Adding a gene expression profile test to aid differential diagnosis and treatment in aggressive large B cell lymphoma: an early exploratory economic evaluation

Cost-effectiveness of gene expression profiling in aggressive large B cell lymphoma

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Conflicts of interest

Bruce Seligmann is a shareholder and employee of BioClavis Limited's parent company, BioSpyder Inc. Pam McKay declares consulting fees/honoraria from Roche, Gilead, KITE, Takeda, Janssen, Beigene, BMS/Celgene and Incyte and conference/travel support from Gilead, Takeda and Janssen. She also declares lecture fees from Janssen, Beigene and Kitex. The remaining authors declare no conflict of interest.

Ethics approval

Ethical approval was not required for this study.

Consent to participate

There were no human participants in this study so no consent to participate was required.

Consent to publish

There were no human participants in this study so no consent to publish was required.

Data availability

No data was generated as a result of this study. Excel-based models are available on request from the corresponding author. Data used in this study are publicly available and referenced in the text with the exception of the West of Scotland aggressive large B cell lymphoma cohort data. This cohort data is subject to UK National Health Service data governance.

Code availability

No code was generated as a result of this study.

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Janet Bouttell and David Hopkins. The first draft of the manuscript was written by Janet Bouttell and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Abstract

Introduction

Adding gene expression profiles (GEP) to the current diagnostic work up of aggressive large B cell lymphomas may lead to the reclassification of patients, treatment changes and improved outcomes. A GEP test is in development using TempO-Seq® technology to distinguish Burkitt Lymphoma (BL) and Primary Mediastinal Large B Cell lymphoma (PMBCL) from Diffuse Large B Cell Lymphoma (DLBCL), and to classify DLBLC patients and predict benefit of (e.g.) adding Bortezomib to R-CHOP therapy (RB-CHOP). This study aims to estimate the potential impact of a GEP test on costs and health outcomes to inform pricing and evidence generation strategies.

Methods

Three decision models were developed comparing diagnostic strategies with and without GEP signatures over a lifetime horizon using a UK health and social care perspective. Inputs were taken

from a recent clinical trial, literature and expert opinion. We estimated the maximum price of the test using a threshold of GBP30,000 per Quality Adjusted Life year (QALY). Sensitivity analyses were conducted.

Results

The estimated maximum threshold price for a combined test to be cost effective is GBP 15,352. At base case values the BL signature delivers QALY gains of 0.054 at an additional cost of GBP 275. This results in a net monetary benefit (NMB) at a threshold of GBP 30,000 per QALY of GBP 1,345. For PMBCL, QALY gains were 0.0011, cost saving GBP406 and NMB GBP437. The hazard ratio for impact of treating BL less intensively must be at least 1.2 for positive NMB. For identifying DLBCL subtype patients responsive to Bortezomib QALY gain was 0.2465 at a cost saving of GBP 6,175, resulting in an NMB of GBP 13,570. In a probabilistic sensitivity analysis using 1,000 simulations, a testing strategy was superior to a treat all with R-CHOP strategy in 81% of the simulations and cost saving in 92% assuming a cost price of zero.

Discussion

Our estimates show that the combined test has a high probability of being cost effective. There is good quality evidence for the benefit of subtyping DLBCL but the evidence on the number of patients reclassified to or from BL and PMBCL and the impact of more precise diagnosis and costs of treatment is weak. The developers can use the price estimate to inform return on investment calculations. Evidence will be required of how well the TempO-Seq® technology performs compared to the testing GEP technology used for sub-typing in the recent clinical trial. For BL and PMBCL elements of the test, evidence would be required of the number of patients reclassified and improved costing information would be useful. The diagnostic and therapeutic environment in haematological malignancies is fast moving which increases the risk for developers of diagnostic tests.

Key points for Decision Makers

A gene expression profiling test to identify sub-types of diffuse large B cell lymphoma patients who would benefit from the addition of Bortezomib is likely to be cost-effective (and cost saving) in a UK setting.

Evidence for the impact of gene expression profiles to distinguish BL and PMBCL from DLBCL is weak. Cost-effectiveness for these elements of the test depends on the relative costs of more and less intensive treatments and the net direction of reclassifications.

