Defining global strategies to improve outcomes in sickle cell disease: a *Lancet Haematology* commission

Authorship

Piel, F.B.*, Rees, D.C., DeBaun, M.R., Nnodu, O., Ranque, B., Thompson, A.A., Ware, R.E., Abboud, M.R., Abraham, A., Ambrose, E.E., Andemariam, B., Colah, R., Colombatti, R., Conran, N., Costa, F.F., Cronin, R.M., de Montalembert, M., Elion, J., Esrick, E., Greenway, A.L., Idris, I.M., Issom, D.-Z., Jain, D., Jordan, L.C., Kaplan, Z.S., King, A.A., Lloyd-Puryear, M., Oppong, S.A., Sharma, A., Sung, L., Tshilolo, L., Wilkie, D.J. & Ohene-Frempong, K.†

** Corresponding author: f.piel@imperial.ac.uk*

† Prof Ohene-Frempong died in May 2022.

Affiliations

** indicates authors involved in more than one section, # indicates section co-leads, $ indicates a retired author.

Executive summary, Introduction, Future perspectives, Conclusions

**Frédéric B. Piel, PhD. Department of Epidemiology & Biostatistics, School of Public Health, Imperial College London, London, UK

David Rees, Department of Paediatric Haematology, King's College London, King's College Hospital, London, UK

Section 1

**Frédéric B. Piel, PhD. Department of Epidemiology & Biostatistics, School of Public Health, Imperial College London, London, UK

$Roshan Colah, PhD. Department of Haematogenetics, Indian Council of Medical Research National Institute of Immunohaematology, Mumbai, India

Raffaella Colombatti. Pediatric Oncology Hematology Unit, Department of Women's and Children's Health, University of Padova, Italy

David-Zacharie Issom. Department of Information Systems, School of Management, HES-SO University of Applied Sciences and Arts Western, Geneva, Switzerland

Kwaku Ohene-Frempong†. Children's Hospital of Philadelphia, Pennsylvania, USA & Komfo Anokye Teaching Hospital, Kumasi, Ghana.

Section 2

Obiageli Nnodu. BMBCH, FWACP (Lab Med) MSc (Lond) DIC, FNAMed. Department of Haematology and Blood Transfusion, College of Health Sciences, University of Abuja, Abuja, Nigeria & Centre of Excellence for Sickle Cell Disease Research and Training, University of Abuja, (CESRTA)

Jacques Elion, MD, PhD, Université Paris Cité and Université des Antilles, Inserm, BIGR, F-75015 Paris, France

Dipty Jain, Department of Paediatrics, Government Medical College, Nagpur, Maharashtra, India.

$Michele Lloyd-Puryear, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20814, USA.

Leon Tshilolo, Institut de Recherche Biomédicale/CEFA-Centre Hospitalier Monkole and Université Officielle de Mbujimayi, Democratic Republic of the Congo.

Section 3

#Brigitte Ranque, Department of Internal Medicine, Hôpital Européen Georges Pompidou, Assistance Publique des Hopitaux de Paris Centre, university of Paris Cité, France.

#Russell E Ware MD PhD, Division of Hematology and Global Health Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

Emmanuela E Ambrose, Department of Paediatrics and Child Health, Bugando Medical Centre, Mwanza, Tanzania.

Biree Andemariam, New England Sickle Cell Institute, University of Connecticut Health, Connecticut, USA.

Nicola Conran, Center of Hematology and Hemotherapy (Hemocentro), University of Campinas - UNICAMP, Brazil.

Fernando F. Costa, Department of Clinical Medicine, School of Medical Sciences, Center of Hematology and Hemotherapy (Hemocentro), University of Campinas - UNICAMP, Brazil.

**Mariane de Montalembert, MD PhD, Department of Pediatrics, Hôpital Necker-Enfants Malades, Assistance Publique des Hopitaux de Paris Centre, France.

Section 4

Alexis A. Thompson, Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Allistair Abraham, Division of Blood and Marrow Transplantation, Children's National Hospital, Washington, District of Columbia, USA.

Erica Esrick, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA.

Akshay Sharma, Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, TN, USA.

Section 5

Michael R. DeBaun, Department of Pediatrics, Vanderbilt-Meharry Center of Excellence for Sickle Cell Disease, Vanderbilt University Medical Center, Nashville, TN 37203

Miguel R. Abboud MD, MHA, Department of Pediatrics and Adolescent Medicine, and Sickle Cell Program, American University of Beirut, Beirut, Lebanon

Robert M. Cronin, MD, MS, Department of Internal Medicine, The Ohio State University, Columbus, OH, USA

**Mariane de Montalembert, MD PhD, Pediatric Department, Sickle Cell Disease Referral Center, Necker Hospital, APHP, Paris, France.

Anthea L Greenway MBBS, FRACP, FRCPA, Department Clinical Haematology, Royal Children's Hospital, Parkville and Department Haematology, Monash Health, Clayton, VIC, Australia

Ibrahim M. Idris, MBBS, MPH, FMCPath, Department of Hematology, Aminu Kano Teaching Hospital/Bayero University Kano, Kano, Nigeria.

Lori C. Jordan, MD, PhD, Department of Pediatrics, Division of Pediatric Neurology, Vanderbilt University Medical Center, Nashville, TN, USA

Zane S. Kaplan MBBS, PhD, FRACP, FRCPA, Department of Clinical Haematology, Monash Health and Monash University, Melbourne, Victoria, Australia.

Allison A. King, MD, MPH, PhD, Departments of Pediatrics and Internal Medicine, Divisions of Pediatric Hematology and Oncology and Hematology, Washington University School of Medicine, St. Louis, MO, USA

Samuel A Oppong, MBChB FWACS, Department of Obstetrics and Gynecology, University of Ghana Medical School, Accra, Ghana

Lillian Sung MD, PhD, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada Diana J. Wilkie, PhD, RN, FAAN, Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, Gainesville, FL 32610

Executive summary

All over the world, patients with sickle cell disease (SCD), an inherited condition, suffer from premature death and preventable severe chronic complications, which considerably affect their quality of life, career progression and financial status. In addition, they are often affected by stigmatisation or structural racism, which can contribute to stress and poor mental health. Inequalities affecting patients with SCD are also reflected in the distribution of the disease, mainly in sub-Saharan Africa, India and the Caribbean, while interventions, clinical trials and funding are mostly available in North America, Europe and the Middle East. Although some of these characteristics also affect patients with other genetic diseases, the fate of patients with SCD seems to be particularly unfair. Simple, effective interventions to reduce the mortality and morbidity associated with SCD are available. The main obstacle preventing better outcomes in this condition is that it is a neglected disease, associated with inequalities affecting populations. One of the aims of this Commission is to highlight the problems associated with SCD and to identify achievable goals to improve outcomes both in the short and longer terms.

The endpoint of the management of patients with SCD is that curative treatment is available to every person with the condition. While this would have seemed unrealistic a decade ago, recent developments in gene therapy make this potentially achievable, albeit in the distant future. Until these curative technologies are fully developed and become widely available, we should make sure that a minimum standard of care, including screening, prophylaxis against infection, acute medical care, safe blood transfusion and hydroxyurea, is available to all patients.

In considering what needs to be achieved to reduce the global burden of SCD and improve the quality of life of patients with SCD, this Commission focuses on five key areas, which are discussed in this report: the epidemiology of SCD (**Section 1**); screening and prevention (**Section 2**); established and emerging treatment for the management of SCD (**Section 3**); cellular therapies for the management of SCD (**Section 4**); and training and education needs (**Section 5**). In **Panel 1**, we summarise key recommendations of the Commission, which are further developed in each section and in **Table 8**. As clinicians, researchers and patients, our objective to reduce the global burden of SCD aligns with wider public health aims to reduce inequalities, improve health for all and develop personalised treatment options. We have observed in recent years some long-awaited momentum following the development of innovative point-of-care testing devices, new approved drugs and emerging curative options. Reducing the burden of SCD will require substantial financial and political commitment, but it will impact the lives of millions of patients and families worldwide and the lessons learned in achieving this goal would unarguably benefit society as a whole.

Panel 1: Key recommendations from the *Lancet Haematology Commission on sickle cell disease*

1. **Enable routine collection of comparable epidemiological data** across all countries by 2025
2. **Make national governments accountable** through monitoring of public health intervention implementation and progress
3. **Ensure that all babies worldwide can be tested** by 2025 to prevent long-term complications
4. **Inform populations affected by SCD about reproductive risks and choices**, tailored to culture and religion
5. **Provide access to minimum specific healthcare to all patients with SCD** no matter where they live
6. **Make hydroxyurea accessible and affordable** (<$0.1 per 500mg capsule) **to all SCD patients** by 2030
7. **Improve blood transfusion supply and safety** (including guidelines for proper use and improvement of haemovigilance) by 2030
8. **Accelerate the development of effective and affordable therapies**, including prioritizing scientific and infrastructure investment to achieve safe and accessible cures globally by 2040
9. **Balance participation of LMICs *vs* HICs in clinical trials for new therapies** by 2030
10. **Educate healthcare professionals and the general public about SCD** and its management
11. **Prioritise funding for SCD research** through dedicated calls
12. **Halve current estimates of the global burden of SCD** by 2050

Introduction

Sickle cell disease (SCD) is probably the most common, serious inherited disease in the world, and one of the top fifty commonest causes of non-communicable death globally, with the most of these deaths occurring in African countries. (1) Whereas the majority of major causes of death are decreasing, the number of deaths due to SCD is increasing globally. (1) Despite this, there are fewer than five effective disease modifying-agents available, and most patients in the world do not have access to any of these. (2) Although curative treatment is possible, by haematopoietic stem-cell transplantation (HSCT) and emerging gene therapies, only a tiny minority of patients are currently treated with these because of the need for infrastructure, the cost and side-effects. (3) In the context of increasing global inequalities, partly driven by racism, previous calls for action on SCD have been largely ineffective. There is an urgent need for the development of research, policies, and public health strategies to reduce the morbidity and mortality associated with this long-neglected condition. (4)

The first paper on SCD was published in 1910 by James Herrick in Chicago, who described the appearance of abnormal, sickle-shaped red cells in a Black dental student from Grenada, who presented with respiratory symptoms. (5) Following this, more clinical and pathophysiological observations emerged, including the identification of haemolysis as a cause of anaemia and jaundice, and vaso-occlusion as a cause of pain and ischaemic tissue damage. (6) In 1948, Janet Watson published the key observation that babies did not develop symptoms of SCD in the first few months of life and attributed this to high levels of foetal haemoglobin (HbF). (7) This realization led to a stream of therapeutic attempts to increase HbF levels to recreate the asymptomatic neonatal state, which resulted in the emergence of hydroxyurea (also known as hydroxycarbamide) as the most effective and widely used drug in SCD, (8) and is also currently the main focus of gene editing trials. (9) In the same year, Linus Pauling published a paper showing that SCD was associated with abnormal electrophoretic mobility of Hb and described it as a ‘molecular disease’ (10) with subsequent studies showing the amino acid change responsible for the abnormal haemoglobin (HbS), and the propensity of HbS to form destructive polymers when deoxygenated. (6) As molecular biology developed, the transcription of globin genes was increasingly understood, and served as a paradigm for other inherited and acquired genetic disorders. (11) These observations form the backbone of our basic understanding of the pathophysiology of SCD: abnormal Hb is inherited, which polymerises when deoxygenated and damages the red cell; the damaged red cell occludes blood vessels causing ischaemic tissue damage, and also lyses prematurely, releasing the toxic erythrocyte contents into the circulation. (12) There has been a large amount of research focusing on the downstream consequences of HbS polymerisation, showing abnormalities in nearly every measurable biological process, including inflammation, oxidative stress, blood coagulability, vascular endothelium function, nitric oxide metabolism, expression of adhesion molecules and immune function. (6) Additionally, there is progressive damage to many organs resulting in hyposplenism, renal impairment, cerebrovascular disease, avascular necrosis of bones and joints, cardiopulmonary disease, retinopathy, hepatopathy and priapism. (6)

In parallel with progress in molecular and clinical understanding of SCD, it became apparent it is distributed very unevenly across different populations, with the majority of patients being of African and African-Caribbean origin. Although most births occur in Nigeria, the Democratic Republic of Congo, and India, (13) SCD is relatively common in the indigenous people of the Middle East and Southern Europe, with significant numbers also occurring in most countries in the world because of population movements. (14) The reason for this uneven distribution was suggested by Haldane in the 1940s, who hypothesised that carriers of SCD (also called sickle cell trait) had relative protection against death from malaria, which resulted in the disease becoming much more common in countries where malaria was or is an important cause of premature death. This 'malaria hypothesis', which was also applies to other inherited red cell disorders such as alpha and beta thalassaemia and glucose-6-phosphate dehydrogenase deficiency, has largely been confirmed by further epidemiological studies, although the exact mechanism of protection is still not known. (15)

Although the molecular and cellular aspects of SCD are fairly well understood, and have often been used as models to understand other molecular conditions, clinical aspects have been relatively neglected. In addition to the progressive organ damage mentioned earlier, SCD is characterised by acute episodes of illness related to vaso-occlusion and infection, causing problems such as acute pain, acute chest syndrome, strokes and in severe cases multi-organ failure and death. (6) The majority of patients are still thought to die in childhood, (16) apart from the relatively small number of patients living in some countries with better outcomes, such as many high-income countries (HICs) and Jamaica, where mean life expectancy is reduced by about 20 years. (17) In 2013, SCD was the 4th commonest cause of death in Nigeria (after malaria, lower respiratory infections and HIV/AIDS) and the 36th commonest globally. (1) In addition to shortened life-expectancy, SCD is also associated with a significant morbidity in all age groups, resulting from unpredictable episodes of acute illness, accumulating organ damage, neuropsychological problems and iatrogenic complications. For example, in 2017, SCD was one of the leading non-communicable disease causes of disability-adjusted life years (DALYs) in the under-fives in African countries (769.4 DALYs per 100 000; [95% uncertainty interval [UI] 432.9 – 1076.4). (1) As previously mentioned, without intervention, this global burden is expected to increase over the coming decades.

Despite the fact that SCD is a common and severe condition, there is little evidence on what constitutes effective clinical management, and relatively few treatment options, certainly when compared with rarer conditions such as haemophilia A and cystic fibrosis. For example, it is unclear how simple supportive measures, such as intravenous fluids and oxygen, should be used during acute complications. There is good evidence to support the use of penicillin prophylaxis (18) and hydroxyurea, (19) but until recently these were the only drugs available to try and prevent complications. With increased commercial interest in orphan diseases and financial incentives to develop drugs for their treatment, more drugs have emerged over the last decade, with crizanlizumab, (20) voxelotor, (21) and L-glutamine (22) being variably licensed for use in different countries around the world. Although these are expensive and non-curative drugs, they are indicative of an increasing academic and commercial interest in SCD, as suggested by the increasing number of publications, and there are currently a large number of drugs in commercial development which may offer further significant benefits. (23) Additionally,

there is rapid progress in the development of stem cell treatments, with advances in haematopoietic stem-cell transplantation and gene therapy, (24) with the potential to make curative treatments available to all patients, although widespread use is still a very long way from clinical reality everywhere, but particularly so in low-income and middle-income countries (LMICs). Importantly, there are also on-going advances in methods for screening and diagnosing patients with SCD. In particular, emerging point-of-care testing (PoCT) devices may facilitate the earlier identification of patients in many LMICs which do not have an established network of laboratories able to perform these tests.

It is difficult to know exactly why SCD has been so neglected, particularly when compared to other less common inherited disorders. To some extent, it has been seen as a disease mainly affecting African countries, and in those countries its relative importance was diminished by the devastation caused by infectious diseases, including malaria, diarrhoea, and HIV. In high income countries, it has occurred predominantly in lower-income populations, lacking political influence, and has been prioritised by few health systems around the world. Equally, the pharmaceutical industry had little or no interest in the condition until recently, although this has changed in the last decade with financial incentives to develop drugs for orphan diseases, and the apparent profitability of selling such drugs. The World Health Organization (WHO) has passed two resolutions on SCD: in 2006 they called for affected countries to strengthen their response to SCD and thalassaemia, and in 2010 WHO made various statements on the prevention and management of SCD and other inherited conditions, encouraging the promotion of awareness, improved access to health services, and support for research. More recently, in August 2022, WHO AFRO, African health ministers and some other interested parties launched a campaign to reduce the burden of SCD in African countries (https://www.afro.who.int/news/african-health-ministers-launch-drive-curb-sickle-cell-disease-toll). Other large organisations, including the United Nations (UN) and the Gates Foundation, have offered limited statements and support for SCD. Although this high-level support is encouraging, there has been very limited progress in actual management of SCD in most parts of the world.

In summary, SCD is a severe condition, affects millions of people, and is increasing in prevalence; very few people have access to disease modifying agents, and even fewer curative treatments. Currently, new diagnostic and treatment options are rapidly emerging, and it is possible for the first time to imagine that most patients could have access to good clinical care and even cure. The aim of this Commission is to describe the current situation for patients with SCD, and to identify the changes which need to be made to the organisation and provision of health care to develop sustainable policies to significantly reduce morbidity and mortality over the coming decades. Although other strategies have been produced previously, most notably the Strategic Plan and Blueprint for Sickle Cell Disease Action in the USA, (25) these have mostly been focused on particular countries, and the aim of this Commission is to take an international perspective, with representative multinational involvement, and broad recommendations relevant to both high-income and low-income regions. The main areas of focus are understanding the epidemiology, the development of screening programmes, providing better

access to established treatments, ensuring that patients in all countries can benefit from new and emerging treatments, and training health care workers and patients themselves to manage SCD.

Section 1: Epidemiology

1.1. Data Quality and Data Quantity

Epidemiological data on disease distribution, prevalence, mortality and morbidity are essential to monitor progress towards reducing the global burden of disease. To sustainably achieve good health and well-being for all people with SCD, identifying and promoting appropriate policies that take into account the priority challenges of the 21st century (e.g. growing inequalities, poverty, climate change) are needed. Public health authorities require precise, reliable, comparable and multi-dimensional data on the burden of disease in order to setup, plan, implement and evaluate policies and break through one-size-fits-all health interventions. Today, in most countries, many gaps in epidemiological data remain. This affects funding allocation and the development of adequate public health policies. In addition, there are substantial disparities in healthcare prevention, coordination, and management programmes between HICs and LMICs, as well as within countries. Reducing these disparities would both decrease the burden caused by SCD and improve the quality of life (QoL) of patients. A first step towards this goal is to agree on minimum accurate standardised epidemiological data to be collected.

1.1.1. Databases, Mapping and Networking

Although a significant body of data has been assembled on the distribution of SCD, (26, 27, 28) reliable, precise and representative data are still lacking on the prevalence and distribution of the condition in most countries. As reflected in discrepancies between existing estimates, including those of the Global Burden of Diseases Study (GBD), (1) there remains a lot of uncertainty in prevalence and burden estimates in many parts of the world. These discrepancies, combined with a long-term neglect of SCD, affect progress improving the management of the disease. These estimates are important to help develop national policies and often highlight the need to use uniform standardized protocols in epidemiological studies. Furthermore, monitoring spatial and temporal changes in the frequencies of SCD, and other malaria-related red cell genetic disorders (e.g. thalassaemia and G6PD deficiency) is essential for public health authorities to develop adequate long-term policies and interventions.

Estimates tend to be based on newborn screening (NBS) and life expectancy data or rely on regional and national registries, natural history studies, clinical and administrative data, and also surveys and cross-sectional reports in sample cohorts whose data are generalized. (29) Many of these data are collected on a voluntary basis or are part of short-term funded research projects. Very few of them are sustained in the long-term with adequate staff or funding.

The development of various international collaborative networks (see examples in **Supplementary Table S1**) has the potential to fill some of these data limitations and to promote the use of standardized protocols. These networks have all shown the benefits of collaborative work. The development of a centralized electronic portal, such as the Sickle Cell Disease Ontology (SCDO), further extended these collaborations to provide tracking systems for recruitment, data quality assurance and reporting of research studies. (30) Similarly, in Europe, collaborations between national registries, for example through EuroBloodNet, have recently increased to

standardise approaches and better monitor changes. In the US, the Centres for Disease Control and Prevention's (CDC) Sickle Cell Data Collection (SCDC) programme developed a population-based longitudinal surveillance system to identify persons living with SCD by centralising data from several sources. (31) Other collaborations, such as the PhenXToolkit, have focused on the development of common data collection. (32) The next steps are to enlarge and join up these collaborative efforts, for example, through more coordinated efforts between anglophone and francophone Sub-Saharan African (SSA) countries; to promote interoperability between data sources; to integrate epidemiological data with emerging omics and real-life data; and to further join up and expand all these national, regional and global efforts to provide near real-time, consistent, and high-quality epidemiological data. Although machine learning algorithms may help fill some of our knowledge gaps, their outputs will largely depend on the quality of input data used.

1.1.2. Data on prevalence and mortality of sickle cell disease

Apart from a few countries with a universal NBS programme (e.g. UK and US), precise data on the annual number of births with SCD are lacking. A review of the burden of SCA in children under five years of age only identified 52 studies containing relevant data on incidence and prevalence and 15 with mortality data, further highlighting the need for better epidemiological data on SCD. (33) Although epidemiological data is not necessary to set up policies and interventions, they are essential to assess changes and measure the impact of public health decisions taken.

Estimates suggest that around 75% of the >300,000 annual global births with sickle cell anaemia (SCA) occur in SSA (**Figure 1**). Data on allele frequencies of HbC and β-thalassaemia are more limited making it difficult to estimate the numbers of births with HbSC disease and HbS/β-thalassaemia. Up-to-date and more meaningful data are required on the frequencies of expected births and outcomes of SCD, particularly in Africa and India. (4) The generation of accurate data requires better screening and diagnostic facilities, with improved staff training. The influence of ethnic, religious and social heterogeneities has so far been poorly studied and data on consanguinity is particularly limited. New large-scale data collection efforts, such as the Statewide Screening Data Interface (SWSDI) in Chhattisgarh, India, and refined modelling work on SCD accounting for these heterogeneities (e.g. scheduled and non-scheduled populations in India) (34) can have a substantial impact on estimates generated. Data on the prevalence of SCA in adults is very limited in all countries worldwide. As a result, there is no reliable estimate of patient numbers either globally or for any country. Even in countries with the best data quality, estimates of the number of patients with SCD remain very crude. (35, 36) Nevertheless, new data from the GBD 2020 estimated that 7.69 million (95% UI: 6.27–9.41) people lived with SCD globally in 2020 [GBD2021, *Pers. Com.*]. Population and fertility projections suggest that this number will increase over the coming decades, particularly in SSA. The implementation of simple measures, such as appropriate prophylaxis, immunization and universal screening, could lead to lower mortality for millions of babies with SCA. (37) High-quality monitoring epidemiological data would allow such estimates to be validated and updated.

The survival of adult patients with SCA has mainly been investigated in specific centres in North America and Europe. (37, 38) Although survival data from well-equipped urban centres in Africa have been published, (39,

40, 41) there is still a lot of uncertainty around mortality rates in SCD in other parts of these countries. (42) Data collected as part of demographic health surveys (DHS) could offer opportunities to collect representative data, as trialled in Nigeria. (43) Prospective studies are required, especially in LMICs, to provide up-to-date data on risk factors for mortality. (30)

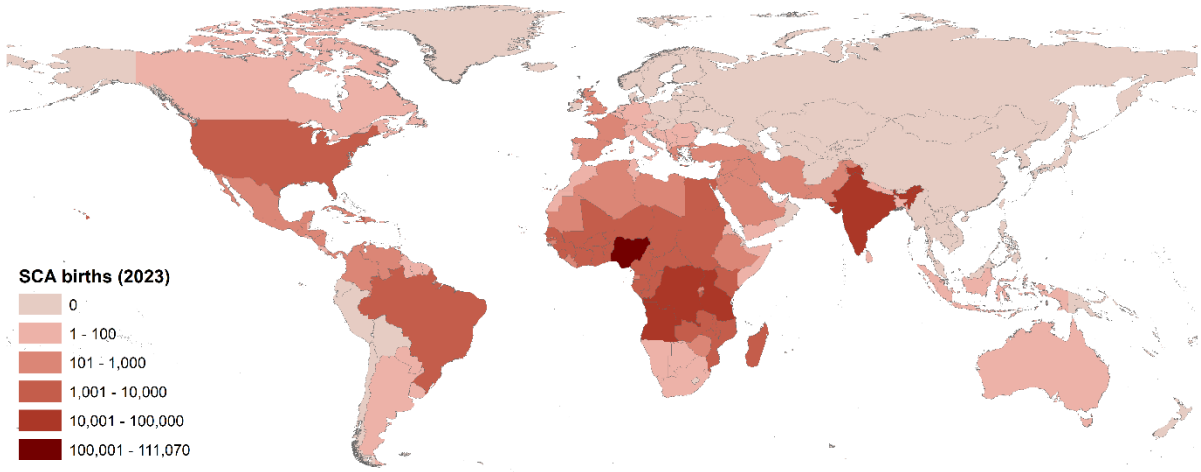


Figure 1: Global distribution of SCD in 2023, illustrated by country-level annual births with sickle cell anaemia (SCA). The estimates are derived from median HbS allele frequencies published in Piel *et al* 2013 (13) and probabilistic birth projections by country for 2023 from the UN' World Population Prospects 2022.

1.1.3. Data on NBS and morbidity

Studies in HICs and Jamaica have shown the importance of NBS with early comprehensive care along with education of the parents to significantly reduce early morbidity and mortality from SCD. (44, 45, 46) Setting up appropriate follow-up of infants with SCD remains a major challenge. Furthermore, data on utilization of healthcare, delivery of services and costs of care are lacking in most countries, including across Europe. (47) Survival beyond 18 years in Europe and North America is common, yet the life expectancy of patients in these countries is still 20 to 30 years lower than in the general population.

Although nationwide universal NBS programmes were launched in 2001 in Brazil and in 2020 in Ghana, there is still very little data available on the natural history of SCD in most areas of high prevalence. The national NBS programme in Ghana screened >200,000 babies over 10 years at nine public institutions and fifteen private clinics, identifying over 3,000 children with SCD and providing care in local clinics. (48) In Uganda, the US3 study demonstrated the feasibility of conducting a large-scale epidemiological study of SCD and sickle cell trait (SCT) on infants of HIV positive mothers using residual dried blood spots. (49) In Tanzania, region and district data are now being generated by analysing repurposed dried blood spots which were part of the HIV infant diagnosis programme utilizing existing infrastructure. (50) In India, there is negligible data on life expectancy of individuals with SCD. Although NBS programmes have been initiated recently in a few Indian states, only two studies from Gujarat and Maharashtra have reported clinical outcomes. (51, 52) The causes of death could not be determined in most children and the follow-up rate was only around 30% in both studies.

Public-private partnerships may be helpful in implementing early diagnosis and sustained care to reduce mortality and improve the quality of data. (53, 54) A village-based model of care using local volunteers has shown the importance of community participation, while the possibility of assessing premature mortality rates and causes of mortality in a remote tribal village in South India has also been demonstrated. (55) One of the main challenges to improve the management of patients in high prevalence countries is reaching rural communities and making sure that patients have access to ongoing care. Inexpensive POCT used in conjunction with immunisation programmes can be a good way to start data collection, to map out and study differences in morbidity, and to setup improved healthcare. (56)

Prenatal diagnosis is acceptable in many countries, but requires a lot of infrastructure, and data on this is limited. (57) Various preventive strategies are needed for the management and control of SCD, including antenatal screening and prenatal diagnosis early in pregnancy to offer parents informed reproductive choices. Antenatal screening is undertaken in the UK, Canada, Australia, some countries across Europe and the Middle East, and in some countries where SCD is prevalent such as India, Cuba and North Israel. The acceptability of prenatal diagnosis and termination of pregnancies varies substantially across the world, reflecting cultural and religious beliefs. In England, although antenatal screening was widely accepted, reproductive choices depended on the timing of prenatal diagnosis, as termination of pregnancies was more acceptable with early diagnosis. (58) In India, prenatal diagnosis and termination of affected pregnancies for SCD is acceptable even among marginalized communities. A single centre experience over 30 years showed that 527 couples opted for prenatal diagnosis of SCD and 30 % of them came prospectively. (57) In Cameroon, physicians considered termination in only 36% of affected pregnancies, while 90% of prospective mothers would opt for termination. (59) In southwestern Nigeria, only 37% of doctors would recommend prenatal diagnosis for SCD, with only 17% of mothers being willing to undergo testing due to the high cost and fear of the procedure. (60) One difficulty of prenatal diagnosis in SCD is that it is a very variable condition and it is hard to predict the clinical severity accurately, making it difficult for parents to make informed choices; increased use of genetic modifiers of SCD, like those associated with higher HbF levels and co-inheritance of α-thalassemia, may help to predict the clinical phenotype. (59) Non-invasive prenatal diagnosis (NIPD) is another option to avoid the small risk of fetal loss associated with invasive methods. Although there is limited data on NIPD for SCD, one of the largest studies on NIPD for SCD showed that 37 out of 44 sample results were concordant with established methods. (61)

1.1.4. Economic Costs

The economic burden of SCD is significant and increasing in most countries. Irrespective of where patients live and their economic situation, the cost of this disease imposes a significant financial burden to patients, their family and society. In the USA, the inpatient costs, outpatient costs and out-of-pocket costs surpass $3 billion per year for about 100,000 patients. Median yearly costs approximate $28,000 and lifetime care cost $460,000 per patient. (62) The indirect economic burden of pain events has also been recognized in the US, (63) where estimates averaged an additional $15,000 per patient per year in terms of productivity loss, and around $20,000 of unpaid work lost per caregiver. In the Netherlands and the UK, studies have recently looked at resource use and costs related to SCD healthcare. (64) In LMICs, there is very limited data on the economic burden, although

SCD can add substantial financial pressure on patients and their families. Such information is essential to advise governments and public health authorities on the future health burden of SCD. A cost-effectiveness analysis of NBS and a few prophylactic interventions conducted across 47 SSA countries could be used to guide policies and pave the way for similar studies in other regions of high prevalence. (65) Further health economics studies, including the costings of a large-scale implementation of key interventions to reduce the burden of SCD, are needed.

1.2. Changing distribution and patient numbers

As witnessed by many haematologists, SCD is the fastest growing genetically inherited condition in many countries worldwide. (14, 66, 67) This increase is due to several different factors that also lead to changing demographics of the patients' cohorts and to a more global distribution of patients in areas of the world were SCD was rare, less known or less reported.

1.2.1. Evidence of increase in patients' numbers in various settings/worldwide

Increasing numbers of patients with SCD started to occur over the past few decades in Europe, North America and Australia. (68, 69, 70) Observed increases in prevalence were mostly the result of gains in life expectancy (due to reduced childhood mortality) and immigration. For example, the UK National Hemoglobinopathy Registry (NHR, https://nhr.mdsas.com/index.php/publications/) reported 1,367 SCD cases in 1979, 7,800 in 2013 and 12,000 in 2019. In France, there were 1,000-3,000 patients with SCD reported in 1992, (71) while the total number of patients with SCD in 2016 was estimated between 19,800 and 32,400. (72) Population movements are also responsible for increased prevalence, for example in Germany and Sweden. (67, 73)

More recently, increasing numbers of patients with SCD have also been reported in LMICs in Africa, South America and Asia and are the result of increased diagnostic and reporting capacity. In Brazil, 45,000 people with SCD were estimated in 1985, (74) while according to reports of the Health Ministry of Brazil, this increased to 60,000-100,000 people with SCD in 2021.

1.2.2. Causes of Changing numbers

1.2.2.1. Increased diagnostic capacity

The implementation of SCD national NBS programmes has allowed the reporting of birth prevalence and demonstrated an increase in the number of patients with SCD in many HICs. This happened in the USA (44) and in many European countries. (29) Birth prevalence from large HIC studies are summarised in **Supplementary Table S2**. In other HICs experiencing immigration, like Italy (75) and Canada, (76) only birth prevalence data from pilot NBS studies are available but data from long-term national sustainable programmes implemented in the health system are still lacking. In African countries, birth prevalence data have also started to become available. The integration of NBS into existing primary health-care immunization programmes or HIV screening programmes has been shown to be feasible and rapidly implemented at limited costs like in Nigeria and Uganda. (56, 77) There have been limited efforts so far to regularly compile prevalence data to update estimates required by public health authorities.

North-South partnerships between research, public or private bodies and regional networking led to the implementation of pilot NBS programmes or screening in LMIC like in Antigua; to diagnostic efforts in remote rural areas of Nepal and Brazil; (78, 79) or to strengthened local effort in the Caribbean. (80) In South Asia, countrywide data and statistics are difficult to gather and there is very limited information available outside India. (81) Although SCD has been reported from Pakistan, Sri Lanka, Nepal, Bangladesh and the Maldives, very little is known about the nature of SCD and the burden of the disease in these countries. Improved data is likely to start to emerge in the near future with the increased use POCT devices in LMICs.

1.2.2.2. Increased reporting

In several countries, the increase in patients' numbers can be estimated from increased reporting of patients' numbers through publication of surveys, clinical cases, research and natural history study results, or enrolment in clinical trials. (82) While all this published information does not allow the determination of precise data on birth prevalence, prevalence and incidence, it does demonstrate an increase in patients' numbers and growing scientific interest towards a neglected public health problem. The past decade also saw reporting from areas that previously had no data or estimates, such as Nepal and rural parts of India.

