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REVIEW ARTICLE

The Use of Cost-Effectiveness Analysis in Sickle Cell Disease: A Critical Review of the Literature

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Abstract

Novel interventions for sickle cell disease (SCD) bring hope to patients, yet concern about the associated economic costs exists. Cost-effectiveness analysis (CEA) uses standardized methods, with robust underpinnings in health economics, to estimate the value of these interventions compared with usual care. However, because of the complexity and lifetime trajectory of SCD, CEAs are challenging to conduct. The objectives of this rapid review were to summarize the main characteristics, components, and results of published CEAs of existing interventions for SCD, identify research gaps, and provide directions for future analyses. We identified records through searches of bibliographic databases, from reference lists of relevant review articles, and through consultation with experts. A total of 13 CEAs met our inclusion criteria and were qualitatively synthesized. These evaluated blood transfusions ($n=2$), hematopoietic stem cell transplantation ($n=1$), pharmaceuticals ($n=2$), hypothetical cell or genetic therapy ($n=1$), screening programs ($n=4$), and interventions for SCD treatment complications ($n=3$). A limited number of potential SCD and treatment complications were evaluated. No study adopted a societal perspective in the base case, six studies examined lifetime cost-effectiveness, seven studies employed a Markov or discrete-event simulation model, and eight studies used an outcome metric that captured both quality and length of life. To better compare the value of emerging and current therapies, future CEAs should adopt a societal perspective incorporating both medical and nonmedical costs, comprehensively model SCD complexity using robust health economic simulation models over the patient's entire lifespan, and capture the intervention's effect on both survival and quality of life.

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1 Introduction

Sickle cell disease (SCD) refers to a group of inherited red blood cell disorders that affects over 20 million people throughout the world. In the USA, the prevalence of SCD is approximately 100,000, and the majority of those affected are Black or African American [1]. SCD can lead to a series of acute and chronic complications, such as acute pain episodes, chronic pain, stroke, acute chest syndrome, symptoms of anemia, and an increased risk of infections and organ damage [1]. These complications significantly impact patients' life expectancy and quality of life [2–4]. Moreover, the economic costs due to SCD are considerable, with annual average healthcare costs ranging from $US15,000 to 30,000 [5–7], placing a large burden on individuals, their caregivers, and the healthcare system.

Several treatments are currently available for SCD. Hydroxyurea, an antimetabolite, and—for certain indications—transfusion, are accepted as standard of care [8, 9]. Allogeneic hematopoietic stem cell transplantation

Key Points for Decision Makers

This is the first literature review to identify published cost-effectiveness analyses (CEAs) of sickle cell disease (SCD) interventions. The identified studies were heterogeneous in terms of geographic setting, intervention type, SCD and treatment complications evaluated, and choice of decision analytic model, time horizon, and outcome metrics. Consequently, the findings were inconsistent across the studies.

This review illuminates the gaps in the existing CEAs in SCD. For example, a limited number of SCD and treatment complications were included, nonmedical costs were not incorporated in the base case, a simulation model or a lifetime horizon was not frequently employed to reflect the complexity of the disease's natural history, and an outcome metric that captured both quality and length of life was not commonly used.

Future CEAs could incorporate the value of an SCD intervention in reducing inequity and reflect the fast-evolving treatment landscape in SCD.

(alloHCT) is the only accepted treatment with curative intent [10]. However, these treatments can cause a wide range of complications. For example, blood transfusions may cause iron overload, alloimmunization, and infections [9] and transplantation may cause graft-versus-host disease, graft failure, and transplantation-related organ toxicities and mortality [10]. Additional healthcare resources are sometimes needed to treat these complications.

Aside from the conventional treatments, several new therapies have recently been approved by the US FDA, including crizanlizumab (a monoclonal antibody), voxelotor (a small molecule), and L-glutamine (a naturally occurring amino acid) [11]. Moreover, initial results of clinical trials of genetic therapy for SCD have been promising [12]. Indeed, the Cure Sickle Cell Initiative, funded by the National Heart Lung and Blood Institute [13], is a large collaborative research effort intended to accelerate the development of genetic therapies to cure SCD. Although the development of novel pharmacologic and stem cell therapies is providing hope to many patients with SCD, the accompanying high costs warrant attention [12]. For instance, the average costs of crizanlizumab and voxelotor range from approximately $US80,000 to 110,000 and from $US100,000 to 250,000 every year, respectively [14, 15]. The cost of one current genetic therapy for beta-thalassemia, another hemoglobin disorder, is approximately $US1.8 million per treatment [16].

The emergence of expensive SCD therapies makes the application of cost-effectiveness analysis (CEA) in this field timely. However, accurately capturing all the significant costs and outcomes in a CEA for SCD can be challenging. Doing so requires the creation of a detailed model that simulates patients' experiences over their lifetime and reflects the complex natural history of the disease. It also requires data to inform model inputs for a disease that is relatively rare. The data may include not only the medical costs and health outcomes associated with SCD, its complications, and treatments but also nonmedical burden such as the impacts on patients' education attainment and work productivity and their caregiver's burden. Despite these limitations, lessons can be learned from published CEAs in SCD.

We conducted this rapid review of published CEAs in SCD as one of a series of landscape analyses we performed as investigators within the Cure Sickle Cell Initiative. The aim of this review was to qualitatively synthesize and evaluate the main characteristics, components, and results of published CEAs of interventions for SCD. We identify current research gaps and provide directions for valuing emerging gene therapies for SCD.