A combined test providing the three elements is likely to be cost-effective in a UK setting.

1. Introduction

Diffuse large B cell lymphoma (DLBCL), Burkitt Lymphoma (BL) and Primary Mediastinal large B cell lymphoma (PMBCL) are large B cell lymphomas, which account for 12.3% of diagnosed haematological malignancies and related premalignant conditions [1]. In the UK, an estimated 4,820 people per year are diagnosed with DLBCL, 130 with PMBCL and a further 240 BL [1]. Diagnosis of these conditions is complex and currently uses a combination of clinical, pathological, immunohistochemical and genetic testing approaches. It has been suggested that the use of gene expression profiles could improve diagnosis [2-4]. Accurate differential diagnosis is important as both BL and PMBCL are typically treated more intensively than DLBCL and recent clinical trial evidence has suggested that two subtypes of DLBCL (Activated B Cell (ABC) and Molecular High Grade (MHG) have better five year survival with the addition of Bortezomib to standard treatment [4] The mainstay first-line treatment for DLBCL is a cancer drug combination known as R-CHOP21 (see glossary for definitions of all regimens) [5]. There is no single standard of care for PMBCL, and options include standard R-CHOP21 or more intensive regimens such as R-CHOP14, R-ACVBP or DA-EPOCH-R possibly followed by mediastinal consolidative radiation therapy [6]. For BL various high intensity regimens are used including LMB, BFM, HOVON and CODOX-M/IVAC [7]. Although response rates and overall survival are relatively good for DLBCL, BL and PMBCL, prospects are poor for patients who relapse or are refractory (i.e., do not respond to first-line treatment). Prompt and accurate differential diagnosis is, therefore, critical to ensure appropriate treatment.

There are some GEP tests in use in research, but no GEP test is in routine clinical use in the UK for these indications. A test is currently at an early stage of development which would provide a gene expression profile for patients with suspected aggressive large B cell lymphoma including DLBCL, BL and PMBCL. The test is based on TempO-Seq® technology which offers several advantages over other techniques of gene expression profiling, including a minimal amount of formalin-fixed paraffin embedded (FFPE) tissue and no RNA extraction required, simplicity of the assay, low turn-around-time, and improved sample-to-sample repeatability [8]. These advantages mean that cost-effective tests can potentially be developed in conditions which would not be possible for more expensive technologies. The test is still in technical development stage and as such, the design is currently undergoing validation testing, including collecting the views of stakeholders and estimating the potential clinical impact of the components of the test. GEP signatures for BL, PMBCL, and DLBCL (ABC, MHG, and Germinal Centre B-cell (GCB) subtypes) could aid the pathologist in diagnosis and, if patients were reclassified or subclassified as a result of the additional information provided, may impact treatment decisions, progression and overall survival. The current analysis explores the potential cost-effectiveness of a GEP test to aid differential diagnosis between BL and DLBCL and between PMBCL and DLBCL as well as between the ABC or MHG and GCB subtypes of DLBCL. We conducted an early exploratory economic evaluation to investigate the potential impact of the GEP signatures for DLBCL sub-types, BL and PMBCL on diagnoses of aggressive B cell lymphoma and

subsequent treatment decisions. We aimed to inform the developers of the technology about the pricing and test performance required for a GEP test to be cost saving and cost effective from a UK health and social care perspective. We also sought to inform evidence generation strategy.

2. Methods

2.1 Study population

The population was all patients with a suspected diagnosis of BL, PMBCL or DLBCL following clinical examination, initial blood and imaging tests, pathologist examination of tumour cells, immunohistochemistry and specific genetic testing. Population characteristics for BL and PMBCL are described in the observational studies from which our parameter estimates were taken [7,9]. As the median age of patients with BL and PMBCL (39 years and 35 years respectively) is young compared to DLBCL, we used data for the 20-59 year old DLBCL group described in Daneels et al as this was the closest match to the BL and PMBCL populations [5]. As the source of the probabilities of progression and survival for DLBCL sub-types are taken from a recently published conference abstract [4] we have assumed population characteristics in line with a large observational cohort [5]

2.2 Setting, location, perspective and discount rate

A cost-utility analysis was conducted to estimate the effects on health outcomes and health service costs of introducing gene expression profiles identifying DLBCL subtypes and distinguishing BL and PMBCL from DLBCL into clinical practice in the UK. A UK health and social care perspective was taken. Costs and health outcomes were discounted at 3.5% in line with the UK NICE reference case [10].