The implementation of standardized data collection is still limited geographically to a few European countries, Brazil and organised networks. Various factors, including the lack of early diagnostic, data entry on a voluntary basis into the registries or databases, and the absence of longitudinal registries, have limited systematic data collection so far. This leads to underestimating real prevalence and to failures to track robust incidence data. Significant trend toward widespread complete coverage of the population at risk should be one of the priorities as SCD patients' numbers continue to increase. (83)

1.2.3. Causes of Changing Distribution/Changing Demographics

The increased prevalence of SCD worldwide is coupled with a change in the distribution of the disease and a change in the demographic of the SCD population. Migration continues to increase the prevalence of SCD in many countries, with movements of people from high prevalence areas in countries where SCD was relatively rare or absent. This phenomenon started a few decades ago in Europe and Australia, with diasporas from Africa and the Middle East. This process is also ongoing in the USA where individuals from SSA represented the fastest growing immigrant population between 2010 and 2018. (84) Population movements are also causing a growing ethnic diversity, increased complexity of the mutations and of disease genotype and phenotype which in turn can make diagnosis and reporting more complex. The interpopulation variation and the mixture with β-thalassaemia mutations are a recognized factor of interpopulation variation and difficult interpretation in South Asia. Therefore, training on laboratory diagnosis for a possible increased variety of compound mutation with increased use of genetic testing as well a clinical alert on increased variety of clinical phenotypes is warranted.

Reduced paediatric mortality also contributed to increased prevalence and will determine a further change in the demographics of the SCD population as its adult component grows and it becomes an ageing population (85), likely to be affected by multi-morbidities.

1.3. Changing life expectancy

1.3.1. Improved survival and comorbidities in high-income countries

The significant impact of SCD on survival was first suggested in reports in the 1950s, mostly from the USA, about the apparent low prevalence rates of severe SCD in older age groups. Diggs estimated a median survival rate of 14.3 years for people with SCD, with one-third of the deaths occurring before age 5 and half occurring between 5 and 30 years of age. (86)

Later on, the largest source of prospective data on survival came from the U.S. Cooperative Study of Sickle Cell Disease (CSSCD; 1978-1998). The CSSCD reported a median survival of 42 years for males and 48 years for females with SCA and, 60 years for males and 68 years for females with HbSC disease. Compared with the general African American population, the probability of death dropped dramatically after the age of 20 years. These survival estimates confirmed the lower life expectancy associated with severe SCD. The CSSCD was not able to establish the exact causes of death in most cases. Of the 209 deaths recorded, 82% occurred in subjects with no clinically diagnosed organ failure but in the circumstances of an acute event (including uncomplicated pain, pain with acute chest syndrome (ACS), stroke, peri-operative complications, infection, and ACS alone).

The CSSCD gave investigators the opportunity to document and carefully determine the causes of the high rates of mortality in children described in earlier reports. After 14,670 person-years of follow-up from 1979 to 1987, the CSSCD determined that the overall mortality rate was 0.5% deaths per 100 person-years, with the highest rates occurring in those less than 1 year of age. The cause of death was known in 54 (74%) of the 73 deaths, and among those, 52% died from bacterial infection.

The Penicillin Prophylaxis Study (PROPS1, 1983-1985) was conducted among young children in the CSSCD. (18) Penicillin prophylaxis may have had a small ameliorative effect on mortality for subjects who were randomized to receive penicillin and a larger group that may have been placed on penicillin after the study was halted when penicillin proved efficacious in reducing incidence of and mortality due to pneumococcal bacteraemia.

Following wide public health adoption of NBS for SCD and penicillin prophylaxis in the context of comprehensive clinical management, several HICs and Jamaica have reported dramatic improvements in survival of children with SCD, raising survival past 18 years of age to levels above 90%. (87)

With the proven effectiveness of NBS and early interventions in reducing childhood mortality in SCD, the expectation would be that overall survival for people with SCD in the HICs would improve steadily. However, the fact that most SCD deaths had been related to acute illness events served as a cautionary note that improved childhood survival may not necessarily reduce mortality in those above five years of age who die unpredictably with no clinically diagnosed organ failure. A review of mortality rates for children and adults with SCD from 1979 to 2005 using the US National Center for Health Statistics multiple cause of death files showed that the median age at death in 2005 was 42 years for females and 38 years for males. While they observed annual decrease in paediatric mortality rate by 3% ($p<0.001$), adult mortality rate increased by 1% ($p<0.001$) each year during the 16 years studied.

The median survival data from Lanzkron and colleagues showed no improvement over those from the 1994 report from the CSSCD. (88) It became clear that saving the lives of people with SCD during childhood may not be sufficient to improve the overall life expectancy of patients. Interventions to reduce both organ failure and improve acute illness management were identified as a need. The switch over from decreasing mortality with age in children to increased mortality with age from 19 years of age corresponded to the switch from paediatric to adult care services in high-income health systems.

The most commonly applied disease modifying intervention to address this has been hydroxyurea (HU) therapy. The broad positive effect of HU on the clinical course of SCD in both children and adults and possibly on survival of adults suggested the need for intensified efforts to encourage hydroxyurea therapy in adults with SCD. (88) The promise of curative interventions, HSCT and gene therapy, is too early in their application to have significant on overall survival of people with SCD, even in high-income, well-funded healthcare systems.

1.3.2. Mortality reduction and sustainable strategies in high-prevalence countries

In SSA, where SCD has been in existence for thousands of years, traditional folklore about SCD typically describe a disease of recurrent pain attacks, small stature, increased mortality, and familial childhood death.

Raper recorded positive sickling test as high as 45% in one community in Uganda but not a single case of SCA. (89) Comparing those findings with data from the USA, Raper suggested in 1950 that “Sickle cell anaemia affects American negroes more frequently than it does Africans” and that “the solution of this paradox may lie in genetic factors associated with the mixture of Black and White strains.” (89) The true solution to the apparent “paradox” was offered in 1952 by the Belgian Lambotte-Legrand paediatrician couple with the advice that “Prevalence of SCA would be found to be high if very young children in Africa were studied”. (90) Even today, without NBS, the impact of SCD on early childhood mortality often escapes public health attention.

The high mortality rate in young children with SCD in SSA was clearly demonstrated by the Garki Malaria Study (1970-1974) conducted in Northern Nigeria. (91) By screening 2,742 subjects in the general population and 534 newborns to determine prevalence of Hb variants and genotypes, they found only one child with SCA in the 1 to 4 years age group, instead of the six expected, and only one child with SCA in those aged 5 years and higher, instead of the expected 53, suggesting that 98% of the people born with SCA had died by age 5 years.

Since the 2006 WHO Report on the impact of SCD on childhood mortality, and the 50%–90% early-life mortality among children born in Africa with SCA estimated by Grosse and colleagues, (42) there has been little evidence of large-scale public health activities that could be expected to lead to substantial reduction in childhood mortality in SCD in SSA. Although pilot and small-scale NBS projects funded largely by foreign grants, may provide reliable birth incidence rates, mortality data remains largely unavailable. Furthermore, such limited efforts are not expected to alter the dire statistics.

The causes of the high mortality in young children with SCD in HICs are likely not to be fundamentally different from those in low-income, high-prevalence countries. In much of Africa, signs of infection, especially fever, are synonymous with malaria and anti-malaria therapy is often administered without prior diagnosis. However,

pneumococcus is as much a major pathogen in malaria endemic regions as it is in countries without malaria. In a large study on bacteraemia in children, conducted in Kenya (1998-2008), the organisms most commonly isolated from children with SCA were *Streptococcus pneumoniae* (41%), non-typhi Salmonella species (18%), and *Haemophilus influenzae* type b (12%). With no penicillin prophylaxis, 23% of children with SCA died. (92)

In the US PROPS1 study, 13 of 110 children on placebo developed pneumococcal bacteraemia and 3 of the 13 died; 2 of 105 children on twice daily penicillin developed pneumococcal bacteraemia and both survived. The three deaths occurred within less than 9 hours from onset of fever. However, penicillin prophylaxis for young children with SCD, even when they are diagnosed with SCD following an acute illness, is not uniformly practiced in many health institutions in Africa.

At the end of the first 10 years of the pilot NBS project conducted in Ghana with support from the US National Institutes of Health, 2,914 out of eligible 3,334 newborns with SCD, had enrolled for care I Kumasi and, 4.6% were known dead after enrolment. All enrolled children had received twice daily penicillin prophylaxis and followed for comprehensive clinical care (Unpublished data, Ohene-Frempong). Ghana has been unable to scale up NBS following the pilot study and is currently screening less than 4% of newborn annually, mostly with foreign grants. This example illustrates the magnitude of the challenges faced by countries of high SCD prevalence.

1.4. Genetic, socio-demographic and environmental risk factors

Although SCD is one of the most common monogenic diseases worldwide and a disease which has been studied for more than a century, our capacity to define and predict disease severity is relatively limited and our understanding of risk factors often remains insufficient to guide the management of patients with SCD. (93) Because SCD is a multi-system disease, which can affect all the organs of the body, defining disease severity is in itself a challenge and remains a controversial topic in the field. The phenotypic variability observed is likely due to a combination of genetic, environmental and socio-economic factors - the respective contribution of each factor remaining relatively poorly understood. (93) Being able to predict the clinical course of patients with SCD and to classify them has long been an important aim for better prognosis and, more recently, personalized treatment. Digital epidemiology initiatives based on at-home study design, wearable devices, pervasive sensors or engaging digital health interventions to capture real-life data (e.g., knowledge, attitude, self-care practices, lifestyle behaviours, exposure to infection) can support the data collection throughout patients' day-to-day life, and machine learning approaches may help infer on a variety of Omics data to propose personalized recommendations supporting decision making. (94)

1.4.1. Genetics risk factors

Objective and quantifiable biomarkers of disease severity in SCD are currently lacking and this has substantially affected drug development and clinical care worldwide. (95) Predicting patients at higher risk for complications using only genetic data remains difficult. Biomarkers can both help classifying patients into sub-groups at the population level or predicting disease severity and progression for individual patients (i.e. personalised medicine). Although the five β-globin-like gene cluster haplotypes – Bantu or Central-Africa Republic (CAR),

Benin (BEN), Cameroon (CAM), Senegal (SEN) and Arab-Indian (ARAB) – originally described may have identified important differences in disease severity at the population level, there is substantial overlap between the characteristics of these haplotypes. For example, data from Central India has shown that severe disease can be commonly observed in patients with the Arab-India haplotype, which is usually considered to be milder than the African haplotypes. Ethnic variability within African haplotypes is starting to be made possible by using large national NBS datasets and international data collected through multi-centre collaborative projects (e.g. SickleInAfrica, BioCADRE).

Over the last couple of decades, genetic association studies have attempted to define disease sub-phenotypes based on markers of anaemia, haemolysis, and vascular complications. (96) More than one hundred blood and urine biomarkers have been correlated to at least one of the complications of SCD (97) but they often explain only a small part of the overall disease variability. More recently, cluster analysis, based on large well-studied cohorts (e.g. CSSCD) have further identified biomarker signatures which could aid the treatment and management of the disease. (98) Although these advances have to some extent guided therapeutic developments and the clinical management of patients with SCD, they have not led to generic biomarkers widely adopted in clinical settings. In the future, omics studies, accounting for genetic and non-genetic factors, might contribute to further improve our understanding of the phenotype-genotype relationships in SCD.

The most established biomarkers of survival and clinical complications in SCD are the levels of HbF and the coinheritance of α-thalassaemia, (93) which both reduce the polymerisation of HbS and therefore results in a milder clinical course. Increasing HbF levels has been underlying the growing use of HU to prevent complications in SCD and the development of new drugs based on endothelial cell activation, cellular adhesion, chronic inflammation, intravascular haemolysis and nitric oxide scavenging (see **Section 3**).

In HICs, the quest for reliable biomarkers is likely to become more complicated with the emergence of comorbidities seen in older patients with SCD. (99) In LMICs, most of current population and burden estimates and projections are based on Hardy-Weinberg Equilibrium assumptions. Better data on key factors underlying these assumptions, consanguinity in particular, will be fundamental to improve such estimates.

1.4.2. Environmental risk factors

A range of environmental factors, including climatic and meteorological variables (temperature, humidity, wind speed or rainfall); air quality (indoors and outdoors pollutants, including PM10, PM2.5, NO2, CO and O3); altitude; and malaria endemicity, can potentially influence the natural history of SCD. It is very difficult to establish a clear link between specific environmental factors and pathophysiological events, and the evidence for these effects is confusing and often contradictory. (100) Similarly, the US Consensus Study Report on SCD concluded that "the exact roles that such [environmental] factors play in influencing symptoms and complications [in SCD] are not well understood" (US Strategic Plan and Blueprint). Most of the evidence generated so far comes from Europe and the USA, although studies are starting to emerge from countries with a high prevalence of SCD. (101) Studies of the general population and of other sub-groups affected by other diseases (e.g. cardiovascular disease, respiratory diseases and cancers) have clearly demonstrated the serious

health effects of poor air quality, even at low levels of exposure. Despite recommendations by the WHO, nine out of ten people are exposed to poor air quality and the GBD estimated that air pollution contributed to 213 million (95% UI 189-240) DALYs and 6.67 million (5.90-7.49) deaths in 2019. (102) As it is highly likely that poor air quality would have adverse effects on individuals with SCD, quantifying risks for each pollutant would help mitigating complications and managing patients. In HICs, the lack of strong associations found so far has likely reduced opportunities for further investigations. In LMICs, ongoing efforts to collect high-resolution data on pollutant concentrations using satellite images or measurements in India, Brazil and African countries represent great opportunities to investigate associations and health risks in SCD.

As the world population becomes increasingly urban and the impact of climate changes becomes apparent, it will be essential to better understand the impact of environmental factors on patients with SCD. Estimates from the UN World Urbanization Prospects suggests that, by 2050, two-thirds of the world population will live in urban areas. These changes will be predominantly driven by changes in SSA and the Indian subcontinent (Our World in Data), which coincide with regions of high prevalence for SCD. Cities represent specific ecosystems in which populations can potentially benefit from easier access to health infrastructures, but also suffer from poor air quality and dramatic inequalities in terms of socio-economic status, as already observed in many megacities (see **1.4.3**).

In parallel, as highlighted in the 6th Assessment Report of the Intergovernmental Panel on Climate Change, millions of people will have to adapt to changing conditions of their local environment or to migrate due to the effects of more severe and more frequent events triggered by climate change (e.g. draughts, storms, wildfires and heatwaves). These local changes will mostly affect the poorest and the most vulnerable, including patients with SCD and their families. For example, good hydration is part of the management of SCD as cell dehydration promotes polymerization and sickling. Local changes will also lead to large numbers of individuals moving within their home country, contributing to urbanisation, or internationally either to neighbouring countries or to countries less affected or with more resources. These large population movements could have an important influence on the global distribution of SCD.

These changes are likely to add to the challenges already faced by SCD patients and their families over the coming decades, making access to quality healthcare more difficult and affecting their mental health. There is limited data on the mental health of SCD individuals. A recent report jointly led by the UK Sickle Cell and Thalassaemia All-Party Parliamentary Group and the UK Sickle Cell Society (103) found that, during the COVID19 pandemic, 75% of patients with SCD and their carers struggled with their mental health. Providing appropriate psychological support to patients with SCD should therefore be more prominent on the policy agenda in both HICs and LMICs.

1.4.3. Socio-demographic risk factors

The COVID19 pandemic has further highlighted growing socio-economic (e.g. access to healthcare and vaccines) and racial (e.g. occupation) disparities as significant determinant of health. As in many other diseases, poverty can have a substantial impact on the health of patients with SCD. Although a large proportion of SCD

complications would be avoidable or treatable with existing medicines (e.g hydroxyurea, penicillin prophylaxis) or interventions (e.g. NBS), the vast majority of patients with SCD worldwide lives in LMICs and suffers from lack of access to proper sanitation, health education and health facilities, combined with poor nutrition, prevalent infectious diseases (such as malaria, tuberculosis and HIV), and exposure to toxic pollutants (e.g. air pollution, heavy metals), highlighting the need for a holistic multi-disciplinary approach, building on ongoing efforts] (56) to improve the management of SCD and reduce health inequalities.

There is some evidence that a higher proportion of patients with SCD live in the lowest socio-economic areas compared to the general population. In the UK, 58% of patients admitted to hospital with a primary or secondary diagnosis of SCA with crisis or without crisis in 2005-2006 lived in areas belonging to the most deprived quintile of the English Index of Multiple Deprivation. (104) In Saudi Arabia, Khan et al (105) found a higher percentage of children in the lowest socio-economic class and a higher frequency of vaso-occlusive crisis (VOC) and adverse events compared to those living in higher classes. In India, SCD is predominantly found amongst scheduled tribes and scheduled castes, which constitute the most socioeconomically disadvantaged population subgroups in the country. (34)

In the UK, SCD patients from the most socio-economically deprived areas and with comorbidities were at highest risk of both SCD readmissions and in-hospital mortality. (104) Similarly, in the US, financial insecurity was associated with three times more hospital admissions and readmissions in adults with SCD. (106) In children, Panepinto and colleagues found that SCD led to a significantly impaired health-related quality of life (HRQL), even after considering the potential detrimental effect of family income on HRQL. (107) Missing school or work for patients and their relatives can have an impact on their education or career progression, further contributing to the long-term disadvantage faced by patients with SCD.

Racism and stigmatisation can aggravate the impact of deprivation on patients with SCD as illustrated by difficulties in accessing opioids; (108) longer waiting times than for other health complications; (109) or the availability of fewer financial resources compared to other diseases (e.g. cystic fibrosis) (110). These inequalities need to be addressed. Additional funding and research for SCD and other diseases that disproportionately affect economically disadvantaged groups could help reducing health care disparities.

In LMICs, although high-quality care is available in well-resourced centres of excellence in cities [e.g. Kilifi, Kenya; (40) Dar-es-Salaam, Tanzania; (39)], the vast majority of patients with SCD do not have access to basic healthcare. In Nigeria, the SPRING trial suggested that poverty was associated with severe anaemia in children with SCD. (111) A cross-sectional descriptive study performed at referral centres for the treatment of haematological diseases in the Northeast of Brazil identified difficulties in obtained medications prescribed by physicians and in transportation. (112) In addition, deficiencies in nutrients associated with malnutrition and undernutrition have been shown to be linked with disease severity and health-related QoL in both adults and children with SCD. (113)

Finally, migrants and refugees can face additional difficulties in relation to legal status, linguistic barriers and cultural differences. Resulting delays in screening and adequate management can lead to severe health complications and to substantial longer term additional healthcare costs. (114)

1.5. Epidemiology recommendations

While the SCD community faces many challenges, proven cost-effective interventions have the potential to identify SCD individuals early, to reduce mortality and to prevent severe chronic complications. These interventions need to be scaled up to reflect the true global burden of SCD. There needs to be an agreement on what standardised epidemiological data is needed, and this data should be collected to track progress towards set milestones, aligned with the UN' Sustainable Development Goals, and to assess the impact of interventions.

Section 2: Screening & Prevention

2.1. Screening for SCD

Detection programmes for any disorder depend on a public health systems and life-course approaches that includes screening, diagnosis, education, treatment, and comprehensive care. Screening can occur at any point throughout life, but is particularly relevant in the newborn period, premaritally and preconceptually, and as part of antenatal care (**Table 1**). (115) Appropriately trained genetic or nurse counsellors play an important part in any screening programme, particularly in the antenatal period, to discuss the possibility of prenatal diagnosis and reproductive choices. (116)

Screening before conception allows the detection of the carrier status of the mother and father. With respect to SCD, during the antenatal period, the mother and foetus can be screened by a variety of tests such as chorionic villus sampling and amniocentesis to find out if the baby will have the disease or be a carrier. (115) These tests are usually conducted at or after twelve weeks of pregnancy and are considered invasive, increasing the risk of miscarriage by up to 1%. Newer methodologies utilising non-invasive techniques employ testing of cell free foetal DNA in the maternal circulation from 8 weeks' gestation.

Postnatally, newborns are identified through newborn screen (NBS) which are sometimes part of broader programmes, for conditions such as phenylketonuria, congenital hypothyroidism and cystic fibrosis. It is vitally important that adequate health care is available for babies identified as having any of these conditions. For SCD, they need to be prescribed penicillin from the age of about 3 months and to be followed up in specialist clinics.

Table 1. Approaches to screening

Type of screening	Screening technology	Advantages	Disadvantages/Challenges	References
		PRECONCEPTUAL		
Testing parents (or young adults)	Blood tests	Widely available on a voluntary basis Evidence of benefit in Saudi Arabia and Bahrain Reliable, able to distinguish most types of SCD, including compound heterozygotes	QA/EQA processes not routine in LMIC with results varying from lab to lab	
	Conventional methods for haemoglobin analysis:			(115, 117)
	- Conventional Electrophoresis		Low sensitivity when compared to HPLC or CE	
	- HPLC*		High cost	
	- CE**		Mostly used in HIC	
	Point of Care Tests (POCTs)	Rapid, sensitive, low cost compared to HPLC and CE in WHO EDL3		(118)
		PRENATAL/ANTENATAL		
Testing pregnant women	Blood tests	Integral part of the UK and Cuban newborn and antenatal screening programme Used for "guided NBS targeting" in India and Benin	Educational and counselling programmes not well established in many countries.	(53, 61, 116, 119, 120)
	Conventional methods for haemoglobin analysis: Same as above			
	POCTs	Used in Republic of Congo, Democratic Republic of Congo, Republic of Guinea, Nigeria, Liberia and Kenya for primary screening		
Testing foetuses	DNA Technology	Available in HICs and in India	High cost Ethical Issues May be unacceptable or prohibited by law in some countries	(116)
	Invasive:			
	- Chorionic villus sampling (10-12 weeks of pregnancy)	Part of the NBS programme in Cuba		
	- Amniocentesis (15-20 weeks of pregnancy)			
	Non-invasive:	No foetal risk during sampling	Still in evaluation phase	

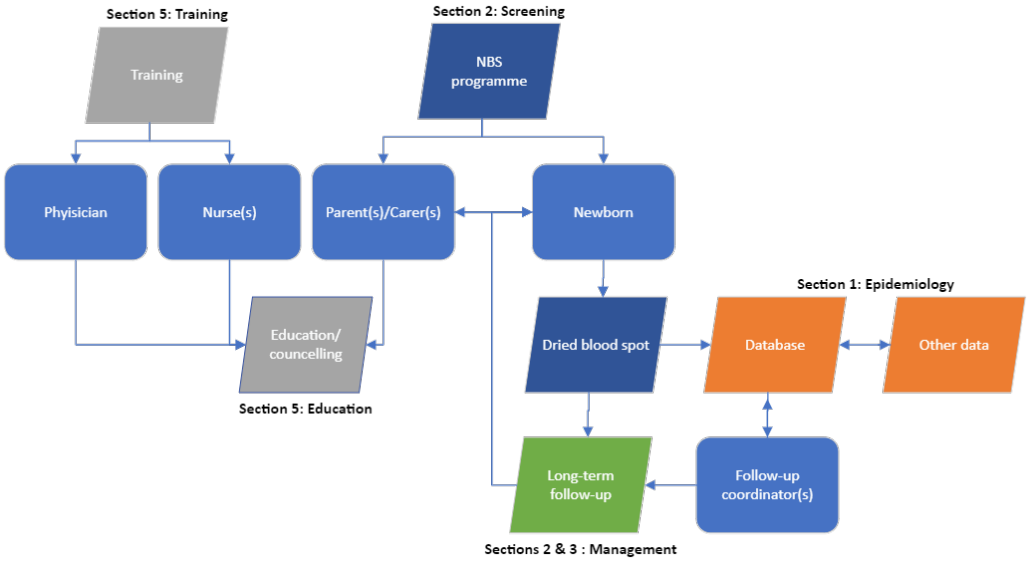
	- Analysis of circulating foetal DNA in mother's blood			
Testing embryos	Preimplantation genetic diagnosis with *in vitro* fertilisation	Alternative to prenatal diagnosis and offer of pregnancy termination in case of an affected foetus	Very high cost, considerable physical and psychological burden for the concerned couples	
		POSTNATAL		
Newborn Screening (NBS)	Blood tests from heelstick	Widely Implemented, extensive experience, benefit demonstrated		(121)
	Conventional methods			
	- IEF***	Mostly used in LMICs	Low cost Labour-intensive Extensive expertise needed	
	- HPLC*	Mostly used in HICs	High cost Require skilled technicians	(122)
	- CE**			
	Mass Spectrometry	Used in UK and France High throughput	Very high cost Require skilled technicians	(123, 124)
	POCTs	Successfully implemented in Nigeria; evidence of benefit in Haiti, Ivory Coast, Ghana, Martinique Easy to use, low cost, does not require electricity		(118)

Screening programs also need to take into account the important stresses that often affect a family's ability to cope with SCD, including the economic and educational consequences of time lost from work and school and the impact of chronic illness on normal family functioning and unaffected siblings. Families live daily with the knowledge that unpredictable acute illnesses may interrupt daily life, and there are often feelings of powerlessness, frustration, and even anger. A general lack of community awareness about SCD and fear of stigmatisation may limit the support available from extended family, friends, and the community at large. Prior experience with health care providers who lack knowledge, sensitivity, and compassion may contribute to delays in seeking appropriate health care and may engender adversarial relationships between families and providers. Failure to appreciate ethnic and cultural differences between providers and patients and families, the effect of stigmatisation and lack of societal education about SCD may also contribute to misunderstanding and lack of trust. Thus, it is imperative that in the design of any screening programme for SCD, providers take time to listen to the concerns of patients and families, are sensitive to psychosocial and medical needs, and that they assist families in accessing available resources as needed.

2.1.1. Data infrastructure and surveillance systems for NBS

Where NBS programmes are established, these programmes are cost effective and their efficiencies and effectiveness depend on the smooth integration of sample collection, laboratory testing, follow-up, diagnosis, and treatment (**Figure 2**). (119, 125, 126, 127, 128) These programmes require information system infrastructure for follow-up and quality assurance. Inequalities between HICs and LMICs are apparent. In LMICs, the absence of data collection and infrastructure makes it very difficult to assess the clinical outcomes for patients, and to monitor the effectiveness of any screening programmes. In addition, training is required in all aspects of establishing and running NBS programmes, with external quality assurance and provision of genetic counselling, follow-up of screen positive babies and provision of comprehensive care. (129)

Figure 2. The network of services associated with NBS and related links between the five core sections of this Commission: Epidemiology in orange, screening in blue, management in green, training and education in grey.



2.1.2. Screening Tests

NBS programmes for SCD have been in place in several regions of the world for more than 40 years (**Table 1**). The first analytical, and still most utilised, techniques for screening (and diagnosis) are based upon the separation of the various haemoglobin species in the newborn blood by their difference in electric charge. (121) These techniques include isoelectric focusing (IEF), cation-exchange high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE). Classical haemoglobin electrophoresis using cellulose acetate electrophoresis at alkaline pH is still a useful technique to screen for and diagnose SCD in older children and adults, and is still used for this in many countries. However, it is not usually recommended for NBS programmes because it maybe too insensitive to reliably detect the small amounts of adult haemoglobins present in newborns. New technologies being developed utilise differences in molecular mass (Mass Spectrometry – MS) or antigenic properties (Immunoassays). MS is used now in some national neonatal screening programmes but relies on the use of equipment which is expensive and requires careful maintenance. Immunoassays are used in particular for point-of-care tests (POCTs), but do not have an established role in screening programmes yet.

The main technical challenge for NBS is that the major haemoglobin constituent in newborn blood is HbF and that the adult haemoglobins (HbA, HbS, HbC, HbDPunjab, HbE, and HbOArab) are minor constituents. Furthermore, it is not only important to detect their presence, but also to be certain if they are absent, particularly in the case of HbA.

2.1.3. Laboratory methods

IEF is a very sensitive method and is widely used in LMICs at relatively low cost. IEF separates haemoglobin species according to their isoelectric point on a gel medium. Bands are very sharp compared to classical electrophoresis, and HbF and HbA bands are clearly distinct. The relevant abnormal haemoglobin variants can be readily detected. A significant disadvantage is that it is a non-automated technique, and therefore time-consuming, and that results rely on accurate interpretation by appropriately trained and experienced staff.

HPLC is based on the sequential elution of positively-charged Hb species (cations) bound to a negatively-charged solid phase in a chromatographic column by buffers, with gradient of increasing ionic strength. Haemoglobin species eluted from the column are detected by a dual-wavelength detector, generating a chromatogram on which each haemoglobin peak is characterised by its elution time, and quantified by integrating its area under the curve. It is a highly resolutive and sensitive technique (detection limit for HbA and HbS ~ 1% of total haemoglobin). The advantages are that it is automated, with computer-aided identification and quantification of the haemoglobin species. Disadvantages are the cost of the equipment, the need for technical support and maintenance, the cost of the reagents, and the need for reliable supplies of electricity. It has become the major first-line screening procedure in HICs and the reference control procedure in many reference centres in LMICs.

CE separates different haemoglobins according to their electrophoretic mobility and an electro-osmotic flow generated by a high-voltage electric field in a glass capillary. Haemoglobin species are prompted to migrate toward a 415-nm wavelength detector generating an electropherogram. Haemoglobin species are identified

according to their migration zones and relatively quantified. Advantages and disadvantages are similar to HPLC, although the procedure is a little bit less costly.

MS-based techniques allow the identification of haemoglobin species according to the difference in molecular mass of globin or peptide chain fragments. Mass spectrometers are highly sophisticated instruments that can be used in different ways. Two variants of the technique are used for SCD NBS: tandem mass spectrometry (MS/MS) (123) and MALDI MS (Matrix-assisted laser desorption/ionisation MS). (124) In the first approach, two mass spectrometers are coupled to separate then identify peptide fragments issued from the tryptic digestion of haemoglobin. The MALDI MS approach uses one single MS machine to analyse the globin chains as a whole or after fragmentation. An advantage of MS/MS is that it is more specific than electrophoretic and chromatographic techniques, allowing the accurate identification of most haemoglobin variants; the disadvantage is that the initial set up is time-consuming (similar to IEF). An advantage of the MALDI MS is that analysis is extremely rapid and thus that the system is amenable to very high throughputs; the disadvantage is that it has been applied to haemoglobin analysis more recently and currently all the variants cannot be identified. Both approaches benefit from a computer-aided identification of the variants removing operator-dependent variability. The cost of the machines is very high, but MS/MS is also used to screen for many other newborn conditions in HIC, and MALDI MS machines routinely equip microbiology laboratories in HIC and an increasing number of reference microbiology laboratories in LMIC.

2.1.4. Point of care tests

Conventional screening programmes as established in North America, Europe, Brazil and some Caribbean countries (119, 125, 126, 127, 128) have not yet been established in LMICs due to the high costs, lack of skilled manpower, inadequate electricity supplies and lack of other basic infrastructure. Several POCTs have recently been developed to overcome some of these barriers, using a variety of approaches, including erythrocyte density, differential mobility of HbS and HbA through filter paper, and antibody-based immunoassays (qualitative lateral flow immunoassays or competitive enzyme-linked immunosorbent assays). (124) These POCTs are inexpensive, reliable, require only a pin prick of blood, and show high specificity and sensitivity in the discrimination of the different haemoglobin phenotypes in the presence of the high HbF levels in newborns. They can easily be administered in rural villages with minimum training, and as such have the potential to reduce health care inequity that has made NBS unattainable in high burden countries. (130) Use of POCTs may increase access to universal NBS, although many problems remain in implementing such schemes and in following-up babies found to have the condition. POCTs have been included in WHO EDL3.

A particular problem with POCTs can be identifying some of the less common genotypes which can cause SCD, such as HbS/β+thalassemia which can be confused with sickle cell carriers. Screening programmes inevitably do not accurately diagnose every case, but clearly very sensitive and highly specific approaches should be used to minimise the number of patients missed as much as possible; to not falsely identify babies as affected; and to prevent unnecessary psychosocial harm to families.

Most techniques detect carriers of haemoglobin variants as a by-product. Some SCD NBS programmes use this information to provide families with reproductive knowledge and informed decision-making regarding SCD. Some other programmes have made the choice not to use this information for feasibility or regulatory reasons.

2.2. The status of NBS

NBS for SCD was initiated in the USA in 1973, but it took more than 30 years to become a national programme, covering all the states of the country in 2006. (125) In Europe, pilot programmes were launched in the early 1980's in France and the UK and on the French island of Guadeloupe in the Caribbean. (126) In high burden countries, the pioneering NBS pilot programs were those simultaneously initiated in Benin and Ghana in 1993. (131) In India, pilot programmes have been initiated since 2010 in Central and Southern Indian states where the incidence of SCD is the highest. (51, 53)

Overall, the situation remains extremely heterogeneous from one country to another from national programmes covering the whole country (USA, 4 European countries, Brazil and 3 countries in the Middle East) to patchy pilot programmes in sub-Saharan Africa and in India (**Table 2**).

In a recent survey of implementation of WHO Strategy in high burden countries in the WHO African Region, it was found that NBS for SCD was being practised in 13 countries (Benin, Nigeria, Uganda, DRC, Mali, Senegal, Ghana, Liberia, Tanzania, Kenya, Zambia, Burkina Faso, and Cameroon). Although substantial progress is being made in Ghana, none of these countries yet has a national programme because of lack of funding and political commitment.

