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SYSTEMATIC REVIEW

Health Economic Evaluations of Hemochromatosis Screening and Treatment: A Systematic Review

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Abstract

Background Hereditary hemochromatosis (HH) is an autosomal recessive disorder that leads to iron overload and multiorgan failure.

Objectives The aim of this systematic review was to provide up-to-date evidence of all the current data on the costs and cost effectiveness of screening and treatment for HH.

Methods We searched PubMed, Cochrane Library, National Health Service Economic Evaluation Database (NHSEED), Cost-Effectiveness Analysis Registry (CEA Registry), Health Technology Assessment Database (HTAD), Centre for Reviews and Dissemination (CRD), and Econlit until April 2023 with no date restrictions. Articles that reported cost-utility, cost-description, cost-minimization, cost-effectiveness, or cost-benefit analyses for any kind of management (drugs, screening, etc.) were included in the study. Patients with HH, their siblings, or individuals suspected of having HH were included in the study. All screening and treatment strategies were included. Two authors assessed the quality of evidence related to screening (either phenotype or genotype screening) and treatment (phlebotomy and electrophoresis). Narrative synthesis was used to analyse the similarities and differences between the respective studies.

Results Thirty-nine papers were included in this study. The majority of the studies reported both the cost of phenotype screening, including transferrin saturation (TS), serum ferritin, and liver biopsy, and the cost of genotype screening (HFE screening, C282Y mutation). Few studies reported the cost for phlebotomy and erythrocytapheresis treatment. Data revealed that either phenotype or genotype screening were cost effective compared with no screening. Treatment studies concluded that erythrocytapheresis might be a cost-effective therapy compared with phlebotomy.

Conclusions Economic studies on either the screening, or treatment strategy for HH patients should be performed in more countries. We suggest that cost-effectiveness studies on the role of deferasirox in HH should be carried out as an alternative therapy to phlebotomy.

1 Introduction

Hereditary hemochromatosis (HH) is a genetic disease mainly affecting Caucasian populations, characterized by iron overload as a result of excessive iron intestinal absorption in the duodenum [1]. The disease was named by von Recklinghausen in 1889 due to the pigment that he thought was of blood origin [2]. The prevalence of HH is 1 in 300–500 individuals [3].

Mutation of the hemochromatosis gene (HFE: C282Y [main mutation], S65C, H63D) is the most common cause of HH [4] that contributes to iron overload in heart, liver, pancreas, and other organs, leading to multiorgan failure. Mutations of transferrin receptor 2, ferroportin protein, or hepcidin antimicrobial peptide (HAMP) are other causes of HH, whereas arrhythmias, diabetes mellitus, arthralgia, impotence, hypermelanotic pigmentation of the skin, cirrhosis of the liver, lethargy, cardiomyopathy, arthritis, and pancreatic disease are some of the complications of HH. Hepatocellular carcinoma is also another result of irreversible damage caused by HH [5, 6]. Men can develop more severe symptoms than women [7].

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Key Points for Decision Makers

Screening of blood donors for hereditary hemochromatosis (HH) can decrease third-party payer health care costs in the long-term.

Population screening programs for HH are cost effective compared with no screening.

Pharmacoeconomic studies for the screening and treatment of HH patients should be performed in more countries.

Since the discovery of HFE gene in 1996, DNA analysis was introduced as a diagnostic strategy for HH; however, different studies revealed that HH is often a neglected or missed diagnosis [8, 9]. The symptoms of the disease become apparent in women later than in men because of iron excretion associated with menstruation, and early detection can improve life expectancy and prevent complications [3].

Serum transferrin saturation (TS), serum ferritin, and unsaturated iron-binding capacity (UIBC) are some of the biochemical tests used for diagnosis and that are further confirmed with HFE genotyping. Studies have reported that TS is increased by 10 years of age [10].

Genetic screening has a relatively low cost [11]. Liver biopsy can be performed to assess the liver damage in severe cases. Screening for HH can contribute to the early detection of patients who are homozygous for the HFE gene, and hence can reduce their risk for severe irreversible diseases [12].

HH treatment is focused on iron excretion. Transferrin saturation screening can be used as an early indicator of the disease, and for the initiation of phlebotomy [13]. Ferritin levels are an indicator for the initiation and frequency of phlebotomies and are used to prevent complications. Therapeutic phlebotomy aims to reduce serum iron indices and iron overload [14]. Removing the excess iron before severe tissue damage significantly increases the survival rate.

Much research has been conducted in relation to HH but only a few recent pharmacoeconomic studies have been carried out. The aim of this review was to summarize and provide up-to-date evidence of all the current data on the costs and cost-effectiveness of screening and treatment for HH. These data can help policy makers to evaluate the cost effectiveness of HH screening and treatment.

2 Methods

2.1 Literature Search and Presentation of the Full Search Strategies for All Databases

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify economic studies on hemochromatosis [15]. A protocol was not prepared and this review was not registered.

We searched the following databases: PubMed, Cochrane Library, National Health Service Economic Evaluation Database (NHSEED), Cost-Effectiveness Analysis Registry (CEA Registry), Health Technology Assessment Database (HTAD), Centre for Reviews and Dissemination (CRD), and Econlit between inception and April 2023, with no date restrictions. For each database, we used the following keywords ('hemochromatosis') and ('economic evaluation' OR 'cost-effectiveness analysis', OR 'cost analysis', OR 'cost benefit', OR 'cost utility', OR 'direct cost', OR 'indirect cost', OR 'health economic').

2.2 Study Design

Articles carried out in any country were included in the study if they contained cost-utility, cost-minimization, cost-description, cost-effectiveness, or cost-benefit analyses for any type of management (drugs, screening, etc.) or intervention. We excluded abstracts, conference papers, reviews, systematic reviews, posters, protocols, and letters to the editors. Two of the reviewers (MH, BZ) independently screened all articles and agreement was reached by consensus. Only articles published in English were included in this systematic review.

2.3 Eligibility

Original articles on hemochromatosis were considered eligible if they reported a full or partial economic estimation comparing intervention(s) and comparator(s) in outcomes and costs. As defined by Drummond et al. [16], a partial economic evaluation study reports the cost examination and/or consequences of one or more interventions, while a full economic evaluation study reports a comparison of either costs or consequences of two or more interventions [16].

All articles that described hemochromatosis as the main outcome with no interventions for treatment or screening were excluded. Studies that did not report health economic data were excluded.

2.3.1 Population

Our population included patients with HH, their siblings, or individuals suspected of having HH. Studies using hypothetical populations in decision models were also included.

2.3.2 Intervention

The interventions were kept broad, and all screening and treatment strategies were included.

2.3.3 Comparators

Sequential screening (phenotype and genotype screening) and therapy (phlebotomy, erythrocytapheresis) were used as interventions/comparators. A no-screening strategy was also used as a comparator.

2.4 Data Extraction

The data extracted from each study included author names, year of publication, country, target group, sample size, time frame, study type, duration, discount rate, comparators, intervention, and outcomes, etc. Two authors collected the data. Incremental cost-effectiveness ratios (ICERs) were extracted from all studies reporting the cost effectiveness of drugs.

