



Reducing Child Mortality in Sierra Leone with a Sustainable Diagnostics Device for Sickle Cell Disease

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Abstract

Sickle cell disease (SCD) is a genetic blood disorder that affects more than 250 million people globally (Ilesanmi, 2010). The disease arises from an abnormal variant of hemoglobin in the bloodstream, which causes healthy red blood cells to assume a sickle shape. Aggregations of these atypical blood cells can inhibit circulation and lead to many health complications that can become fatal if left untreated. When the disease reached the United States during the 20th century, there were sufficient resources for the innovation of advanced diagnostic procedures to identify SCD in its early stages. However, low-to-middle income countries (LMICs) in Sub-Saharan Africa lack the means to effectively cope with the disease, thus demonstrating the healthcare inequalities between LMICs and developed countries. Between 50-90% of SCD-affected individuals in this region die before the age of 5, accounting for over half of the global SCD-related deaths in children under 5 (Tshilolo, 2019). To address this health crisis, the Lehigh University Sickle Cell Diagnostics team (SickLED) is developing a low-cost, point-of-care screening device for SCD that is designed for implementation as a neonatal standard operating procedure (SOP) in local hospitals. Because the lateral flow device is paper-based, its fabrication is sustainable and easily constructible without advanced medical training. With help from sponsors and the team's established network of healthcare and social workers in Sierra Leone, SickLED's plan is to assist the efforts present in Sub-Saharan Africa to help raise public awareness of the importance of healthcare and definitively diagnose SCD in these regions.

Keywords: sickle cell disease, lateral flow device, test strips, sustainable global health, low-cost diagnostic, LMIC

Purpose

Universal screening and early intervention programs for SCD are crucial to preventing patient fatality, as they are proven to increase the life expectancy of those who have the disease (Kanter, 2015). However, LMICs such as Sierra Leone lack the resources and knowledge to definitively test for SCD. While primary diagnostic methods used in high resource countries include Isoelectric Focusing (IEF) and High-Performance Liquid Chromatography (HPLC), these technologies are costly, limited to a lab, and require a continuous reliable supply of electricity (Ilesanmi, 2010), thus making them unfeasible in LMICs. Additionally, Sierra Leone is one of the least developed countries worldwide, with uneven distribution of resources throughout the country (Caviglia, 2021). The vast majority of hospitals are concentrated in the country's capital, Freetown, thus preventing

individuals living in rural communities from access to healthcare. Furthermore, the poor service quality and lack of skilled medical staff contribute to increasing out-of-pocket expenses, as this high demand towards a low supply exacerbates the issue and skyrockets prices (Caviglia, 2021). With 53% of the population living below the poverty income line of \$1.25 U.S. dollars a day, medical care is not feasible unless it is cost-effective (World Food). Therefore, with an already existing lack of education and awareness about the disease, there are scarce opportunities for SCD diagnosis.

While several small-scale screening initiatives have been implemented throughout LMICs, these initiatives were time-consuming and expensive, thus making it infeasible to continue these practices in LMIC and furthering the disparity between health care between high- and low-income countries. Two such programs were initiated in Angola and Uganda, and involved collecting dried blood spot (DBS) samples from newborns in high-risk areas, and sending them to centralized laboratories for isoelectric focusing analysis (Mvundura, 2019).

These programs had costs estimated to be \$15.36 and \$9.94 per test, respectively, and the time-consuming operations of the initiatives did not account for the need for early diagnosis of SCD. Evidently, the lack of a low-cost, point-of-care screening device in LMICs leads individuals with SCD to be left undiagnosed until they are present with clinical symptoms in late childhood, when treatments such as folic acid penicillin prophylaxis are less effective (Italia, 2019). This makes the illness a multifaceted issue in these regions, requiring not only the innovation and implementation of an accurate screening device, but also a campaign to spread awareness about the disease and its trajectory to local communities. SickLED acknowledges each dimension of the required solution to the problem by addressing aspects of SCD education, device cost and accessibility, and testing accuracy to advocate for sustainable global health.