2.3 Comparators and modelling approach

We developed three separate models in order to estimate the cost-utility of GEP for DLBCL sub-typing and the differential diagnosis of BL and PMBCL. All models are decision-tree based and figures illustrating the decision trees are included in the Online Resources. All models explicitly model first line treatment choice, then use progression and survival data over either a five or eight year period (depending on evidence available) to estimate probabilities for branches. Survival beyond the period covered by the decision-tree is added to each branch as appropriate using life tables. All survival is discounted except for those patients who died during the decision-tree period. For clarity, the main features of the three models are set out in Table 1.

2.4 Health outcomes

The health outcome considered was quality adjusted life years (QALYs) gained.

2.5 Time horizon

Decision trees were used to model first-line treatment, progression and survival over a lifetime horizon. A lifetime horizon was chosen as more accurate treatment selection impacts survival and adverse effects over the longer term.

2.6 Costs

Detail of costing calculations (including currency, price dates and conversions) and sources of parameter estimates are given in the model-specific sections below and in the on-line material.

Table 1 Characteristics of models

	DLBCL sub-typing	BL versus DLBCL	PMBCL versus DLBLC
Intervention strategy	Diagnostic pathway including GEP test classifying patients as ABC, MHG or GCB and treating ABC and MHG with RB-CHOP and GCB patients with R-CHOP	Current clinic-pathological diagnostic pathway with the addition of GEP test	Current clinic-pathological diagnostic pathway with the addition of GEP test
Comparator strategy	Treat all DLBCL patients with R-CHOP	Current diagnostic pathway	Current diagnostic pathway
Assumption about test accuracy	Assumes new test is equivalent to test used in REMODL-B trial with no false positives or negatives. Model has capacity for false positives and negatives to be included when data is available.	Assumes diagnosis with GEP accurately classifies patients as BL or DLBCL and that diagnosis without GEP leaves patients wrongly diagnosed who were reclassified in Dave et al (2)	Assumes diagnosis with GEP accurately classifies patients as PMBCL or DLBCL and that diagnosis without GEP leaves patients wrongly diagnosed who were reclassified in Mottok et al (3)
Decision tree period and source of progression and survival within that period	5 years based on Davies et al which is an abstract reporting 5 year follow up data from the REMODL-B trial (4)	8 years based on Daneels et al (5) for DLCBL and Oosten et al (7) plus standard life tables for years 6-8.	8 years based on Daneels et al (5) for DLCBL and Giulino-Roth et al (9) plus standard life tables for years 6-8.
Survival of patients who died within decision tree period	One year based on median survival of patients who died in the 60-69-year-old age group in Daneels et al (5)	BL patients - Six months based on median survival of patients who died in Oosten et al (7). DLBCL patients – fifteen months based on median survival in 20-59 age category in Daneels et al (5).	PMBCL patients – 6.5 months based on median survival of patients who died in Guilino-Roth et al (9). DLBCL patients – fifteen months based on median survival in 20-59 age category in Daneels et al (5).
Survival of patients who survived the decision tree period	Based on average life expectancy for 70-year-olds (65 years median age in REMODL-B trial plus five year decision tree period (4))	Based on average life expectancy for 47-year-olds (39 years median age at diagnosis per Oosten et al (7) plus eight year decision tree period)	Based on average life expectancy for 42-year-olds (34 years median age at diagnosis per Guilino-Roth et al (9) plus eight-year decision tree period)
Impact of false positive	Not applicable	Receive more intensive treatment regimen. No impact on health outcomes.	Receive more intensive treatment regimen. No impact on health outcomes.
Impact of false negative	Not applicable	Receive a less intensive regimen. Estimated double risk of progression (11)	Receive a less intensive regimen. Higher probability of receiving radiotherapy with increased chance of long-term CVD and BC.

