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ORIGINAL ARTICLE

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Health economic evidence for the use of molecular biomarker tests in hematological malignancies: A systematic review

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Abstract

Objectives: Molecular biomarker tests can inform the clinical management of genomic heterogeneous hematological malignancies, yet their availability in routine care largely depends on the supporting health economic evidence. This study aims to systematically review the economic evidence for recent molecular biomarker tests in hematological malignancies.

Methods: We conducted a systematic search in five electronic databases for studies published between January 2010 and October 2020. Publications were independently screened by two reviewers. Clinical study characteristics, economic methodology, and results were extracted, and reporting quality was assessed.

Results: Fourteen studies were identified, of which half (n = 7; 50%) were full economic evaluations examining both health and economic outcomes. Studies were predominantly conducted in a first-line treatment setting (n = 7; 50%) and adopted a non-lifetime time horizon to measure health outcomes and costs (n = 7; 50%). Five studies reported that companion diagnostics for associated therapies were likely cost-effective for acute myeloid leukemia, chronic myeloid leukemia, diffuse large B-cell lymphoma, and multiple myeloma. Four studies suggested molecular biomarker tests for treatment monitoring in chronic myeloid leukemia were likely cost-saving.

Conclusions: Although there is initial confirmation of the promising health economic results, the present research for molecular biomarker tests in hematological malignancies is sparse with many applications of technological advances yet to be evaluated.

KEYWORDS
cost-effectiveness, costs, health services, hematological malignancies, molecular biomarker

Novelty statement
This systematic review synthesized and appraised the health economic evidence for molecular biomarker tests in hematological malignancies. Although several molecular biomarker tests represent cost-effective and cost-saving use of health resources, more studies are required to provide further health economic evidence on the promising and emerging application of these technologies across hematological malignancies. By doing so, health economic research in this area can further support payor reimbursement and access of molecular biomarker testing services for patients with a hematological malignancy.

1 | INTRODUCTION

Collectively, hematological malignancies were the fourth most commonly diagnosed cancer worldwide in 2020 and responsible for a significant cancer burden.[1] The 5-year survival from diagnosis in the United States (US) is 64% for leukemias, 87% for Hodgkin lymphomas, 73% for non-Hodgkin lymphomas, and 54% for myelomas, and challenges remain in managing relapsed disease and the long-term effects of cancer treatments on patients.[2-4] The economic cost of hematological malignancies is substantial, estimated at €12 billion in Europe 2012 arising from direct healthcare consumption, productivity losses, and informal care.[5] This all emphasizes the importance of providing better treatments and controlling overall costs.

Molecular biomarker tests are assisting clinicians to optimize treatment strategies specific to the molecular profile for each individual patient.[6-8] The benefit for molecular biomarker tests to personalize treatment and improve patient outcomes is demonstrated across numerous predictive and prognostic applications and is consequently endorsed by several clinical guidelines. This includes testing for the *TP53* mutations and *IGHV* somatic hypermutation in predicting response to chemoimmunotherapy for chronic lymphocytic leukemia (CLL)[9] and testing for the *ASXL1*, *CEBPA*, *FLT3*, *NPM1*, *RUNX1*, and *TP53* gene mutations for refining diagnosis in acute myeloid leukemia (AML).[10] Several targetable gene mutations such as *FLT3*, *IDH1*, and *IGH2* in AML are also clinically recognized important predictive biomarkers for treatment selection.[11] There are many different types of genetic and genomic technologies that are used to detect actionable molecular changes in hematological malignancies, including next-generation sequencing (NGS) platforms for targeted DNA sequencing and whole-genome sequencing (WGS) and whole-transcriptome sequencing (WTS), but they vary in their technical and analytical capacities.[12,13] However, technological advancements for clinical decision making are not being matched by their uptake in the health system.[6,8,14-16]

Health economic considerations regarding the cost-effectiveness of molecular biomarker tests are pivotal in overcoming regulatory policy hurdles that have traditionally prohibited payor coverage and reimbursement to these services. In this regard, health technology assessments (HTA) of new medical products guide payor decisions concerning their benefits, harms, and costs to patients and society. Both as HTA mainstays, economic evaluations inform allocation of health resources that will maximize population benefits whereas budget impact analysis assesses the consequences of an intervention on resource consumption and costs.[17,18] Understanding the available economic evidence is important to support reimbursements and widespread use of accurate and reliable molecular biomarkers tests, such as NGS testing. It is necessary to consider these health economic aspects to highlight potential gaps between clinical and economic evidence. Therefore, the objective of this systematic review was to identify and appraise the current health economic evidence for molecular biomarker tests used for the clinical care of hematological malignancies.

2 | MATERIALS AND METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (International Prospective Register of Systematic Reviews [PROSPERO] registration number CRD42020212798).

2.1 | Eligibility criteria

Publications were included if target population comprised of patients with a hematological malignancy irrespective of age, gender, stage, or treatment received. Publications had to evaluate at least one of the following technology platforms: karyotyping, fluorescence *in situ* hybridization (FISH), single nucleotide polymorphism microarray, polymerase chain reaction (PCR)-based techniques (e.g., real-time quantitative polymerase chain reaction [qPCR], reverse transcriptase polymerase chain reaction [RT-PCR], or quantitative reverse transcriptase PCR [RT-qPCR]), gene expression profiling (e.g., gene expression microarray or WTS), or DNA sequence analysis (e.g., Sanger sequencing, targeted DNA sequencing, whole-exome sequencing [WES] or WGS). Trial-based or model-based economic analyses that were either full or partial economic evaluations (i.e., cost analysis, cost-consequence, cost-minimization, cost-effectiveness, cost-utility, cost-benefit), or a budget impact analysis, comparing at least two alternative interventions, were considered. Only publications in the past decade were included to maintain relevancy with current clinical practice. Publications that involved non-malignant hematological diseases or did not report on health economic indicators, as well as conference papers, abstracts, or reviews, or not published in English, were excluded.

2.2 | Search strategy

A systematic search was conducted using the Ovid® platform for electronic databases consisting of MEDLINE, Embase, Cochrane Library (Cochrane), Health Technology Assessment, and National Health Services Health Economic Evaluation Database (NHSEED). Each database was individually searched from January 1, 2010, up until October 9, 2020. The search strategy consisted of free key words and subject headings related to blood cancers, molecular biomarker tests, and health economic studies. Medical subject headings (MeSH) were used for MEDLINE, Cochrane, Health Technology Assessment, and NHSHEED databases, while Embase subject headings (EMTREE) were used for the Embase database. Full search strategy for each database is available in Tables S1-S5.

