INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES
(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijcrcps Coden: IJCROO(USA) Volume 12, Issue 10- 2025

Review Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2025.12.10.003

Algorithmic Pathways for Early Diagnosis of Sickle Cell Anemia: Integrating Hematologic, Genetic, and Imaging Markers

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Abstract

Early diagnosis of sickle cell anemia (SCA) remains critical for reducing childhood morbidity and mortality, yet diagnostic delays persist in many regions where the disease burden is highest. Emerging advances in hematologic profiling, genetic testing, and imaging technologies are reshaping the diagnostic landscape and enabling more precise, multi-layered approaches. This narrative review examines the development and application of integrated algorithmic pathways that combine accessible hematologic indices, definitive genetic assays, and early imaging markers of organ stress. We highlight how these complementary tools enhance the accuracy, speed, and reliability of SCA detection across diverse healthcare settings, including environments with limited resources. The review also evaluates current challenges, implementation considerations, and future directions for algorithm-driven diagnostics. By synthesizing evidence across diagnostic modalities, we demonstrate that integrated algorithmic pathways offer a powerful framework for earlier identification, improved risk stratification, and more personalized care for individuals with SCA.

Keywords: Sickle cell anemia, diagnostic algorithms, hematologic markers, genetic testing, imaging biomarkers

Introduction

Sickle cell anemia (SCA) remains one of the most prevalent and clinically significant monogenic disorders worldwide, affecting millions of individuals and contributing substantially to early childhood morbidity and mortality. The condition arises from a single-point mutation in the beta-globin gene, yet its clinical expression is profoundly heterogeneous, shaped by genetic modifiers, environmental influences, and early-life interventions. Timely diagnosis is central to improving outcomes: children diagnosed during the newborn period benefit from comprehensive care pathways that include prophylactic antibiotics, vaccination, parental education, nutritional support, and timely screening for complications. These measures have dramatically reduced the incidence of life-threatening infections, stroke, and early organ damage in regions where early detection is routine. Unfortunately, large segments of the global population, particularly in sub-Saharan Africa and parts of Asia, still lack systematic newborn screening programs, leading to delayed identification and preventable early deaths [1-2].

Traditionally, the diagnostic process for SCA has relied on a combination of clinical features, hemoglobin electrophoresis, and basic hematologic parameters. While effective, these methods are often applied only after symptoms develop, narrowing the window for preventive intervention. In the past decade, advances in hematology, molecular diagnostics, medical imaging, and data science have catalyzed a shift toward algorithmic diagnostic pathways. These approaches integrate biologic signals across multiple domains, enabling clinicians to detect subtle patterns that might otherwise be overlooked. Automated hematology analyzers now provide detailed red blood cell indices and reticulocyte parameters that can differentiate SCA from other causes of pediatric anemia. Genetic testing, once limited to specialized laboratories, has evolved into rapid, cost-effective, point-of-care platforms capable of identifying hemoglobin variants in minutes. Complementary imaging tools such as transcranial Doppler ultrasonography help reveal early cerebrovascular changes that strengthen diagnostic confidence in ambiguous cases and signal heightened risk long before clinical events occur [3-4].

The value of diagnostic algorithms lies not just in combining tests but in creating structured, sequential decision pathways. These models use hematologic markers as the frontline screen, incorporate genetic assays for definitive confirmation, and apply imaging markers to assess early organ involvement and refine risk stratification. Increasingly, artificial intelligence and machine learning models are being trained on large datasets of hematologic, genomic, and clinical variables to generate predictive tools that support clinicians, optimize resource allocation, and reduce time to diagnosis. Such integrated frameworks are especially promising for low-resource settings where laboratory infrastructure and specialist availability remain limited [5-6].Despite this progress, challenges persist. The unequal distribution of diagnostic technologies, variability in healthcare worker training, and the need for population-specific validation of predictive models continue to limit widespread adoption. Ethical concerns around data use and sustainability of advanced diagnostic platforms also require careful consideration. Still, the growing convergence of technological innovation, global health commitments, and research investment signals a future where early, algorithm-driven diagnosis of SCA becomes standard practice rather than an exception [7-8].This narrative review synthesizes current evidence on the role of hematologic, genetic, and imaging markers within algorithmic diagnostic pathways for SCA. It discusses emerging approaches, evaluates practical considerations for diverse healthcare settings, and outlines how integrated diagnostic strategies can transform early detection and long-term clinical outcomes.

