Health Technology Assessment in India (HTAIn)

स्वास्थ्य अनुसंधान विभाग
Department of Health Research

PGI School of Public Health

To determine Cost-effectiveness of Rapid Diagnostic Tests (Hemo-Type-Sc, Sickle Scan and Gazelle) in comparison to solubility test followed by HPLC for Sickle Cell Disease/Trait diagnosis among high-risk population in India

Policy Brief

Recommendations

- ICER per case detected for Hemotype SC is 3,46,437 and 3,47,466 for 2-30 years and 0-30 years, respectively.
- ICER per case detected for Sickle Scan is 3,04,090 and 3,04,284 for 2-30 years and 0-30 years, respectively.
- ICER per case detected suggests that if Hemotype SC Kit and Sickle SCAN Kit can be procured below INR 100, it will become cost-effective.
- POC tests may be considered for adoption in Sickle cell screening programmme of neonates and children 0-2 years as existing solubility test cannot be used
- POC tests are useful in identifying the SCTs and its health benefits will be reflected in next generation along with its economic benefits
- Screening may be rolled out in a phased manner; Phase 1: 0-2 years; Phase 2: 2-18 years (traits), and antenatal population as well

Summary

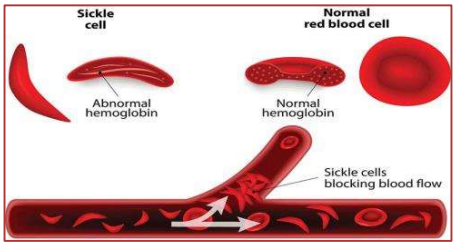
Sickle Cell Disease (SCD) is a common genetic disorder prevalent in Sub-Saharan Africa, the Mediterranean, the Middle East, and the Indian subcontinent. Three nations, including India, bear over half of the world's SCD burden. SCD has a large impact on childhood morbidity and mortality. In India, where 1.5 lakh children are affected, 20% of infants die before the age of two. The high SCD prevalence is also reflected in the high proportion of individuals who are carriers of the sickle cell gene, also known as sickle cell trait (SCT). The overall prevalence of SCD among tribal population of India varies from 1-34%. Madhya Pradesh, has the highest load of prevalence that varies from 10%-33 % followed by Maharashtra with 0-35%, Kerala (18.2%-34.1%), Gujarat (6.3%-22.7%). With more than 5200 affected new-born with SCD each year, it is a serious public health issue in India.

The Guidelines from Ministry recommend screening and early diagnosis of SCD. Solubility test followed by confirmation with HPLC is the standard screening modality currently available in public health program. However, newborn screening cannot be performed using this method due to presence of fetal hemoglobin.

Recently, many Point of Care diagnostic tests are commercially available (not manufactured in India) for screening SCD. An HTA analysis was recommended to be carried out to assess the most cost-effective point of care test that could be used for mass scale screening of SCD.

Research Question:

Which is the age group and method of population-based screening/ high-risk screening for Sickle Cell disease/traits?



Objectives:

- To collate evidence on clinical-effectiveness of rapid tests (Hemo Type Sc, Sickle Scan and Gazelle) vs HPLC and solubility test to diagnose sickle cell trait/disease
- To estimate cost per test of detection with rapid tests (Hemo Type Sc, Sickle Scan and Gazelle)
- To assess the budget impact of using rapid test/s (Hemo Type Sc, Sickle Scan and Gazella) for universal screening vs targeted screening in the national health program

