Outcome Report

Rapid Health Technology Assessment to Determine Cost-effectiveness of Rapid Diagnostic Tests (HemoType-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

Compiled by

HTAIn, Department of Health Research, MOHFW, GOI
HTA Resource Hub, ICMR NIRRCH Mumbai
HTA Resource Hub, School of Public Health, PGIMER, Chandigarh

2022

Outcome report for Rapid Health Technology Assessment

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

Compiled by

HTAIn, Department of Health Research, MOHFW, GOI

HTA Resource Hub, ICMR NIRRCH Mumbai

HTA Resource Hub, School of Public Health, PGIMER, Chandigarh

Research Question:

This HTA proposes to answer the question proposed by the user department- which is the age group and method of population-based screening/ high-risk screening for Sickle Cell disease/traits.

Objectives:

1. 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
2. To estimate cost per test of detection with rapid tests (Hemo Type Sc, Sickle Scan and Gazelle)
3. To estimate cost-effectiveness of using rapid tests (Hemo Type Sc, Sickle Scan and Gazelle) for universal screening vs targeted screening at public health facilities for sickle cell trait/ disease compared to standard of care
4. 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

PICOT

Population	1. Newborns and children up to 24 months of age who come for immunization and are not screened earlier 2. General population between 2 - 30 years 3. General population between 0 - 30 years
Intervention	Sickle Screening with Rapid Tests (Hemo Type C, Gazelle, Sickle Scan) with confirmation of positives with HPLC
Comparator	Standard of care (screening by solubility test followed by confirmation with HPLC)* except in newborns where HPLC will be done on DBS samples
Outcome	Health system costs, ICER. Cost per case detected, cost per test

Population: A hypothetical cohort of a) all newborns being born in the public health facilities or home in tribal districts of India where SCD is endemic will be the population who will be included in the model along with all the children who avail services for immunization up to 18 months of age but have missed newborn screening and b) general population between 2- 30 years.

Intervention: Rapid tests for sickle cell screening (Hemotype SC, Sickle Scan and solubility test) followed by confirmation of sickle cell disease (SS) with by HPLC at 9-12 months of age. Note: This test will be used for screening and diagnosis of all newborns using cord blood or heel prick and by heel prick when they come for immunization if not tested earlier.

Comparator: Standard of care tests recommended as per the guidelines for screening newborns/ adult population. There is no point of care test recommended for newborn screening. Note: The recommended test is Using DBS by heel prick wherein samples sent for testing using HPLC.

Outcomes:

1. **Primary outcome:** Health system costs, ICER, Cost per case detected, cost per test
2. **Secondary outcomes**: ICER per case detected
3. **Perspective:** Health system perspective

Methodology

The HTA is structured to answer the policy question put forward by the Ministry about which rapid diagnostic tests (Hemo-type-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.

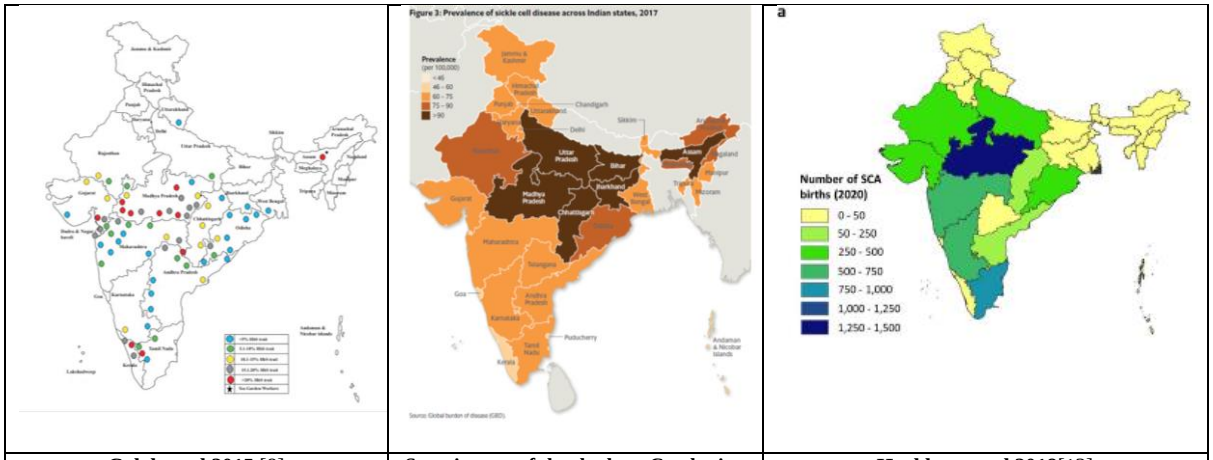
1. Evidence collation on thorough literature review of literature

1.1 Burden of disease in India

More than 300,000 babies are thought to be born each year with sickle cell disease (SCD) globally, and it is predicted that this number would rise from 305,800 in 2010 to 404,200 in 2050. SCD, 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. [1]. The majority of these infants are born in India and sub-Saharan Africa [2–4], where SCD has a large impact on childhood morbidity and mortality [5–7]. While the death rate for children under five with SCD can reach as high as 90% in some low-income nations [5–7]. In India, where 1.5 lakh children are affected, 20% of infants die before the age of two [7]. 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) (13–20%) [6].

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%) and few other states as shown in figure below [8]. Kaur et al have summarized from individual states that there are still many gaps in our knowledge about the distribution of the HbS gene in tribal communities in India [9].

With more than 5200 affected new-borns with SCD each year [10,11], it is a serious public health issue in India. SCD is common across several ethnic groups in India, a huge country with many different ethnic groups. India's central region has the highest frequency of the SCD, with Chhattisgarh, Bihar, Uttar Pradesh, Madhya Pradesh, Jharkhand, Assam, Meghalaya, Arunachal Pradesh, and Rajasthan among the states with the highest prevalence. SCD is most frequent among tribal cultures, but as more people move into cities, it is becoming more widespread [12].



Colah et al 2015 [8]	**Stepping out of the shadows Combating sickle cell disease in India, 2017** [12]	**Hockham et al 2018**[13]

Figure: Shows the prevalence of SCD in districts as well as in the states

Out of six studies only one study was based on new-borns, rest all other five studies included all age-groups. Only one study showed prevalence by male-female, while other represented the overall SCD ranges between 0.1 to 9.02 % while SCT ranges from 1.3-88.7% respectively. four studies adapted HPLC as a screening test, while one with solubility test and one with sickling test followed by HPLC (see table 1 below).

