Health Technology Assessment of Cost-effectiveness of High-Performance Optical Spectroscopy (HPOS) Diagnostic Test (SickleCert)

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Summary

SickleCert is India's first indigenous Point-of-Care Sickle Cell kit, developed by Indian Institute of Science (IISc), Bengaluru, that can be used for both screening and diagnosis of Sickle-Cell Anemia (SCA). It is a quantitative, single-step, low-cost method with an accuracy, sensitivity, and specificity of 97.25%, 97.4%, and 97.5%, respectively. It was found to be a **Cost-Effective intervention** compared to the traditional Solubility Test for screening followed by confirmatory HPLC Test (with an ICER of 1,15,051 per case detected), when per test cost is Rs 114 or below. Cost of rolling out screening program with SickleCERT + HPLC was calculated to be 444.60 Crores. With the potential for effective point-of-care use and minimal training, SickleCert offers a cost-effective solution for SCA elimination programme.

Policy Recommendations

1. HPOS Based **SickleCert Is Effective For Diagnostic Testing** of Sickle Cell Anemia In Remote Areas, Primary, Secondary As Well As Tertiary Healthcare Settings **when charged at Rs.114/- or below per test.**
2. HPOS Considered As **Quantitative Point-Of-Care Test** Based On Feasibility Studies Conducted by ICMR Institutes.
3. HPOS was Recommended For The **Age Group Of 5- 60 Years.**

Background

The Disease: Sickle cell anemia (SCA) is a hereditary blood disorder characte rized by abnormal sickle-shaped Red Blood Cells (RBCs) caused by a point mutation[1] distorting RBCs shape into a sickle under low oxygen conditions. These abnormal RBCs have a shortened lifespan (10-20 days) compared to normal RBCs (120 days), leading to anemia[2]. SCA categorized into sickle cell trait (SCT) – a milder form of anemia and sickle cell disease (SCD) which is a severe form of anemia, based on zygosity [3,4].

Disease Burden: SCA is of global importance with economic as well as clinical significance. In India, 1.5 lakh children are affected, and 20% die before age two and 30% during adulthood [5]. The disease is more prevalent in Madhya Pradesh, Tamil Nadu, Maharashtra, Gujarat, Odisha and Chhattisgarh [6]. Prevalence among tribal populations is highest in Madhya Pradesh followed by Maharashtra, Kerala and Gujarat [7].

Screening Tests for Sickle Cell Anemia:

Solubility Test: National Guidelines on hemoglobinopathies recommend screening for sickle cell disease (SCD) using a Solubility Test followed by a confirmatory test through Hemoglobin Electrophoresis or High-Performance Liquid Chromatography (HPLC). For newborn, a dried blood spot (DBS) with HPLC is recommended due to the limitations of the solubility test in the presence of high HbF levels [8]. The solubility test cannot distinguish between sickle cell trait (SCT) and sickle cell disease (SCD) [9,10]. Despite their specificity, these tests are expensive, time-consuming, and require specialized labs and personnel, restricting their use at the point of care.

SickleCert: Research team from the Department of Instrumentation and Applied Physics (IAP) at **Indian Institute of Science (IISc)** has developed India's first indigenous kit, SickleCert, that can be used for **both screening and diagnostic testing of Sickle-Cell Anaemia.** ***It is a single-step, low-cost method for rapid and accurate screening and diagnosis of SCT as well as SCD*** (Fig. 1). ***This test can provide its results in 15-20 minutes with a throughput of 30 test per hour.***

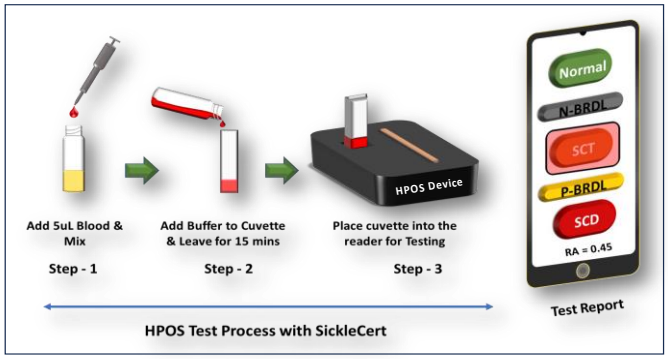


Figure 1: Schematic of the sickle cell test using the optical absorbance spectrometry method [11].

Validated with 438 patient samples it demonstrated an average accuracy of 97.6%, sensitivity of 96.9%, and specificity of 98.6%[11].