Hematologic Markers: Foundation of Algorithmic Screening

Hematologic markers form the earliest and most accessible diagnostic gateway for sickle cell anemia, particularly in regions where genetic

testing and imaging technologies are not routinely available. The complete blood count (CBC) remains the cornerstone of initial screening because it captures the physiologic consequences of chronic hemolysis, ineffective erythropoiesis, and red blood cell deformability long before complications become clinically apparent. Although no single hematologic parameter is pathognomonic for SCA, characteristic patterns emerge when markers are interpreted together, creating a powerful foundation for algorithm-based diagnostic pathways [9-10].Children with SCA typically present with chronic anemia, reflected by reduced hemoglobin and hematocrit values, often accompanied by a markedly elevated reticulocyte count due to compensatory marrow hyperactivity. Automated hematology analyzers now quantify not only absolute reticulocyte counts but also the immature reticulocyte fraction, which tends to rise sharply during hemolytic stress. This additional layer of reticulocyte data improves differentiation between SCA and other anemia etiologies such as iron deficiency or aplastic conditions. Similarly, an increased red cell distribution width (RDW) and profound anisopoikilocytosis on peripheral smear analysis provide early morphological clues consistent with sickling and hemolytic turnover [11-12].

Advances in analyzer technology have further expanded the diagnostic value of CBC-derived parameters. Many modern platforms generate red cell population data (RCPD), measuring factors such as hyperchromic cell percentage, hypochromic cell fraction, and reticulocyte hemoglobin content. In SCA, the presence of dense, dehydrated RBCs and abnormal hemoglobinization patterns often produces distinctive RCPD signatures that can be incorporated into algorithmic decision models. When combined with platelet indices and leukocyte profiles, these hematologic patterns strengthen the signal-to-noise ratio for early screening [13-14].Machine learning applications have accelerated the utility of hematologic markers by uncovering subtle relationships among CBC parameters that escape conventional clinical interpretation. Predictive models built on tens of thousands of CBC results have successfully classified hemoglobin genotypes with high accuracy, even in the absence of confirmatory genetic data. These models leverage multidimensional relationships among hemoglobin levels, reticulocyte patterns, RDW, mean corpuscular volume (MCV), and other indices to identify phenotypic “fingerprints” of SCA. This capability is particularly valuable in rural settings where advanced diagnostics may be unavailable or cost-prohibitive [15-16].Peripheral blood smear analysis remains a valuable complement to automated markers in algorithmic screening. The presence of sickled cells, target cells, nucleated RBCs, and Howell-Jolly bodies can reinforce findings from the CBC and suggest functional asplenia. With the emergence of smartphone-based microscopy and AI-enhanced image recognition tools, smear interpretation is becoming increasingly standardized and accessible, reducing reliance on expert hematologists and enabling more consistent early diagnosis [17].

Genetic Diagnostics: Definitive Confirmation and Subtype Discrimination

Genetic diagnostics represent the definitive cornerstone ofSCA confirmation, providing precise identification of hemoglobin variants and enabling accurate differentiation between homozygous disease, compound heterozygous states, and benign carrier conditions. While hematologic markers raise suspicion, genetic assays establish the diagnosis with certainty by detecting the underlying point mutation in the beta-globin gene (HBB), where valine replaces glutamic acid at position six. This molecular clarity is crucial not only for confirming SCA but also for delineating related hemoglobinopathies whose clinical trajectories differ significantly [18].Historically, genetic confirmation relied on laboratory-based techniques such as hemoglobin electrophoresis, isoelectric focusing (IEF), high-performance liquid chromatography (HPLC), and PCR-based methods. These platforms remain widely used due to their reliability and ability to separate hemoglobin fractions. HPLC and IEF, in particular, provide robust identification of HbS, HbC, HbA2, fetal hemoglobin, and other variants

essential for distinguishing HbSS from conditions such as HbSC, HbS/beta-thalassemia, or rare double heterozygous states. However, these technologies require trained personnel, electricity, and controlled laboratory environments, limiting their use in rural or resource-constrained settings where the burden of SCA is highest [19].