The SickLED screening device provides an affordable and effective solution for SCD testing in LMIC. The paper-based test strip is designed to differentiate between individuals who have SCD, carry the sickle cell trait (SCT), or are healthy. Additionally, SickLED pushes forth an educational campaign by informing locals of what SCD is and how early detection is crucial to increasing the life expectancy of an affected individual. With increased awareness, people in LMICs will be more inclined to use the device, thus promoting long-term healthy living. These plans have been made possible through the connections that SickLED has been fostering with in-country organizations such as World Hope International, the Sickle Cell Carers Awareness Network, and Sickle Cell Society in Sierra Leone. This collaborative combination of screening, education, and treatment led by partnerships between SickLED and other SCD organizations, as well as local physicians, clinics, and hospitals, will promote well-being across all ages to ensure and maintain standards of healthy living in accordance with local community life. Upon success in Sierra Leone, the device will maintain sustainability through its implementation into Sierra Leone's health infrastructure through the Free Healthcare Initiative (FHCI), which provides basic health services to pregnant women and children under five (Witter, 2016). Upon local implementation, SickLED operations will be handed off to the Sierra Leone Ministry of Health, where the device can continue to be developed and optimized further without SickLED's involvement. Successful SickLED operations have the potential to expand to other Sub-Saharan countries to improve the life quality and life expectancy of SCD-

affected individuals, thus creating value for patients, their families, and the global healthcare system overall.

Design and Approach

The SickIED device design meets standards of accuracy, sustainability, affordability, and portability such that unnecessary costs are minimized and accurate results are guaranteed. In alignment with the sustainable development goals (SDG) of the United Nations (UN), the SickIED diagnostic device will reduce financial burden and healthcare inequality by improving long-term health outcomes for SCD-affected individuals. While SickIED's primary focus is to lower the SCD-related child mortality rate in Sierra Leone and other LMICs, the concentrations and volumes of the antibodies in the SickIED screening device are designed to be manipulated and optimized for use with varying forms and concentrations of hemoglobin across all age ranges. Thus, the test strip is designed to have a wide dynamic range between infants and adults, with the ability to distinguish between individuals who have SCD, SCT, and are healthy.

Beginning with screening and diagnosis of diseases, SickIED promotes the well-being of individuals at all ages and allows for the administration of proper treatment. This will significantly reduce the number of preventable deaths and promote good health as outlined in SDG 3. Additionally, the SickIED implementation phase, which includes collaboration with multiple SCD advocacy networks in Sierra Leone, demonstrates alignment with SDG 10 because of its commitment to reducing global healthcare inequalities.

The SickIED test strip employs simplified immunoassay techniques with small quantities of reagent, thus ensuring accurate results without compromising device affordability. Modeled after the common pregnancy test, the structure of the SickIED test strip is built based on a lateral flow sandwich assay (Figure 1), where an antigen-antibody complex with conjugated beads allows for control or test lines to appear. Lateral flow immunoassays are largely employed in point-of-care settings due to their simplicity and the minimal resources required (Easthope, 2021), the SickIED device adopted its paper-based design as a lateral flow assay with an assembly that does not require advanced medical training. Thus, the SickIED test strip will allow for increased SCD diagnostics accessibility within local health clinics in Sierra Leone and other LMICs, given that local healthcare workers will be able to construct and administer the SickIED device without more than an information manual for both purposes. In this way, a method for SCD diagnostics will become widely available and accessible in LMICs.

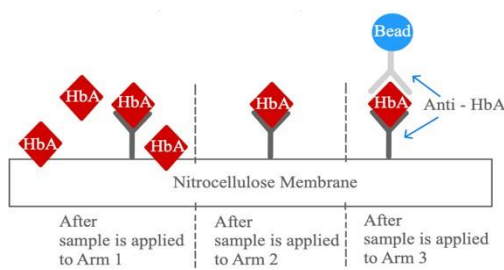


Figure 1: The sandwich structure formation

Blue latex beads conjugated with an anti-HbA/ anti-HbS antibody detect the HbA/HbS analyte in the sample and create visible test lines. The blue test lines then indicate whether the patient has normal blood, SCD, or sickle cell trait.