Table 1: Prevalence studies from India

S no.	Title	Time period	age	place	Sample size	Population	Prevalence	screen test adapted
1	Ahmed et al 2018 [14]	2 years	0-10 11-15 16-20 Above 20	Amravati, Maharashtra	2,50,424	(SC & ST) tribal	Over all =0.1%, SC= 0.0015%, ST=0.0013%, Male=0.176%,female=0.106%	Solubility test
2	Italia et al 2015 [15]	2 years period	newborns were screened	Community (newborn screening) (South Gujarat)	5467 (samples collected from 13 different centres)	tribal populations	SCD - 0.60%, SCT - 12.5	HPLC
3	Patel et al 2012 [16]	4 Years (Sept. 2004 to Nov.2008)	<17 17-35 35+	Community based (Gujarat)	168495 persons from tribal areas,149044 from non tribal areas	tribal and non tribal population	SCT - 6.54% SCT (tribal) - 11.38% SCT (nontribal) - 1.1%, male- 11.6%, female- 11.13%	HPLC
4	Patel et al 2012 [17]	-	<18 18+	Gujarat	35857,<18 n >18	tribal	SCD - 0.03%, SCT - 1.3%	HPLC
5	Balgir et al 2005 [18]	-	0-61+	Odisha	836 (primary data collection)	tribal village	SCT=5.3%, SCD=0.3	HPLC
6	Mistry et al 2018 [19]	January 2015 to December 2016	All age group	Valshad, Gujarat	1186 were tested positive with Sickling test (DTT test)	Tribal	SCD= (107/1186)= 9.02%, SCT= (1052/1186)=88 .7%	sickling test+ HPLC (either SCD or SCT)

References

[1] 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 Medicine 2013;10:e1001484. https://doi.org/10.1371/journal.pmed.1001484.

[2] 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. The Lancet 2013;381:142–151.

[3] Serjeant G. World sickle cell day: lessons for India. The Indian Journal of Medical Research 2017;145:705.

[4] Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. The Lancet 2017;390:311–323.

[5] Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. American Journal of Preventive Medicine 2011;41:S398–S405.

[6] 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:e14699.

[7] Tewari S, Rees D. Morbidity pattern of sickle cell disease in India: a single centre perspective. The Indian Journal of Medical Research 2013;138:288.

[8] Colah RB, Mukherjee MB, Martin S, Ghosh K. Sickle cell disease in tribal populations in India. The Indian Journal of Medical Research 2015;141:509.

[9] Kaur M, Dangi CBS, Singh M, Singh H, Kapoor S. Burden of sickle cell diseases among tribes of India-a burning problem. International Research Journal of Pharmaceutical and Applied Sciences 2013;3:60–80.

[10] Verma IC. Burden of genetic disorders in India. The Indian Journal of Pediatrics 2000;67:893–898.

[11] Verma IC, Bijarnia S. The burden of genetic disorders in India and a framework for community control. Public Health Genomics 2002;5:192–196.

[12] Stepping out of the shadows Combating sickle cell disease in India. The Economist Intelligence Unit Limited; 2020.

[13] Hockham C, Bhatt S, Colah R, Mukherjee MB, Penman BS, Gupta S, et al. The spatial epidemiology of sickle-cell anaemia in India. Scientific Reports 2018;8:1–10.

[14] Ahmad MM, Gupta HN, Shinde DS, Ruparel ND. The Prevalence and Severity of Sickle Cell Disease in Amravati District of Maharashtra. Indian Journal of Pharmacy Practice 2018;11.

[15] 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. Journal of Medical Screening 2015;22:1–7.

[16] Patel AP, Naik MR, Shah NM, Sharma NP, Parmar PH. Prevalence of common hemoglobinopathies in Gujarat: an analysis of a large population screening program. National Journal of Community Medicine 2012;3:112–116.

[17] Patel AG, Shah AP, Sorathiya SM, Gupte SC. Hemoglobinopathies in South Gujarat population and incidence of anemia in them. Indian Journal of Human Genetics 2012;18:294.

[18] Balgir RS. The spectrum of haemoglobin variants in two scheduled tribes of Sundargarh district in north-western Orissa, India. Annals of Human Biology 2005;32:560–573.

[19] Mistry S, Shah K, Patel J. Prevalence of sickle cell disease in tribal peoples of Valsad district region in Gujarat, India. Tropical Journal of Pathology and Microbiology 2018.

1.2Evidence on Cost-effectiveness Analysis for SCD screening in other countries

We found four cost-effectiveness studies that examined screening vs no screening strategy[1-4]. We did not find any cost-effectiveness study that looked at POC tests. In the base-case scenario, three studies [1-3] used the healthcare system perspective, while one [4] did not. All four studies were model-based, while one used a discrete-event simulation model [3]. The lifetime horizon were used in two of the model-based studies, while one used 10 years as a time horizon for new-borns.

The screening studies have different effectiveness measure. In Spain during a 10-year period (fiscal year 2013), Sub-Saharan Africa (fiscal year 2014) and Angola (fiscal year 2012–2014), the ICER for new-born screening vs no screening was €34,169 ($US45,445) per LYG, $US213 every DALY averted, and $US2214–2824 each HLY gained over a lifetime horizon (fiscal year not available) [2-4]. In comparison to a midwife care strategy (sequential testing at the first midwife consultation) over a 10-week period in the UK, the primary care parallel strategy (testing mother and father at the same time in primary care) and primary care sequential strategy (testing mother in primary care and then the father if the mother is a carrier) resulted in an ICER of £25 ($US39) and £13 ($US20) per woman screened, respectively (fiscal year 2010) [1].

SCD complications were examined in two studies [2,3]. Stroke (two studies) [2-3], vaso-occlusive crisis or pain crisis (one study) [2], and acute chest syndrome (one study) [2] were the most frequent problems in those studies. Healthy life-years (HLYs; one study) [2], life-years gained (LYG; one study) [3], Disability adjusted life-years (DALYs; one study) [4] and were three effectiveness measures that captured both quality and length of life. One antenatal screening study measured the number of women screened [1].

References

[1] Bryan S, Dormandy E, Roberts T, Ades A, Barton P, Juarez-Garcia A, et al. Screening for sickle cell and thalassaemia in primary care: a cost-effectiveness study. British Journal of General Practice 2011;61:e620–e627.

[2] 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. The Journal of Pediatrics 2015;167:1314–1319.

[3] Castilla-Rodríguez I, Cela E, Vallejo-Torres L, Valcárcel-Nazco C, Dulín E, Espada M, et al. Cost-effectiveness analysis of newborn screening for sickle-cell disease in Spain. Expert Opinion on Orphan Drugs 2016;4:567–575.

[4] 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 Services Research 2016;16:1–12.

Table 1: Cost-effectiveness Analysis for SCD

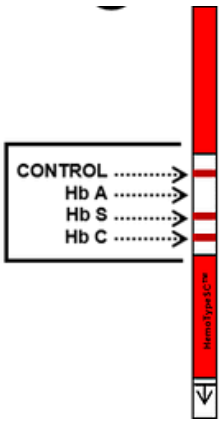
S.No	Study	Study design	Region	Perspective	Intervention type	Study Population	Time Horizon	Intervention/Comparator	Effectiveness Measure
1	Castilla-Rodríguez et al 2016	Model-based study	Spain	Healthcare system	Screening	New-borns	10 years	Intervention: Newborn screening program Comparator: No screening	LY The ICER for newborn screening versus no screening was €34,169 ($US45,445) per LYG in Spain over 10 years
2	Kuznik et al. 2016	Model-based study	Sub-Saharan Africa	Healthcare system	Screening	New-borns	Lifetime	Intervention: Newborn screening and prophylactic intervention Comparator: No screening	DALY $US213 per DALY averted in SubSaharan Africa (fscal year 2014
3	McGann et al. 2015	Model-based study	Angola	NA	Screening	New-borns	Lifetime	Intervention: Newborn screening and treatment program for sickle cell anemia Comparator: No screening	HLY $US2214–2824 per HLY gained in Angola over a lifetime horizon
4	Bryan et al. 2011	Model-based study	UK	Healthcare system	Screening	Pregnant women (biological moth-ers); their partners (biological fathers)	Pregnancy to conclusion	Intervention: Primary care sequential Comparator: Midwife care Intervention: Primary care parallel Comparator: Midwife care Intervention: Primary care parallel Comparator: Primary care sequential	woman screened £13 ($US20) per woman screened £25 ($US39) per woman screened More costly, less effective

1.3 Description of various tests being considered for Sickle Cell Disease Screening:

As per National Guidelines on hemoglobinapahies, screening of sickle cell disease has been recommended using solubility test followed by confirmation either by Iso electric Focussing or HPLC. For newborn screening solubility test is not useful due to the presenece of high levels of HbF. In newborns DBS with HPLC is the recommended test. However, the positive ones need to be re confirmed of their diagnosis at the age of 9 months to 1 year.