2.5 Synthesis (Methods)

Narrative synthesis was used to assess the similarities and differences between the respective studies. Due to the heterogeneity of the studies, we classified them into either screening or treatment studies. The screening strategies studies were synthesized into two different tables—CEA or non-CEA studies. The information recovered from the studies was synthesized in different columns in the respective tables to make it easier for readers to view the similarities and compare the data. Discrepancies were double-checked and discussed between MH and BZ.

2.6 Effect Measures

Health economic metrics such as ICER and quality-adjusted life-years (QALYs) were reported for the CEA studies. In addition, we reported all cost values in the original currency, as well as in current (Euros [€]) currency (year 2023).

2.7 Outcomes

The mean cost and cost effectiveness of phlebotomy and erythrocytapheresis are reported as the main outcomes in the economic studies on the treatment strategies included in this review. Moreover, the phenotype versus genotype screening costs are also reported as the main outcomes in the economic studies on the screening strategies included in this article.

2.8 Risk-of-Bias Assessment and Quality Assessment

Two reviewers independently selected the studies and assessed the respective interventions and outcomes of the studies—either the reported outcomes, or the missing outcomes. Agreement was reached by consensus. The sample size may have introduced bias in different studies, estimating the cost to the population level.

The British Medical Journal (BMJ) checklist [17] was used to assess the quality of the economic studies included in this current study. The BMJ checklist is made up of 35 items, each of which require a 'yes', 'no', or 'not applicable' answer, which were each given a score of '1' when the task was carried out and '0' when the task was not executed. The total scores were converted and reported in percentages.

We assessed the certainty of evidence as high, moderate, or low quality. High-quality studies were considered as those with a total percentage of 75% from the BMJ checklist, moderate-quality studies as those with 50–75%, and low-quality studies as those with a total percentage of <50% from the BMJ checklist [18]. The relevant information is reported in Tables 1, 2, and 3 in the Results section.

2.9 Reporting Bias Assessment

Multiple databases with no date restrictions were used to recover the data. MH and BZ double-checked the papers to avoid potential duplication. Tables were used to report and compare the BMJ checklist, and the outcomes for each eligible study were included in this review.

3 Results

3.1 Overview of Selected Studies

As shown in Fig. 1, we identified 590 articles, of which 252 were duplicates and were hence removed. Fifty-five articles were excluded based on title and abstract screening. Other

Table 1 All cost-effectiveness analysis reporting the screening strategy included in this review

No.	References	Country/ currency/ perspective	Study Type	BMJ check-list score	Population	Duration/ discount rate (Cost)	Interven-tion	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
1	Adams et al. [19], 1995	Canada/ CAN$/ Third-party payer	Decision tree model; CUA; CEA	91%	Hypothetical cohort of blood donors (10,000) and siblings	lifetime/3%	Phenotype screening strategy (sequential testing of UIBC, TS, SF, and hepatic iron index)	No screening	The cost utility ratio: $4082 per QALY $312,456 (NPV) for non screening versus $307,567 (NPV) for screening donors and siblings	1. Screening of blood donors: Incremental cost savings of $3.19/ blood donor 2. Screening of homozygous siblings: incremental cost savings of $12.57/ person screened	1. Screening of blood donors: 0.84 QALY 2. Screening of asymptomatic homozygous siblings: 1.18 QALY	The cost utility ratio: $7,056.71 per QALY $540,154.47 (net present value-NPV) for non screening versus $531,702.67 (NPV) for screening donors and siblings **ICER**: 1. Screening of blood donors: Incremental cost savings of $5.51/ blood donor 2. Screening of homozygous siblings: Incremental cost savings of $21.73 person screened **QALY**: Cost-utility ratio: $5,274.38/ QALY	The cost utility ratio: €4,841.82 per QALY €370,616.19 (net present value-NPV) for non screening versus €364,817.15 (NPV) for screening donors and siblings **ICER**: 1. Screening of blood donors: Incremental cost savings of €3.78/ blood donor 2. Screening of homozygous siblings: Incremental cost savings of €14.91 person screened **QALY**: Cost-utility ratio: €3,618.91/ QALY

Table 1 (continued)

No.	References	Country/ currency/ perspective	Study Type	BMJ check-list score	Population	Duration/ discount rate (Cost)	Interven-tion	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
2	Rogowski [22], 2009	Germany/€/ Third-party payer	CEA, Markov model, proba-bilistic decisio-nanalytic model	97%	Male Cau-casians aged 30	Lifetime/3%	Strategy 1: no screening Strategy 2: screening by 2 inde-pendent TS tests Strategy 3: sequen-tial TS and HFE screen-ing on the same blood sample Strategy 4: Genotype screen-ing HFE (C282Y homozy-gosity) mutation screening	Strategy 1: no screening Strategy 2: screening by 2 independ-ent TS tests Strategy 3: sequential TS and HFE screening Strategy 4: Genotype screen-ing HFE (C282Y homozy-gosity) mutation screening	ICER (€/LYG)/ Strategy 1: no screening 3c: male cascade TS+HFE screening €41,425 3p: male population TS+HFE screening €123,996 4p: male popu-lation HFE screening €161248	DNA test (primary screening test): has a higher ICER (161 000 €/LYG) in comparison to sequential TS/HFE screening (124 000 €/ LYG)	N.R.	**ICER**: (€/LYG)/ Strategy 1: no screening 3c: male cascade TS+HFE screen-ing €54,144.32 3p: male popula-tion TS+HFE screening €162,068.30 4p: male popula-tion HFE screen-ing €210,758.32 **ICER**: DNA test (primary screen-ing test): has a higher ICER (210,434.18 €/ LYG) in compari-son to sequential TS/HFE screen-ing (162,073.53€/ LYG)	**ICER**: (€/LYG)/ Strategy 1: no screening 3c: male cascade TS+HFE screen-ing €54,144.32 3p: male popula-tion TS+HFE screening €162,068.30 4p: male popula-tion HFE screen-ing €210,758.32 **ICER**: DNA test (primary screen-ing test): has a higher ICER (210,434.18 €/LYG) in comparison to sequential TS/ HFE screening (162,073.53€/ LYG)
3	Gagné et al. [23], 2007	Canada/ CAN$/ Health system	CEA, Computer stimu-lation model, Decision tree	94%	Quebec popula-tion	Lifetime/ N.R.	Phenotype screening	Genotype screening	The cost of phenotype screening is 121 CAN $ for UIBC1 TS4 versus no screening (143 CAN$)	N.R.	N.R.	The cost of phe-notype screening is 164.32 CAN $ for UIBC1 TS4 versus no screening (194.20 CAN$)	The cost of phe-notype screening is €112.74 for UIBC1 TS4 ver-sus no screening (133.25 €)

Table 1 (continued)