2 Methods

2.1 Search Methods and Sources

We conducted a rapid literature review following Agency for Healthcare Research and Quality guidance for rapid reviews and adopted the population, intervention, comparator, outcomes, timing, and setting/study design (PICOTS) framework to establish eligibility criteria (Appendix 1 in the electronic supplementary material [ESM]) [17]. This framework reflects deliberations and decisions made over a 3-month period in late 2019 by an expert panel that included a molecular biologist, clinicians who care for patients with SCD, health economists, evidence synthesis scientists, and librarians. These stakeholders represent academia, clinical practice, and the federal government. The framework was executed as a search strategy in PubMed, Embase, the National Health System Economic Evaluation Database, the Tufts University CEA Registry, and EconLit by two experienced health sciences librarians and one health economist with expertise in evidence synthesis (search terms can be found in Appendix 2 in the ESM). Additional articles were identified from the reference lists of relevant review articles and through consultations with experts. The content of this report aligns with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement for reporting of systematic reviews [18].

2.2 Eligibility Criteria

We included English language articles published in peer-reviewed journals from January 2008 to June 2021 and white papers published from January 2018 to June 2021. Eligible articles included CEAs of SCD interventions with costs, effectiveness, and incremental cost-effectiveness ratios (ICERs) as the outcomes. All types of interventions for patients with SCD, treatment complications, and screening programs targeting newborns or pregnant people were included, whereas treatments targeting patients with sickle cell trait were excluded (Appendix 1 in the ESM).

2.3 Study Selection

Records identified through the databases, found from reference lists of relevant review articles, and from consultations with experts were merged. After duplicate records were removed, the primary reviewer (BJ) independently screened the titles and abstracts of all references and assessed the full text of all remaining articles for eligibility. The second reviewer (DQ) reviewed 10% of randomly selected references. Discrepancies between reviewers' judgments were discussed and resolved through consensus.

2.4 Data Extraction

The primary reviewer (BJ) extracted the main characteristics of included studies (intervention type, study design, geographic region, and perspective), main components of each study (time horizon, model type, cost type, effectiveness measure, source of health utilities, discounting), disease characteristics (SCD complications and treatment complications), and study results (costs, effectiveness, and ICER). To convert countries' currencies to $US, we applied the average annual exchange rates for the fiscal years [19–21]. The second reviewer (DQ) verified the extracted data.

2.5 Critical Appraisal

We evaluated the adherence of the cost-effectiveness studies to the health economic evaluation reporting guidelines (The Consolidated Health Economic Evaluation Reporting Standards [CHEERS]), which was developed by a task force supported by the International Society for Pharmacoeconomics and Outcomes Research [22]. Eighteen items from the CHEERS statement were used to assess the proper description of methods and the complete presentation of results (Appendix 3 in the ESM). Each item was judged using the following options: yes, no, partially or implied, or not applicable.

3 Results

3.1 Study Selection

The PRISMA flow diagram outlines study selection and reasons for exclusion (Fig. 1). Our search identified 166 references. One additional study was identified through consultation with experts. No additional studies that were not already contained in our search were identified from the reference lists of relevant literature review articles. After removing the duplicate articles, we screened the titles and abstracts of the remaining 128 articles and included 44 articles for full-text assessment. In total, 13 articles met our final inclusion criteria, and data from these were extracted.

3.2 Overview of Included Studies

The main characteristics of the included studies are presented in Table 1. Two studies estimated the value of the intervention of blood transfusion [23, 24], one study evaluated transplantation [25], two studies evaluated pharmaceuticals for SCD (hydroxyurea, crizanlizumab, voxelotor, and L-glutamine) [26, 27], one study evaluated a hypothetical cell or genetic therapy [28], four studies examined screening programs [29–32], and the remaining three studies evaluated interventions for SCD treatment complications [33–35].

Five studies were set in the context of the USA [25, 27, 28, 33, 34], four in the UK [23, 24, 32, 35], one in Jamaica [26], one in Spain [29], one in Angola [31], and one in Sub-Saharan Africa [30]. In the base-case scenario, nine studies adopted the healthcare system perspective [23, 24, 26–30, 32, 35], three studies adopted the healthcare institution or hospital perspective [25, 33, 34], and one study did not mention the perspective [31]. One study also adopted a modified societal perspective as a scenario analysis [27].

3.3 Study Design

The key components of the study design can be found in Table 2. Eleven studies were model-based [23, 24, 27–35], six used a Markov model [23, 27, 28, 30, 33, 34], one used a discrete-event simulation model [29], one used a life table model [31], and three did not explicitly mention the model type [24, 32, 35]. The lifetime horizon was used in five of the model-based studies [23, 27, 28, 30, 31]. The remaining two studies summarized the costs and effectiveness outcome directly, based on longitudinal data without building a decision model [25, 26]. One study followed the patients over 1 year and also predicted the lifetime cost-effectiveness [25]. The mean follow-up time of the other study was approximately 4 years [26].

