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GUIDELINES - CONSENSUS-BASED

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EHA Recommendations for preconceptual and antenatal screening and prenatal diagnosis for hemoglobinopathies

Mariane de Montalembert[1,2] | Maria D. Cappellini[3] | Achille Iolascon[4,5] | Lucia de Franceschi[6,7] | Eda Ömur[8] | Michele Abi Saad[9] | Immacolata Andolfo[4,5] | Celeste Bento[10] | Maria Berghs[11] | Doris Bonnet[12] | Andreas Glenthoj[13] | Beatrice Gulbis[14] | Tuphan K. Dolai[15] | Jorge Lima[16,17,18] | Irene Motta[19] | Roberta Russo[4,5] | Ali Taher[20] | Leon Tshilolo[21,22] | Antonio Almeida[23,24] | David Rees[25,26]

Correspondence: Mariane de Montalembert (mariane.demontal@aphp.fr)

Abstract

Thalassemia and sickle cell disease (SCD) are among the most common monogenic disorders worldwide. They cause chronic hemolytic anemia, the consequences and prognosis of which vary considerably depending on the genetic characteristics of patients and the healthcare system in their country of residence. Both diseases are autosomal recessive in their transmission, with carriers generally being asymptomatic. Informing carriers of thalassemia or SCD about reproductive risks and choices, while taking into account cultural and religious considerations, is a priority within global strategies to improve outcomes for these diseases. The European Hematology Association (EHA)'s Topic In Focus (TIF) Hemoglobinopathies Group created a focus group of hematologists, patients, anthropologists, and an obstetrician from Europe, the Middle East, India, and Africa. The Group considered that preconceptual screening tests would correspond to tests conducted before pregnancy (screening for carriers before marriage/conception), antenatal screening referred to tests completed on pregnant women, and prenatal diagnosis referred to tests performed on the fetus. It proposed guidelines addressing optimal timing of screening, appropriate laboratory tests, and communication strategies, taking into account the great diversity of regions and cultures where thalassemia and SCD are present. A main discussion point was that no recommendations would be given for couples about reproductive decisions, and that the aim was to present the existing and available options in different countries. Eight questions were examined using available literature, leading to the formulation of seven recommendations, which were submitted to a vote using the Delphi method. Consensus agreement was obtained for all recommendations.

[1]Department of General Pediatrics and Pediatric Infectious Diseases, Sickle Cell Center, Necker-Enfants Malades Hospital, Assistance Publique – Hôpitaux de Paris (AP-HP), Paris, France
[2]Université Paris-Cité, INSERM, EFS, BIGR U1134, Paris, France
[3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SC Medicina ad Indirizzo Metabolico, Milan, Italy
[4]Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Naples, Italy
[5]CEINGE Biotecnologie Avanzate Franco Salvatore, Naples, Italy
[6]Dept of Engineering for Innovative Medicine, University of Verona, Verona, Italy
[7]Azienda Ospedaliera Universitaria integrata di Verona, Verona, Italy
[8]Sickle cell patient representative, Voices of Sicklecell, Deventer, The Netherlands
[9]Chronic Care Center, Hazmieh, Lebanon
[10]Hematology Department, University Hospital Coimbra, Coimbra, Portugal
[11]Department of Psychiatry, Herchel Smith Building, Robinson Way, University of Cambridge, Cambridge, UK
[12]Institut de Recherche pour le développement Ceped, UMR 196, Université de Paris Cité, Paris, France
[13]Danish Red Blood Cell Center, Department of Hematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[14]Center of Human Genetics, Hôpital Universitaire de Bruxelles - U.L.B, Brussels, Belgium
[15]Department of Hematology, NRS Medical College and Hospital, Kolkata, West Bengal, India

INTRODUCTION

Thalassemia and sickle cell syndromes are among the most common monogenic disorders worldwide. Both are responsible for chronic hemolytic anemia and have an autosomal recessive transmission, with carriers being largely asymptomatic.

Thalassemic syndromes result from an impaired synthesis of α- or β-globin chains. Their severity varies greatly depending on the extent of the imbalance in the α/β chain ratio. Thalassemia is clinically heterogeneous because various genetic variants impair globin-chain synthesis. Patients on the most severe end of the spectrum depend on regular transfusions for survival (called transfusion-dependent thalassemia, TDT); thus, their life expectancy depends mainly on the availability and safety of blood supplies and treatment of transfusion-related complications, primarily through iron chelators, and disease-related complications.[1] Thalassemia is mostly prevalent in the Mediterranean region, North Africa, the Middle East, and Asia. The 2021 assessment of the global burden of thalassemia estimated that there were 1,310,407 cases worldwide (95% CI: 1,099,973–1,572,220).[2]

Sickle cell disease (SCD) syndromes are characterized by the presence of abnormal hemoglobin S, which polymerizes in deoxygenated conditions, leading to sickling of red blood cells (RBCs). The entrapment of abnormal RBCs, associated with inflammatory vasculopathy and over-activation of neutrophils, results in vascular obstruction and the generation of vaso-occlusive crises (VOC). There are three main phenotypes, the most common being homozygous HbS mutation (HbSS patients), with other forms including compound heterozygous conditions such as HbS with HbC (HbSC patients), and HbS with β-thalassemia ($HbS\beta^0$ and $HbS\beta^+$ phenotypes). Given the multiplicity of causative factors, SCD is characterized by a remarkable phenotypic complexity, making individual prognosis very difficult. SCD is mainly prevalent across sub-Saharan Africa, India, and Mediterranean areas,[3] although the increase in worldwide migration patterns has led to the widespread presence of patients in the USA, Latin America, Caribbean, the Arab Peninsula, and Central/Northern Europe. A study estimated that 7.74 million people (95% uncertainty interval: 6.51–9.20 million) were living globally with SCD in 2021.[4]

Giving birth to children affected by a severe condition is a major cause of suffering for people who are carriers of genetic diseases. Following a comprehensive review of the SCD disease landscape, an expert panel from the Lancet Hematology Commission reported that information about reproductive risks and choices, tailored to cultures and religions, requiring action by governments, national health authorities, public health organizations, and patient support organizations, was in the top five priorities of global strategies to improve outcomes in SCD.[4] This recommendation is equally applicable to people affected by thalassemia.