Solubility test is a very cheap test that uses phosphate buffer a hemolyzing agent and sodium diothenate. Due to insolubility of HbS in presence of these solutions, the HbS crystalises resulting in precipitation of the the cells causing turbidity

Hemotype Sc, manufactured by Silverlake Corporation USA, is a rapid diagnostic test that utilises 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 study. It can remain viable at 15°C- 40°C for upto 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 microlitres of blood. The limitation of the test include the inability to detect haemoglobin variants like HbD, HbE and HbF. It also cannot differentiate between HbSS and sickle- β0-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 pre treatment 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 microlitres. 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.

Gazelle POC test

1.3.1 Review of literature on Sensitivity – Specificity of the tests under consideration:

A scoping review was performed using a comprehensive search strategy on Pubmed and Google Scholar databases, to review literature evidence on sensitivity specificity of tests used for screening (i) in the current program ie Solubility Test followed by HPLC for adults and HPLC alone for newborns vs (ii) the three point of care tests namely Hemotype SC, Sickle Scan and Gazelle. The articles were first screened at the abstract level for specified exclusions and potentially eligible articles were retrieved and reviewed in their entirety. Screening studies irrespective of the age group of the participants were included for review.

The search yielded twenty-two studies that were reviewed in whole for extracting the sensitivity, specificity, PPV and NPV of all the above mentioned tests used for screening Sickle Cell Disease.

Among the 22 studies, one study was a recent review of all tests that are used for diagnosis of sickle cell disease, 3 studies validated solubility test, 7 primary studies were about screening with Hemotype SC vs HPLC/IEF/PCR, 6 studies evaluated Sickle Scan, 3 studies compared Hemotype SC with Sickle Scan and only 2 studies evaluated Gazelle. One article was a review paper that described all tests used for diagnosing Sickle cell disease.

Solubility Test (Table 1):

Three studies from literature were reviewed to extract the diagnostic effectiveness of **Solubility test**, two of which were Indian studies and one from Uganda. The comparators were either HPLC or Hb Electrophoresis. While the Indian study conducted in Gadchiroli had a high sensitivity and specificity of 93.8% and 100% respectively, the one conducted in Gujarat had a very low specificity of 29.6% and a high specificity of 96.8%. However, the study conducted in Uganda had a low sensitivity of 45% in comparison to the specificity of 90%.

Hemotype SC (Table 2):

Of the seven studies on **Hemotype SC**, one study validated this POC against HPLC among all age groups in India, one in USA and the rest five in different African countries. While four had electrophoresis, two studies had HPLC and one had PCR as the reference tests.

The Indian study by Mukherjee et al, published in 2020, carried out in Nagpur & Chandrapur in Maharashtra, Valsad & Jagadia in Gujarat, which had screened over 1559 individuals,

including new born and infants reported an overall sensitivity and specificity of 98.2% and 98.9% respectively. However, the sensitivity among new-borns were lower in comparison to the adult population, 85.7 and 99.5 respectively. Of the five African studies three had a cohort inclusive of new-borns.

Studies conducted in South West Nigeria, Cote d Ivoire and USA by Olatunya et al, Danho et al and Quinn et al respectively reported 100% sensitivity and specificity.

We could not find any published evidence which assessed the diagnostic effectiveness of Hemotype SC among pregnant women.

Every study reviewed had reported an overall sensitivity and specificity above 95% except the study conducted in Nigeria by Nnodu et al, with new-born and infant as the study population. The study reported a sensitivity of 90% for HbSS, which is the lowest value reported.

Sickle Scan (Table 3):

Six studies reported diagnostic effectiveness of **SickleScan** in comparison to standard of care tests. Only one study was conducted in India, at AIIMS Nagpur, but is yet to be published. However, an interim report was available for review. This study compared Sickle Scan against HPLC among children above two years of age and adults. It reports a sensitivity and specificity with respect to HbSS as 100% and 99.1% and HbAS as 92.4% and 99.1% respectively.

Three from Africa and one each from USA and Haiti are the other studies available in literature assessing the diagnostic accuracy of Sickle Scan. The comparator in these studies were either HPLC or electrophoresis technique. Most of the studies had reported a sensitivity and specificity above 95%. However, the Indian study as mentioned earlier had reported a sensitivity of 92.4% for HbAS. While the study conducted in Haiti reported a lower sensitivity of 90%, the study in Tanzania stated a lower specificity of 91.1%. These are the two studies, which validated Sickle scan among new- born.

The study conducted in Congo among pregnant women, also reported a lower sensitivity of 50% for HbSS, probabaly as the number of pregnant ladies with Sickle Cell Disease in the cohort were only two with Sickle Scan diagnosing one. To our best knowledge, this is also the only study available in the literature which validates a rapid diagnostic test for sickle cell disease among pregnant women.

Studies comparing Hemotype Sc with Sickle Scan (Table 4):

Three studies, Nnodu et al 2020, Olaniyan et al 2021 and Christopher et al 2022 had compared the diagnostic effectiveness of **Hemotype SC and Sickle Scan** in three different African countries. Nnodu et al reports a 100% sensitivity and specificity for both Hemotype SC and Sickle Scan in all Hb variants. Christopher et al reports 100% specificity for both the tests,

sensitivity is 100% for Hemotype Sc in all Hb variants and for Sickle Scan in all except HbAS which is estimated as 97%. Olaniyan et al, has compared Hemotype SC and Sickle Scan on the basis of time taken for conduct of study, percentage of tests repeated and incorrect readings. Time for conduct of study was measured as 15 mins and 7 mins for Hemotype SC and Sickle Scan respectively, while 6.8% tests were repeated with Hemotype SC only 0.2% was repeated with Sickle Scan. When 0.4% incorrect readings were made with Hemotype SC around 1.1% were made with Sickle scan.

Gazelle (Table 5)

There are limited studies in literature validating **Gazelle** for diagnosing Sickle Cell Disease. Of the two studies available in the literature one was conducted exclusively in India and the other included both Indian and Nigerian cohort. Both the studies reported a sensitivity and specificity above 98%.

