health services for rare diseases in Europe: The example of haemoglobin disorders. Sci World J. 2013; 2013:727905.*

Appendix
Definitions of migrants, asylum seekers and refugees
Migrants include those who move, either temporarily or permanently from one place, area or country of residence to another for reasons such as work or seeking a better life (i.e. economic migrants), for family reasons or to study. People also migrate to flee conflict or persecution, which is where the definition converges with the terms (Source: United Nations High Commission for Refugees. Global trends: forced displacement in 2016. Geneva, 2017).
Asylum seekers are individuals who have sought international protection and whose claims for refugee status have not yet been determined, irrespective of when they may have been lodged. An asylum seeker has applied for asylum on the grounds of persecution in their home country relating to their race, religion, nationality, political belief or membership of a particular social group. This population remains classified as asylum seeker for as long as the application is pending (Source: United Nations High Commission for Refugees. Global trends: forced displacement in 2016. Geneva, 2017).
Refugees have been forced to leave their country in order to escape war, persecution or natural disaster. The 1951 Convention relating to the Status of Refugees describes a refugee as "a person who owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group, or political opinion, is outside the country of this nationality and is unable to or, owing to such fear, is unwilling to avail himself of the protection of that country". A refugee is an asylum seeker whose application has been successful (Source: United Nations High Commission for Refugees. Global trends: forced displacement in 2016. Geneva, 2017).

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