No.	References	Country/currency/perspective	Study Type	BMJ check-list score	Population	Duration/discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/QALD	Cost values in original currency	Cost values in current (EUR) currency
4	Buffone and Beck [24], 1994	USA/$/Societal	CEA, Markov model	66%	Men ≥ 25 years old with no history of alcoholism and no pre-existing conditions that would predispose to iron loading	Lifetime/N.R.	Phenotype screen (TS, SF, liver biopsy) and treatment (phlebotomy)	No screening	Testing, early detection, and treatment are only slightly more costly than waiting to treat at onset of symptoms; on average, $605 per life-year gained	Marginal cost/marginal effect, $/LYr gained=605	N.R.	Testing, early detection, and treatment are only slightly more costly than waiting to treat at onset of symptoms; on average, $1,245.55 per life-year gained **ICER**: Marginal cost/marginal effect, $/LYr gained=1,245.55	Testing, early detection, and treatment are only slightly more costly than waiting to treat at onset of symptoms; on average, €1151.69 per life-year gained **ICER**: Marginal cost/marginal effect, €/LYr gained=1151.69
5	El-Serag et al. [25], 2000	USA/$/Societal	CEA, Decision tree	63%	Children of 10 years of age or 45 years of age (siblings)	lifetime/3%	Four screening strategies phenotype (serum iron studies), and genotype screening	No screening	ICER (screening of one child): $508 per life-year saved ICER (screening two or more children): $3665 per life-year saved	ICER = $508 per life-year saved for screening 1 child versus ICER = $3665 per life-year saved for screening 2 or more children	N.R.	ICER (screening of one child): $900.09 per life-year saved ICER (screening two or more children): $6493.75 per life-year saved **ICER**: ICER = $900.09 per life-year saved for screening 1 child versus ICER = $6493.75 per life-year saved for screening 2 or more children	ICER (screening of one child): €832.2 per life-year saved ICER (screening two or more children): €6004.39 per life-year saved **ICER**: ICER = €832.26 per life-year saved for screening 1 child versus ICER= €6004.39 per life-year saved for screening 2 or more children

Table 1 (continued)

No.	References	Country/ currency/ perspective	Study Type	BMJ check-list score	Population	Duration/ discount rate (Cost)	Interven-tion	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
6	Balan et al. [37], 1994	USA/US$/ Service Provider	CEA	20%	12,258 consecu-tive blood samples from Mayo Clinic patients having diagnostic laboratory studies	For a period of 12 con-secutive week days in October 1990/N.R.	Phenotype screening (TS, SF)	No screening	$33,787 (total cost) $8447 (cost/case detected if based on ascertainment of four cases with HH) $563 (cost/ case detected if based on ascertainment of six cases with HH)	The incremen-tal cost of $1.50/speci-men may be added to other chem-istry tests if the serum iron test is used as a preliminary screening test	N.R.	$69,559.50(total cost) $17,390.39 (cost/case detected if based on ascertainment of four cases with HH) $1159.08 (cost/case detected if based on ascertainment of six cases with HH) **ICER**: The incre-mental cost of $3.09/specimen may be added to other chemistry tests if the serum iron test is used as a preliminary screening test	€64,317.57 (total cost) €16,079.87 (cost/case detected if based on ascertain-ment of four cases with HH) €1071.73 (cost/ case detected if based on ascer-tainment of six cases with HH) **ICER**: The incre-mental cost of €2.86/specimen may be added to other chemistry tests if the serum iron test is used as a preliminary
7	Bassett et al. [26], 1997	Australia/$/ Govern-ment	Decision Tree, CEA	68%	Hypotheti-cal popu-lation	life-time/< 3%	Phenotype screening and liver biopsy versus phe-notype screen-ing, liver biopsy and cascade versus phe-notype screen-ing and genotype screening	Phenotype screening and liver biopsy versus phenotype screening, liver biopsy and cascade versus phenotype screen-ing and genotype screening	Screening by liver biopsy: US$5079 -US%8813/ HH case detected. Screen-ing with DNA test: US$3954-US$4410/HH case detected	US$960	N.R.	Screening by liver biopsy: US$10,339.30-US$17,940.58/ HH case detected. Screening with DNA test: US$8049.14-US$8977.42/HH case detected **ICER**: US$1954.27	Screening by liver biopsy: €6464.54-€11,217.17/HH case detected. Screening with DNA test: €5032.64-€5613.04/HH case detected **ICER**: €1221.89

Table 1 (continued)

No.	References	Country/currency/perspective	Study Type	BMJ check-list score	Population	Duration/discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/QALD	Cost values in original currency	Cost values in current (EUR) currency
8	de Graaff et al. [27], 2017	Australia/AUD$/Government	CEA, Markov Model	97%	30-year-old males and 45-year-old females, of northern European ancestry	Lifetime/0 and 7%	Genotypic screening	Phenotypic screening (TS)	Genotyping (blood) was the most cost-effective approach, with an ICER of AUD1810/QALY gained, followed by TfS screening (AUD4225/QALY gained), and genotyping (buccal) (AUD15,371/QALY gained)	The incremental costs for: genotyping (blood): 56 Australian Dollar (AUD) TfS: 45 AUD genotyping (buccal): 56 AUD, having an ICERs of AUD1673, 4103 and 15,233/QALY gained, respectively	Effectiveness of the TfS strategy: 0.002 QALY	Genotyping (blood) was the most cost-effective approach, with an ICER of AUD2216.73/QALY gained, followed by TfS screening (AUD5419.35/QALY gained), and genotyping (buccal) (AUD18,825.05/QALY gained) **ICER**: The incremental costs for: Genotyping (blood): 68.58 Australian Dollar (AUD) TfS: 55.11 AUD Genotyping (buccal): 68.58 AUD, having an ICERs of AUD2048.94, 5024.99, and 18,656.04/QALY gained, respectively	Genotyping (blood) was the most cost-effective approach, with an ICER of €1385.99/QALY gained, followed by TfS screening (€3388.39/QALY gained), and genotyping (buccal) (€11,770.17/QALY gained) **ICER**: The incremental costs for: Genotyping (blood): 42.88 € TfS: 34.46 €Genotyping (buccal): 42.88 €,having an ICERs of €1281.08, 3141.82, and 11,664.50/QALY gained, respectively
9	Schoffski et al. [31], 2000	Germany/€/third-party payer	Decision Tree, CEA	71%	Cohort of men aged 25	Lifetime/5%	Genotype screening	No screening	7.26 €/person versus 1.62 €/non tested person. The cost for one life year: 4441 €	N.R.	The costs of HH screening per life year gained: 4441 euro	11.47€/person versus 2.56 €/non tested person. The cost for one life year: 7017.90 €	11.47€/person versus 2.56 €/non tested person. The cost for one life year: 7017.90 €

Table 1 (continued)

No.	References	Country/ currency/ perspective	Study Type	BMJ check-list score	Population	Duration/ discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
10	Smith et al. [49], 1997	USA/US$/ third-party payer	CEA	66%	Workplace (8087 employees of the Polaroid Corporation)	1987–1993/ N.R.	Phenotype screening (TS, liver biopsy)	No screening	$39.32/ employee screened versus no screening $18,041/ program; $90,205 for the total study population	UIBC was a cost-effective screening with an incremental cost of $3.19/each donor	N.R.	$74.75/employee screened versus no screening $34,295.77/ program; $171,478.86 for the total study population **ICER**: UIBC was a cost-effective screening with an incremental cost of $6.06/each donor	€69.12/employee screened versus no screening €31,711.28/ program; €158,556.38 for the total study population **ICER**: UIBC was a cost-effective screening with an incremental cost of €5.60/ each donor

CAN$ Canadian dollar, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *ICER* incremental cost-effectiveness ratio, *QALD* quality-adjusted life-year, *QALY* quality-adjusted life-year, *TS* transferrin saturation, *SF* serum ferritin, *UIBC* unsaturated iron-binding capacity, *US$* United States dollar, *AUS$* Australian dollars, *€* Euros, *N.R.* not reported, *NPV* negative predictive value, *LYG* life-year gained, *BMJ* British Medical Journal

studies that did not fulfil the eligibility criteria, i.e. review articles, systematic reviews, abstracts, poster presentations, and studies not reporting full or partial economic evaluation of HH, were also excluded ($n = 244$). Of 590 identified records, 39 were selected for inclusion in our systematic review.