The SickIED E-junction lateral flow test strip is constructed from four main components: a nitrocellulose membrane, an adhesive polystyrene backing card, a CF5 absorbent pad, and conjugate release pad (Figure 2). The nitrocellulose membrane of the test strip contains the printed antibody lines, which include a control line and a test line for each antigen in the sample deposited on the test strip. The paper-based absorbent pad (5mm x 15mm) is attached on the end, nearest to the antibody lines, as the sample is located at the ends of each arm where the sample will be applied. The backing card is beneath the nitrocellulose membrane, absorbent pad, and sample pads, providing the device with structure and support. These materials each have a paper base, thus providing for the sustainable qualities of the SickIED test strip, which range from its availability to its biodegradability. While lateral flow devices that are based on polymer microfabrication lack environmental qualities and will likely contribute to the accumulation of plastics in the environment (Saidykhan, 2021), the SickIED device avoids this issue, thus providing a rapid, affordable, and environmentally sustainable method for SCD diagnosis.

Paper is not only manufactured locally in an abundance of locations around the world, but is often available in various engineered forms, giving it a range of material properties. Given its paper base, SickIED test strip administration does not rely on an active pump or external power source, and instead relies on the advantageous capillary effects of paper to carry the necessary reagents up the strip for diagnosis (Chiang, 2019). This is an essential aspect of the device, considering that many health clinics in sub-Saharan Africa do not have reliable access to electricity. Similarly, the small size of the SickIED test strips and their requirement of only small volumes of samples and reagents for diagnosis makes the device easily distributable, thus contributing to the sustainable cost and local accessibility of the SickIED test strip. With paper-based microfluidics that benefit the environment in Sierra Leone, SickIED serves a valuable purpose in LMICs with regard to healthy and sustainable living.

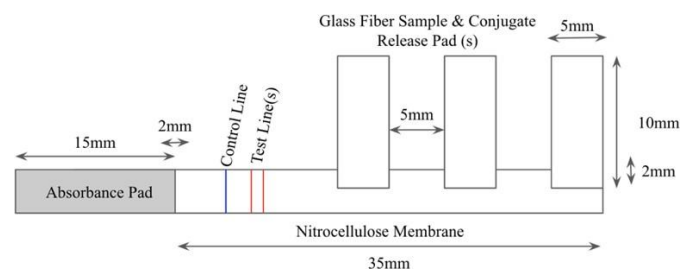


Figure 2: E-junction test strip assembly.

The E-junction design incorporates three sample pads (5mm x 10mm), attached 5mm apart and positioned perpendicular to the nitrocellulose membrane (5mm x 35 mm) with clear laboratory tape. The sample pads and absorbent pads overlap the nitrocellulose membrane by 2mm, respectively. The nitrocellulose membrane facilitates capillary action such that the analyte, wash

buffer, and beads are pulled up to the absorbent pad, which increases the volume drawn and allows for the sample to fully travel to the test lines. The control, HbA, and HbS antibodies are printed right below the absorbent pad.

Translation of SickLED's technology into practice will be conducted through the Lehigh University Office of Creative Inquiry and its close collaborations with clinics in Sierra Leone. The SickLED team has recently received Institutional Review Board (IRB) approval from the Sierra Leonean Pharmacy Board Control to conduct alpha testing groundwork and is in the process of receiving IRB approval from Lehigh University. Once the device reaches clinical testing stages, SickLED will work towards district, regional, and national care system approvals before clinical and hospital implementation. In-country partnerships and mass manufacturing by Wancheng Bioelectron Co. is anticipated to supply distribution to hospital and physician health units; the team will then work with World Hope International and local health ministries to distribute materials. In-country partnerships and mass-manufacturing by Wancheng Bioelectron Co. is anticipated to supply distribution to hospital and physician health units; the team will then work with World Hope International and local health ministries to distribute materials. Upon successful implementation in local healthcare clinics, SickLED operational management will be given to the Sierra Leone Ministry of Health, which will continue to sustain and build upon progress.

Aside from diagnosis, education and treatment are essential components of the SickLED venture that contribute to its alignment with the SDGs. Raising awareness of SCD symptoms in Sierra Leonean communities and incorporating the screening device into the FHCI will allow for the SickLED to become integrated into local infrastructure, thus definitively promoting a reduction in healthcare inequities between LMICs and developed countries. In-country healthcare providers will be trained to operate the test strip and teach other clinicians, thus promoting widespread free and easy access to screening. Once patients are diagnosed, they will be connected to receive proper treatment at a nearby hospital. These elements contribute to increasing the likelihood of life quality and life expectancy for children and adults affected by SCD. As more information about the experience of SCD patients in LMIC is collected, the SickLED education campaign will be further developed to address additional needs. This knowledge will further increase the long-term sustainability of the SickLED device as it will improve the understanding of the need to be screened.