Policy Brief

Tests for Sickle Cell Disease Screening

Introduction

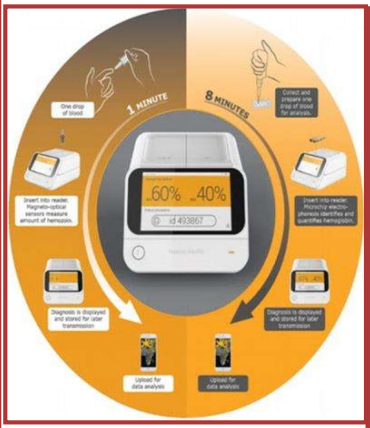
Sickle cell disease (SCD), an autosomal recessive disorder of the red blood cell, is the most common monogenic disease with more than 300 000 affected births annually worldwide, mostly in low- and middle-income countries. An estimated 7% of the world population carry an abnormal hemoglobin gene, while about 300,000 - 500,000 are born annually with significant hemoglobin disorders. They consist of two major groups –Thalassemia and Sickle cell syndromes. Sickle cell syndromes are more frequent and constitute 70% of affected births world-wide, the rest are due to Thalassemia. Sickle cell syndromes include Sickle Cell Disease (SCD, HbSS), also called Sickle Cell Anemia (SCA), as well as disorders due to sickle cell gene combined with another hemoglobinopathy such as Hb C, E, or β thalassemia. Persons carrying only one of these genes are called 'carriers' as they do not suffer from any disease but carry the abnormal gene and transmit it to the next generation. Carriers cannot be recognized clinically but only by performing special blood tests. Where both mother and father are 'carriers', there is a chance that their children may inherit the abnormal gene from both parents and thus suffer from a severe thalassemia syndrome or a Sickle Cell syndrome or may be normal without any abnormal gene or carriers like their parents. Screening prior to conception or during pregnancy can help controlling hemoglobinopathies by preventing birth of affected children by – avoiding marriage between two carriers or by Prenatal diagnosis in pregnancies of couples where both partners are carriers, with the option of termination of pregnancy in case of an affected fetus. Newborn screening can detect abnormal hemoglobin variants like HbS, both carriers as well as those with disease (HbSS) states. SCD requires lifelong management and contributes to infant and childhood morbidity and mortality. Cost effective population screening programs are possible for detection of diseased or carriers, as low-cost screening tests with high negative predictive value are available. Genetic counseling, community education and awareness play a very important role in successful implementation of prevention programs.

Hemotype Sc:

Manufactured by Silverlake Corporation USA, is a rapid diagnostic test that utilizes the competitive lateral flow immunoassay incorporating monoclonal antibodies for detection of Hb A, HbS and HbC. The kit includes, single-use test strips, single-use blood sampling devices and three reusable dropper pipette and does not need a separate buffer solution. However, it would require test vials and test tube racks for the conduct of test. It can remain viable at 15°C- 40°C for up to five years and for 30 days once opened. The time taken for carrying out the test ranges from 8 - 15 mins and requires around 1.5 microliters of blood. The limitation of the test includes the inability to detect hemoglobin variants like HbD, HbE and HbF. It also cannot differentiate between HbSS and sickle- 60-thalassemia. Misinterpretation of the result in cases with recent blood transfusion is also reported.

Sickle Scan

Manufactured by Biomedomics Inc is yet another point of care for detection of sickle cell disease and works on the principle of sandwich-type lateral flow immunoassay utilizing polyclonal antibodies. It identifies HbA, HbS & HbC. The Sickle Scan test kit includes, Sickle SCAN cartridges, capillary sampler and pretreatment modules (buffer) and package insert. The time taken for carrying out the test is reported to be less than other POC tests and ranges between 5 mins to 8 mins. However, the amount of blood sample required for carrying out the test is around 5 microliters. The storage temperature is reported to be between 2 °C and 30 °C. Its ease of performance and interpretation makes it suitable to be used by non-skilled personnel. Similar to Hemotype SC, Sickle Scan cannot detect Hemoglobin variants like HbD, HbE and HbF and also cannot differentiate between HbSS and sickle- β0-thalassemia.



Gazelle

Manufactured by Hemex health is a HemeChip cellulose acetate paper-based microchip electrophoresis system consists of Gazelle reader and Cartridge. The reader is a touch-screen tablet computer with an integrated imaging system and has a rechargeable battery. The cartridge consists of a single strip of cellulose acetate paper, a pair of blotting pads and integrated stainless-steel electrodes. Apart from HbA, HbS and HbC detected by other POCs it also detects HbA, HbF, HbA2, and HbE, thereby making it capable of differentiating between HbSS and sickle- β0-thalassemia. The time required for completion of one test by Gazelle is reported to be 13 mins and the blood volume utilized per test is approx. 0.2 microliter. It is however expected to require a skilled interpretation and web-based image processing application for automated results.

Methods & Approach:

The HTA is structured to answer the policy question put forward by the Ministry about which rapid diagnostic tests (Hemotype-Sc test, Gazelle, Sickle Scan and solubility test) is more cost effective than current standard of care in population level screening for sickle cell disease/trait. Mathematical modelling, one way and probabilistic sensitivity analysis and budget impact analysis was conducted. It was assumed that screening will be predominantly performed at primary level (70%) and rest of the screening at secondary and tertiary level.

Review of literature was conducted to assess clinical effectiveness of all POCs. Robust published studies on Sickle Scan were not available in Indian settings. Gazelle was not considered a POC test due to its operational feasibility issues regarding high cost of machine, need for electric charging and expertise needed to interpret the results. The same was vetted by an experts working in the area of SCD screening.

