Chapter 11
Haemoglobinopathies: Genetic Services in India

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Abstract Genetic testing is an integral component of a birth defects service. Using the example of haemoglobinopathies, the most common single-gene disorder, this chapter presents the magnitude of these disorders and describes their consequences on patients and their families. Haemoglobinopathies impact the public health system, because of the chronicity and expensive treatment modalities. Genetic testing and screening are key prevention tools. This chapter discusses the need for development of genetic services in India by describing the magnitude of these conditions and tracks the history of development of services for haemoglobinopathies till the launch of the national guidelines on prevention and control of haemoglobinopathies in India. The relevance of these guidelines and their similarity to global guidelines have been discussed. The need for the programme to be ethical and culturally sensitive in order for it to be successful has also been deliberated. Monitoring of such a programme is important, and the available indicators for monitoring the programme have been examined.

Keywords Haemoglobinopathies · Beta thalassemia · Sickle cell anaemia · Public health · India

Thalassemia, sickle cell anaemia, muscular dystrophy and haemophilia are examples of common genetic (monogenic or single gene) disorders. Single-gene disorders are caused by mutations in a single gene whose function is of critical importance in one or more metabolic pathway(s) of the body. Genetic disorders can be classified based on their pattern of inheritance that is whether they are sex-linked or autosomal, recessive or dominant. Clinical manifestation of the disorder depends on the number of copies of the mutation (recessive or dominant), location (X-linked, Y-linked or autosomal), penetrance, epistatic interactions, presence of secondary modifiers and others. Though individually monogenic disorders are less prevalent than other common diseases and disorders, collectively they affect a significant proportion of the global population. The chronic, often life-threatening nature of the conditions adversely impacts the quality of life of patients and their families. In

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low-income countries, subsidized care is limited or may not be available for all types of genetic disorders. This limited or absence of services causes physical, economic and emotional distress to patients and caregivers. Where available, these services may primarily be available through private medical services which impose considerable financial burden on families.

From a public health perspective, the expenditure needed for patient management, the different clinical types of genetic disorders, their varied diagnoses and treatment modalities make it difficult to view genetic services through the prism of public health services, especially in resource limited settings. Genetic disorders are accorded a low priority in these regions primarily because their management is long term and expensive, and there are more urgent public health challenges in the form of infectious diseases, malnutrition and perinatal complications that are major contributors to child mortality [1]. Public health activities to address prevalent genetic disorders have however started emerging in low- and low-middle-income countries (LMICs). This article focuses on the guidelines for a national prevention and control programme for haemoglobinopathies in India. These guidelines form a first step towards development of a public health genetic service in India.

Haemoglobinopathies

Thalassemias are inherited haemoglobin disorders which together with sickle cell anaemias and other haemoglobin disorders are referred to as haemoglobinopathies. Thalassemias are caused by mutations in the alpha or beta globin gene, resulting in a quantitative deficiency in the synthesis of alpha or beta globin, causing reduced haemoglobin in red blood cells, decreased red blood cell production and anaemia [2]. Sickle cell anaemia is caused by a structural alteration in the beta globin subunit of haemoglobin. Haemoglobin polymerization leading to red cell damage causes vaso-occlusion, leading to infarction, anaemia, inflammation, hypercoagulability, oxidative stress and vascular endothelial dysfunction [3]. Mutations causing severe alpha thalassemia are less common in India, but the beta thalassemias pose a considerable public health challenge in the country [4].

Beta thalassemia and sickle cell anaemia are autosomal recessive disorders, with asymptomatic carriers (heterozygotes) (referred to as beta thalassemia trait and sickle cell trait, respectively) transmitting the mutation to the next generation. Individuals homozygous for beta thalassemia (beta thalassemia major/intermedia) are present with chronic, haemolytic anaemia. Heterozygote carriers are mostly asymptomatic, presenting with mild anaemia. The clinical manifestations of thalassemia and their management are summarized in Box 11.1 [5–12]. Sickle cell disease is marked by periodic episodes of pain (crises), organ ischemia and severe systemic complications. Organ failure is the primary cause of death [13]. Pain, infections and anemia result in frequent hospitalization [14]. Stroke is common in children with sickle cell disease, but there is limited data from India [13].