2.2.1. An example of NBS programme in sub-Saharan Africa: Ghana

Ghana is probably the best example of an African country with a well-planned NBS programme for SCD. (132) The pilot NBS programme commenced in 1993 and was supported in 1996 with three five-year cycles of NIH funding at the Komfo Anokye Teaching Hospital (KATH), and Kwame Nkrumah University of Science and Technology (KNUST) in collaboration with the Minister of Health and the Ghana Health Service. Sample collections are done at the place of birth prior to discharge or at immunisation sites. Data collection, collation, and handling of samples are performed by nursing staff of the screening healthcare facilities. The structured programme has facilitators and coordinators at site, district and regional levels overseeing sample collection, communication and shipment to the centralised screening laboratory with a Nurse Coordinator supervising all the NBS activities of the coordinators of the programme. Data from the programme since inception have been managed in a backed-up database with secure access to staff only. 87.4% of babies diagnosed with SCD have been located and enrolled into comprehensive care and follow-up. Recently the programme transitioned to mobile data collection using the specially developed Ghana NBS App for all NBS-related data at screening sites and at the National NBS Laboratory at Noguchi to enhance accuracy in data collection and easier and faster management of NBS data. Workshops were conducted to train genetic counsellors. The government and health insurance supports NBS at the sites in Kumasi and surrounding communities but not sufficiently to allow scaling up to a national programme. Over the years, the NBS has been sustained by external funding through

international collaboration with the Government of Brazil, NGOs, the American Society of Hematology (ASH), and pharmaceutical companies including a formal public/private agreement with the Government of Ghana. A recent public-private partnership aims to scale up the programme cover the whole country, but this has not been achieved yet.

Table 2. Newborn screening programmes in different regions of the world

Region	Type of programme	Date of programme initiation/ full national coverage	Country, Coverage/Efficiency	Comment
Africa	Regional/Pilot	1993	Benin	Pioneer projects
		1993	Ghana	Supported by NGOs, HIC Agencies, Public/Private initiatives
			Cameroon, DR Congo, Gabon, Ghana, Guinea, Mali, Senegal, Tanzania, Uganda, Zambia	Regional projects partially supported by govt funding
			Burkina Faso, Kenya, Liberia, Niger, Nigeria	
Europe	*National programmes* - *universal*	2002/2014	UK* (coverage: >99%, survival at 16yo: 99%)	*Coupled newborn and antenatal screening meme
		2003/2015	Spain	
		2007	The Netherlands	
		2017	Malta	
		2020	Germany	
	- *targeted*	1995/2000	France (coverage: >99%, survival at 16yo: 97%)	Target: geographical ancestry of the mother
	Regional/Pilot	2003	Ireland[a]	
		1994	Belgium[b]	
		2007	Italy: 3 of 20 regions[c]	
Middle East	National programmes - universal	2002/2005	United Arab Emirates	
		2007	Bahrain	
		2007	Qatar	
	Regional/Pilot	2005	Oman	

India	Regional	2010	6 of the 31 states and Union Territories[d]	
North America	National - universal	1973-2006	USA (survival at 18yo: 94%)	
	Regional – universal		Canada: 8 of 13 Provinces/Territories[e]	
Latin America	National - universal	1995	French Guiana (coverage: >99%)	
	Regional – pilot	2010/2014	Brazil (coverage: 83%)	
		2000	Colombia	
		2013	Costa Rica	
		2013	Uruguay	
West Indies	National - universal	1983	Cuba*	*Coupled antenatal screening and prenatal testing
		1984	French West Indies (coverage: >98%)	
		1995/2015	Jamaica (coverage: >98%)	
		1977/1987	Puerto Rico & the Virgin Islands (USA)	
		2015	Dutch Caribbean	
	Regional – pilot		Tobago, Grenada, Saint Lucia, Saint Vincent and the Grenadines, Antigua and Barbuda, Haiti	

[a] NGO funded

[b] Regions of Brussels and Liège

[c] Regions of Veneto, Sicilia (universal), and Emilia-Romagna (targeted on ethnicity)

[d] States of Gujarat, Maharashtra, Madhya Pradesh, Chhattisgarh, Odisha, Tamil Nadu. Depending on the programme, screening is untargeted or targeted to tribal newborns, and/or to newborns of HbAS mothers

[e] Provinces of Ontario, British Colombia, Yukon, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, and Alberta

2.2.2. An example of NBS programme in Europe: the UK

The history of NBS for SCD in Europe goes back almost 40 years from the first pioneering pockets of screening in France and England to full implementation of NBS covering the whole countries in 2000 for France (targeted) and 2014 for the UK (universal). (126) In both countries, it is now part of national screening programmes integrated into a comprehensive free-of-charge system to ensure a complete medical support of prevention and care. The chosen strategy in the UK is that of a linked antenatal and neonatal screening programme. In addition, women and couples with carrier status known before pregnancy are offered genetic counselling to consider options as soon as they present in pregnancy. The antenatal programme offers screening to all pregnant women by 10 weeks of gestation. All the fathers of carrier women are fast-tracked, offered information and testing. Genetic counselling is provided, and prenatal diagnosis offered to carrier couples early enough to complete prenatal diagnosis by 12+6 weeks' gestation if the option is chosen. The same procedure is offered to carrier women when the biological father is unavailable. Independently from the results of the antenatal screening, all the newborns in the UK are tested at 5 days of age via the national blood spot screening programme for nine conditions including SCD. For SCD, testing of the blood spot is performed in 13 accredited laboratories by at least two analytical methods including HPLC, CE, IEF and MS/MS. The overall efficiency and quality of the programme are regularly evaluated to optimally ensure that the main objective of the programme is met: prompt identification of babies born with SCD and timely transition into clinical care. Advantages of coupling antenatal and neonatal programmes are: i) to support parents at risk to make informed choices during pregnancy (and before conception); ii) to prepare them for their NBS result; and iii) to check, as a part of the quality control, that the antenatal and postnatal results are congruent. Evaluation shows that the programme is well accepted by professionals and by the public. Still, timeliness of the antenatal phase has to be improved to meet the standards for 10 weeks. Coverage of the NBS was 97,8% in 2018 and 2019. Survival of the SCD patients at 16-year-old in the UK is 99%. (133)

2.2.3. An example of NBS programme in the Middle East: the Kingdom of Bahrain

In the Middle East, three countries are running NBS programmes for SCD: universal national programmes in the United Arab Emirates and the Kingdom of Bahrain; and a pilot programme in Muscat, the capital city of the Sultanate of Oman. NBS in Bahrain was included in 2007 in the national programme to control genetic diseases, the first to be initiated in a Middle East country in 1984 with the support from religious scholars, and the Parliament. (134) It is conducted on cord blood samples collected for all deliveries in all the public maternities of the Kingdom. A leaflet detailing the purpose, process, and outcomes of the screening is provided to the parent(s) before screening and the possibility to opt out of testing is mentioned. Information regarding demographic characteristics, parental age group, and consanguinity is also recorded. Cord blood analysis is performed by HPLC in a centralised reference laboratory. Interestingly, by raising the awareness of the population about genetic diseases and haemoglobinopathies in particular, the number of babies born with SCD has declined by 75% since the initiation of the national programme in 1984. Addition of NBS to the programme has ensured prompt identification of the affected babies and early transition into clinical care.

2.2.4. Differences among different regions of the world

There are marked differences in the nature of the screened populations in different parts of the world, particularly the prevalence of SCD, which determines the most effective approach to screening. While in most programmes, screening is universal, meaning that all the newborns using some form of haemoglobin analysis, some programmes aim to do blood tests only on those deemed to be at high risk of having SCD. Targeting may be "guided" in programmes testing only newborns of carrier mothers as in Benin (120) and in some local programmes in India (51, 53) and in Cuba. (119) Alternatively, targeting addresses "populations at risk" based on geographic origin or ethnicity as in France, Ireland, or one of the Italian programmes. Some programmes in India target the "tribal" populations. (34)

Sampling can be done at birth or soon after at all levels of health care by a variety of health care workers, mostly nurses and midwives and, sometimes also by laboratory personnel and doctors. In Africa, the services are generally provided only in tertiary health facilities except in parts of Mali, DR Congo, Uganda and Ghana where samples for NBS are collected at all levels of the health system and transported to tertiary facilities for analysis. Sometimes sampling is performed at the first immunisation visit because it is integrated into immunisation programmes (e.g. in Nigeria and Ghana). In some countries, it is linked to reproductive, maternal, newborn and child health (RMNCH) programmes (DR Congo, Gabon, Ghana, Guinea, Tanzania and Uganda) and/or into HIV screening programmes (Burkina Faso and Uganda). Most often, sample analysis is performed in dedicated NBS laboratories using mostly IEF as the first-tier method in Africa, HPLC in the USA, Europe, and India, mass-spectrometry in England and France. However, this situation is changing as some countries have reported the use of POCTs for primary screening (Republic of Congo, DR Congo, Guinea, Liberia, and Kenya). In counties where a national programme is in place, NBS is fully covered most often by public funding and/or sometimes by insurance companies (USA, Europe, Middle East, Cuba, Brazil). Elsewhere, the tests are paid for by a variable combination of government, non-governmental organisations (NGOs) and patients themselves in many countries. In Uganda, the government pays for the test while in Kenya, the payment source is a combination of the government, insurance companies and patients.

Effectiveness of the different programmes is difficult to appreciate as data are scarce and highly heterogeneous. The coverage of national programmes is high (> 98% in the UK, France, the Netherlands and USA; 85% in Brazil). (126, 128) Because of imprecise addresses and ever-changing phone numbers in Africa, a major challenge of many programmes is to locate affected newborns and to enrol them in follow-up and care (54% in Angola, up to 85-87% in Benin and Ghana). But these figures depend very much on the setting, the chosen strategy, including the point of sampling, and awareness about the disease. Linkages to HIV and/or Reproductive, Maternal, Newborn, Child and Adolescent Health programmes improve early detection, enrolment into follow-up, and management of SCD as they deliver a package of educational and counselling services.

Data are lacking concerning the general effect of NBS on the first-year mortality or the under-5 mortality rate (U5MR) of affected children. In Angola, the first-year mortality rate for affected babies compares favourably to the national infant mortality rate (6.8 vs. 9.8%). (135) In Benin, U5MR was 15.5 per 1000 in the cohort of enrolled

affected children, i.e. 10 times lower than the U5MR of the general population. (120) In HICs with NBS programmes (UK, France, USA), survival into adulthood is higher than 98%. (87, 133, 136) Data are lacking concerning cost/efficiency of the various programmes. In Angola the estimated cost per healthy life-years (HLYs) gained was $1380-$3565, i.e. less than the gross domestic product per capita. (137)

2.2.5. Barriers to screening

Cost is one of the main barriers to screening with other barriers existing at policy, health system, institutional and personal levels. Conventional screening requires leadership, detailed planning, expensive equipment, and reagents, technical personnel, stable power source, logistic support (supply chain management) education of and buy-in of stakeholders and communities. Without enabling policies, budgetary allocation, and a functional public health system, NBS even when started by well-intentioned foreign NGOs are often unsustainable, hence the reason for failure to progress beyond pilot programmes in many high burden countries. Equally important barriers are the lack of awareness and acceptability of the programme. Raising the awareness of the target population is key to a successful screening programme. (138) Myths and misconceptions about SCD must be addressed while ensuring the availability of adequate screening tests kits, trained manpower and follow up services.

2.3. The Effectiveness of NBS and early clinical interventions

The effectiveness of NBS and early clinical interventions has been evident from the experience of HICs (87, 133)with some rarer examples of improved outcomes in LMICs, most notably Jamaica. (139) However, the six-part system that includes education, screening, short-term follow-up, diagnosis, management, and evaluation (140) has not been widely implemented in high-burden countries due to limited government capacity and funding. (141)

2.4. Examples of best practices

Best practice in screening requires that all the people with SCD in each population are identified as early as possible along with those having the trait. The design of any screening programme will depend on the resources available, the incidence of SCD and the existence of other health infrastructure, such as screening programmes for other conditions. The full details about where and when the samples will be collected are important. This can be at birth, post-natal (2-6 weeks) or immunisation clinic either at first immunizations, immunizations at birth (BCG) or later. A protocol outlining the type of tests to be used for screening and confirmation, the screening laboratory, what happens to the result, the person responsible for parental follow-up, the scheduling of clinical visits and the comprehensive care centres should be established. The data management workflow and the personnel charged with this as well as quality control should be designated. While this is best done at or soon after birth in NBS, every contact with health care centres, educational institutions in high burden countries should be used to achieve universal coverage. POCTs may be particularly suited to universal screening in countries with limited resources.

2.4.1. Consortium on NBS in Africa

An example of initiative aimed to change this is the Consortium for NBS in Africa (CONSA), a collaboration between ASH and haematologists across Africa aiming to increase the region's capacity for NBS and to demonstrate the benefits of screening and early therapeutic interventions for babies with SCD, working in partnership with local governments to ensure the long-term sustainability of these efforts. (142) When establishing the consortium, careful preparation was made to develop governance structure and protocols, and site inspection visits were carried out to assess Consortium member readiness. The Consortium negotiated lower equipment and reagent costs for NBS using IEF. Seven countries have so far been admitted into the Consortium i.e., Ghana, Tanzania, Nigeria, Liberia, Uganda, Kenya and Zambia. Babies with SCD detected in the programme will be followed up for five years to document the effectiveness of NBS to encourage African governments to implement universal NBS. The protocol, checklist and forms developed by CONSA could be a valuable resource for NBS programmes. (143)

2.5. Prevention of SCD

Primary prevention in this context refer to action aimed at reducing the number of babies born with SCD. This includes premarital testing and genetic counselling, with the potential to choose partners partly based on their haemoglobinopathy status. Prenatal diagnosis with termination of pregnancy is not widely practiced in most African countries where abortion is illegal and cultural and ethical considerations still favour the protection of life of the unborn. However, this approach, with selective termination of affected foetuses, is an integral part of screening programmes for SCD in some countries, such as the UK. *In-vitro* fertilisation with preimplantation genetic diagnosis, which is available in some HICs, is not feasible in most African countries.

Genetic counselling for persons who are at high risk of having a child with SCD can be considered a method of primary prevention. For persons who are heterozygous for the sickle cell allele, education should be provided regarding the probability of having a child with SCD. This can be implemented in the screening of adolescents within the school system.

The fact that SCD is inherited as an autosomal recessive disease which is potentially preventable has been known for decades by the scientific community. However, this knowledge has not been translated into action in many high burden countries resulting in low levels of awareness of SCD and its implications, limited availability of genetic counselling, and the absence of effective policies for universal screening and public health measures for primary prevention.

2.5.1. Genetic Counselling for SCD

Genetic counselling is an educational procedure, the nature of which varies with the objectives. Genetic counselling in SCD is a cost-effective strategy in reducing the burden of the disease. It is a communicative process which can help to decrease the overall incidence of SCD.

The goals of genetic counselling in SCD are to: i) provide an understanding of the inheritance of SCD; and ii) provide those counselled with the information needed to make family planning decisions. Reproductive genetic

counselling in SCD can be predominantly divided in to pre-marital, prenatal and neonatal. Counselling is designed to assist in decision making. It provides objective information to individuals at risk of having a child with SCD. This information enables the individuals to make informed decisions. The counselling should also include specific information on the natural history of the type of SCD that may affect the offspring and the resources that will be required to care for an affected child. Counselling should be nondirective and objective. Counsellors should not introduce personal biases or offer specific recommendations. Counselling and education of parents of a child with SCD should be done in a kind and sensitive manner as the parents frequently have feelings of grief, guilt, anxiety, or anger. Counselling sessions should stress the importance of health care maintenance, compliance with prescribed prophylactic penicillin and prompt medical evaluation of infants at the time of acute illness.

Utilisation and awareness of genetic counselling and testing for SCD is variable across countries and is unacceptably low in high disease burden countries where such services should be greatest. This will not only adversely continue to fuel the already high carrier rate of the S gene in these countries but, will also add to the high morbidity and mortality in individuals born with the disease.

2.5.2. Sickle Cell Trait (SCT)

Counselling of individuals with SCT relates predominantly to the risks of having a child with SCD. Subjects are largely fit and healthy and hence, such counselling is necessary to increase the general public's awareness of SCT to the level that people with SCT can make informed reproductive choices about pregnancies.

2.6. Screening and prevention recommendations

The discrepancy in access to NBS and early intervention between HICs and LMICs needs to be reduced. Screening for SCD is technically possible in nearly all healthcare settings and is becoming more possible with POCT devices. Based on the evidence discussed above, we recommend that by 2025, policies, resources and facilities are in place to allow all babies worldwide to be tested for SCD, so that they can enter into clinical care and avoid premature death or organ damage. Related to this, we also recommend that all populations at increased risk of SCD are given culturally appropriate information and counselling regarding their reproductive choices. (144)

Section 3: Disease management - Established and emerging treatments

3.1. Treatment and prevention of complications

3.1.1. Acute clinical events

Acute complications are common in SCD and have a characteristic abrupt onset. Whether presenting with fever, pain, dyspnea, or other specific symptoms such as priapism or hemiplegia, patients with acute clinical events warrant urgent intervention and treatment. Current medical management is frequently based on clinical experience and expert opinion, highlighting the need for prospective research. While appropriate treatment of acute events is an important part of SCD management, their prevention is an equally important goal. In this section, three common acute clinical complications are discussed: fever, VOC, and ACS. Organ specific damage such as stroke or splenic sequestration are also acute events but typically managed by transfusions, so are discussed later.

3.1.1.1. Infection

Fever must be systematically evaluated, as bacteraemia/sepsis is the leading cause for death in children, because of functional hypo- or asplenia. Although there is limited high-quality evidence to guide recommendations, especially in adults and low-income countries, fever is typically managed aggressively in all patients with SCD. Penicillin prophylaxis and immunizations greatly reduce the risk of infection with encapsulated bacteria and especially invasive pneumococcal diseases, but nonvaccine serotypes are emerging. (145) All patients with temperature >38.5˚C should be urgently investigated with a full blood count, blood and other relevant cultures, chest X-ray for any respiratory symptoms, and empirical antibiotics covering pneumococcus. Osteomyelitis, typically from Staphylococcal or Salmonella bacteria, have an increased frequency in SCD and may be difficult to distinguish from local vaso-occlusive events, especially since leukocytosis and inflammatory markers such as elevated C-reactive protein occur in both settings. Malaria must be suspected in febrile patients living in endemic regions or after traveling to these regions.

3.1.1.2. Vaso-occlusive crises

VOCs are the hallmark complication of SCD that manifest as severe acute pain, typically in the back, trunk, or limbs, and last several hours to several days. Diagnosis relies on the patient's self-report as there are no specific laboratory biomarkers or imaging abnormalities. This unfortunately often leads to delayed and inadequate management and many patients are wrongfully stigmatized as drug-seeking opioid addicts. (146) Where available, national guidelines appropriately recommend that patients presenting for emergency care should be treated with respect and offered rapid and effective analgesia. (147) Hospital personnel must be trained in pain monitoring and treatment, and should have access to local protocols for managing VOC. Despite its frequency and importance, acute pain management remains unsatisfactory for many patients, and preventive VOC treatment should be a priority.

Optimal management of VOC is primarily for symptomatic pain control, and is based mainly on expert consensus due to lack of available evidence. Mild to moderate pain can be managed at home using paracetamol, non-steroidal anti-inflammatory drugs (NSAID) and weak oral opioids. (148) When pain cannot be relieved at home, appropriate analgesia should be rapidly administered at a healthcare facility or hospital. The choice of drug, dose, and administration route is guided by the severity of the pain, the history of use of analgesia for this episode of pain, previous experience with analgesic efficacy, and side-effects. Ideally, an individualized prescribing and monitoring protocol, established by the patient's SCD provider, should be available. (149) For severe pain, parenteral opioid treatment is usually necessary; typically intravenously or subcutaneously: however alternative routes including transmucosal and intranasal analgesia can be used effectively, especially when intravenous access is delayed or difficult. (150) Pain must be reassessed and treated frequently until pain relief is achieved. Regular opioid administration by patient-controlled analgesia or frequent scheduled doses is then recommended, rather than "as requested" administration. Continuous opioid infusions and long-acting oral opioids can provide good pain control, but due to irregular pain intensity, some patients may become over-sedated with risk of hypoventilation, and should be administered with close monitoring. Frequent assessment of sedation, respiration, and oxygen saturation, as well as pruritus, nausea, and constipation are recommended.

Due in part to lack of evidence-based data, existing guidelines have different recommendations, and several aspects of VOC management remain controversial. For example, normal saline bolus therapy for initial pain treatment is common, yet may be deleterious due to cellular dehydration that promotes sickling. (151) Similarly, while patients should receive paracetamol for synergistic analgesic effects with opioids, NSAID therapy is recommended by NIH and UK guidelines but discouraged by Brazilian and French experts for adults, fearing long-term renal toxicity. (152) Corticosteroids are typically not recommended due to the potential for rebound pain, while incentive spirometry is important to help prevent hypoventilation and development of ACS. (153)

Adjunctive non-pharmacological approaches to treat pain may be useful, such as local heat, massage, distraction, meditation, exercise and encouraging oral fluids. Nasal oxygen, intravenous fluids, oral alkaline water, and preventive anticoagulation have theoretical justification but need prospective data to strengthen the evidence. Blood transfusion is not recommended for acute pain management unless there are other clinical indications, yet many patients receive blood during hospitalisations for VOC. After hospital discharge, weaning of opioids is also controversial, as NIH and UK guidelines recommend converting to oral long- and short-acting opioid prescriptions, while home-based morphine is strongly discouraged in France.

3.1.1.3. Acute chest syndrome

The acute onset of lower respiratory tract signs and symptoms (cough, shortness of breath, tachypnea, retractions, or wheezing) requires evaluation and management for ACS. Minimal investigation includes chest X-ray and serial measurement of oxygen saturation by pulse oximetry, although this may not be possible in many low-income settings. By general consensus, patients with signs of ACS should be hospitalized to allow close monitoring and avoid progression to respiratory failure and even death. Microbiological documentation including blood and sputum cultures, and nasopharyngeal aspirate for viral testing, is recommended. (147)

Supplemental oxygen is recommended to maintain oxygen saturations greater than 92-95%, depending on the patient's baseline value, and close clinical monitoring is required for hypoxemia and bronchospasm. Bronchodilators are commonly used to help relieve reactive airway disease, but corticosteroids have been associated with late-onset clinical rebound and hospital readmission. (154)

Pulmonary embolism, fat embolism, fluid overload, opiate narcosis and hypoventilation may cause or worsen ACS. Pulmonary infection with *Chlamydia pneumonia, Mycoplasma pneumonia, Streptococcus pneumoniae, Staphylococcus aureus* and *Haemophilus influenzae* have been documented in ACS, (155) hence most national guidelines recommend an intravenous cephalosporin and oral macrolide antibiotic. (147) However, bacterial infection is documented in a minority of cases and in France, antibiotic use is relatively restricted unless fever and X-ray consolidation are present. Blood transfusion for ACS, discussed below, can help prevent rapid clinical deterioration and thus be lifesaving. For respiratory failure, high-flow humidified oxygen is recommended to reduce the need for mechanical ventilation.

3.1.1.4. Chronic organ damage

Acute complications in SCD are the most frequent reason for clinical evaluation and intervention, particularly early in life, but the development of progressive damage to internal organs remains a leading cause of morbidity and mortality among adults. Repeated sickling events with tissue ischaemia, as well as chronic haemolysis and inflammation, inexorably leads to chronic organ damage. Over time, older patients with SCD commonly develop kidney disease, retinopathy, pulmonary hypertension, cerebral vasculopathy, leg ulcers, avascular necrosis, and hepatobiliary complications. Management involves organ-specific screening and treatment (**Table 3**). (156, 157) As described below, early use of transfusions or hydroxyurea may ameliorate organ damage. (158, 159)

3.2. Standard Interventions

3.2.1. Blood transfusion

Red blood cell (RBC) transfusions are an important and life-saving treatment for SCD, so access to safe, sufficient, and affordable blood represents a key element to the optimal management of SCD. About 90% of adults with SCD will receive at least one RBC transfusion in their lifetime; (160) many receive sporadic transfusions for acute clinical complications, while some receive regular transfusions for chronic organ damage such as stroke.

3.2.1.1. Indications for Transfusions

All individuals with SCD have chronic haemolytic anaemia, yet most adapt to their steady-state low haemoglobin level such that anaemia *per se* is not an indication for blood transfusion. Acute exacerbation of chronic anaemia, however, can occur in the settings of acute splenic sequestration, transient red cell aplasia associated with parvovirus B19 infection, and increased haemolysis, notably during severe infection such as bacterial sepsis or malaria. In these settings, a simple transfusion is indicated to increase oxygen-carrying capacity. In all cases, the post-transfusion haemoglobin concentration should not usually exceed the baseline value by more than ~2 g/dL or exceed 10 g/dL to avoid hyperviscosity. (147) For children who have recurrent splenic sequestration, repeated transfusions can be helpful but if life-threatening anaemia develops, surgical splenectomy provides a better

outcome. The optimal age for splenectomy in this setting is debated, but surgery should be delayed until all vaccinations are completed to reduce the post-operative infectious risks.

RBC transfusion also reduces the percentage of erythrocytes containing HbS, which reduces the percentage of cells sickling and improves blood flow. Whenever feasible, exchange transfusion should be performed instead of simple transfusion in the setting of severe acute organ damage such as stroke, ACS, acute intrahepatic cholestasis, and multi-organ failure, because exchange transfusion reliably decreases the HbS to below 30% and thereby reduces *in vivo* sickling. (161) Exchange transfusion can be performed either manually or as an automated erythrocytapheresis procedure where facilities permit.

The NHLBI guideline panel has recommended transfusion before surgery requiring general anaesthesia and lasting more than one hour in patients with HbSS or HbS/β^0 thalassaemia, with individualized discussion according to type of surgery, known organ damage, or other medical co-morbidities. (147) Long-term regular transfusions to maintain HbS <30% have demonstrated efficacy in reducing the risk of a first stroke in children with abnormal transcranial Doppler. (158) Initially this transfusion regimen was recommended to be lifelong, (162) but more recently hydroxyurea was shown to be non-inferior to transfusion for primary stroke prevention in children without severe vasculopathy who received transfusion for at least a year. (163) Lifelong chronic transfusion should be offered to patients who have suffered a previous clinical ischaemic stroke, although HLA-matched hematopoietic stem cell transplantation offers an alternative. Regular transfusions also prevent stroke in children with silent cerebral infarcts, but the benefits of long-term transfusion in this setting must be weighed against their risks. Although randomized studies are lacking, chronic transfusion can be effective for patients with recurrent ACS or recurrent VOCs, but should be considered a second-line therapy after hydroxyurea. (161) Where available, automated exchange transfusion is usually preferable to simple transfusion because of the efficiency of the procedure to remove sickled erythrocytes and lower the risk of iron overload. (160)

3.2.1.2. Complications of transfusions

Long-term complications of transfusions vary in frequency and severity according to the individual country. In low-resource countries, blood is not always screened adequately so may transmit infections such as HIV, hepatitis B and C, syphilis, and malaria. (164) In high-resource countries, blood supplies are readily available and routinely screened for blood-borne pathogens, so carry a very low risk of transmitting infections. Instead, the main complications are erythrocyte alloimmunization and iron overload. Lack of venous access may also be very problematic and require insertion of indwelling catheters, which carry risks of infection and thrombosis.

Erythrocyte antigens are highly polymorphic and antigenic mismatches are common between blood donors and recipients; differences in Rh and Kell antigens are particularly immunogenic and frequently lead to alloantibody formation. Alloimmunization causes premature immune-mediated clearance of transfused erythrocytes, and can lead to clinical complications including immediate or delayed haemolytic transfusion reactions (DHTR). Once present, alloimmunization makes finding matched blood difficult and can limit the ability to transfuse safely, particularly in countries with less developed blood transfusion services. In some cases, DHTRs can be very severe, and cause a life threatening fall in haemoglobin below its pretransfusion level, which is sometimes referred to

as hyperhaemolysis. Management of this sort of very severe DHTR requires a high level of expertise since additional transfusions should be avoided if possible, even in highly anaemic patients, and immunomodulatory agents may be necessary. (165) To prevent alloimmunization, a proper transfusion history is needed, and ideally an extended red cell antigen profile by serology or genotyping, with prophylactic red cell antigen matching for Rh and Kell antigens performed in all patients. (160)

Transfusional iron overload is common among multiply transfused patients, although erythrocytapheresis limits this risk. In contrast to thalassaemia, heart function in SCD is usually preserved, although the liver can be seriously damaged. Serum ferritin levels are not specific or accurate to measure the iron burden, since ferritin is increased in SCD secondary to chronic inflammation, but can provide a general assessment in low-resource settings. The NHLBI guideline panel suggests iron overload screening by MRI for liver iron every one to two years in regularly transfused patients. (147) Iron chelation is needed for patients on regular transfusions; the level of intra-hepatic iron typically guides the chelation dose.

3.2.2. Hydroxyurea

Treatment with hydroxyurea currently constitutes the standard of care for prevention of painful VOC in both paediatric and adult patients, and is available in many parts of the world. Hydroxyurea is a cytostatic agent that induces HbF production via inhibition of ribonucleotide reductase, prolonging the S-phase of the cell cycle. Daily oral administration of hydroxyurea results in dose-related marrow suppression with stress erythropoiesis, (166) which may be a critical mechanism for HbF induction, due to the proliferation and release of early erythroid progenitor cells that synthesize more HbF. Sustained increases in HbF reduce RBC sickling and ameliorate RBC hydration, with consequent clinical benefit.

Hydroxyurea also has some HbF-independent benefits. Treatment-associated macrocytosis improves erythrocyte deformability and reduces blood viscosity. (159) Leukocytes, especially granulocytes, participate in the initiation of vaso-occlusion by adhering to activated endothelium and producing inflammatory molecules that propagate vessel occlusion. (167) The reduction in leukocytosis and inflammation by hydroxyurea is therefore likely to be beneficial, although excessive myelosuppression should be avoided. Furthermore, hydroxyurea may exert additional benefits by virtue of *in vivo* nitric oxide donor properties, thereby activating intracellular soluble guanylyl cyclase. (168) In vivo evidence of hydroxyurea's immediate anti-vaso-occlusive actions suggests that this agent could even be exploited in acute settings, including patients hospitalized for vaso-occlusive episodes. (169)

The clinical benefits of hydroxyurea therapy for SCD are numerous and well established. In 1995, the randomized controlled Multicenter Study of Hydroxyurea (MSH) documented a decreased incidence of painful VOE and ACS, as well as fewer blood transfusions and hospitalisations. (170) Long-term follow-up of these patients revealed a significant reduction in mortality, (171) which has been observed in other adult and paediatric populations. (172, 173) Among infants, the BABY HUG trial demonstrated reduced numbers of VOC, ACS, and transfusions even with a low fixed dose of 20 mg/kg/day. (174)

National guidelines provide evidence-based recommendations for initiating and monitoring the use of hydroxyurea therapy in SCD, and consensus treatment protocols for its implementation. (147, 175) Indications for the initiation of hydroxyurea vary among countries, typically based on the frequency and severity of vaso-occlusive complications. All guidelines emphasize the importance of informed joint decision-making between patients and care providers regarding the risks and benefits of treatment. For children, hydroxyurea has the additional potential to prevent or ameliorate future organ damage and chronic complications, hence the current consensus is to offer hydroxyurea to all children with SCA. (147) However, there is not yet strong evidence that long-term hydroxyurea therapy, given either during childhood or later in life, can prevent organ damage during adulthood. Treatment guidelines in low-resource countries are emerging despite limited drug access and affordability. (176)

The HbF response to hydroxyurea depends on the average daily dose, with optimal effects observed when the dose is escalated to produce mild marrow suppression, typically an absolute neutrophil count around 2.0 x 10^9/L. This type of escalation has historically been referred to as the maximum tolerated dose (MTD), although optimal dosing may be a more accurate designation. While HbF induction is the main treatment effect, the amount of induction is heterogeneous and unpredictable, probably reflecting the numerous genetic modifiers of HbF (see **Section 1.4.1**). (177)

Administered orally as a single daily dose, hydroxyurea should be escalated every 4 to 12 weeks. An initiation dose of 15-20 mg/kg/day is well tolerated in both adults and children with SCD, and the optimal dose is typically 25-30 mg/kg/day, with a dose of 30 mg/kg/day recently shown to be superior to 20 mg/kg/day. (19) Importantly, dose escalation does not aim to achieve a specific %HbF goal, but rather to achieve an acceptable level of mild myelosuppression; patients who achieve the greatest myelosuppression often achieve the highest %HbF levels, which correlates with improved clinical status and survival. (178) Once a stable hydroxyurea dose is established, monitoring with full blood counts, including differential leukocyte counts and reticulocytes, should be performed at periodic intervals. (147, 179) Interruption of treatment is indicated only if clinically significant neutropenia, thrombocytopenia, or reticulocytopenia is detected.

Hydroxyurea treatment has almost exclusively focused on individuals with severe SCD (HbSS or HbS/β^0thalassemia), but there is some evidence to support the safety and benefits of hydroxyurea therapy for reducing pain and hospitalization in other genotypes, including HbSC disease. A retrospective analysis of 133 adult and paediatric HbSC patients treated with hydroxyurea reported significant decrease in painful events, especially among adults. (180) However, prospective controlled trials of hydroxyurea for HbSC are warranted.