2.3 | Study selection

After removing duplicates, study selection occurred in two stages and a publication was excluded if it did not meet one or more of

the eligibility criteria. Initially, two reviewers (M.V. and K.D.) independently performed title and abstract screening for the first 10% of publications identified, with no differences in the inclusion of publications between both reviewers. For the remaining 90% of publications, title and abstract screening was completed by one reviewer (M.V.). All full-text publications were then independently assessed by two reviewers (M.V. and K.D.) for eligibility. Disagreement regarding publication eligibility was resolved through consensus.

2.4 | Data extraction and synthesis

One reviewer (M.V.) read the full-text and supplemental materials to extract relevant study and methodological data using a prespecified extraction template. General article and clinical information were extracted for year of publication, journal of publication according to specialist area (i.e., clinical, or economic or HTA journal), funding classification (i.e., non-industry or industry funding), country of evaluation, study population, primary hematological malignancy, molecular biomarkers and technology testing platform, purpose of the test (i.e., prognosis, diagnosis, treatment selection, dosing, monitoring), treatment line, and treatment received (where applicable). If there was no information regarding funding sources from the publication, funding classification was based on the affiliation of the primary author. The European Society of Medical Oncology (ESMO) guidelines were used as a reference for clinically relevant molecular testing strategies to investigate whether all endorsed strategies have been evaluated.[19] The incidence of each hematological malignancy for included studies was assessed based on 2019 Global Burden of Disease data.[20]

Data extraction for methodological information included type of health economic study, whether a decision analytic model was used, study perspective, time horizon, annual discount rate, currency and currency index year, economic and effectiveness outcomes considered, economic and effectiveness data sources, willingness-to-pay thresholds, validation efforts, and sensitivity and uncertainty analyses. For publications with a decision analytic model, model-specific characteristics were assessed, including type of decision analytic model, model structure, cycle length (if applicable), and structural and methodological assumptions reported. Economic and/or effectiveness results per strategy, including the incremental cost-effectiveness ratio (ICER), were also reported.

Economic outcomes were converted to 2020 US dollars (US$) by adjusting for inflation to the year 2020 using the average Organization for Economic Co-operation and Development (OECD) Consumer Price Index (CPI) for the country reported in the study and then an exchange rate to 2020 US$ using the average OECD Purchasing Power Parity (PPP) conversion factor.[21,22] If no index year for economic

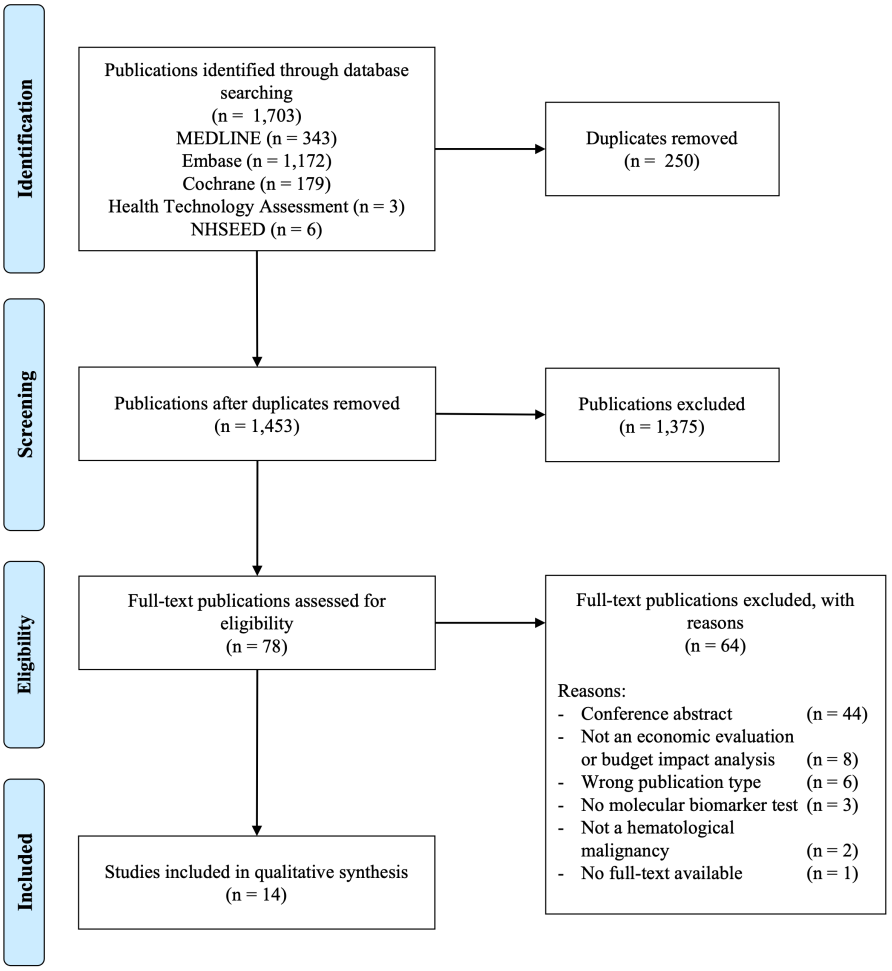

FIGURE 1 PRISMA flowchart diagram of publication selection process including reasons for exclusion

TABLE 1 Overview of study characteristics, clinical and intervention considerations, and health and economic outcomes

