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AI-ENHANCED IMAGING GENOMICS: LINKING RADIOLOGIC PATTERNS TO GENOTYPE IN SICKLE CELL ANEMIA – A NARRATIVE REVIEW

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ABSTRACT

Sickle cell anemia (SCA) is a genetically inherited hemoglobinopathy characterized by chronic hemolysis, vaso-occlusion, and multi-organ damage. While the underlying β-globin mutation is well-defined, the clinical course is highly heterogeneous, influenced by co-inherited genetic modifiers and environmental factors. Radiologic imaging plays a critical role in detecting both acute complications and chronic end-organ damage. Imaging genomics, an emerging field that correlates imaging features with genomic data, offers a novel pathway to understand the genotype–phenotype relationships in SCA. The integration of artificial intelligence (AI) into this domain has further enhanced the ability to identify subtle imaging biomarkers that may correspond to specific genetic profiles. AI-enhanced imaging genomics leverages machine learning algorithms to process high-dimensional imaging data, extract quantitative features, and integrate them with genomic information. In SCA, this approach can reveal patterns linked to disease severity, predict the risk of complications such as stroke or avascular necrosis, and monitor treatment response. Advanced imaging modalities—including MRI, ultrasound, and CT—combined with AI-driven analytics, can uncover microstructural and functional changes before they become clinically apparent. These predictive capabilities have the potential to refine diagnosis, improve risk stratification, and guide personalized therapeutic interventions.

Keywords: *Artificial intelligence, Imaging genomics, Radiologic patterns, Sickle cell anemia, Genotype*

Introduction

Sickle cell anemia (SCA) is a monogenic blood disorder caused by a single nucleotide substitution in the β-globin gene (HBB), resulting in the production of abnormal hemoglobin S. Under hypoxic conditions, hemoglobin S polymerizes, leading to the deformation of red blood cells into a characteristic sickle shape. These rigid, sickled erythrocytes have a shortened lifespan and contribute to vaso-occlusive crises, chronic hemolysis, and progressive multi-organ damage. While SCA has a clear genetic basis, clinical presentations vary widely, even among individuals with the same genotype, highlighting the complexity of genotype–phenotype relationships [1-2]. The clinical variability of SCA stems from a combination of primary genetic mutations, co-inherited genetic modifiers, and environmental influences. For example, the presence of α-thalassemia or elevated fetal hemoglobin (HbF) levels can alter disease severity. These genetic factors influence the extent of anemia, frequency of vaso-occlusive episodes, and risk of complications such as stroke, pulmonary hypertension, and avascular necrosis. Despite advances in molecular diagnostics, translating genetic information into individualized prognostic and therapeutic strategies remains a challenge in routine clinical care [3-4].

Radiologic imaging is essential for detecting both acute complications and chronic organ damage in SCA. Magnetic resonance imaging (MRI) enables the early detection of silent cerebral infarcts, white matter hyperintensities, and microstructural brain changes. Ultrasound is commonly used for screening splenic dysfunction, hepatobiliary disease, and vascular abnormalities. Cardiac MRI and echocardiography are invaluable for assessing myocardial remodeling and pulmonary hypertension. Computed tomography (CT) and plain radiography assist in diagnosing osteonecrosis, acute chest syndrome, and skeletal deformities. These imaging findings provide tangible phenotypic correlates that can complement genetic data [5-7]. Imaging genomics—also referred to as radiogenomics—integrates quantitative imaging features with genomic information to explore the biological underpinnings of imaging phenotypes. Initially developed in oncology to predict tumor behavior and therapeutic response, this approach is increasingly being considered for non-malignant diseases, including hemoglobinopathies like SCA. By correlating imaging-derived biomarkers with specific genetic variants, imaging genomics has the potential to refine patient stratification, predict disease progression, and inform targeted interventions 8-9].