Recent innovations have ushered in a new era of molecular diagnostics tailored for decentralized and point-of-care (POC) applications. Isothermal amplification assays, loop-mediated amplification (LAMP), microfluidic genotyping chips, and lateral-flow DNA-based devices have demonstrated strong accuracy while drastically reducing turnaround times. Many of these platforms bypass the need for thermal cycling and complex equipment, enabling frontline healthcare workers to confirm SCA rapidly in newborns, infants, and symptomatic individuals. Their portability and low cost make them particularly attractive for national newborn screening programs in sub-Saharan Africa and South Asia [20].Genetic diagnostics also play a pivotal role in distinguishing SCA subtypes and predicting disease severity. Compound heterozygous conditions such as HbSC disease or HbS/beta-thalassemia can mimic or diverge from classical HbSS in terms of anemia severity, vaso-occlusive patterns, and risk of complications. Precise genotyping ensures appropriate clinical management and avoids misclassification, which can lead to delays in initiating prophylaxis or inappropriate therapeutic decisions. Additionally, the identification of genetic modifiers, including alpha-thalassemia deletions, BCL11A and HBS1L-MYB variants, or polymorphisms affecting fetal hemoglobin production, is increasingly recognized as vital for risk stratification. These modifiers help explain inter-individual variability and can be integrated into predictive algorithms to refine prognostic accuracy [21].

As algorithmic diagnostic pathways evolve, genetic confirmation sits at the center of multi-tiered diagnostic models. Hematologic screening algorithms can rapidly filter high-risk individuals, who then undergo confirmatory genotyping to verify diagnosis and elucidate subtype. This systematic approach minimizes unnecessary testing while ensuring timely identification of affected infants. In settings with emerging digital health infrastructure, genetic results can be uploaded into electronic diagnostic platforms, allowing automated algorithms to combine genotype data with hematologic and clinical indicators for more comprehensive patient profiling [22].

Imaging Markers: Early Detection of Subclinical Organ Stress

Imaging markers are emerging as valuable adjuncts in the early diagnostic landscape ofSCA, offering insights into organ dysfunction that may precede overt clinical symptoms. While imaging is not typically the first diagnostic step, its integration into algorithmic pathways provides an important layer of specificity and risk stratification. By detecting early cerebrovascular, splenic, hepatic, and cardiopulmonary alterations, imaging modalities help clinicians identify subtle physiologic changes that complement hematologic and genetic findings, ultimately guiding early intervention strategies [23].Transcranial Doppler (TCD) ultrasonography has become one of the most widely used imaging tools in pediatric SCA care, owing to its ability to identify elevated cerebral blood flow velocities associated with increased stroke risk. Children with SCA often exhibit compensatory cerebral hyperemia due to chronic anemia and endothelial dysfunction. TCD captures these changes long before clinical neurologic compromise occurs, making it an essential element of early risk assessment. Incorporating TCD findings into diagnostic algorithms enhances early disease profiling by distinguishing infants and children with early cerebrovascular stress who may benefit from preventive therapies such as chronic transfusion programs [24].

The spleen is another organ where early imaging provides substantial diagnostic and prognostic value. Ultrasound imaging can detect splenomegaly, progressive splenic infarction, and eventual autosplenectomy, which are hallmarks of

SCA even in early childhood. These findings may support suspicion of SCA when hematologic results are inconclusive or complicated by coexisting conditions such as malaria or iron deficiency anemia. Moreover, early detection of splenic dysfunction is critical because it signals increased susceptibility to invasive bacterial infections, reinforcing the need for aggressive prophylaxis and vigilant monitoring [25].Abdominal ultrasound also provides valuable information about hepatobiliary complications, which often begin insidiously. Children with SCA may develop gallstones, bile duct dilation, or early hepatic fibrosis, detectable before clinical symptoms manifest. While these findings are not diagnostic in isolation, their presence helps strengthen the cumulative evidence in complex diagnostic scenarios, especially when integrated with laboratory markers of hemolysis or genetic results [26].