The technology has been patented in India, United States and Africa, and it is licensed for commercialization by ***ShanMukha Innovations Pvt Ltd, an IISc start-up.***

Health Technology Assessment of Rapid Diagnostic Test (SickleCERT)

Estimation of Cost: Costs for screening SCD involved utilizing standard treatment guidelines, package rates from Ayushman Bharat, CHSI costing study, and other published data. Expert opinions were sought for certain cost components, such as kit price. The aim was to compare the expenses of POC testing to the current standard care, encompassing screening, diagnosis, and health system costs. Various heads of costing, including human resources, area cost, drugs, consumables, and overhead costs, were considered.

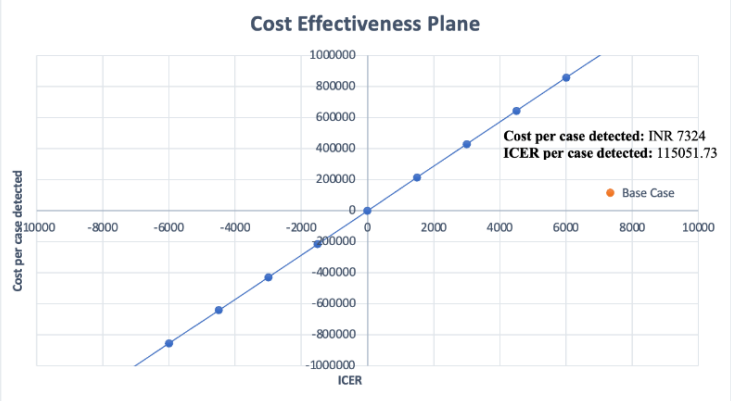


Figure 2: Cost-effectiveness plane showing ICER per case detected of the intervention - POC test with HPOS principle in comparison with solubility + HPLC

Cost-Effectiveness Analysis (CEA): CEA of SickleCert was carried out in comparison with SolubilityTest Followed by HPLC employing a Mathematical Modelling, One-way and Probabilistic Sensitivity Analysis were conducted. It was assumed that screening will be predominantly performed at primary level (70%) and rest of the screening at secondary and tertiary level.

Table 1: Model Outcomes

Parameters	In 5-40 years, Population (95% CI)
Population to be screened	3.73 Crores
Cases detected by SickleCERT +HPLC	6,07,091 (5,46,382 – 6,67,800)
Cases detected by Solubility + HPLC	5,84,652 (5,26,187 – 6,43,118)
Cases remaining undetected in population: SickleCERT	16,205 (14,585 – 17,826)
Cases remaining undetected in population: Solubility + HPLC	38,644 (34,779 – 42,508)
Cost/ Case detected: Sickle CERT	7,324 (6,596 – 8,051)
Cost/ Case detected: Solubility + HPLC	3,189 (2,875 – 3,503)
ICER (per Case Detected): SickleCERT	115051.73 (103552.1 – 126556.52)

Budget-Impact Analysis: A budget impact analysis was conducted to find the total health system costs of rolling out screening program with, SickleCERT and solubility + HPLC. Table 2 lists the respective detailed costs.

Table 2: Budget impact of rolling out screening in different age groups using SickleCERT + HPLC and solubility + HPLC.

Strategy	In 5-40 years, Population (95% CI)
Cost of rolling out screening program with SickleCERT + HPLC	444.60 (360.4 – 537.64) Crores
Cost of rolling out screening program with Solubility + HPLC	186.4(151.3 – 225.3) Crores

The analysis reveals that SickleCert falls within the first quadrant of the cost-effectiveness plane when considering the Incremental Cost-Effectiveness Ratio (ICER) per detected case. Although, the cost for screening with SickleCERT followed by HPLC as confirmatory test for borderline cases is INR 444.60 crores which is higher than screening with solubility + HPLC (Table 2), 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 intervention. (ICER) per case detected (ICER) (Fig. 2) for SickleCERT 1,15,051 (1,03552 – 126556), as shown in table 1.

Feasibility Tests

To enhance the utility and feasibility of SickleCert, based on expert recommendations, field testing and validation studies across diverse populations and conditions were conducted, ensuring its effectiveness in real-world scenarios that included Borderline Cases (Fig. 3). Individual field studies were carried out by (i) ICMR-BMHRC, Bhopal (ii) ICMR-CRMCH, Chandrapur, Maharashtra and the detailed results have been reported in the full HTAIn report. A consolidated performance metrics were derived by combining the true positives (TP), True negatives (TN), False positives (FP), and False negatives

(FN) from all the evaluations carried out till date including CDSCO clinical evaluations and data that has already been published. The overall performance showed an **accuracy, sensitivity,** and **specificity** of **97.25%, 97.4%**, and **97.5%** respectively.