Continued advances in genetic testing and obstetric techniques have enabled routine prenatal diagnosis (PND) in high-income countries (HICs).[5] PND allows couples to determine whether the child is affected by the disease, to make informed decisions regarding the pregnancy, and to prepare for the child's birth, if that is the parents' choice, or to opt for pregnancy termination.

However, PND is not available in many regions due to a lack of resources. In addition, the psychological and social impact of being identified as a carrier must not be underestimated and may be particularly poignant in low-income countries (LICs). This negative impact highlights the need for the dissemination of knowledge and education about hemoglobinopathies.

Several national guidelines on the screening and diagnosis of hemoglobinopathies have been developed by expert hematologists.[6,7] In reality, screening practices for hemoglobinopathies vary considerably worldwide. Some countries implement carrier screening programs during high school or as part of premarital testing, whereas others primarily rely on prenatal screening strategies, often integrated into routine antenatal care. In 2023, a group of experts from the European Hematology Association (EHA) Topic-in-Focus (TIF) Hemoglobinopathies Group identified the development of the first interprofessional and intercultural consensus on the screening and diagnosis of hemoglobinopathies as a priority during its inaugural meeting.

METHODS

The EHA-TIF Hemoglobinopathies Group includes experts and patients from Europe and the Middle East. Experts were specialized in clinical and biological hematology, pediatrics, genetics, and obstetrics. Two patient representatives (one being a patient) joined the group. After deciding to draft guidelines on preconceptual and antenatal screening and prenatal diagnosis of hemoglobinopathies, in order to take into consideration the differences in various regions and cultures where hemoglobinopathies are present, the EHA-TIF Hemoglobinopathies Group invited additional experts interested in screening, notably from LICs, and anthropologists. These experts were required to disclose conflicts of interest, and the EHA supervised the project, ensuring that the guidelines complied with the methodology adopted by its Guidelines Committee. The EHA also provided organizational and logistical assistance, and funding for the necessary face-to-face meetings or teleconferences.

The Group confirmed the following definitions:

- Preconceptual screening: tests performed before pregnancy (screening for carriers before marriage/conception).
- Antenatal screening: tests performed on a pregnant woman.
- Prenatal diagnosis: tests performed on a fetus.

A main point was that no recommendations would be given for couples about reproductive decisions, and that the aim was to present the existing and available options in different countries only.

A literature search was conducted via PubMed online using the keywords “genetic counseling,” “premarital OR preconceptual,” “carrier screening,” “antenatal screening,” “prenatal diagnosis,” “genetic counseling,” “reproductive choice,” “thalassemia,” and “sickle cell disease,” selecting articles published after 2000. Abstracts of 476 papers were analyzed, of which 205 papers relevant to this manuscript were selected for review. Selection was finalized after excluding duplicates and papers

[16]Department of Obstetrics and Gynecology, Hospital da Luz Lisboa, Lisboa, Portugal
[17]Comprehensive Health Research Centre, NOVA Medical School, Lisboa, Portugal
[18]Católica Medical School, Rio de Mouro, Portugal
[19]Department of Clinical Sciences and Community Health, Dipartimento di Eccellenza 2023-2027, University of Milan, Milan, Italy
[20]Division of Hematology & Oncology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon
[21]Institut de Recherche Biomédicale 1-Health/CEFA-Monkole, Kinshasa, Democratic Republic of the Congo
[22]Département de Pédiatrie, Université Officielle de Mbujimayi, Mbuji-Mayi, Democratic Republic of the Congo
[23]Faculdade de Medicina, Universidade Católica Portuguesa, Lisboa, Portugal
[24]Hospital da Luz, Lisboa, Portugal
[25]School of Cancer and Pharmaceutical Sciences, Faculty of Life Sciences Medicine, King's College London, London, UK
[26]Department of Hematological Medicine, King's College Hospital, London, UK

focusing only on molecular biology techniques, epidemiologic analyses, or newborn screening (NBS) techniques. Two groups of experts were then formed, one focused on "methodology, tests, and strategies," the other on "cultural behaviors, education, and communication of results," led by AI (methodology) and MC (cultural behaviors), respectively. Each group produced four questions, and AI, MC, and MM selected the most relevant articles for each.

The "Methodology, Tests, and Strategies" group selected the following questions:

Regarding preconceptual screening and antenatal screening

Q1. At what age/when should screening be done?

Q2. What type of laboratory test should be used for screening?

Regarding prenatal diagnosis

Q3. With regard to genetic counseling: what are the possibilities for couples at risk of having an affected fetus?

Q4. What type of laboratory test should be used for diagnosis?

The "Cultural behaviors, Education, and Communication of results" group selected the following questions:

Q5. How to increase awareness regarding preconceptual and antenatal screening and prenatal diagnosis?

Q6. How to communicate the results of a carrier status or disease in a fetus?

Q7. What are the competencies required of a genetic counselor for hemoglobinopathies? How to train a genetic counselor, including in LICs?

Q8. What is the proposed process for genetic counseling?