In higher-resource settings, advanced imaging modalities further deepen the ability to detect subclinical organ injury. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are particularly useful for identifying silent cerebral infarcts, white matter abnormalities, early renal dysfunction, and cardiac remodeling that may escape detection by ultrasound. These modalities have revealed that many children with SCA sustain silent organ damage early in life, reshaping the understanding of disease progression. Although resource-intensive, the findings generated by these modalities are crucial for validating imaging-based algorithms that can later be adapted for simpler technologies in lower-resource environments [27].Emerging imaging technologies, such as portable ultrasound and smartphone-connected Doppler devices, are making it increasingly feasible to integrate imaging markers into diagnostic pathways even outside tertiary hospitals. These innovations expand access to TCD and general ultrasound services, allowing frontline clinicians to incorporate organ-level assessments into early SCA evaluation workflows. In algorithmic models, imaging serves as the third tier of diagnostic verification and risk refinement, triggered once hematologic and genetic markers point strongly toward SCA [28].

Towards Integrated Algorithmic Pathways: A Multi-Modal Approach

The growing convergence of hematologic, genetic, and imaging diagnostics has paved the way for truly integrated algorithmic pathways capable of transforming early detection in SCA. Rather than relying on a single test or clinical cue, multi-modal diagnostic frameworks synthesize complementary markers into coherent, stepwise decision models. This approach mirrors the complexity of SCA itself, acknowledging that no single modality captures the full breadth of disease biology, especially in early infancy when symptoms remain subtle. By structuring diagnostic steps into a tiered algorithm, clinicians can move systematically from suspicion to confirmation and early risk stratification with improved accuracy, speed, and resource efficiency [29].At the first tier, hematologic screening functions as the primary filtering mechanism. CBC-derived parameters, reticulocyte profiles, and morphological cues help flag individuals whose red cell patterns are consistent with hemolytic disease. Automated algorithms can rapidly score these hematologic markers to prioritize infants at highest suspicion. In settings with limited laboratory infrastructure, this initial filter ensures that only those truly needing further assessment proceed to more specialized testing, conserving valuable resources [30].

Once hematologic indicators raise suspicion, the second-tier centers on genetic diagnostics as the definitive confirmatory step. Rapid genotyping platforms enable immediate identification of HbSS, HbSC, or HbS/beta-thalassemia variants. Integrating these results into the algorithm not only verifies the diagnosis but also assigns each patient to a biologically meaningful subtype. In many algorithmic models, genetic confirmation acts as the pivotal decision point around which all subsequent clinical actions are organized, from caregiver counseling and prophylaxis initiation to follow-up scheduling [31].The third tier

introduces imaging markers, which serve to refine early risk profiles by revealing subclinical organ stress. TCD ultrasonography, splenic and hepatic ultrasound, or more advanced MRI findings can be incorporated into algorithmic models to stratify children into low-, intermediate-, or high-risk categories. This approach ensures that early interventions such as chronic transfusion therapy, hydroxyurea initiation, or enhanced monitoring are allocated to those most likely to benefit. Even in resource-limited settings, simplified imaging inclusion, such as portable ultrasound or targeted TCD assessment, strengthens early risk recognition without adding excessive cost [32].

The power of a multi-modal algorithm lies in its ability to unify diverse data streams into a structured, interpretable pathway. Digital health platforms are increasingly being used to automate this integration. Mobile applications, cloud-based diagnostic systems, and AI-enabled decision-support tools can merge hematologic data with genotyping results and imaging outputs to generate patient-specific diagnostic profiles. These systems reduce reliance on specialist interpretation, improve consistency in rural clinics, and shorten the time between initial suspicion and confirmed diagnosis[30].Importantly, integrated algorithms also enhance equity in care. By minimizing subjective interpretation and standardizing diagnostic steps, they help ensure that infants in high-burden, under-resourced regions receive diagnostic quality comparable to that in high-income settings. Moreover, multi-modal pathways support the wider implementation of universal newborn screening programs by offering scalable, reproducible workflows that adapt to local resources [31].Still, algorithmic integration requires careful contextualization. Variability in laboratory capacity, cost constraints, and the availability of imaging tools mean that pathways must be flexible, allowing modular adoption based on local resources. In practice, this means building tiered diagnostic pathways that can function fully with low-cost hematologic and genetic tools alone, while incorporating imaging enhancements where feasible. Sustainable implementation also depends on workforce training, digital literacy, and stable supply chains for diagnostic reagents and consumables [32].