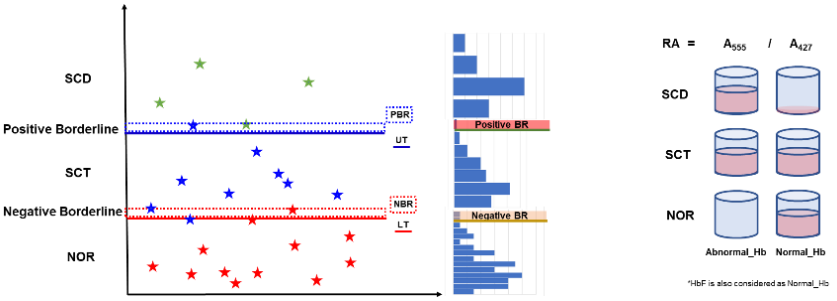


Figure 3. Scattered plot depicting **borderline cases** and threshold values.

Overall, SickleCert **field performance demonstrated accurate detection of Sickle cell cases** even in the presence of Sickle-Thal co-morbidity. Extreme condition analysis (4°C-50°C) showed consistent performance as room temperature, but challenges were observed at 4°C where samples struggled to deoxygenate. Despite this, the Single-Test Kit proved effective and user-friendly for door-to-door testing.

Borderline Cases

Borderline Cases: In the context of the HPOS Technology, the term "Borderline" refers to cases where the Ratio of Abnormal-Hb to Normal-Hb Absorbance (RA) falls very close to the established thresholds. Borderline cases shown in the fig. 5:

- Negative & Borderline (NBR): If RA is very close to the Lower Threshold (LT) of 0.29.

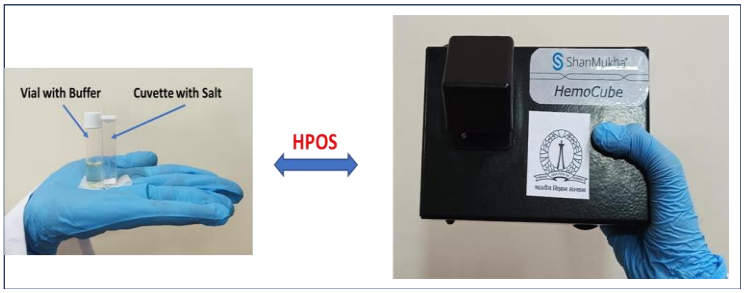
- Positive & Borderline (PBR): If RA is very close to the Upper Threshold (UT) of 0.53.

These Borderline cases indicate a proximity to the classification thresholds, and as a precautionary measure, re-testing is recommended for confirmation with HPLC to ensure accurate and reliable results.

It is recommended to provide the RA values as well as reference ranges for classification along with the final test reports for prognosis and reference for clinicians.

SickleCert

- First **Indigenous** Sickle Cell Disease Screening Kit.
- HPOS based a **Single-step, Low-Cost method for Rapid and Accurate screening** and Diagnosis of Sickle Cell Trait as well as Sickle Cell Disease.
- Portable Device with Minimal Training Required.
- **Approved by DCGI-CDSCO's** as a Class-C Medical Device



Key Findings

- ICER per case detected for SickleCERT when compared with Solubility + HPLC is 1,15,051 at **per test cost of Rs 114 or below** for population-based screening.
- ICER per case detected suggests that screening with SickleCERT kit is a cost-effective strategy in **5 – 40 years of age group**.
- **Cost of rolling out screening at public health facilities** in 5-40 years of age group is 444.60 (360.4 – 537.64) Crores.
- POC testing with principle of lateral flow was found to be cost - effective below Rs 100, and the current POC based on High performance optical spectroscopy **(HPOS) technology is cost effective if procured at Rs 114 or below.**
- This POC test **cannot be used for screening neonatal population, due to lack of validation**. Further validation studies are required in testing with neonates, and blood samples from sources other than cord blood should be considered.
- There is **no data available for validity of this test in beta thalassemia.**
- Limited peer reviewed publication on SickleCERT validation in India. It is essential for DHR to **plan a multicentric study for further kit validation as a scaling up for population wide screening and a study eventually for newborn screening.**
- The cost of screening will increase with increase in case load of screening, wherein extra HR cost will have to be considered.

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