	Study characteristics				
Publication	**Health economic analysis type**	**Country**	**Perspective, time horizon**	**Test purpose**	**Strategies evaluated**
ALL ($n = 1$)					
Donnan et al. (2011)	Cost-effectiveness analysis	Canada	Healthcare system, 3 months	Treatment dosage	a. No test (weight-based dosing) b. Enzymatic test c. *TPMT* genotype test
AML ($n = 2$)					
Cressman et al. (2016)	Cost-utility analysis	Canada	Healthcare system, 10 years	Treatment selection	a. Standard molecular analysis of 3 genes b. Targeted genomic analysis of 10 genes
Hörster et al. (2017)	Cost-effectiveness analysis	Germany	Healthcare system. 10 years	Treatment selection	a. Conventional cytogenetics diagnostics b. Molecular genetic diagnostics
CLL ($n = 2$)					
Al Zaabi et al. (2010)	Cost analysis	Canada	Health service, *not reported*	Prognostication	a. FISH b. MLPA
Buchannan et al. (2017)	Cost-effectiveness analysis and cost-utility analysis	UK	Healthcare system, 30 years (lifetime)	Treatment selection	a. No genetic test (no ibrutinib) b. Genetic test (no ibrutinib) c. Genetic test (refractory ibrutinib treatment) d. Genomic test (first-line ibrutinib in chemoimmunotherapy non-responders) e. Genomic test (refractory ibrutinib in chemoimmunotherapy non-responders)
CML ($n = 6$)					
Cayuella et al. (2011)	Cost-minimization analysis	France	Societal, *not reported*	Treatment monitoring	a. Non-automated RT-qPCR (dedicated equipment) b. Non-automated RT-qPCR (shared equipment) c. Automated RT-qPCR
Gaultney et al. (2011)	Cost-effectiveness analysis and cost-utility analysis	Netherlands	Healthcare system, 2 years	Treatment selection	a. No test (dasatinib) b. Microarray

Molecular biomarker(s)	Treatment line	Treatment type	Health economic outcomes[a]		
			Cost (2020 US$)	Effectiveness	Conclusions
TPMT	*Not reported*	Chemotherapy	a. $655 b. $1022 c. $1092	a. 0.25 LY b. 0.25 LY c. 0.25 LY	*TPMT* genotype test for chemotherapy treatment dosing in pediatric ALL is associated with no survival benefit at a higher cost compared to no test (weight-based dosing) strategy.
FLT3-ITD, *NPM1*, *CEBPA*, *IDH1*, *IDH2*, *TET2*, *KMT2A*, *KMT2A-PTD*, *PHF6*, *ASXL1*, *DNMT3A*	First-line	Chemotherapy and HSCT	a. $144 738 b. $156 424	a. 3.48 QALY b. 3.74 QALY	Targeted genomic analysis of 10 genes for treatment selection in AML is likely cost-effective compared to standard molecular analysis at a willingness-to-pay of CAD$100 000 per QALY in Canada.
FLT3-ITD, *NPM1*, *CEBPA*	First-line	Chemotherapy and HSCT	a. $93 498 b. $129 604	a. 0.94 LY b. 3.83 LY	Molecular genetic diagnostics for treatment selection in AML is likely cost-effective compared to conventional cytogenetic diagnostics at a willingness-to-pay between simple and three times GDP per capita in Germany.
del(2p), del(6q), del(8q), del(9p), del(10q), del(11q), del(12p), del(13q), del(17p), +12	Previously untreated and treated (not otherwise specified)	*Not applicable*	a. $328 b. $45	*Not applicable*	FISH for prognostication in CLL cost more than MLPA.
TP53	All	Chemo-immunotherapy, BTK inhibitors and HSCT	a. $107 920 b. $110 818 c. $166 752 d. $184 379 e. $142 115	a. 6.37 LY/5.60 QALY b. 6.61 LY/5.82 QALY c. 7.63 LY/6.44 QALY d. 7.45 LY/5.60 QALY e. 6.65 LY/5.93 QALY	Genomic test strategies for treatment selection in CLL is not cost-effective compared to no genetic test strategy at a willingness-to-pay threshold of £30 000 per QALY in the UK.
BCR-ABL1	*Not reported*	TKI therapy	a. $168 b. $178 c. $294	*Not applicable*	Automated RT-qPCR for treatment monitoring in CML cost more than non-automated RT-qPCR at an annual activity level greater than 300 cases.
T315I	Second-line	TKI therapy, chemotherapy and HSCT	a. $151 798 b. $133 104	a. 1.74 PFLY/1.61 QALY b. 1.84 PFLY/1.63 QALY	Microarray platform for treatment selection in CML is cost-effective (greater health gains at a lower cost) compared to no test strategy in the Netherlands.

TABLE 1 (Continued)

Publication	Study characteristics				
	Health economic analysis type	Country	Perspective, time horizon	Test purpose	Strategies evaluated
Guérin et al. (2014)	Cost analysis	US	Healthcare system, 1 year	Treatment monitoring	a. 0 qPCR test per year b. 1–2 qPCR tests per year c. 3–4 qPCR tests per year
Latremouille-Viau et al. (2017)	Cost analysis	US	Healthcare system, 1 year	Treatment monitoring	a. 1 qPCR test per year b. 2 qPCR tests per year c. 4 qPCR tests per year
Jabbour et al. (2018)	Cost analysis	US	Payor, *not reported*	Treatment monitoring	a. 0 RT-qPCR test per year b. 3 RT-qPCR test per year
Yamazaki et al. (2020)	Budget impact analysis	Japan	Payor, 3 years	Treatment monitoring	a. Quarterly RT-qPCR tests (TKI continuation strategy) b. Quarterly RT-qPCR tests during treatment followed by monthly RT-qPCR tests for treatment-free remission eligible patients in the first year and then quarterly thereafter (TKI discontinuation strategy)
Non-Hodgkin lymphoma (DLBCL, FL) and Hodgkin lymphoma ($n = 1$)					
Costa et al. (2016)	Cost analysis	Canada	Health service, *not reported*	Prognostication	a. Targeted capture sequencing (DLBCL and FL patients) b. Digital gene expression profiling (DLBCL and Hodgkin lymphoma patients) c. FISH (DLBCL patients)
DLBCL ($n = 1$)					
Chen et al. (2018)	Cost-utility analysis	US	Payor, lifetime	Treatment selection	a. No test (chemotherapy) b. No test (R2CHOP treatment) c. Gene expression profile test
MM ($n = 1$)					
Gaultney et al. (2018)	Cost-utility analysis	Multiple European countries	Healthcare system, lifetime	Treatment selection	a. No test (bortezomib-based regimens) b. International Staging System and FISH c. SKY92 signature test d. International Staging System, FISH and SKY92 signature test

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; FISH, fluorescence in situ hybridization; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; LY, life years; MLPA, multiplex ligation-dependent probe amplification; MM. multiple myeloma; PFLY, progression free life year; QALY, quality-adjusted life years; qPCR, quantitative real-time polymerase chain reaction; R2CHOP, lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; RT-qPCR, reverse transcription quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor; UK, United Kingdom.