Results:

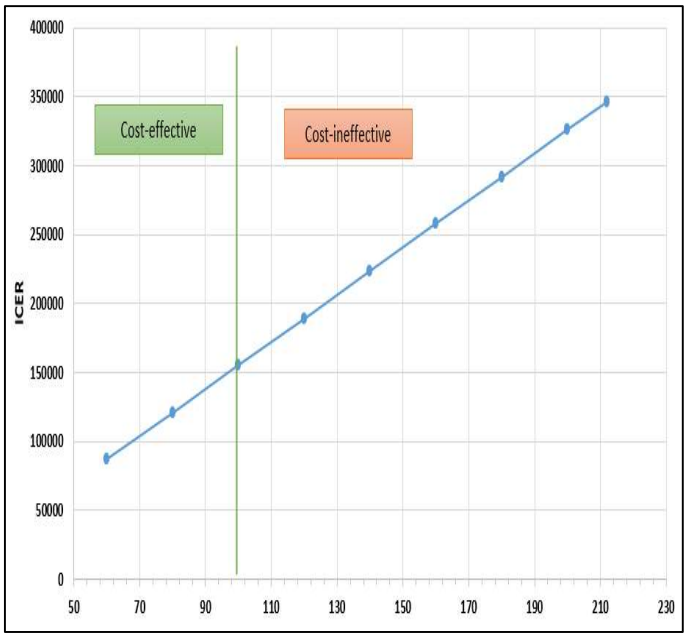
The population to be screened was considered in a Decision Tree analytical model and analysed in three different age groups. The cohort size for age group 0 to 2 years, 2 to 30 years and 0 to 30 years was 1.37 crores, 3,07 crores and 3,41 crores, respectively. These populations were selected from the tribal districts of the 6 highest burden states (Hockham *etal.,* 2018) i.e Tamil Nadu, Chhattisgarh, Maharashtra, Odisha, Gujarat and MP (Census 2011) for sickle cell disease. According to the model, cost per individual screened using the POC tests Hemotype SC and Sickle Scan is INR 250.17 and for solubility test followed by HPLC as a confirmatory test is INR 53.32. Screening through Hemotype SC could detect 56,180 cases, 4.97 lakh and 5.52 lakh in age group 0 to 2 years, 2 to 30 years and 0 to 30 years, respectively. Screening through Sickle Scan could detect 56,465, 5 lakh and 5.55 lakh cases in age group 0 to 2 years, 2 to 30 years and 0 to 30 years, respectively. If solubility followed by HPLC is used for screening, then 4.79 lakh and 5.32 lakh cases could be detected in age group 2 to 30 years and 0 to 30 years, respectively. Table 1 (with 95% CI values) describes all model parameters, such as, cost of rolling out screening programme in target population using the two POC tests and solubility test followed by HPLC.

One-way sensitivity Analysis (OWSA) for Price Threshold:

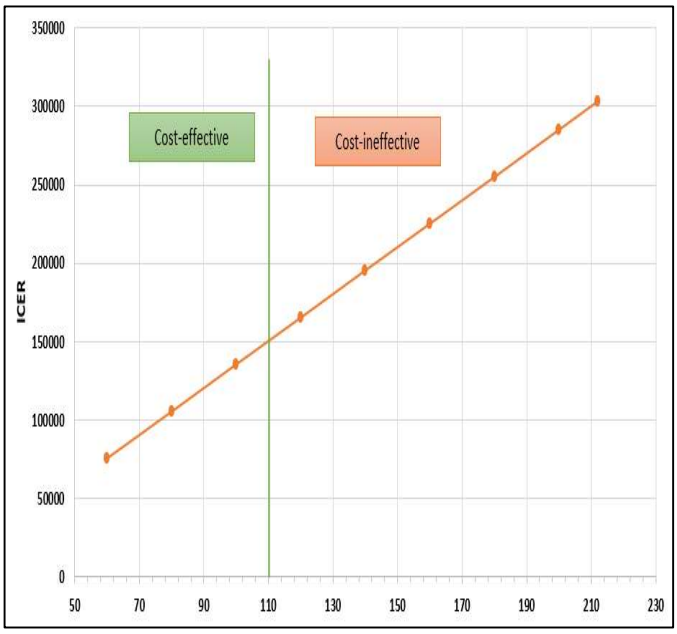
ICER per case detected suggests that if Hemotype SC Kit can be procured below INR 100 it will become cost effective. Similarly, if Sickle SCAN Kit can be procured below INR **110,** it will become cost-effective.

Probabilistic Sensitivity Analysis PSA:

To check the robustness of the model and address uncertainty, probabilistic sensitivity analysis (PSA) was also conducted. Using monte carlo simulation method, we ran 1000 simulations for various parameters, such as, prevalence, cost etc. Median of 999 values and lower and upper limits of 95% CI intervals were ascertained corresponding to 2.6 percentile and 97.5 percentile values.