A summary of the study characteristics of all the articles included in this current study is reported in Tables 1, 2, and 3. The studies were variable and the study design included population, intervention, comparator, intervention duration, outcomes, perspectives, and ICER; the QALYs were heterogeneous.

Thirty-three percent of the studies evaluated the modeled screening programs over a lifetime [19–31]. Six studies were conducted in Canada [7, 19–21, 23, 35], 13 in the US [24, 25, 30, 34, 37, 39, 40, 45, 48, 49, 52, 53, 55], 3 in Germany [22, 31, 47], 2 in Norway [32, 33], 3 in The Netherlands [29, 50, 51], 4 in the UK [28, 36, 38, 41], 6 in Australia [26, 27, 42–44, 46], 1 in Switzerland [54], and 1 in Italy [56]. The timeline of publications was from 1992 to 2020, and the currency evaluated was €, Canadian dollars (CAN$), US dollars (US$), Australian dollars (AUS$), and Great Britain pounds (£). Other than the original cost values in the original currency (outcome, ICER), we also added two additional columns reporting all the current cost values in the original currency, as well as the cost values in the current currency (€). Taking into consideration the heterogeneity of all the economic published data, we expressed the cost data in the same year using the standard inflator for the country on which the analysis is focused. The average daily exchange rates for the period from 1 January 2023 to 30 June 2023 were taken into consideration when calculating the cost values in the current (€) currency.

The majority of the studies reported both phenotype screening, including TS, serum ferritin, and liver biopsy, and genotype screening (HFE screening, C282Y mutation) [7, 20–23, 25–27, 29, 30, 32, 35, 36, 38, 42]. A few studies reported on phlebotomy and erythrocytapheresis treatment [50–56].

Of the 39 papers accepted, most studies used a cost-effectiveness analysis ($n = 20$) [7, 19, 21–27, 29, 31, 32, 34, 36–38, 41, 48, 49]; 23.1% of studies used a decision tree ($n = 9$) [17, 18, 21, 24, 25, 30, 35, 37, 40]. There were eight non-experimental screened studies that included a cost description [28, 30, 42, 43, 45, 47, 52, 53]. Four studies employed a cost-utility analysis [19, 20, 33, 44], and a Markov model was applied in four studies [22, 24, 27, 33].

Overall, 12.8% of studies reported an annual discount rate of 3%, while other studies reported a discount rate of 5% [31] or 0–7% [27]. No discounting of costs was reported in 80.5% of screening studies [7, 21, 28–30, 32–56].

Table 2 An overview of all the economic studies, other than CEA studies, on the screening strategies included in this review

No.	References	Country/ currency/ perspective	Study type	BMJ checklist score	Population	Duration/ discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
1	Asberg et al. [33], 2002	Norway/ US$/ Third-party payer	CUA, Markov Model	75%	Cohort of 1000 men (30 years old)	1 year/N.R.	Phenotype screening (TS)	No screening	The screening cost was $250 per QALY gained	N.R.	Phenotype screening: 7.65 QALY	Screening cost: $424.00 per QALY gained	Screening cost: €392.05per QALY gained
2	Adams and Kertesz [35], 1992	Canada/ US$/ Third-party payer	CA	57%	105 siblings (median age 55 years old) of 35 proband cases of HH	5 year follow up/N.R.	Phenotype screen (TS, iron overload)	Genetic screen (HLA typing)	Total cost: $1800–$2100/screening of a family with four members	N.R.	N.R.	Total cost: $3243.24-$3783.77/ screening of a family with four members	Total cost: €2225.28 -€2596.16/ screening of a family with four members
3	Montanez et al. [39], 2020	USA/US$/ Health System	CA	63%	Patients with HH from contracted clinical laboratory	October–December 2015/N.R.	Genotype screening (ordered test)	Recommended testing	Testing for HH cost: $357 versus $143 cost of recommended testing	N.R.	N.R.	Testing for HH cost: $420.86 versus $168.58 cost of recommended testing	Testing for HH cost: €389.14 versus €155.88 cost of recommended testing

Table 2 (continued)

No.	References	Country/ currency/ perspective	Study type	BMJ checklist score	Population	Duration/ discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
4	Elsaid et al. [40], 2019	USA/US$/ Health System	CA; Wilcoxon signed rank tests	71%	Adult participants in the Truven Health MarketScan Commercial Claims database	January 1, 2010–December 31, 2015/N.R.	Screening of HH (not specified)	No screening	$3118/new HH diganosed patient yearly	The incremental difference in annual health care cost after in comparison to the period before having the HH diagnosis was due to $84 (inpatient costs), $46 (emergency department costs), $2032 (outpatient visits costs), $957 (prescription costs)	N.R.	$3721.11/new HH diagnosed patient yearly **ICER**: The incremental difference in annual health care cost after in comparison to the period before having the HH diagnosis was due to $100.25 (inpatient costs), $54.90 (emergency department costs), $2425.05 (outpatient visits costs), $1142.11 (prescription costs)	€3440.69/new HH diagnosed patient yearly **ICER**: The incremental difference in annual health care cost after in comparison to the period before having the HH diagnosis was due to €92.70 (inpatient costs), €50.76 (emergency department costs), €2242.30 (outpatient visits costs), €1056.04 (prescription costs)
5	Hickman, et al. [42], 2000	Australia/ AUD$/ Service Provider	CD	81%	Patients in a tertiary hospital	Four week period in November and December 1997/N.R.	UIBC	Phenotype screening (TS, SF) and genotype screening	AUD$2268.777HH diagnosis (approximately US$1496)	N.R.	N.R.	AUD$4321.41 HH diagnosis	€2701.92 HH diagnosis

Table 2 (continued)

No.	References	Country/ currency/ perspective	Study type	BMJ checklist score	Population	Duration/ discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
6	de Graaff et al. [43], 2016	Australia/ AUD$/ Societal, government and patient perspectives	CUA	77%	National cohort	November 2013–February 2015/N.R.	Health sector costs (prescribed and non-prescribed medications and supplements; medical appointments, investigations and interventions; hospitalisations; specialised equipment)	Other sector costs (transport), time loss cost	Estimated annual cost of HH: AUD$274 million. The mean cost for symptomatic patients versus that of asymptomatic patients (A$10 030 (7705–12670) vs A$3701 (2423–5296)	N.R.	N.R.	Estimated annual cost of HH: AUD$342.03 million. The mean cost for symptomatic patients versus that of asymptomatic patients (A$12,520.31 (9618.04–15,815.78) vs A$4619.91 (3024.60–6610.92)	Estimated annual cost of HH: €213.85 million. The mean cost for symptomatic patients versus that of asymptomatic patients (€7828.20 (6013.58–9888.66) vs €2888.55, (1891.10–4133.41)
7	de Graaff, et al. [44], 2016	Australia/ AUD$/ Patient perspective	CUA	80%	Volunteers with HH	November 2013-November 2014/N.R.	HH screening	No screening	Mean (standard deviation) utilities were 0.76 (0.21), 0.81 (0.18), 0.60 (0.27), and 0.50 (0.27) for categories 1–4 HH respectively	N.R.	N.R.		