For each question, a summary of publications was prepared. Key information from consolidated summaries, combined with the experts' opinions, was used to form these guidelines. These guidelines were then submitted to expert panels from both the working groups (i.e., "Methodology, Tests, and Strategies" and "Cultural behaviors, Education, and Communication of results"). The manuscript was modified in accordance with the requests of each co-author. The drafting of the recommendations was the subject of two discussions within the two subgroups, "methodology, testing, and strategies" and "cultural behaviors, education, and communication of results." Questions 1, 2, 5, 6, and 7 each resulted in one recommendation. Question 3 resulted in two recommendations (recommendations 3 and 4). Conversely, the answers to question 4 depended heavily on the infrastructure of each country and did not result in any consensus recommendations. Similarly, question 8 did not result in any recommendations, as we felt that the key elements of this message had already been discussed. We preferred to propose an algorithm for diagnosis and counseling pathways (Figure 1). After establishing the recommendations, in a second step, during a global discussion, the 20 authors of the article voted on all the recommendations during the Delphi panel. An agreement was reached using a Delphi method. Voting options were "agree" or "disagree" and consensus was reached when >75% of experts chose to "agree" with a particular statement. Note that ethical approval was not applicable to this consensus manuscript.

RESULTS

Q1: Regarding preconceptual screening and antenatal screening: at what age/when should screening be done?

Preconception and prenatal screening should be accessible to all, leaving it up to each individual to decide whether or not to use them. A literature review shows that it has mainly been offered to the following groups

a. Individuals before they enter into a relationship, for example, in high school;
b. In the premarital period, particularly in the case of arranged marriages (often called premarital screening);
c. To couples before conception; or
d. Early in pregnancy.[6–10]

Extended familial screening after the identification of a case within a family is also effective.[11] Almost all hemoglobinopathies (with the exception of very rare forms of thalassemia) can be detected using phenotypic screening, without the need for molecular genetic testing, which makes the screening easier. The Cyprus national thalassemia screening program, launched in the early 1970s, is a good illustration of this. It focused first on the screening of high-school students and conscripts, as well as the parents of affected individuals, and, after the early 1980s, on the issue of a prenuptial certificate (couples wishing to marry in the Greek Orthodox Church were required by church authorities to provide proof that they had been screened and had received appropriate counseling at the National Thalassemia Center). Although this screening approach was not mandatory, it was widely adopted, and the use of prenatal diagnosis and termination of pregnancy in cases of fetal disease led to a dramatic reduction in the prevalence of β-thalassemia at birth.[10] Since this pivotal experience, different strategies have been developed around the world.[10] Structured national/regional antenatal screening programs for hemoglobinopathies have been developed across Europe: in Greece, Italy, United Kingdom, France, Netherlands, Denmark, and Spain.[12,13] Thalassemia screening is offered in high schools in Malaysia, Singapore, Thailand, and other Asian countries.[14] Premarital screening for thalassemia and SCD is mandatory for any couple planning to marry in Saudi Arabia; after completion of screening, couples are issued a certificate enabling them to proceed to marriage. Nevertheless, around 80% of at-risk couples still choose to marry.[15–17] Additionally, programs have been implemented in Africa and India.[18]

Some observations and lessons can be drawn from these experiences:

- It can be hypothesized that the decision to implement a large-scale national screening program depends as much on the burden of the disease on the healthcare system and the ability of health authorities to cover the costs as on the religious and legal framework of each country.
- Awareness of the population and healthcare providers is a key factor. Uninformed people have no tools to make a choice, with the risks of developing distress, anxiety, and fear of stigmatization in those identified as carriers. This point will be developed in Q5.
- While preconceptual/antenatal screening has previously been associated with a decline in the number of children born with hemoglobinopathies, the advent of curative treatments, currently available primarily in HICs, may alter this pattern.[17]
- The offer of hemoglobinopathy screening can be a source of great difficulty for an individual or a couple. Should they talk to their family about it? The two partners in a couple may have different opinions, with the risk of conflict or even separation.
- In some settings, access to prenatal services, such as diagnostic testing or termination, may be legally or practically contingent on spousal or paternal consent.

Although having the option to engage with carrier screening at the preconception stage is the best option according to literature reviews,[19,20] few countries have implemented large-scale screening programs, meaning that screening is most often proposed during pregnancy. We will thus provide detailed recommendations concerning antenatal screening.