Review on Effectiveness of tests under consideration for Sickle Cell Disease Screening

Table 1: Studies discussing the diagnostic effectiveness of Solubility Test

Sl.No	STUDY	REFERENCE TEST	LOCATION	POPULATION	SAMPLE SIZE	SENSITIVITY	SPECIFICITY	PPV	NPV
1.	Surve et al, 2000 [1]	HPLC, Hb electrophoresis	Dhule, Gadchiroli	Adults	3246	93.8	100		
2.	Okwi Andrew et al. 2010 [2]	Hb electrophoresis	Uganda	6 months – 5 years	200	45%	90%		
3.	Richa Jain et al 2020 [3]	HPLC	Gujarat		1890	96.8%	29.6%	87.9%	64%

Table 2: Studies discussing the diagnostic effectiveness of Hemotype SC

Sl.No	STUDY	REFERENCE TEST	LOCATION	POPULATION	SAMPLE SIZE	SENSITIVITY			SPECIFICITY			PPV	NPV
						AA	AS	SS	AA	AS	SS		
1.	Mukherjee et al, 2020 [4]	HPLC	Nagpur & Chandrapur in Maharashtra, Valsad & Jagadia in Gujarat	Newborns, Pediatric & Adults	1559	NB: 97.9 A: 100	NB: 91.7 A:100	NB: 85.7 A: 99.5	NB: 92.2 A: 100	NB: 97.9 A: 99.7	NB: 99.9 A: 100	NB: 97.1 A: 99.8	NB: 98.6 A: 99.9
						98.3	97.2	99.1	98.3	98.5	99.9	98.1	99.1
2.	Steele et al, 2019 [5]	Ghana: Agarose gel electrophoresis Martinique: IEF USA: Capillary zone electrophoresis	Ghana (n=383), Martinique (n=46, of which 39 - newborn)), and USA (n=158)	Newborns, 1 month - 5 years 5 years and above	587	Gha: 99.3 Mar: 100 US: 100	Gha: 100 Mar: 100 US: 100	Gha: 100 US: 100	Gha: 100 Mar: 100 US: 100	Gha:99.7 Mar: 100 US: 100	Gha: 100 US: 100	99.7	99.9
						99.7	100	100	100	99.8	100	99.7	99.9
3.	Olatunya et al, 2021 [6]	PCR	South West Nigeria	4 - 23	156	100	100	100	100	100	100	100	100
4.	Danho et al, 2021 [7]	Hb Electrophoresis	Cˆote d'Ivoire	0-15	336	100	100	100	100	100	100	100	100

Sl.No	STUDY	REFERENCE TEST	LOCATION	POPULATION	SAMPLE SIZE	SENSITIVITY			SPECIFICITY		
						AA	AS	SS	AA	AS	SS
5.	Nnodu et al, 2019[8]	HPLC	Nigeria	Newborns & Infants	1121	98.9	96.1	90	97.2	98.5	99.4
6.	Aime et al, 2022 [9]	Hb Electrophoresis	Congo	Less than 5 years	448	96.8-100			98.5-100		
7.	Quinn et al, 2016 [10]	HPLC Capillary Zone Electrophoresis	USA		100	100			100		

Table 3: Studies discussing the diagnostic effectiveness of Sickle scan

1.	Segbena et al, 2018 [11]	Togo: Capillary Electrophoresis Mali: HPLC	West Africa(Togo & Mali)	>= 6 months	520	100	95.6	94.6	100	99.6	99.6
2.	AIIMS Nagpur, Unpublished [12]	HPLC	Nagpur	> 2 years	404		92.4	99.7		100	99.1
3.	Kanter et al, 2015 [13]	Hb Electrophoresis, HPLC	USA	All age groups	137	>99	>99	>99	>99	>99	>99
4.	Mungu et al, 2020 [14]		Kisangani, Congo	14-43 Pregnant women	245	99.7	98.4	50 (n=2)	99.4	96.3	99.6
5.	Smart et al, 2018 [15]	Hb Electrophoresis	Tanzania	1 day – 20 years	752	98.1			91.1		
6.	Alvarez et al, 2019 [16]	HPLC	Haiti	Newborns & Infants	2159	90			97		

Table 4: Studies comparing the diagnostic effectiveness of Hemotype SC and Sickle Scan:

	Sl.No.	Article	Reference Test	Location	Population	Sample size	Comparison					
Comparative Study: SickleScan & Hemotype Sc	1.	Olaniyan et al, 2021 [17]	IEF	Luanda, Angola	Infants, 6 months age	2000 (1000 each)				**Time**	**Repeated Tests**	**Incorrect Readings**
							Hemotype			15 mins	6.8%	0.4%
							Sicklescan			7 mins	0.2%	1.1%
	2.	Christopher et al, 2022 [18]	IEF	Tanzania	Newborns	706		**PPV**	**NPV**	**Sensitivity & Specificity**		
										AA	AS	SS
							Hemo type	100	100	100	100	100
							Sickle Scan	100	99.7	100	97 Spec.100	100
	3.	Nnodu et al, 2020 [19]	HPLC	Nigerai	Newborns & infants	3603	Hemotype & SS	100	100	100	100	100

Table 5: Studies discussing the diagnostic effectiveness of Gazelle

Sl. No	STUDY	REFERENCE TEST	LOCATION	POPULATION	SAMPLE SIZE	SENSITIVITY		SPECIFICITY		PPV	NPV
						Sickle Trait	Sickle Disease	Sickle Trait	Sickle Disease		
1.	Srivas et al, 2021 [20]	Hb electrophoresis & HPLC	Chattisgarh & Madhya Pradesh	6 months to 65 years	1050	98.2	100	99.6	99.3	SCD:91.8 Trait: 98.9	SCD:100 Trait: 99.3
2.	Hasan et al, 2020 [21]	Lab electrophoresis, HPLC	India & Nigeria	6 weeks to 5 years	566	100	100	100	98.7	SCD:78.6 Trait:100	SCD:100 Trait:100

References:

1.Surve R, Mukherjee M, Kate S, et al. Detection of the βs gene: An evaluation of the solubility test against automated chromatography and haemoglobin electrophoresis. *British journal of biomedical science*. 2000;57:292-294.

2.Andrew O, Byarugaba W, Parkes A, Ocaido M. The Reliability of Sickling and Solubility Tests and Peripheral Blood Film Method for Sickle Cell Disease Screening at District Health Centers in Uganda. *Clinics in Mother and Child Health*. 2010;7:1-5. doi:10.4303/cmch/C101947

3.Jain R, Saxena S. The efficacy and reliability of Solubility test followed by High-Performance Liquid Chromatography (HPLC) for sickle cell disorders in Gujarat- An original research article. *Tropical Journal of Pathology and Microbiology*. 2020;6(2):199-204. doi:10.17511/jopm.2020.i02.13

4.Mukherjee MB, Colah RB, Mehta PR, et al. Multicenter Evaluation of HemoTypeSC as a Point-of-Care Sickle Cell Disease Rapid Diagnostic Test for Newborns and Adults Across India. *Am J Clin Pathol*. 2020;153(1):82-87. doi:10.1093/ajcp/aqz108

5.Steele C, Sinski A, Asibey J, 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. doi:10.1002/ajh.25305

6. Olatunya OS, Albuquerque DM, Fagbamigbe AF, et al. Diagnostic Accuracy of HemotypeSC as a Point-of-Care Testing Device for Sickle Cell Disease: Findings from a Southwestern State in Nigeria and Implications for Patient Care in Resource-Poor Settings of sub-Saharan Africa. *Glob Pediatr Health*. 2021;8:2333794X211016789. doi:10.1177/2333794X211016789