Concerns have been raised regarding the effects of hydroxyurea on fertility for both males and females, but a limited analysis of testicular biopsies of children on hydroxyurea revealed no differences in spermatogonial cells. (181) Potential for teratogenicity has also been questioned, but data from the USA (182) and Europe (183) have documented hundred exposed offspring without congenital anomalies, and a large review concluded that hydroxyurea at pharmacological dosing does not have *in vivo* mutagenicity or carcinogenicity. (184) In addition,

a recent prospective study concluded that hydroxyurea exposure through lactation was safe for infants, and thus breastfeeding should not be contraindicated for women with SCD on hydroxyurea therapy. (185)

3.3. Newer disease-modifying therapies

With our improved understanding of sickling, vaso-occlusion, and other pathophysiological abnormalities of SCD, an unprecedented biopharmaceutical interest has emerged that has largely focused on agents that modify cellular adhesion, oxygen affinity, and inflammation. Given the reduction in morbidity and mortality with hydroxyurea, there is also interest in identifying novel agents that induce HbF with potentially greater potency and less myelosuppression.

3.3.1. Induction of HbF

Elevated HbF expression in SCD, whether from inherited hereditary persistence or hydroxyurea-related reactivation, significantly ameliorates clinical manifestations, limits organ damage and improves survival. Although decades of evidence have consistently documented the efficacy of hydroxyurea, its widespread use is limited, especially among adults. In addition, despite the lack of hydroxyurea-related mutagenicity or carcinogenicity, ongoing concerns exist about long-term treatment side-effects, as well as recommended avoidance during preconception, pregnancy, and lactation, which affect drug acceptance and utilisation. There are several HbF inducers in clinical development that might overcome some of these limitations, as outlined below.

3.3.1.1. Cyclic GMP increase

Tovinontrine (IMR-687) is an oral highly selective inhibitor of phosphodiesterase-9 (PDE9), which increases intracellular cyclic GMP levels, boosting HbF and reducing markers of haemolysis. (186) An added benefit of PDE9 inhibition is that this enzyme is almost exclusively expressed in haematopoietic cells, in addition to the brain, thereby providing semi-targeted therapy for HbF induction with some anti-adhesive benefits. While earlier trials in adults with SCD showed that IMR-687 was generally well-tolerated as monotherapy and in combination with hydroxyurea, recent interim results from the Ardent phase 2b clinical trial showed no significant improvement in vaso-occlusive crises or HbF in a high-dose treatment group versus placebo-treated population.

3.3.1.2. Histone deacetylase (HDAC) inhibition

HDAC inhibition can induce HbF in SCD. (187) A small study using vorinostat showed that it was welltolerated but caused no significant HbF increases. Panabinostat, an oral pan-HDAC inhibitor, is currently under investigation in adults with SCD (NCT01245179).

3.3.1.3. DNA methyltransferase 1 (DNMT1) inhibition

DNA methyltransferase 1 (DNMT1) is an enzyme that epigenetically silences HbF. Decitabine, an FDA-approved DNMT inhibitor used to treat myelodysplastic syndrome, can increase HbF in adults with SCD, including those without significant HbF responses to hydroxyurea. (188) Its intravenous administration and short biological half-life are limitations, but oral decitabine with tetrahydrouridine to block enzymatic degradation appears safe and

can boost both haemoglobin and HbF. (189) A large global randomized clinical trial has recently begun enrolment (NCT05405114).

3.3.2. Anti-sickling compounds

Since the initial demonstration almost 50 years ago that polymerisation of deoxy HbS is the first and essential step in SCD pathophysiology, the search for therapeutic agents with anti-sickling activity and clinical efficacy has been largely unsuccessful. Very recently, however, several new mechanisms and compounds have become available that offer that promise to interrupt this critical early step of erythrocyte sickling.

3.3.2.1. Increased oxygen affinity

Voxelotor is an FDA and and EMA approved once daily oral small molecule that reversibly binds to haemoglobin to increase the oxygen affinity of haemoglobin, and stabilize the oxygenated haemoglobin state. In a global, double-blind, randomized, placebo-controlled trial, voxelotor met its primary clinical trial endpoint of an absolute haemoglobin increase of at least 1.0 g/dL (1,500mg *vs*. placebo; 59% *vs*. 9%). (190) Common side effects include headache, diarrhoea, and abdominal pain. Safety and efficacy on haemoglobin level were also demonstrated in children aged 4 to 11 years. Trials aimed at defining a clinical benefit such as arterial cerebral blood flow (NCT04218084) and delayed progression of nephropathy (NCT04335721) are currently underway. Additionally, GBT021601, a highly potent, second generation HbS polymerization inhibitor shown in SCD mouse models to normalize haemoglobin has recently entered early-stage clinical trials. One important concern is that a left-shifted oxygen dissociation curve could inhibit oxygen delivery to tissues. (191)

3.3.2.2. Pyruvate Kinase activation

Haemoglobin polymerisation and red cell stability is modified by erythrocyte metabolites adenosine triphosphate (ATP) and 2,3-diphosphyglycerate (2,3-DPG). Activation of erythrocyte pyruvate kinase lowers 2,3-DPG levels, which increases haemoglobin oxygen affinity and inhibits HbS polymerisation. Additionally, increased pyruvate kinase activity leads to higher erythrocyte ATP levels, improving many aspects of erythrocyte health and potentially reducing haemolysis. Two oral small molecule pyruvate kinase activators, FT-4202 (192) and mitapivat, (193) are currently under investigation for safety, tolerability and efficacy in adolescents and adults with SCD (NCT04624659, NCT04000165). Pyruvate kinase activation might also reduce ineffective erythropoiesis, which could provide additional benefits for patients with SCD. (194)

3.3.3. Additional therapeutic approaches

3.3.3.1. Anti-adhesion agents

Adhesive interactions among leukocytes, reticulocytes, endothelial cells, and platelets are all contributory to SCD-related vaso-occlusion. Evidence supports a key role for membrane-bound selectins in mediating adhesion. Accordingly, selectin inhibition has been a major therapeutic focus for both prevention and treatment of acute vaso-occlusive pain. Rivipansel, a monoclonal pan-selectin inhibitor, failed to demonstrate statistically significant improvement over placebo in reducing the length of an acute VOC in hospitalised patients, although a recent phase 3 clinical trial indicated that the timing of rivipansel administration after the onset of pain onset may be

critical for accelerating acute VOC resolution (NCT02187003; NCT02433158). At the moment, there is no evidence that rivipansel is an effective treatment in SCD and it should not be used unless as part of a clinical trial. In contrast, prophylactic monthly treatment with crizanlizumab, a monoclonal anti-P-selectin antibody, significantly reduced VOE pain compared to placebo, which led to US-FDA and EMA approvals. Studies at higher doses (NCT03814746), in children (NCT03474965), and for the prevention of priapism (NCT03938454) and progression of renal disease (NCT04053764) are ongoing. Inclacumab, a fully humanized and potentially more potent monoclonal anti- P-selectin antibody, is under investigation in adults with a 3-month dosing interval for VOC prevention (NCT04935879) and a one-time dose following an admission for acute VOC to reduce re-hospitalisation (NCT04927247).

3.3.3.2. Anti-platelet agents and anti-coagulants

Because SCD is known to be a hypercoagulable state with widespread inflammation, which contributes to vaso-occlusion and vasculopathy through *in vivo* fibrin formation, the potential therapeutic role of anti-platelet agents and anticoagulants has been considered. However, meaningful clinical trials have been limited by concerns over bleeding risks, especially intracranial. Sevuparin, a low molecular weight heparin, was recently shown to have no benefit for reducing the duration of acute VOC episodes in hospitalized patients. (195) Prasugrel, an oral anti-platelet agent, did not show benefit in reducing the rate of VOCs in children ages 2 to 17 years with SCD. (196) Whether other similar agents such as clopidogrel or even rivaroxaban have utility in SCD will require further investigation.

3.3.3.3. Agents targeting vasculopathy, inflammation, and iron

A wide variety of additional therapeutic compounds have potential benefit for SCD. Hemopexin (CL889), canakinumab, IVIG, simvastatin, omega-3 fatty acid supplementation, the endothelin receptor antagonist ambrisentan, and complement inhibitor crovalimab are under consideration for clinical trials in the near future. An oral ferroportin inhibitor (vamifeport) has some reported benefits in a murine model. (197) Vitamin D has myriad effects and has been purported to reduce infections and VOC. (198)

3.3.3.4. Glutamine

L-glutamine was approved by the FDA in 2017 to reduce acute complications of SCD in adults and children 5 years and older. This was based on a randomized double-blinded placebo-controlled trial that demonstrated a reduction in median annual VOE rate (3 *vs* 4, p=0.0005), time to 1st VOE (2.8 *vs* 1.8 months, p=0.02), and time to 2nd VOE (7 vs. 4.4 months, p=0.03). (22) Side effects were mostly gastrointestinal likely due to the powder formulation of the medication and limited medication adherence. Based on that trial, L-glutamine was approved by the FDA in 2017 to reduce acute complications of SCD. However, the molecule was rejected by the EMA in 2019 and no additional data on the clinical benefits of L-glutamine have been published since the original study.

3.4. Considerations for low-resource settings

LMICs have both the highest number of SCD births and the least access to disease-modifying treatments, especially transfusions and hydroxyurea the most common disease-modifying treatments. In SSA, where the

prevalence of SCD is particularly high, these treatments are essential and life-saving. Transfusions are especially important for the management of acute clinical complications that require emergency care and hospitalisation, while hydroxyurea can reduce the incidence of acute complications, including painful VOC, ACS, infection, stroke and death, whilst also preserving organ function.

Due to high demand, low supply and blood safety issues, all countries in SSA fail to collect enough blood to meet their transfusion needs and have frequent shortages. Individuals with SCD are especially affected by such shortages, since available units are used in other life-threatening emergencies related to obstetrics, trauma, and malaria, especially in the under-5s. (199) In a recent questionnaire-based study of 31 sickle cell centres in Nigeria, 78% of hospitals were unable to transfuse patients with SCD regularly due to blood scarcity. (200)

Several modifiable factors contribute to the inadequate blood supply for SCD patients in many African countries. For logistical and cultural reasons, a very low percentage of individuals living in LMIC donate blood; according to 2015 WHO data, the median blood donation rate in LMIC is three to ten-fold lower than in HICs. (199) Donation may be also limited by nutritional deficiencies, mainly iron deficiency, in potential blood donors. Blood donations in LMICs often come from paid donors and replacement donations (family members donate blood to replace that used by their relative), but less frequently from voluntary unpaid donors.

In addition to blood scarcity, there are serious concerns about the quality of blood and related monitoring systems. Most blood collected in LMICs undergoes laboratory testing only to identify the ABO group and RhD type, without any screening of serum to identify antibodies that might affect the transfusion. (200, 201) In addition, transfused blood units are often selected by ABO/RhD typing alone, without a formal cross-match to ensure accuracy in testing and labelling. Moreover, in some low-resource countries whole blood transfusions are still performed, further increasing the risk of alloimmunization and transfusion reactions. Better phenotyping, screening, and cross-matching are needed to decrease the risk of developing acute and delayed haemolytic transfusion reactions.

Transfusion safety must also be addressed because especially in SSA, blood is not always tested for blood-borne pathogens such as HIV, hepatitis B and C, and syphilis. Rapid diagnostic tests are sometimes available, but have variable reliability, and consequently transfusion-transmitted infections remain a substantial concern for families and patients with SCD. Moreover, safe blood transfusions are often expensive, and not affordable for many families. Finally, national SCD guidelines need to be developed to include the appropriate indications for transfusion in a particular country, which may well be different from guidelines currently used in Europe and North America. Treatment recommendations should consider the scarce and potentially unsafe blood supply; previous transfusion thresholds and volumes have recently been challenged. (202)

Given the myriad of challenges toward ensuring a safe and reliable blood supply for SCD globally, wider use of hydroxyurea is an attractive treatment alternative. Decades of consistent and compelling data confirm its safety, efficacy, and effectiveness in adults and children with SCD. After suitable dose escalation to achieve mild myelosuppression, hydroxyurea can significantly reduce rates of VOE, ACS, hospitalisation, and transfusion even in low-resource settings. (176) Reports from Africa are now also documenting its benefits for primary and

secondary stroke prevention. (203) Hydroxyurea is a relatively cheap drug, and has been listed by WHO as an Essential Medicine for over a decade, and is recommended for both children and adults with SCD.

Despite this, hydroxyurea is only minimally used in many LMIC. Challenges for the effective introduction and utilisation of hydroxyurea have been recently described but primarily relate to the lack of drug availability and affordability in low-resource settings. (204) Lack of drug registration with national drug authorities is another potentially limiting factor, although hydroxyurea is already registered in many countries for the treatment of chronic myelogenous leukaemia. Lack of national treatment guidelines is also limiting, although several countries are now generating their own guidelines that are based on published treatment guidelines from the US and Europe. Lack of prescriber familiarity with hydroxyurea, including the need for monitoring blood counts and dose adjustments is another significant factor, but one that is amenable to training. Cost of the drug itself and associated laboratory monitoring is also prohibitive for many families in LMICs, but recent efforts by pharmaceutical companies to lower prices may bring treatment closer to the affordable range.

Hydroxyurea has become the standard of care for SCD in HICs. To work toward health equity for SCD, it must be introduced widely in LMICs, especially SSA. To achieve this goal, urgent efforts should be made to address the lack of treatment guidelines, inadequate clinical infrastructure and training, and drug accessibility and affordability. (204) As an example worthy of mention, the public healthcare system of Brazil, a middle-income country, now offers universal newborn screening for SCD, and transfusions and hydroxyurea are available free of charge in several specialised centres across the country. Before new expensive treatments can be considered for SCD in low-resource settings, including potentially curative treatment options, hydroxyurea must first become widely available.

3.5. Recommendations on established and emerging treatments

Currently, effective treatment requires access to prophylaxis against and treatment of infections, hydroxyurea and safe blood transfusions. **Table 3** summarises recommendations for basic care, based on the consensus guidelines from the USA, UK and France. Although some LMICs, such as Uganda, Tanzania or Kenya, do have national guidelines, these tend to be aspirational and based on the recommendations summarised in this table. (205) Although precise figures are not available, the majority of patients in the world do not have access to this basic level of care. We therefore recommend that policies and resources focus on providing access to these treatments for all patients across the world, with a particular goal that affordable hydroxyurea is available to all patients by 2030. It is important that further new treatments are developed, and that they are tested in all appropriate healthcare settings, and are made affordable to all patients and healthcare systems throughout the world.

Table 3. Summary of consensual expert guidelines and national guidelines in the USA, UK, and France for various complications of SCD

	Consensual expert guidelines	**UK national guidelines (2nd edition, 2018) (206)**	**France national guidelines (2nd edition, 2015) (157)**	**USA national guidelines (NIH 2014, ASH 2020) (156)**	**Level of evidence***
RETINOPATHY					
Monitoring	Retinal examination after 10 years old	- Every year in asymptomatic SC patients and on desferoxamin/deferasirox - More often in symptomatic patients or with history of ophthalmopathy - Every 2 or 3 years for other patients	At least every year for all patients, + slit lamp, colour vision and electroretinogram if treatment with deferoxamin or deferasirox	Every 1-2 years if normal	Very low
Prevention	Laser photocoagulation if proliferative retinopathy	- No intervention required for small, asymptomatic neovascular fronds - Consider treatment for large, elevated sea fans, rapid growth of retinal neovascularisation	Photocoagulation of ischemic zones	Photocoagulation in stage III retinopathy	Moderate
Treatment	Vitreoretinal surgery		Surgery under local anaesthesia, oxygenotherapy, no		Low

	in case of vitreous haemorrhage or retinal detachment		acetazolamide, no sympathomimetic, discuss transfusion		
OSTEONECROSIS					
Monitoring	- Imaging only if intermittent or chronic hip pain - Start with plain radiographs - Perform MRI if normal Xray and persistent symptoms or before surgery				Low
Treatment -early stages (I or II stage)	Conservative management: physiotherapy, walking aid	Injections of local anaesthetic into the joint	Consider HSCT in the femoral head	Not mentioned	Very low
Treatment-advanced stages	Joint replacement surgery	- Prefer the use of cementless prosthetic devices. - Prophylaxis of post-operative infection and thrombosis	Not detailed	Not detailed	High
PRIAPISM (RECURRENT/STUTTERING)					
Prevention	Hydration			Avoid tobacco and hashish, night oxygen if nocturnal desaturation	Very low

Treatment	Hydration, exercise and urination, pain killer, alpha agonists and anti-androgens		Hydration, exercise and urination, pain killer, alpha agonists and anti-androgens + consult a urologist	Blood letting to maintain Hb<10 g/dl in SS, 11 g/dl in SC, referral to a psychologist	Very low
LEG ULCERS					
Monitoring	Clinical, look for veinous insufficiency and infection				
Prevention	Eat a nutritious and well-balanced diet; local moisturisers; wear socks and well fitted shoes, insect repellents; avoid injury; treat minor trauma quickly, avoid blood test or IV lines in the lower limbs, wear compression stocking				Very low
Local treatment	Debridement, moist wound surface,		Alginate phase cleaning, then vaselinated bandages then hydrocelllar dressings +/- discuss negative pressure (VAC) with surgeons		Low
Other	Antibiotics	Not detailed	Reserved to culture-proven bacterial infections	Reserved to culture-proven bacterial infections	Very low
	Pain management, compression, bed rest	Pentoxiphilin for marge veinous ulcers, zinc supplementation if zinc deficiency, do not stop hydroxurea	Sulfate de zinc can be tried, discuss a reduction of hydroxyurea dose, try local injection of GM-CSF	Not mentioned	Very low
Transfusion	Trial of blood transfusion if untractable ulcer			Not mentioned	Very low

Surgery	Microsurgery with free flap transfer and skin grafting for some intractable ulcers			Not mentioned	Very low (high risk of failure)
PULMONARY HYPERTENSION (PH)					
Monitoring	Cardiac echography with measure of TRV	At least once at adult age then every 3 to 5 years if normal or every year if TRV>2.5 m/s	At least once at adult age then if evocative clinical signs	If suggestive clinical signs (exercice intolerance, chest pain, fatigue, oedema)	Low
	If TRV>2.5 m/s	Refer to PH center if >2.9m/s or if >2.5 m/s + raised NT-proBNP or reduced 6min walk test	To be repeated after 6 months if TJV >2.5 m/s, right heart catheterization if >2.8 m/s at 6 months	Echography confirmed by right heart catheterization	Moderate
Work out	Only for symptomatic patients	ECG, look for chronic lung disease (chest radio, pulmonary function test, 6 min walk test, arterial blood gas), thromboembolism, HIV, sleep disordered breathing, autoimmune disease, hypertension, renal and liver function			Moderate
Treatment		Consider disease modifying therapy with hydroxyureaor blood transfusion vasodilator therapy for selected patients with precapillary PH under the supervision of PH specialist	Consider blood exchanges or hydroxycarbamide, refer to PAH specialist, avoid sildenafil (triggers VOC), anticoagulation if no Moya Moya	Refer to PAH specialist	Low

NEPHROPATHY					
Monitoring	Microalbuminuria + proteinuria every year				Low
Prevention of CKD: general measures	High fluid intake, especially if hyposthenuria, avoid NSAID	NSAIDs should be avoided in patients with stage 3-5 CKD; Blood pressure target of <130/80 mmHg if ACR >3.5 mg/mmol	Avoid NSAIDs in all adults systolic blood pressure target <130 mmHg, add anticalcic if necessary,	Not mentioned	Low
Prevention of CKD	ACE inhibitors or angiotensin receptor blockers	If uPCR >50 mg/mmol + add hydroxyurea	If macroalbuminuria or proteinuria + avoid NSAID and iodide	In adults, if microalbuminuria or uPCR	Moderate
Treatment of CKD	Usual treatment of CKD renal replacement if needed		Non contraindication for renal transplant unless another organ failure reduces life expectation <2 years		Low
Haematuria	High fluid intake, refer to urologist	Look for renal (medullary) carcinoma, calculi or non-sickle related glomerular disease	Look for renal cancer or renal venous thrombosis, consider desmopressin if massive	Not mentioned	Very low
CEREBRAL VASCULOPATHY/STROKE					
Monitoring	Annual transcranial Doppler velocity (TCD) in SCD children	Inadequate evidence to recommend routine	Brain angio IRM or CT at least once at adult age	Perform IRM and ARM at least once at children and adult age	Moderate for TCD in SS or

	and at least one brain IRM in SS/Sbeta0 adults	screening by TCD or brain MRI to predict stroke risk in adults			Sbeta0 pts, low for other genotypes, low for imaging
Primary prevention in case of abnormal TCD	Long term exchange transfusion therapy in children with abnormal TCD (objective = HbS<30%)	Hydroxyurea after normalization of TCD even in adults; management of risk factors for stroke (hypertension, anaemia, chronic lung disease, avascular necrosis, retinopathy)	Long term exchange programme until 18, unknown duration at adult age, no antiaggregant or anticoagulant in case of Moya Moya	Maintain the haemoglobin level >9.0 g/dL) . Hydroxyurea if long term exchange transfusion therapy not possible or after one year	High for SS/Sbeta 0, low for other genotypes
Secondary prevention after a stroke	Long term exchange transfusion therapy (objective = HbS<30%)	To be continued in adulthood; NSAID as per non SCD patients; in adults with silent infarction or overt stroke, offer interval MRI scanning: consider intervention if there is progressive ischaemia or discuss stopping exchanges if no progression.	Long term exchange program in children, unknown duration in adults, no antiaggregant or anticoagulant in case of Moya Moya	Exchange transfusion monthly (haemoglobin above 9 g/dL at all times) or HU if regular exchanges are not possible. Multidisciplinary evaluation for revascularization surgery in addition	Moderate for exchange transfusion, very low for revascularizatio n

		Consider hydroxyurea when transfusion is not possible or acceptable			
COGNITIVE IMPAIRMENT					
	Surveillance in children and adults	Use simplified signalling questions. cognitive and medical evaluation to diagnose any related disorders and to identify modifiable risk factors for developmental delays or cognitive impairments	Not mentioned	Refer the patient to a specialist who may better evaluate the magnitude of the cognitive impairments and provide rehabilitative approaches	Low
CHRONIC PAIN					
Pharmacological treatment		- Use opioid with caution, avoid escalating doses, identify key prescriptors, elaborate a prescribing plan	Not mentioned Opioid use strongly discouraged at home	No specificity for SCD: follow the general guidelines for chronic pain	Low

		with chronic pain team and GP - Atypical analgesics are useful (gabapentin, amitriptyline, pregabalin, duloxetine)			
Other therapies		Cognitive behavioural therapies or acceptance based approaches (need further evaluation)	Not mentioned	Not mentioned	Very low
PSYCHOTHERAPY					
	Psychologists should be an integral part of multidisciplinary teams for the management of SCD	- Routinely assess a patient's desire for psychological intervention/support -encourage patients to practice cognitive behavioural therapies techniques such as relaxation - specialist staff should be aware of the importance of psychosocial issues and	Propose psychological assessment during hospitalization or in case of recurrent VOC or severe morbidity Cultural issues must be taken into account since many children are migrants or children of migrants.	Not mentioned	Very low

		have access to training, support, consultation or supervision from a psychologist			

*gradation of evidence quality using the same methods as in Yawn *et al*. JAMA 2014 (147).

ACE=angiotensin converting enzyme. CKD= chronic kidney disease. ECG= electrocardiogram. NSAID=non steroid anti-inflammatory drugs. PH=pulmonary hypertension. TCD=transcranial Doppler. TRV=tricuspid regurgitant velocity. uPCR=urine protein creatinine ratio. VOC=vaso-occlusive crisis. proBNP: N-terminal pro B-type natriuretic peptide

Section 4: Management – Cellular therapies

4.1. Allogeneic haematopoietic stem-cell transplantation

4.1.1. HLA matched sibling hematopoietic stem-cell transplantation

Haematopoietic stem-cell transplantation (HSCT) for SCD using an HLA matched sibling donor (MSD) was first described in 1984 in a child with AML and SCD. Since then, the approach has become the most common and arguably most effective cure for SCD. Recent investigations have focused on reducing toxicity without impacting curative potential. (207)

4.1.1.1. Myeloablative conditioning based approaches

Myeloablative conditioning based HSCT was developed as a treatment for children using busulfan and cyclophosphamide became the predominant approach in the late 1990's and early 2000's. Outcomes were promising in these early studies with event-free survival (EFS) around 84-86% and overall survival (OS) of 93-94%. (208) A number of refinements led to an increase in EFS to 98% in patients under 30 years and 100% survival in the under 5 age group. Now considered a standard of care at many centres worldwide, myeloablative MSD HSCT provides a high chance of cure, with immunological complications like graft-versus-host disease (GVHD) occurring in only a minority of patients and less than 5% needing long term systemic immune suppression. (209)

Generally, short-term toxicities of HSCT are reversible, but the morbidity associated with myeloablative conditioning can negatively impact the quality of life during the peri-transplant period. Although infrequent, long-term risks of myeloablative conditioning-based HSCT could include increased risk of secondary cancer, infertility, exacerbation of SCD-induced organ dysfunction, and metabolic syndrome. (3)

To minimize the toxicity associated with MSD HSCT, several less intense regimens have recently been developed. The well-tolerated immunosuppressant fludarabine has been incorporated into conditioning regimens to limit the need for alkylating drugs that are responsible for the toxicity of myeloablative regimens. A commonly used reduced intensity conditioning (RIC) regimen is a combination of fludarabine, the lymphodepleting antibody alemtuzumab and the alkylator melphalan. This low-toxicity regimen has a similar disease-free survival compared to busulfan based myeloablative regimens. There is some preliminary data suggesting that fertility may be preserved in females because this reduced toxicity regimen limits alkylator exposure. (3)

4.1.1.2. Non-myeloablative

Non-myeloablative regimens are sufficiently low intensity such that, following conditioning, in the absence of a donor stem cell infusion, autologous blood count recovery occurs universally. Adult patients with SCD have suffered cumulative organ injury, making the use of higher intensity conditioning regimens untenable due to the risk of further organ damage during HSCT. However, the nonmyeloablative alemtuzumab and low-dose total body irradiation-based approach has now been shown in a primarily adult cohort of 122 patients to have an OS of 93% and EFS of 85% at 5 years. (210) Similarly encouraging results have been reported in 16 paediatric patients with an OS and EFS of 100% and is being studied further in a Phase 2 trial (NCT03587272). (211) While toxicity

is minimal and there have been no cases of severe GVHD reported, the long-term effects are still to be examined and are of particular importance in the paediatric population.

4.1.2. Alternative donor HSCT

As the chance of a patient with SCD finding a MSD is approximately 15%, alternative donor HSCT has been investigated to increase the donor pool. To date none of the alternative donor HSCT approaches are comparable to the current success of MSD HSCT, but significant improvements have been made in the last decade. Investigation into adapting conditioning and GVHD prevention continue.

4.1.2.1. Unrelated bone marrow donors

Unrelated bone marrow derived graft from 8/8-HLA-matched donors was investigated on the BMTCTN 0601 trial. The observed two-year EFS of 69% in this paediatric cohort of 29 patients was lower than the contemporary MSD HSCT and was attributed to the high rates of GVHD (69% chronic GVHD, of which 38% were classified as extensive). (212) Recently, 7/8 HLA-matched donors have been investigated to address the challenges of finding an 8/8 donor. To address the risk of GVHD, the co-stimulatory blockade agent abatacept is being evaluated as a part of the GVHD prophylaxis regimen in several studies with promising results. (213)

4.1.2.2. Unrelated cord blood

Historically, graft failure was an issue in unrelated cord blood transplants for SCD occurring in about 50% cases. However, in a Phase I study of 9 patients, the addition of thiotepa to an alemtuzumab, fludarabine, melphalan based regimen improved the sustained engraftment rate to 78%. (3) Cell dose requirements limit the use of cord blood HSCT to smaller patients usually around 4 years of age. To address this limitation, ex-vivo culture expansion of cord units for transplant has been recently investigated in clinical trials. In a study of cord units expanded with nicotinamide-derivative, the median age of HSCT recipients was 13 years and an 85% EFS was observed in patients receiving an expanded plus un-expanded double cord transplant. (214) Further investigation is required to assess the applicability of this approach for older patient populations.

4.1.2.3. Haploidentical donors

The advantage of using HLA-half-matched related or haploidentical donors is that most patients have such a donor in the form of a parent. However, the inherent risks of severe GVHD and rejection with HLA-mismatched donors have plagued early studies. Currently two approaches for HSCT using haploidentical donors are being employed, and recent results are encouraging. (3)

4.1.2.4. Post-transplant cyclophosphamide

Initial results with this approach using a non-myeloablative conditioning regimen resulted in only about 50% being disease-free post-HSCT. (215) With the addition of thiotepa to a reduced intensity regimen, 93% EFS and 100% OS were seen in 15 patients with only one developing mild chronic GVHD. A multicentre study is ongoing to verify these results (NCT03263559).

4.1.2.5. Ex-vivo graft manipulation

Historically, this approach was impacted by both severe GVHD and graft rejection with only half of patients being cured. Two recent studies using a CD34+ cell selection have shown OS and EFS of 84-90% and 69-90%. (216, 217) Future investigations will likely utilize more modern manipulation methods that better maintain cells in the graft that are important to engraftment and immune recovery.

Panel 2. Essential medications for haematopoietic stem-cell transplantation (HSCT)

- Filgrastim
- Ceftazidime
- Cefepime
- Vancomycin
- Fluconazole
- Magnesium sulfate
- Levetiracetam
- Amlodipine
- Hydralazine
- Labetalol

4.1.3. Conclusion:

MSD HSCT using myeloablative conditioning is now a standard curative approach requiring a relatively small number of essential medications (**Panel 2**) and future investigations are expected to focus on lessening toxicities by reducing the intensity of conditioning regimens. Alternative donors are however needed for most patients with SCD seeking cure and new approaches to make these transplants safer is an area of active research.

4.2. Gene Addition Therapy

Despite improving outcomes, allogeneic transplant may still not be a feasible option for many SCD patients, so genetic modification of autologous hematopoietic stem and progenitor cells (HSPCs) has become an area of rapidly expanding interest for the haemoglobinopathy community. Autologous genetic therapies offer two major benefits over allogeneic HSCT: eliminating the need to find a suitable donor, and eliminating the risk of GVHD and immune-mediated graft rejection. *Ex-vivo* viral-based gene therapy has now amassed broad experience in treating genetic disorders including immunodeficiencies, neurodegenerative disorders and bone marrow failure syndromes. (218) Early experience with gammaretroviral and early lentiviral vectors demonstrated proof of principle by effectively supplying the gene that was lacking in ADA and X-lined severe combined immunodeficiency (SCID), (219, 220) but the field suffered a setback when insertional mutagenesis led to acute leukaemia in multiple patients. (221) Alterations were made to vector design, and a new generation of self-inactivating lentiviral vectors has proven well-tolerated and effective, thus far without evidence of insertional oncogenesis. More than 300 patients have now been treated with HSPC gene therapy in clinical trials. (222) Haemoglobinopathies are particularly well-suited to correction by gene therapy because even a partial correction of the defect can lead to major clinical benefit. A gene therapy product using the addition of a modified β-globin gene to treat transfusion-dependent β-thalassemia was among the first to receive regulatory approval by the EMA and the FDA. (223)

Strategies of lentiviral gene therapy for SCD include either the addition of an exogenous globin gene that will pair with α-globin to produce a non-sickling haemoglobin, or the addition of a regulatory construct that will act on the cell's endogenous globin genes to switch expression from the mutated β-globin to γ-globin, thus inducing production of HbF. Regardless of the strategy, the metrics of success in a gene therapy trial include: i) features of the medicinal product such as cell number and vector copy number (VCN); ii) quantification of the non-sickling haemoglobin; iii) clinical outcomes; iv) durability; and v) avoidance of adverse events.

The gene therapy treatment process is similar in all open clinical trials. First, autologous HSPCs must be collected from the patient. After early attempts to collect HSPCs directly via bone marrow harvest resulted in poor cell yield, several studies demonstrated that the CXCR4 antagonist plerixafor could effectively be used as a single-drug stem cell mobilizing agent followed by collection using apheresis in SCD patients. (224, 225, 226) After collection and selection of CD34+ cells, transduction with the lentiviral vector is performed. After clinical release criteria are met (including, among other features, sufficient VCN in the product and adequate cell number), the modified cells are infused in the patient after preparation with an alkylator-based (generally Busulfan) conditioning regimen.

Clinical trials that have reported initial results after treating SCD patients with lentiviral gene therapy are listed in the text below, and all SCD GT trials registered as enrolling are shown in **Table 4**.