Price of Hemotype SC Kit in INR



Price of Sickle Scan Kit in INR

Budget impact analysis showing Total health system Cost of rolling out screening populations residing in tribal districts of 6 high prevalence states in different age groups using Hemotype SC, Sickle Scan and solubility + HPLC.

Strategy	In 0-2 years Population (95% CI) 34,56,509 Population	In 2-30 years, Population (95% CI) 3,06,75,481 Population	In 0-30 years, Population (95% CI) 3,41,31,990 Population
Cost of rolling out screening program with Hemotype SC	89.58 (84.11 – 94.91) Crores	797.71 (746.38 – 841.86) Crores	885.53 (834.18 – 942.87) Crores
Cost of rolling out screening program with Sickle SCAN	89.59 (84.04 – 95.43) Crores	795.38 (846.40 – 846.40) Crores	885.53 (836.66 - 938.24) Crores
Cost of rolling out screening program with Solubility + HPLC	Solubility can still be used for children above 9 months of age	175.08 (167.25 – 183.12) Crores	194.64 (185.74 – 203.10) Crores

A budget impact analysis was conducted to find the total health system costs of rolling out screening program with Hemotype SC, Sickle Scan and solubility + HPLC.

Conclusion

To summarize, both the Hemotype Sc and Sickle Scan POC tests to diagnose Sickle Cell Disease/Trait will be cost-effective for screening. The screening strategy could be rolled out in the six states of Tamil Nadu, Chhattisgarh, Maharashtra, Odisha, Gujarat and MP (Top 6 are states with high prevalence of Sickle Cell Disease among newborns. Screening may be rolled out in a phased manner, with phase one being 0-2 years and phase 2 being 2-30 years, including antenatal population as well. HPLC is only required for tertiary care.

References:

1. Kaur M, Das GP, Verma IC. Sickle cell trait & disease among tribal communities in Orissa, Madhya Pradesh & Kerala. Indian J Med Res. 1997;105:111–6.
2. Dash BP, Das RK: Age, sex and seasonal variations of sickle cell disorder cases in Orissa. J Hum Ecol 1998, 9:281–284.
3. Mukherjee MB, Surve RR, Gorakshakar AC, et al.: Symptomatic presentation of a sickle cell heterozygote: an evaluation of genetic factors. Am J Hematol 2001, 66:307–308.
4. Mohanty D, Mukherjee MB. Sickle cell disease in India. Current Opinion in Hematology 2002;9:117–122.
5. Mohanty PK, Meher S. Mortality risk factors in hospitalised late adolescent and adult sickle cell disease patients. J Evid Based Med Health Care 2018;5:135–9.
6. Shah P, Bhagat VM, Patel K, Patel C. Pattern of mortality in sickle cell disease: an autopsy study. International Journal of Research in Medical Sciences. 2017;5(5):2115-2119. doi:10.18203/2320-6012.ijrms20171853
7. Newborn Screening and Clinical Profile of Children With Sickle Cell Disease in a Tribal Area of Gujarat | SpringerLink. Accessed August 4, 2022. https://link.springer.com/article/10.1007/s13312-022-2476-7
8. 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. doi:10.1371/journal.pone.0147081
9. Purohit P, Mantri S, Nayak J, Mahapatra B. Factors responsible for mortality in patients with sickle cell disease: A hospital-based study. Natl J Physiol Pharm Pharmacol. 2019;(0):1. doi:10.5455/njppp.2020.10.0932225102019
10. Thaker P, Colah RB, Patel J, et al. Newborn Screening for Sickle Cell Disease Among Tribal Populations in the States of Gujarat and Madhya Pradesh in India: Evaluation and Outcome Over 6 Years. Front Med (Lausanne). 2022;8:731884. doi:10.3389/fmed.2021.73188
11. Balgir RS. The spectrum of haemoglobin variants in two scheduled tribes of Sundargarh district in north-western Orissa, India. Annals of Human Biology. 2005;32(5):560-573. doi:10.1080/03014460500228741
12. Jain DL, Apte M, Colah R, et al. Efficacy of fixed low dose hydroxyurea in Indian children with sickle cell anemia: a single centre experience. Indian Pediatr. 2013;50(10):929-933. doi:10.1007/s13312-013-0264-0
13. Bhatwadekar SS, Deshpande SV, Khadse SV, Shah B, Desai D. Morbidity Pattern in Sickle Cell Disease in Central Gujarat, India — Single Centre Perspective. Blood. 2017;130:4785. doi:10.1182/blood.V130.Suppl_1.4785.4785
14. Silva-Pinto AC, Costa FF, Gualandro SFM, et al. Economic burden of sickle cell disease in Brazil. PLoS One. 2022;17(6):e0269703. doi:10.1371/journal.pone.0269703