Table 2 (continued)

No.	References	Country/ currency/ perspective	Study type	BMJ checklist score	Population	Duration/ discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
8	Stave et al. [45], 1999	USA/US$/ Third-party payer	CD	37%	All employees seen at onsite occupational health clinics and scheduled for venipuncture for other reasons	First year of a newly initiated corporate screening program/N.R.	Phenotype screening (transferrin index)	N.R.	The cost of the screening program: $27,850. $9283/diagnosis, cost per year of life saved: $928	N.R.	N.R.	The cost of the screening program: $51,004.12. $17,000.76/ diagnosis, cost per year of life saved: $1699.53	The cost of the screening program: €47,160.50. €15,719.60/ diagnosis, cost per year of life saved: €1571.46
9	Dye et al. [46], 2011	Australia/ US$/ Service provider	CA	23%	Western Australia Hospital Morbidity Data system	7-year period/ N.R.	N.R.	N.R.	21,349$/patient versus 2827$ cost/ admission	N.R.	N.R.	29,279.73 $/ patient versus 3877.17 $ cost/admission	18,306.86 €/ patient versus €2424.16 € cost/ admission
10	Timms et al. [28], 2002	UK/£/ Service Provider	CD	9%	128 patients with chondrocalcinosis recruited from the Nuffield Orthopaedic Centre	Lifetime/N.R.	Genotype screening (PCR/ SSP) and genotypes for the C282Y polymorphism	Genotype screening (PCR/ RFLP)	Cost of £1/each test and £64/each case of HH identified	N.R.	N.R.	Cost of £2.08/ each test and £133.21/each case of HH identified	Cost of €2.37/each test and €151.86/ each case of HH identified

Table 2 (continued)

No.	References	Country/currency/perspective	Study type	BMJ checklist score	Population	Duration/discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/QALD	Cost values in original currency	Cost values in current (EUR) currency
11	Stuhrmann et al. [47], 2005	Germany/€/Third-party payer	CD	81%	5882 health insurant patients	January 2001-August 2002/N.R.	Genetic screening through two of the following methods: 1.PCR and restriction digest, 2. 2. Reverse allele-specific oligonucleotide hybridisation 3.Solid-phase oligonucleotide ligation assay (SPOLA) 4. Microarray (DNA-chip)	1. PCR and restriction digest, 2. 2. Reverse allele-specific oligonucleotide hybridisation 3.Solid-phase oligonucleotide ligation assay (SPOLA) 4. Microarray (DNA-chip)	11.20/test, €16.35/test, €13.79/test, €15.70/test	N.R.	N.R.	15.85/test, €23.13/test,€19.51/test, €22.21/test	15.85/test, €23.13/test, €19.51/test, €22.21/test
12	Beutler and Gelbart [30], 2000	USA/$/Laboratory	CD	51%	500 blood samples	Lifetime/N.R.	Phenotype screening	Genetic screen (HFE gene mutations)	Cost of determining two mutations on 500 samples is $4310 or $8.62/test	N.R.	N.R.	Cost of determining two mutations on 500 samples is $7636.58 or $15.27/test	Cost of determining two mutations on 500 samples is €7061.09 or €14.12/test

Table 2 (continued)

No.	References	Country/ currency/ perspective	Study type	BMJ checklist score	Population	Duration/ discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
13	Adams and Valberg [20], 1999	Canada/$/ Third-party payer	Decision tree model, CUA	78%	Hypothetical cohort of blood donors (10,000) and their siblings (50)	Lifetime/3%	Genotype screening (C282Y mutation), and phenotype screening (TS, SF)	No screening	Cost of phenotypic screening with confirmatory genetic testing: $2711/per homozygote with life-threatening complications	1. Phenotyping with transferrin saturation: 0.97 $ incremental cost Saving/ person screened 2. Genotyping: − $151 Incremental cost saving/ person screened versus no-screening strategy	1. Genotypic screening: 2.75 QALD/ person screened for a cost-utility of $20,042 per QALY	Cost of phenotypic screening with confirmatory genetic testing: $4419.09/ per homozygote with life-threatening complications **ICER**: Phenotyping with TS: 1.58$ incremental cost Saving/person screened 2. Genotyping: − $246.14 Incremental cost saving/person screened versus no-screening strategy. **QALY**: Genotypic screening: 4.48. QALD/person screened for a cost-utility of $32,669.64 per QALY	Cost of phenotypic screening with confirmatory genetic testing: €3032.07/per homozygote with life-threatening complications **ICER**: Phenotyping with transferrin saturation: 1.08€ incremental cost Saving/person screened 2. Genotyping: − €168.88 Incremental cost saving/person screened versus no-screening strategy **QALY**: Genotypic screening: 3.07 QALD/person screened for a cost-utility of € 22,415.62 per QALY
14	Adams et al. [7], 2000	Canada/ US$/ Service Provider	CD	25%	5211 voluntary blood donors	N.R./N.R.	Phenotype (unbound iron-binding capacity (UIBC), TS	Genotype screening (genetic testing for the C282Y mutation of the HFE gene)	Screening strategy through UIBC: $5570/per homozygote HH detected. TS cost: $5–$22	N.R.	N.R.	Screening strategy through UIBC: $8839.06/per homozygote HH detected. TS cost: $7.93–$34.91	Screening strategy through UIBC: €6064.74/per homozygote HH detected. TS cost: €5.44–€23.95

Table 2 (continued)

No.	References	Country/currency/perspective	Study type	BMJ checklist score	Population	Duration/discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/QALD	Cost values in original currency	Cost values in current (EUR) currency
15	Adams [21], 1998	Canada/US$/Health service	CD	42%	291 children of homozygotes	Lifetime/N.R.	Phenotype screening (HLA typing, TS, SF)	Genotype screening	Phenotype screening ($58 200) vs genotype screening ($35,600)	N.R.	N.R.	Phenotype screening ($96,515.27) vs genotype screening ($59,036.83)	Phenotype screening (€66,222.02) vs genotype screening (€40,506.94)
16	Asberg et al. [32], 2001	Norway/$/Third-party payer	CD	34%	Population above 20 years of age in Nord-Trøndelag county	August 1995–June 1997/N.R.	Sequential screening (phenotype screening (TS))	Followed by genotype screening	US$1.6/subject screened; US$390/newly discovered HH subject	N.R.	N.R.	US$2.76/subject screened; US$671.89/newly discovered HH subject	€2.55/subject screened; €621.26/newly discovered HH subject
17	Baer et al. [34], 1995	USA/US$/Third-party payer	CA	31%	3977 men ≥30 years old who received multiphasic check-ups	January–November 1989/N.R.	Phenotype screening (liver biopsies, TS)	No screening	$17,000/case of genetic HH identified (including affected relatives), or $65,000/HH identified case	N.R.	N.R.	$34,034.47/case of genetic HH identified (including affected relatives), or $130,131.79/HH identified case	€31,469.67/case of genetic HH identified (including affected relatives), or €120,325.19/HH identified case
18	Patch et al. [36], 2005	UK/£/Government	Decision Tree, RCT, CD	76%	3000 participants from the general practice lists of two general practices, stratified for sex and two age groups (30–50, 51–70)	February 2001-February 2003/N.R.	Phenotypic—TS, iron overload	Genotype screening	The cost of £1440/case detected requiring further management versus £2358 for genetic testing	N.R.	N.R.	The cost of £2750.99/case detected requiring further management versus £4504.74 for genetic testing	The cost of €3136.13/case detected requiring further management versus €5135.41 for genetic testing