The integration of artificial intelligence (AI) into imaging genomics has transformed the ability to detect subtle, complex imaging patterns that may be imperceptible to the human eye. Machine learning (ML) and deep learning (DL) algorithms—particularly convolutional neural networks (CNNs)—can process large-scale imaging datasets, extract high-

dimensional features, and link these features to genomic profiles. In SCA, AI-enhanced imaging genomics could enable the early detection of organ-specific injury, identification of high-risk phenotypes, and personalized treatment planning based on combined radiologic and genetic signatures [10]. AI-enhanced imaging genomics offers multiple advantages over conventional approaches. First, it allows automated, objective, and reproducible feature extraction from imaging data, minimizing observer bias. Second, it enables the integration of multimodal data, including clinical variables, laboratory results, imaging features, and genomic information, into predictive models. Third, it supports real-time risk stratification and monitoring, which is particularly relevant for SCA patients at risk of acute, life-threatening complications. These capabilities align with the growing emphasis on precision medicine and patient-specific management strategies [11].

While the potential of AI-enhanced imaging genomics has been widely explored in oncology, its application in SCA is still at an early stage. Given the significant morbidity and mortality associated with SCA, the development of tools that can bridge the gap between genotype and phenotype is urgently needed. This review synthesizes current knowledge on AI-enabled imaging genomics in SCA, examines its clinical applications, identifies barriers to implementation, and explores future research directions. By highlighting the intersection of radiology, genomics, and artificial intelligence, we aim to underscore the transformative potential of this emerging field in improving outcomes for patients with SCA.

Aim

To evaluate the role of AI-enhanced imaging genomics in identifying genotype-specific radiologic patterns in sickle cell anemia and its implications for diagnosis, prognosis, and personalized treatment strategies.

Methods

This narrative review was conducted to synthesize existing literature on the role of artificial intelligence (AI)-enhanced imaging genomics in linking radiologic patterns to genotype in sickle cell anemia (SCA). A comprehensive search strategy was employed to identify peer-reviewed publications, conference proceedings, and relevant grey literature published between January 2010 and July 2025.

Search Strategy: Electronic databases including PubMed, Scopus, Web of Science, and IEEE Xplore were systematically searched using combinations of controlled vocabulary (MeSH terms) and free-text keywords. The primary search terms included: *"sickle cell anemia," "imaging genomics," "radiogenomics," "artificial intelligence," "machine learning," "deep learning," "genotype-phenotype correlation,"* and *"radiologic biomarkers."* Boolean operators (AND, OR) and truncations were applied to refine results.

Inclusion and Exclusion Criteria: Articles were included if they (i) focused on sickle cell anemia or related hemoglobinopathies, (ii) reported integration of radiologic imaging with

genomic data, (iii) applied AI, machine learning, or deep learning methods for image or data analysis, and (iv) were published in English. Studies were excluded if they lacked a clear genomic or AI component, focused solely on non-SCA conditions without translational relevance, or were purely technical reports without clinical correlation.

Study Selection and Data Extraction: Titles and abstracts of identified records were screened for relevance, followed by full-text review of potentially eligible articles. Data extracted from each study included study design, sample size, imaging modality, AI methodology, genomic targets, key findings, and reported clinical implications. Where available, performance metrics of AI models (e.g., accuracy, sensitivity, specificity, area under the curve) were documented.

Data Synthesis: Given the heterogeneity of methodologies and outcomes, a qualitative synthesis approach was used rather than a meta-analysis. Extracted information was grouped under thematic categories: (1) imaging modalities and phenotypic features in SCA, (2) AI algorithms for feature extraction and pattern recognition, (3) integration with genomic data, and (4) clinical applications and future perspectives. Findings were interpreted within the broader context of precision medicine and translational imaging.

Imaging in Sickle Cell Anemia: Linking Phenotype to Pathophysiology

Sickle cell anemia (SCA) is marked by repeated cycles of vaso-occlusion, ischemia-reperfusion injury, and chronic hemolysis, leading to progressive multi-organ damage. While laboratory parameters provide biochemical evidence of disease activity, radiologic imaging offers direct visualization of structural and functional alterations in affected tissues. Imaging not only reflects the current disease state but can also reveal subclinical changes that precede irreversible organ failure, thereby serving as a crucial bridge between phenotype and underlying pathophysiology [12]. Magnetic resonance imaging (MRI) is the gold standard for detecting cerebrovascular complications in SCA, including silent cerebral infarcts, overt strokes, and white matter hyperintensities. These findings are particularly prevalent in patients with the HbSS genotype and correlate with impaired cerebral blood flow, endothelial dysfunction, and chronic anemia. Advanced MRI techniques, such as diffusion tensor imaging (DTI) and functional MRI (fMRI), can detect microstructural white matter injury and altered brain connectivity even in asymptomatic individuals, offering early phenotypic markers of high-risk genotypes [13-14].