[a]Health economic outcomes are reported as discounted costs and effectiveness where appropriate.

			Health economic outcomes[a]		
Molecular biomarker(s)	**Treatment line**	**Treatment type**	**Cost (2020 US$)**	**Effectiveness**	**Conclusions**
BCR-ABL1	First-line	TKI therapy	a. $20 539 b. $18 827 c. $16 712	*Not applicable*	Regular treatment monitoring of *BCR-ABL1* transcripts in CML via qPCR is associated with lower healthcare costs.
BCR-ABL1	First-line	TKI therapy	*Not reported*	*Not applicable*	Regular treatment monitoring of *BCR-ABL1* transcripts in CML via qPCR is associated with lower healthcare costs.
BCR-ABL1	First-line	TKI therapy	a. $7372 b. $1206	*Not applicable*	Regular treatment monitoring of *BCR-ABL1* transcripts in CML via RT-qPCR is associated with lower healthcare costs.
BCR-ABL1	First and second-line	TKI therapy	a. $148 383 396 b. $74 659 666	*Not applicable*	Increased treatment monitoring of *BCR-ABL1* transcripts in CML via RT-qPCR in treatment-free remission eligible patients (TKI discontinuation strategy) is associated with cost saving compared to regular quarterly monitoring for all patients (TKI continuation strategy).
Although full list of molecular biomarkers not reported, study specified number of genes for each panel and FISH break-apart probes used in genetic analysis	*Not reported*	*Not applicable*	a. $940 b. $821 c. $545	*Not applicable*	Targeted capture sequencing for prognostication in DLBCL and FL cost more than digital gene expression profiling (DLBCL and Hodgkin lymphoma) and FISH (DLBCL).
Not reported	First-line	Chemotherapy and chemoimmuno-therapy	a. $57 590 b. $120 605 c. $92 850	a. 9.85 QALY b. 12.02 QALY c. 12.02 QALY	Gene expression profile test for treatment selection in DLBCL is likely cost-effective compared to no test (chemotherapy) strategy in the US although factors such as treatment survival benefit and cost are likely to influence findings.
t(4;14), del(17p), SKY92 signature	First-line	Chemotherapy, proteasome inhibitor	a. $302 225–$508 982 b. $282 981–$455 246 c. $327 445–$465 878 d. $289 046–$463 967	a. 4.24–4.72 QALY b. 4.24–4.73 QALY c. 4.27–4.76 QALY d. 4.26–6.76 QALY	International Staging System and FISH and/or SKY92 signature test for treatment selection in MM is cost-effective (greater health gains at a lower cost) compared to no test strategy across multiple European countries

outcomes was reported, the year prior to the publication was used instead. Likewise, if the currency was not specified, it was assumed that the currency is based on the country of publication.

2.5 | Quality assessment and risk of bias

One reviewer (M.V.) assessed the publication quality using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. The CHEERS checklist provides a minimum set of health economic study aspects that should be reported.[23] Each publication was scored under each criteria item, being awarded a score of 1 if a criterion was satisfactorily reported and a score of 0 if unsatisfactorily reported. Depending on the study, not all items were applicable, and so no score was given for that item. When there was scoring doubt, the input of a second reviewer (K.D.) was conferred. Overall reporting compliance was calculated based on proportion of satisfactory criteria items compared to the total number of applicable criteria items in the checklist.

Risk of bias was not assessed as no established risk of bias assessment tools currently exist for health economic studies.

3 | RESULTS

The PRISMA diagram presented in Figure 1 details the selection of publications under each review stage. The search strategy identified 1453 unique publications, of which 1375 were excluded following title and abstract screening. Of the remaining 78 publications, 64 publications were excluded based on full-text review. Finally, 14 publications met the inclusion criteria and were included in this review.

3.1 | General characteristics

Table 1 outlines the general study characteristics and health and economic outcomes, grouped by primary hematological malignancy. Nine (64%) of the fourteen studies were published between 2015 and 2020,[24-32] while five (36%) studies were published between 2010 and 2014.[33-37] The country of evaluation was mostly from Canada[24,25,33,35] or the US[28,29,31,37] (both n = 4; 29%). Majority of studies were published in a clinical journal (n = 11; 79%)[24,25,27-30,32-36] rather than an economic or HTA journal (n = 3; 21%).[26,31,37] More studies declared non-industry (i.e., government, non-government, and academia) funding (n = 8; 57%)[24-27,29,33-35] compared to industry funding (n = 6; 43%).[28,30-32,36,37]

3.2 | Reporting quality

Figure 2 presents the percentages of publications that have satisfactorily reported applicable CHEERS checklist item, and a more detailed scoring for each publication is provided in Table S6. Reporting compliance ranged between 42% and 100% with a median CHEERS score of 90%. Most studies (n = 10; 71%) were categorized as high reporting quality (CHEERS score >80%).[25-30,32,35-37] Patient preferences and characterizing heterogeneity were not applicable for many publications since studies did not seek to elicit preferences nor