Box 11.1 Clinical manifestations and management of beta thalassemias

- **Genotype**
  Thalassemia major/intermedia: $\beta^{\circ}/\beta^{\circ}$, β°/β^{+}, β^{+}/β^{+}
  Thalassemia minor: β°/β^{N}, β^{+}/β^{N}
  Prevalent mutations in India
  IVS 1–5 (G → C), 619 bp del, IVS 1–1 (G → T), Cd 41/42 (−TCTT), Cd 8/9 (+G), Cd 15 (G → A), Cd 30 (G → C), Cap site +1 (A → C), Cd 5 (−CT), Cd 16 (−C) [5].
- **Pattern of inheritance**: Autosomal recessive.
- **Phenotype**
  Beta thalassemia major, beta thalassemia intermedia, beta thalassemia minor/trait/carrier.
- **Clinical manifestations in under-transfused patients with beta thalassemia major**
  Chronic anaemia, pallor, growth retardation, poor musculature, craniofacial abnormalities often referred to as thalassemic facies (frontal bossing, prominent malar eminence, depression of the bridge of the nose, mongoloid slant of the eye, hypertrophy of the maxillae), genu valgum and hepatosplenomegaly [6].
- **Beta thalassemia intermedia**
  Craniofacial deformities, gallstones, leg ulcers, thrombosis leading to pulmonary embolism.
- **Beta thalassemia minor**
  Clinically asymptomatic, may have mild anaemia.
- **Management**
  - Blood transfusions
    Frequency increases with age and may range from 3 to 20 transfusions in a year (unpublished data).
  - Iron chelation therapy
    Desferrioxamine, deferiprone and desirox to be prescribed at the discretion of the clinician [7].
- **Quality of life**
  Eighty-six percent of parents reported emotional stress, anxiety and depression [8].
  Physical, psychological, social, school functioning and environmental domains were affected, and discontinuation of schooling was reported [9–12].

Patients with beta thalassemia major are treated with repeated blood transfusions to correct anaemia and with iron chelation that removes the excess iron that accumulates in the body due to repeated transfusions. The importance of iron chelation therapy is evidenced in the survival rates of patients who are chelated and those

who are not [2]. Survival of patients without iron chelation is 35 years [15], whereas well-transfused and well-chelated patients survive up to 45 years [16]. The Standardized Mortality Ratio (SMR) was estimated to reduce from 28.9 to 13.5 after introduction of iron chelation [17]. The current iron chelation therapies recommend initiation of therapy at the age of 2–3 years. Hydroxyurea is the main treatment for sickle cell disease [13], as it has been shown to reduce the frequency and severity of crises episodes and may even reduce the risk of stroke in children [18]. Treatment options focus on prevention and management of complications. Median life expectancy remains 30–40 years, but life expectancy data from India are limited [3].

Epidemiology

Prevalence of thalassemia/sickle cell carriers is the indicator used to determine the magnitude of thalassemia and sickle cell anaemia. Globally, the thalassemias are prevalent through the Mediterranean, sub-Saharan Africa, Middle East, Indian subcontinent, Southeast Asia, Melanesia and the Pacific islands (global carrier prevalence: 0.5–20%) (Fig. 11.1). Haemoglobin variants such as sickle cell anaemia (global carrier prevalence: 1–38%) and HbE disorders (global carrier prevalence: 1–70%) are also reported from these regions [19, 20]. Among the thalassemias, beta thalassemia, sickle cell anaemia and HbE disorders are more prevalent in India and constitute a public health problem. The reasons for the widespread and increasing prevalence of haemoglobin disorders has been attributed to natural selection for protection against malaria (the prevalence of haemoglobin disorders varies with that of malaria), consanguineous marriages (increasing the frequency of the Mendelian recessive disorder), epidemiological transition resulting in increasing visibility of the disorder due to reducing rates of other causes of mortality, and population migration from high prevalent regions to areas where the condition was not present [20–24]. The increasing detection of patients and lack of access to care have been brought to public attention by pronounced advocacy by patient organizations.

The prevalence rate of beta thalassemia in India has been estimated to be 0.2 [25]–37.9% [26] by various studies panning all over India. This huge variation in prevalence estimates can be attributed to different case definitions used, incorrect sampling methods and heterogeneous populations screened. On an average, the prevalence of beta thalassemia is between 3 and 4%, translating into 35–45 million carriers in India [27]. Using a systematic review and meta-analysis, the pooled prevalence of beta thalassemia carriers in India has been estimated to be 3.9% (95% CI 3.15–4.84) and estimated 8740 children with beta thalassemia are likely to be born each year with thalassemia major [Dharmarajan, unpublished data]. There may be as many as 100,000 patients with beta thalassemia in India [27]. Considering India's large population, there is a possibility that these may be underestimates, as there may be a significant number who could be beta thalassemia carriers, many of whom would be undiagnosed and unaware of their carrier status.