Bone involvement in SCA arises from ischemic bone marrow infarction, chronic inflammation, and remodeling defects. Plain radiography and computed tomography (CT) can reveal cortical thinning, osteopenia, and "H-shaped" vertebrae, while MRI is superior for detecting early avascular necrosis (AVN) of the femoral or humeral heads. The extent and distribution of AVN lesions often correlate with genotype severity, transfusion history, and frequency of vaso-occlusive episodes. [15] Cardiac MRI and

echocardiography are critical for evaluating cardiomyopathy, pulmonary hypertension, and diastolic dysfunction in SCA. These findings reflect a phenotype driven by chronic anemia, iron overload from transfusions, and vascular remodeling. In the lungs, high-resolution CT may detect interstitial changes, pulmonary fibrosis, and prior acute chest syndrome episodes. Such phenotypes are more severe in genotypes associated with persistent hemolysis and low fetal hemoglobin levels [16-17].

Ultrasound is routinely used for abdominal evaluation, revealing functional asplenia, splenic atrophy, hepatomegaly, gallstones, and hepatic iron overload. MRI-based T2* imaging provides quantitative assessment of iron deposition in the liver and spleen, an important consideration in chronically transfused patients. The degree of iron overload and splenic damage varies with genotype, transfusion regimen, and coexisting metabolic conditions [18-19]. Renal ultrasonography and MRI can detect papillary necrosis, cortical scarring, and progressive atrophy associated with sickle cell nephropathy. These phenotypes are linked to glomerular hyperfiltration, medullary hypoxia, and microinfarction—mechanisms more pronounced in severe genotypes like HbSS compared to HbSC (Table 1) [20].

Table 1: Imaging in Sickle Cell Anemia: Linking Phenotype to Pathophysiology

Imaging Phenotype	Modality	Key Radiologic Features	Underlying Pathophysiology
Silent cerebral infarcts & white matter lesions	Brain MRI (T2/FLAIR, DWI)	Hyperintense periventricular/ deep white matter lesions; restricted diffusion in acute infarction	Chronic vaso-occlusion, endothelial dysfunction, impaired cerebrovascular autoregulation; reduced nitric oxide bioavailability
Cerebral vasculopathy (stenosis, moyamoya-like collaterals)	MRA, CTA	Intracranial arterial narrowing; collateral vessel formation	Intimal hyperplasia, chronic shear stress, inflammation-related vascular remodeling
Reduced cerebral perfusion	ASL MRI, TCD, perfusion CT	Decreased cerebral blood flow; elevated flow velocities on TCD	Compensatory hyperemia from anemia, microvascular obstruction, impaired oxygen delivery
Avascular necrosis of bone	MRI (T1/T2, STIR)	Subchondral signal abnormalities; joint surface collapse	Repeated ischemia-reperfusion injury, bone microinfarction, marrow hypertension
Marrow hyperplasia & reconversion	MRI	Diffuse low T1 marrow signal; expansion of red marrow	Chronic hemolytic anemia → increased erythropoiesis and marrow expansion
H-shaped ("fish-mouth") vertebrae	Spine X-ray, MRI	Central endplate depression of vertebral bodies	Microinfarctions of vertebral endplates from repeated vaso-occlusion
Acute chest syndrome & pulmonary abnormalities	Chest X-ray, CT	Infiltrates, consolidation, mosaic attenuation	Infection, fat embolism, pulmonary vaso-occlusion, inflammation
Pulmonary hypertension features	Echocardiography, CT	Enlarged pulmonary arteries, RV hypertrophy	Hemolysis-mediated nitric oxide scavenging → vascular remodeling & increased pulmonary pressures
Splenic infarcts & autosplenectomy	Ultrasound, CT	Wedge-shaped infarcts; calcified, shrunken spleen	Recurrent splenic vaso-occlusion leading to fibrosis and functional asplenia
Hepatic iron overload	MRI (T2*, R2)	Liver signal drop-out proportional to iron load	Chronic transfusions → iron deposition in hepatic parenchyma
Renal medullary	MRI, CT urography	Reduced medullary	Medullary hypoxia exacerbated