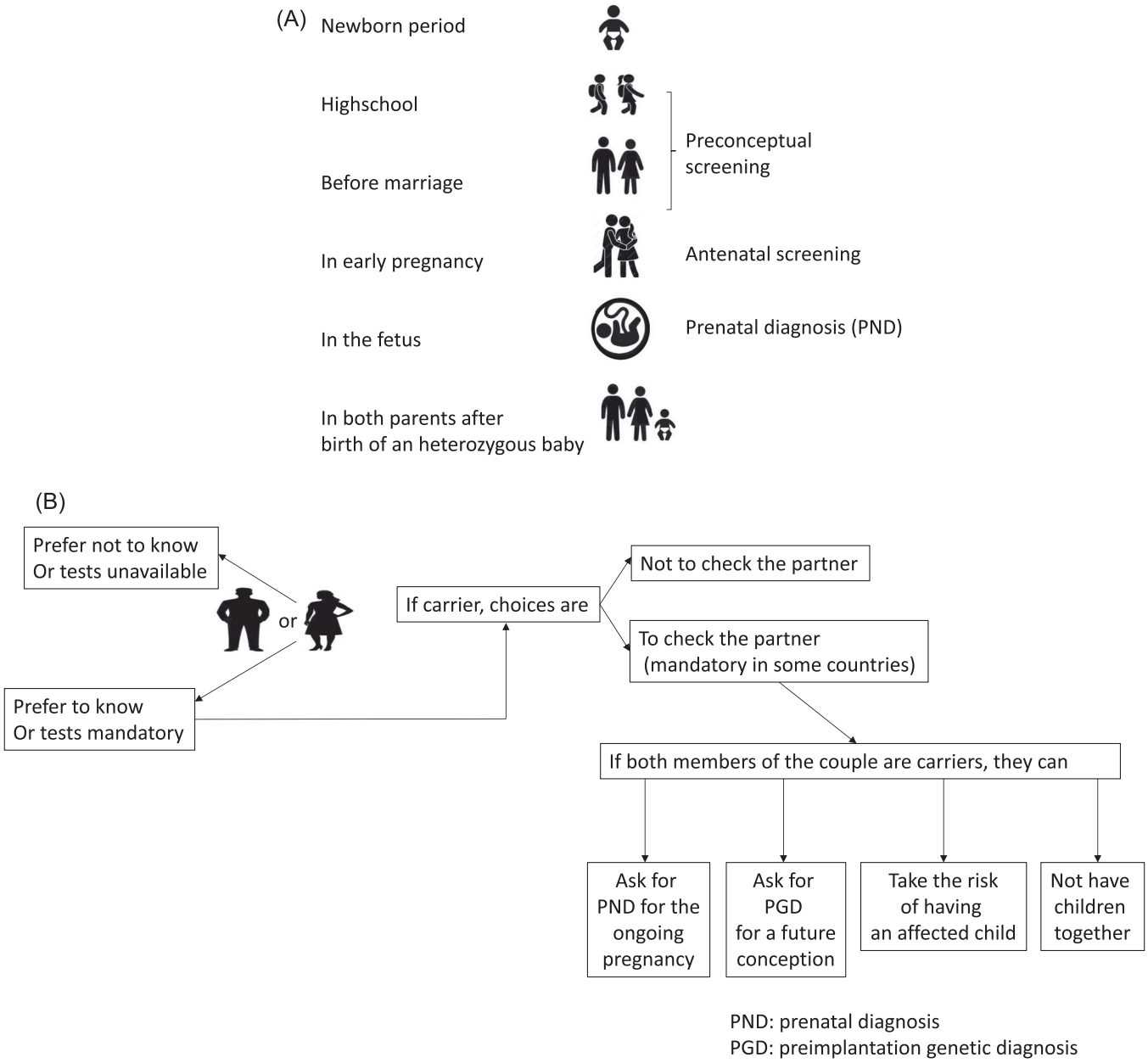

FIGURE 1 **(A)** When to perform screening tests? **(B)** Options regarding reproductive choices when at risk for hemoglobinopathies.

Antenatal screening

The appropriateness of different screening strategies will depend on the prevalence of the conditions in a given country and the resources available in that country.[6] Broadly, two main screening strategies are used:

- Universal screening (or one-step screening): each person is screened for hemoglobinopathies using laboratory tests, usually a complete blood count (CBC) and hemoglobin analysis to measure HbA_2 and identify variants.
- Selective screening (or two-step screening): the risk of individuals is first assessed using some sort of ethnicity assessment, and only those at higher risk proceed to laboratory testing. This may be appropriate in countries with a very low prevalence of hemoglobinopathies, such as some countries in northern Europe,[13] and in settings with limited healthcare resources, where screening can be focused on high-risk groups. Extended family screening is useful.[21] Nevertheless, targeted screening can be perceived as discriminatory.[19]

The target is to offer screening by 8–10 weeks of gestation to allow sufficient time to perform PND and offer informed reproductive choice.[6,22–25] Several approaches are possible:

a. In primary care, at the time of pregnancy confirmation, with parallel partner testing;
b. In primary care at the time of pregnancy confirmation, with sequential partner testing; or
c. In secondary care by midwives, with sequential partner testing.

A randomized controlled trial conducted in the United Kingdom did not demonstrate the superiority of any method, with an acceptance or refusal rate for screening after receiving all necessary information of only around 30%; this low rate was generally attributed to a lack of knowledge.[24] It is recommended to prioritize tailored programs for women from ethnic minority groups who are not often screened before 10 weeks, and to monitor any delays between pregnancy confirmation in primary care and the first midwifery appointment.[9,22] To this end, the involvement of primary care professionals/general practitioners and nurses to enable rapid screening should be proactive and collaborative, in order to expedite referral processes[25,26] (Table 1).

The Group agreed to recommend the United Kingdom strategy: if the disease is prevalent across the population, to perform universal screening; if the disease is concentrated within specific subgroups, to choose targeted screening.

Priority groups for screening using hemoglobin analysis

The following groups should be considered a priority with regard to screening at a population and individual level:

- People of specific ethnic origins or those residing in a region with a known high prevalence of hemoglobinopathies
- **SCD**: people of Greek, Turkish, Middle Eastern, Asian, and African descent[13,19,20]
- Since these can be small populations with a high prevalence of SCD, extended family history and regional epidemiology are important
- **Thalassemia:** People of Mediterranean, African, Middle Eastern, and Asian descent[7,19,20]
- Individuals with a family history of thalassemia or microcytic anemia with a negative history of iron deficiency.[7,11]
- Individuals with persistent microcytic anemia despite an adequate intake of supplemental iron.[7]
- Both members of a couple, when NBS has revealed that their baby is heterozygous for HbS (heterozygosity for β-thalassemia is not detected by NBS). Due to logistical difficulties, many parents do not receive this information. Screening of parents is also mandatory when NBS reveals that a baby is affected by hemoglobinopathy.

The group considered that these recommendations were grounded in solid experience in screening practices[6,28,30,31] and, therefore, did not deem it necessary to submit to a formal vote. In contrast, the group agreed that particular emphasis should be placed on the recommendation underscoring the importance of nondirective strategies, highlighting the need for parents to have full and autonomous decision-making power regarding their reproductive choices. A wording was drafted and submitted to a Delphi vote.

Recommendation 1

Screening aims to offer individuals and couples the timely opportunity to choose between different reproductive options, among which termination of pregnancy is only one option, and to prepare for the birth of an affected child, should that be their choice. The main aim is to support couples in their decisions based on personal wishes, cultural and religious beliefs, and the legal framework, and should not be focused on public health measures or the aim of eradicating the disease.

Consensus agreement: 100%

Q2: Regarding preconceptual screening and antenatal screening: What type of laboratory tests should be used for screening?