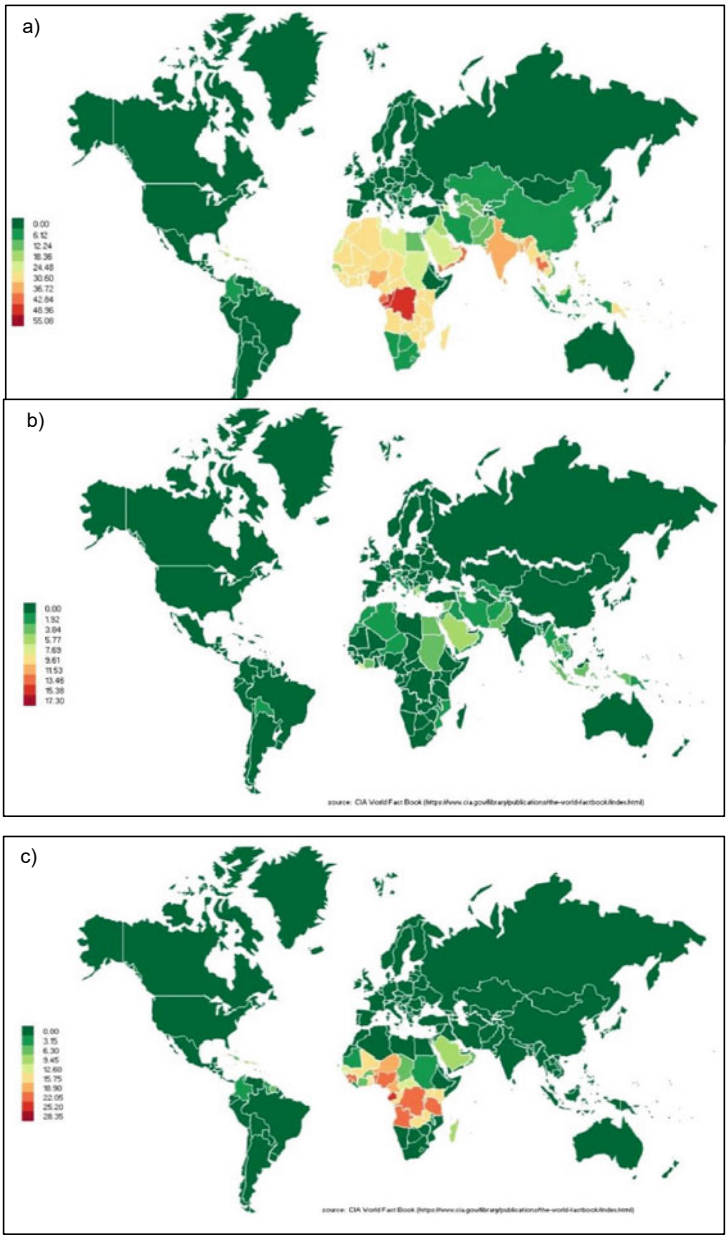

Fig. 11.1 Global distribution of haemoglobinopathies. **a** Heterozygous alpha thalassemia (prevalence range 5–60%), **b** heterozygous beta thalassemia (prevalence range 0.5–20%) and **c** sickle cell carriers (prevalence range 1–38%). Cyprus and Maldives which have the highest prevalence rates for beta thalassaemia carriers 15% and 17%, respectively, and are not visible in this map. Data from Ref. [29]

Due to the same methodological issues, the prevalence of sickle cell trait has to be interpreted with caution, with estimates varying from 5 to 35%. The condition is more prevalent in Scheduled Tribes and Scheduled Castes, but the distribution varies even within local areas. Sickle cell disease is frequently associated with beta thalassemia, but here again, the data vary. For example, 40% of patients in a hospital-based study had sickle cell-beta thalassemia, and 16% had sickle cell-alpha thalassemia. This was in contrast to studies conducted in Odisha and Gujarat that had reported 50 and 85% sickle cell-alpha thalassemia, leading to an erroneous assumption that sickle cell disease was more frequently associated with alpha thalassemia [30]. Non-randomly conducted small studies have also propagated the perception of sickle cell disease being restricted to tribal communities. These data have also been used to generate spatial maps of sickle cell disease in the country [31]. This is best reflected in a recently conducted study by the laboratory in Pune, India. The study screened a random sample of 360 pregnant women attending antenatal clinics in government hospitals in Pune, Maharashtra. Pune is the second largest city in Maharashtra, a western state in India. The study detected that 6.3% women were haemoglobinopathy carriers, of which 3.3% were beta thalassaemia carriers, 1.7% were sickle cell carriers and 1.4% were HbE carriers. Of these, sickle cell and HbE carriers have been considered to be prevalent in tribal areas and north-east India, respectively, but migration has resulted in persons carrying these mutations to be found in urban areas. The range of these mutations has diagnostic and treatment implications [28]. This highlights that multiple studies need to be conducted in different areas of India using appropriate study designs and correct diagnostic techniques. It is a lack of such studies resulting in data quality issues associated with measuring the magnitude of the disorder that makes it difficult to understand the true prevalence of haemoglobinopathies in India. Based on these best available data, it is estimated that there may be as many as 150,000 patients with sickle cell disease in India.

Impact of Thalassemia on Patients and Families in Low-Income Settings

Quality of Life (QoL)

Like parents of children with other genetic disorders, studies indicate that QoL of patients with thalassemia and their parents are affected. QoL studies report that the physical, psychological, social domains, as well as school functioning and home environment were affected. A study reported that patients were not satisfied with their body image and were depressed and anxious. They were more likely not to discuss the disorder with their friends and only depend on parents for their emotional support. This often resulted in patients dropping out from school and an adverse home environment, especially among older children [32, 33].