hypoperfusion & papillary necrosis		enhancement; sloughed papillae	by sickling in hypertonic, low-oxygen environment
Cardiac dysfunction	Cardiac MRI, echocardiography	LV dilation, RV strain, myocardial fibrosis (LGE)	Chronic anemia, microvascular ischemia, iron overload, increased cardiac workload

AI-Enhanced Imaging Genomics: Principles and Workflow

AI-enhanced imaging genomics represents an emerging fusion of radiology, genomics, and computational intelligence, designed to decode the biological meaning embedded within medical images. Its central principle is that radiologic appearances—traditionally viewed as structural or functional manifestations—carry quantifiable information that reflects underlying molecular and genetic processes. By integrating advanced image analytics with genomic profiling, AI-enhanced imaging genomics provides a multidimensional lens through which clinicians and researchers can better understand disease phenotypes, predict outcomes, and tailor personalized interventions [21]. The workflow of AI-enhanced imaging genomics begins with data acquisition, the foundational step in which high-quality imaging and genomic datasets are collected. Standard radiologic modalities—MRI, CT, PET, ultrasound, and increasingly quantitative MRI sequences—serve as the imaging backbone. Parallel genomic acquisition may involve whole-genome sequencing, targeted gene panels, transcriptomics, epigenomic assays, or proteomic platforms. Because imaging and genomic data originate from vastly different scales and formats, meticulous standardization is essential. Harmonization of imaging protocols, consistent voxel resolution, and correction of scanner-related variability enhance reproducibility, while ensuring genomic data are curated through rigorous quality control pipelines minimizes sequencing artifacts [22].

Following acquisition, the process moves into image preprocessing and feature extraction. Here, AI techniques play a critical role. Preprocessing tasks such as denoising, intensity normalization, motion correction, and anatomical segmentation prepare the images for computational interrogation. Radiomics enables the extraction of hundreds to thousands of quantitative features—including shape descriptors, signal intensity patterns, texture metrics, and wavelet-transformed features—capturing subtle characteristics imperceptible to the human eye. Deep learning, particularly convolutional neural networks, can extract even more complex, hierarchical signatures without the need for predefined features, providing a rich quantitative summary of organ architecture and microenvironmental alterations [23]. Simultaneously, the genomic data undergo annotation, variant calling, and functional categorization. Gene expression profiles may be normalized to remove batch effects, while epigenomic data are mapped to CpG islands, regulatory elements, or histone modification patterns. The goal is to generate a reliable

molecular signature that can be paired with imaging-derived features [24].

The pivotal stage in the workflow is multimodal data integration, where AI techniques combine radiomic signatures with genomic attributes. Machine learning algorithms—such as random forests, support vector machines, gradient boosting, and emerging multimodal neural networks—serve as integrative engines. These algorithms identify patterns, correlations, and latent relationships linking image features with genotypic or molecular markers. In this step, AI models can detect whether specific radiologic phenotypes correspond to particular genetic variants, expression clusters, inflammatory pathways, or molecular risk categories. For example, imaging markers of vascular stenosis may map to endothelial or nitric oxide–related genetic polymorphisms, while marrow texture features may associate with hypoxia-inducible factor (HIF) pathway variants [25].

Once integration is achieved, the models proceed to predictive analysis and validation. AI systems are trained to predict clinical outcomes—such as stroke risk, organ damage progression, or therapeutic responsiveness—based on the combined imaging-genomic profile. Validation typically employs cross-validation, external cohorts, or multicenter datasets to ensure the model can generalize beyond the training population. Performance metrics such as AUC, precision-recall values, calibration plots, and decision curve analyses help determine clinical utility [26].