4.2.1. LentiGlobin – addition of modified β-globin gene

In 2008, the first haemoglobinopathy patient was treated with gene therapy using a vector called HPV569 that delivered a modified β-globin gene ($\beta^{A(T87Q)}$) designed to inhibit HbS polymerization. (227, 228) Subsequent modifications to this vector resulted in the vector LentiGlobin BB305. (229) This vector is first being tested in SCD patients in the Phase 1/2 HGB-206 trial (NCT02140554) with interim results presented at major haematology meetings in recent years. (230) In an initial cohort of seven patients (referred to as "Group A"), the subjects all engrafted but CD34 cell yield and peripheral VCN was low. (231) Study modifications were put into place for later cohorts, including addition of a transfusion regimen prior to collection of autologous cells, alteration of the transduction protocol to increase VCN, and use of peripheral stem cell mobilization instead of bone marrow harvest for collection of CD34+ cells. A publication of the latest cohort in this trial (referred to as "Group C") noted that 25 patients had been treated. Of 16 patients with at least six months of follow-up, total haemoglobin was 11.5 (9.6-16.2) g/dL with median HbS ≤ 60% of total haemoglobin. 14 patients with ≥ 6 months of follow-up had 4.0 (2.0-14.0) episodes per year of VOC or ACS during the two years prior to treatment, and these patients had no ACS or serious VOCs after treatment. (232, 233)

4.2.2. BCH-BB694 – knockdown of *BCL11A* to increase HbF

The protein BCL11A (B cell lymphoma/leukaemia 11A) is an important developmental regulator of both the initial haemoglobin switch from γ-globin to ß-globin expression in infants and young children, and of the persistent silencing of γ-globin expression in adults. BCL11A, a zinc-finger protein encoded by a gene on chromosome 2p15, was not a known regulator of globin expression. In 2007-2008, genome-wide association studies (GWAS) reported that variation at the *BCL11A* locus is responsible for a significant degree of the variation

in HbF levels. (234, 235) Preclinical studies demonstrated that down-regulation of *BCL11A* expression in adult human erythroid precursor cells, (236) and inactivation of BCL11A in a sickle cell mouse model, (237) resulted in HbF induction and correction of the SCD defect. These data made clear that inactivating BCL11A in patients with β-haemoglobinopathies would hold promise as an effective way to increase levels of HbF, and thus to decrease disease severity. A current clinical trial is utilizing lentiviral gene therapy to downregulate *BCL11A* in HSC-derived erythroid precursors via shRNA knockdown. The vector in this study, BCH-BB694, is driven by β-globin promotor and regulatory sequences to ensure that expression is limited to the erythroid lineage. The vector contains a short hairpin RNA (shRNA) targeting *BCL11A* embedded within an endogenous microRNA scaffold. Data from the first six patients (ages 7-25 years old) with a follow-up of 7-29 months showed that total HbF as a component of the total haemoglobin [HbF/(HbF+HbS)] was 21-42% at last follow up, and HbF was broadly distributed based on F-cell percent of 59-94%. Treatment was well-tolerated without safety concerns beyond expected adverse effects of conditioning. (238)

4.2.3. ARU-1801 – addition of γ-globin gene

In 2018, two patients were treated with autologous cells containing a modified γ-globin transgene. Data presented in 2020 showed HbF levels of 22% in the first two patients at 30 months after treatment, but with only 31% F-cells. A third patient has been treated after modifying the manufacturing process with improvement in cell number and VCN in the product and early suggestion of improved transgene production. (239)

4.2.4. Long-term safety

Long term safety is one of the most critical questions that must be investigated for all novel genetic therapies. With the newer generation of lentiviral vectors, insertional oncogenesis has not been reported, however careful monitoring of clinical status and insertion site analysis is required, typically for 15 years after treatment. However, vector-mediated insertional mutagenesis is not the only cause of malignancy risk in trials of autologous genetic therapy. In February 2021, the LentiGlobin lentiviral SCD gene therapy trial was temporarily halted due to a reported suspected unexpected serious adverse reaction (SUSAR) of acute myeloid leukaemia (AML). Earlier, another patient had been reported in 2020 to have developed myelodysplastic syndrome three years after infusion of the genetically modified cells. (240) In that patient however, lack of vector within the blasts indicated that vector insertion was not implicated in leukemogenesis, and this was presumed to be secondary to busulfan-related genotoxicity. The second patient developed AML 5.5 years after gene therapy. In this case, the blasts did contain the vector and transgene, but there was no evidence that this integration was a driver of the malignancy. Therefore, additional investigation is needed to fully understand why at least two out of 47 SCD patients (4.25%) treated (241) with lentiviral gene therapy have developed AML, including the possibility of an underlying increased malignancy risk in SCD, and whether there are ways to mitigate this risk.

Table 4. Overview of ongoing or recently completed gene addition therapy studies

Strategy	Modality	Lead group	Status	Clinical trial number	Results	References
Globin gene addition	Addition of modified β globin gene β^{T87Q} (LentiGlobin = lovotibeglogene autotemcel; bb1111)	bluebird bio	Phase 3; recruiting	NCT02140554 and NCT04293185	35 Group C patients infused by 7/2021 with a median duration of follow-up 20.9 (range 8.5-28.5) months. 28 of 29 evaluable patients were free of severe VOEs.	(232)
Globin gene addition	Addition of gamma globin gene (ARU-1801)	Aruvant	Phase 1/2; not recruiting	NCT02186418	As of 11/2021, 4 patients infused. 3 patients with >12 mo follow up had reduced or absent VOEs.	(242)
Globin gene addition	Addition of modified β globin gene βAS3 (DREPAGLOBE)	Assistance Publique - Hôpitaux de Paris	Phase 1/2; not recruiting	NCT03964792	No clinical trial results posted yet.	
Globin gene addition	Addition of modified β globin gene βAS3-FB	UCLA	Phase 1; recruiting	NCT02247843	No clinical trial results posted yet.	
HbF induction	shRNA knockdown of *BCL11A* gene (BCH-BB694)	Boston Children's Hospital	Phase 2; recruiting	NCT03282656 and NCT05353647	10 patients infused infused by 11/2022 with a median duration of follow-up of 30.5 (range 2-50) months. 9 of 10 patients had reduced or absent VOEs.	(238)

4.3. Gene Editing

Editing the genetic code to correct disease causing mutations has been the holy grail of molecular genetics. Monogenic disorders, especially those due to single point mutation such as SCD, are the most amendable to genetic code correction. Several groups had previously attempted, and many successfully achieved correction of the SCD mutation in primary human CD34+ cells or induced pluripotent stem cells (iPSCs) using zinc-finger nucleases (ZFNs) or transcription activator-like effector nucleases (TALENs). (243) However, the advent of precise and efficient, programmable, clustered regularly interspaced short palindromic repeat (CRISPR)associated protein 9 (Cas9) system has fast forwarded genome editing to treat SCD from the laboratory bench to the bedside. (244, 245) Novel genome editing techniques along with the newfound understanding of the genetic regulation of the globin-like genes have ushered in an era of therapeutic genetic manipulation to treat SCD. There are several target sites and gene editing methods that are currently being investigated to either increase HbF or change the sickle mutation, (243, 244) and many new editing tool-target site combinations are being constantly described in the literature.

While the direct correction of the mutant SCD codon (GTG, coding for valine), either to normal (GAG, coding for glutamic acid) or to another benign, non-sickling variant is most desirable, it has some inherent technical challenges (described below). (244) However, reversing the haemoglobin switch has been a rather simplistic and achievable alternative. Induction of HbF as a therapeutic strategy for SCD is based on the observation that individuals with SCD who co-inherit hereditary persistence of foetal haemoglobin (HPFH), a naturally occurring benign genetic condition which results in persistently elevated HbF levels, exhibit few or no SCD effects. (246) HbF inhibits HbS polymerization. (247) Additionally, induction of γ-globin genes (*HBG1/2*) leads to competition with β-globin gene (*HBB*) locus for the locus control region (LCR), a globin gene enhancer, which results in suppression of the mutant HBB^S gene expression. (248, 249) Several genome editing methods have been developed that induce HbF to levels sufficient to ameliorate SCD pathologies. These genome editing methods that induce HbF are also less likely to induce globin chain imbalance, due to balanced production of β-like chains (β^S+γ), in comparison to the lentiviral gene addition approaches wherein the transgenic globin molecule is produced independently of the β^S production. Systematic evaluation of patients undergoing treatment with gene addition methods and genome editing techniques should assess for chain imbalance and resultant ineffective erythropoiesis from unmatched globin chain aggregate deposition.

There are four main genome editing based approaches, in various pre-clinical and clinical stages of development to treat SCD. These are listed in the order of those which are most advanced in clinical development to those which only have proof of concept pre-clinical data available below:

4.3.1. Conventional gene editing

Conventional gene editing approaches involve making a double stranded break (DSB) in the genome at a precise location. The DSB is then re-ligated by the DNA repair machinery of the cell, most frequently via the non-homologous end joining (NHEJ) pathway and rarely, in the presence of a template DNA, by homology directed repair (HDR). The NHEJ repair pathway leads to stochastic insertions or deletions (indels) which may disrupt

either the protein coding exon sequences or functional non-coding regulatory elements in the intronic DNA. This approach has been leveraged to disrupt the regulatory elements essential to globin switching from γ-globin *(HBG1/2)* - which is expressed during the foetal life, to ß-globin *(HBB)* - which is expressed during the adult life.

4.3.1.1. Editing of BCL11A erythroid specific enhancer

After GWAS led to the discovery of sequence variants in the gene *BCL11A* that are associated with elevated HbF levels, (250) BCL11A was identified as a potent repressor of HbF in humans. (236) Early genome editing attempts used ZFN to disrupt exon 2 of *BCL11A* by introducing bi-allelic frameshift mutations which led to complete inactivation of *BCL11A.* (251) However, global knockdown of BCL11A not only adversely affected erythroid maturation but also impacted hematopoietic stem cell expansion and engraftment. (251, 252) Later, pooled CRISPR screens for fine-mapping of the *BCL11A* intronic region identified a developmental stage-specific, erythroid lineage-restricted enhancer. (253) Canver *et al* further identified discrete vulnerabilities of these erythroid specific enhancers which could be disrupted to selectively decrease BCL11A transcription in the erythroid lineage while mitigating the HSC growth disadvantage resulting from complete BCL11A loss. (254) Given the specificity of BCL11A restriction by editing of the erythroid specific enhancer and the plethora of data on these enhancers that has been generated over the past decade, (255) this strategy has become the most widely adopted genome editing method and several individuals with SCD have been treated using autologous CD34 cells edited at this locus (Table 5). This approach is the most clinically developed and in phase III clinical trials currently. Several independent groups are using this approach to disrupt the erythroid specific enhancer of *BCL11A* using CRISPR/Cas9 (256) or ZFN. (257, 258) Both these nucleases have produced comparable preliminary data.

4.3.1.2. Editing of globin locus

Several cis-regulatory elements have been identified within the extended globin locus on chromosome 11, specifically in the *HBG1/2* promoters, where various repressors of HbF such as BCL11A (259, 260) and LRF/ZBTB7A (261, 262) bind leading to haemoglobin switching from *HBG1/2* to *HBB.* (263) Disrupting these transcription factor binding motifs using CRISPR-Cas9 has been considered as another potential therapeutic strategy for HbF induction. (264) While the efficacy and safety of the conventional gene editing approaches at the BCL11A erythroid specific enhancer and the globin locus have not yet been systematically compared, there are some key differences between these two genomic targets. Disruption of the regulatory elements in the *HBG1/2* promoters represents a more targeted approach than eliminating BCL11A expression in erythroid progenitors, which could potentially have deleterious consequences. Preliminary data suggest that disruption of the *BCL11A* erythroid enhancer in HSPCs could impair erythropoiesis. (265) *BCL11A* erythroid-enhancer edited cells were found to have an erythroid differentiation defect in a mouse model, and increased apoptosis during erythroid differentiation in *ex vivo* erythroid cultures. (265) Secondly, editing at the globin locus recapitulates some mutations that cause HPFH, which is a naturally occurring benign condition. Individuals with HPFH are not known to have any long-term adverse consequences affecting erythropoiesis. However, editing the *HBG1/2* promoters presents a challenge that optimal HbF induction may require efficient editing at four separate loci

(two *HBG1* alleles and two *HBG2* alleles) compared to editing of just two (or maybe even just one) alleles of the *BCL11A* locus. These challenges may not result in any clinically significant differences or adverse outcomes, but future clinical trials with correlative mechanistic studies to closely examine these different approaches are highly recommended.

There are at least two ongoing clinical trials, one using *Streptococcus pyogenes* Cas9 (SpCas9) (NCT04443907) protein and another using *Acidaminococcus* sp. Cas12a (AsCas12a) protein to create indels at the *HBG1/2* promoters. Preliminary results from the clinical trial using the SpCas9 for editing at the *HBG1/2* locus suggest clinically relevant HbF induction and symptom control in two patients who have undergone treatment so far. (266) This approach could be an alternative to the *BCL11A* erythroid-specific enhancer editing.

4.3.2. Precise correction of the sickle mutations

4.3.2.1. Homology directed repair for direct correction of the SCD mutation

Delivery of an extrachromosomal wild-type donor DNA sequence along with the nuclease allows the double-stranded (DSB) to be precisely corrected via the homology-directed repair (HDR) pathway. (267) This approach aims at replacing the sickle mutation with the wild-type sequence. (268, 269, 270, 271, 272) While it is indeed desirable to revert the genotype of the edited cells to 'normal' rather than to induce HbF, there are some inherent challenges associated with this method. High degree of SCD mutation correction by HDR based methods is challenging in HSCs given their quiescent nature. (271, 273) Concomitant formation of indels during the nuclease mediated DSB may disrupt the *HBB* reading frame leading to a thalassaemia phenotype. (271, 274) The delivery of an exogenous DNA template for HDR is not only challenging but also potentially cytotoxic to the HSCs. (275) Lastly, given the sequence homology between different globin-like genes, there is a high risk of off target editing. (245) At the same time, monoallelic correction may be sufficient to convert SCD to SCT phenotype. (245) Lastly, conversion to the wild-type sequence with subsequent production of adult haemoglobin would be the most desirable and natural resolution of SCD. While current nucleases are fairly precise in their targeting of the DNA to introduce break points, repair efficiency with HDR remains low and off-target breaks remain a concern. Reported attempts at HDR correction have reported modest success in xenotransplantation and non-human primate experiments. (269, 276) Perhaps insufficient to produce clinical benefit as they currently stand, these methods are likely to continue to improve as methods to enhance HDR frequency or selection of HSCs with the editing of interest are developed. (264) An ongoing clinical trial is attempting this approach in humans with no clinical results available yet (NCT04819841).

4.3.2.2. Base Editing

Base editors are the next generation of gene editing nucleases that directly introduce base changes without DSBs, thus bypassing the low-efficiency HDR as well as NHEJ mediated indels and off-target effects. (277, 278) Nuclease-induced DSBs activate the p53 damage-response pathway (279) which can result in prolonged cell-cycle arrest, compromise HSC viability, reduce repopulating potential, induce apoptosis, and sometime lead to TP53 gene loss which could promote malignant transformation of the edited cells. (280) Single base edits disrupting the GATA1 motif within the *BCL11A* erythroid enhancer (281) as well as editing of the *HBG1/2*

promoter disrupting the BCL11A binding motif in the *HBG1/2* promoters (282) led to potent induction of HbF similar to indels produced by conventional CRISPR-Cas9 editing at those respective sites. (283) A clinical trial exploring base editing of the *HBG1/2* promoters is ongoing and recruiting participants (NCT05456880).

While base editors are currently unable to execute a base change from T to A, required for correcting the sickle mutation to normal, recently, adenine base editors have been shown to effectively convert SCD codon (GTG) to a variant haemoglobin G-Makassar (Hb G-Makassar, codon GCG). (284) Hb G-Makassar is a rare naturally occurring, benign, non-sickling variant found in people in Southeast Asia. Individuals who are heterozygotes for Hb G-Makassar exhibit normal RBC indices. In a xenotransplantation model, this mutation successfully rescued the sickling phenotype of erythroid progeny of edited human CD34+ cells derived from donors with SCD. (284) This approach provides an efficient alternative to the HbF induction strategies but without introduction of DSBs.

However, given the novelty of base editing technique, little data exists on the guide RNA dependent and independent off-target activity of these nucleases, hence comprehensive off-target analysis needs to be performed before base editing moves to clinical application.

4.3.2.3. Prime editing

Prime editors are the latest generation of gene editors which can directly copy sequence information from a prime editing guide RNA (pegRNA) into a target DNA locus, thus introducing precise changes. (285) Prime editing has been shown to convert the SCD mutation to normal at relatively high efficiencies in HEK293 cells but requires further optimization for high frequency targeted modification of human HSCs. (285)

Table 5. Overview of ongoing gene editing studies *(data in the table updated as of January 11, 2023 based on ClinicalTrials.GOV)*

Strategy	**Modality** (Drug Product)	**Lead Group** (Study Name)	**Status**	**Clinical Trial Number**	**Results**	**Reference**
HbF induction	Cas9 mediated NHEJ; disruption of erythroid specific enhancer in *BCL11A* gene (CTX001 or Exagamglogene autotemcel)	Vertex Pharmaceuticals/CRISPR Therapeutics (CLIMB SCD 121 Study)	Phase I/II/III (Study closed to accrual, licensing application pending)	NCT03745287 and NCT05329649	31 patients with SCD (median age 22.5 [range 12-34] years) infused. All patients were VOC-free with a median duration of follow-up 9.6 (range 2.0-32.3) months after infusion.	(286)
HbF induction	Cas9 mediated NHEJ, disruption of a regulatory element in the *HBG1/HBG2* promoters (OTQ923)	Novartis Pharmaceuticals	Phase I/II	NCT04443907	2 patients with SCD (aged 22 and 21 years) infused. Both patients were VOC-free with a follow-up of 6 and 12 months after infusion.	(266)
HbF induction	ZFN mediated NHEJ; disruption of erythroid specific enhancer in *BCL11A* gene (BIVV003)	Sangamo Therapeutics (PRECIZN-1 Study)	Phase I/II	NCT03653247	4 adult patients with SCD infused. All patients were VOC-free with a follow-up of 13-65 weeks after infusion.	(287)
HbF induction	Cas12a (Cpf1) mediated editing of the *HBG1/HBG2* promoters (EDIT-301)	Editas Medicine (RUBY Trial)	Phase I/II	NCT04853576	No clinical trial results posted yet.	
HbF induction	Base editing of the *HBG1/HBG2* promoters (BEAM-101)	Beam Therapeutics (BEACON Trial)	Phase I/II	NCT05456880	No clinical trial results posted yet.	
Correction of sickle mutation	Cas9 mediated HDR (CRISPR_SCD001)	UCSF Benioff Children's Hospital, Oakland; University of California,	Phase I/II	NCT04774536	No clinical trial results posted yet.	

		Los Angeles; University of California, Berkeley			
Correction of sickle mutation	Cas9 mediated HDR (GPH101 or nulabeglogene autogedtemcel)	Graphite Bio (CEDAR Trial)	Phase I/II (Study Paused)	NCT04819841	No clinical trial results posted yet.

4.4. *In-Vivo* Gene Therapy

In vivo gene therapy at present is the least mature platform for genetic interventions for the hemoglobinopathies, yet it has the greatest promise, particularly as it relates to delivering more definitive targeted treatment to individuals living in LMICs, or are otherwise without access to highly specialized academic medical centres.

A collaboration was formed between the National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation in 2019 to support the development of safe and effective *in vivo* gene therapies for HIV and SCD that could be scalable and sustainable in parts of the world such as SSA where the burden of these conditions is high, and access to definitive therapies is limited. (288) Lessons learned from *ex vivo* gene therapy have informed several key considerations for the development of *in vivo* approaches. (289)

Today, there are several notable impediments to *in vivo* gene therapy for SCD. True hematopoietic stem cells (HSC) are a remarkably small subpopulation of marrow-based progenitor cells and are typically nondividing. Lentiviral vectors used in current *ex vivo* gene therapy approaches utilize the lentiviral vesicular stomatitis viral G (VSVG) protein to promote fusion with CD34+ stem cells in the more quiescent G0 state through a low-density lipoprotein receptor in culture during the transduction process. (290) *In vivo* approaches will therefore need to overcome this relative resistance of HSC in resting state to uptake of viral vectors or nanoparticles without the ability for cell selection or stimulation in culture, perhaps by employing new methods for targeting stem cells *in situ*. The use of myeloablation for *ex vivo* gene therapy has ostensibly been needed to free up stem cell niches in an otherwise hypercellular marrow and to reduce the absolute numbers of unmodified stem cells competing with genetically modified stem cells for these spaces. (291) Ideally *in vivo* gene therapy would not require conditioning so the design approach must consider how effective disease amelioration can be accomplished if a limited percentage of stem cells are altered. Gene-editing approaches that rely upon gene disruption of targeted sequences typically utilize non-homologous end joining (NHEJ) for DNA repair, however other approaches for direct gene correction through homologous directed repair (HDR) are cell cycle dependent, given that HDR occurs at the S/G2 transition, not the usual G0/G1 phase of HSC. (292) Driving HSC into cell cycle or otherwise activating HSC, and then maintaining them for an extended period of time to achieve the correction would be needed in order to use HDR-mediated gene editing *in vivo*.

Certain parameters that have been deemed essential in manufacturing vectors for *ex vivo* gene therapy may require reconsideration for *in vivo* applications. (293) One example is the target vector copy number (VCN) and the general range for multiplicity of infection (MOI) needed to achieve this VCN that have been optimized in current *ex vivo* gene therapy approaches. If *in vivo* gene therapy approaches involve viral vectors that are delivered by direct intravenous infusion, some (likely most) of the aliquot will be trapped in the liver, thus it is not clear if the MOI used to achieve current target VCN in the laboratory will be sufficient. For *ex vivo* gene therapy, the percentage of CD34+ cells transduced with lentiviral vectors (%LVV) is another critical feature of success. The interrelationship of the efficiency of VCN and %LVV will need to be reconsidered for *in vivo* approaches.

In vivo gene therapy for SCD will likely require development of delivery systems currently not used in *ex vivo* studies. Recent studies using HdAd5/35++vector system have yielded promising results in animal models that target HSC, which are mobilized into the bloodstream prior to intravenous infusion of the vector which either deliver the gamma globin transgene, or enable CRISPR-Cas gene editing of a gamma globin repressor binding site and targets the CD46 receptor of primitive hematopoietic cells. (294)

Studies must continue to advance our understanding of the HSC microenvironment to increase homing efficiency of modified HSC and to optimize mobilization to facilitate *in vivo* editing of HSC. The HSC-specific surface markers may differ between species and are altered in mobilized HSC versus the marrow niche. More studies in various mouse models as well as larger animal species will be critical prior to human studies.

Lipid nanoparticles (LNP) have emerged as a new nonviral strategy for *in vivo* delivery of CRISPR-Cas9 gene editing tools that can target HSC. (295) Nucleoside-modification of mRNA that has been shown to increase translation combined with highly efficient transfection will be needed. LNP that target specific cell types can deliver mRNA for gene editing reagents. Delivery of the components relative to the appropriate cell cycle phase of target cells will be important for different gene-editing platforms that seek to utilize HDR- or NHEJ-mediated DNA repair.

While it is expected that *in vivo* gene therapy approaches will obviate the need for prolonged inpatient hospitalizations in resource-intensive settings, it is not clear if the overall costs will necessarily be lower at the outset. Manufacturing reagents and facilities for preparation of viral vectors and nanoparticles are expensive. It is possible to achieve lower costs over time, which should be pursued vigorously as these tools are being developed so that ultimately broad access to gene therapy is achieved.

Even in HICs, individuals with SCD face barriers that prevent more than relatively small numbers from realizing the full benefits of scientific advances. Some of the conditions that contribute to overall disparities in outcomes in SCD also limit the use of HSCT. (296) These include lack of awareness among patients and their care providers of the availability of curative options, lack of access to specialized care centres, and restrictions imposed by certain insurance models commonly used by sickle cell patients. Potential solutions include greater direct engagement of patients, creation and dissemination of multimedia, open-access educational materials describing current approaches and advocacy for innovation in payment models.

Curative therapies for SCD currently available in clinical practice and research trials require highly complex services and facilities not likely available in LMICs where the majority of the global sickle cell population live. Collaborations between academic institutions, private industry and governments should be encouraged. (288, 297) Key considerations include prioritizing technologies that allow for single infusions with durable effects, insuring that the local healthcare systems have adopted early detection of SCD and provision of evidence-informed early interventions, and finally devising financial and workflow models to democratize access to curative options.

4.5. Recommendations on established and emerging treatments

While endorsing population-based public health priorities, such as newborn screening and early intervention, the ultimate aim is to provide access definitive or curative therapies for every patient with SCD, irrespective of where they live, and it seems likely that this will involve some form of gene therapy. However, it will require planning and investment that will need to begin in the near term. We firmly recommend prioritizing ongoing scientific and infrastructure investment to achieve effective, safe and accessible cures globally by 2040.

Autologous curative approaches are maturing and will likely play an important role in the future given that most individuals with SCD seeking potentially curative options will still not have a HLA-matched sibling donor. We believe that most approaches currently in late-phase clinical trials have an acceptable safety and efficacy, however modifications in future trials or development of treatment centers must evolve to improve safety further, and consider cost containment to insure more global access.

Finally, it should be noted that this discussion does not address the use of germline stem cell modifications as there is not as yet international consensus on safety and ethics. However, given the global burden of SCD in the future a case may be made to consider germline or heritable gene therapy in order to reduce the population at risk.

Section 5: Global strategies for training and educating health-care providers: improving evidence-based medicine and nursing care

The increasing global burden of SCD is now well established. Despite the enhanced development of evidenced-based strategies for decreasing morbidity and mortality, few individuals with SCD in LMICs receive evidence-based medical and nursing care, resulting in thousands of preventable deaths every year. The gap in health-care practice for prevention of death and lifelong morbidities such as SCD-related strokes in children and young adults is in part related to the mismatch between evidenced-based strategies for disease management and the clinical practice in low-middle and high-income settings. SCD has evolved from a life-threatening illness of childhood with a shortened lifespan to a chronic disease where most children are expected to live to be middle-aged.[1,2] As the life-course of children with SCD has changed, so have the patterns of the mortality and co-morbidities associated with SCD.

The changing global demographics of SCD present unique challenges in developing a pipeline of knowledgeable medical and nursing providers. In Africa, where more than 70% of the children with SCD are born, few formal medical and nursing haematology programmes exist to ensure SCD evidence-based practice. In many locations in Africa, most children and adults with SCD receive nursing and medical care from health-care providers without any formal SCD training. In some cases, patients receive SCD care from nurses alone or nurses and medical officers (recent medical school graduates without any specialty training) with limited training in evidence-based strategies for primary care and SCD practices. Countries with a traditionally low SCD prevalence, such as most European and Asian countries, have recently had a significant influx of African and Middle Eastern individuals with SCD and SCT who are at risk of having offspring with SCD. The focus of our global panel of medical and nursing experts is to: 1) define gaps in implementing evidence-based guidelines for SCD management across the lifespan; 2) identify best strategies for educating a multidisciplinary SCD health-care workforce in low-middle and high-income settings; 3) identify novel health-care delivery models for implementing SCD evidence-based guidelines for nurses, neurologists, obstetricians, haematologists, and primary care physician; the subspecialities that have pre-existing evidence based guidelines for management of SCD. We acknowledge that people with SCD, their families and allied health professionals all need education about SCD to provide comprehensive care.

For this manuscript, we are focusing on the education and training of health-care providers.

Educating medical and nursing students about the inheritance pattern of SCD and non-directive genetic counselling

Medical and nursing students are typically not exposed to a formal curriculum on how to provide non-directive genetic counselling for SCD. We are unaware of any actively implemented medical school and nursing school curriculum to educate students about the inheritance pattern of SCD that includes non-directive genetic counselling learning objectives. The absence of a universal curriculum that includes genetic counselling is a missed opportunity to ensure appropriate reproductive counselling for individuals at risk for having a child with SCD. Furthermore, the lack of genetic counsellors combined with the prevalence of SCT, particularly in people

of African and Asian descent, ranging from one in four individuals in West Africa to one in 12 African Americans living in the USA, highlights the need for development of a specific curriculum to both expand the knowledge of non-directive genetic counselling techniques and increase the number of providers certified to deliver genetic counselling. The Saudi Ministry of Health has developed training modules for genetic counselling materials used for training health care professionals in urban and rural primary care centres. This training must have a common core content /syllabus, taking into account the religious and cultural sensitivities unique to the populations and regions where they are being employed.

5.2. Existing SCD education curricula with learning objective for medical students

Most medical schools provide one to two lectures on SCD or haemoglobinopathies. The panel was aware of a few current SCD curriculae with learning objectives adjusted for educational training (pre-graduate versus post-graduate) that would assess a minimum core competency required for acute and chronic management of SCD. As an exception, faculty in Senegal and the University of Paris developed French curricula focused on these topics (**Table 6**).

A major gap in developing SCD education curricula is the absence of a minimum set of teaching objectives or content knowledge required to ensure a uniform knowledge base from year to year. The panel identified one systematic guideline for developing a minimum knowledge base for primary care providers to become proficient in the acute and chronic management of SCD in primary care settings in Africa. (http://ceasamef.sn/wp-content/uploads/2019/09/Guide-La-Drepanocytose-en-Afrique-senegal-.pdf)

In Lebanon, at the American University of Beirut, the first-year medical students have one lecture on SCD as part of the haematology course, and all third-year medical students attend the comprehensive sickle cell clinic once a week for 8 weeks. This rotation is structured with reading materials and recently included genetic counselling for all patients with hemoglobinopathies. A newly established National Committee on SCD will evaluate and recommend introducing a module on SCD to all medical school curricula in Lebanon.

In Nigeria, where the greatest number of children and adults with SCD live, medical schools offer on average three-hours of lectures on SCD and thalassaemia; however, in the country where approximately 150,000 babies with SCD are born annually, there has been no systematic approach to assess core competency in SCD care at the postgraduate, residency programme level or in nursing schools. At the federal level, a national guideline for SCD management was developed by an expert committee and published by the Nigeria's Minister of Health in November 2014. (298) Effective strategies are required to increase the dissemination and adoption of the national guideline into the medical and nursing curricula. A task shifting approach should be recommended to train the Community Health Extension Workers (CHEWs), who are responsible for the vast majority of primary care provision in all rural and underserved communities of Nigeria, based on the national guideline for SCD management.

5.3. Existing SCD education curriculum with learning objective for nursing students

Comprehensive care for people with SCD relies on the chronic care model, (299) and nurses are crucial members of these teams. Nursing education programmes emphasize the role of nurses as health educators and care coordinators. Pre-licensure nursing education includes generalist education in the genetics of SCD. Education about the genetics of SCD in nursing school may allow nurses to provide genetic counselling to parents of children with SCD and preconception counselling to adolescents and young adults with SCD. Nurses also manage chronic complications of pain and the comorbidities of asthma by educating families on symptom management.

A precious human resource is the small cadre of nurse educators and scientists committed to the next generation of SCD nurse providers, educators, and investigators. We believe that foundations and government agencies would dramatically impact the care of individuals, particularly maternal child health if more resources are placed in creating regional SCD nursing centres of excellence or at the very least providing a nurse-focused SCD curriculum.

5.4. Existing SCD education curriculum with learning objective for internal medicine and paediatric trainees

The absence of a universally accepted curriculum to provide expected SCD primary care management, despite formal evidence-based guidelines specifically developed for primary care providers (147), is a missed opportunity to building a knowledgeable SCD healthcare workforce. An easy and efficient approach is to develop a consensus health care curriculum with learning objectives for nursing and primary care providers.

Primary care providers are an under-recognized yet crucial part of the medical care for persons with SCD. Individuals with SCD who have primary care providers have lower hospitalizations, readmissions, and better hydroxyurea adherence. (300, 301, 302) Globally, SCD care largely relies on access to primary care providers and primary care nurses. Several healthcare issues typically screened and treated in the primary care setting can significantly impact people with SCD. Mental health, women's health including contraception, hypertension, diabetes, cancer, smoking, asthma, and vaccinations are among these topics.

A global curriculum that educates primary care providers and primary care nurses about SCD and the nuances of caring for this population is critical. Due to the missed opportunity for educating medical and nursing students and primary care residents mentioned previously, curriculums that target post-residency primary care providers are another potential opportunity to bridge the gap. Two of the authors of this section, a haematologist and a primary care provider, developed a curriculum to help primary care providers overcome established barriers, learn evidence-based guidelines for SCD care, and embrace the care of children and adults with SCD. As outlined in **Table 6**, the curriculum takes about 24-32 hours on average and includes approximately ten sessions that address the specific components of SCD care. (303) The curriculum uses evidence-based methods to overcome barriers to care and could be used to educate primary care providers across the USA. The team developed a

booklet of the 2014 NHLBI guidelines adapted for the education of individuals with SCD, their families, and primary care providers to augment this curriculum. (304)

Other initiatives in this area include developing a core curriculum for practitioners charged with the management of children and adults with SCD. The online course (https://odf.u-paris.fr/fr/offre-de-formation/diplome-d-universite-1/sciences-technologies-sante-STS/du-enseignement-on-line-sur-la-drepanocytose-I73G5WVE.html) addressed the management of children and adults with SCD. The course, developed in 2013, includes topics such as diagnosis, treatment, psychological and social aspects (70 hours), and offers validated training in therapeutic education (40 hours). Approximately 200 health care providers from France, Africa, and the West Indies have already completed the course. The University of Paris Cite acknowledges the graduates.

Although in many situations, evidence-based treatments and appropriate resources need to be established before education can be fully effective, there are also many areas where education of health care professionals can make a very big difference. Children and adults with SCD have one of the highest incidence rates of acute and chronic neurologic morbidities of any monogenic disease. Without the establishment of primary stroke prevention programmes with transcranial Doppler screening coupled with regular blood transfusions for abnormal velocities, approximately 11% of the children with SCA will develop overt strokes. (305) After introducing stroke prevention programmes in HICs, the stroke incidence rate dropped by at least 80% in a population-based study (306) and decreased by 10-fold in a single-centre study. (307) Since 2006 and subsequently, in 2011 and 2019, the American Heart Association has published evidence-based guidelines for stroke prevention and management that include SCD. (305, 308, 309, 310) Additionally, since 2020, the ASH has published evidence-based guidelines for the treatment and prevention of neurologic morbidity in SCD. (156) Despite the presence of these guidelines coupled with the high prevalence of stroke-related morbidity and mortality in SCD, to our knowledge, a formal curriculum with learning objectives has not been established for neurologists-in-training regarding acute and chronic neurological complications of SCD across the lifespan, which is a critical need. Further, neurologists are not always readily available. Thus, all healthcare providers who care for children or adults with SCD need to be educated about the neurological complications of SCD, how to detect them by history and neurological examination, and potential treatments. A northern Nigeria research and clinical care team worked to educate nurses and non-neurologist physicians on how to perform a standardized neurological examination for stroke detection. Ultimately, this group formed stroke prevention teams. (311) This low cost-model to improve prevention and treatment of strokes should be possible to implement in other LMICs. Such a strategy is required because of the lack of haematologists, neurologists, and radiologists to establish a systematic approach to primary stroke prevention and provide acute and chronic medical management.