SickLED operates under the strong belief that early detection of SCD is crucial to proper treatment and a healthy life. Beyond testing, the team strives to collaboratively contribute to educational efforts in LMIC, beginning in Sierra Leone. The connections that SickLED has fostered with in-country organizations such as World Hope International, Sickle Cell Carers Awareness Network, and Sickle Cell Society in Sierra Leone will allow for community members to be properly educated on the effects of the disease and subsequently connected to affordable treatment options including folic acid and penicillin prophylaxis (Italia, M. et al 2019). This collaborative combination of screening, education, and treatment led by partnerships between SickLED and other SCD organizations will promote well-being across all ages and ultimately help reduce the healthcare inequalities present between high and low income countries.

Findings

Findings by the team involve multiple aspects of laboratory and sociodemographic research results, which influenced changes in the device configuration and the approach that SickIED will take in implementation. In designing the test strip, SickIED team members evaluated antibodies which respectively target HbA and HbS in varying combinations of volume and concentration to maximize test line intensities of the device and improve dynamic range of the device. The dynamic range of the device is important to ensure that the SickIED device is usable across a wide variety of individuals, while test line intensity, indicated by the darkness of the blue lines on the strip, visibly demonstrates the specific detection of HbA and HbS by the antibodies, despite varying concentrations of antigen. These two design factors were found as important metrics of the SickIED device diagnostic ability as they affect the extent to which the use of the test strip can impact the healthcare community.

Evaluation of device performance was performed using straight-line test strips dipped into wells of analyte, wash buffer, and conjugated beads. SickIED utilizes two specific capture antibodies, antibody HbA and antibody HbS, from Rockland Antibodies and Assays Inc. to help form the antigen-antibody complex on the test strip with purified antigens acquired from Sigma-Aldrich. Quantification of the test line intensities involved the use of ImageJ software to analyze and compare test line intensities from multiple test strips. Once a test strip was completely developed, images were taken under uniform lighting and with consistent camera settings to minimize variation in image quality. ImageJ subsequently served to standardize the intensity and create an equal platform for comparison. Following a phase of experimentation with the test strips, a predetermined background intensity value is found from an unused test strip and is used as a baseline for comparison when ascertaining test line intensity values for each test line. The background value is then subtracted from the test line value, and this computed intensity is then compared between remaining developed test strips.

However, initial results (Figure 3a) showed low intensity values, which is an indication of cross-reactivity between the test line and the antibodies placed on the strip. Hence, recent efforts in the lab have focused on optimizing the biofunctionality of the test strip and finding the most efficient buffer to reduce cross reactions, which helps to improve sensitivity and specificity. Sensitivity and specificity are metrics of the device's dynamic range, thus allowing for more widespread detection of SCD and equal access to the device by diverse individuals. To this effect, an aspect of recent laboratory findings included the balance in concentrations which minimize cross-reactivity between antibody-antigen complexes on the test strip.

After varying the concentrations of different blocking agents in the running buffer, SickIED has determined that the combination of 2.5% nonfat dairy milk (NFDM) diluted in phosphate-buffered saline (PBS) and Tween-20 efficiently minimize antigens from binding to the antibodies spotted on the membrane nonspecifically and to decrease background noise. The volume of beads on the strip and printed antibody concentrations were also optimized, reducing the amount of beads from 2uL to 1uL to reduce nonspecific binding. The intensities of the test lines with 1uL remain visible with 0.2mg/mL (20% diluted) anti-HbA, whereas with 0.2mg/mL (20% diluted) anti-HbS, the test

line was difficult to visualize therefore the HbS test line will remain at 1mg/mL (100%) anti-HbS undiluted.