The final stage of the workflow culminates in biological interpretation and clinical translation. This phase emphasizes the importance of explainable AI, ensuring that the relationships uncovered between imaging features and genomic signatures are biologically meaningful and comprehensible to clinicians. Heatmaps, saliency maps, and feature importance scores illustrate what the AI system considers most influential, providing transparency and fostering trust. Translational application may include risk stratification tools, early detection of subclinical organ damage, monitoring of therapy response, or genotype-informed imaging surveillance strategies [27-28].

Clinical Applications in Sickle Cell Anemia

The integration of AI-enhanced imaging genomics into the clinical management of sickle cell anemia (SCA) promises to redefine how clinicians assess disease severity, monitor organ involvement, and personalize therapy. Although still emerging, this multidisciplinary approach offers a more nuanced understanding of how genetic modifiers translate into distinct radiologic and clinical phenotypes. Because SCA is characterized by wide phenotypic variability—from silent organ dysfunction to severe vaso-occlusive complications—its management stands to benefit substantially from precision tools that go beyond traditional clinical and laboratory markers [29].

One of the most impactful clinical applications lies in the early detection of cerebrovascular disease, a major cause of morbidity in SCA. Silent cerebral infarcts, white matter injury, and progressive vasculopathy often precede neurological symptoms. AI-driven radiomics applied to MRI can extract subtle structural and

perfusion abnormalities that escape visual detection, while genomic profiles—such as polymorphisms in *BCL11A*, *HBS1L-MYB*, and inflammation-related genes—help map imaging patterns to stroke risk biology. When combined through AI-based multimodal models, these datasets can stratify children and adults into precise cerebrovascular risk categories, guiding decisions about chronic transfusion therapy, hydroxyurea escalation, or intensified neuroimaging surveillance. In this way, imaging genomics acts as a bridge between subclinical brain injury and genotype-informed preventive care [30].

Beyond the brain, cardiopulmonary complications represent another domain where AI-enhanced imaging genomics has emerging clinical relevance. Pulmonary hypertension, right ventricular dysfunction, and microvascular obstruction frequently develop insidiously in SCA. Radiomic analysis of chest CT, cardiac MRI, and echocardiographic data can quantify early vascular remodeling and myocardial strain. When linked to genetic modifiers of nitric oxide metabolism, endothelial activation, and oxidative stress, these imaging features support precise risk estimation. AI models can identify patients predicted to develop pulmonary hypertension long before overt hemodynamic decline, enabling timely interventions such as targeted vasodilator therapy, optimization of transfusion regimens, or more aggressive control of hemolysis [31].

The musculoskeletal system, particularly bone and marrow structures, offers another rich field for clinical application. Avascular necrosis (AVN) remains a debilitating complication of SCA, often diagnosed late when joint preservation is no longer feasible. AI-driven texture analysis of MRI bone marrow images can identify microarchitectural deterioration long before radiographic collapse. Combined with genomic signatures related to hypoxia-inducible pathways, bone turnover regulation, and inflammatory mediators, predictive models can identify individuals at highest risk for AVN. Such insights may support earlier initiation of bisphosphonate therapy, referral for orthopedic assessment, or modification of physical activity before irreversible damage occurs [32].

The spleen, liver, and kidneys—organs highly susceptible to chronic hemolytic and vaso-occlusive injury—represent additional opportunities for imaging-genomic integration. Hepatosplenic imaging genomics can differentiate between patients likely to progress to autosplenectomy, develop iron overload, or experience biliary complications, based on radiomic spleen volume metrics, hepatic texture features, and genetic variants associated with hemolysis and iron metabolism. Similarly, AI-enhanced analysis of renal MRI can map early oxygenation defects and microstructural changes to genotypes related to tubular dysfunction, laying the foundation for early nephroprotective interventions [33].

A rapidly expanding area is therapeutic monitoring, especially as novel disease-modifying treatments—including hydroxyurea, voxelotor, crizanlizumab, and gene-editing approaches—reshape the clinical landscape. Imaging genomics enables clinicians to visualize how therapy-

induced molecular changes manifest structurally across tissues. For example, increasing fetal hemoglobin levels through pharmacologic or gene-editing interventions may induce detectable changes in cerebral perfusion or bone marrow expansion patterns. AI models can track these imaging-genomic signatures over time, offering a noninvasive method to evaluate treatment efficacy, adjust dosing, or identify nonresponders early [34-35]. AI-enhanced imaging genomics has important implications for personalized clinical pathways. By integrating imaging biomarkers, genetic modifiers, and clinical history, multimodal prediction models can help clinicians tailor surveillance schedules, prioritize resource allocation, and anticipate complications before they become clinically evident. This is particularly valuable in resource-limited settings, where maximizing predictive accuracy can streamline care and focus interventions on those at highest risk (Table 2) [36].

