I'm not a bot

 . 2021 May 5;12(5):519. doi: 10.3390/mi12050519 Sickle cell disease (SCD) is a widespread disease caused by a mutation in the beta-globin gene that leads to the production of abnormal hemoglobin called hemoglobin S. The inheritance of the mutation could be homozygous or heterozygous combined with another hemoglobin mutation. SCD can be characterized by the presence of dense, sickled cells that causes hemolysis of blood cells, anemia, painful episodes, organ damage, and in some cases death. Early detection of SCD can help to reduce the mortality and manage the disease effectively. Therefore, different techniques have been developed to detect the sickle cell disease and the carrier states with high sensitivity and specificity. These techniques can be screening tests such as complete blood count, peripheral blood smears, and sickling test; confirmatory tests such as hemoglobin separation techniques; and genetic tests, which are more expensive and need to be done in centralized labs by highly skilled personnel. However, advanced portable point of care techniques have been developed to provide a low-cost, simple, and user-friendly device for detecting SCD, for instance coupling solubility tests with portable devices, using smartphone microscopic classifications, image processing techniques, rapid immunoassays, and sensor-based platforms. This review provides an overview of the current and emerging techniques for sickle cell disease detection and highlights the different potential methods that could be applied to help the early diagnosis of SCD. Keywords: sickle cell anemia, hemoglobinopathies, detection, diagnosis, point of care Sickle-cell disease (SCD) is a multisystem disorder related to acute illness, painful episodes, and gradual organ damage [1]. Sickle cell anemia is caused by point mutations in the HBB gene, which codes for β-subunit, where adenine is substituted by thymine (GAG > GTG) at codon 6 of the HBB gene. As a result of nucleotide substitution, the amino acid is altered, and glutamic acid is replaced by valine resulting in hemoglobin S (HbS) formation. Hb S polymerizes in a deoxygenated state and forms rigid, less soluble sickle-shaped cells [1,2]. SCD arises when inheriting two mutated alleles βS/βS (homozygous) or in the case of inheriting different types of mixed heterozygous alleles such as sickle-β-thalassemia HbSβ-thalassemia, sickle-hemoglobin C disease (HbSC), and other combinations. When the sickle cell trait (SCT)is heterozygous βA/βS, it means only one allele is affected and produces insoluble hemoglobin, and the other gene is wildtype and produces normal hemoglobin [3]. The pathogenesis mechanism of SCD depends on the polymerization of hemoglobin S, which is triggered by the lower oxygen affinity [4]. Polymerization alters the physical properties of red blood cells, such as shape and cell membrane, leading to dehydration of cells and increased polymerization. Repeated polymerization and sickling of cells lead to the formation of irreversibly sickle cell [4]. This accelerates cell destruction and reduces cells' lifespan by ≥75%, resulting in hemolytic anemia [5]. In addition, the polymerized cell cannot move easily in the small blood vessels, resulting in the blockage of the vessel, i.e. vaso-occlusion [5,6]. The most common acute complication of SCD is acute vaso-occlusive crises (VOC) that cause pain crisis and acute chest syndrome, which is considered the major cause of hospitalization and death among SCD patients [4,7]. Chronic complications of SCD start to appear with age as organ failure due to the progressive ischemia leads to earlier death, cerebrovascular disease, pulmonary hypertension, retinopathy, and priapism. In addition, complications during pregnancy include preeclampsia and preterm delivery [8,9]. Children with SCD who live in Sub-Saharan Africa have a high mortality rate estimated at 50–80% by five years old. The most common cause of death in children is infection, including invasive pneumococcal disease and malaria [1,9]. In developed countries, the life expectancy of SCD patients has been improved by early diagnosis, comprehensive treatment, and general medical care. Therefore, early detection supports the effective management of the disease [10]. Detection of hemoglobin S and diagnosis of sickle cell disease depend mainly on the clinical laboratory, where a combination of biochemical and molecular tests is used in the detection and confirmation of the diagnosis [11]. The most popular methods for detecting these diseases are the full count of blood cells, Hb electrophoresis, and high-performance liquid chromatography (HPLC). These methods are considered the gold standard in the diagnosis of SCD [12]. Sickle cell disease causes a variety of different illnesses; the most common disorder is sickle cell anemia HbSS with the genotype βs/βs. Other forms of the SCD are formed with a combination of βS mutation with other HBB mutations, such as sickle-hemoglobin C disease (HbSC) and sickle-β-thalassemia (either HbSβ+ or HbSβ0). β0 means there is no β-globin synthesis, while β+ means reduced production of β-globin [13]. The most severe forms of SCD are HbSS and HbSβ0, and they show same clinical picture. HbSC and HbSβ+ are considered the less severe forms of SCD [14]. The clinical picture of the sickle-β-thalassemia ranges from asymptomatic to severe state similar to HbSS sickle cell anemia [15], while, in some HbSC cases, severe and life-threatening complications will appear [16]. Some genetic factors can modify the sickle cell's clinical expression when co-inherited with the βS gene, such as α-globin gene mutations, either one-gene deletion or two-gene deletion [17]. Several techniques and assays are used for the detection and monitoring of the sickle disease. These techniques can be divided into two main categories: (1) currently used methods in the diagnosis of SCD; and (2) innovative techniques which are mostly still in the research stage. Several reviews have been published related to the development of point of care (POC) SCD detection [18,19,20]. Table 1 lists the different technologies developed for the diagnosis and monitoring of the SCD. Technologies for sickle-cell disease (SCD) diagnosis and monitoring. Technique Sensitivity Specificity Accuracy Advantages Disadvantage Result Ref. Peripheral blood smear (PBF) 35.0%. 96.7% 90.5% Simple preparation, inexpensive, Turnaround time (TAT) is 44 min Dependence on the pathologist's skills, does not differentiate between different types of SCD Detect sickle cells [22] Solubility and Sickling Sickling: 65.0%Solubility: 45.0%. Sickling: 95.6%Solubility: 90.0%. Sickling: 92.5%Solubility: 85.5%. Easy, inexpensive, fast, affordable, TAT 38 min for sickling, TAT for solubility 70 min Testing newborns shows false-negative result, does not differentiate between SCD types Detect the sickling event. [27] Capillary electrophoresis Not reported Not reported Not reported Reliable, ability todistinguish most types of sickle cell disease including heterozygous. Expensive, requires skilled technicians identify and quantify HbF, Hb A, Hb A2, Hb S, Hb C, Hb Barts and other [36] Isoelectric focusing (IEF) Not reported Not reported Not reported Detect HbS and HbA easily in a high concentration of HbF, Hb D-Punjab easily separated from HbS, need small volume of the sample, able to use dried blood spot, TAT is 45 min. Expensive, requires highly trained staff to interpret the results. Hb A, Hb F, Hb C, Hb S, Hb E and Hb O Arab [38] High-performance liquid chromatography (HPLC) Not reported Not reported Not reported Reliable, ability todistinguish most types of sickle cell disease including heterozygous, fully automated Misdiagnoses the new variants that mimic HbS, Expensive and needs trained personnel, not practical in limited resources areas Detect Hb F, Hb A2, Hb S, Hb C, Hb Barts, and other Hb variants. [18,44] Amplification-refractory mutation system (ARMS) polymerase chain reaction (PCR) for prenatal analysis 75% Not reported Not reported Simple, can be used for prenatal diagnosis Low sensitivity,maternal cell DNA contamination βSβSβAβSβAβA [49] Allele-Specific Recombinase Polymerase Amplification 100% βA: 94.7%βS:97.1%