The SickLED device is currently able to identify purified hemoglobin-HbA and hemoglobin-HbS. The antigen binds specifically to the printed HbA/HbS test line antibody; however, the future optimization of the device will include further minimization of the test line antibody interactions, quality control of temperature conditions and storage life-span of the buffers. Furthermore, clinical testing of the device using whole blood samples will be carried out such that the SickLED device will be run with healthy, SCD, and SCT whole blood samples.

Each diagnosis will be compared against the gold standard (HPLC/IEF) to determine a false positive/negative statistic. Initial clinical testing will be completed within the lab using obtained blood samples from the local hospital. Following successful device results from in lab testing, clinical testing will be carried out in the field. Using connections, developed through World Hope International and the Sickle Cell Cares Awareness Network in Sierra Leone (SCCAN), the device will be run on confirmed SCD and SCT individuals to further confirm device accuracy and ensure device usability in a LMIC setting.

To facilitate transport of materials for fieldwork, SickLED adapted the running buffer used on the test strips to carry antigen up the device arms; thus leading to more findings with regards to the buffer's shelf life. To prepare for travel, the team stored the nonfat dairy milk (NFDM) powder separately from the liquid component of the buffer, thereby allowing for longer shelf life, as the NFDM usually aggregates into clumps, making the buffer ineffective during the running of the strip. The buffer is stored at room temperature; therefore, no electricity for refrigeration is required, making the test strip a portable and sustainable option for SCD diagnosis. The SickLED laboratory stores reagents and conducts experiments with temperature and humidity conditions like those of Sierra Leone to replicate the in-country environment and optimize development.

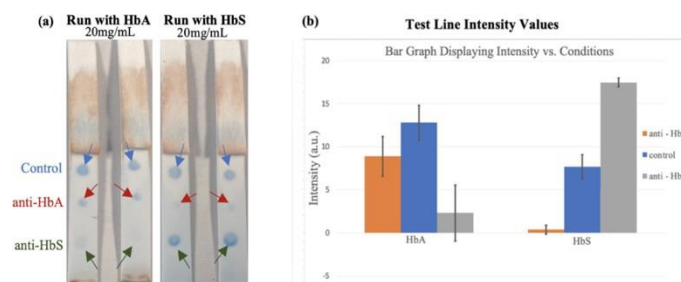


Figure 3: SickLED evaluatory phase of HbS and HbA antibody concentrations for the test strip.

(a) Experimental straight test strip results; 20mg/mL of HbA/HbS concentration resulted in minimal cross-reactivity on the test strip. (b) ImageJ quantification of test line intensities presenting a promising result of low level of cross reactivity.

Additional previous work in the SickLED laboratory utilized enzyme-linked immunosorbent assays (ELISA) to confirm antibody bead conjugation; however, ELISA was labor-intensive, expensive

and was highly variable. Successful bead conjugation is now confirmed through the development of the control and test line intensities. It was evident that the aspects of the previous design of our lateral flow strip could potentially infringe on current patents; therefore, SickLED research into patents led to findings of current SCD diagnostic methods on the market. For example, a prominent US patent that exists for the device is a lateral flow immunoassay rapid test detecting the presence of hemoglobin A, C, and S (US20160116489A1). In this patent, the claims protect specific antibodies used for the detection of these hemoglobin types and their amino acid sequences, immunoassays using these antibodies (including competitive and noncompetitive immunoassays), and a lateral flow device using these antibodies.

In further evaluating current SCD devices on the market, several substantially equivalent SCT and SCD diagnostic devices were found. Analogous devices, such as SickleSCAN, are classified as a class II device and serve as a predicate example for substantial equivalency.

Another device that can qualify as being substantially equivalent is Arlington Scientific, Inc.'s Sickle Cell Test Kit, found in the FDA 510(k) database by the reference number K960947. This kit uses a number of reagents to detect the presence of HbA or HbS hemoglobin, but does not differentiate between SCD and SCT. The SICKLEDEX kit, located in the FDA 510(k) database by reference number K013316, is also approved by the FDA and may be another potential device that can qualify as substantially equivalent to as the device uses a number of reagents to differentiate between SC blood and normal blood by solubility differences. Finally, SickLED identified a CE-marked device that does not have FDA approval called HemoTypesSC. This device is also a lateral flow test and differentiates between HbA, HbS and HbC by mixing the blood samples with reagent before depositing them onto the strip.