ABC – activated B cell sub-type of DLBCL, BC – breast cancer, BL – Burkitt lymphoma, CVD – cardio-vascular disease, DLBCL – diffuse large B cell lymphoma, GCB – germinal centre B cell sub-type of DLBCL, GEP – gene-expression profiling, MHG – molecular high grade sub-type of DLBCL, PMBCL – primary mediastinal B cell lymphoma, RB-CHOP – R-CHOP with the addition of Bortezomib, R-CHOP – rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone

2.7 DLBCL sub-typing model

The DLBCL sub-typing model compares treating all patients with R-CHOP to including the GEP test and treating ABC and MHG sub-types with R-CHOP plus Bortezomib (RB-CHOP) and remaining patients with R-CHOP. In both the treat all with R-CHOP and test and treat strategies of the decision tree, the probabilities of progression and subsequent survival at five years are taken from the latest follow-up data from the REMoDL-B randomised clinical trial including 801 patients with GEP subtypes. These results are reported in Abstract form only at the time of writing [4]. It is assumed that patients who died within the first five years had an average survival of one year. This is based on median survival of those who died in the 70-79 year old age group in Daneels et al [5]. For patients who survive the initial five-year period it is assumed that mortality reverts to standard life expectancy. Costs are included for treatment only and are mainly taken from Wang et al [12] a 2015 UK paper with costs uplifted to mid-2022. Wang et al based their costings on treatments current in 2013 and did not include CAR-T therapy. We based the additional cost of Bortezomib on dosage and cycle data from the REMoDL-B trial [13]. We based the proportions of patients receiving second and subsequent line treatments, except for CAR-T therapy on data from Daneels et al [5] and Moertl et al [14]. The proportion of patients receiving CAR-T therapy was based on a 2019 cohort from the West of Scotland, UK, data which is currently unpublished. Further detail about the calculation of the cost of treatments and proportion of patients receiving treatments is given in the Online Resources.

2.8 Differential diagnosis between BL and DLBCL and PMBCL and DLBCL models

The BL and PMBCL models explored the impact of adding a GEP test to the current diagnostic work-up. The current diagnostic strategy includes clinical aspects (such as the age of the patient and the location of the tumour), the appearance of the tumour under the microscope, immunohistochemistry (IHC) tests and some genetic tests including MYC and BCL2 and BCL6. The decision trees capture the reclassification of patients between a diagnosis of DLBCL and PMBCL or BL. No gold standard exists for the diagnosis of these conditions. Given that this is an early exploratory assessment, we have assumed that the introduction of a GEP would lead to more accurate classification of patients in line with estimates in the literature [2,3]. In the standard of care arm, there are a number of false positives (DLBCL cases diagnosed as either BL or PMBCL). This results in those patients receiving a more intensive treatment regimen at higher cost and lower utility value. There is some evidence of the impact on health outcomes of DLBCL patients being treated with DA-EPOCH-R which suggests that outcomes are equivalent [15]. We have assumed in the base case, that the same applies for DLBCL cases treated with an intensive regimen. In the standard of care arm there are also patients with BL or PMBCL who are diagnosed as suffering from DLBCL, which leads to less intensive treatment. For BL, Wasterlid et al, 2013, a small retrospective cohort analysis, found that high intensity regimens were associated with a hazard ratio of 2 (95% CI 1-4.1, $p = 0.04$) for overall survival at 2 years compared to low intensity regimens such as R-CHOP [11]. For PMBCL, a greater proportion of patients treated with R-CHOP will require radiotherapy to consolidate first-line chemotherapy [16]. This results in a higher proportion of late adverse events in the false negative population but is unlikely to directly impact response or survival in the short term [16].