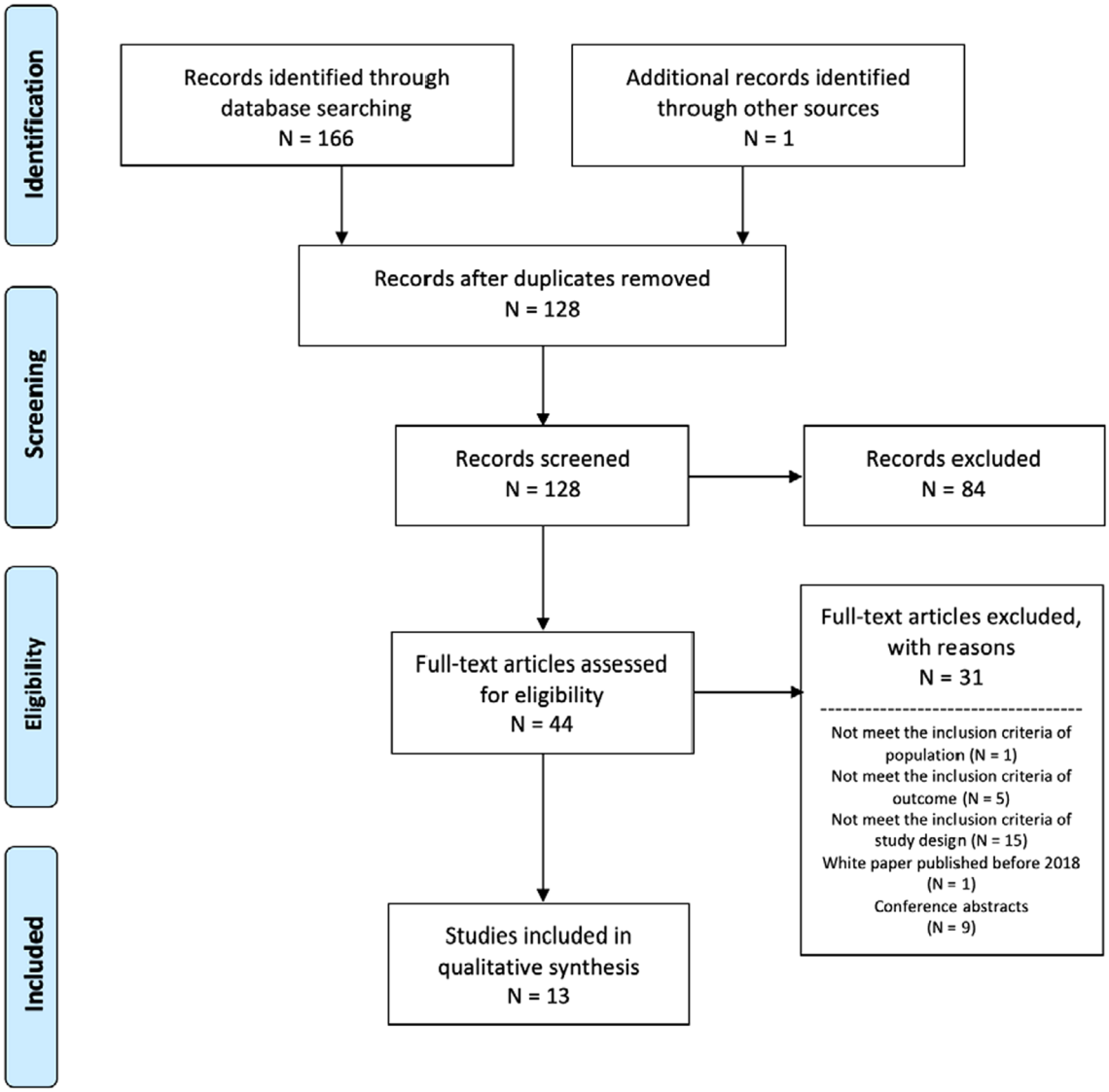

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow diagram of studies included in this systematic review and reasons for exclusion

3.4 Cost Inputs

Table 2 displays the types of cost inputs and effectiveness measures found in each study. All 13 studies included costs of the healthcare intervention. Twelve studies also included costs of the healthcare consequences due to the intervention (i.e., downstream healthcare resource use) [23–34]. One study considered costs outside the formal healthcare sector in their scenario analysis, such as the effect of SCD on caregiver burden, education, and productivity [27].

3.5 Utility Inputs

Six studies employed the quality-adjusted life-year (QALY) as the effectiveness measure [23–25, 27, 28, 35]. Although four studies used health utility values that were empirically elicited from an SCD population [24, 25, 27, 28], all six also relied on assumptions by the authors without referencing an empirical study or values empirically elicited for non-SCD-specific populations [23–25, 27, 28, 35].

3.6 Clinical Inputs: Disease and Treatment Complications

Seven studies considered SCD complications [23, 25–29, 31]. The most common complications in those studies were stroke (six studies) [23, 25–27, 29, 31], vaso-occlusive crisis or pain crisis (five studies) [23, 25, 27, 28, 31], and acute chest syndrome (four studies) [23, 25, 27, 31] (Appendix 4 in the ESM). Seven studies considered treatment complications

Table 1 Main characteristics of included cost-effectiveness analyses

Study	Study design	Region	Perspective	Intervention type
Cherry et al. [23]	Model-based study	UK	Healthcare system	Blood transfusion
Spackman et al. [24]	Model-based study	UK	Healthcare system	Blood transfusion
Arnold et al. [25]	Observational study	USA	Healthcare institution or hospital	Transplantation
Cunningham-Myrie et al. [26]	Observational study	Jamaica	Healthcare system	Pharmaceuticals
Bradt et al. [27]	Model-based study	USA	Healthcare system, modified societal	Pharmaceuticals
Salcedo et al. [28]	Model-based study	USA	Healthcare system	Hypothetical cell or genetic therapy
Castilla-Rodríguez et al. [29]	Model-based study	Spain	Healthcare system	Screening
Kuznik et al. [30]	Model-based study	Sub-Saharan Africa	Healthcare system	Screening
McGann et al. [31]	Model-based study	Angola	NA	Screening
Bryan et al. [32]	Model-based study	UK	Healthcare system	Screening
Kacker et al. [33]	Model-based study	USA	Hospital	Intervention for treatment complications
Kacker et al. [34]	Model-based study	USA	Hospital	Intervention for treatment complications
McLeod et al. [35]	Model-based study	UK	Healthcare system	Intervention for treatment complications

NA not available

[23–25, 27, 33–35]. Treatment complications from blood transfusions were most common, such as iron overload (three studies) [23, 27, 35] and alloimmunization (three studies) [23, 33, 34]. One study considered complications of alloHCT, such as acute and chronic graft-versus-host disease, cytomegalovirus reactivation, and primary graft failure [25] (Appendix 4 in the ESM).