Challenges and Considerations in Implementation

Despite the growing promise of integrated algorithmic pathways for early diagnosis of SCA, real-world implementation is shaped by a complex set of logistical, economic, ethical, and infrastructural considerations. These challenges must be acknowledged and addressed to ensure that multi-modal diagnostic frameworks can be effectively translated into clinical practice across diverse global settings [33].One major challenge is the variability in resource availability. Many regions with the highest SCA burden still rely on limited laboratory infrastructure, intermittent power supply, and constrained access to trained personnel. While hematologic screening tools are increasingly low-cost and decentralized, genetic testing and imaging availability vary widely. Even point-of-care molecular platforms require consistent reagent supply chains, device maintenance, and quality assurance systems. Diagnostic algorithms must therefore be designed with flexible tiers that allow each step to function independently, ensuring that absence of one modality does not halt the entire diagnostic workflow [34].

Financial considerations also play a significant role. Introducing multi-modal diagnostics requires investment not only in equipment but also in training, data systems, and ongoing operational support. Although newer POC genetic tools reduce long-term costs, the upfront expenditure may be prohibitive for underfunded health systems. Policymakers must weigh the benefits of early diagnosis and prevention against immediate budget constraints, planning for sustainable financing models such as centralized procurement, donor partnerships, or integration into national newborn screening programs [35].Another concern relates to workforce capacity. Accurate interpretation of TCD velocities, ultrasound findings, and even some hematologic patterns requires trained clinicians or technicians. Efforts to scale algorithmic pathways

must therefore be coupled with training programs, competency assessments, and ongoing mentorship. Digital tools can help compensate for personnel shortages by automating aspects of data interpretation, but they rely heavily on consistent internet connectivity and device availability, which cannot be assumed in all settings [36].

Data management and interoperability are additional considerations. Multi-modal algorithms generate diverse data types, from CBC outputs to genotype results and imaging measurements. Integrating these into unified patient profiles demands secure digital systems capable of storing, analyzing, and sharing information across care levels. Without careful planning, poorly integrated platforms can create fragmentation or introduce delays rather than improving efficiency. Ensuring data privacy and ethical governance is equally important, especially when handling genetic information in regions where regulatory frameworks may be evolving [37].Cultural and ethical dimensions also influence implementation. Misunderstandings about genetic testing, stigma around hereditary conditions, and mistrust of health systems may reduce community acceptance of newborn screening or early diagnostic interventions. Effective communication, culturally sensitive education campaigns, and involvement of community leaders are key components of successful implementation. Families must be given clear information about the purpose, benefits, and implications of diagnostic testing to support informed decision-making [38]. Sustaining algorithmic pathways requires continuous evaluation and adaptation. As new diagnostic technologies emerge and costs shift, algorithms must be updated to reflect current evidence. Surveillance systems and operational research can help identify bottlenecks, measure diagnostic turnaround times, and assess real-world effectiveness. Without such iterative feedback loops, algorithms risk becoming outdated or misaligned with local realities.

Conclusion

Early diagnosis of sickle cell anemia is undergoing a quiet but transformative shift, driven by the convergence of hematologic analytics, molecular diagnostics, and increasingly sensitive imaging tools. Each modality contributes a different layer of insight, but their real power emerges when they are woven together into integrated, algorithmic pathways. These multimodal strategies not only sharpen diagnostic accuracy but also accelerate identification of at-risk infants, help clinicians classify disease subtypes earlier, and enable proactive monitoring of organ health long before irreversible damage occurs.

Yet the promise of these pathways depends on thoughtful implementation. Infrastructure gaps, cost constraints, unequal access to genetic testing, and limited availability of advanced imaging remain real barriers, especially in regions where SCA is most prevalent. Addressing these challenges will require sustained investment, coordinated policy support, and scalable innovations that balance sophistication with practicality.As diagnostic tools continue to evolve, algorithm-driven approaches provide a blueprint for a more equitable and responsive model of SCA care. By integrating hematologic, genetic, and imaging markers into cohesive decision frameworks, healthcare systems can move toward earlier detection, more personalized management, and ultimately better outcomes for individuals living with sickle cell anemia.

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DOI: 10.22192/ijcrcps.2025.12.10.003

How to cite this article:
Emmanuel Ifeanyi Obeagu. (2025). Algorithmic Pathways for Early Diagnosis of Sickle Cell Anemia: Integrating Hematologic, Genetic, and Imaging Markers. Int. J. Curr. Res. Chem. Pharm. Sci. 12(10): 24-33.
DOI: http://dx.doi.org/10.22192/ijcrcps.2025.12.10.003