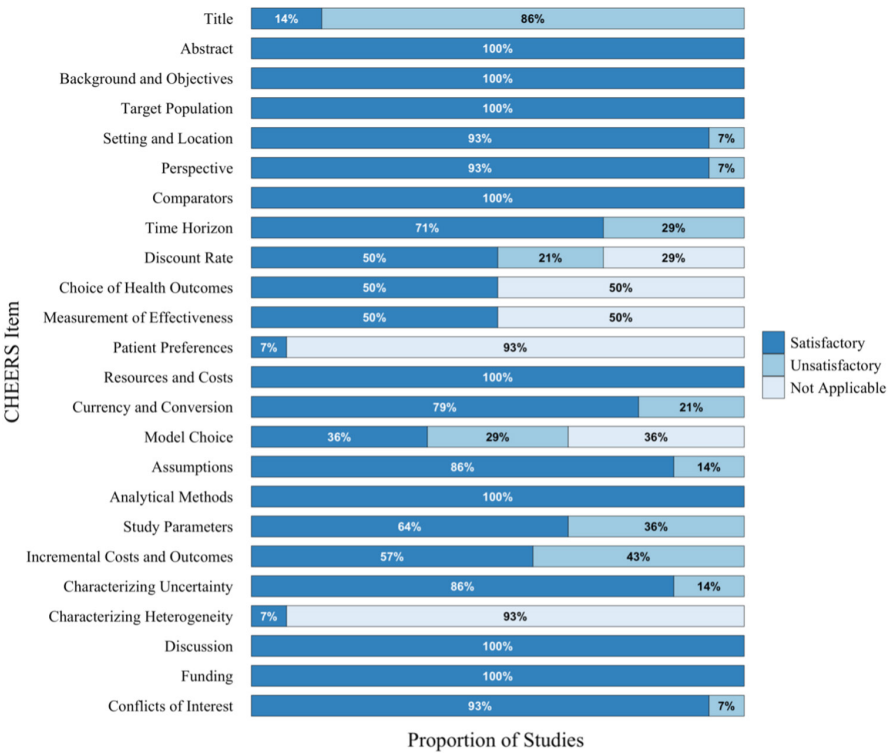

FIGURE 2 Overview of the percentage of publications reporting on each criteria item on the CHEERS checklist

TABLE 2 Summary of hematological malignancy incidence and molecular biomarkers clinically recommended and evaluated by health economic studies

Hematological malignancy[a]	2019 GBD incidence rates per 100 000[b]	ESMO recommended molecular biomarkers		Molecular biomarkers evaluated in systematic review	
		Chromosomal aberrations	Gene mutations	Chromosomal aberrations	Gene mutations
ALL	1.98	−7, +8, abn11q23, abn14q32, del(6q), del(7p), t(1;19), t(12;21), t(4;11), t(8;14), t(9;22), del(17p), hyperdiploidy, low hypodiploidy	*ABL1*, *CLRF2*, *CREBBP*, *FBXW7*, *FLT3*, *IKZF1*, *JAK2*, *KRAS*, *NF1*, *NOTCH1*, *NRAS*, *PDGFR-β*, *RAS/PTEN*, *TP53*	No chromosomal aberrations included in review	*TPMT*
AML	1.61	−5, −7, del(17p), inv(3), inv(16), t(8;21), t(9;22), t(15;17), t(16;16)	*ASXL1*, *CEBPA*, *FLT3*, *IDH1*, *IDH2*, *KMT2A*, *NPM1*, *RUNX1*, *TP53*	No chromosomal aberrations included in review	*FLT3-ITD*, *NPM1*, *CEBPA*, *IDH1*, *IDH2*, *TET2*, *KMT2A*, *KMT2A-PTD*, *PHF6*, *ASXL1*, *DNMT3A*
Myelodysplastic, myeloproliferative, and other hematopoietic neoplasms	5.20	MDS: 5q31, 7q31, 20q, cen7, cen8, cenY MPN: No recommendations made on testing for molecular biomarkers	MDS: *SF3B1*, *TP53* MPN: *CALR*, *JAK2*, *MPL*		
CLL	1.34	del(17p)	*IGHV*, *TP53*	del(2p), del(6q), del(8q), del(9p), del(10q), del(11q), del(12p), del(13q), del(17p), +12	*TP53*
CML	0.85	+8, +19, +22q, iso(17-q), t(9;22), chromosome 3 aberrations	*BCR-ABL1*, T315I	No chromosomal aberrations included in review	*BCR-ABL1*, T315I
Other leukemia	2.50	HCL: No recommendations made on testing for molecular biomarkers	HCL: *BRAF*, *IGHV*, *TP53*		
Hodgkin lymphoma	1.13	No recommendations made on testing for molecular biomarkers	No recommendations made on testing for molecular biomarkers	Not reported in study	Not reported in study
Non-Hodgkin lymphoma	5.91	*DLBCL*: No recommendations made on testing for molecular biomarkers *FL*: No recommendations made on testing for molecular biomarkers *MCL*: t(11;14) *MZL*: t(11;18) *PCL*: No recommendations made on testing for molecular biomarkers *PMBCL*: No recommendations made on testing for molecular biomarkers *PTCL*: t(2;5) *WM*: No recommendations made on testing for molecular biomarkers	*DLBCL*: *BCL2*, *MYC* *FL*: No recommendations made on testing for molecular biomarkers *MCL*: No recommendations made on testing for molecular biomarkers *MZL*: *MYD88* *PCL*: *TCR* *PMBCL*: No recommendations made on testing for molecular biomarkers *PTCL*: No recommendations made on testing for molecular biomarkers *WM*: *CXCR4*, *MYD88*	*DLBCL*: Not reported in study *FL*: Not reported in study	*DLBCL*: Not reported in study *FL*: Not reported in study
MM	2.01	del17p, t(4;14), t(11;14), t(14;16), ampl 1q/+1q	No recommendations made on testing for molecular biomarkers	t(4;14), del(17p)	Not reported in study

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; ESMO, European Society for Medical Oncology; FL, follicular lymphoma; GBD, Global Burden of Disease; HCL, hairy cell leukemia; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasms; MZL, marginal zone lymphoma; PCL, primary cutaneous lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; WM, Waldenström's macroglobulinemia.

[a]Hematological malignancy classified according to causes of diseases used by 2019 GBD.

[b]The incidence of each hematological malignancies based on 2019 GBD data.

TABLE 3 Methodological and decision analytic model characteristics including reporting quality assessment of publications

	Economic analysis		
Publication	**Model approach**	**Model structure**	**Cycle length**
ALL ($n = 1$)			
Donnan et al. (2011)	Decision tree model	Health: adverse drug events and severity	*Not applicable*
AML ($n = 2$)			
Cressman et al. (2016)	Decision tree and state-transition cohort model	Health: relapse, complete remission, death	90 days
Hörster et al. (2017)	State-transition cohort model	Health: induction, remission, relapse, death	1 month
CLL ($n = 2$)			
Al Zaabi et al. (2010)	*Not applicable*	*Not applicable*	*Not applicable*
Buchannan et al. (2017)	State-transition cohort model	Health and treatment	28 days
CML ($n = 6$)			
Cayuella et al. (2011)	*Not applicable*	*Not applicable*	*Not applicable*
Gaultney et al. (2011)	Decision tree model	Health: treatment response and PD	*Not applicable*
Guérin et al. (2014)	*Not applicable*	*Not applicable*	*Not applicable*
Latremouille-Viau et al. (2017)	*Not applicable*	*Not applicable*	*Not applicable*
Jabbour et al. (2018)	Decision tree model	Health: PD	*Not applicable*
Yamazaki et al. (2020)	State-transition cohort model	Health and treatment	1 year
Non-Hodgkin lymphoma (DLBCL, FL) and Hodgkin lymphoma ($n = 1$)			
Costa et al. (2016)	*Not applicable*	*Not applicable*	*Not applicable*
DLBCL ($n = 1$)			
Chen et al. (2018)	State-transition patient model	Health: PFS, relapse, death	3 weeks
MM ($n = 1$)			
Gaultney et al. (2018)	State-transition cohort model	Health: PFS, PD, death	1 month