Parental quality of life was also affected with the earliest study in 1990 reporting that 86% of parents of patients with beta thalassemia reported emotional stress, anxiety and depression [8]. A smaller number of families reported experiencing social stigma. Majority of parents were diagnosed with psychological conditions such as depression and anxiety. Parents of newly diagnosed and older patients were most affected. The major cause for concern was expenses for treatment of thalassemia [9–12].

Out-of-Pocket Expenditure

India has the largest incidence of catastrophic health spending, wherein the largest proportion of the spending is on medications [34, 35]. There are only three cost-of-care studies conducted in India. Sangani et al. [8] estimated that the cost of blood transfusion services to be Rs. 900–3780 per year and reported that families spent 20–30% of income on management of the disorder [8]. Moirangthem and Phadke [36] reported that families spent 19,150–439,500 rupees per annum on management of the disorder with highest expenditure incurred on medications [36]. Families spent 29–67% of their family income on management with caregivers of older patients spending more on treatment. These data were reported from a government hospital where families from below the poverty line receive compensation for selected expenditures [33].

Emotional and financial costs of sickle cell disease have also been reported from across the world [37]. Indian studies report the economic burden on individuals and families. For example, a study on treatment of patients with sickle cell trait/disease observed that while 17% and 26% of patients availed free of charge services from the Primary Health Centres and the District Hospitals, respectively, majority (60%) made out-of-pocket payments for consulting private practitioners. Nearly 70% of transfusion was availed from government blood banks, where patients with haemoglobinopathies are not charged for the service. Among patients requiring hospital admissions, nearly 60% used a combination of government and private hospitals. For supporting treatment costs, 11% of families availed of loans [38].

Basic Components of a Genetic Service

The impact of thalassemia on patients and families in the absence of a genetic service is catastrophic. The number of patients, the widespread and increasing prevalence of haemoglobinopathies, and the severe consequences on those with the homozygous disorder were the main factors mobilizing the demand for recognition of the problem by the public health system in India and the development of a genetic service for these conditions in the country.

Genetic services should combine patient care and provide genetic counselling to families at risk (medical genetics services) and include population-based prevention strategies (public health genetics programmes). These services should be integrated and be an essential component of the maternal and child health services [39]. Development of such genetic services for haemoglobinopathies is important in LMICs because of (i) limited availability of management/treatment services which makes these disorders burdensome for patients and their families, (ii) prevention is a relatively low-cost tool that will reduce the prevalence of the disorder and consequently prevent the adverse impact on families, and (iii) diagnosis methods are inexpensive especially as the use of screening followed by diagnosis has reduced these costs. There is evidence from several countries on the reduction in birth prevalence of haemoglobinopathies due to introduction of genetic services as a component of public health services (discussed below). A study in Israel reported that the cost ratio of prevention to treatment was 1:4, illustrating the benefits of prevention [40].

A population-based genetic service can be organized only if the disorder to be screened is common, a clear diagnosis is possible, natural history of the condition is well understood, management strategy is available and acceptable and the programme is cost-effective [41]. Such a service is organized into primary, secondary and tertiary levels of prevention (Table 11.1). Primary prevention aims at reducing the incidence of genetic disorders. Secondary prevention aims at avoiding the birth of an affected child and minimizing the severity of clinical manifestations by early diagnosis. Tertiary prevention aims at proper management of the condition, thereby

Table 11.1 Primary, secondary and tertiary prevention of genetic disorders

Level of prevention	Interventions (with examples of thalassemia)
Primary	
Health promotion	Community education and awareness through Information, Education and Communication (IEC) on signs and symptoms of the disorder, mode of transmission, prevention and health facilities offering preventive services
Specific protection	Assessment of family history risk for genetic disorders among all women registering for antenatal care
	Voluntary premarital, preconception and antenatal screening and counselling: e.g. screening for beta thalassemia carriers in adolescents, in couples before marriage, after marriage before conception, pregnant women; cascade screening of extended family members
Secondary	Newborn screening
	Monitoring of child growth and development to identify sick children or children with developmental disabilities
Tertiary	Averting complications of diseases, e.g. transfusion, chelation or bone marrow transplant for patients with thalassemia
	Routine monitoring of patients, e.g. monthly monitoring for haemoglobin level and amount of blood transfused; periodic anthropometric assessment, liver biochemistry, kidney functioning, testing for transfusion transmitted infections and hemosiderosis

reducing complications including disability and providing psychosocial support to patients and their family members.