7. Kakou Danho JB, Atiméré YN, Koné D, Yéo DD, Couitchéré L. Feasibility Study of the "HemoTypeSC" Test for the Rapid Screening of Sickle Cell Disease in Côte D'Ivoire. *Adv Hematol*. 2021;2021:8862039. doi:10.1155/2021/8862039

8.Nnodu O, Isa H, Nwegbu M, et al. HemoTypeSC, a low-cost point-of-care testing device for sickle cell disease: Promises and challenges. *Blood Cells Mol Dis*. 2019;78:22-28. doi:10.1016/j.bcmd.2019.01.007

9.Aimé AK, Etienne SM, Mbongi D, et al. Dépistage hospitalier de la drépanocytose en République Démocratique du Congo (RDC) par HemoTypeSC: cas de la ville de Kindu. *Pan Afr Med J*. 2022;41:134. doi:10.11604/pamj.2022.41.134.30187

10.Quinn CT, Paniagua MC, DiNello RK, Panchal A, Geisberg M. A rapid, inexpensive and disposable point-of-care blood test for sickle cell disease using novel, highly specific monoclonal antibodies. *Br J Haematol*. 2016;175(4):724-732. doi:10.1111/bjh.14298

11.Segbena AY, Guindo A, Buono R, et al. Diagnostic accuracy in field conditions of the sickle SCAN® rapid test for sickle cell disease among children and adults in two West African settings: the DREPATEST study. *BMC Hematol*. 2018;18:26. doi:10.1186/s12878-018-0120-5

12. Project Report : Evaluation of Lateral Flow Immunoassay Based Rapid Test (Sickle Scan) or Point of Care Testing for Sickle Cell Disease in Hospital Setting. All India Institute of Medical Sciences, New Delhi & All India Institute of Medical Sciences, Nagpur; 2021.

13.Validation of a novel point of care testing device for sickle cell disease | BMC Medicine | Full Text. Accessed August 4, 2022. https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-015-0473-6
14. Mungu YNU, Juakali-Sihalikyolo JJ, Marini RD, et al. Performance of Sickle SCAN® in the Screening of Sickle Cell Disease in Kisangani Pregnant Women and Attitude towards Results. *OJBD*. 2020;10(02):23-36. doi:10.4236/ojbd.2020.102003

15. Smart LR, Ambrose EE, Raphael KC, et al. Simultaneous Point-of-Care Detection of Anemia and Sickle Cell Disease in Tanzania: The RAPID Study. *Ann Hematol*. 2018;97(2):239-246. doi:10.1007/s00277-017-3182-8

16. Alvarez OA, Hustace T, Voltaire M, Mantero A, Liberus U, Saint Fleur R. Newborn Screening for Sickle Cell Disease Using Point-of-Care Testing in Low-Income Setting. *Pediatrics*. 2019;144(4):e20184105. doi:10.1542/peds.2018-4105

17.Olaniyan HS, Briscoe C, Santos B, Pascoal R, Armando A, McGann PT. Comparison of Sickle SCAN and Hemotype SC As Point-of-Care Newborn Screening Diagnostics for Sickle Cell Disease in Luanda, Angola. *Blood*. 2021;138:913. doi:10.1182/blood-2021-151028

18.Christopher HH, Burns A, Josephat E, et al. Evaluation of Newborns Screening Laboratory Tests for Sickle Cell Disease and Other Haemoglobinopathies in Tanzania. *Blood*. 2019;134(Supplement_1):4817. doi:10.1182/blood-2019-129900

19.Nnodu OE, Sopekan A, Nnebe-Agumadu U, 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-e540. doi:10.1016/s2352-3026(20)30143-5
20. Shrivas S, Patel M, Kumar R, et al. Evaluation of Microchip-Based Point-Of-Care Device "Gazelle" for Diagnosis of Sickle Cell Disease in India. *Front Med (Lausanne)*. 2021;8:639208. doi:10.3389/fmed.2021.639208

21..Hasan MN, Fraiwan A, An R, et al. Paper-based microchip electrophoresis for point-of-care hemoglobin testing. *Analyst*. 2020;145(7):2525-2542. doi:10.1039/c9an02250c

22. Arishi WA, Alhadrami HA, Zourob M. Techniques for the Detection of Sickle Cell Disease: A Review. *Micromachines (Basel)*. 2021;12(5):519. doi:10.3390/mi12050519

1.4 Review of studies reporting clinical events among diagnosed patients:

The incidence of most clinical complications of SCD varies markedly both with time in the same individual and between different individuals. It can range from mild to severe. Children with SCD begin to show signs of the disease during the first year of life, usually around 5 months of age. In the initial period of infant's life, the fetal hemoglobin protects the red blood cells from sickling. When the infant is around 4 to 5 months of age, the fetal hemoglobin is replaced by sickle hemoglobin and the cells begin to sickle.

Over the entire life span these children have repeated bouts of illness majorly caused by vaso-occulsion such as pain, hand foot syndrome, severe anemia needing blood transfusions, bacterial infections most common being acute chest syndrome commonly due to pneumonia, acute symptoms of abdominal pain, breathlessness, thirst, weakness and tachycardia indicating splenic sequestration that might need blood transfusion or splenectomy. Leg ulcers, stroke, organ failures, joint problems, eye problems including retinal detachment in severe cases are other documented health problems that these children face.

The three most common presenting features of SCD in children remarked as the SCD Triad include, Infections, Acute Pain and Anemia. They are manifested before 5 years of age in around 80% of the children with SCD.
An ICMR survey reports a SCD mortality as 20 per cent by the age of two and 30 per cent before adulthood. In India, the major clinical manifestation among is vasoocclusion [1] with the highest incidence during rainy season followed by winter.[2] Patients complain mostly of periodic pain all over the body or in joints and limbs. Some carriers of SCD also complain of painful crisis.[3] The sickle cell disease patient survival rate in India is reported to be about 40 years [4]. In a study of SCD patients in Odisha over the age of 14, it was discovered that the death rate was 48% for those in the age groups of 15-25, 24% for those in 26-35, 20% for those in 36-45, and 8% for those over the age of 45 [5].

In an autopsy study to describe the pattern of mortality in SCD by Shah et al, 2017, the mean age at death was estimated as 30 years, a male/female ratio of 1.5:1 and peak mortality in the 2^{nd} to 4^{th} decades of life was reported. The cause of death in middle aged patients was reported as vaso occlusive crisis, and in paediatric patients and older patients as infection and chronic organ damage respectively. [6]

There are few studies in literature which estimated the incidence of events in SCD patients in India. These studies were majorly carried out in the high risk sickle belt of India including the states of Gujarat, Madhya Pradesh, Maharashtra and Odisha.