Table 2 (continued)

No.	References	Country/ currency/ perspective	Study type	BMJ checklist score	Population	Duration/ discount rate (Cost)	Intervention	Comparator/s	Outcomes	ICER	QALY/ QALD	Cost values in original currency	Cost values in current (EUR) currency
19	Bhavnani et al. [38], 2000	UK/£/Laboratory	CD	37%	Hospital inpatients, outpatients and genetic HH patients	8 months/N.R.	Sequential screening (phenotype screening)	Genotype screening	£117/HH patient identified	N.R.	N.R.	£251.96/HH patient identified	€287.23/HH patient identified
20	Cooper et al. [41], 2008	UK/£/Government	Decision analytic models, Decision tree, Cost-saving analysis	94%	Hypothetical cohort of people with suspected HH	Monitoring of offspring until the disease manifests/ N.R.	Genotypic screening	Liver biopsy	DNA strategy screening (total costs):73,823 £ versus 83,068 £ for liver biopsy	N.R.	N.R.	DNA strategy screening (total costs): 126,021.87 £ versus 141,803.84 £ for liver biopsy	DNA strategy screening (total costs): €143,665.18versus €161,656.66 for liver biopsy
21	Jacobs et al. [29], 2005	Netherlands/€/ Third-party payer	CD	40%	Hospital inpatients	Lifetime/N.R.	Sequential screening	No screening	Diagnostic costs of €2380/diagnosed patient before and €2600 after introduction of the guideline	N.R.	N.R.	Diagnostic costs of €3367.42/ diagnosed patient before and €3678.70 after introduction of the guideline	Diagnostic costs of €3367.42/ diagnosed patient before and €3678.70 after introduction of the guideline
22	Barton et al. [48], 2002	USA/$/ Third-party payer	CD	44%	2199 employers at Forest Products Mill	January 1990-July 2001/N.R.	Phenotype screening (TS)	Phenotype screening (SF)	$8826/HH case	N.R.	N.R.	$14,968.83/HH case	€13,840.79/HH case

AUS$ Australian dollars, *BMJ* British Medical Journal, *CA* cost analysis, *CEA* cost-effectiveness analysis, *CD* cost description, *CUA* cost-utility analysis, *ED* Emergency Department, *€* Euros, *HH* hemochromatosis, *HLA* human leukocyte antigen, *ICER* incremental cost-effectiveness ratio, *N.R.* not reported, *PCR/SSP* polymerase chain reaction using sequence specific primers, *PCR* polymerase chain reaction, *QALD* quality-adjusted life-day, *QALY* quality-adjusted life-year, *RCT* randomized clinical trial, *RFLP* restriction fragment length polymorphism, *SD* standard deviation, *SF* serum ferritin, *SPOLA* solid-phase oligonucleotide ligation assay, *SSP* sequence specific primer, *TS* transferrin saturation, *UIBC* unsaturated iron-binding capacity, *US$* US dollars

Table 3 An overview of all the economic studies on the treatment strategies included in this review

No.	References	Country/currency/perspective	Study type	BMJ checklist score	Population	Discount rate (Cost)/duration	Intervention	Comparator/s	Outcomes	Cost values in original currency	Cost values in current (EUR) currency
1	Rombout et al. [50], 2012	Netherlands//€/ Societal	RCT; CA	79%	Newly HFE-HC patients from four hospitals in the region of Sanquin Blood Bank South East Division (Netherlands)	N.R./Between December 2005 and November 2008	Treatment (ERY)	Treatment(PHL)	71.49 €/PHL versus 251.18 €/ERY. Total cost for PHL: 4438 € versus 3005 € for ERY	87.34€/PHL versus 306.85 €/ERY Total cost for PHL: 5421.69 € versus 3671.06 € for ERY	87.34 €/PHL versus 306.85 €/ERY Total cost for PHL: 5421.69 € versus 3671.06€ for ERY
2	Rombout et al. [51], 2016	Netherlands//€/ Societal	RCT	63%	HH patients receiving PHL as maintenance treatment from three hospitals (Maastricht University Medical Centre, Radboud University Medical Centre Nijmegen, Zuyderland Medical Center, Heerlen/Brunssum/Sittard	N.R./May 2008–May 2011	Treatment (ERY)	Treatment (PHL)	235 €/PHL versus 511 €/ERY	281.27 €/PHL versus 611.62€/ERY	281.27 €/PHLY versus 611.62€/ERY
3	McDonnel et al. [52], 1999	USA/US$/ Health system	CD	49%	Patients with HH	N.R./September 1, 1996–August 31, 1997	Treatment (PHL)	n/a	Mean cost: $90/PHL in hospitals and $52/PHL in blood centers	Mean cost: $164.82/PHL in hospitals and $95.23/PHL in blood centers	Mean cost: €152.4/PHL in hospitals and €88.05/PHL in blood centers
4	Flynn et al. [53], 2011	USA/US$/ Health system	CD	49%	62 HH patients	N.R./13-month period (October 200–October 2009	Therapeutic PHL	N.R.	Financial gain of $36,000 during the 13-month study period	Financial gain of $48,830.68 during the 13-month study period	Financial gain of €45,150.85 during the 13-month study period

Table 3 (continued)

No.	References	Country/currency/perspective	Study type	BMJ checklist score	Population	Discount rate (Cost)/duration	Intervention	Comparator/s	Outcomes	Cost values in original currency	Cost values in current (EUR) currency
5	Stefashyna, et al. [54], 2014	Switzerland/US$/Service Provider	CA	40%	Asymptomatic volunteers with suspicion of HH	N.R./January 2004	WBD	DEC	186 USD/WBD, versus 238 USD/DEC	239.72 USD/WBD, versus 306.74USD/DEC	221.65 €/WBD, versus 283.62 €/DEC
6	Gribble et al. [55], 2009	USA/US$/Service Provider	CD	40%	HH blood donors	N.R./January 2008–December 2008	PHL	DEC	The total cost for WBC is $6000 versus $23,595 for DEC	The total cost for WBC is $8533.05 versus $33,556.20 for DEC	The total cost for WBC is €7890.01 versus €31,027.44 for DEC
7	Mariani et al. [56], 2005	Italy/€/Service Provider	CA	54%	3 patients with severe HH	N.R./N.K	ERY	PHL	Mean costs for ERY plus erythropoietin is €602 versus PHL €35	Mean costs for ERY plus erythropoietin is €851.76 versus PHL €49.52	Mean costs for ERY plus erythropoietin is €851.76 versus PHL €49.52
8	Buffone and Beck [24], 1994	USA/US$/Societal	CEA, Markov model	63%	Men ≥ 25 years old with no history of alcoholism and no preexisting conditions that would predispose to iron loading	N.R../Lifetime	Phenotype screen (TS, SF, liver biopsy) and treatment (PHL)	No screening	$605 per life-year gained	$1245.55 per life-year gained	€1151.69 per life-year gained