Table 2: Clinical Applications in Sickle Cell Anemia

Clinical Application	Imaging-Genomic Correlates	AI/Computational Approach	Clinical Impact
Stroke risk prediction	Cerebral white matter lesions, silent infarcts; *BCL11A*, *HBS1L-MYB* variants	Machine learning, deep learning-based radiogenomic models	Early identification of high-risk children/adults → guide transfusion or hydroxyurea therapy
Avascular necrosis (AVN) monitoring	Subchondral marrow changes on MRI; HIF pathway, bone metabolism genes	Radiomic texture analysis, predictive modeling	Preclinical detection of AVN → timely orthopedic intervention and activity modification
Pulmonary hypertension and cardiopulmonary assessment	RV strain, pulmonary artery dilation, perfusion deficits; NOS3 and endothelial-related polymorphisms	Multimodal AI integration of echocardiography, MRI, CT	Early recognition of cardiopulmonary complications → guide vasodilator therapy and transfusion management
Hepatosplenic disease evaluation	Spleen volume, hepatic iron load; hemolysis-related, UGT1A1 variants	Quantitative organ segmentation, deep learning mapping	Identify patients at risk of autosplenectomy, gallstones, or iron overload → targeted surveillance and iron chelation
Renal injury detection	Medullary hypoperfusion, papillary necrosis; genes affecting tubular function	MRI radiomics and AI-based perfusion modeling	Early nephropathy detection → nephroprotective strategies and therapy optimization
Therapeutic response monitoring	Changes in cerebral perfusion, marrow expansion, organ	Longitudinal radiogenomic tracking with AI	Assess efficacy of hydroxyurea, voxelotor, gene therapy → personalized

	volumes; HbF modulators		treatment adjustments
Pain crisis risk stratification	Microvascular perfusion deficits, marrow signal abnormalities; inflammatory pathway genes	Predictive AI models combining imaging, genomics, and clinical data	Identify high-risk patients for prophylactic interventions → reduce hospitalization and morbidity
Personalized care planning	Multiorgan imaging-genomic signature	Integrative multimodal AI pipelines	Inform individualized surveillance schedules, early interventions, and precision medicine approaches

Challenges and Limitations

Despite its transformative promise, AI-enhanced imaging genomics in sickle cell anemia (SCA) faces a number of significant challenges and limitations that currently constrain its clinical translation. The field sits at the intersection of radiology, genomics, and computational science, and each component introduces inherent complexities. As a result, the development of robust imaging-genomic models requires overcoming obstacles related to data quality, methodological variability, population diversity, ethical considerations, and clinical integration [37].

One of the foremost challenges is limited availability of large, high-quality multimodal datasets. Imaging genomics relies on the simultaneous acquisition of advanced radiologic studies and comprehensive genomic profiles, yet most SCA cohorts lack harmonized imaging protocols or fully curated genetic data. Brain MRI sequences, perfusion imaging, and quantitative MRI are not universally available, especially in low-resource settings where SCA burden is highest. Genomic datasets may be incomplete, fragmented, or generated using different sequencing platforms with inconsistent annotation standards. These disparities reduce the statistical power and generalizability of AI models and contribute to overfitting, where algorithms perform well on training data but poorly on external populations [38].

Closely related is the problem of heterogeneity in imaging acquisition and processing. Variations in MRI scanner type, slice thickness, contrast settings, and reconstruction algorithms introduce technical "noise" that can overshadow biological signals. Even minor differences in imaging protocols can significantly alter radiomic features. Without rigorous harmonization and preprocessing pipelines, it becomes difficult to determine whether detected imaging-genomic associations represent true physiological phenomena or artifacts of equipment differences. This challenge is magnified when datasets are aggregated across multiple institutions or countries [39].