In the study by Dave et al 2021, conducted in the tribal area of Gujarat following up 87 new borns diagnosed with SCD, 80.5% babies had at least one clinical complication during the follow-up period. The rates of acute febrile illness, painful crisis, hospitalization and severe anemia were 42.9, 14.9, 14.9 and 4.5 per 100 person-year, respectively.[7]

In a study by Upadhaye et al, 2016 a cohort of 104 SS babies (Males-59, Females-45) was followed up clinically every month for a year and then every 3 months for 3–4 years for hematological and clinical evaluation, the study reported painful events followed by blood transfusions and acute febrile illness as the main clinical complications with the overall incidence of 59.7, 45.1 and 42.6 per 100 person years respectively. Vasoocclusive crisis (VOC), sequestration crisis and death were observed at 9.7, 3.0 and 3.65 per 100 person years respectively. [8]

In another study by Purohit et al, 2019 a hospital based study in Odisha, the demographic features, hematological, and clinical investigations in the deceased SCD patients were compared with age- and gender-matched hospitalized sickle cell disease patients who survived and were discharged during the study period . They reported 43.18% had fever in the survived group in comparison to 76.19% in the deceased group, similarly pain and anaemia were reported as 52.27% and 61.36% in the survived group in comparison to 86.36% and 52.38% in the deceased cohort respectively. [9]

The study by Thaker et al, 2022 conducted in Gujarat 87 new born SCD babies were followed for 0.5–6.6 years. The study reported 27.5% babies presented with fever and 17.4%, 2.9%, 21.8% presented pain, acute chest syndrome and anaemia respectively. The study also reported a death of 4.3%. [10]

The study conducted by Dr R.S. Balgir reports 11.5% fever, 4.9%, 13.1%, 9.8% abdominal, joint, chest pains respectively in the cohort of 61 HbAS phenotypes among the Bhuyan and Kharia tribes in North West Odisha.[11]

The study by Jain et al, 2013 conducted in Nagpur which assessed the efficacy of Fixed Low Dose Hydroxyurea in Indian Children with Sickle Cell Anaemia, on a cohort consisting of 144 children (<18 years of age) with SCA, reported baseline characteristic of various SCD events. The cohort presented with 4.27±1.99 events per year vasoocclusive crisis and 0.04±0.21,

0.03±0.18, 0.04±0.21 events per year of cerebrovascular events, acute chest syndrome and sequestration crisis respectively.[12]

In a hospital based study conducted by Bhatwadekar et al in Vadodara with SCD patients of age ranging between 7 to 57 years, Vaso-occlusive crisis was reported as the most common morbid event (58%) followed by Acute chest syndrome (11%), Hepatic cell crisis (10%), Septicemia (7.5%) and Splenic sequestration (3.7%). [13]

The study conducted by Silva Pinto et al in Brazil, to estimate SCD societal costs based on disease burden modelling, reviewed studies describing the clinical events of SCD. It reported 55% and 30% of acute chest syndrome among children and adults respectively. Vaso-occlusion, splenic sequestration and infections were reported as 59.5%, 34.9%, 50% among children and 75%, 2% and 32% among adults respectively. [14]

Table 1: Incidence of clinical events in SS cases per 100 person years

Sl No	Study	Cohort Size	Location	Time Period	Painful events/ crisis	Acute Chest Syndrome	Vaso occlusive Crisis	Splenic sequestration	Fever	Severe anaemia	Death
1.	Dave et al 2021 [7]	8916 new born	Gujarat, MP	6 years	14.9	5.9			42.9	4.5	0.9
2.	Upadhaye et al 2015 [8]	104 new born	Govt Medical College, Nagpur	Follow up monthly for one year and 3 monthly for next 3-4 years	59.7		9.7	3	42.6		3.65

Table 2: Clinical events in SS cases expressed as percentage or proportions:

S no.	Author	Title	Location	Sample Size	age-group	Fever	Painful events	Acute Chest Syndrome	Anaemia	Vaso-occlusion	Splenic sequestration	Death
1	Purohit et al 2019 [9]	Factors responsible for mortality in patients with sickle cell disease: A hospital-based study	Medical College, Berhampur, Odisha	44 SCD patients	13-50	43.18 survived, 76.19 died	52.27 survived, 86.36 died		61.36 survived, 52.38 died			
2	Silva-Pinto AC et al 2022 [14]	Economic burden of sickle cell disease in Brazil	Brazil	-	Adult and children			55(children) 30(adults)		59.5 (children) 75(adults)	34.9 (children) 2(adults)	
3	Balgir et al 2005 [11]	The spectrum of haemoglobin variants in two scheduled tribes of Sundargarh district in north-western Orissa, India	Sundargarh district in north-western Orissa	1603	0-61+	11.5	4.9 (abdominal pains), 13.1 (joint pain), 9.8 (chest pain)				3.3(splenomegaly)	
4	Thaker et al 2022 [10]	Newborn Screening for Sickle Cell Disease Among Tribal Populations in the States of Gujarat and Madhya Pradesh in	Gujarat and Madhya Pradesh	8,916 newborn babies 8,411 from Gujarat and 505 from Madhya Pradesh	new-borns	27.5	17.4	2.9	21.8			4.3

		India: Evaluation and Outcome Over 6 Years										
5	Jain et al 2013 [12]	Efficacy of fixed low dose hydroxyurea in Indian children with sickle cell anemia: a single centre experience	Nagpur	144	Less than 18 years				0.03±0.18	4.27±1.99	0.04±0.21	
6	Bhatwadekar et al [13]	Morbidity Pattern in Sickle Cell Disease in Central Gujarat, India — Single Centre Perspective	Gujarat		7-57			11%		58%	3.7%	

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.2021.731884

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

1.5 Estimation of costs:

Health system costs for screening of the disease in the public health system were estimated using standard treatment guidelines and package rates from Ayushman Bharat. Costs were also derived from CHSI costing study and other published data. Expert opinion was also sought for deriving few of the cost components, such as, kit price. Threshold analysis was be performed as part of the cost analysis.

The aim was to estimate the cost of providing point of care testing as compared to standard care currently available along with health system cost for diagnosing the cases. Cost of screening included the economic cost of sample collection, supplies, personnel and additionally transport and laboratory processing cost for HPLC confirmation. Other costing heads included human resources, area cost, drugs and consumables, medical and non-medical equipment and overhead costs. The sources to obtain this data was secondary sources of available data.

Expert Opinion:

Several clinicians and researchers were consulted to get a perspective of their experiences in screening diagnosis and management of sickle cell patients using various POC tests as well as standard modalities.

Disease progression and most common clinical presentations were agreed upon and algorithms to manage the same were discussed.

In these interactions it was agreed that Gazelle is not an ideal POC to be considered for this analysis due to high cost of machine, need for electric charging and expertise needed to read the results although it has several additional advantages of diagnosing other hemoglobinopathies.

Experts also noted that there was no good published evidence of validation of Sickle Scan in India in various age groups. The need for a buffer solution to carry out the tests was an additional consumable that would be needed unlike Hemotype Sc where only distilled/tap water could be used.

Experts suggested need for generating more evidence on the use of Sickle Scan in India.

According to them two groups were most important to be screened

(i) Newborns/ children coming for immunisation who have missed screening
This group can be put on prophylactic antibiotics and preventive immunisations like pneumococcal vaccines that could reduce morbidities and under two age mortalities.

(ii) Pregnant women who need to ne screened in first trimester or early second trimester who could be given an option for abortion before 20 weeks as prenatal diagnosis.