It is assumed that patients who died within the first eight years had an average survival of six months for BL and 6.5 months for PMBCL. This is based on median survival of those who died in Oosten et al and Guilino-Roth et al respectively [7, 9]. For patients who survive the initial eight-year period it is assumed that mortality reverts to standard life expectancy. Costs are included for treatment only. For DLBCL and for second and subsequent line (excluding CAR-T) costs are taken from Wang et al adjusted for the proportion of patients receiving stem cell transplants [12]. Costs

for first line treatment for BL is based on Oosten et al [7] and for PMBCL based on the cost of first line treatment for DLBCL from Wang et al uplifted in line with data from Dholaria et al [15]. We based the proportions of patients receiving second and subsequent line treatments, except for CAR-T therapy on data from Daneels et al [5] and Moertl et al [14] for DLBCL and Oosten et al and Guilino-Roth et al for BL and PMBCL respectively [7,9]. No BL or PMBCL patients received CAR-T therapy based on the 2019 West of Scotland cohort. Further detail about the calculation of the cost of treatments and proportion of patients receiving treatments is given in the Online Resources. For the PMBCL and DLBCL model, long term adverse events (increased incidence of breast cancer and cardiovascular disease) are introduced for those patients who were treated with radiotherapy. Incidence and mortality were based on studies in patients with Hodgkin's lymphoma, but radiotherapy doses and location of treatment were similar to those described for PMBCL [17, 18].

2.9 Parameter estimates common to all three models

We used estimated incidence data for the UK from the Haematological Malignancies Research Network [1]. Health state utilities were applied to life years to estimate QALYs. Utility weights were taken from Knight et al, 2005 [19]. We applied a lower utility for intensive treatment to reflect increased short term adverse events with intensive treatment. We used a single utility for the disease-free state regardless of age, although as patients aged, QALYs would be subject to discounting. The only cost included were the costs of treatment. Existing diagnostic testing was not included as these costs were assumed not to vary between the treatment arms. Costs of palliative care were not included as they would only vary slightly between arms and they are small relative to other treatment costs. The cost of the test was not included as the maximum price will be the result of our threshold analysis. Resource costs were taken from the literature and converted to UK sterling (where necessary) using the average of the year the costs were incurred then uplifted to reflect 2022 prices using the consumer price inflation time series: health, from the UK Office for National Statistics [20]. As costs could change significantly due to drug price changes, we checked for significant changes from the source year to 2022 using the British National Formulary [21] and confirmed with clinical experts that no significant change had occurred. Only the cost of rituximab had changed significantly and clinical experts confirmed that this would affect low and high intensity regimens by a similar amount. Further information on sources of costs is included in the Online Resources. We calculated net monetary benefit (NMB) assuming a willingness to pay threshold of GBP 30,000 per QALY. NMB is calculated by multiplying QALYs gained by GBP 30,000 and adjusting for incremental costs. A positive NMB indicates that a technology is cost-effective at the chosen willingness to pay threshold (here GBP 30,000).

2.10 Characterising uncertainty

We calculated a base case threshold analysis for the maximum price of the DLBCL sub-typing, BL and PMBCL GEP signatures individually and in combination. We also conducted threshold analysis to determine the minimum hazard ratio for less intensive treatment in BL at a range of test prices. For the DLBCL sub-typing test, where we had robust trial data, we conducted a probabilistic sensitivity analysis. We also conducted one way sensitivity analyses for each model, varying one parameter at a time over a plausible range (95% confidence intervals for proportions, probabilities and utilities, up/down 20% for costs and estimated life years) to determine which parameters are the most influential on cost-effectiveness. Probabilistic sensitivity analysis was not carried out at this stage on the BL and PMBCL models due to the under-developed evidence base leading to a high level of uncertainty in key parameters. Internal validity of the models was independently verified. Additional sensitivity analysis was undertaken for the DLBCL sub-typing model including a treat-all strategy with RB-CHOP and performing analyses over 5 years as well as a lifetime horizon.

2.11 Approach to engagement with patients and others affected by the study

Patients were not actively involved in the formation of this study, but the developers plan to consult patient groups should the development progress.

2.12 Other relevant information

Except where explicitly noted modelling has been carried out in accordance with the ISPOR best practices guidelines [22] and the study has been reported according to CHEERS guidelines [23]. The models are available from the corresponding author on request. The study was carried out as part of an Innovate UK Knowledge Transfer Partnership (012321) between the University of Glasgow and BioClavis Limited. Innovate UK had no role in the design, conduct or reporting of the analysis.