With this research into account, the SickLED team began experimentation with unique test strip configurations to prevent contravention of any patents in place. Before landing on the E-junction geometry, SickLED considered the T-junction and Y-junction test strips, and experimentation with these configurations led to the finding of the "hook effect", which occurs when the antigen is present in very high amounts of concentration, blocking all the capture and detection antibody binding sites. This obstructs the sandwich structure of the device mechanism from forming, consequently revealing no visible line and producing false negatives and false positives. In the case of the "hook effect", the blood sample is directly deposited onto the test strip, but the exact concentration of the hemoglobin in a single drop of blood is unknown, so the oversaturation phenomenon of the hook effect could inhibit the intensities of the test lines that form. The E-junction configuration of the test strip helps minimize this occurrence, with the incorporation of two wash steps which helps reduce the concentration of antigen present on the test strip.

SickLED's collaboration with World Hope International (WHI), a multinational, nonprofit organization dedicated to alleviating global poverty and improving global health, has allowed the team to access networking opportunities within Sierra Leone during the developmental phase of the device. For example, through connections with WHI, SickLED met with other SCD advocacy networks in Sierra Leone which provided access to local healthcare clinics and patients. Specifically, WHI's network team has allowed for connection with the Sickle Cell Society, the

Sickle Cell Cares Awareness Network (SCAAN), as well as the Masanga Hospital. These organizations and individuals identified the pressing need for a low-cost screening device and expressed an interest in SickLED's proposed solution. In this way, SickLED has grown in ways that are truly beneficial for the local community. Metrics of success in this regard are the direct feedback from the local health workers who SickLED works with to administer the test.

During each fieldwork cycle, the team continues to explore implementation strategies that follow the FHCI of Sierra Leone which provides free healthcare for children and nursing mothers. The plan for this exploration is to administer diagnoses to children before the age of 5 years or neonatal screening. Through this screening program, children will receive preventative treatments early and begin practicing methods of symptom management at a young age, which has been proven to be beneficial in reducing the intensity of SCD symptoms.

Research Limitations/Implications

The lack of community understanding in Sierra Leone with regards to preventative medicine is one of the primary difficulties of improving healthcare in local, non-urban areas (Rahimy et al., 2009). Parental understanding, voluntary participation, and informed consent are instrumental to the success of projects intended to reduce SCD burden. Because there are only a small number of newborn screening (NBS) programs in Sierra Leone, many parents are skeptical when informed that their seemingly healthy infant has SCD. It is increasingly more difficult to spread awareness about SCD diagnosis, considering the stigma that surrounds healthcare facilities in countries like Sierra Leone. During 2019 fieldwork, a Peace Corps volunteer in Sierra Leone shared with the team that the community often considers hospitals to be "the place where you go to die," indicating that healthcare is only sought out in times of need, instead of for preventative measures. As per these shared beliefs, many individuals in local communities refuse preventative treatments due to their lack of understanding about the long-term purpose. This mindset is also reflected in follow up appointments, as individuals that do seek treatment often do not return for subsequent visits (Kachimanga et al., 2021). As a result of this lack of educational awareness about the healthcare system, it is difficult for physicians to hold their patients accountable. There is a lack of structure in healthcare, as patients do not recognize the importance of follow-up treatments, and clinics often have scarce resources that limit the amount of days they can consistently remain open. The negative stigma surrounding the healthcare system has also been found to apply to the specific illness that the patient suffers from. For example, when SickLED team members conducted fieldwork in 2019 and visited a local clinic, one of the maternal and child health aids expressed that, "If someone has sickle cell, they tie them up and tie them down because they believe the devil is inside them... so they don't come here." These stigmas and misconceptions about SCD in the Sierra Leonean community prevent locals from going to the clinic. This underscores the importance of educational efforts on NBS and SCD in order to increase public awareness and combat the stigma that leads community members to put their lives at risk by avoiding healthcare facilities despite their clear need.