History of Development of Thalassemia Services in India

Perceiving the consequences of the thalassemia, other haemoglobinopathies and other genetic disorders, the World Health Organization (WHO) released a report in 1966, describing the pathology and clinical manifestations of these disorders [42]. The WHO emphasized the need for further research to investigate the distribution of these disorders, particularly in Africa, Asia, Oceania and some parts of Europe [43]. Subsequently, a Memorandum was released by the WHO in 1983, reporting expert recommendations to initiate national haemoglobinopathy control programmes, with prevention as the main component. The public health strategies recommended to be adopted were community awareness, foetal diagnosis and genetic counselling [44]. An updated set of guidelines were published in 1989 [45]. The guidelines included methods for determining the epidemiology of the condition, treatment guidelines, carrier screening methods, education and awareness, genetic counselling and prenatal diagnosis, service requirements for a control programme detailing personnel and equipments, and encouraging patient support groups in providing care and support to patients and families. The costing of such a programme and the suggested evaluation indicators are valid and relevant for India and other developing countries even today. The WHO in 2006 passed a resolution urging member states to regard genetic disorders such as haemoglobinopathies as a public health problem and introduce public health programmes for prevention and care for these disorders [46].

In India, thalassemia was not given a public health priority and development of services was on an ad hoc basis across different states. Early on, thalassemia services in India were spearheaded by a collaborative effort of parent–patient organizations, supported by the International Thalassemia Foundation, clinicians and the Indian Red Cross Society. Prolonged advocacy, together with the burgeoning HIV epidemic, was instrumental in ensuring free of charge transfusion from government blood banks. In the meantime, studies identified the high prevalence of thalassemia and its consequences on patients and their families [8]. Recognizing the chronicity of the disorder, the states of Odisha, Madhya Pradesh and Rajasthan started providing blood, free of charge, to patients with thalassemia and iron chelation, either free or at subsidized costs [47–49]. Other Indian studies identified the high prevalence of sickle cell disease among tribal populations. Certain states with high densities of these vulnerable populations initiated services for sickle cell anaemia. A programme for screening, followed by counselling and provision of care for patients with sickle cell disease, was initiated in 2006 in Gujarat and 2008 in Maharashtra.

Since the early 2000, studies reported not only a high prevalence of haemoglobinopathies in India, but the challenge of diagnosing the disease in remote and far-flung areas of the country (inhabited by tribal populations). A number of research studies implemented under a special funding scheme, the Jai Vigyan project,

identified that a package of low-cost diagnostics (Naked Eye Single Tube Red Cell Osmotic Fragility Test (NESTROFT) test, red blood cell indices, solubility tests and di-chloro phenol indophenol (DCIP) test) could identify majority of beta thalassemia, sickle cell and HbE cases [7]. This package of diagnostics could make it feasible for screening among populations living in rural and remote communities. In 2014, the National Blood Transfusion Council declared blood and its components to be provided free of cost for patients with thalassemia and sickle cell anaemia, across the country [50].

It is important to note that while programmes for providing services for thalassemia patients were spearheaded by the non-governmental organization, Thalassemics India, programmes to provide services for sickle cell anaemia patients were initiated by the state governments. Parents of patients with thalassemia have needed to approach state governments to provide free of cost transfusion services and iron chelation, petition courts and approach the Prime Minister's Office in order to treat their child by bone marrow transplantation. In contrast, as sickle cell disease primarily affected vulnerable populations, prevention and care programmes were primarily initiated by state governments. Development of care and prevention services for the haemoglobinopathies and other genetic disorders therefore originated from piecemeal services, implemented in response to demand from patient support organizations. Unlike a public health service with defined goals and objectives, there are no achievable targets and no direction in terms of what these services were intended to achieve, other than providing some relief to patients.

As of now, thalassemia patients receive free blood and iron chelators, but leucocyte filters and other consumables have to be procured by patients. For patients with sickle cell disease living in remote areas, Primary Health Centres provide pain killers and antibiotics, and folic acid and hydroxyurea prophylaxis have been initiated at a few centres. In 2013, a programme to address birth defects was introduced through the launch of the Rashtriya Bal Swasthya Karkyakram (RBSK) (Chap. 13). It advocated screening of thalassemia carriers where the prevalence of the disorder was high [51]. In December 2016, there were specific guidelines launched for diagnosis, management and prevention of haemoglobinopathies in India. These guidelines closely follow the WHO guidelines [45], according to an adequate and necessary importance to prevention. The national guidelines form the first steps towards the development of genetic services in the country. The availability of these guidelines provides a basis for states to put in place services for providing care and offer services for prevention of haemoglobinopathies.

Guidelines on Haemoglobinopathies in India

The stated mission of the guidelines for the prevention and control of haemoglobinopathies in India is to improve care for patients with thalassemia and sickle cell disease, and lower the prevalence of these conditions through screening and awareness programmes [7].