5.5. Existing SCD education curriculum with learning objective for obstetric-gynaecologic residents

Informed reproductive decision-making is critical in family planning of a monogenic disease. The American College of Obstetricians and Gynaecologists recommends carrier screening for hemoglobinopathies to prepare women for the chance of delivering a child with sickle trait or disease. (312) However, past studies show that some OB/GYN providers have used sickle-dex tests for screening instead of haemoglobin analysis tests. (313) As a result, other traits such as HbC and thalassaemia are missed. Prenatal counselling and follow-up represent an essential part of care and must be included in OB/GYN training. The committee was unaware of any formal learning objectives for OB/GYN residents. However, women with SCD have significant mortality and morbidity during pregnancy. Women with SCD, when compared to women without SCD, have a substantial increase in maternal mortality. Using a large administrative data set, the maternal mortality rate was at least 10 times greater among women with SCD (1.6 per 1000 deliveries) compared to women without SCD (0.1 per 1000 deliveries). (314) In low-income countries, where most children with SCD are born, the maternal mortality rate is between 7,000 and 12,000 per 100,000 live births (315, 316, 317) in comparison to the maternal mortality rate of 17.4 and 9.5 per 100,000 live births in the USA (318) and the UK, (319) respectively.

Even with the high rate of maternal-foetal mortality in women with SCD, few formal health-care delivery strategies have been developed to address this issue. At Korle Bu Teaching Hospital, Accra, Ghana, the baseline maternal mortality rate was 10,000 per 100,000 live births in women with SCD, compared to 1,000 per 100,000 live births in women without SCD. (320) After implementing a multidisciplinary team, there was an 89% relative risk reduction of maternal mortality that was sustained three years after the intervention. (321) The primary interventions were all low budget interventions including adding standard clinical care management strategies, routine assessment of haemoglobin oxygen saturation measurements at baseline and during admissions with clinical action if more significant than a 3% drop from baseline; standardizing nursing care guidelines; and ongoing quality control assessment of care with initially weekly meetings. These results clearly demonstrated that improvement in obstetrician and nursing care knowledge could result in a dramatic decrease in maternal mortality rates. The comprehensive SCD obstetric care programme at the Korle Bu Teaching Hospital in Ghana recently published its management protocol (322) that can serve as important guidelines for the training of midwives, medical students, residents, and maternal-foetal medicine fellow across Ghana and in other LMICs.

Despite the higher incidence of SCD related morbidity during pregnancy, the panel was unaware of formal curriculum to educate obstetric residents and nurses about the prevention and treatment of complications of SCD during pregnancy outside of the Ghana experience above. Two evidenced-based guidelines for the management of pregnancy in women with SCD, from the USA and the UK, could be used to establish the expected learning objective. (312, 323, 324, 325)

5.6. SCD curriculum with learning objectives for health-care professionals

There are some examples of the development of curricula specifically focusing on SCD, with clear learning objectives for healthcare providers. Recently a member of the panel (MRA) was actively involved with the Thalassemia International Federation in developing an online course on SCD for health-care providers. The course is available, free of charge since April 2021, and has modules on different aspects of SCD, including clinical complications (infections, pain, neurologic complications, pregnancy etc.), treatment, and care organization. The European Hematology Association (EHA) has also developed a haematology curriculum which includes a specific and detailed description of the knowledge necessary to care for patients with SCD, mostly from a European perspective. We did identify one institutional collaboration between those living in a high-income setting and those living in a low-middle-income setting, the University of Paris Cité and health-care providers in Senegal (https://odf.u-paris.fr/plugins/odf-web/uparis/_content/program-diu-international-franco-africain-prise-en-charge-de-la-drepanocytose/DIU%20International%20%20franco-africain%20-%20%20Price%20en%20charge%20de%20la%20dr%C3%A9%20Panocytose.pdf).

Additionally, the West African Genetic Medicine Center, a World Bank Center of Excellence, located at the University of Ghana has recently started a genetic counselling master of science programme (MSc) to train genetic counsellors for the region (https://www.ug.edu.gh/news/university-ghana-partners-national-institute-genetics-strengthen-its-genetics-programmes). Trainees are drawn from wide biomedical and clinical backgrounds including physicians, nurses, biomedical scientists and psychologists; the programme offers appropriate detail related to inherited blood disorders incorporating practical counselling courses focused on SCD.

It is particularly important that training programmes in each country or region reflect the availability of resources. For example, the use of blood transfusions to treat cerebrovascular disease is not possible in most LMICs, and evidence-based clinical practice from Europe and the USA would not be appropriate. Training programmes need to be developed using the best available evidence adapted to local conditions. A good example of this is the way in which the Jamaica Sickle Cell Unit Clinical Care Guidelines were developed by adapting North American and UK guidelines to local needs; these guidelines have subsequently been used a basis for training throughout the English-speaking Caribbean.

Overall, the panel believes the absence of a core set of expected SCD competencies for haematology fellows globally significantly impairs implementing and disseminating SCD evidenced-based practice. Further, the lack of SCD learning objectives and evaluation during annual competency service examinations explicitly lowers expectations of haematology training programme directors and trainees about the importance of SCD in their current and future clinical practice.

5.7. Improving the pipeline of investigators to advance discovery in sickle cell disease

Although precise figures are not available, there is relatively little research funding reserved specifically to investigate SCD, particularly when compared to many other comparable conditions, such as cystic fibrosis and haemophilia. This leads to shortage of trained investigators in SCD, and is a disincentive for new researchers to become interested in the condition. Private foundations have targeted grant funding for haematologists and multidisciplinary research teams focused on SCD related problems (https://www.novartis.com/our-impact/global-health/sickle-cell-disease). The Doris Duke Charitable Foundation offered SCD specific research funding opportunities for 7 years (2009-'15), a total of $17 million or approximately $2.4 million per year. In contrast, the US Cystic Fibrosis Foundation spends greater than $100 million per year. A total of 28 new grants were provided, $450,000 for direct cost over three years, and seven grants were renewed. Subsequently, based on this pilot funding, the Doris Duke awardees received $55.6 million from the NIH. (326) The ASH also supports junior investigators with 2-3 year awards for research and training activities, and SCD focused trainees have been among the recipients. (327) To our knowledge, there is no current foundation devoted to specific funding of fellows or new faculty focused on a research career in SCD, in contrast to many other much rarer diseases.

5.8. Evidence-Based Medicine as a Bridge to Improve and Expand the Pipeline of Medical and Nursing Care in Sickle Cell Disease

Evidence-based medicine is the purposeful use of current best evidence in making decisions about the care of individual patients. Evidence-based medicine integrates provider clinical expertise with the best available external clinical evidence from systematic research and patient preferences. In 2020, the ASH produced evidence-based guidelines in SCD for the management of heart, lung, neurological and kidney disease, (328) (156) the use of blood transfusion, (329) and acute and chronic pain management. (330) The ASH guidelines serve as a starting point for implementing and adopting regional-specific SCD evidenced-based guidelines. However, bridging the gap between optimal management and bedside patient management requires a paradigm shift in training physicians and nurses in low-middle- and high-income settings, to improve access to treatment. Further, the value of such guidelines is undermined by the relative lack of high-grade evidence to support them, particularly when the guidelines refer to LMICs.

5.9. Opportunities for Training in Sickle Cell Disease

There is a shortage of haematologists and medical providers trained in SCD. Rural America lacks providers for a large portion of adults with SCD. SSA, where 75% of all children with SCD are born, the demand for SCD health-care providers far exceeds available personnel. As a result, some organizations have invested in training programmes to increase the number of fellowship-trained haematologists, primary care providers, and advanced practice providers to deliver evidence-based care to children and adults with SCD.

In the USA, the Health Resources and Services Administration (HRSA) funded five regional SCD Treatment and Demonstration Programs (SCDTDP) awards to support the education of providers to learn more about evidence-based care of people with SCD. A learning collaborative is an initiative in which peers come together to study and apply quality improvement methods to a focused topic area. Learning collaboratives have also been funded to support communities learning about SCD. In the SCDTDP awards supported by HRSA, the regions also formed learning collaboratives across the participating state. HRSA tasked awardees to work on quality improvement activities to increase the uptake of evidence-based guidelines such as TCD screening of children 2-16 years with SCA, prescribing of hydroxyurea, vaccinating, and using child to adult SCD care transition planning tools. Another learning collaborative focused on SCD care is being created by ASH in 2021. Several organizations have invested in learning modules to create SCD education programmes available to individuals living in low- middle-income countries. See **Table 7**.

Although opportunities for training in SCD are relatively limited in the USA, the situation is probably worse in most other countries, particularly in Africa and India where the disease is most prevalent. There is also a significant problem in many European countries where there has been a recent marked increase in the numbers of patients with SCD, with the means to train the medical and other staff to manage the condition.

5.9.1. The gap in dissemination and implementation research for evidence-based medical and nursing practice in SCD

After curricula for practitioners in SCD are established, the dissemination and implementation of the objectives are required. In recent years, implementation science has evolved as a much-needed set of tools to increase the uptake of evidence-based clinical guidelines. (331, 332, 333) The same approaches of identifying the evidence-based practice or learning objectives, assessing the organization's culture or setting, and working through strategies to deliver the education or training are relevant to implementing curricula. (334, 335)

In implementation research, the RE-AIM is a framework commonly used in public health to reduce the gap between evidence-based practice and actual activities. (336) Reach and Effectiveness of the intervention, Adoption, and Implementation (individual and organizational), and Maintenance of the intervention is assessed after planning and intervening. A recently published modification of the RE-AIM framework (337) purposely brought the concept of equity into the maintenance to enhance sustainability. Given the inequities of the population of patients, their daily settings, and the settings of their medical care, this adapted version of RE-AIM (337) could be considered in future dissemination and implementation of training curricula.

5.10. Recommendations on training and education

Across HICs and LMICs, we could not identify an ideal model for training and educating physicians and nurses to look after patients with SCD. There is an urgent humanitarian need to educate healthcare professionals and the general public about SCD across the world, to prevent death and decrease life-long sequelae of SCD, particularly in in Africa, where 70% of newborns with SCD are born. However, all global regions lack an adequate approach

for preparing the next cadre of leaders focused on SCD medical and nursing care and research. Relatively small investments in training and education can lead to marked improvement in health outcomes, as shown by exemplar programmes, such as those to prevent the deaths of pregnant women with SCD and to diagnose strokes in young children with SCD living in Ghana and Nigeria. These programmes should be highlighted to allow replication across the settings most in need of investment (low/ middle resource and lower incidence) to facilitate improvements in care.

A comprehensive partnership between private foundations, professional medical and nursing societies, and government agencies is required to tilt the global scale toward medical justice for children and adults with SCD (**Table 8**).

Table 6: Curriculum Overview for training PCPs about SCD. These are didactic and case-based sessions in person or done remotely through educational platforms. The sessions are primarily geared towards how a PCP manages SCD in an outpatient setting.

Overview of SCD	**Topics**
PCP management	Genetics and pathophysiology of the disease, psychosocial factors, poverty, and other socioeconomic factors, how PCPs fit into the care model
The SCD perspective – Individuals with SCD and/or caregivers	Vaccines and screening (SCD related: Eye screening, heart, lung, and kidney screening, neurological screening, SCD specific vaccines (NHLBI guidelines (147)) and non-SCD related – USPSTF guidelines), penicillin (NHLBI guidelines), depression, women's health, hypertension, diabetes, vitamin D and bone health, sleep, acute issues Resources for the PCP: Guidelines (2014 NHLBI (147), 2019 ASH), checklists, patient resources, the patient portal, apps
Acute and chronic pain in SCD	Their perspectives of their disease. The positives of the care they receive. The challenges of their care (like wait times in the emergency room, providers in care). What they would hope their primary care physicians would, what is most important to them as individuals with SCD and their caregivers
Acute complications in SCD	Acute pain episodes and chronic pain (avascular necrosis, musculoskeletal issues). Include pathophysiology and treatment and NHLBI/ASH guidelines (330).
Chronic complications in SCD	Acute chest syndrome, fever and infection, priapism, splenic sequestration, abdominal pain, vision changes, venous thrombosis (NHLBI/ASH guidelines)
Wellness in SCD	Heart, lung, and kidney issues, (328) leg ulcers, central nervous system complications – strokes, silent strokes, and cognition (156) (NHLBI/ASH guidelines). Other problems that may exacerbate SCD such as diabetes, tobacco use, etc.
Care coordination in SCD	Preventing life-threatening infections, avoiding sickle cell pain triggers, managing stress, taking care of your teeth, healthy diet, staying active, safe sex, tobacco use, alcohol, and drug use
Disease-modifying therapies	Medical home model, and the role of the nurse case manager/care coordinator in the coordination of care

Curative therapies	Medications (hydroxyurea, L-glutamine, voxeletor, crizanlizumab), chronic transfusion therapy. Recognizing indications and exclusions, complications, efficacies, dosing, and side effects/toxicities. Transfusion support, including RBC transfusions, requires extra matching (specifically at the Rh and Kell loci) (ASH guidelines) (329). How to manage hydroxyurea as the PCP (NHLBI guidelines)
SCD: Sickle cell disease; PCP: primary care provider; USPSTF: United States Preventive Services Taskforce; NHLBI: National Heart, Lung, and Blood Institute; ASH: American Society of Hematology; RBC: red blood cell.	Transplant (ASH guidelines) (338), post-transplant knowledge for the PCP, how to talk to patients about curative therapies

Table 7. Sample of available training modules for sickle cell disease education programmes

Organization	Title	Objectives	Language	Access
American Society of Hematology	Benign Hematology Curriculum - SCD	• pathophysiology and clinical Management of people with SCD • increase knowledge and awareness • 13 modules	English	https://academy.hematology.org/local/catalog/view/product.php?productid=35
European Union's Horizon 2020 Marie Skłodowska-Curie programme for education and training	ARISE: African Research and Innovative Initiative for Sickle cell Education: Improving Research Capacity for Service Improvement	• Sickle Cell Disease (SCD) prevalence • genotypes and phenotypes • existing "best practices" for Newborn Screening and early diagnosis • engagement with patients, families and policy makers to determine barriers to Newborn Screening • lab diagnosis and quality assurance systems for population screening; • treatment protocols for the Management of common SCD complications and transition from paediatric to adult care, health promotion strategies and nutrition	English	https://www.ariseinitiative.org/education-training/arise-virtual-teaching-programme/

University of Paris	Diplôme Universitaire Enseignement on line sur la Drépanocytose	Diagnosis, treatment, psychological and social aspects of paediatric and adults with SCD (70 hours), and offers validated training in therapeutic education (40 hours)	French	https://odf.u-paris.fr/fr/offre-de-formation/diplome-d-universite-1/sciences-technologies-sante-STS/du-enseignement-on-line-sur-la-drepanocytose-I73G5WVE.html
Senegal and University of Paris	Diplôme Universitaire International Franco-Africain	Pathophysiology and clinical Management of people with SCD with special focus on the facilities available in Africa	French	https://odf.u-paris.fr/plugins/odf-web/uparis/_content/program-diu-international-franco-africain-prise-en-charge-de-la-drepanocytose/DIU%20International%20%20franco-africain%20-%20%20Price%20en%20charge%20de%20la%20dr%C3%A9%20Panocytose.pdf
Thalassemia International Foundation	TIF SCD e-Course, reviewed and endorsed for its quality by the European Hematology Association	Clinical complications (infections, pain, neurologic complications, pregnancy etc.), treatment, and care organization	English	https://academy.thalassaemia.org.cy/
Saudi Ministry of Health	Sickle Cell Disease in KSA	Genetic counselling and modules on clinical care to be used in primary care and remote centres	English	See Appendix for slides

Future challenges and opportunities

There have been many warnings in the past about the neglect of SCD and frequent calls to reduce the global burden of SCD and to better managed and treat patients with SCD. So far, these calls, including those from WHO, have had limited impact. Given growing inequalities within most countries and internationally, and substantial financial pressures to improve the health of a growing and ageing population, it will require substantial commitments to achieve the recommendations outlined in this Commission.

The number of patients with SCD globally is expected to increase, bringing new challenges, for example, in terms of multimorbidity in HICs and of developing adequate healthcare strategies for numbers of patients in LMICs considerably larger than those currently managed in HICs.

The development of innovative POCT devices, new drugs and promising therapies in recent years all offer great opportunities to scale up the availability and accessibility of existing tools in areas of high prevalence, and to pursue further developments through ethical and equal collaborations.

As illustrated by a couple of multibillion-dollar acquisitions of drug companies interested in sickle cell disease treatments, there is growing awareness about SCD and the development of a cure for SCD currently has a high profile. The main challenge going forward will be to maximise the impact of investments for the benefits of patients and society overall.

To guide future progress, this Commission makes 12 key necessary and realistic recommendations for reducing the global burden of SCD (**Panel 1**) which are further expanded in **Table 8**.

Conclusions

Overall, improvements for patients with SCD worldwide have been really limited over the past few decades. Until recently, HU was the only available drug for the treatment of SCD, while most individuals with SCD in high prevalence areas remain undiagnosed. Furthermore, throughout their lives, most patients do not receive adequate healthcare and are victims of racism and stigmatisation.

The beginning of the journey would seem to be starting neonatal screening programmes in every country with significant numbers of patients with SCD; although the technology to do this is increasingly available, with point of care testing and widespread use of mobile phones, it is still a huge undertaking to establish even the most basic programme in most African countries. The end of the journey is also imaginable, in which every patient in the world is offered curative treatment, possibly through the emerging field of *in vivo* gene editing, although this requires major technical, logistical and economic advances, and it would take substantial commitment to make this a reality within the next three decades.

Education has often been shown to be a driver of societal, economic and health improvements. Awareness and understanding of the disease within the general population, training and knowledge of SCD within healthcare

professionals, familiarity with the challenges faced by public health services amongst decision makers would all contribute to improve the life and quality of care for patients with SCD and their families.

Although there remains many unknowns concerning the natural history of the disease and uncertainties in relation to the exact burden of SCD, a series of inexpensive and effective tools to identify patients with SCD, to reduce early mortality, and to prevent severe chronic complications, is readily available to rolled out at scale. There is strong evidence about their benefits and cost-effectiveness, and strategies building on existing infrastructure to maximise investments and impact.

This Commission brings together the enthusiasm and ambitious aspirations of a diverse and multi-disciplinary group of international experts of SCD, complemented by input from advisory board members from academia, advocacy groups, pharmaceutical industry, policy institutions and funders, to seize current opportunities to make the world a better place for all patients with SCD by defining priorities and setting short-term, mid-term and long-term recommendations to guide public health policies and investments. Our ambition is to monitor and document progress towards these recommendations and to evaluate achievements and shortfalls within the next decade, while curative treatments continue to be developed in parallel.

Contributions

Contributors FBP and DR were the lead authors of the Commission and participated in the writing, editing, and review of all sections. The Introduction lead author was DR (correspondence to david.rees@kcl.ac.uk). FBP led the writing of section 1 (correspondence to f.piel@imperial.ac.uk). DZI, KOF, RC and RC participated in the writing and editing of section 1. ON led the writing of section 2 (correspondence to oennodu@gmail.com). JE, DJ, MLP and LT participated in the writing and editing of section 2. BR and REW led the writing of section 3 (correspondence to Russell.Ware@cchmc.org). EEA, BA, MdM, NC and FC participated in the writing and editing of section 3. AAT led the writing of section 4 (correspondence to thompsona7@chop.edu). AA, As and EE participated in the writing and editing of section 4. MRDB led the writing of section 5 (correspondence to m.debaun@vumc.org). MRA, RMC, MdM, ALG, IMI, LCJ, ZSK, AAK, SAO, LS and DJW participated in the writing and editing of section 5. FBP and DR wrote the conclusions and reviewed the entire commission in detail (correspondence to f.piel@imperial.ac.uk). All authors reviewed and approved the final version of the Commission.

Declarations of interest

MRA has received grants or contracts with Novartis, Pfizer, GBT and Forma Therapeutics and participated in Data Safety Monitoring Boards or Advisory Boards for Vertex, GBT, Forma, Novartis and Aggios. BA has participated in Data Safety Monitoring Boards or Advisory Boards for Agios, Aruvant, bluebird bio, CRISPR, CVS/Accordant, Emmaus, Forma Therapeutics, Fulcrum, Global Blood Therapeutics, Hemanext, Novartis, NovoNordisk, and Vertex. RF has received grants from the European Horizon 2020 and Horizon Europe schemes and a contract with Global Blood Therapeutics; consulting fees from Novartis and Global Blood Therapeutics; honoraria for a Physicians' Education Resource and from Global Blood Therapeutics; has participated in Data Safety Monitoring Boards or Advisory Boards for Vertex, Addmedica and Novonordisk; and has a leadership or fiduciary role as a member of the Steering Committee and Coordinator of the Red Cell Disorder Working Group of the Italian Association of Pediatric Hematology Oncology (AIEOP). NC has received a research grant for Novartis Precision Medicine. MdM has received honoraria for presentations by Addmedica and Novartis and support from Addmedica for attending a conference; and has participated in a Data Safety Monitoring Board or Advisory Board for Addmedica, Vertex and Novartis. JE has received grants from the European Horizon 2020 scheme and participated in the Data Safety Monitoring Board or Advisory Board of the Fondation Pierre Fabre. EE has received consulting fees from bluebird bio. ALG has an honorary advisory role on the Australian Sickle Cell Advisory Board. IMI has received a grant from the American Society of Hematology; consulting fees from Agios Pharmaceuticals, and honoraria from the American Society of Hematology. LCJ received royalties for a book chapter. AAK has received support from the Health resources and Services Administration. MLP has received consulting fees from the American College of Medical Genetics and Genomics; and participated in a Data Safety Monitoring Board or Advisory Board for the American College of Medical Genetics and Genomics and the

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Advisory Board

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Table 8. Overall Commission Recommendations

SECTION 1	Concern	Setting	Short-term solutions (1-3 years)	Long-term solutions (more than 3 years)
Epidemiology	Limited availability of standardised epidemiological data	Worldwide	To develop standards for minimum epidemiological data needed to monitor changes and progress	To support the implementation of robust, standardised electronic data collection systems, particularly in LMICs
			To build on existing infrastructures, software and networks used for other diseases (e.g. immunisation programmes)	To monitor progress to reduce the burden of SCD through an online interactive portal
			To enable data sharing across datasets and registries	To inform policies through reliable regular updated global, regional and national burden estimates
	Neglected large numbers of patients with SCD	High-prevalence countries	To develop tailored public health strategies, based on a better understanding of the natural history of SCD	To demonstrate the societal and economic benefits of implementing sustainable public health policies for SCD

SECTION 2	Concern	Setting	Short-term solutions (1-3 years)	Long-term solutions (more than 3 years)
Screening & Prevention	Lack of NBS policies and guidelines	High-prevalence countries	To develop policies on NBS with budgetary allocation for implementation	To establish universal NBS as a public health programme with adequate provision for follow up of babies affected
	Lack of stable consistent and sufficient funding	High-prevalence countries	To allocate specific budgets for NBS	To develop a global funding mechanism for NBS and other SCD prevention and management interventions
		LMICs	To provide tailored preconceptual programs/offer and genetic counselling	To establish national preconceptual screening programmes as part of standard of care

	Lack of organised national NBS programmes		To prioritize the implementation of NBS programmes	To establish newborn screening programmes in birthing hospitals
				To develop Centres of Excellence with multi-disciplinary providers

SECTION 3	Concern	Setting	Short-term solutions (1-3 years)	Long-term solutions (more than 3 years)
Disease management - Established and emerging treatments	Need for comprehensive national SCD programmes	Worldwide	To write guidelines that are geographically and socioeconomically appropriate	To arrange low-cost distribution of vaccines, antibiotics, analgesics, and hydroxyurea
	Poor management of VOCs and other acute events	Worldwide	To set up facilities with Transcranial Doppler screening	To increase awareness of psychosocial issues
			To create local protocols for managing pain	To create practical tools for evaluation and improvement of treatment adherence
			To provide adequate opioid analgesics	
			To encourage incentive spirometry	
			To treat fever with antibiotics and antimalarials as appropriate	
	Poor access to safe blood transfusions	LMICs	To write guidelines for proper use of blood transfusions, limiting paid donors	To establish a national transfusion programme
			To screen serum for RBC alloantibodies	To develop tools for recording historical RBC alloantibodies

			To cross-match blood before releasing units	To improve haemovigilance and blood safety
		Worldwide	To increase blood supply for SCD patients	
	Poor access to affordable HU	LMICs	To register HU nationally for the treatment of SCD	To improve clinical infrastructure for drug distribution and treatment
			To write treatment guidelines adapted to the socioeconomic setting	To increase accessibility to drug supply and avoid stock-outs
				To improve affordability to below $1 USD per week

SECTION 4	**Concern**	**Setting**	**Short-term solutions (1-3 years)**	**Long-term solutions (more than 3 years)**
Management – Cellular therapies	Limited awareness of curative therapies	Worldwide	To enhance education and advocacy of governmental agencies	To create educational materials that are multimedia and in appropriate languages
	Limited access to allogeneic HSCT	Worldwide	To secure essential medications for HSCT	To increase accessibility to drug supply
			To improve coverage in national plans or through insurance payors	To improve affordability
		HICs	To provide safe universal HLA typing of all SCD children, covered by insurance where applicable	
			To enhance blood banking capabilities for safe collection and storage of components, especially platelets	

		To establish radiotherapy services to deliver irradiation for conditioning (total body) and to irradiate blood products	
	LMICs	To develop capacity for transplant and access to clinical trials	To identify additional centres with sufficient infrastructure to perform safe and effective allo-HSCT
		To develop patient selection criteria based on local considerations	
Limited access to autologous HSCT for gene therapy	HICs	To support late-stage clinical trials that will support registration of commercial gene therapy	
		To encourage additional early phase studies of innovative approaches that may be safer, more effective and less costly	
	LMICs		To identify additional centres for autologous HSCT
Lack of investment in development of in vivo gene therapy	Worldwide	To encourage and support ongoing research and innovation	To explore technology solutions such as closed systems for point of care manufacturing that will reduce dependence on specialized centres
		To prioritize investments in systems that support in vivo delivery of genetic therapies	To support ongoing studies on non-genotoxic preparative regimen to eliminate the need for radiation or chemotherapy

SECTION 5	**Concern**	**Setting**	**Short-term solutions (1-3 years)**	**Long-term solutions (more than 3 years)**

Global strategies for training and educating health-care providers: improving evidence-based medicine and nursing care	Limited global curriculum for training/certification of SCD care providers- incorporate recent guidelines/updates/utilize existing resources and programs.	Worldwide	To develop a global curriculum and adapt it to local circumstances	To foster an international multidisciplinary educational meeting (IT solution) for SCD clinicians
			To facilitate advocacy for inclusion in health care worker training by local practitioners	To update curriculum every 2 years
			To create regional SCD nursing centres of Excellence or at the very least provide a nurse-focused SCD curriculum	
			To develop educational resources for health professionals such as social workers, genetic counsellors, PT/OT/speech/ psychologist	
			To target curriculum development for PCP, obstetricians, and midwives for improved identification and counselling of carriers/couples	
		Worldwide	To capitalize on expansion of online training/ telemedicine to standardize and disseminate	To set up secondary and tertiary consultation to facilitate evidence-based care and support local practitioners
		1) Lead by centres of excellence 2) Support provided to groups of similar providers		To develop sanctioned education/clinical support partnerships: centres of excellence linked with geographic zones of LMICs
				Example: quarterly succinct online meetings with short update, new learning or cases with learning moderated by centres of excellence

	Should be regionalized/ aligned to care settings	
Lack of funding	Worldwide	Foundation funding for fellows or new faculty to focus a career of research in SCD

LMICs=low-income and middle-income countries. MICs=middle-income countries. HICs=high-income countries. NBS= newborn screening. VOC= vaso-occlusive crisis. HSCT=haematopoietic stem-cell transplantation.

Bibliography

1. Gouda HN, Charlson F, Sorsdahl K, Ahmadzada S, Ferrari AJ, Erskine H, et al. Burden of non-communicable diseases in sub-Saharan Africa, 1990-2017: results from the Global Burden of Disease Study 2017. Lancet Glob Health. 2019;7(10):e1375-e87.
2. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010.
3. de la Fuente J, Gluckman E, Makani J, Telfer P, Faulkner L, Corbacioglu S. The role of haematopoietic stem cell transplantation for sickle cell disease in the era of targeted disease-modifying therapies and gene editing. Lancet Haematol. 2020;7(12):e902-e11.
4. Chakravorty S, Williams TN. Sickle cell disease: a neglected chronic disease of increasing global health importance. Arch Dis Child. 2015;100(1):48-53.
5. Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. 1910. Yale J Biol Med. 2001;74(3):179-84.
6. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376(9757):2018-31.
7. Watson J. The significance of the paucity of sickle cells in newborn Negro infants. Am J Med Sci. 1948;215(4):419-23.
8. Charache S, Dover GJ, Moore RD, Eckert S, Ballas SK, Koshy M, et al. Hydroxyurea: effects on hemoglobin F production in patients with sickle cell anemia. Blood. 1992;79(10):2555-65.
9. Mussolino C, Strouboulis J. Recent Approaches for Manipulating Globin Gene Expression in Treating Hemoglobinopathies. Front Genome Ed. 2021;3:618111.
10. Pauling L, Itano HA, et al. Sickle cell anemia a molecular disease. Science. 1949;110(2865):543-8.
11. Vinjamur DS, Bauer DE, Orkin SH. Recent progress in understanding and manipulating haemoglobin switching for the haemoglobinopathies. British Journal of Haematology. 2018;180(5):630-43.
12. Hebbel RP. Reconstructing sickle cell disease: a data-based analysis of the "hyperhemolysis paradigm" for pulmonary hypertension from the perspective of evidence-based medicine. Am J Hematol. 2011;86(2):123-54.
13. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet. 2013;381(9861):142-51.
14. Piel FB, Tatem AJ, Huang Z, Gupta S, Williams TN, Weatherall DJ. Global migration and the changing distribution of sickle haemoglobin: a quantitative study of temporal trends between 1960 and 2000. Lancet Glob Health. 2014;2(2):e80-9.
15. Weatherall DJ. Genetic variation and susceptibility to infection: the red cell and malaria. British Journal of Haematology. 2008;141(3):276-86.
16. Ranque B, Kitenge R, Ndiaye DD, Ba MD, Adjoumani L, Traore H, et al. Estimating the risk of child mortality attributable to sickle cell anaemia in sub-Saharan Africa: a retrospective, multicentre, case-control study. Lancet Haematol. 2022;9(3):e208-e16.
17. Gardner K, Bell C, Bartram JL, Allman M, Awogbade M, Rees DC, et al. Outcome of adults with sickle cell disease admitted to critical care – experience of a single institution in the UK. British Journal of Haematology. 2010;150(5):610-3.
18. Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med. 1986;314(25):1593-9.
19. John CC, Opoka RO, Latham TS, Hume HA, Nabaggala C, Kasirye P, et al. Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med. 2020;382(26):2524-33.
20. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017;376(5):429-39.

21. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8(5):e323-e33.
22. Niihara Y, Miller ST, Kanter J, Lanzkron S, Smith WR, Hsu LL, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. N Engl J Med. 2018;379(3):226-35.
23. Telen MJ, Malik P, Vercellotti GM. Therapeutic strategies for sickle cell disease: towards a multi-agent approach. Nat Rev Drug Discov. 2019;18(2):139-58.
24. Rosanwo TO, Bauer DE. Editing outside the body: Ex vivo gene-modification for β-hemoglobinopathy cellular therapy. Mol Ther. 2021;29(11):3163-78.
25. National Academies of Sciences E, Medicine, Health, Medicine D, Board on Population H, Public Health P, et al. In: Martinez RM, Osei-Anto HA, McCormick M, editors. Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action. Washington (DC): National Academies Press (US)

26. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. PLoS Med. 2013;10(7):e1001484.
27. Livingstone FB. Frequencies of hemoglobin variants. Oxford: Oxford University Press; 1985.
28. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ. 2008;86(6):480-7.
29. Lobitz S, Telfer P, Cela E, Allaf B, Angastiniotis M, Backman Johansson C, et al. Newborn screening for sickle cell disease in Europe: recommendations from a Pan-European Consensus Conference. Br J Haematol. 2018;183(4):648-60.
30. Wonkam A, Makani J. Sickle cell disease in Africa: an urgent need for longitudinal cohort studies. Lancet Glob Health. 2019;7(10):e1310-e1.
31. Kaur M, Brown M, Love TW, Thompson A, Treadwell M, Smith-Whitley K. Understanding sickle cell disease: impact of surveillance and gaps in knowledge. Blood Adv. 2020;4(3):496-8.
32. Eckman JR, Hassell KL, Huggins W, Werner EM, Klings ES, Adams RJ, et al. Standard measures for sickle cell disease research: the PhenX Toolkit sickle cell disease collections. Blood Adv. 2017;1(27):2703-11.
33. Wastnedge E, Waters D, Patel S, Morrison K, Goh MY, Adeloye D, et al. The global burden of sickle cell disease in children under five years of age: a systematic review and meta-analysis. J Glob Health. 2018;8(2):021103.
34. Hockham C, Bhatt S, Colah R, Mukherjee MB, Penman BS, Gupta S, et al. The spatial epidemiology of sickle-cell anaemia in India. Sci Rep. 2018;8(1):17685.
35. Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med. 2010;38(4 Suppl):S512-21.
36. Dormandy E, James J, Inusa B, Rees D. How many people have sickle cell disease in the UK? J Public Health (Oxf). 2018;40(3):e291-e5.
37. Lee A, Thomas P, Cupidore L, Serjeant B, Serjeant G. Improved survival in homozygous sickle cell disease: lessons from a cohort study. BMJ. 1995;311(7020):1600-2.
38. Maitra P, Caughey M, Robinson L, Desai PC, Jones S, Nouraie M, et al. Risk factors for mortality in adult patients with sickle cell disease: a meta-analysis of studies in North America and Europe. Haematologica. 2017;102(4):626-36.
39. Makani J, Cox SE, Soka D, Komba AN, Oruo J, Mwamtemi H, et al. Mortality in sickle cell anemia in Africa: a prospective cohort study in Tanzania. PLoS One. 2011;6(2):e14699.
40. Uyoga S, Macharia AW, Mochamah G, Ndila CM, Nyutu G, Makale J, et al. The epidemiology of sickle cell disease in children recruited in infancy in Kilifi, Kenya: a prospective cohort study. Lancet Glob Health. 2019;7(10):e1458-e66.