BMJ British Medical Journal, *CA* cost analysis, *CD* cost description, *CEA* cost-effectiveness analysis, *DEC* double erythrocytapheresis, *ERY* erythrocytapheresis, *HH* hemochromatosis, *N.K.* not known, *NR* not reported, *PCR/RFLP* polymerase chain reaction using restriction fragment length polymorphism, *PHL* phlebotomy, *RCT* randomized clinical trial, *SF* serum ferritin, *TS* transferrin saturation, *WBD* whole blood donation, € Euro

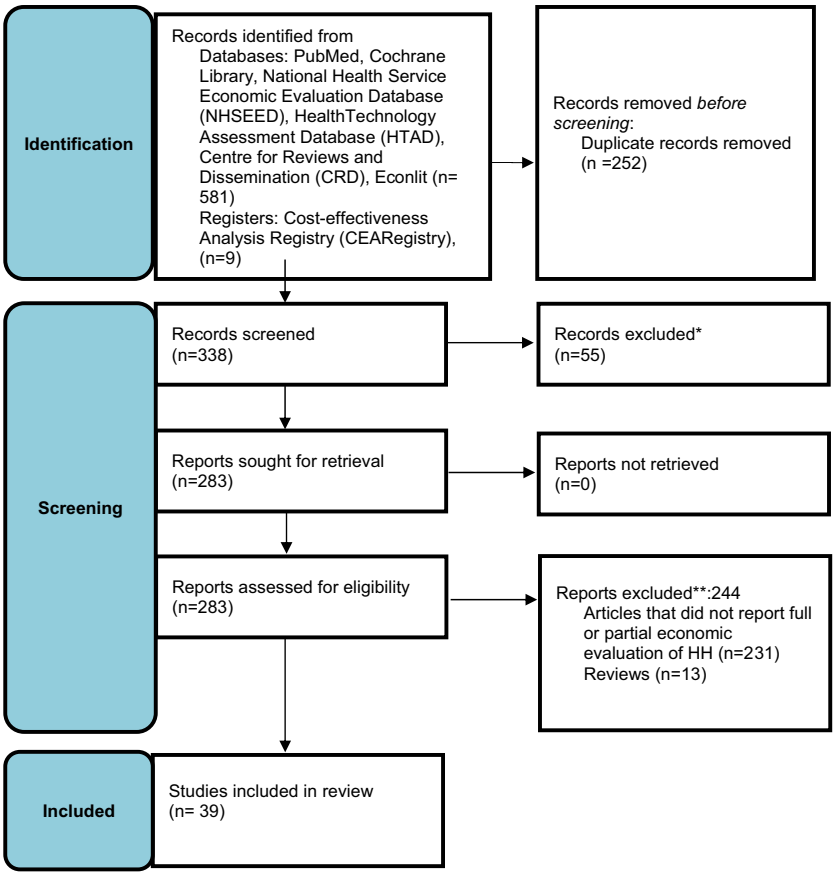

Fig. 1 PRISMA flow diagram of the literature search and selection of articles included in this systematic review. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *HH* hereditary hemochromatosis

* Studies not eligible excluded based on their abstracts

** Reviews and articles that did not report full or partial economic evaluation of HH were excluded.

3.2 Screening

Thirty-two studies that reported the screening strategy were identified (Tables 1, 2). The majority of the studies reported a sequential screening, a combination of both the genotypic and phenotypic screening programs. We identified 10 CEA studies on screening, which are all reported in Table 1, whereas Table 2 reports all the economic studies, other than CEA studies on the screening strategies included in this review. The phenotype screening included TS, UIBC, and serum ferritin, with a confirmation of liver biopsy. HFE mutation identification was used to confirm the HH diagnosis.

The QALYs or quality-adjusted life-days (QALDs) were reported in a few studies [19, 20, 27, 33]. Adams et al. showed that in a hypothetical cohort of 10,000 blood donors and siblings, the screening of blood donors showed a QALY of 0.84, versus a QALY of 1.18 for the screening of asymptomatic homozygous siblings [19]. In line with these findings, Adams and Valberg showed a QALD of 2.75 per genotypic screening per person screened in a hypothetical cohort of 10,000 blood donors and their siblings [20]. In both studies, a discount rate of 3% was reported and the third-party payer perspective was reported. The incremental cost saving per person was US$0.97 in 1999 for phenotyping TS versus US$151 for genotyping, in comparison with the no-screening strategy [20]. However, when converted to the current currency (€), the genotyping cost was €168.88 of incremental cost saving/person screened versus the no-screening strategy. The incremental cost savings were higher for homozygous siblings screened versus blood donors, and when the values were converted to Euros (current currency), the incremental cost savings were €14.91 per person screened versus €3.78 for the screening of blood donors [19].

A cost-utility analysis carried out in a cohort of 30-year-old men in Norway reported a QALY of 7.65 for phenotype screening, with a screening cost of US$250 per QALY gained [33]. Using a DNA test as the primary screening test resulted in a higher ICER (€210,434.18) in comparison with sequential TS/HFE screening (€162,073.53/life-year gained [LYG]) [22]. The incremental cost of US$1.50 per specimen could be added to other chemistry tests if the serum iron test

is used as a preliminary screening test [37]. In a cost analysis, it was reported that a new HH diagnosis results in an additional health care cost of US$3118/patient yearly [40]. Other cost-description studies showed that the estimated cost for newly identified HH patients was US$390 [32], or £117 for each HH patient identified, which, when converted to Euros in the current currency, would be €621.26/newly identified HH subject and €287.23/HH patient identified, respectively [38]. The TS strategy was cost effective, with an ICER of AUS$10,195/QALY gained [27]. In line with these findings, UIBC was determined to be a cost-effective screening, with an incremental cost of US$3.19/each donor [49]. Other cost-description papers compared phenotype versus genotype screening [7, 21, 23, 36, 38]. Genotyping the spouse of a homozygote is the best cost-efficient strategy in pedigree studies [21]. The cost of phenotype screening for UIBC per HH detected was reported in different studies [7, 23]. In a quasi-experimental cost-analysis study of 105 siblings with a median age of 55 years from 35 proband cases of HH, it was revealed that the screening of siblings with ferritin and TS may be adequate in many families, with a total cost of US$1800–$2100/screening of a family with four members [35]. However, other studies showed that the uptake of screening with the genotypic strategy was not inferior to that in the phenotypic strategy [36]. The cost for different screening programs was reported in a few studies conducted in four different countries (USA, Germany, UK, Australia) [27, 28, 30, 42, 45, 47]. A cost-utility analysis reported that the symptomatic stages of HH and the presence of multiple self-reported symptoms were associated with decreasing utility [44]. In addition, we noticed a lack of utility weight sources in the cost-utility studies on either phenotype, or genotype screening, despite reporting the utility weights for diabetes, heart failure, and cirrhosis [19, 20, 33]. In their cost-of-illness study, De Graaff et al. reported for the first time the HH cost estimate for the Australian population, showing that reducing the clinical penetrance of HH can result in a significant reduction in cost [44].