The first stage of screening may involve the use of a family origin questionnaire to assess individual risk and facilitate the interpretation of laboratory tests. A CBC and hemoglobin fraction analysis by quantitative tests, such as high-performance liquid chromatography (HPLC) or capillary electrophoresis (CE), is a mandatory initial test for the screening of hemoglobinopathies. The main cut-offs used to define suspected hemoglobinopathy in a person above the age of 12 are a mean corpuscular hemoglobin content (MCH) <27 pg (and <25 pg for a significant α-thalassemia); and/or a HbA2 below or above the reference range of the test used; and/or a fetal hemoglobin ≥5%; and/or

TABLE 1 Recommendations for tailored screening programs according to prevalence within the general population.

Scenario	Recommended timing/process
High prevalence settings (≥2% of the antenatal booking bloods positive for SS/SC, SE, and E/β, Hb Bart's hydrops fetalis)[6,22,23,26–28]	Testing should be completed before 10 weeks, and the whole process, including testing of the biological father, should be completed within the first 12–13 weeks of pregnancy
Low prevalence settings (<1% of the screened antenatal booking bloods positive for Hb variants)[6,13,20,27]	Offer testing according to ancestry, using a standard family origin questionnaire to determine the family origins of the mother and the baby's biological father, with specific tests subsequently employed
Primary care consultations[9,23,26,29]	Offer antenatal screening for SCD and thalassemia at a visit for confirmation of pregnancy to increase the chances of women being screened before 10 weeks of gestation. Monitor any delays between pregnancy confirmation in primary care and the first midwifery appointment

Abbreviations: Hb, hemoglobin; SCD, sickle cell disease.

TABLE 2 First-line preconceptual and antenatal screening tests for hemoglobinopathies

Who?	Which tests?
Anyone of childbearing age except of Northern European ancestry[6,30,31] and All egg donors and sperm donors[6]	• CBC and • Separation of the hemoglobin fractions by a quantitative technique such as HPLC or CE[6,30] ◦ In the presence of a significant hemoglobin variant, confirmation testing (alternative from the screening test used) is mandatory

Abbreviations: CE, capillary electrophoresis; HPLC, high-performance liquid chromatography.

the presence of a hemoglobin variant. Recommendations for interpretation of MCH and hemoglobin fraction results have been described in detail previously,[6,30,31] and are summarized below (Table 2).

The recommendations for first-line preconceptual and antenatal screening tests for hemoglobinopathy include:

- Preconceptual screening for hemoglobinopathy must be encouraged.
- Egg or sperm donors must always be screened for a hemoglobinopathy.
- Of the red blood cell indices, MCH is recommended as an indicator to suspect thalassemia.
- Screening for α- and β-thalassemia requires a quantitative technique such as HPLC or CE.

Point-of-care testing for SCD is already available and at a low cost. In low-resource settings, the main challenges are related to public health national strategies and the acceptability of testing by the population rather than techniques.[32,33]

Recommendation 2

Point-of-care testing may contribute to genetic counseling for SCD in low- and middle-income countries (LMICs).

Consensus agreement: 94%

Q3: Regarding prenatal diagnosis and genetic counseling: what are the possibilities for couples at risk of having an affected fetus?

People may conceive without a prenatal test, by personal choice or because a test is unavailable. People who have benefited from preconceptual screening can choose not to marry or conceive with a partner carrying a trait that could result in a fetus with a significant hemoglobinopathy (this option is mandatory in some countries, see above). A couple may also choose to have a child with a serious condition, or not to have children, to adopt a child, or to undergo preimplantation genetic diagnosis or prenatal diagnosis, when available.[34] The use of a gamete donor is possible in certain countries. Genetic counseling should also be provided to couples after the birth of an affected child to inform them about the genetic transmission of the disease, the fact that they are both carriers, and that they may conceive another child with the disease. Parents must be informed about the course of the disease, the quality of life of affected individuals, and the possible treatment options. Receiving this information may be extremely stressful, and it should be communicated by experts or people with specific training in genetic counseling and knowledge of hemoglobinopathies, and should be adapted to the cultural background and knowledge. In our experience, information about reproductive choices is often not presented during the initial consultation, disclosing the newborn's diagnosis, in order to avoid further stress about the baby's future.

Preimplantation genetic diagnosis (PGD) and in vitro fertilization give couples the choice of having an unaffected child without needing to consider pregnancy termination.[7,35–39] Most parents are not aware of this technique; it is not accessible in LICs and limited in HICs by the small number of accredited centers and the cost of the procedure.[38] Increasing access to PGD will require collaboration with public health programs and consideration of each country's legal framework. PGD may be coupled with human leukocyte antigen (HLA) typing of an unaffected fetus (PGD-HLA) to potentially select a hematopoietic stem cell donor for future transplantation of an affected sibling. However, PGD-HLA is technically challenging; the birth rate of unaffected HLA-identical babies rarely surpasses 10%–15% for any cycle initiated,[37] and so very few countries offer it. In the opinion of the expert panel, families are also frequently deterred by the low success rate and high cost of the procedure.

After conception, prenatal diagnosis (PND) using invasive or noninvasive (NIPT) methods is required to determine whether the fetus is affected by the disease. In countries where PND is available and affordable, couples can decide whether to request this procedure, a decision that involves balancing the risks of PND against the usefulness of the knowledge gained (the possible risks are discussed in more detail below). When performed, PND is recommended early in pregnancy. Uptake may be low in LICs due to the nonavailability of tests or very high costs. Worldwide, low uptake can also be due to cultural or religious restrictions, social or familial pressure, personal history, or lack of awareness about the disease.[6,7,34–36,40–42] It is important to discuss PND with all mothers/couples in the same way, and not make assumptions about their wishes based on their ethnic or religious backgrounds. Many couples wish to use PND even if they do not intend to terminate the pregnancy, but to find out whether the fetus is affected and to prepare for the birth of the baby.