41. Mbiya BM, Kalombo DK, Mukendi YN, Daubie V, Mpoyi JK, Biboyi PM, et al. Improvement of SCD morbimortality in children: experience in a remote area of an African country. BMC Health Serv Res. 2021;21(1):294.
42. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med. 2011;41(6 Suppl 4):S398-405.
43. Nnodu OE, Oron AP, Sopekan A, Akaba GO, Piel FB, Chao DL. Child mortality from sickle cell disease in Nigeria: a model-estimated, population-level analysis of data from the 2018 Demographic and Health Survey. Lancet Haematol. 2021;8(10):e723-e31.
44. Therrell BL, Jr., Lloyd-Puryear MA, Eckman JR, Mann MY. Newborn screening for sickle cell diseases in the United States: A review of data spanning 2 decades. Semin Perinatol. 2015;39(3):238-51.
45. Streetly A, Sisodia R, Dick M, Latinovic R, Hounsell K, Dormandy E. Evaluation of newborn sickle cell screening programme in England: 2010-2016. Arch Dis Child. 2018;103(7):648-53.
46. Mason K, Gibson F, Gardner RA, Serjeant B, Serjeant GR. Prevention of sickle cell disease: observations on females with the sickle cell trait from the Manchester project, Jamaica. J Community Genet. 2016;7(2):127-32.
47. Colombatti RS, L. Management of children with sickle cell disease in Europe: current situation and future perspectives. EMJ Hematology. 2016;4(1):129-35.
48. Ohene-Frempong K, Oduro J, Tetteh H, Nkrumah F. Screening newborns for sickle cell disease in Ghana. Pediatrics. 2008;121:S120-S1.
49. Ndeezi G, Kiyaga C, Hernandez AG, Munube D, Howard TA, Ssewanyana I, et al. Burden of sickle cell trait and disease in the Uganda Sickle Surveillance Study (US3): a cross-sectional study. Lancet Glob Health. 2016;4(3):e195-200.
50. Ambrose EE, Smart LR, Charles M, Hernandez AG, Latham T, Hokororo A, et al. Surveillance for sickle cell disease, United Republic of Tanzania. Bull World Health Organ. 2020;98(12):859-68.
51. Italia Y, Krishnamurti L, Mehta V, Raicha B, Italia K, Mehta P, et al. Feasibility of a newborn screening and follow-up programme for sickle cell disease among South Gujarat (India) tribal populations. J Med Screen. 2015;22(1):1-7.
52. Upadhye DS, Jain DL, Trivedi YL, Nadkarni AH, Ghosh K, Colah RB. Neonatal Screening and the Clinical Outcome in Children with Sickle Cell Disease in Central India. PLoS One. 2016;11(1):e0147081.
53. Colah RB, Mehta P, Mukherjee MB. Newborn Screening for Sickle Cell Disease: Indian Experience. Int J Neonatal Screen. 2018;4(4):31.
54. Odame I, Jain D. Sickle cell disease: Progress made & challenges ahead. Indian J Med Res. 2020;151(6):505-8.
55. Raman V, Seshadri T, Joice SV, P NS. Sickle cell disease in India: a scoping review from a health systems perspective to identify an agenda for research and action. BMJ Glob Health. 2021;6(2).
56. Nnodu OE, Sopekan A, Nnebe-Agumadu U, Ohiaeri C, Adeniran A, Shedul G, et al. Implementing newborn screening for sickle cell disease as part of immunisation programmes in Nigeria: a feasibility study. Lancet Haematol. 2020;7(7):e534-e40.
57. Colah RB, Nadkarni AH, Gorakshakar AC, Sawant PM, Mehta PR, Gorivale MS, et al. The Changing Trends in Prenatal Diagnosis of Hemoglobinopathies in India: The Quest of a Single Center to Reduce the Burden of Disease over Three Decades. Hemoglobin. 2021;45(2):112-8.
58. Weil LG, Charlton MR, Coppinger C, Daniel Y, Streetly A. Sickle cell disease and thalassaemia antenatal screening programme in England over 10 years: a review from 2007/2008 to 2016/2017. J Clin Pathol. 2020;73(4):183-90.
59. Wonkam A, Ngo Bitoungui VJ, Ngogang J. Perspectives in Genetics and Sickle Cell Disease Prevention in Africa: Beyond the Preliminary Data from Cameroon. Public Health Genomics. 2015;18(4):237-41.
60. Olatunya OS, Babatola AO, Ogundare EO, Olofinbiyi BA, Lawal OA, Awoleke JO, et al. Perceptions and Practice of Early Diagnosis of Sickle Cell Disease by Parents and Physicians in a Southwestern State of Nigeria. ScientificWorldJournal. 2020;2020:4801087.

61. Daniel Y, Van Campen J, Silcock L, Yau M, Ahn JW, Ogilvie C, et al. Non-Invasive Prenatal Diagnosis (NIPD) of Sickle-Cell Disease By Massively Parallel Sequencing of Cell-Free Fetal DNA in Maternal Serum. Blood. 2019;134(2085).
62. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. Am J Hematol. 2009;84(6):323-7.
63. Holdford D, Vendetti N, Sop DM, Johnson S, Smith WR. Indirect Economic Burden of Sickle Cell Disease. Value Health. 2021;24(8):1095-101.
64. Thielen FW, Houwing ME, Cnossen MH, Al Hadithy-Irgiztseva IA, Hazelzet JA, Groot CAU, et al. Cost of health care for paediatric patients with sickle cell disease: An analysis of resource use and costs in a European country. Pediatr Blood Cancer. 2020;67(9):e28588.
65. Kuznik A, Habib AG, Munube D, Lamorde M. Newborn screening and prophylactic interventions for sickle cell disease in 47 countries in sub-Saharan Africa: a cost-effectiveness analysis. BMC Health Serv Res. 2016;16:304.
66. Colombatti R, Dalla Pozza LV, Mazzucato M, Sainati L, Pierobon M, Facchin P. Hospitalization of children with sickle cell disease in a region with increasing immigration rates. Haematologica. 2008;93(3):463-4.
67. Kunz JB, Cario H, Grosse R, Jarisch A, Lobitz S, Kulozik AE. The epidemiology of sickle cell disease in Germany following recent large-scale immigration. Pediatr Blood Cancer. 2017;64(7).
68. Davis LR, Huehns ER, White JM. Survey of sickle-cell disease in England and Wales. Br Med J (Clin Res Ed). 1981;283(6305):1519-21.
69. Corriveau-Bourque C, Bruce AA. The Changing Epidemiology of Pediatric Hemoglobinopathy Patients in Northern Alberta, Canada. J Pediatr Hematol Oncol. 2015;37(8):595-9.
70. Crighton G, Wood E, Scarborough R, Ho PJ, Bowden D. Haemoglobin disorders in Australia: where are we now and where will we be in the future? Intern Med J. 2016;46(7):770-9.
71. Lena-Russo D, North ML, Girot R. [Epidemiology of genetic hemoglobin diseases in metropolitan France]. Rev Prat. 1992;42(15):1867-72.
72. Leleu H, Arlet JB, Habibi A, Etienne-Julan M, Khellaf M, Adjibi Y, et al. Epidemiology and disease burden of sickle cell disease in France: A descriptive study based on a French nationwide claim database. PLoS One. 2021;16(7):e0253986.
73. Hemminki K, Li X, Försti A, Sundquist J, Sundquist K. Thalassemia and sickle cell anemia in Swedish immigrants: Genetic diseases have become global. SAGE Open Medicine. 2015;3:2050312115613097.
74. Salzano FM. Incidence, effects, and management of sickle cell disease in Brazil. Am J Pediatr Hematol Oncol. 1985;7(3):240-4.
75. Colombatti R, Martella M, Cattaneo L, Viola G, Cappellari A, Bergamo C, et al. Results of a multicenter universal newborn screening program for sickle cell disease in Italy: A call to action. Pediatr Blood Cancer. 2019;66(5):e27657.
76. Yorke D, Mitchell J, Clow C, Nuguid E, Cadogan R, Sinclair D, et al. Newborn screening for sickle cell and other hemoglobinopathies: a Canadian pilot study. Clin Invest Med. 1992;15(4):376-83.
77. Hernandez AG, Kiyaga C, Howard TA, Ssewanyana I, Ndeezi G, Aceng JR, et al. Trends in sickle cell trait and disease screening in the Republic of Uganda, 2014-2019. Trop Med Int Health. 2021;26(1):23-32.
78. Marchand M, Gill C, Malhotra AK, Bell C, Busto E, McKeown MD, et al. The Assessment and Sustainable Management of Sickle Cell Disease in the Indigenous Tharu Population of Nepal. Hemoglobin. 2017;41(4-6):278-82.
79. Souza RC, Miranda Neto PAD, Santos JRN, Monteiro SG, Goncalves MC, Silva FB, et al. Sickle Cell Anaemia Prevalence Among Newborns in the Brazilian Amazon-Savanna Transition Region. Int J Environ Res Public Health. 2019;16(9).
80. Antoine M, Lee K, Donald T, Belfon Y, Drigo A, Polson S, et al. Prevalence of sickle cell disease among Grenadian newborns. J Med Screen. 2018;25(1):49-50.

81. Darshana T, Rees D, Premawardhena A. Hydroxyurea and blood transfusion therapy for Sickle cell disease in South Asia: inconsistent treatment of a neglected disease. Orphanet J Rare Dis. 2021;16(1):148.
82. Gibbons C, Geoghegan R, Conroy H, Lippacott S, O'Brien D, Lynam P, et al. Sickle cell disease: time for a targeted neonatal screening programme. Ir Med J. 2015;108(2):43-5.
83. World Health Organization & March of Dimes. Management of birth defects and haemoglobin disorders : report of a joint WHO-March of Dimes meeting. Geneva, Switzerland; 2006 17-19 May 2006.
84. Cintron-Garcia J, Guddati AK. Effect of immigration on mortality trends in sickle cell patients. Am J Blood Res. 2020;10(5):172-8.
85. Thein SL, Howard J. How I treat the older adult with sickle cell disease. Blood. 2018;132(17):1750-60.
86. Diggs LM. Anatomic lesions in sickle cell disease. In: Abramson H, Bertles JF, Wethers DL, editors. Sickle cell disease: diagnosis, management, education, and research. St. Louis: C.V. Mosby; 1973. p. 189-229.
87. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood. 2010;115(17):3447-52.
88. Lanzkron S, Strouse JJ, Wilson R, Beach MC, Haywood C, Park H, et al. Systematic review: Hydroxyurea for the treatment of adults with sickle cell disease. Ann Intern Med. 2008;148(12):939-55.
89. Raper A. Sickle-Cell Disease in Africa and America-a Comparison. The Journal of tropical medicine and hygiene. 1950;53:49-53.
90. Lambotte-Legrand J, Lambotte-Legrand C. [Sickle cell anemia in the native child of Belgian Congo]. Ann Soc Belg Med Trop (1920). 1951;31(2):207-34.
91. Fleming AF, Storey J, Molineaux L, Iroko EA, Attai ED. Abnormal haemoglobins in the Sudan savanna of Nigeria. I. Prevalence of haemoglobins and relationships between sickle cell trait, malaria and survival. Ann Trop Med Parasitol. 1979;73(2):161-72.
92. Williams TN, Uyoga S, Macharia A, Ndila C, McAuley CF, Opi DH, et al. Bacteraemia in Kenyan children with sickle-cell anaemia: a retrospective cohort and case-control study. Lancet. 2009;374(9698):1364-70.
93. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. N Engl J Med. 2017;376(16):1561-73.
94. Issom DZ, Hardy-Dessources MD, Romana M, Hartvigsen G, Lovis C. Toward a Conversational Agent to Support the Self-Management of Adults and Young Adults With Sickle Cell Disease: Usability and Usefulness Study. Front Digit Health. 2021;3:600333.
95. Kalpatthi R, Novelli EM. Measuring success: utility of biomarkers in sickle cell disease clinical trials and care. Hematology Am Soc Hematol Educ Program. 2018;2018(1):482-92.
96. Dubert M, Elion J, Tolo A, Diallo DA, Diop S, Diagne I, et al. Degree of anemia, indirect markers of hemolysis, and vascular complications of sickle cell disease in Africa. Blood. 2017;130(20):2215-23.
97. Rees DC, Gibson JS. Biomarkers in sickle cell disease. Br J Haematol. 2012;156(4):433-45.
98. Du M, Van Ness S, Gordeuk V, Nouraie SM, Nekhai S, Gladwin M, et al. Biomarker signatures of sickle cell disease severity. Blood Cells Mol Dis. 2018;72:1-9.
99. Sandhu MK, Cohen A. Aging in Sickle Cell Disease: Co-morbidities and New Issues in Management. Hemoglobin. 2015;39(4):221-4.
100. Tewari S, Brousse V, Piel FB, Menzel S, Rees DC. Environmental determinants of severity in sickle cell disease. Haematologica. 2015;100(9):1108-16.
101. Asnani MR, Knight Madden J, Reid M, Greene L-G, Lyew-Ayee P. Socio-environmental exposures and health outcomes among persons with sickle cell disease. PLOS ONE. 2017;12(4):e0175260.
102. Collaborators GBDRF. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1223-49.

103. The Sickle Cell and Thalassaemia All-Party Parliamentary Group (SCTAPPG). Cast Aside and forgotten. A report into the experiences of those living with sickle cell or caring for someone with sickle cell during the COVID-19 pandemic. 2021.
104. Aljuburi G, Laverty AA, Green SA, Phekoo KJ, Bell D, Majeed A. Socio-economic deprivation and risk of emergency readmission and inpatient mortality in people with sickle cell disease in England: observational study. J Public Health (Oxf). 2013;35(4):510-7.
105. Khan SA, AlSiny F, Makki A, Ali A, AlAnsari I, Khan S. Socioeconomic status dependent medical complexities in children with sickle cell disease in Saudi Arabia. Saudi J Biol Sci. 2020;27(7):1781-7.
106. Cronin RM, Hankins JS, Byrd J, Pernell BM, Kassim A, Adams-Graves P, et al. Risk factors for hospitalizations and readmissions among individuals with sickle cell disease: results of a U.S. survey study. Hematology. 2019;24(1):189-98.
107. Panepinto JA, Pajewski NM, Foerster LM, Sabnis S, Hoffmann RG. Impact of family income and sickle cell disease on the health-related quality of life of children. Qual Life Res. 2009;18(1):5-13.
108. Fearon A, Marsh A, Kim J, Treadwell M. Pediatric residents' perceived barriers to opioid use in sickle cell disease pain management. Pediatr Blood Cancer. 2019;66(2):e27535.
109. Haywood C, Jr., Tanabe P, Naik R, Beach MC, Lanzkron S. The impact of race and disease on sickle cell patient wait times in the emergency department. Am J Emerg Med. 2013;31(4):651-6.
110. Farooq F, Mogayzel PJ, Lanzkron S, Haywood C, Strouse JJ. Comparison of US Federal and Foundation Funding of Research for Sickle Cell Disease and Cystic Fibrosis and Factors Associated With Research Productivity. JAMA Netw Open. 2020;3(3):e201737.
111. Bello-Manga H, Galadanci AA, Abdullahi S, Ali S, Jibir B, Gambo S, et al. Low educational level of head of household, as a proxy for poverty, is associated with severe anaemia among children with sickle cell disease living in a low-resource setting: evidence from the SPRING trial. Br J Haematol. 2020;190(6):939-44.
112. Fernandes TA, Medeiros TM, Alves JJ, Bezerra CM, Fernandes JV, Serafim ES, et al. Socioeconomic and demographic characteristics of sickle cell disease patients from a low-income region of northeastern Brazil. Rev Bras Hematol Hemoter. 2015;37(3):172-7.
113. Kamal S, Naghib MM, Al Zahrani J, Hassan H, Moawad K, Arrahman O. Influence of Nutrition on Disease Severity and Health-related Quality of Life in Adults with Sickle Cell Disease: A Prospective Study. Mediterr J Hematol Infect Dis. 2021;13(1):e2021007.
114. Canatan D, Vives Corrons JL, Piacentini G, Kara F, Keskinkilic B, Tezel B, et al. Immigration and screening programs for hemoglobinopathies in Italy, Spain and Turkey. Acta Biomed. 2021;92(4):e2021410.
115. Ghosh K, Ghosh K, Agrawal R, Nadkarni AH. Recent advances in screening and diagnosis of hemoglobinopathy. Expert Rev Hematol. 2020;13(1):13-21.
116. Chakravorty S, Dick MC. Antenatal screening for haemoglobinopathies: current status, barriers and ethics. Br J Haematol. 2019;187(4):431-40.
117. Memish ZA, Saeedi MY. Six-year outcome of the national premarital screening and genetic counseling program for sickle cell disease and beta-thalassemia in Saudi Arabia. Ann Saudi Med. 2011;31(3):229-35.
118. Dexter D, McGann PT. Saving lives through early diagnosis: the promise and role of point of care testing for sickle cell disease. Br J Haematol. 2022;196(1):63-9.
119. Marcheco-Teruel B. Sickle Cell Anemia in Cuba: Prevention and Management, 1982-2018. MEDICC Rev. 2019;21(4):34-8.
120. Rahimy MC, Gangbo A, Ahouignan G, Alihonou E. Newborn screening for sickle cell disease in the Republic of Benin. J Clin Pathol. 2009;62(1):46-8.
121. Frömmel C. Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies: A Short Review on Classical Laboratory Methods-Isoelectric Focusing, HPLC, and Capillary Electrophoresis. Int J Neonatal Screen. 2018;4(4):39.

122. Mvundura M, Kiyaga C, Metzler M, Kamya C, Lim JM, Maiteki-Sebuguzi C, et al. Cost for sickle cell disease screening using isoelectric focusing with dried blood spot samples and estimation of price thresholds for a point-of-care test in Uganda. J Blood Med. 2019;10:59-67.
123. Moat SJ, Rees D, George RS, King L, Dodd A, Ifederu A, et al. Newborn screening for sickle cell disorders using tandem mass spectrometry: three years' experience of using a protocol to detect only the disease states. Ann Clin Biochem. 2017;54(5):601-11.
124. Naubourg P, El Osta M, Rageot D, Grunewald O, Renom G, Ducoroy P, et al. A Multicentre Pilot Study of a Two-Tier Newborn Sickle Cell Disease Screening Procedure with a First Tier Based on a Fully Automated MALDI-TOF MS Platform. Int J Neonatal Screen. 2019;5(1):10.
125. El-Haj N, Hoppe CC. Newborn Screening for SCD in the USA and Canada. Int J Neonatal Screen. 2018;4(4):36.
126. Daniel Y, Elion J, Allaf B, Badens C, Bouva MJ, Brincat I, et al. Newborn Screening for Sickle Cell Disease in Europe. Int J Neonatal Screen. 2019;5(1):15.
127. Knight-Madden J, Lee K, Elana G, Elenga N, Marcheco-Teruel B, Keshi N, et al. Newborn Screening for Sickle Cell Disease in the Caribbean: An Update of the Present Situation and of the Disease Prevalence. Int J Neonatal Screen. 2019;5(1):5.
128. Silva-Pinto AC, Alencar de Queiroz MC, Antoniazzo Zamaro PJ, Arruda M, Pimentel Dos Santos H. The Neonatal Screening Program in Brazil, Focus on Sickle Cell Disease (SCD). Int J Neonatal Screen. 2019;5(1):11.
129. Diallo DA, Guindo A. Sickle cell disease in sub-Saharan Africa: stakes and strategies for control of the disease. Curr Opin Hematol. 2014;21(3):210-4.
130. Steele C, Sinski A, Asibey J, Hardy-Dessources MD, Elana G, Brennan C, et al. Point-of-care screening for sickle cell disease in low-resource settings: A multi-center evaluation of HemoTypeSC, a novel rapid test. Am J Hematol. 2019;94(1):39-45.
131. Rahimy MC. [Early detection and medical management of sickle cell anemia: five years of experience in Cotonou]. Arch Pediatr. 1999;6 Suppl 2:343s-4s.
132. Segbefia CI, Goka B, Welbeck J, Amegan-Aho K, Dwuma-Badu D, Rao S, et al. Implementing newborn screening for sickle cell disease in Korle Bu Teaching Hospital, Accra: Results and lessons learned. Pediatr Blood Cancer. 2021;68(7):e29068.
133. Telfer P, Coen P, Chakravorty S, Wilkey O, Evans J, Newell H, et al. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. Haematologica. 2007;92(7):905-12.
134. Al Arrayed S, Al Hajeri A. Newborn Screening Services in Bahrain between 1985 and 2010. Adv Hematol. 2012;2012:903219.
135. McGann PT, Ferris MG, Ramamurthy U, Santos B, de Oliveira V, Bernardino L, et al. A prospective newborn screening and treatment program for sickle cell anemia in Luanda, Angola. Am J Hematol. 2013;88(12):984-9.
136. Couque N, Girard D, Ducrocq R, Boizeau P, Haouari Z, Missud F, et al. Improvement of medical care in a cohort of newborns with sickle-cell disease in North Paris: impact of national guidelines. Br J Haematol. 2016;173(6):927-37.
137. McGann PT, Grosse SD, Santos B, de Oliveira V, Bernardino L, Kassebaum NJ, et al. A Cost-Effectiveness Analysis of a Pilot Neonatal Screening Program for Sickle Cell Anemia in the Republic of Angola. J Pediatr. 2015;167(6):1314-9.
138. James J, Dormandy E. Improving Screening Programmes for Sickle Cell Disorders and Other Haemoglobinopathies in Europe: The Role of Patient Organisations. Int J Neonatal Screen. 2019;5(1):12.
139. King LG, Bortolusso-Ali S, Cunningham-Myrie CA, Reid ME. Impact of a Comprehensive Sickle Cell Center on Early Childhood Mortality in a Developing Country: The Jamaican Experience. J Pediatr. 2015;167(3):702-5.e1.

140. Brousse V, Arnaud C, Lesprit E, Quinet B, Odievre MH, Etienne-Julan M, et al. Evaluation of Outcomes and Quality of Care in Children with Sickle Cell Disease Diagnosed by Newborn Screening: A Real-World Nation-Wide Study in France. J Clin Med. 2019;8(10).
141. Regional Committee for Africa. Progress in the implementation of the African Region sickle-cell strategy 2010–2020: information document. Brazzaville: World Health Organization. Regional Office for Africa; 2020.
142. Therrell BL, Jr. U.S. newborn screening policy dilemmas for the twenty-first century. Mol Genet Metab. 2001;74(1-2):64-74.
143. Green NS, Zapfel A, Nnodu OE, Franklin P, Tubman VN, Chirande L, et al. The Consortium on Newborn Screening in Africa for sickle cell disease: study rationale and methodology. Blood Advances. 2022;6(24):6187-97.
144. Okeke CO, Chianumba RI, Isa H, Asala S, Nnodu OE. Using dried blood spot on HemoTypeSC™, a new frontier for newborn screening for sickle cell disease in Nigeria. Frontiers in Genetics. 2022;13.
145. Oligbu G, Fallaha M, Pay L, Ladhani S. Risk of invasive pneumococcal disease in children with sickle cell disease in the era of conjugate vaccines: a systematic review of the literature. Br J Haematol. 2019;185(4):743-51.
146. Ballas SK. Opioids and Sickle Cell Disease: From Opium to the Opioid Epidemic. J Clin Med. 2021;10(3).
147. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. Jama. 2014;312(10):1033-48.
148. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet. 2017;390(10091):311-23.
149. Tanabe P, Silva S, Bosworth HB, Crawford R, Paice JA, Richardson LD, et al. A randomized controlled trial comparing two vaso-occlusive episode (VOE) protocols in sickle cell disease (SCD). Am J Hematol. 2018;93(2):159-68.
150. Telfer P, Bahal N, Lo A, Challands J. Management of the acute painful crisis in sickle cell disease- a re-evaluation of the use of opioids in adult patients. Br J Haematol. 2014;166(2):157-64.
151. Carden MA, Patil P, Ahmad ME, Lam WA, Joiner CH, Morris CR. Variations in pediatric emergency medicine physician practices for intravenous fluid management in children with sickle cell disease and vaso-occlusive pain: A single institution experience. Pediatr Blood Cancer. 2018;65(1).
152. Bartolucci P, El Murr T, Roudot-Thoraval F, Habibi A, Santin A, Renaud B, et al. A randomized, controlled clinical trial of ketoprofen for sickle-cell disease vaso-occlusive crises in adults. Blood. 2009;114(18):3742-7.
153. Bellet PS, Kalinyak KA, Shukla R, Gelfand MJ, Rucknagel DL. Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. N Engl J Med. 1995;333(11):699-703.
154. Sobota A, Graham DA, Heeney MM, Neufeld EJ. Corticosteroids for acute chest syndrome in children with sickle cell disease: variation in use and association with length of stay and readmission. Am J Hematol. 2010;85(1):24-8.
155. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000;342(25):1855-65.
156. DeBaun MR, Jordan LC, King AA, Schatz J, Vichinsky E, Fox CK, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv. 2020;4(8):1554-88.
157. Habibi A, Arlet JB, Stankovic K, Gellen-Dautremer J, Ribeil JA, Bartolucci P, et al. Recommandations françaises de prise en charge de la drépanocytose de l'adulte : actualisation 2015. La Revue de Médecine Interne. 2015;36(5, Supplement 1):5S3-5S84.
158. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339(1):5-11.

159. Ware RE. Optimizing hydroxyurea therapy for sickle cell anemia. Hematology Am Soc Hematol Educ Program. 2015;2015:436-43.
160. Chou ST. Transfusion therapy for sickle cell disease: a balancing act. Hematology Am Soc Hematol Educ Program. 2013;2013:439-46.
161. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. Br J Haematol. 2017;176(2):192-209.
162. Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med. 2005;353(26):2769-78.
163. Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, Sarnaik S, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. Lancet. 2016;387(10019):661-70.
164. Candotti D, Tagny-Tayou C, Laperche S. Challenges in transfusion-transmitted infection screening in Sub-Saharan Africa. Transfus Clin Biol. 2021;28(2):163-70.
165. Pirenne F, Yazdanbakhsh K. How I safely transfuse patients with sickle-cell disease and manage delayed hemolytic transfusion reactions. Blood. 2018;131(25):2773-81.
166. Socolovsky M. Molecular insights into stress erythropoiesis. Curr Opin Hematol. 2007;14(3):215-24.
167. Conran N, Belcher JD. Inflammation in sickle cell disease. Clin Hemorheol Microcirc. 2018;68(2-3):263-99.
168. Cokic VP, Andric SA, Stojilkovic SS, Noguchi CT, Schechter AN. Hydroxyurea nitrosylates and activates soluble guanylyl cyclase in human erythroid cells. Blood. 2008;111(3):1117-23.
169. Conran N, de Alvarenga Maximo C, Oliveira T, Fertrin KY, Lobo C, Costa FF. Safe use of hydroxycarbamide in sickle cell disease patients hospitalized for painful vaso-occlusive episodes during the randomized, open-label HELPS study. Br J Haematol. 2022;199(1):153-7.
170. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med. 1995;332(20):1317-22.
171. Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong FD, Smith W, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. Am J Hematol. 2010;85(6):403-8.
172. Voskaridou E, Christoulas D, Bilalis A, Plata E, Varvagiannis K, Stamatopoulos G, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). Blood. 2010;115(12):2354-63.
173. Lobo CL, Pinto JF, Nascimento EM, Moura PG, Cardoso GP, Hankins JS. The effect of hydroxcarbamide therapy on survival of children with sickle cell disease. Br J Haematol. 2013;161(6):852-60.
174. Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet. 2011;377(9778):1663-72.
175. Qureshi A, Kaya B, Pancham S, Keenan R, Anderson J, Akanni M, et al. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. Br J Haematol. 2018;181(4):460-75.
176. Tshilolo L, Tomlinson G, Williams TN, Santos B, Olupot-Olupot P, Lane A, et al. Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med. 2019;380(2):121-31.
177. Menzel S, Thein SL. Genetic Modifiers of Fetal Haemoglobin in Sickle Cell Disease. Mol Diagn Ther. 2019;23(2):235-44.
178. Fitzhugh CD, Hsieh MM, Allen D, Coles WA, Seamon C, Ring M, et al. Hydroxyurea-Increased Fetal Hemoglobin Is Associated with Less Organ Damage and Longer Survival in Adults with Sickle Cell Anemia. PLoS One. 2015;10(11):e0141706.

179. Qureshi A, Kaya B, Pancham S, Keenan R, Anderson J, Akanni M, et al. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. Br J Haematol. 2018;181(4):460-75.
180. Luchtman-Jones L, Pressel S, Hilliard L, Brown RC, Smith MG, Thompson AA, et al. Effects of hydroxyurea treatment for patients with hemoglobin SC disease. Am J Hematol. 2016;91(2):238-42.
181. Gille AS, Pondarré C, Dalle JH, Bernaudin F, Chalas C, Fahd M, et al. Hydroxyurea does not affect the spermatogonial pool in prepubertal patients with sickle cell disease. Blood. 2021;137(6):856-9.
182. Ballas SK, McCarthy WF, Guo N, DeCastro L, Bellevue R, Barton BA, et al. Exposure to hydroxyurea and pregnancy outcomes in patients with sickle cell anemia. J Natl Med Assoc. 2009;101(10):1046-51.
183. de Montalembert M, Voskaridou E, Oevermann L, Cannas G, Habibi A, Loko G, et al. Real-Life experience with hydroxyurea in patients with sickle cell disease: Results from the prospective ESCORT-HU cohort study. Am J Hematol. 2021;96(10):1223-31.
184. Ware RE, Dertinger SD. Absence of hydroxyurea-induced mutational effects supports higher utilisation for the treatment of sickle cell anaemia. Br J Haematol. 2021;194(2):252-66.
185. Ware RE, Marahatta A, Ware JL, McElhinney K, Dong M, Vinks AA. Hydroxyurea Exposure in Lactation: a Pharmacokinetics Study (HELPS). J Pediatr. 2020;222:236-9.
186. McArthur JG, Svenstrup N, Chen C, Fricot A, Carvalho C, Nguyen J, et al. A novel, highly potent and selective phosphodiesterase-9 inhibitor for the treatment of sickle cell disease. Haematologica. 2020;105(3):623-31.
187. Perrine SP, Ginder GD, Faller DV, Dover GH, Ikuta T, Witkowska HE, et al. A short-term trial of butyrate to stimulate fetal-globin-gene expression in the beta-globin disorders. N Engl J Med. 1993;328(2):81-6.
188. Koshy M, Dorn L, Bressler L, Molokie R, Lavelle D, Talischy N, et al. 2-deoxy 5-azacytidine and fetal hemoglobin induction in sickle cell anemia. Blood. 2000;96(7):2379-84.
189. Molokie R, Lavelle D, Gowhari M, Pacini M, Krauz L, Hassan J, et al. Oral tetrahydrouridine and decitabine for non-cytotoxic epigenetic gene regulation in sickle cell disease: A randomized phase 1 study. PLoS Med. 2017;14(9):e1002382.
190. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med. 2019;381(6):509-19.
191. Quinn CT, Ware RE. Increased oxygen affinity: to have and to hold. Blood. 2021;138(13):1094-5.
192. Shrestha A, Chi M, Wagner K, Malik A, Korpik J, Drake A, et al. FT-4202, an oral PKR activator, has potent antisickling effects and improves RBC survival and Hb levels in SCA mice. Blood Adv. 2021;5(9):2385-90.
193. Matte A, Federti E, Kung C, Kosinski PA, Narayanaswamy R, Russo R, et al. The pyruvate kinase activator mitapivat reduces hemolysis and improves anemia in a β-thalassemia mouse model. J Clin Invest. 2021;131(10).
194. El Nemer W, Godard A, El Hoss S. Ineffective erythropoiesis in sickle cell disease: new insights and future implications. Curr Opin Hematol. 2021;28(3):171-6.
195. Biemond BJ, Tombak A, Kilinc Y, Al-Khabori M, Abboud M, Nafea M, et al. Sevuparin for the treatment of acute pain crisis in patients with sickle cell disease: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Haematol. 2021;8(5):e334-e43.
196. Heeney MM, Hoppe CC, Abboud MR, Inusa B, Kanter J, Ogutu B, et al. A Multinational Trial of Prasugrel for Sickle Cell Vaso-Occlusive Events. N Engl J Med. 2016;374(7):625-35.
197. Nyffenegger N, Zennadi R, Kalleda N, Flace A, Ingoglia G, Buzzi RM, et al. The oral ferroportin inhibitor vamifeport improves hemodynamics in a mouse model of sickle cell disease. Blood. 2022;140(7):769-81.