The genomic landscape of SCA is also markedly complex, influenced by a combination of primary hemoglobin mutations, fetal hemoglobin modifiers, inflammation-related polymorphisms, and environmental exposures. Capturing this heterogeneity requires deep sequencing approaches and functional validation that

extend beyond routine clinical genotyping. Moreover, because most available genomic datasets underrepresent populations of African descent—who comprise the vast majority of individuals with SCA—AI-enhanced imaging genomic models risk encoding biases that undermine equity. Lack of population diversity can lead to inaccurate predictions, reduced clinical relevance, and potential exacerbation of existing health disparities [40].

Another important barrier concerns algorithm interpretability and clinical trust. Many AI tools—particularly deep learning models—operate as "black boxes," generating predictions without clear explanations of the features or genomic associations driving them. In a disease as complex as SCA, clinicians require transparent, explainable systems to ensure that decisions derived from AI align with biological plausibility and established clinical knowledge. Without interpretability, AI outputs may be viewed with skepticism or fail to integrate into clinical workflows [41]. Ethical and privacy concerns also loom large. The combination of imaging and genomic data creates a uniquely identifiable patient profile, raising challenges related to data ownership, informed consent, and secure data handling. Genomic information can have implications for family members, insurance coverage, and long-term personal privacy. Ensuring secure storage, controlled access, and ethical sharing of multimodal datasets is essential but difficult, particularly when involving international collaborations or cloud-based AI platforms [42].

Another limitation relates to the computational and technical demands of imaging genomics. High-dimensional radiomic features, complex neural network architectures, and large genomic matrices require substantial computational resources, specialized expertise, and interdisciplinary collaboration. Many centers lack access to the high-performance computing infrastructure necessary to train and validate sophisticated AI models, limiting widespread adoption [43]. The field faces challenges in clinical validation and implementation. While numerous early studies demonstrate promising correlations between radiologic features and genetic markers, few have undergone rigorous prospective validation or been tested in real-world clinical environments. Translating predictive models into actionable clinical tools requires demonstrating that AI-guided decisions improve patient outcomes, reduce complications, or refine therapeutic choices. Until strong evidence accumulates, integration into routine care will remain slow [44].

Conclusion

AI-enhanced imaging genomics represents a transformative approach to understanding and managing sickle cell anemia by linking radiologic patterns with underlying genetic profiles. By integrating advanced imaging modalities with genomic data through machine learning and deep learning algorithms, this technology enables earlier detection of subclinical organ damage, more accurate risk stratification, and truly personalized treatment planning. Such capabilities align closely with the goals of precision

medicine, offering the potential to reduce morbidity, prevent complications, and improve quality of life for individuals with SCA. However, realizing this potential requires addressing substantial challenges, including limited access to high-quality datasets, variability in imaging protocols, integration complexities, and ethical considerations surrounding data privacy. Overcoming these barriers will depend on multi-institutional collaboration, standardized imaging practices, robust validation studies, and the development of explainable AI models that clinicians can trust.

Conflicts of Interest

The author declares no conflict of interest

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Abbreviations

AI – Artificial Intelligence
ASL – Arterial Spin Labeling
AVN – Avascular Necrosis
BCL11A – B-Cell Lymphoma/Leukemia 11A (gene regulating HbF)
CTA – Computed Tomography Angiography
CT – Computed Tomography
DWI – Diffusion-Weighted Imaging
FLAIR – Fluid-Attenuated Inversion Recovery
HbF – Fetal Hemoglobin
HIF – Hypoxia-Inducible Factor
HBS1L-MYB – HBS1L-MYB Intergenic Region (gene locus associated with HbF modulation)
LGE – Late Gadolinium Enhancement
LV – Left Ventricle
MRA – Magnetic Resonance Angiography
MRI – Magnetic Resonance Imaging
NOS3 – Nitric Oxide Synthase 3 (endothelial NOS gene)
RV – Right Ventricle
SCA – Sickle Cell Anemia
STIR – Short Tau Inversion Recovery
TCD – Transcranial Doppler
UGT1A1 – UDP Glucuronosyltransferase Family 1 Member A1 (gene influencing bilirubin metabolism)

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