Prevention Strategies

Prevention of haemoglobinopathies is to be implemented through screening at various stages of the life cycle. Newborn screening that is screening of newborns at birth for a panel of genetic disorders including haemoglobinopathies is mandated in order to improve the quality of life of the newborn. The guidelines mandate that children with anaemia (haemoglobin levels <7 g/dl) should be referred from community settings (i.e. playschools (*anganwadis*) and schools where screening for haemoglobin levels is routinely conducted) to district health facilities for further investigation. Adolescent screening implies intervention in the school age group. The guidelines suggest that school children should be provided information on haemoglobinopathies, their pathology, inheritance and the necessity of prevention, followed by screening after informed consent. Carriers are to be 'counselled' regarding avoiding marriage to another carrier and also informed about the availability of prenatal diagnosis.

The other stages when screening can be offered are during the preconceptional or the antenatal periods. Preconceptional screening involves screening of couples who are planning their pregnancy, and if both are carriers the option of prenatal diagnosis with pregnancy termination is provided. Antenatal screening involves universal screening of all pregnant women during the first trimester, screening husbands of those testing positive and provision of prenatal diagnostic services when both partners are positive. The guidelines suggest screening of siblings and cascade screening of other family members. Cascade screening involves screening of extended family members of patients and carriers, but the guidelines recommend caution as screening may not be accepted by extended family members [7, 52].

Key to identification of patients is the choice of screening and diagnostic tools. There are multiple methods available for screening and diagnosis of beta thalassemia. Choice of screening method is primarily governed by the specificity and sensitivity of the method, the range of mutations covered, ease of set-up, availability of technical knowledge and infrastructure, and its ease of use in remote and rural settings. As iron deficiency anaemia is widely prevalent in India, and its manifestations overlap with that of beta thalassemia carriers, it is important for the tests to provide a differential diagnosis between these two conditions.

The national guidelines recommend low-cost tests with high negative predictive value, such as NESTROFT, solubility test (for sickle cell trait/disease), DCIP, complete blood count or a peripheral blood smear as the first line of screening in community settings. Dried blood spots can be collected from newborns after informed consent. Diagnosis can be done using cellulose acetate electrophoresis (CAE), isoelectric focusing (IEF), capillary electrophoresis, cation-exchange high-performance liquid chromatography (CE-HPLC) using HbA_2 level indicator cut-offs at 3.5% (haemoglobin A_2 is a normal variant of haemoglobin, which is elevated in beta thalassemia carriers and patients), and molecular methods such as allele-specific oligonucleotide (ASO) hybridization, amplification-refractory mutation system polymerase chain reaction (ARMS PCR) and gap PCR [53].

It is worth noting that the national guidelines recommend cut-offs for diagnosis of carriers at HbA_2 values of 4% and further investigations for individuals with values between 3.5 and 3.9% [7]. International guidelines however recommend HbA_2 <

3.5% as diagnostic for beta thalassemia carriers and HbA_2 levels between 3.5 and 4.0% for further investigation [54]. The use of such cut-offs in the national guidelines will reduce the comparability of the data for making global estimates.

Pretest and Post-test Counselling in Community-Based Screening Programmes

Genetic counselling is the process through which information about the genetic aspects of illnesses is shared by trained professionals with those who are at an increased risk of having a heritable disorder or of passing it on to their unborn offspring [55]. Genetic counselling is composed of pretest and post-test counselling components. Pretest genetic counselling is offered before individuals undergo the genetic test. It is used to inform the utility, sensitivity and specificity of the test, what the test results will convey. In India's socio-cultural milieu, it can be used to sensitize the recipient and the partner, the necessity of the test and the impact of a positive diagnosis [56, 57].

Post-test counselling is offered to all individuals irrespective of the result of the test. In case of a negative test, the chances of an affected pregnancy in case of thalassemia disorders are low, but not zero due to prevalence of less severe and silent mutations. In case of a positive test, the partner needs to be screened. If both partners are carriers, the diagnosis and prognosis of the disorder for the child have to be explained. Availability of health services for the child has to be explained, and the alternative provision of termination of pregnancy services, if preferred, has to be explained. Appropriate referral linkages with the obstetrician are essential. All this counselling has to be non-directive, enabling an autonomous decision to be taken by the couple [56, 57].

Genetic Counselling Education, Testing Laboratories in India

There is no structured teaching programme in medical genetics in the undergraduate and postgraduate medical curriculum in the country [58]. The Indian Academy of Medical Genetics which has the objective of promoting the science and practice of medical genetics lists a single super-speciality course (DM Medical Genetics). Diplomate of National Board (DNB) Medical Genetics is offered/proposed to be offered from a few institutes. Master courses in Biomedical Genetics and Genetic Counselling, and a certificate course in Genetic Counselling are also being offered. There is a Board of Genetic Counselling registered in the state of Telangana. Prenatal diagnosis using invasive techniques is available at several centres, with the majority being at private medical facilities [58].