(iii) Reproductive age group to be considered for screening which could cover maximum population of marriageable age for counselling and preconception care. As per discussions age group upto 30 years was agreed upon

Analysis

Mathematical modelling, one way and probabilistic sensitivity analysis and budget impact analysis were conducted. We assumed that screening will be predominantly performed at primary level (70%) and rest of the screening at secondary and tertiary level.

Results

The population screened with a Markov model was 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 population of the 6 highest burden states (Tamil Nadu, Chhattisgarh, Maharashtra, Odisha, Gujarat and MP) for sickle cell disease. According to the model, cost per individual screened (also, cost per test) using the POC tests Hemotype SC and Sickle Scan is INR 250.17 and for solubility test

Table 1: Cost* per individual screened using different strategies

Solubility Test: Primary Level- HR, Capital and Other Cost	28.172
Solubility Test: Primary Level- Consumables Cost	17.32
Total	**45.492**
Solubility Test: Secondary Level- HR, Capital and Other Cost	52.98
Solubility Test: Secondary Level- Consumables Cost	17.32
Total	**70.3**
Solubility Test: Tertiary Level- HR, Capital and Other Cost	34.16
Solubility Test: Tertiary Level- Consumables Cost	17.32
Total	**51.48**
Solubility test is followed by HPLC of screened positives. In our analysis, we have taken cost of HPLC as INR 500, as costing data was not available. Using the current prevalence, using HPLC in screened positives will increase the cost/individual screened by INR 7.83.	
HemotypeSC: Primary Level- HR, Capital and Other Cost	38.17
HemotypeSC: Primary Level- KIT Cost	212
Total	**250.17**
HemotypeSC: Secondary Level- HR, Capital and Other Cost	91.08
HemotypeSC: Secondary Level- KIT Cost	212
Total	**303.08**
HemotypeSC: Tertiary Level- HR, Capital and Other Cost	59
HemotypeSC: Tertiary Level- KIT Cost	212
Total	**271**
Sickle SCAN: Primary Level- HR, Capital and Other Cost	38.172
Sickle SCAN: Primary Level- KIT Cost	212
Total	**250.172**
Sickle SCAN: Secondary Level- HR, Capital and Other Cost	91.08
Sickle SCAN: Secondary Level- KIT Cost	212
Total	**303.08**
Sickle SCAN: Tertiary Level- HR, Capital and Other Cost	59
Sickle SCAN: Tertiary Level- KIT Cost	212
Total	**271**

(*Source: CHSI Study data and expert opinion)

followed by HPLC as a confirmatory test is INR 53.32. Table 1 further elaborates the cost component breakdown for primary, secondary and tertiary levels.

In this cohort, screening through Hemotype CS 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 2 (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.

Table 2: Model Outcomes for different age groups:

	In 0-2 years Population (95% CI)**	**In 2-30 years, Population (95% CI)**	**In 0-30 years, Population (95% CI)**
Population to be screened	1.37 Crores	3.07 Crores	3.41 Crores
Cases detected by HemotypeSC	56,180 (50,866 – 61,635)	4,97,722 (4,46,798 – 5,48,736)	5,52,376 (4,98,950 – 6,07,175)
Cases detected by Sickle SCAN	56,465 (51,146 – 62,049)	5,00,048 (4,49,290 – 5,52,365)	5,55,371 (5,02,248 – 6,10,799)
Cases detected by Solubility + HPLC**	0	4,79,790 (4,30,897 – 5,29,487)	5,32,422 (4,81,582 – 5,85,764)
Cases remaining undetected in population: HemotypeSC	1,560 (1271 – 1,897)	13,736 (11,062 – 16,878)	15,255 (12,381 – 18,932)
Cases remaining undetected in population: Sickle SCAN	1,260 (993 – 1,578)	11,325 (8,744 – 14,213)	12,409 (9,518 – 15,842)
Cases remaining undetected in population: Solubility + HPLC**	-	31,728 (28,469 – 34,997)	35,206 (31,805 – 38,706)
Cost/ Case detected: HemotypeSC	16,056 (14,377 – 17,993)	15,985 (14,140 – 17,968)	16,056 (14,377 – 17,993)
Cost/ Case detected: Sickle SCAN	15,958 (14,250 – 17,908)	15,844 (14,183 – 17,998)	15,958 (14,250 -17,908)
Cost/ Case detected: Solubility + HPLC**	0	3,640 (3314 – 4021)	3,652 (3,332 – 4,025)
ICER (per Case Detected): HemotypeSC	-	3,46,437 (2,88,345 – 4,32,023)	3,47,466 (2,90,295 – 4,35,444)
ICER (per Case Detected): Sickle SCAN	-	3,04,090 (2,56,004 – 3,69,291)	3,04,284 (2,60,597 – 3,65,470)

**** In age group 0-2 years; Solubility + HPLC: Literature review and expert consultation done as a part of landscape analysis of this study suggested that solubility test is not suitable for testing Sickle cell disease and trait in newborns, as number of false negatives will be high. Therefore, in this part of the model, we have not considered solubility as a comparator.**

Although, the cost for screening (table 2) with Hemotype SC [INR 797.71 crores (2-30 years); INR 885.53 (0-30 years)] and Sickle Scan [INR 795.38 crores (2-30 years); INR 885.53 (0-30 years)]is higher than screening with solubility + HPLC, it may be noted that the number of undetected cases is highest in screening with solubility + HPLC, which makes it a less reliable test as compared to the interventions. Incremental cost effectiveness ratio per case detected (ICER) for Hemotype SC ranges between 2,88,345 – 4,32,023 and 2,90,295 – 4,35,444; in 2-30 years and 0-30 years age groups, respectively, as shown in table 2. Similarly, Incremental cost effectiveness ratio per case detected (ICER) for Sickle Scan ranges between 2,56,004 – 3,69,291 and 2,60,597 – 3,65,470 in 2-30 years and 0-30 years age groups, respectively, as shown in table 2.

One way sensitivity Analysis (OWSA) for Price Threshold:

The price at which these POC kits are procured plays a huge role in determining the overall cost of screening, therefore one way sensitivity Analysis (OWSA) was performed. 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.

Price of HemotypeSC Kit	ICER
212	346662.6
200	326132.2
180	291915
160	257697.7
140	223480.4
120	189263.1
100	155045.9
80	120828.6
60	86611.29

Table 3a and 3b: Threshold analysis shows change in ICER value with change in kit price for Hemotype SC and Sickle Scan, respectively.