"Brain drain," or the departure of educated healthcare workers to countries with higher compensation (Merriam Webster Dictionary), has also been a challenge to third-world countries

when it comes to improving healthcare operations. The problem is rooted in lower compensation for medical technologists and medical doctors in Sierra Leone, where they only make a monthly income of approximately \$659 and \$1370, respectively. Meanwhile, the same professions can earn an income that exceeds \$5,850 and \$24,500 per month in other countries. As educated workers voluntarily depart the region, citizens face diminished resources and personnel required for conducting intensive blood tests. There also exists a scarcity of resources for advanced blood work procedures in Sierra Leone and other Sub-Saharan African countries. Companies such as LabCorp and Quest Diagnostics in the United States are responsible for running blood tests that diagnose for SCD, and prices range from \$50 to \$100. As follows, healthcare providers face a financial burden to obtain the diagnostic tools needed to ascertain early intervention, an instrumental step to preventing such elevated childhood mortality rates. This creates a need for a simple, yet affordable, diagnostic tool that can be rapidly utilized for early detection. The SickIED screening device is easy to assemble and operate, so it's feasible for current healthcare workers in the system to readily understand the mechanism and learn how to use it. While successful implementation of the device in Sierra Leone for early SCD diagnosis can help lower the staggering mortality rate, the most important aspect of the procedure is making sure that patients who test positive have access to treatment and support that they need. These patients are not guaranteed to seek out necessary treatment post-diagnosis – however, education and collaboration with SickIED can encourage them to do so. Patient attendance needs to be advocated for; keeping electronic records to track the patients' health history will help generate a more structured and organized plan of care.

NBS benefits to patient outcomes have been proven in many regions of Sub-Saharan Africa. Successful implementation of NBS in Angola, with an SCD clinic established at the National Children's Hospital in the capital city of Luanda, serves as evidence of success, as approximately 1000 patients are seen there annually (Therrell et al., 2020). As follows, infants with abnormal FS or FSC patterns were enrolled in a newborn clinic (McGann et al., 2020). During the first clinical visit, all newborns received medication, such as the first dose of the 13-valent pneumococcal conjugate vaccine (PCV-13, Pfizer, Inc.), an insecticide-treated mosquito bed net for malaria prophylaxis, and initiated Penicillin prophylaxis, as well as comprehensive sickle cell education. As a result, the calculated first-year mortality rate for babies with SCD compared favorably to Angola's national initial mortality rate, where 3.6% of enrolled infants have died during the follow-up period. According to this aforementioned success, our initiative of promoting NBS as well as serving SCD education to the broader community yields a promising outcome to combat the SCD burden in Sierra Leone. At the first and subsequent clinic visit, families were educated in the warning signs of emergency complications (fever, pallor, splenomegaly), and were instructed to seek emergency care if they noted any of the signs. The majority of the families did seek care as instructed. However, gaps in the medical system and the lack of awareness among Angolan healthcare providers prevented these children from receiving appropriate and timely care.

A study from 2015 on cost-effective analysis reveals that the NBS program in Angola is cost-effective; however, the downstream medical costs, including acute care were not included in the report (Therrell et al., 2020). The screening costs included supplies for sample collection, maternity nurses labor for specimen collection, transport of samples to the central laboratory, and laboratory

costs for personnel to perform isoelectric focusing on all samples. SickLED aims to eliminate the demanding cost of isoelectric technology through the point-of-care approach.

SickLED's long-term goals aim to screen all newborns for SCD while also spreading awareness of the effects of SCD. These factors will depend on strengthening the communities' positive attitudes towards the idea of diagnosing SCD. SickLED success will not be labeled by the completion of the diagnostic device, but through ensuring that the diagnostic device is implemented in LMICs followed by the receipt of treatments to those in need.

Value

The SickLED effort towards implementation of the diagnostic device has significant value with regards to reducing inequities in healthcare on a global level. It is understood that diagnosis is merely the first step towards improving the life quality of SCD subjects, and access to SCD treatment is necessary to combat the high child mortality rate in Sierra Leone and other LMIC. The multidimensional approach by SickLED to reduce child mortality in Sierra Leone requires collaboration across the board, from Western donors and funding agencies to local government, non-profit organizations, clinics, and healthcare providers at different levels in Sierra Leone.