Since the establishment of the first genetic diagnostic laboratories in India, genetic testing capabilities have proliferated in the country [59, 60]. Table 11.2 shows the number of genetic diagnostic clinics in India [61]. This list is incomplete as there is no centralized data on the numbers of genetic clinics in India. The list does not include over ten large private genetic diagnostic laboratories, many of which are Indian offices of international diagnostic companies. The private diagnostic services also have a network of sample collection centres. Table 11.2 shows the variation in the number of genetic diagnostic companies by states of India. The socio-economically developed states, which also have several non-medical and medical universities and research institutions, tend to have greater numbers of genetic diagnostic testing facilities. It is notable that while the UK has 25 genetic testing centres catering to a population of 56 million [62], India has already established over one hundred such laboratories.

Table 11.2 Genetic clinics in India

State/Union	Genetic clinics	Area km^2	Population (census 2011)	Genetic clinics/100,000 population
Andhra Pradesh and Telangana	19	275,045	84,580,777	0.22
Chandigarh	3	114	1,055,450	0.28
Chhattisgarh	2	135,192	25,545,198	0.007
Gujarat	8	196,244	60,439,692	0.013
Haryana	8	44,212	25,351,462	0.031
Jammu & Kashmir*	2	222,236	12,267,032	0.016
Karnataka	14	191,791	61,095,297	0.022
Kerala	6	38,852	33,406,061	0.017
Madhya Pradesh	3	308,252	72,626,809	0.004
Maharashtra	23	307,713	112,374,333	0.02
Odisha	1	155,707	41,974,219	0.002
Punjab	2	50,362	27,743,338	0.007
Rajasthan	1	342,239	68,548,437	0.001
Tamil Nadu	17	130,060	72,147,030	0.02
Uttar Pradesh	5	240,928	199,812,341	0.002
West Bengal	3	88,752	91,276,115	0.003
Delhi	11	1483	16,787,941	0.065

*- The states in this table have been listed as in [61]

Medical Care

The national guidelines have proposed free of cost blood transfusion therapy with leuco-depleted, packed red blood cells (pRBCs). Chelation for iron overload is recommended to be initiated when the iron ferritin values are higher than 1000 μg/l. The iron chelators to be provided free of charge are desferrioxamine, deferiprone and deferasirox. Continuous monitoring for endocrine, cardiac, skeletal and other complications due to the disease and treatment of these complications is recommended. Monthly monitoring for haemoglobin level and amount of blood transfused and six monthly anthropometric assessments, liver biochemistry, kidney functioning, testing for transfusion transmitted infections and hemosiderosis are to be undertaken. Bone marrow transplantation (BMT)/hematopoietic stem cell transplant (HSCT) as the ultimate curative therapy is recommended, although these services are limited. For patients with sickle cell disease, prompt treatment of fever, penicillin prophylaxis and compulsory pneumococcal vaccination are recommended. Pain relief with non-steroidal anti-inflammatory drugs is recommended. Hydroxyurea therapy for decreasing pain and improving HbF levels is recommended. The guidelines recommend psychological support services for parents. Day care centres have been established at district hospitals providing transfusion services and are to be set up at District Early Intervention Centres [7].

Few state governments have put in place services for patients with haemoglobinopathies in India. Leuco-depleted, packed red blood cells are not available at all blood banks, so that patients have to travel long distances for transfusion. Iron chelators, if supplied, are predominantly desferioxamine. Due to the high reactions and the visible distress of patients, it is necessary to provide oral chelators. If supplied at some centres, the services are erratic. At present, treatment from private practitioners, through personal expenditure, remains the main source of treatment for patients. For patients with sickle cell disease, accessing treatment is a greater challenge due to the difficult terrain of tribal areas where the disease is most prevalent. Non-governmental organizations have been instrumental in providing care.

Global Strategies for Prevention of Haemoglobinopathies

A genetic service with prevention at its core can only be successful if it is acceptable to the community at large. Prevention and control is largely dependant on availability of services to terminate a pregnancy, if required, after a positive genetic test. The type of carrier screening (premarital, prenatal or antenatal) to be introduced, depends on acceptance of this ethically difficult decision by the cultural leaders and subsequently the larger community. In certain high burden countries such as Cyprus, Greece and Italy, thalassemia screening was voluntary and premarital and antenatal screening services, and prenatal diagnostic services were available [63]. Screening was mandated in most Islamic countries such as Iran, Turkey, Jordan and Saudi

Arabia, due to high prevalence of haemoglobinopathies and high consanguinity rates. Only premarital screening was provided in these countries resulting in a high marriage cancellation rate among carrier couples. Due to limited abortion services and strict laws, carrier couples in these countries were *counselled* to and opted to cancel their marriage [64].

Such strategies raise the public health debate of ethics of individual choice versus reducing the magnitude of a chronic debilitating disorder. Cyprus has the highest carrier prevalence rates in the world, and thalassemia screening is mandatory [65]. Despite debates surrounding ethics, mandatory screening had yielded effects, as all countries with thalassemia screening programmes had reported a reduction. Maldives and Iran showed 55–80% reduction in the number of affected births after implementation of the programme [64, 66]. In all these countries, screening programmes were accompanied by extensive media campaigns for increasing the awareness about the thalassemias, which has been attributed to the successful uptake of the thalassemia screening services. Cost-benefit analysis supports preventive services to treatment programmes [8, 63, 64, 66–68].