198. Lee MT, Kattan M, Fennoy I, Arpadi SM, Miller RL, Cremers S, et al. Randomized phase 2 trial of monthly vitamin D to prevent respiratory complications in children with sickle cell disease. Blood Adv. 2018;2(9):969-78.
199. World Health Organization (WHO). Blood safety and availability Geneva, Switzerland: World Health Organization; 2020 [Available from: https://www.who.int/news-room/fact-sheets/detail/blood-safety-and-availability.
200. Diaku-Akinwumi IN, Abubakar SB, Adegoke SA, Adeleke S, Adewoye O, Adeyemo T, et al. Blood transfusion services for patients with sickle cell disease in Nigeria. Int Health. 2016;8(5):330-5.
201. Diop S, Pirenne F. Transfusion and sickle cell anemia in Africa. Transfus Clin Biol. 2021;28(2):143-5.
202. Maitland K, Kiguli S, Olupot-Olupot P, Engoru C, Mallewa M, Saramago Goncalves P, et al. Immediate Transfusion in African Children with Uncomplicated Severe Anemia. N Engl J Med. 2019;381(5):407-19.
203. Lagunju I, Brown BJ, Oyinlade AO, Asinobi A, Ibeh J, Esione A, et al. Annual stroke incidence in Nigerian children with sickle cell disease and elevated TCD velocities treated with hydroxyurea. Pediatr Blood Cancer. 2019;66(3):e27252.
204. Power-Hays A, Ware RE. Effective use of hydroxyurea for sickle cell anemia in low-resource countries. Curr Opin Hematol. 2020;27(3):172-80.
205. Paintsil V, Ally M, Isa H, Anie KA, Mgaya J, Nkanyemka M, et al. Development of multi-level standards of care recommendations for sickle cell disease: Experience from SickleInAfrica. Frontiers in Genetics. 2023;13.
206. Sickle Cell Society. Standards for the clinical care of adults with sickle cell disease in the UK. 2018.
207. Abraham AA, Tisdale JF. Gene therapy for sickle cell disease: moving from the bench to the bedside. Blood. 2021;138(11):932-41.
208. Gluckman E, Cappelli B, Bernaudin F, Labopin M, Volt F, Carreras J, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood. 2017;129(11):1548-56.
209. Eapen M, Brazauskas R, Walters MC, Bernaudin F, Bo-Subait K, Fitzhugh CD, et al. Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study. Lancet Haematol. 2019;6(11):e585-e96.
210. Alzahrani M, Damlaj M, Jeffries N, Alahmari B, Singh A, Rondelli D, et al. Non-myeloablative human leukocyte antigen-matched related donor transplantation in sickle cell disease: outcomes from three independent centres. Br J Haematol. 2021;192(4):761-8.
211. Guilcher GMT, Monagel DA, Nettel-Aguirre A, Truong TH, Desai SJ, Bruce A, et al. Nonmyeloablative Matched Sibling Donor Hematopoietic Cell Transplantation in Children and Adolescents with Sickle Cell Disease. Biol Blood Marrow Transplant. 2019;25(6):1179-86.
212. Shenoy S, Eapen M, Panepinto JA, Logan BR, Wu J, Abraham A, et al. A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. Blood. 2016;128(21):2561-7.
213. Ngwube A, Shah N, Godder K, Jacobsohn D, Hulbert ML, Shenoy S. Abatacept is effective as GVHD prophylaxis in unrelated donor stem cell transplantation for children with severe sickle cell disease. Blood Adv. 2020;4(16):3894-9.
214. Parikh S, Brochstein JA, Galamidi E, Schwarzbach A, Kurtzberg J. Allogeneic stem cell transplantation with omidubicel in sickle cell disease. Blood Adv. 2021;5(3):843-52.
215. Fitzhugh CD, Hsieh MM, Taylor T, Coles W, Roskom K, Wilson D, et al. Cyclophosphamide improves engraftment in patients with SCD and severe organ damage who undergo haploidentical PBSCT. Blood Adv. 2017;1(11):652-61.
216. Gaziev J, Isgro A, Sodani P, Paciaroni K, De Angelis G, Marziali M, et al. Haploidentical HSCT for hemoglobinopathies: improved outcomes with TCRalphabeta(+)/CD19(+)-depleted grafts. Blood Adv. 2018;2(3):263-70.

217. Foell J, Schulte JH, Pfirstinger B, Troeger A, Wolff D, Edinger M, et al. Haploidentical CD3 or alpha/beta T-cell depleted HSCT in advanced stage sickle cell disease. Bone Marrow Transplant. 2019;54(11):1859-67.
218. Dunbar CE, High KA, Joung JK, Kohn DB, Ozawa K, Sadelain M. Gene therapy comes of age. Science. 2018;359(6372).
219. Cavazzana-Calvo M, Hacein-Bey S, de Saint Basile G, Gross F, Yvon E, Nusbaum P, et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science. 2000;288(5466):669-72.
220. Blaese RM, Culver KW, Miller AD, Carter CS, Fleisher T, Clerici M, et al. T lymphocyte-directed gene therapy for ADA- SCID: initial trial results after 4 years. Science. 1995;270(5235):475-80.
221. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, McCormack MP, Wulffraat N, Leboulch P, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science. 2003;302(5644):415-9.
222. Ferrari G, Thrasher AJ, Aiuti A. Gene therapy using haematopoietic stem and progenitor cells. Nat Rev Genet. 2021;22(4):216-34.
223. Thompson AA, Walters MC, Kwiatkowski J, Rasko JEJ, Ribeil JA, Hongeng S, et al. Gene Therapy in Patients with Transfusion-Dependent beta-Thalassemia. N Engl J Med. 2018;378(16):1479-93.
224. Tisdale JF, Pierciey FJ, Jr., Bonner M, Thompson AA, Krishnamurti L, Mapara MY, et al. Safety and feasibility of hematopoietic progenitor stem cell collection by mobilization with plerixafor followed by apheresis vs bone marrow harvest in patients with sickle cell disease in the multi-center HGB-206 trial. Am J Hematol. 2020;95(9):E239-E42.
225. Esrick EB, Manis JP, Daley H, Baricordi C, Trebeden-Negre H, Pierciey FJ, et al. Successful hematopoietic stem cell mobilization and apheresis collection using plerixafor alone in sickle cell patients. Blood Adv. 2018;2(19):2505-12.
226. Lagresle-Peyrou C, Lefrere F, Magrin E, Ribeil JA, Romano O, Weber L, et al. Plerixafor enables safe, rapid, efficient mobilization of hematopoietic stem cells in sickle cell disease patients after exchange transfusion. Haematologica. 2018;103(5):778-86.
227. Cavazzana-Calvo M, Payen E, Negre O, Wang G, Hehir K, Fusil F, et al. Transfusion independence and HMGA2 activation after gene therapy of human beta-thalassaemia. Nature. 2010;467(7313):318-22.
228. Pawliuk R, Westerman KA, Fabry ME, Payen E, Tighe R, Bouhassira EE, et al. Correction of sickle cell disease in transgenic mouse models by gene therapy. Science. 2001;294(5550):2368-71.
229. Negre O, Eggimann AV, Beuzard Y, Ribeil JA, Bourget P, Borwornpinyo S, et al. Gene Therapy of the beta-Hemoglobinopathies by Lentiviral Transfer of the beta(A(T87Q))-Globin Gene. Hum Gene Ther. 2016;27(2):148-65.
230. Kanter JW TJ, Mapara MY, Kwiatkowski JL, Krishnamurti L, Schmidt M, Miller AL , Pierciey FJ, Huang W, Ribeil JA, Thompson AA, Walters MC. Resolution of Sickle Cell Disease Manifestations in Patients Treated with Lentiglobin Gene Therapy: Updated Results from the Phase 1/2 Hgb-206 Group C Study [abstract]. Blood. 2019;134:990.
231. Kanter J, Walters MC, Hsieh M, Krishnamurti L, Kwiatkowski JL, Kamble R, von Kalle C, Joseney-Antoine M, Pierciey FJ, Shi W, Asmal M, Thompson AA, Tisdale JF. Interim Results from a Phase 1/2 Clinical Study of Lentiglobin Gene Therapy for Severe Sickle Cell Disease [abstract]. Blood. 2017;130:527.
232. Kanter J, Walters MC, Krishnamurti L, Mapara MY, Kwiatkowski JL, Rifkin-Zenenberg S, et al. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. N Engl J Med. 2021.
233. Thompson AA WM, Mapara MY, Kwiatkowski JL, Krishnamurti L, Aygun B, Kasow KA, Rifkin-Zenenberg S, Schmidt M, DelCarpini J, Pierciey FJ, Miller AL, Gallagher ME, Chen R, Goyal S, Kanter J, Tisdale JF. Resolution of Serious Vaso-Occlusive Pain Crises and Reduction in Patient-Reported Pain Intensity: Results from the Ongoing Phase 1/2 HGB-206 Group C Study of LentiGlobin for Sickle Cell Disease (bb1111) Gene Therapy [abstract]. Blood. 2020;136:16-7.

234. Menzel S, Garner C, Gut I, Matsuda F, Yamaguchi M, Heath S, et al. A QTL influencing F cell production maps to a gene encoding a zinc-finger protein on chromosome 2p15. Nat Genet. 2007;39(10):1197-9.
235. Lettre G, Sankaran VG, Bezerra MA, Araujo AS, Uda M, Sanna S, et al. DNA polymorphisms at the BCL11A, HBS1L-MYB, and beta-globin loci associate with fetal hemoglobin levels and pain crises in sickle cell disease. Proc Natl Acad Sci U S A. 2008;105(33):11869-74.
236. Sankaran VG, Menne TF, Xu J, Akie TE, Lettre G, Van Handel B, et al. Human fetal hemoglobin expression is regulated by the developmental stage-specific repressor BCL11A. Science. 2008;322(5909):1839-42.
237. Xu J, Peng C, Sankaran VG, Shao Z, Esrick EB, Chong BG, et al. Correction of sickle cell disease in adult mice by interference with fetal hemoglobin silencing. Science. 2011;334(6058):993-6.
238. Esrick EB, Lehmann LE, Biffi A, Achebe M, Brendel C, Ciuculescu MF, et al. Post-Transcriptional Genetic Silencing of BCL11A to Treat Sickle Cell Disease. N Engl J Med. 2021;384(3):205-15.
239. Grimley M AM, Shrestha A, Felker S, Lutzko C, Arumugam PI, Witting S, Knight-Madden J, Niss O, Quinn CT, Lo C, Little CR, McIntosh JW, Malik P. Early Results from a Phase 1/2 Study of Aru-1801 Gene Therapy for Sickle Cell Disease (SCD): Manufacturing Process Enhancements Improve Efficacy of a Modified Gamma Globin Lentivirus Vector and Reduced Intensity Conditioning Transplant [abstract]. Blood. 2020;136:20-1.
240. Hsieh MM, Bonner M, Pierciey FJ, Uchida N, Rottman J, Demopoulos L, et al. Myelodysplastic syndrome unrelated to lentiviral vector in a patient treated with gene therapy for sickle cell disease. Blood Adv. 2020;4(9):2058-63.
241. Leonard A, Tisdale JF. A pause in gene therapy: Reflecting on the unique challenges of sickle cell disease. Mol Ther. 2021;29(4):1355-6.
242. Grimley M, Asnani M, Shrestha A, Felker S, Lutzko C, Arumugam PI, et al. Safety and Efficacy of Aru-1801 in Patients with Sickle Cell Disease: Early Results from the Phase 1/2 Momentum Study of a Modified Gamma Globin Gene Therapy and Reduced Intensity Conditioning. Blood. 2021;138(Supplement 1):3970-.
243. Bhoopalan SV, Yen JS, Levine RM, Sharma A. Editing human hematopoietic stem cells: advances and challenges. Cytotherapy. 2022.
244. Doerfler PA, Sharma A, Porter JS, Zheng Y, Tisdale JF, Weiss MJ. Genetic therapies for the first molecular disease. J Clin Invest. 2021;131(8).
245. Drysdale CM, Nassehi T, Gamer J, Yapundich M, Tisdale JF, Uchida N. Hematopoietic-Stem-Cell-Targeted Gene-Addition and Gene-Editing Strategies for beta-hemoglobinopathies. Cell Stem Cell. 2021;28(2):191-208.
246. Forget BG. Molecular basis of hereditary persistence of fetal hemoglobin. Ann N Y Acad Sci. 1998;850:38-44.
247. Eaton WA, Bunn HF. Treating sickle cell disease by targeting HbS polymerization. Blood. 2017;129(20):2719-26.
248. Bartman CR, Hsu SC, Hsiung CC, Raj A, Blobel GA. Enhancer Regulation of Transcriptional Bursting Parameters Revealed by Forced Chromatin Looping. Mol Cell. 2016;62(2):237-47.
249. Palstra RJ, Tolhuis B, Splinter E, Nijmeijer R, Grosveld F, de Laat W. The beta-globin nuclear compartment in development and erythroid differentiation. Nat Genet. 2003;35(2):190-4.
250. Uda M, Galanello R, Sanna S, Lettre G, Sankaran VG, Chen W, et al. Genome-wide association study shows BCL11A associated with persistent fetal hemoglobin and amelioration of the phenotype of beta-thalassemia. Proc Natl Acad Sci U S A. 2008;105(5):1620-5.
251. Chang KH, Smith SE, Sullivan T, Chen K, Zhou Q, West JA, et al. Long-Term Engraftment and Fetal Globin Induction upon BCL11A Gene Editing in Bone-Marrow-Derived CD34(+) Hematopoietic Stem and Progenitor Cells. Mol Ther Methods Clin Dev. 2017;4:137-48.
252. Psatha N, Reik A, Phelps S, Zhou Y, Dalas D, Yannaki E, et al. Disruption of the BCL11A Erythroid Enhancer Reactivates Fetal Hemoglobin in Erythroid Cells of Patients with beta-Thalassemia Major. Mol Ther Methods Clin Dev. 2018;10:313-26.

253. Bauer DE, Kamran SC, Lessard S, Xu J, Fujiwara Y, Lin C, et al. An erythroid enhancer of BCL11A subject to genetic variation determines fetal hemoglobin level. Science. 2013;342(6155):253-7.
254. Canver MC, Smith EC, Sher F, Pinello L, Sanjana NE, Shalem O, et al. BCL11A enhancer dissection by Cas9-mediated in situ saturating mutagenesis. Nature. 2015;527(7577):192-7.
255. Wu Y, Zeng J, Roscoe BP, Liu P, Yao Q, Lazzarotto CR, et al. Highly efficient therapeutic gene editing of human hematopoietic stem cells. Nat Med. 2019;25(5):776-83.
256. Frangoul H, Altshuler D, Cappellini MD, Chen YS, Domm J, Eustace BK, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and beta-Thalassemia. N Engl J Med. 2021;384(3):252-60.
257. Lessard S, Rimmele P, Ling H, Moran K, Vieira B, Lin Y-D, et al. Zinc Finger Nuclease-Mediated Disruption of the BCL11A Erythroid Enhancer Results in Enriched Biallelic Editing, Increased Fetal Hemoglobin, and Reduced Sickling in Erythroid Cells Derived from Sickle Cell Disease Patients. Blood. 2019;134(Supplement_1):974-.
258. Moran K, Ling H, Lessard S, Vieira B, Hong V, Holmes MC, et al. Ex Vivo Gene-Edited Cell Therapy for Sickle Cell Disease: Disruption of the BCL11A Erythroid Enhancer with Zinc Finger Nucleases Increases Fetal Hemoglobin in Plerixafor Mobilized Human CD34+ Cells. Blood. 2018;132(Supplement 1):2190-.
259. Metais JY, Doerfler PA, Mayuranathan T, Bauer DE, Fowler SC, Hsieh MM, et al. Genome editing of HBG1 and HBG2 to induce fetal hemoglobin. Blood Adv. 2019;3(21):3379-92.
260. Traxler EA, Yao Y, Wang YD, Woodard KJ, Kurita R, Nakamura Y, et al. A genome-editing strategy to treat beta-hemoglobinopathies that recapitulates a mutation associated with a benign genetic condition. Nat Med. 2016;22(9):987-90.
261. Weber L, Frati G, Felix T, Hardouin G, Casini A, Wollenschlaeger C, et al. Editing a gamma-globin repressor binding site restores fetal hemoglobin synthesis and corrects the sickle cell disease phenotype. Sci Adv. 2020;6(7).
262. Antoniani C, Meneghini V, Lattanzi A, Felix T, Romano O, Magrin E, et al. Induction of fetal hemoglobin synthesis by CRISPR/Cas9-mediated editing of the human beta-globin locus. Blood. 2018;131(17):1960-73.
263. Masuda T, Wang X, Maeda M, Canver MC, Sher F, Funnell AP, et al. Transcription factors LRF and BCL11A independently repress expression of fetal hemoglobin. Science. 2016;351(6270):285-9.
264. Humbert O, Radtke S, Samuelson C, Carrillo RR, Perez AM, Reddy SS, et al. Therapeutically relevant engraftment of a CRISPR-Cas9-edited HSC-enriched population with HbF reactivation in nonhuman primates. Sci Transl Med. 2019;11(503):eaaw3768.
265. Chang K-H, Sanchez M, Heath J, deDreuzy E, Haskett S, Vogelaar A, et al. Comparative Studies Reveal Robust HbF Induction By Editing of HBG1/2 Promoters or BCL11A Erythroid-Enhancer in Human CD34+ Cells but That BCL11A Erythroid-Enhancer Editing Is Associated with Selective Reduction in Erythroid Lineage Reconstitution in a Xenotransplantation Model. Blood. 2018;132(Supplement 1):409-.
266. Sharma A, Boelens JJ, Cancio MI, Hankins J, Bhad PA, Lewandowski A, et al. Treatment of Individuals with Severe Sickle Cell Disease with OTQ923, an Autologous, Ex Vivo, CRISPR/Cas9-Edited, CD34+ Hematopoietic Stem and Progenitor Cell Product, Leads to Durable Engraftment and Fetal Hemoglobin Induction. Blood. 2022;140(Supplement 1):1906-8.
267. Urnov FD, Miller JC, Lee YL, Beausejour CM, Rock JM, Augustus S, et al. Highly efficient endogenous human gene correction using designed zinc-finger nucleases. Nature. 2005;435(7042):646-51.
268. Pattabhi S, Lotti SN, Berger MP, Singh S, Lux CT, Jacoby K, et al. In Vivo Outcome of Homology-Directed Repair at the HBB Gene in HSC Using Alternative Donor Template Delivery Methods. Mol Ther Nucleic Acids. 2019;17:277-88.
269. Wilkinson AC, Dever DP, Baik R, Camarena J, Hsu I, Charlesworth CT, et al. Cas9-AAV6 gene correction of beta-globin in autologous HSCs improves sickle cell disease erythropoiesis in mice. Nat Commun. 2021;12(1):686.

270. Cai L, Bai H, Mahairaki V, Gao Y, He C, Wen Y, et al. A Universal Approach to Correct Various HBB Gene Mutations in Human Stem Cells for Gene Therapy of Beta-Thalassemia and Sickle Cell Disease. Stem Cells Transl Med. 2018;7(1):87-97.
271. Hoban MD, Cost GJ, Mendel MC, Romero Z, Kaufman ML, Joglekar AV, et al. Correction of the sickle cell disease mutation in human hematopoietic stem/progenitor cells. Blood. 2015;125(17):2597-604.
272. Hoban MD, Lumaquin D, Kuo CY, Romero Z, Long J, Ho M, et al. CRISPR/Cas9-Mediated Correction of the Sickle Mutation in Human CD34+ cells. Mol Ther. 2016;24(9):1561-9.
273. Park SH, Lee CM, Dever DP, Davis TH, Camarena J, Srifa W, et al. Highly efficient editing of the beta-globin gene in patient-derived hematopoietic stem and progenitor cells to treat sickle cell disease. Nucleic Acids Res. 2019;47(15):7955-72.
274. Dever DP, Bak RO, Reinisch A, Camarena J, Washington G, Nicolas CE, et al. CRISPR/Cas9 beta-globin gene targeting in human haematopoietic stem cells. Nature. 2016;539(7629):384-9.
275. Yang H, Ren S, Yu S, Pan H, Li T, Ge S, et al. Methods Favoring Homology-Directed Repair Choice in Response to CRISPR/Cas9 Induced-Double Strand Breaks. Int J Mol Sci. 2020;21(18).
276. Uchida N, Li L, Nassehi T, Drysdale CM, Yapundich M, Gamer J, et al. Preclinical evaluation for engraftment of CD34(+) cells gene-edited at the sickle cell disease locus in xenograft mouse and non-human primate models. Cell Rep Med. 2021;2(4):100247.
277. Gaudelli NM, Komor AC, Rees HA, Packer MS, Badran AH, Bryson DI, et al. Programmable base editing of A*T to G*C in genomic DNA without DNA cleavage. Nature. 2017;551(7681):464-71.
278. Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature. 2016;533(7603):420-4.
279. Haapaniemi E, Botla S, Persson J, Schmierer B, Taipale J. CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response. Nat Med. 2018;24(7):927-30.
280. Leibowitz ML, Papathanasiou S, Doerfler PA, Blaine LJ, Sun L, Yao Y, et al. Chromothripsis as an on-target consequence of CRISPR-Cas9 genome editing. Nat Genet. 2021;53(6):895-905.
281. Zeng J, Wu Y, Ren C, Bonanno J, Shen AH, Shea D, et al. Therapeutic base editing of human hematopoietic stem cells. Nat Med. 2020;26(4):535-41.
282. Wang L, Li L, Ma Y, Hu H, Li Q, Yang Y, et al. Reactivation of gamma-globin expression through Cas9 or base editor to treat beta-hemoglobinopathies. Cell Res. 2020;30(3):276-8.
283. Li C, Georgakopoulou A, Mishra A, Gil S, Hawkins RD, Yannaki E, et al. In vivo HSPC gene therapy with base editors allows for efficient reactivation of fetal gamma-globin in beta-YAC mice. Blood Adv. 2021;5(4):1122-35.
284. Newby GA, Yen JS, Woodard KJ, Mayuranathan T, Lazzarotto CR, Li Y, et al. Base editing of haematopoietic stem cells rescues sickle cell disease in mice. Nature. 2021;595(7866):295-302.
285. Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature. 2019;576(7785):149-57.
286. Frangoul H, Locatelli F, Bhatia M, Mapara MY, Molinari L, Sharma A, et al. Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Severe Sickle Cell Disease. Blood. 2022;140(Supplement 1):29-31.
287. Alavi A, Krishnamurti L, Abedi M, Galeon I, Reiner D, Smith SE, et al. Preliminary Safety and Efficacy Results from Precizn-1: An Ongoing Phase 1/2 Study on Zinc Finger Nuclease-Modified Autologous CD34+ HSPCs for Sickle Cell Disease (SCD). Blood. 2021;138(Supplement 1):2930-.
288. Cohen J, Kaiser J. Gates and NIH join forces on HIV and sickle cell diseases. Science. 2019;366(6465):558-9.
289. Cannon P, Asokan A, Czechowicz A, Hammond P, Kohn DB, Lieber A, et al. Safe and Effective In Vivo Targeting and Gene Editing in Hematopoietic Stem Cells: Strategies for Accelerating Development. Hum Gene Ther. 2021;32(1-2):31-42.
290. Amirache F, Levy C, Costa C, Mangeot PE, Torbett BE, Wang CX, et al. Mystery solved: VSV-G-LVs do not allow efficient gene transfer into unstimulated T cells, B cells, and HSCs because they lack the LDL receptor. Blood. 2014;123(9):1422-4.

291. Ikawa Y, Miccio A, Magrin E, Kwiatkowski JL, Rivella S, Cavazzana M. Gene therapy of hemoglobinopathies: progress and future challenges. Hum Mol Genet. 2019;28(R1):R24-R30.
292. Kesavan G. Innovations in CRISPR-Based Therapies. Mol Biotechnol. 2021.
293. Urbinati F, Campo Fernandez B, Masiuk KE, Poletti V, Hollis RP, Koziol C, et al. Gene Therapy for Sickle Cell Disease: A Lentiviral Vector Comparison Study. Hum Gene Ther. 2018;29(10):1153-66.
294. Li C, Wang H, Georgakopoulou A, Gil S, Yannaki E, Lieber A. In Vivo HSC Gene Therapy Using a Bi-modular HDAd5/35++ Vector Cures Sickle Cell Disease in a Mouse Model. Mol Ther. 2021;29(2):822-37.
295. Cullis PR, Hope MJ. Lipid Nanoparticle Systems for Enabling Gene Therapies. Mol Ther. 2017;25(7):1467-75.
296. Lee L, Smith-Whitley K, Banks S, Puckrein G. Reducing Health Care Disparities in Sickle Cell Disease: A Review. Public Health Rep. 2019;134(6):599-607.
297. McCune JM, Stevenson SC, Doehle BP, Trenor CC, 3rd, Turner EH, Spector JM. Collaborative science to advance gene therapies in resource-limited parts of the world. Mol Ther. 2021;29(11):3101-2.
298. Olatunya O, Adekile A. What every physician should know about the national guidelines for the control and management of sickle cell disease and the parent handbook for sickle cell disease in Nigeria. Nigerian Journal of Clinical Practice. 2017;20(1):123-5.
299. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. Milbank Q. 1996;74(4):511-44.
300. Mainous AG, 3rd, Rooks B, Tanner RJ, Carek PJ, Black V, Coates TD. Shared Care for Adults with Sickle Cell Disease: An Analysis of Care from Eight Health Systems. J Clin Med. 2019;8(8).
301. Brodsky MA, Rodeghier M, Sanger M, Byrd J, McClain B, Covert B, et al. Risk Factors for 30-Day Readmission in Adults with Sickle Cell Disease. Am J Med. 2017;130(5):601.e9-.e15.
302. Crego N, Douglas C, Bonnabeau E, Earls M, Eason K, Merwin E, et al. Sickle-Cell Disease Co-Management, Health Care Utilization, and Hydroxyurea Use. J Am Board Fam Med. 2020;33(1):91-105.
303. Quality NIfCsH. NICHQ.Org | Sickle Cell Disease: Transition Resources 2014 [cited 2016 November 28]. Available from: http://sicklecell.nichq.org/resources/scd-transition-resources.
304. Cronin RM, Mayo-Gamble TL, Stimpson SJ, Badawy SM, Crosby LE, Byrd J, et al. Adapting medical guidelines to be patient-centered using a patient-driven process for individuals with sickle cell disease and their caregivers. BMC Hematol. 2018;18:12.
305. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288-94.
306. Fullerton HJ, Adams RJ, Zhao S, Johnston SC. Declining stroke rates in Californian children with sickle cell disease. Blood. 2004;104(2):336-9.
307. Enninful-Eghan H, Moore RH, Ichord R, Smith-Whitley K, Kwiatkowski JL. Transcranial Doppler ultrasonography and prophylactic transfusion program is effective in preventing overt stroke in children with sickle cell disease. J Pediatr. 2010;157(3):479-84.
308. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke. 2006;37(2):577-617.
309. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2011;42(1):227-76.
310. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines

for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-e418.
311. Ghafuri DL, Abdullahi SU, Dambatta AH, Galadanci J, Tabari MA, Bello-Manga H, et al. Establishing Sickle Cell Disease Stroke Prevention Teams in Africa is Feasible: Program Evaluation Using the RE-AIM Framework. J Pediatr Hematol Oncol. 2021.
312. Adamski C, Terhaar C, DaRe J, Fernandes P, Settler C, Dohany L. Hemoglobinopathy Evaluation in Routine Carrier Testing: Results to Inform Guidelines and Protocols [5O]. Obstetrics & Gynecology. 2019;133:163.
313. Moerdler S, Fraint E, Silver E, Dolan SM, Demasio KA, Roth ME, et al. Prenatal Hemoglobinopathy Screening Practices: Areas for Improvement. Blood. 2019;134(Supplement_1):2298-.
314. Alayed N, Kezouh A, Oddy L, Abenhaim HA. Sickle cell disease and pregnancy outcomes: population-based study on 8.8 million births. J Perinat Med. 2014;42(4):487-92.
315. Odum CU, Anorlu RI, Dim SI, Oyekan TO. Pregnancy outcome in HbSS-sickle cell disease in Lagos, Nigeria. West Afr J Med. 2002;21(1):19-23.
316. Wilson NO, Ceesay FK, Hibbert JM, Driss A, Obed SA, Adjei AA, et al. Pregnancy outcomes among patients with sickle cell disease at Korle-Bu Teaching Hospital, Accra, Ghana: retrospective cohort study. Am J Trop Med Hyg. 2012;86(6):936-42.
317. Muganyizi PS, Kidanto H. Sickle cell disease in pregnancy: trend and pregnancy outcomes at a tertiary hospital in Tanzania. PLoS One. 2013;8(2):e56541.
318. Hoyert DL, Miniño AM. Maternal Mortality in the United States: Changes in Coding, Publication, and Data Release, 2018. Natl Vital Stat Rep. 2020;69(2):1-18.
319. Knight M, Bunch K, Kenyon S, Tuffnell D, Kurinczuk JJ. A national population-based cohort study to investigate inequalities in maternal mortality in the United Kingdom, 2009-17. Paediatr Perinat Epidemiol. 2020;34(4):392-8.
320. Oppong SA, Asare EV, Olayemi E, Boafor T, Dei-Adomakoh Y, Swarry-Deen A, et al. Multidisciplinary care results in similar maternal and perinatal mortality rates for women with and without SCD in a low-resource setting. Am J Hematol. 2019;94(2):223-30.
321. Asare EV, Olayemi E, Boafor T, Dei-Adomakoh Y, Mensah E, Ghansah H, et al. Implementation of multidisciplinary care reduces maternal mortality in women with sickle cell disease living in low-resource setting. Am J Hematol. 2017;92(9):872-8.
322. Oppong SA, Stewart J-A, DeBaun MR. Management of Pregnant Women and Newborns With Sickle Cell Disease. Sickle Cell Disease. 2021:195.
323. No G. Management of sickle cell disease in pregnancy. London: Royal College of Obstetricians and Gynaecologists. 2011.
324. Amer YS, Sabr Y, ElGohary GM, Altaki AM, Khojah OT, El-Malky A, et al. Quality assessment of evidence-based clinical practice guidelines for the management of pregnant women with sickle cell disease using the AGREE II instrument: a systematic review. BMC Pregnancy and Childbirth. 2020;20(1):595.
325. on Obstetrics AC. ACOG Practice Bulletin No. 78: hemoglobinopathies in pregnancy. Obstetrics and gynecology. 2007;109(1):229-37.
326. Escobar Alvarez SN, Myers ER. Impact of a grant program to spur advances in sickle cell disease research. Blood Adv. 2021;5(19):3855-61.
327. Broxmeyer H. Scholarships and Awards Ensure the Future of Hematology. The Hematologist. 2010;7(3).
328. Liem RI, Lanzkron S, T DC, DeCastro L, Desai AA, Ataga KI, et al. American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease. Blood Adv. 2019;3(23):3867-97.
329. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4(2):327-55.

330. Brandow AM, Carroll CP, Creary S, Edwards-Elliott R, Glassberg J, Hurley RW, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. Blood Adv. 2020;4(12):2656-701.
331. Luo L, King AA, Carroll Y, Baumann AA, Brambilla D, Carpenter CR, et al. Electronic Health Record-Embedded Individualized Pain Plans for Emergency Department Treatment of Vaso-occlusive Episodes in Adults With Sickle Cell Disease: Protocol for a Preimplementation and Postimplementation Study. JMIR Res Protoc. 2021;10(4):e24818.
332. Hankins JS, Shah N, DiMartino L, Brambilla D, Fernandez ME, Gibson RW, et al. Integration of Mobile Health Into Sickle Cell Disease Care to Increase Hydroxyurea Utilization: Protocol for an Efficacy and Implementation Study. JMIR Res Protoc. 2020;9(7):e16319.
333. Duckworth L, Black LV, Ezmigna D, Green J, Yao Y, Grannis S, et al. Spirometry use in Patients with Sickle Cell Disease with and without asthma and acute chest syndrome: A Multicenter Study. EJHaem. 2020;1(1):239-42.
334. Price DW, Wagner DP, Krane NK, Rougas SC, Lowitt NR, Offodile RS, et al. What are the implications of implementation science for medical education? Medical Education Online. 2015;20(1):27003.
335. McGaghie WC, Barsuk JH, Cohen ER, Kristopaitis T, Wayne DB. Dissemination of an innovative mastery learning curriculum grounded in implementation science principles: a case study. Acad Med. 2015;90(11):1487-94.
336. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. American journal of public health. 1999;89(9):1322-7.
337. Shelton RC, Chambers DA, Glasgow RE. An Extension of RE-AIM to Enhance Sustainability: Addressing Dynamic Context and Promoting Health Equity Over Time. Frontiers in Public Health. 2020;8(134).
338. Kanter J, Liem RI, Bernaudin F, Bolaños-Meade J, Fitzhugh CD, Hankins JS, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. Blood Adv. 2021;5(18):3668-89.