Price of Sickle SCAN Kit	ICER
212	303331.9
200	285367.8
180	255427.7
160	225487.6
140	195547.5
120	165607.3
100	135667.2

80	105727.1
60	75786.98

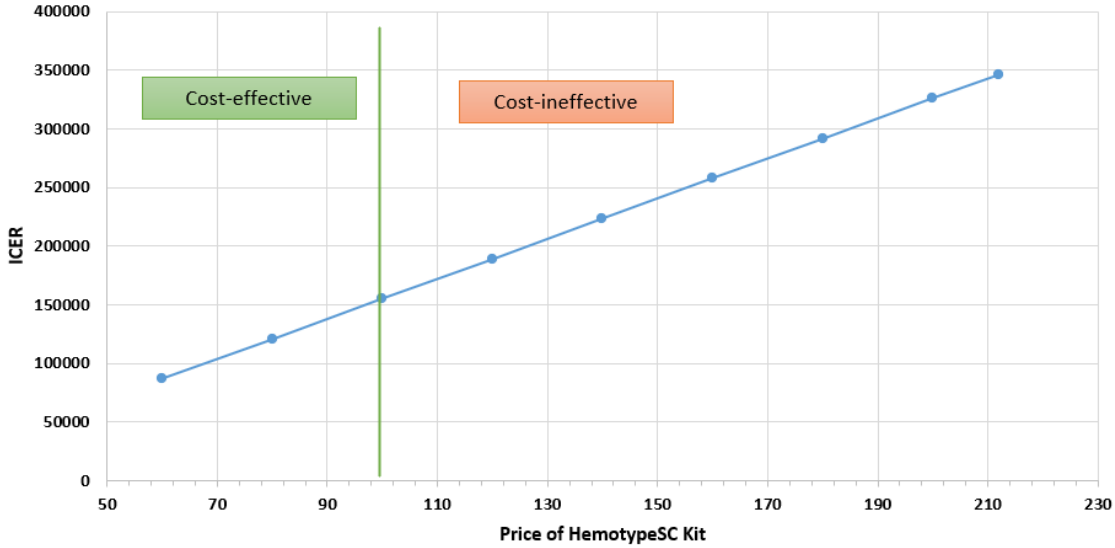
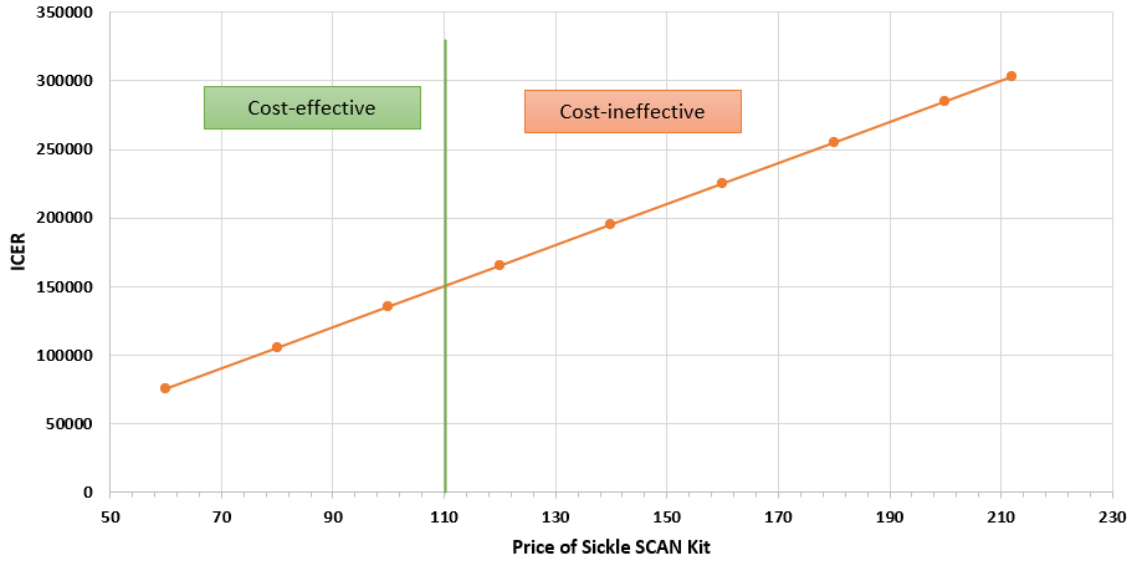


Figure 1a and 1b: Graphical representations of change in ICER upon changing the kit prices of Hemotype SC and Sickle Scan, respectively.



Probabilistic Sensitivity Analysis PSA

To check the robustness of the model and address uncertainity, 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. The results of which have been presented in table 2.

Budget Impact Analysis (BIA)

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. Table 4 lists the respective detailed costs.

Strategy	In 0-2 years Population (95% CI)	In 2-30 years, Population (95% CI)	In 0-30 years, Population (95% CI)
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

Table 4: Budget impact analysis showing cost of rolling out screening in different age groups using Hemotype SC, Sickle Scan and solubility + HPLC.

Landscape Analysis using expert opinion

Additionally, experts in the field were also consulted at the stage of model development and also when deriving parameter values. The findings of this consultation are:

- Solubility + HPLC: Literature review and expert consultation done as a part of landscape analysis of this study suggested that solubility test is not suitable for testing Sickle cell disease and trait in newborns, as number of false negatives will be high due to the presence of foetal haemoglobin (Hb F) interferes with the results.
- Solubility test cannot identify sickle cell trait (SCT). However, the two POC tests, as also suggested by literature can successfully identify traits and hence can lead to long term health and economic benefits.
- Gazelle has been eliminated from the analysis, as it is not a POC test.
- POC tests can be done by ASHA workers/ technicians, does not require skilled manpower.

- It will be ideal to use age group of 0-30 years in high risk population for modelling.

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.
- The POC tests as compared to HPLC is cost effective in 0-2 years as solubility test cannot be done for newborns due to interference of foetal hemoglobin.
- POC tests may be considered for adoption in Sickle cell screening programme of neonates 0-2 years
- POC tests are useful in identifying the SCTs and its health benefits will be reflected in next generation along with its economic benefits with a cost reduction below Rs.100.
- 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.
- Cost of rolling out screening at public health facilities in age groups.
    a) **0-2 years** (34,56,509) is **INR 89.58 crore** for **Hemotype SC**; **INR 89.59 crore** for **Sickle Scan**,
    b) **2-30 years** (3,06,75,481) is **INR 797.71 crore** for **Hemotype SC**; **INR 795.38** crore for **Sickle Scan** and **INR 175.08** for **Solubility + HPLC** and
    c) **0-30 years** (3,41,31,990) is **INR 885.53 crore** for **Hemotype SC**; **INR 795.38 crore** for **Sickle Scan** and **INR 194.64** for **Solubility + HPLC**, respectively.
- Solubility although incurs less cost, but is not appropriate for neonate screening.

Limitations

- No peer reviewed publication on Sickle Scan validation in India
- Sensitivity and specificity data was derived using targeted literature review. A systematic literature review may be performed to estimate more accurate estimates.
- This analysis takes into account the economic consequences of screening for Sickle Cell Disease only. There are many more benefits of identifying Sickle Cell Disease and Trait, which the POC tests impart. These benefits will be reflected in terms of better health outcomes and lesser management cost because of early detection and prompt treatment in SCD patients, as well as in the forthcoming birth cohort in SCT patients and may be modelled in subsequent analysis.
- Indigenous POC tests need to be validated further.

Conclusion

To summarise, both the POC tests to diagnose Sickle Cell Disease/Trait will be cost-effective for screening only if it is procured below Rs. 100. The screening strategy could be rolled out in the six states of Tamil Nadu, Chhattisgarh, Maharashtra, Odisha, Gujarat and MP (Top 6 are

high prevalent sickle cell states in new-borns). Screening may be rolled out in a phased manner, with phase one being 0-2 years and phase 2 being 2-30 years, including anti-natal population as well.

Compiled by

HTAIn, Department of Health Research, MOHFW, GOI
HTA Resource Hub, ICMR NIRRCH Mumbai
HTA Resource Hub, School of Public Health, PGIMER, Chandigarh