3.7 Effectiveness Measures

Apart from the QALY as the effectiveness measure in six studies [23–25, 27, 28, 35], other similar measures capturing both quality and length of life included disability-adjusted life-years (DALYs; one study) [30], healthy life-years (HLYs; one study) [31], and equal value of life-years gained (evLYG; one study) [27]. DALYs combine years of life lost due to early death and years lost due to disability. HLYs measure disability-free life expectancy. The metric of evLYG combines quality and length of life, as do QALYs, during the baseline survival period, adding gains in length of life (not considering quality of life during added life-years). Three studies used life-years gained (LYG) as the measure of effectiveness [27–29]. Three studies measured health events, such as stroke, death, and alloimmunization [26, 33, 34]. One antenatal screening study measured the number of women screened [32].

3.8 Cost-Effectiveness Results

The costs, effectiveness, and ICERs of each intervention versus its comparator can be found in Table 3. If the studies presented the total costs and effectiveness for the entire cohort, the costs and effectiveness were converted to per-person values (calculated as total costs or effectiveness divided by cohort size). The original numbers from the references can be found in Appendix 5 in the ESM.

3.8.1 Blood Transfusion

The ICER for blood transfusion for primary stroke prevention in one study was estimated to be £24,075 ($US37,316) per QALY gained versus no transfusion over a lifetime horizon (fiscal year 2010) [23]. The other study found that preoperative blood transfusion was less costly and more effective (dominant) than no transfusion over 1 year (fiscal year 2011) [24].

3.8.2 Transplantation

The study assessing alloHCT versus no alloHCT presented an "ICER" over 1 year post transplantation and another over a lifetime horizon [25]. However, the "ICER" presented was not calculated as incremental costs divided by incremental

Table 2 Summary of components of included cost-effectiveness analyses

Study	Study population	Mean age (years)	Intervention	Time horizon	Model type	Cost type	Effectiveness measure	Source of health utility	Discounting
Cherry et al. [23]	Children with SCD; no prior history of stroke	2	TCD scans followed by blood transfusion where the scan revealed a blood velocity of > 200 cm/s	Lifetime	Markov model	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	QALY	Empirically elicited for non-SCD-specific population; assumed by the authors without referencing empirical study	3.5%
Spackman et al. [24]	Patients with SCD undergoing low- or medium-risk surgery	17.3	Preoperative transfusion	1 year	NA	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	QALY	Empirically elicited from SCD population; assumed by the authors without referencing empirical study	Not discounted
Arnold et al. [25]	Children with SCD	Intervention: 9.10 (SD 6.25) Comparator: 4.23 (SD 3.74)	alloHCT	1 year; lifetime	Not a modeling study	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	QALY	Empirically elicited for SCD population; empirically elicited for non-SCD-specific population	Not discounted
Cunningham-Myrie et al. [26]	Children with SCD; first clinical stroke	NA	Hydroxyurea	Mean study duration: 3.82 years for intervention group; 4.47 years for control group	Not a modeling study	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	Stroke, death	Utilities not used	Not discounted
Bradt et al. [27]	Patients with SCD; baseline rate of three acute pain crises per year	24	Voxelotor, crizanlizumab, L-glutamine	Lifetime	Markov model	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention Costs within the informal health care sector: caregiver time costs Costs within the nonhealth-care sector: productivity; education	LY, QALY, evLYG	Empirically elicited for SCD population; empirically elicited for non-SCD-specific population; assumed by the authors without referencing empirical study	3%

Table 2 (continued)

Study	Study population	Mean age (years)	Intervention	Time horizon	Model type	Cost type	Effectiveness measure	Source of health utility	Discounting
Salcedo et al. [28]	Newborns with SCD	At birth	Hypothetical cell or genetic therapy	Lifetime	Markov model	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	LY, QALY	Empirically elicited for SCD-specific population; empirically elicited for non-SCD-specific population	3%
Castilla-Rodríguez et al. [29]	Newborns	At birth	Newborn screening program	10 years	Discrete-event simulation model	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	LY	Utilities not used	3%
Kuznik et al. [30]	Newborns	At birth	Newborn screening program	Lifetime	Markov model	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	DALY	Utilities not used	3%
McGann et al. [31]	Newborns	At birth	Newborn screening program	Lifetime	Life table	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	HLY	Utilities not used	3%
Bryan et al. [32]	Pregnant women (biological mothers); their partners (biological fathers)	NA	Primary care parallel; primary care sequential	Pregnancy to conclusion	NA	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	Woman screened	Utilities not used	Not discounted
Kacker et al. [33]	Patients with SCD undergoing chronic blood transfusion	Equivalent to mean age of the US population	Prospective antigen-matching; perfectly informed antigen-matching; imperfectly informed antigen-matching	10 years; 20 years	Markov model	Costs within the formal health-care sector: of the intervention; of consequences due to the intervention	Alloimmunization event	Utilities not used	3%

Table 2 (continued)