Ethical Considerations for Indian Genetic Screening Services

One of the key issues of the genetic service is that interventions should be ethical, upholding the four key principles of ethics that is autonomy, justice, beneficence and non-maleficence. A genetic service only focused on prevention and not on treatment is unethical. Hence, a comprehensive programme encompassing preventive and treatment services is a must. This has been highlighted in each of the statements and guidelines released by the WHO. Following these recommendations, the Indian guidelines on haemoglobinopathies have also given appropriate weightage to treatment. Newborn screening, for example, has little utility if it is not followed by access to appropriate treatment.

One of the major issues of concern is the marriage counselling strategies being used by different state agencies and some NGOs. The Gujarat sickle cell anaemia programme, for example, provides colour-coded cards, with patients given a yellow card, carriers given a yellow and white card and non-carriers a white card (Fig. 11.2) [69]. Providing such cards may appear an effective public health tool to increase awareness about carrier status among populations with low literacy levels. This method however is highly unethical, as it violates the principle of autonomy of choosing a partner and causes psychosocial harm to the individual. In the social–cultural milieu of India, adolescent screening and premarital screening strategies suggested in the guidelines for detecting both thalassaemia and sickle cell anaemia carriers place adolescents and young adults at risk, with the risk being higher in girls. The potential of screening strategies in stigmatizing individuals might impact the acceptance of screening by the community [70]. Lack of community acceptance will lead to failure of an otherwise well-structured genetic services programme.

Fig. 11.2 Sickle cell anaemia counselling cards. Counselling cards issued to persons screened for sickle cell anaemia. The white shaded portion indicates a normal beta globin allele, and yellow shaded portion indicates a mutant allele. A non-carrier will be issued a white card, a sickle cell carrier will be issued a card shaded white and yellow, whereas a patient with sickle cell anaemia will be issued a yellow card. From [69]

The methods that will be most acceptable to the community without violating the principles of ethics are the antenatal and cascade screening strategies, wherein carriers can be detected through screening, and prenatal diagnosis can be provided on time. This indicates that the timing of provision of carrier screening strategies is vital for ensuring success of a genetic services programme in a community which is governed by strict religious and cultural norms. Integrating genetic services with maternal health services and ensuring that such a programme is governed by strict guidelines safeguarding the interests of patients, parents and persons screened for genetic disorders are imperative.

Monitoring

Important for a genetic service is monitoring, particularly when there are multiple programme components. Periodic monitoring will ensure correction of programmatic approaches and modification of interventions as and when needed. Modell and Darlison have prepared a list of such indicators that will be useful for determining the progress of the service towards achieving its stated goals [71] (Box 11.2).

Box 11.2 Programme indicators for a genetic service [71]

- **Indicator for patient care**: Annual conceptions with a haemoglobin disorder in the absence of prevention.
- **Indicator for carrier screening**: Annual number of carrier tests required.
- **Indicator for carrier information and offer of partner testing**: Annual number of carriers detected using the chosen strategy.

- **Indicator for expert risk assessment and genetic counselling**: Annual at-risk pregnancies of carrier couples detected by screening using the chosen strategy.
- **Indicator for the offer of prenatal diagnosis**: Annual pregnancies at risk detected.

Research

There are multiple institutes across India researching thalassemia and sickle cell anaemia. The major publications from these institutes involve molecular characterization of *HBB* mutations. The research has determined the most prevalent mutations in India, thereby reducing costs of diagnostic testing. Other research studies have yielded data on the usefulness of low-cost diagnostics that have come into routine use in rural and remote settings. Description of clinical manifestations and effectiveness of medications have informed which treatment modalities are acceptable and effective. The clinical and large technical competency in India to offer genetic testing is apparent.

There are however a number of research gaps. First and foremost, systematic studies are required to understand the true prevalence of haemoglobinopathies in India, as existing studies have methodological limitations described earlier in the article. Appropriately powered studies, using globally relevant case definitions and cut-offs, are essential. Such studies are important not only to identify the true magnitude of the problem, but also to understand whether the problem extends beyond the selected communities that have been repeatedly studied. Clinical research also needs to be systematic [72]. The natural history of haemoglobinopathies needs to be studied, preferably through cohort studies, so that the clinical course of disease and the effectiveness of health interventions can appropriately inform public health service providers. There is limited research on the quality of life of patients with genetic disorders and their parents, limited needs assessment studies, cost of care studies and investigations on genetic counselling in context to India's cultural milieu. Such studies, conducted across the country, are urgently required to provide evidence for further developing the proposed programme for the prevention and control of haemoglobinopathies in India, which can be generally applicable at the national level and streamlined to meet the local needs.

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