Parallel to the SickLED lab efforts in technical development and clinical evaluation, SickLED has established connections with various healthcare sectors in Sierra Leone over time, with contributions from the Lehigh University Office of Creative Inquiry. Partners such as Dr. Cheedy Jaja, SickleSCAN and World Hope International have provided us with insight on the current local community in Sierra Leone. This deeper understanding of the environment has significantly helped us in optimizing the test strip to be as useful as possible for the environment it will be implemented in.

The education and advocacy of SCD prevention presents value to researchers already conducting studies in Sierra Leone. In the summer of 2019, SickLED had the opportunity to validate the developing device, where the team gained a greater understanding of the device's current limitations and its usability in the field through Dr. Jaja and his medical team. He and his team have experience with diagnosing and treating SCD in Sierra Leone due to the numerous clinics they operate in. He has provided numerous resources that were crucial to SickLED development.

After lab validation of the diagnostic device in the US using blood samples from healthy, SCT and SCD subjects, field evaluation of the diagnostic device will be carried out in collaboration with Dr. Cheedy Jaja. Dr. Jaja's research team has been investigating the feasibility of point-of-care tests (POCT) to diagnose newborns with SCD in low-resourced community healthcare settings in Sierra Leone since 2017. Specifically, within the framework of the Sierra Leone Sickle Cell Disease Data Collection Project, Dr. Jaja works to determine the best practices for the implementation and routine adoption of POCT diagnostic tools, such as SickleSCAN and HemoTypeSC across different clinical settings (including rural and urban hospitals, clinics and health care centers) by involving nurses, midwives, and health workers. His group has extensive experience screening patients with the SickleSCAN device, strong support from the Government of Sierra Leone, and

strong commitments from local partners (SCCAN & AMMCHC). Integral to the Sierra Leone Sickle Cell Data Collect Project is planned care management for confirmed cases, care coordination, and active patient/caregiver engagement. These are crucial steps in providing comprehensive care and tackling the vexingly high rates of infant mortality associated with SCD. SickLED's partnerships with organizations rich in clinical experience involving POCT diagnostics will be leveraged to translate the proposed device for utilization. Through developing the screening device in parallel with the translational research of Dr. Jaja's team in the implementation of POCT for SCD screening, especially the effort with newborn screening, the operation and performance specifics of the device will evolve with and be optimized for proper settings to facilitate downstream wide adoption.

After successful implementation on a small scale, widespread implementation throughout Sierra Leone and other LMICs will be pursued. Widespread implementation of the diagnostic device will be in conjunction with the development of infrastructure to treat diagnosed SCD individuals. In addition to the collaboration with Dr. Jaja, SickLED has sought out continuous feedback on device development from partners in Sierra Leone. Partner relationships were formed during the initial visit (August, 2019) to Sierra Leone to distinguish developmental frameworks for the device. The SCCAN and the Sickle Cell Society allowed SickLED access to patients and local healthcare workers who provided insight with regards to the current screening situation as well as the socioeconomic and demographic impact on individual's outcome. Mutual collaboration between the groups is beneficial to each party as we all share the same interest of lowering the high mortality rate of SCD disease in Sierra Leone. While SCANN and Sickle Cell Society provide us with information on the social aspects of SickLED, we help solve the problem at its root with a technical device. With continuation of SickLED partnerships, the goal of lowering mortality while providing necessary treatments to those in need will be feasible. Upon implementation, the device will be an asset to these two organizations and their SCD diagnosis and treatment facilities.

The SickLED device will be optimized to be affordable for clinical implementation in low resource areas that are highly affected by SCD. The screening device is capable of sustaining functionality without the usage of electricity or large equipment currently required for diagnosis. The lateral flow technology combined with the geometry of the test strip eliminates the cost of reagents. Affordability is important in LMICs, such as Sierra Leone, due to the health inequities present. Families in Sierra Leone have limited access to resources due to their income, which makes it difficult for them to prioritize health as a concern. Due to the current high financial costs of healthcare, individuals tend to invest their financial resources into other concerns such as food, clean water, and housing. However, the World Health Organization's ASSURED framework defines the most suitable screening devices for use in LMICs as affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end-users (Kosack). Therefore, the application of the lateral flow mechanism represents the ability to adapt healthcare technology such that inequalities such as cost and accessibility within LMICs due to lack of resources may be alleviated.

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