Study	Study population	Mean age (years)	Intervention	Time horizon	Model type	Cost type	Effectiveness measure	Source of health utility	Discounting
Kacker et al. [34]	Patients with SCD undergoing chronic blood transfusion	NA	Prospective limited matching; prospective extensive matching	10 years; 20 years	Markov model	Costs within the formal healthcare sector: of the intervention; of consequences due to the intervention	Alloimmunization event	Utilities not used	3%
McLeod et al. [35]	Patients with beta-thalassemia major or SCD	Stratified by age ranging from 2 to ≥ 18	Deferasirox	1 year	NA	Costs within the formal healthcare sector: of interventions	QALY	Empirically elicited for non-SCD-specific population; assumed by the authors without referencing empirical study	Not discounted

alloHCT allogeneic hematopoietic cell transplantation, *DALY* disability-adjusted life-year, *evLYG* equal value of life-year gain, *HLY* health life-year, *LY* life-year, *NA* not available, *QALY* quality-adjusted life-year, *SCD* sickle cell disease, *SD* standard deviation, *TCD* transcranial doppler ultrasound

effectiveness, as is standard for CEAs. This issue was also addressed in a letter to the editor by Thielen et al. [36]. The results of this study revealed that alloHCT was more costly than the comparator (median $US430,816 vs. 8245) and produced fewer QALYs (mean 0.78 vs. 0.91) over the post-alloHCT year (fiscal year not available). The lifetime cost and effectiveness values of the intervention and comparator were not available. The original "ICER" can be found in Appendix 5 in the ESM.

3.8.3 Pharmaceuticals

One study, conducted in Jamaica, estimated the ICER for hydroxyurea versus no hydroxyurea at J$169,238 ($US1917) per stroke averted and J$635,843 ($US7203) per death averted over an approximate 4-year mean follow-up (fiscal year 2009) [26]. Separately, the lifetime ICER of newer drugs (crizanlizumab, voxelotor, and L-glutamine) versus optimal usual care (e.g., hydroxyurea, blood transfusion) ranged from $US604,000 to 1,086,000 per QALY gained in the USA (fiscal year 2019), under the assumption that the treatment effects of those new therapies do not wane over time [27].

3.8.4 Hypothetical Cell or Genetic Therapy

One US-based study examined the cost-effectiveness of a hypothetical one-time administration cell or genetic therapy for newborns with SCD, relative to standard of care (including antibiotics, vaccinations, pain-relief medications, hydroxyurea, transfusions, and transplantation) [28]. In the base case, they assumed a lifetime durability of cure and a price of $US2,100,000 for the hypothetical therapy. The ICER was $US140,877 per QALY gained (fiscal year 2018) under these assumptions.

3.8.5 Screening

The effectiveness measure varied among the screening studies. The ICER for newborn screening versus no screening was €34,169 ($US45,445) per LYG in Spain over 10 years (fiscal year 2013) [29], $US213 per DALY averted in Sub-Saharan Africa (fiscal year 2014) [30], and $US2214–2824 per HLY gained in Angola over a lifetime horizon (fiscal year not available) [31]. The primary care parallel strategy (testing mother and father at the same time in primary care) and primary care sequential strategy (testing mother in primary care and subsequently the father if the mother is a carrier) led to an ICER of £25 ($US39) and £13 ($US20) per woman screened, respectively, compared with a midwife care strategy (sequential testing at the first midwife consultation) over 10 weeks in the UK (fiscal year 2010) [32].

Table 3 Results of the base-case scenario in included cost-effectiveness analyses of interventions for sickle cell disease

Study	Study population	Time horizon	Intervention vs. comparator	Currency (fiscal year); effectiveness measure	Costs (per person) of intervention vs. comparator[a]	Effectiveness (per person) of intervention vs. comparator[a]	ICER as reported by authors of original publication
Blood transfusion							
Cherry et al. [23]	Children with SCD; no prior history of stroke	Lifetime	Intervention: TCD scans followed by blood transfusion where the scan revealed a blood velocity of >200 cm/second. Comparator: TCD scans only	£ (2010); QALY	52,472 vs. 38,720	14.87 vs. 14.30	£24,075 ($US37,316) per QALY gained
Spackman et al. [24]	Patients with SCD undergoing low- or medium-risk surgery	1 year	Intervention: Preoperative transfusion. Comparator: No transfusion	£ (2011); QALY	1706 vs. 2442	0.71 vs. 0.70	Less costly, more effective
Transplantation							
Arnold et al. [25]	Children with SCD	1 year	Intervention: alloHCT. Comparator: Referred but without alloHCT	$US (NA); QALY	430,861 vs. 8245	0.78 vs. 0.91	More costly, less effective[b]
		Lifetime			NA	NA	NA[b]
Pharmaceuticals							
Cunningham-Myrie et al. [26]	Children with SCD who had a first clinical stroke	Mean study duration: 3.82 years for intervention group; 4.47 years for control group	Intervention: Hydroxyurea. Comparator: No hydroxyurea	J$ (2009); stroke	86,710 vs. 69,941	0.03 vs. 0.13	J$169,238 ($US1917) per stroke averted
				J$ (2009); death		0.00 vs. 0.00	J$635,843 ($US7203) per death averted

Table 3 (continued)