From a medical standpoint, there is consensus to offer PND when the risk to the baby is linked to the HbSβ^0-thalassemia and HbSS genotypes, but no consensus exists for the HbSβ$^+$-thalassemia, HbSC, or other less-severe genotypes. For thalassemia, there is consensus to offer PND for TDT, but no consensus for non-transfusion-dependent thalassemia.[43] The difficulty lies in the marked phenotypic variability associated with each genotype, which makes it very difficult to accurately predict clinical severity. For families where one parent is homozygous for the disease, or where the first child is affected, the severity of the disease in future children may differ greatly from that of the parent or sibling, again making it difficult to predict severity.

In some cases, the mother may be found to carry a significant hemoglobinopathy, but the partner may not be available for testing, either because he is absent, not known, or refuses to be tested. In these circumstances, the mother should be counseled about the risks of having an affected baby and of invasive PND, and PND should be offered if she wishes to know the phenotype of the fetus.

Recommendation 3

The decision to perform PND is up to the parents. This decision must be respected even if pregnancy termination is not planned in the event of a disease in the child.

Consensus agreement: 88%

Recommendation 4

PND can be offered for the potentially less-severe phenotypes, such as HbSβ+ and HbSC SCD phenotypes, or non-transfusion-dependent thalassemia, if fully informed parents request it.

Consensus agreement: 94%

Q4: Regarding prenatal diagnosis: What type of laboratory test should be used for diagnosis?

Genetic analysis of fetal or embryonic material as part of PND is highly sensitive and should be carried out by experienced laboratory geneticists in collaboration with experts in other relevant medical disciplines, in accordance with local/national legislation and accepted social, cultural, and religious norms.[37,44]

PND by invasive sampling of amniotic fluid or chorionic villi may be offered to pregnant women to diagnose hemoglobinopathies. In the United Kingdom, SCD is the most common monogenic indication for invasive prenatal diagnostic testing, with approximately 350 tests performed each year (information provided by the author David Rees via personal communication). PND is performed in many parts of the world, including the United States, the United Kingdom, Europe, Asia, India, and the Middle East.[6,7,28,34–37,40–42,44–46] However, many women are discouraged from opting for invasive PND because of the perceived increased risk of miscarriage.[47] A meta-analysis published in 2015 analyzing publications from Europe, the United States, Hong Kong, China, and Thailand demonstrated the weighted pooled procedure-related risks of miscarriage for amniocentesis and chorionic villus sampling as 0.11% (95% CI: −0.04 to 0.26%) and 0.22%

(95% CI: −0.71 to 1.16%), respectively.[48] Another 2019 meta-analysis of miscarriages occurring after amniocentesis or chorionic villus sampling reported that the procedure-related risk of miscarriage is 0.30% after amniocentesis, while there is no significant risk associated with chorionic villus sampling.[49]

More recently, non-invasive prenatal testing (NIPT) has been proposed for hemoglobinopathies through the analysis of fetal DNA circulating in maternal blood.[47,50] This technique is preferred by parents, who find it simpler and less stressful.[51] However, in a 2020 publication on its use for SCD in the United Kingdom, only 83% (35/42) of the samples analyzed yielded accurate results; in six cases, the amount of free fetal DNA was insufficient to establish a diagnosis, and in one case, a fetus with HbAS was misdiagnosed as having normal Hb levels (HbAA).[47] Overall, the performance of NIPT in this study and other similar studies remains significantly inferior to that of invasive PND, and further progress is needed.[52] For example, the Netherlands, Belgium, and the United Kingdom have integrated NIPT into national screening programs, but not for hemoglobinopathies. The latter is available in the USA, but it is covered by patients' private insurances.

Table 3 summarizes the current state of conventional invasive PND vs NIPT.

Q5: How to increase awareness regarding preconceptual and antenatal screening, and prenatal diagnosis?

According to the literature, education at the preconception stage on the importance of screening carriers is the best option.[19,20,53–56] Educational and screening strategies have been implemented among university students in the Middle East,[57,58] Africa,[59] Asia,[60–63] the United Kingdom,[64] and the United States.[65] The publications converge in revealing gaps in students' knowledge, with the majority of students unaware of basic information about hemoglobinopathies, such as genetic transmission, the difference between carrier state and disease, or prognosis. Adolescents and adults may encounter difficulties in obtaining parental consent for screening,[62] and the fear of stigma is commonly mentioned.[62] It is suggested that education in schools would be more effective if it were conducted in parallel with a community awareness program.[63] The use of interactive e-learning modules is recommended,[61,62] and social networks and the media (television, interactive theater, documentaries, animated cartoons) can be used as tools for raising public awareness in countries with high disease prevalence. However, there is concern that testing during childhood may be inefficient because the results may be forgotten or lost by the time the individual is considering parenthood, and repeat testing is always necessary antenatally.

Premarital screening is an important option in countries where PND and abortion are not possible for logistical or religious reasons.[54] Screening is often offered to women who have not been previously tested at the beginning of their pregnancy.

In a study conducted in Cameroon, Ghana, and Tanzania, participants mentioned that women bore an increased decision-making burden in sickle cell trait screening because they were at higher risk of rejection by their in-laws/potential partners if identified as a carrier, as well as the possibility of divorce if they had a child with SCD.[55] The risk in African communities of blaming mothers for their children's illness was also highlighted during a 3-day workshop in Ghana, which involved community leaders as lay advisors to assist with the development and implementation of a Sickle Cell Counselor Training and Certification Program. The workshop suggested involving stakeholders such as elders and religious and traditional leaders. The dissemination of information to young people was recommended in churches, mosques, and other traditional places of worship, particularly during religious events such as baptisms or puberty rites, with the help of traditional or religious leaders respected within the community.[66]

Some countries have established local or national associations to raise public awareness and support families with thalassemia and SCD. These associations can act as mediators within the community to build trust and disseminate information. Parent associations can also play an important role in providing psychological support to parents and patients, and in mobilizing the efforts of parents as an influential group.[9]

Recommendation 5

Awareness campaigns should be encouraged in close collaboration with patients' associations and, in some countries, health authorities, religious, and community leaders.