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; PD, progressive disease; PFS, progression free survival.

perform subgroup analysis. Not all model-based studies provided justification to model choice ($n = 4$; 29%).[31,32,35,36]

3.3 | Clinical test application

Studies analyzed the impact of molecular biomarker tests across numerous hematological malignancies, including chronic myeloid leukemia (CML) ($n = 6$, 43%),[28,31,32,34,36,37] AML ($n = 2$; 14%),[25,27] and CLL ($n = 2$; 14%).[26,33] Single studies (each 7%) considered acute lymphoblastic leukemia (ALL),[35] diffuse large B-cell lymphoma (DLBCL)[29] and multiple myeloma (MM),[30] or both non-Hodgkin lymphoma (specifically, DLBCL and follicular lymphoma [FL]) and Hodgkin lymphoma.[24] Three (21%) studies assessed the use of NGS testing strategies on patient management,[24-26] while other studies used a variety of molecular techniques, such

		Data sources		
Annual discount rate	Uncertainty and sensitivity analysis	Effectiveness data	Cost data	CHEERS score
Not applicable	One-way sensitivity analysis, probabilistic analysis	Literature sources	Public health insurance data, case costing data	95%
3%	One-way sensitivity analysis, probabilistic analysis, scenario analysis	Patient-level hospital medical records	Literature sources, hospital cost data, national health insurance data	91%
3%	One-way sensitivity analysis, scenario analysis	Literature sources	Physicians' fee schedule	95%
Not reported	*Not reported*	*Not applicable*	Internal institution data	42%
3.5%	One-way sensitivity analysis, probabilistic analysis, scenario analysis	Literature sources	National health insurance data, clinical trial data	100%
5%	Scenario analysis	*Not applicable*	Internal institution data	74%
1.5% (Health); 4% (Costs)	One-way sensitivity analysis, scenario analysis	Literature sources	National health insurance data, clinical trial data	91%
Not applicable	*Not reported*	*Not applicable*	Administrative claims data	83%
Not applicable	Probabilistic analysis	*Not applicable*	Administrative claims data	83%
Not reported	One-way sensitivity analysis, probabilistic analysis	*Not applicable*	Literature sources	70%
Not reported	One-way sensitivity analysis, scenario analysis	*Not applicable*	Literature sources, national health insurance data	89%
Not reported	One-way sensitivity analysis	*Not applicable*	Internal institution data	74%
3%	Probabilistic analysis, scenario analysis	Literature sources	Physicians' fee schedule, literature sources	91%
Country specific discount rates	One-way sensitivity analysis	Patient-level clinical trial data	Clinical trial data, literature sources, national health insurance databases	95%

as karyotyping, FISH, qPCR, RT-qPCR, or gene expression profile test. These tests were mostly evaluated to match patients to a specific therapy (i.e., as a companion diagnostic) ($n = 6$; 43%) comparing a risk-stratified treatment approach for existing and novel therapies versus a conventional or no testing strategy.[25-27,29,30,36] Other applications included monitoring of therapeutic response ($n = 5$; 36%),[28,31,32,34,37] or informing prognosis ($n = 2$; 14%)[24,33] and treatment dosing ($n = 1$; 7%).[35] All five publications that assessed the test to monitor treatment were in CML for *BCR-ABL1* transcript levels using either qPCR or RT-qPCR technology in determining treatment discontinuation with tyrosine kinase inhibitor (TKI) therapies (i.e., imatinib, dasatinib, and nilotinib).[28,31,32,34,37] Seven (50%) studies focused on first-line treatment,[25,27-31,37] one study (7%) on second-line treatment,[36] and three (21%) on multiple treatment lines either across the entire treatment pathway,[26] within first-line and second-line treatment only,[32] or in previously

untreated and previously treated patient cohorts with no differentiation in treatment line for previously treated patients.[33] However, three (21%) publications did not report on the treatment line.[24,34,35] Four (57%) of the seven studies in first-line treatment only were on companion diagnostics[25,27,29,30] and three (43%) were for treatment monitoring.[28,31,37]

Fourteen out of 17 different ESMO guideline documents for the management of different hematological malignancies included recommendations for either cytogenetic or molecular testing according to implication for clinical practice, clinical trials, and targeted trials from the ESMO guidelines as summarized in Table 2. Of which, four (29%) ESMO guidelines include biomarkers that have been the subject of health economic studies in AML,[25,27] CLL,[26,33] CML,[28,31,32,34,36,37] and MM[30] evaluated molecular biomarkers that were the subject of ESMO guidelines.