Study	Study population	Time horizon	Intervention vs. comparator	Currency (fiscal year); effectiveness measure	Costs (per person) of intervention vs. comparator[a]	Effectiveness (per person) of intervention vs. comparator[a]	ICER as reported by authors of original publication
Bradt et al. [27]	Patients with SCD; baseline rate of three acute pain crises per year	Lifetime	Intervention: L-glutamine Comparator: Optimal usual care alone	$US (2019); LY	1,414,000 vs. 1,174,000	15.35 vs. 14.34	$US238,000 per LY gained
				$US (2019); evLYG		8.96 vs. 8.07	$US270,000 per evLYG gained
				$US (2019); QALY		8.47 vs. 8.07	$US604,000 per QALY gained
			Intervention: Crizanlizumab Comparator: Optimal usual care alone	$US (2019); LY	2,046,000 vs. 1,174,000	16.36 vs. 14.34	$US432,000 per LY gained
				$US (2019); evLYG		9.78 vs. 8.07	$US509,000 per evLYG gained
				$US (2019); QALY		8.87 vs. 8.07	$US1,086,000 per QALY gained
			Intervention: Voxelotor Comparator: Optimal usual care alone	$US (2019); LY	2,291,000 vs. 1,174,000	16.37 vs. 14.34	$US550,000 per LY gained
				$US (2019); evLYG		9.96 vs. 8.07	$US589,000 per evLYG gained
				$US (2019); QALY		9.10 vs. 8.07	$US1,082,000 per QALY gained
Hypothetical cell or genetic therapy							
Salcedo et al. [28]	Newborns with SCD	Lifetime	Intervention: Hypothetical cell or genetic therapy Comparator: Standard of care	$US (2018); LY	2,372,482 vs. 1,175,566	29.9 vs. 26.2	NA[c]
				$US (2018); QALY		26.4 vs. 17.9	$US140,877 per QALY gained
Screening							
Castilla-Rodríguez et al. [29]	Newborns	10 years	Intervention: Newborn screening program Comparator: No screening	€ (2013); LY	5 vs. 6	8.66 vs. 8.66	€34,169 ($US45,445) per LY gained
Kuznik et al. [30]	Newborns	Lifetime	Intervention: Newborn screening and prophylactic intervention Comparator: No screening	$US (2014); DALY	16 vs. 0	NA[d]	$US213 per DALY averted
McGann et al. [31]	Newborns	Lifetime	Intervention: Newborn screening and treatment program for sickle cell anemia Comparator: No screening	$US (NA); HLY	44 vs. 0	NA[e]	$US2214–2824 per HLY gained

Table 3 (continued)

Study	Study population	Time horizon	Intervention vs. comparator	Currency (fiscal year); effectiveness measure	Costs (per person) of intervention vs. comparator[a]	Effectiveness (per person) of intervention vs. comparator[a]	ICER as reported by authors of original publication
Bryan et al. [32]	Pregnant women (biological mothers); their partners (biological fathers)	Pregnancy to conclusion	Intervention: Primary care sequential Comparator: Midwife care	£ (2010); woman screened	18 vs. 15	0.29 vs. 0.03	£13 ($US20) per woman screened
			Intervention: Primary care parallel Comparator: Midwife care		20 vs. 15	0.26 vs. 0.03	£25 ($US39) per woman screened
			Intervention: Primary care parallel Comparator: Primary care sequential		20 vs. 20	0.26 vs. 0.29	More costly, less effective
Intervention for SCD complications							
Kacker et al. [33]	Patients with SCD undergoing chronic blood transfusion	10 years	Intervention: Prospective antigen-matching Comparator: History-based antigen-matching	$US (2012); alloimmunization event	247,201 vs. 162,623	0.25 vs. 0.46	$US412,132 per alloimmunization event averted
			Intervention: Perfectly informed antigen-matching Comparator: History-based antigen-matching		164,866 vs. 162,623	0.25 vs. 0.46	$US10,934 per alloimmunization event averted
			Intervention: Imperfectly informed antigen-matching Comparator: History-based antigen-matching		164,556–185,700 vs. 162,623	0.25–0.31 vs. 0.46	$US12,558–147,915 per alloimmunization event averted
		20 years	Intervention: Prospective antigen-matching Comparator: History-based antigen-matching		433,064 vs. 287,313	0.41 vs. 0.60	$US759,799 per alloimmunization event averted
			Intervention: Perfectly informed antigen-matching Comparator: History-based antigen-matching		288,721 vs. 287,313	0.41 vs. 0.60	$US7344 per alloimmunization event averted
			Intervention: Imperfectly informed antigen-matching Comparator: History-based antigen-matching		288,619–325,057 vs. 287,313	0.41–0.46 vs. 0.60	$US9082–261,638 per alloimmunization event averted

Table 3 (continued)

Study	Study population	Time horizon	Intervention vs. comparator	Currency (fiscal year); effectiveness measure	Costs (per person) of intervention vs. comparator[a]	Effectiveness (per person) of intervention vs. comparator[a]	ICER as reported by authors of original publication
Kacker et al. [34]	Patients with SCD undergoing chronic blood transfusion; had been transfusion naive initially	10 years	Intervention: Prospective limited matching Comparator: History-based limited matching	$US (2012); alloimmunization event	456,376 vs. 236,978	0.08 vs. 0.36	$US369,479 per alloimmunization event averted
			Intervention: Prospective extensive matching Comparator: History-based extensive matching		286,025 vs. 195,959	1.06 vs. 1.30	$US769,344 per alloimmunization event averted
		20 years	Intervention: Prospective limited matching Comparator: History-based limited matching		502,938 vs. 344,544	1.86 vs. 2.10	$US640,814 per alloimmunization event averted
			Intervention: Prospective extensive matching Comparator: History-based extensive matching		799,565 vs. 15,649	0.13 vs. 0.41	$US1,364,247 per alloimmunization event averted
	Patients with SCD undergoing chronic blood transfusion; included patients with a prior history of transfusion and possible alloimmunization	10 years	Intervention: Prospective limited matching Comparator: History-based limited matching		169,720 vs. 127,562	0.64 vs. 0.81	$US252,708 per alloimmunization event averted
			Intervention: Prospective extensive matching Comparator: History-based extensive matching		271,488 vs. 162,016	0.04 vs. 0.25	$US541,939 per alloimmunization event averted
		20 years	Intervention: Prospective limited matching Comparator: History-based limited matching		271,272 vs. 201,192	1.05 vs. 1.25	$US355,630 per alloimmunization event averted
			Intervention: Prospective extensive matching Comparator: History-based extensive matching		433,806 vs. 254,993	0.07 vs. 0.30	$US775,069 per alloimmunization event averted

Table 3 (continued)