Consensus agreement: 100%

Q6: How to communicate the result of a carrier status or disease in a fetus?

There is agreement that it is very important to communicate the results of hemoglobinopathy screening to all tested individuals, including carriers.[65,67] The recipients of the information may learn both that they are carriers of a genetic disease and that they can pass this disease on to their children. It is often difficult for the general public to understand the difference between being a carrier of a disease and having a disease. Furthermore, carrier status is not well characterized, and it is not correct to assume that carriers are always asymptomatic. Carriers of thalassemia may have mild anemia. There is evidence to confirm a positive association between carrying sickle hemoglobin and the risk of pulmonary embolism, proteinuria, and chronic kidney disease.[68] Case reports describe vaso-occlusive events and splenic infarction in conditions of hypoxia, such as those observed at high altitudes.[17] Disclosure of carrier status may cause some recipients significant anxiety and fear of blame and stigma, and they may become unable to take in any further information, particularly regarding reproductive choices (patient-reported outcomes based on experts' clinical experience). A cross-sectional study conducted in the United States in 2018 found that participants were dissatisfied with the different ways in which they learned about their carrier status (e.g., through a healthcare professional or by mail), as these methods were not accompanied by additional information, or left them too frightened to consult a healthcare professional or genetic counselor to find out more about the implications.[65] A prospective follow-up protocol was launched in the United States in 2003 regarding the communication of information on abnormal hemoglobin carriers

TABLE 3 Invasive PND and NIPT

Information	Conventional (invasive) PND	NIPT
Timing	Chorionic villus sampling: 10–12 weeks of gestation Amniocentesis: 15th week of gestation onward	As early as 9 weeks of gestation
Accuracy	>99%	Needs progress
Disadvantages	Invasive (minimal risk of procedure-related miscarriage)	High associated cost Lack of availability

Abbreviations: NI, non-invasive; PND, prenatal diagnosis; PT, prenatal testing.

during newborn screening. It included letters, phone calls, educational videos, and genetic counseling by phone or in person. Communication of results by mail was often ineffective, as many people did not respond, and there was no way to determine their level of understanding of the information provided. Genetic counseling by telephone and educational videos were well received. Among those who declined expanded family screening, 26% preferred to consult their pediatrician.[69] A French randomized study compared three methods of communicating carrier status results after observation of carriers during newborn screening, with a recommendation to parents to undergo parental screening for sickle cell carrier. The methods used were standard letters, telephone calls, or text messages. The authors concluded that phone calls or text messages resulted in higher screening rates than the standard "letter only" approach and that it was necessary to train healthcare professionals in different communication methods and set up a helpline for parents informed of their child's carrier status.[70]

Studies conducted in Europe and the United States evaluating the effectiveness of different methods of communicating carrier test results indicate that risk-based counseling is effective if tailored to the literacy level of the individual or couple, their perception of the disease, their previous experiences, and their cultural and religious beliefs.[17] In all cases, it can be difficult to understand information if it is not provided in the local language. Every effort should be made to use understandable language, possibly with the help of a translator.

After consulting rural communities in Kenya, Marsh et al. concluded that screening for sickle cell trait was beneficial but reported community concerns about the risk of stigmatization of mothers, the refusal of some fathers to accept their genetic role, particularly that of being a carrier of sickle cell trait and the parent of a child with the condition, with a risk of parental separation and stigmatization of the child. This emphasized the need to accompany disclosure of status with detailed explanations.[71]

Communication should always be followed with a clear, detailed plan of the coming steps, and to double-check that the individuals clearly understand the plan. Learning that the child they are expecting has thalassemia or SCD is often a tragedy for couples who have seen a family member or neighbor die prematurely from this disease, or who come from a country where the future and quality of life of such an individual living with this condition would be perceived as low. Only experienced healthcare professionals should deliver this news. In countries strongly influenced by religion (mainly Islam and Christianity), termination of pregnancy is not an option for couples due to religious beliefs or legal restrictions. Psychologists, the community, and patient associations' support can be very helpful. For couples who are allowed to terminate a pregnancy, the decision is extremely difficult to make, and attitudes may vary between the father and the mother. Genetic counselors must explain the consequences of the disease, which are, in reality, unpredictable. Many couples may have heard about curative treatment options for hemoglobinopathies (hematopoietic stem cell transplantation and gene therapy), which discourage them from requesting PND. The genetic counselor must make it clear that these options are virtually unaffordable in LICs and are currently only offered to a very small minority of patients in HICs for reasons of safety, feasibility, and economic constraints. Alternatively, the counselor can talk about the use of modifying drugs, such as hydroxyurea. There is the additional possibility for parents to discuss this with their family, doctors, or patient associations, but this option is often ignored by couples who prefer to maintain their privacy.

Recommendation 6

Information about thalassemia or sickle cell trait should be accompanied by a clear explanation of the genetic risk and reassuring information, possibly in the form of a video or online, about its characteristics, lack of serious risk to the carrier, the possibility of passing it on to children, the reproductive choices, and where to find further explanations in an appropriate language, respectful to people's privacy.

Consensus agreement: 94%

Q7: What are the competencies required of a genetic counselor for hemoglobinopathies? How to train a genetic counselor, even in LICs?