3.4 | Economic analysis

Studies were either full economic evaluations considering both health and economic outcomes (n = 7; 50%),[25-27,29,30,35,36] partial economic evaluations considering economic outcomes only (n = 6; 43%),[24,28,31,33,34,37] or a budget impact analysis (n = 1; 7%).[32] Of the seven full economic evaluations, two (29%) studies were cost-effectiveness analyses with life years (LY) as health outcome,[27,35] three (43%) studies were cost-utility analysis with QALY as health outcome,[25,29,30] and two (29%) studies were both a cost-effectiveness and cost-utility analysis.[26,36] Conversely, the six partial economic evaluations were comprised of five (83%) cost analyses[24,28,31,33,37] and one (17%) cost-minimization analysis[34] assuming interventions are non-inferior in health outcomes. Five out of six (83%) publications on CML were partial economic evaluations[28,31,34,37] or a budget impact analysis,[32] with one (17%) publication in CML a cost-effectiveness and cost-utility analysis.[36]

Most health economic studies utilized a decision analytic model (n = 9; 64%) (Table 3).[25-27,29-32,35,36] All five publications that did not use any modeling were either a cost analysis[24,28,33,37] or a cost-minimization analysis.[34] Studies were mostly assessed from the healthcare system perspective (n = 8; 57%),[25-28,30,35-37] followed by a payor (n = 3; 21%),[29,31,32] health service (n = 2; 14%),[24,33] and societal (n = 1; 7%) perspective.[34] Although Cayuella et al.[34] reported a societal perspective, it was classified as a health service perspective because only direct cost and indirect cost arising from health labor and equipment were accounted but not non-medical costs. Half (n = 7; 50%) of all studies applied a time horizon of less than 10 years[25,27,28,32,35-37] and three (21%) studies used the lifetime analytic approach measuring the health outcomes and costs throughout the entire patient life duration in the study.[26,29,30] Four (29%) studies did not state a time horizon.[24,31,33,34]

Many studies used multiple literature sources[26,27,29,35,36] or patient-level hospital medical records[25] for effectiveness data, with one study deriving model parameter input values from patient-level clinical trial data.[30]

3.5 | Decision analytic model characteristics

Table 3 provides additional methodological characteristics and model-specific information. Among the nine model-based studies, cohort-level modeling techniques (n = 8; 89%)[25-27,29-32,35,36] were more common than patient-level models (n = 1; 11%).[29] The latter was a patient-level state-transition model (STM).[29] Cohort-level models were either decision trees (n = 3; 33%),[31,35,36] cohort-level state-transition models (STM) otherwise known as Markov models (n = 4; 44%),[26,27,30,32] or a two-part modeling approach encompassing both these techniques (n = 1; 11%).[25] Model structures were mostly health-state driven (n = 7; 78%)[25,27,29-31,35,36] using a series of health states such as progression-free survival, progressive disease, treatment response, adverse events and severity, relapse, and death. Two studies (33%) additionally defined health states for each treatment line in their model structure.[26,32] Relevant only to STM studies, cycle lengths were either 3 weeks (n = 1),[29] 28 days/1 month (n = 3),[26,27,30] 90 days (n = 1),[25] or 1 year (n = 1).[32]

3.6 | Sensitivity analysis and validation efforts

Sensitivity analysis for the characterization of model assumptions and model parameter inputs on health economic outcomes was reported by most studies (n = 12; 86%).[24-32,34-36] Specifically, nine (64%) studies conducted a one-way sensitivity analysis (i.e., deterministic analysis),[24-27,30-32,35,36] to assess the impact of variations of a particular model input on study results. Six (64%) studies performed a probabilistic analysis estimating the joint uncertainty of model inputs.[25,26,28,29,31,35] Seven (50%) studies incorporated a scenario analysis varying a combination of two or more model inputs.[25-27,29,32,34,36] Model validation efforts were reported in a single study.[26]

3.7 | Cost and cost-effectiveness outcomes

Five (71%) out of seven cost-effectiveness publications suggested cost-effective use of healthcare resources when molecular biomarker tests were used as a companion diagnostic for identifying population groups most likely to respond to treatment.[25,27,29,30,36]

Two of these publications evaluated between two diagnostic approaches in AML. One study compared between a multigene targeted genomic analysis and standard molecular analysis in determining optimal consolidation therapies following complete remission from induction chemotherapy for AML, with an ICER of Canadian dollars (CAD) $49 493/QALY gained and a 58% chance of cost-effectiveness at CAD$100 000/QALY.[25] Similarly, molecular genetic diagnostics used for the characterization *FLT3-ITD*, *NPM1*, and *CEBPA* mutational status were compared to conventional cytogenetic diagnostics for first-line treatment of AML, whereby the molecular genetic diagnostics strategy was cost-effective in Germany

based on an ICER of US$59 136/LY gained and a willingness-to-pay range of one-to-three times Germany's gross domestic product (GDP) per capita.[27]

The three other publications evaluated predictive biomarker testing against a "no testing" comparator. Firstly, a microarray platform for targeted second-line treatment (TKI therapies, interferon-alpha plus low-dose cytarabine, or HSCT) compared to a no testing strategy (dasatinib treatment for all patients) in CML was more effective and less costly in the Netherlands.[36] Secondly, although no definitive conclusions were drawn, a favorable cost-effectiveness was suggested for a gene expression profile test to stratify patients with DLBCL into receiving either first-line novel treatment or chemotherapy based on patient's germinal center B-cell-like subtype compared to the no testing strategy (chemotherapy for all patients) at an ICER of US$15 015/QALY in the US.[29] Finally, a risk-stratified treatment approach (combination of International Staging System, FISH for t(4;14) and del(17p) and/or SKY92 gene expression classifier) for transplant-eligible patients with MM to differentiate between first-line bortezomib-based regimens and chemotherapy-based regimens compared to a no testing strategy (bortezomib-based regimens for all patients) was more effective and less costly across multiple European countries.[30]

Similarly, four (57%) out of seven partial economic evaluations and budget impact analysis studies showed that increased frequency of molecular monitoring of *BCR-ABL1* in CML is associated with lower healthcare resource utilization and medical costs.[28,31,32,37] This was likely due to TKI therapy discontinuation in patients who are no longer responsive to treatment or are likely to develop disease progression or adverse events.

Several economic evaluations reported assumptions regarding treatment effectiveness for associated therapies with companion diagnostics.[26,29,36] Sensitivity analyses suggested that the cost-effectiveness of the molecular biomarker test used for treatment selection was more influenced by both the cost and long-term health benefits for treatments following testing, including quality of life, rates of treatment relapse, and mortality than the cost of the test itself.[25,26]

4 | DISCUSSION

This systematic review identified fourteen publications from the past decade investigating the cost and cost-effectiveness of complex molecular biomarker testing strategies in hematological malignancies. Companion diagnostics for AML, CML DLBCL, and MM were likely cost-effective, whereas regular molecular monitoring of *BCR-ABL1* transcripts in CML with TKI therapy was likely cost-saving. Despite high compliance to reporting standards, the paucity of health economic studies precludes meaningful comparisons across studies, and therefore, the economic value of other testing strategies is not fully understood.