Study	Study population	Time horizon	Intervention vs. comparator	Currency (fiscal year); effectiveness measure	Costs (per person) of intervention vs. comparator[a]	Effectiveness (per person) of intervention vs. comparator[a]	ICER as reported by authors of original publication
McLeod et al. [35]	Patients with beta-thalassemia major or SCD, stratified by age ranging from 2 to ≥18 years	1 year	Intervention: Deferasirox Comparator: Deferoxamine/ desferrioxamine	£ (2007); QALY	4386–18,594 vs. 2733–7219	0.84 vs. 0.66	£9232 ($US18,464)–£63,195 ($US126,390) per QALY gained
			Intervention: Deferasirox Comparator: Deferiprone		4386–18,594 vs. 2194–5565	0.84 vs. 0.66	£12,224 ($US24,448)–£72,386 ($US144,772) per QALY gained

alloHCT allogeneic hematopoietic cell transplantation, *DALY* disability-adjusted life-year, *ESM* electronic supplementary material, *evLYG* equal value of life-year gain, *HLY* health life-year, *ICER* incremental cost-effectiveness ratio, *J$* Jamaican dollars, *LY* life-year, *NA* not available, *QALY* quality-adjusted life-year, *SCD* sickle cell disease, *TCD* transcranial doppler ultrasound

[a]The costs and effectiveness were converted to per person values if not reported. The original number from the references can be found in Appendix 5 in the ESM

[b]The ICER provided by Arnold et al. [25] was not calculated as incremental costs divided by incremental effectiveness. The original ICER can be found in Appendix 5 in the ESM

[c]Salcedo et al. [28] provided the ICER measured as costs per QALY gained but did not provide the ICER measured as costs per LY gained

[d]Kuznik et al. [30] provided the DALYs averted but did not provide the mean DALYs for intervention and for comparator

[e]McGann et al. [31] provided the HLYs gained but did not provide the mean HLYs for intervention and for comparator

3.8.6 Interventions for Treatment Complications

The ICER for a prospective antigen-matching strategy versus history-based antigen-matching strategy to prevent alloimmunization following transfusion ranged from $US10,934 to 769,344 per alloimmunization event averted over 10 years and from $US9,082 to 1,364,247 per alloimmunization event averted over 20 years in the USA (fiscal year 2012) [33, 34]. The ICER for deferasirox, the drug used to treat iron overload, ranged from £9232 ($US18,464) to £63,195 ($US126,390) per QALY gained versus deferoxamine/desferrioxamine. When compared with deferiprone, the ICER for deferasirox ranged from £12,224 ($US24,448) to £72,386 ($US144,772) per QALY gained over 1 year in the UK (fiscal year 2007) [35].

3.9 Critical Appraisal

Appendix 3 in the ESM presents the results of the critical appraisal of each CEA. In general, most of the items in the reporting guideline were followed. Nonetheless, several studies did not explicitly present or correctly calculate the incremental costs and effectiveness [25, 30, 31], did not report the uncertainties [25, 26], and did not report the heterogeneity of cost-effectiveness between subgroups with different characteristics [26, 32].

4 Discussion

Few CEAs of SCD treatments have been published to date, and existing studies have been limited in scope. There are some similarities across the 13 studies that met our inclusion criteria. For example, the studies adopted the perspective of the healthcare system, and most included only costs within the formal healthcare sector. However, our results revealed that published CEAs in SCD are quite heterogeneous in terms of geographic setting, intervention type, SCD and treatment complications included, choice of model and time horizon, and effectiveness measures used. As a consequence, cost-effectiveness findings are inconsistent across studies.

Our rapid review found that most studies were limited to a very narrow subset of disease complications and treatments. Admittedly, modeling such a complex disease, with so many complications occurring over the lifetime horizon, is challenging. Estimates of necessary model input parameters require data sources that include information about the trajectory of the disease burden, treatments, and treatment complications; these data sources are few in SCD. Nevertheless, models need to incorporate these elements, as many of the complications have significant implications for survival, quality of life, and economic costs. Unfortunately, real-world datasets necessary to quantify SCD incidence, costs, and

outcomes are limited. There are no large comprehensive national registries, and extraction from electronic medical records and claims data is fraught with complications, such as inaccurate or inconsistent coding, limited clinical information, and incomplete record of care received [37]. Nonetheless, the estimates may be derived from the existing large cohort studies [38–40]. In addition to needing higher-quality databases, eliciting input from stakeholders, especially patients, on their perceptions about which of the complications are most troubling, is critical in guiding model development.

Over the past 30 years, efforts to bring increased rigor to, and standardize the methodological practices and improve the comparability and quality of, CEAs have been ongoing. Transparent and complete reporting of methods and findings remains critical to the CEAs in SCD, as we note that several included studies did not explicitly present or correctly calculate the incremental costs and effectiveness and did not report the uncertainties or heterogeneity of the findings. The CHEERS statement can be a reliable tool to enhance the quality of reporting in future studies [22]. In 2016, the Second Panel on Cost-Effectiveness in Health and Medicine (hereafter 'Second Panel') also provided guidance for future studies, which has been widely referenced since then [41]. The panel recommend that all studies report reference case analyses from a healthcare sector perspective and a societal perspective. The societal reference case analysis should consider all parties affected by the medical interventions and include all significant outcomes and costs (i.e. those in formal and informal healthcare sectors as well as nonhealthcare sectors). They also recommend that health effects should be measured in terms of QALYs in the reference case analysis. Moreover, they recommended that the time horizon should be long enough to capture all relevant outcomes.