3.3 Treatment

This review identified eight economic evaluation studies on HH treatment (Table 3). The most recent study, a randomized, crossover clinical trial was carried out in 2016. Two studies concluded that whole blood donation (WBD) was a more cost-effective treatment than double erythrocytapheresis (DEC). Gribble et al. concluded that in an economic study performed in HH blood donors from a social provider perspective during the period January 2008–December 2008, the total cost for WBD was US$6000 versus US$23,595 for DEC [55].

In line with these findings, Stefashyna et al. showed that the cost of a single DEC was higher (US$238) in respect to WBD (US$186) [54]. In a randomized controlled trial carried out in HH patients from three hospitals, the mean treatment costs for phlebotomy was lower (€235) than the cost for erythrocytapheresis (€511); the results showed that erythrocytapheresis is the preferred treatment method [51]. In line with this study, Mariani et al. showed that in a non-experimental descriptive case-series study that included three patients with severe HH, the total mean costs for erythrocytapheresis was higher (€602) in respect of phlebotomy (€35) [56]. Rombout et al., reported that erythrocytapheresis might be a cost-saving therapy [50]. The mean cost of phlebotomy varied from US$90 in hospitals to US$52 in blood centers, which, when converted to the current currency (€), would be €152.4 and €88.05, respectively [52]. Discounting costs are not reported in all studies. Two of the selected studies were randomized clinical trials, both performed in The Netherlands, with a duration of 3 years, and from a societal perspective [50, 51]. The cost-analysis studies were carried out in Italy and Switzerland, both from a service provider perspective [54, 56]. A further two cost-description papers were identified, one of which reported a financial gain of US$36,000 for the therapeutic phlebotomy program during the 13-month study period conducted in a rural hospital in the US [53, 55]. One of the studies was included in both Table 1 and Table 3 because it reported data from both a screening and treatment strategy point of view [24]. In that study, a Markov model was used in a group of males aged ≥25 years, with no pre-existing conditions that would predispose to iron loading. The data showed that early detection and treatment was slightly more costly than treatment at the onset of symptoms, with an average cost of US$605 per life-year gained [24]. However, the cost-effectiveness results obtained with this hypothetical cohort of 25-year-old males were based on certain assumptions, some of which have moderate-to-high degrees of uncertainty.

In conclusion, treatment economic studies performed in four different countries showed that erythrocytapheresis was more costly than phlebotomy [50–52, 56]; however, the most recent economic study on the treatment strategy of HH included in this review was published in 2016 [51].

4 Discussion

This systematic review summarizes all health economics data, either full or partial economic evaluations on the screening (phenotypic and genetic) and treatment of HH. No recent systematic reviews have been conducted in this field; to our knowledge, the latest systematic review in this field was published in 2015 [18]. Our review reports additional economic evaluation studies published until April 2023, either on phenotype or genotype screening, or treatment of HH, that were classified into two groups, i.e. screening or

treatment economic studies. We were unable to perform a meta-analysis due to the heterogeneity of the studies.

Most of the studies reported the screening strategies. Studies have mostly shown that either phenotype or genotype screening were cost effective compared with no screening. In addition, treatment studies concluded that erythrocytapheresis might be a cost-effective therapy compared with phlebotomy. Phenotype screening with a confirmation of genetic screening is an optimal strategy for HH diagnosis. Rombout et al. revealed that erythrocytapheresis is a highly effective treatment to reduce iron overload and might potentially also be a cost-saving therapy compared with phlebotomy [50]. In addition, phenotyping with transferrin saturation and genotyping are cost-saving strategies compared with the no-screening strategy [19, 20]. The studies were heterogeneous, including either individuals suspected of having HH or patients with HH, or their siblings; however they all concluded that population screening programs for HH are cost-effective compared to no screening. El-Serag showed that HFE gene testing was less costly compared with serum iron screening [25]. In an Australian decision model study with a hypothetical cohort, it was shown that asymptomatic hemochromatosis subjects had higher costs than symptomatic patients, reflecting the low clinical penetrance estimate used. The authors showed that health sector and the time related to the productivity were the main cost drivers, and that the clinical penetrance estimate had a significant role on the assessment of cost effectiveness [23].

In a German cost-description study in which the presence of C282Y mutation was tested using different methods, such as PCR and restriction digest, reverse allele-specific oligonucleotide hybridization, solid-phase oligonucleotide ligation assay (SPOLA), and microarray (DNA-chip) [47], the respective costs were reported. Elsaid et al. reported that the annual health care costs were higher in HH patients with hypertension, arthritis, type 2 diabetes, and chronic kidney disease, but without HH [40].

Only a few cost-utility studies were observed and future studies should include reliable utility weights. The majority of the studies modeled screening programs over a lifetime.

Deferasirox is an iron chelator administered orally once daily in patients with transfusion-dependent anemias and other iron overload syndromes. We identified a review on the pharmacoeconomic benefits of deferasirox, but unfortunately it did not meet the eligibility criteria of this study. Furthermore, we did not identify any original articles on the economic aspects of deferasirox as a potential alternative therapy to phlebotomy in HH patients [57]. Various studies have been carried out on the role of deferasirox in different iron overload syndromes, but no cost-effectiveness, cost-analysis, or cost-utility studies have been conducted in HH patients.

There are limitations of this current review that warrant consideration. First, the quality of the data was variable, and an evaluation of the quality of the studies and the credible measurement of costs should be reported in the future. Second, the search was limited to articles published in English only, and including articles in other languages would have extended our results.

5 Conclusions

This systematic review provides up-to-date evidence on the economic data regarding either screening or treatment for HH. We noted that the current studies were only performed in a few countries. The lack of high-quality economic studies is an obstacle for population screening programs, which are considered as an approach to reduce clinical penetrance.

No original article on the economic aspects of deferasirox as a potential alternative therapy to phlebotomy in HH patient was found. We believe that despite assessing the cost of erythrocytapheresis and phlebotomy, it would be of great interest to carry out cost-effectiveness studies on the role of deferasirox in HH other than in different iron overload syndromes. There are still evidence gaps that need to be addressed.

Declarations

Conflicts of interest Malvina Hoxha, Visar Malaj, and Bruno Zappacosta certify that they have no affiliations with, or involvement in, any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Availability of data and material The authors confirm that the data supporting the findings of this study are available within the article.

Author contributions Conceptualization and methodology: All authors. Database search, study selection, and data extraction: MH and BZ. Data synthesis: MH, BZ, and VM; First draft preparation: All authors. Draft review and editing: All authors. All authors read and approved the final manuscript.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication (from patients/participants) Not applicable.

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Code availability Not applicable.

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