There are conflicting requirements regarding the characteristics of an optimal genetic counselor. They must not only be able to explain the genetic transmission of the disease but also be able to describe the manifestations and outcomes of the specific disease in a simple, understandable way. In addition, they should preferably communicate in the language of the patient or couple, have an awareness of the cultural and religious requirements of their audience, and, ideally, be close to the community concerned. It is virtually impossible to present all these capabilities, and it therefore seems desirable for genetic counseling to bring together several people, each with their own area of expertise; this is a possibility that is almost never realized in practice. Healthcare professionals that parents can engage with include trained medical geneticists, obstetricians, genetic counselors, trained midwives, and specialist screening nurses, with the likelihood that primary care providers and local screening practitioners will serve as the first and regular point of contact.[72]

In Ghana, a study of a selected group of doctors and midwives found that young doctors (with less than 6 years' experience) and nurses/midwives were less likely to inform patients of a negative carrier status. Practices regarding referral for genetic counseling varied: 26.5% of professionals referred patients systematically, 28.4% never did so, and 45.1% only did so if the patient asked questions.[73] A study led in 2013 in 118 Malaysian non-geneticist healthcare workers found that all the nurses and 50 doctors (96.1%) were in favor of discussing PND for thalassemia major. However, only 29 doctors (58%) and 33 nurses (50%) were willing to discuss the option of pregnancy termination. The main reasons given for declining to discuss pregnancy termination were views that "the condition was not serious enough" (54.9%), "termination of pregnancy is not permissible by their religion" (17.6%), and "abortion for this indication was illegal" (13.7%).[74] While couples may express a desire to receive information from their primary care physician or pediatrician,[69] many primary care physicians believe they do not have the necessary skills to provide effective genetic counseling.[67,75] Specific programs (small group discussions, role play and simulation, collaborative learning, and project-based learning and inquiry) have been set up in Indonesia to improve nurses' knowledge and skills in providing genetic counseling to patients with thalassemia.[76]

In all cases, in countries where religion has a strong influence, religious and traditional leaders, as well as family elders, are considered to be important stakeholders for the training of lay counselors.[66]

Recommendation 7

Primary healthcare professionals, general practitioners, nurses, or midwives can be trained to provide genetic counseling in countries with restricted resources, where specialist counselors are not readily available, but must undergo specific training.

Consensus agreement: 100%

Q8: What is the proposed process for genetic counseling?

This analysis of the literature and our experience shows that it is highly preferable for persons or couples to know their hemoglobinopathy status before conceiving a child. Even information about carriers is sensitive, as it is a source of anxiety and possible fear of discrimination. It is desirable that countries with a large at-risk

population, whether endogenous or due to migration, develop policies to inform the general population and provide access to specialized centers where people can be screened and receive detailed genetic information. In countries where the frequency of people at risk is low, communities and patient associations can spread the word about the benefits of hemoglobinopathy screening programs, and healthcare workers should consider offering screening to people coming from high-risk countries. In all cases, religious and community leaders should be involved. After a child is conceived, it is essential to carry out early hemoglobinopathy screening of the couple to give parents as much time as possible to make their decision. The freedom of choice available to couples is generally limited by cultural, religious, and societal constraints. We have in this paper considered together thalassemia and SCD, but it seems that SCD in Africa weighs particularly heavily on mothers, who may feel solely responsible for their child's illness.

As these reflections stemmed from previous considerations and the key messages had already been addressed in recommendations and votes, no additional recommendations or votes were linked to this final question. Instead, we proposed an algorithm summarizing and structuring the overall process (Figure 1).

CONCLUSION

This EHA-TIF Hemoglobinopathies Group was a multidisciplinary group of experts and brought together people from diverse geographic backgrounds.

These consensus guidelines provide a framework that can be adapted to different countries. By implementing these recommendations, healthcare providers and policymakers can improve carrier detection and ensure that at-risk couples receive appropriate counseling and options. Such objectives require the large-scale development of awareness campaigns, in close collaboration with patient associations and, in some countries, health authorities, religious leaders, and community leaders.

The scope of these guidelines is limited by the fact that they are based largely on the experience of the experts involved and patients' perspectives, which are obviously shaped by the cultural contexts of the authors' countries of origin. This limitation also reflects the scarcity of robust evidence-based literature addressing such sensitive and culturally nuanced topics.

The strength of these guidelines, therefore, lies not in scientific innovation but in the collaborative process that brought together 20 experts from diverse professional, cultural, and geographic backgrounds. Despite these differences, a broad consensus was achieved on the need to ensure that individuals and couples receive comprehensive information about their reproductive options, information that respects their personal wishes, cultural and religious beliefs, and the applicable legal framework.

Ongoing evaluation of these programs and periodic updates to the guidelines will be important as new technologies and insights emerge. Future changes are probably related to the evolution of whole genome sequencing, at least in HIC, which will raise new ethical and even practical counseling challenges.

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AUTHOR CONTRIBUTIONS

Mariane de Montalembert: Conceptualization; investigation; writing—original draft; methodology; validation; visualization; writing—review and editing; data curation; supervision; resources. **Maria D. Cappellini**: Investigation; methodology; validation; visualization; supervision; resources. **Achille Iolascon**: Investigation; methodology; validation; visualization; supervision; resources. **Lucia de Franceschi**: Methodology; validation; visualization; supervision; investigation. **Eda Ömur**: Validation; supervision; investigation; visualization. **Michele Abi Saad**: Investigation; validation; supervision; visualization. **Immacolata Andolfo**: Investigation; validation; supervision; visualization. **Celeste Bento**: Investigation; validation; supervision; visualization. **Maria Berghs**: Investigation; validation; visualization; supervision. **Doris Bonnet**: Investigation; validation; visualization; supervision. **Andreas Glenthoj**: Investigation; validation; visualization; supervision. **Beatrice Gulbis**: Investigation; writing—original draft; validation; visualization; supervision. **Tuphan K. Dolai**: Investigation; validation; visualization; supervision. **Jorge Lima**: Investigation; validation; visualization; supervision. **Irene Motta**: Investigation; validation; visualization; supervision. **Roberta Russo**: Investigation; writing—original draft; validation; visualization; supervision. **Ali Taher**: Investigation; validation; visualization; supervision. **Leon Tshilolo**: Investigation; validation; visualization; supervision. **Antonio Almeida**: Investigation; validation; supervision; visualization. **David Rees**: Investigation; validation; visualization; supervision.

CONFLICT OF INTEREST STATEMENT

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ORCID

Mariane de Montalembert https://orcid.org/0000-0002-4900-4753

Irene Motta https://orcid.org/0000-0001-5701-599X

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