Health economic studies can be used to improve the availability of molecular biomarker tests and support their optimal allocation and delivery in health systems. Several studies in this review evaluated companion diagnostics used in a single line of treatment, typically first-line treatment. Of the economic evaluation studies that support the cost-effectiveness of companion diagnostics in hematological malignancies, SKY92 signature test measuring gene expression levels in MM has not yet been clinically recommended. Likewise, a multigene targeted genomic analysis was evaluated as cost-effective for AML, but not all genes in the panel are currently recommended in the ESMO clinical guidelines. Nevertheless, it is likely that companion diagnostics will become more prominent for patient clinical management with the expenditure of treatment contingent on the likelihood of patient response, especially as more novel, costly targeted therapies enter the market.[3] However, as most studies are from European countries and from the healthcare system perspective, results may not be directly applicable to other settings. This review identified several other challenges, such as that the cost-effectiveness of these tests is sensitive to the long-term treatment outcomes, health state utility, rates of treatment relapse, and mortality along with the cost of associated treatment.[25,26] Furthermore, studies suggest that appropriate adherence to the clinical recommendations of molecular monitoring of *BCR-ABL1* transcripts in CML using either qPCR or RT-qPCR technologies may reduce the economic burden of the disease. These studies demonstrate the potential value of regular molecular monitoring and may encourage appropriate measures to better align real-world clinical testing practices with recommended clinical guidelines.[38]

With the publication scarcity in health economic studies of molecular biomarker tests for hematological malignancies, distinct research gaps are evident. Based on published ESMO clinical guidelines,[39-54] not all molecular biomarkers that are recommended for testing have been investigated. For instance, no health economic studies have considered the predictive significance of *IGHV* mutation status testing prior to first-line therapy in CLL.[9,53] Hematological malignancies such as myelodysplastic syndromes and myeloproliferative neoplasms were also absent. There is also a shortage of health economic research for NGS notwithstanding its utility regarding the molecular aspects of the World Health Organization (WHO) diagnostic classification for hematopoietic and lymphoid malignancies.[55] Novel complex genomic testing was assessed in a cost analysis for targeted DNA sequencing in non-Hodgkin and Hodgkin lymphoma,[24] a cost-effectiveness analysis genomic testing in CLL,[26] and a cost-utility analysis of multigene targeted genomic analysis in AML.[25] However, other than the study in AML, these interventions were either more expensive than other diagnostic strategies or not cost-effective. Unless further health economic research is developed for these genomics platforms, the capacity to widely embed genomics within clinical care for hematological malignancies will be further delayed.

Although the methodological quality of the health economic studies seems fair, there are several opportunities to expand the evidence base. Studies that either adopted a relatively short time horizon or single treatment-line evaluations may not fully account the impact of these tests on sequential clinical processes

or downstream consequences from changes to care from molecular biomarker testing.[56,57] Therefore, the longer-term economic impacts on cancer management needs to be examined. This is, however, underpinned by availability of data sources needed to populate decision analytic models. Health outcomes from studies were mostly evidence driven from published clinical trials, with fewer studies using individual patient clinical, observational, or other real-world data. Health economic studies in precision medicine research are increasingly using real-world data to assess the effectiveness of interventions in practice, patient heterogeneity, and non-health outcomes associated with molecular diagnostics.[58-60] This is a possible future direction for this field of clinical molecular biomarkers in blood cancers. Nonetheless, challenges in patient consent and data sharing may influence access to real-world patient-level health outcomes data for research, but guidance is available to incorporate such evidence into HTA for oncology and precision medicine.[61,62] These technical issues are consistent with previous research commenting on the complexities in the design of economic evaluations of precision medicine (albeit not hematological malignancy specific).[14,63-70]

This review has recognized that the limited number of health economic studies in recent years is concerning, but there is another layer of complexity to the conduct of health economic research for HTA purposes. This includes small market sizes given the rarity of many hematological malignancies,[20] expensive drug prices, health economic outcomes above payor's willingness-to-pay, and insufficient market incentives (evidenced by the small number of industry-funded research studies in this review), in addition to technical difficulties regarding evaluation design and data acquisition.[71-73] While economic evaluations and budget impact analysis are conventionally focused on a single intervention on a single population using traditional value metrics such as health gains (i.e., LY and QALY), cost savings, and/or productivity,[74,75] it is also important to consider other value elements beyond these core health outcomes that are a direct consequence of molecular biomarker tests.[65,75-77] Technologies like NGS impart greater diagnostic certainty and generate patient information that supports present-day and future clinical decisions, with potential psychological gains and personal utility for which payors (and patients) may be willing to pay. HTA agencies are yet to extensively consider patient-centered value propositions, but value elements should be more akin to how molecular biomarker tests affect patients in making treatment choices. To incentivize research in this area and promote efficiency of health systems from these innovations over time, ongoing policy discussions will need to determine how payors can accept assessments of molecular biomarker tests in hematological malignancies consorted with the value of these services for patients.[77,78]

There are limitations to this systematic review. Findings from this review are subjected to publication bias as there may be a bias toward publications with more favorable cost-effectiveness results in journals. Secondary publications of HTA reports across different healthcare systems were not considered, which may introduce unforeseen bias, but this review is focused on the publicly available economic literature. Moreover, the CHEERS checklist was used to assess the quality of reporting, but the checklist was not originally developed to score publications, thereby introducing subjectivity in methodology appraisal. Finally, with a range of analytical methods assessing the health outcomes and costs attributable to these interventions, the study results were summarized at the discretion of the reviewers.

4.1 | Conclusions

There are a limited number of health economic studies for molecular biomarker tests in hematological malignancies to facilitate clinical incorporation into routine clinical management. Although the cost and cost-effectiveness evidence in this disease were promising, further research is needed to examine the health economic impact of molecular biomarker tests across different biomarkers and technologies, including NGS, to support implementation and reimbursement decisions.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Contribution: All authors contributed to the review protocol study; M.V., K.D., and M.I.J. prepared the search strategy approved by all authors; M.V. performed the search strategy; M.V. and K.D. conducted the screening and selection process. M.V. extracted and analyzed the data; M.V., K.D., and M.I.J. interpreted the results and M.V. prepared the first draft of the manuscript and was critically reviewed by all authors; and all authors approved the submitted final version of the manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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