While the healthcare costs attributable to SCD are substantial, the nonhealthcare costs are likely substantial as well, placing high burdens on patients and families. Those costs can arise from but are not limited to the impact of SCD on work productivity, education, household activities, and caregiver's time use [42–45]. Neglecting those costs may substantially underestimate the economic value of SCD interventions. Our review found that only one study adopted a modified societal perspective in a scenario analysis, incorporating a portion but not all of the costs that may be incurred outside the healthcare system [27]. This study has shown that including such costs would substantially decrease the ICER estimates [27]. Consistent with the Second Panel's recommendation, we recommend that future CEAs in SCD adopt a societal perspective, explicitly incorporating the costs outside the formal healthcare sectors.

Preventing SCD complications can not only lower the risk of death but also promote improved quality of life [2–4]. Hence, we recommend that both of these effects should be captured in CEAs using outcome measures such as QALYs. We found that only eight studies used QALYs or similar measures. One possible explanation for this gap might be that health utility data in the SCD population are sparse. Most of the studies relied on utility values for non-SCD-specific populations (to inform the utility decrement due to complications) or based on assumptions. Additionally, in the absence of QALYs or DALYs as outcome measures, it is difficult to draw a conclusion about whether the intervention is cost-effective, as most established willingness-to-pay thresholds are based on QALYs gained or DALYs averted, both metrics that can be compared across disease states [46].

Since SCD interventions are likely to have long-term health and economic impacts, using a lifetime horizon is recommended for future CEA in SCD. This is also in line with the Second Panel's recommendation. Another important aspect of the natural history of SCD is that the rate and spectrum of complications varies throughout the patient's lifespan [47]. Further, patients receive different types of medical care across the life stages (e.g. pediatric care vs. adult care, primary care vs. specialty care) [48]. To reflect the long-term and time-varying features of SCD, a simulation model (e.g. state-transition, microsimulation, or discrete-event model) with a lifetime horizon would be beneficial for valuing the emerging treatments.

Admittedly, the CEAs conducted to date in the context of SCD provide limited information. These analyses do not typically incorporate the value of a treatment in reducing inequity in resources and expenditures for patients with SCD [49]. Some argue that research funding and pharmaceutical investment for a rare disease such as SCD are not commensurate with funding and investment for more prevalent diseases [50]. Inequity is also reflected in the lack of access to necessary healthcare among underserved populations, such as patients with SCD. To incorporate the equity issue in economic evaluations, future studies will likely employ innovative, emerging methods, such as distributional CEA [51]. Additionally, it is clear that treatment approaches for SCD continue to evolve, and both newly approved therapeutics and those under investigation appear promising [52–54]. A single CEA has limited ability to reflect this dynamic treatment landscape. CEAs could be updated to reflect changes in treatment modalities.

We provide recommendations to increase the rigor and comparability of future CEAs in SCD. However, global heterogeneity should be addressed. Our review identified the existing CEAs conducted globally; these countries have various SCD burdens, financial resources, healthcare systems, and preferences for types of SCD interventions [55–57]. Thus, the model inputs should be customized to the local population using country-specific information for input parameters. Additionally, our study revealed the issue of global inequity in terms of CEA research. Although the

prevalence and incidence of SCD is substantially higher in Africa and Latin America than in North America and Europe [55], the former regions produced a much lower volume of CEA studies than the latter. The studies conducted in North America and Europe might shed light on the value of SCD interventions for the other regions, yet the relative ranking of the cost-effectiveness of SCD interventions possibly differs across the regions. For example, a screening program is likely to be more cost-effective in a region with a higher incidence and prevalence of SCD. To better inform healthcare resource allocation decisions in countries with high SCD burden and poverty rates, it is imperative to provide them with more research resources.

Finally, we found that the ICER estimates were inconsistent across studies. This might be due to not only the properties of interventions assessed but also the study designs (e.g., short term vs. long term) and global heterogeneity. Of note, the study by Bradt et al. [27] was part of the assessment of the Institute of Economic and Clinical Review in the USA, revealing that the ICERs of those newly approved SCD therapies ranged from approximately $US600,000 to 1 million per QALY gained. Although high, these estimates were lower than those for therapies for some other rare diseases. For instance, other assessments from the Institute for Clinical and Economic Review suggested that the ICERs for lanadelumab and the C1 esterase inhibitors for hereditary angioedema ranged from approximately $US1 million to 6 million per QALY gained [58], and ICERs for modulator treatments for cystic fibrosis were over $US1 million per QALY gained [59]. Caution is needed in drawing conclusions from these "high" ICERs about whether the treatments are cost-effective, since there is a general recognition that a higher value-based price can be justified for rare diseases that have a catastrophic impact on health [60].

Considering the uncertainties in modeling the cost-effectiveness of SCD, making comparisons across existing studies can inform the accuracy and validity of results. Although limited in their scope, the estimates we summarized in this review may be a useful resource against which to compare the results of future CEAs. Specifically, if a future CEA compares a genetic therapy against a conventional treatment found in this review, the projected costs and effectiveness of the conventional treatment in that new study can be compared with the estimates for that same treatment summarized in this review. Of course, researchers must use caution when making these comparisons because, as seen here, studies vary widely in many ways.

Our review is subject to several limitations. First, only English articles were included in our review. Second, we included only peer-reviewed journal articles published since 2008 and white papers published since 2018. However, a previous study suggested that decision analytic studies were rarely published prior to 2009 [61]. Finally, a quantitative synthesis (meta-analysis) of the ICER estimates was not feasible because of the large degree of heterogeneity among the studies.

5 Conclusion

Our review provides direction for future research. Published CEAs of SCD are not comprehensive yet may serve as a basis for comparisons with more robust CEAs conducted in the future. Specially, future studies should adopt a societal perspective, examine effects of interventions on both quality and length of life, and use an advanced simulation model design to capture a wide range of SCD complications and treatment complications over patients' lifetimes. These modeling strategies will be essential to accurately value emerging genetic therapies and other novel agents under investigation.

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