3. Results

3.1 Study parameters

Details of all analytic inputs are provided in the Online Resources.

3.2 Test cost threshold analysis

Combined threshold analysis results are reported in Table 2.

Table 2 Base case results comparing diagnostic pathway with and without gene expression profile test

GEP test	Incremental costs/(cost saving) (GBP)	Incremental QALYs	Maximum price of test (GBP)
DLBCL sub-typing	(6,175)	0.2465	13,570
BL	275	0.0540	1,345
PMBCL	(406)	0.0011	437
Total	**(6,306)**	**0.3016**	**15,352**

BL – Burkitt lymphoma, DLCBL – diffuse large B cell lymphoma, GBP – Great Britain Pound, GEP – gene expression profile, LY – Life years, PMBCL – primary mediastinal B cell lymphoma, QALY – quality adjusted life year. Maximum price based on net monetary benefit (QALY gain valued at GBP 30,000 minus incremental cost or plus cost saving).

We estimate that the addition of GEP testing for subtypes of DLBCL and for BL and PMBCL would have a positive net monetary benefit of GBP 15,352 at a threshold of GBP 30,000 per QALY, which is the upper limit of the range used in the UK to determine whether health technologies should be reimbursed [9]. This means that the developers could potentially charge up to GBP 15,352 for the combined test and it would still remain cost effective. At base case values the DLBCL subtyping signature delivers an average QALY gain per patient of 0.2465 as the addition of bortezomib to the standard R-CHOP treatment improves survival in the ABC and MHG subtypes (approximately 40% of the DLBCL population). This signature delivers cost savings of over £6,000 per patient, primarily as a result of less patients having expensive second and subsequent line treatments which include stem cell transplants and CAR-T therapy. At base case values the BL and PMBCL signatures deliver small increases in QALYs, as a result of a small proportion of patients moving diagnosis and changing treatment regimen when the GEP signature is added to existing diagnostic procedures. The BL signature increases costs as a result of an increase in the proportion of patients treated with more intensive therapy. The addition of the PMBCL signature results in a smaller proportion of patients receiving intensive therapy and radiotherapy thus delivering a small average cost saving per patient.

3.3 Sensitivity and hazard ratio threshold analysis

A probabilistic sensitivity analysis was carried out for the DLBCL sub-typing test and results are shown in Figure 1. At a threshold of GBP 30,000 per QALY gained, the testing strategy is cost-effective compared to treat all with R-CHOP in 82% of 1,000 Monte Carlo simulations and cost-saving in 92%.

Figure 1 – Cost-effectiveness plane for Diffuse Large B Cell Lymphoma sub-typing test

[Figure 1 here]

One-way sensitivity analysis (Figure 2) showed that the DLBCL sub-typing result is most sensitive to the progression of patients with both ABC and GCB sub-types treated with R-CHOP, to the progression of patients with ABC sub-type treated with RB-CHOP and the mortality rate for all patients treated with R-CHOP (in the treat all with R-CHOP strategy).

Figure 2 – One way sensitivity analysis for diffuse large B cell subtyping test and treat strategy compared with treat all with R-CHOP

[Figure 2 here]

We undertook an analysis which included a treat-all with RB-CHOP strategy as a comparator, rather than treat-all with R-CHOP. This was a sensitivity, rather than the main analysis as RB-CHOP is not currently used as the standard of care in this population. The lifetime horizon results for the testing strategy compared to treat-all RB-CHOP result in a cost saving of £5,205, reduced QALY gains of 0.152 so an overall NMB of £630. This is considerably lower than the NMB when R-CHOP is used as the comparator. A five-year time-horizon was also considered in sensitivity analysis as this was the period for which we had robust trial data. Using treat-all R-CHOP as comparator with a five-year time horizon results in an NMB of £8,405, reduced from the lifetime horizon of £13,570 because the QALY gain is reduced. The corresponding figure for testing strategy versus treat-all RB-CHOP strategy is £4,126 increased from the lifetime horizon NMB of £630. This increase is because the QALY difference between the two strategies is captured for a shorter period so has less influence on the results. Both five year and lifetime results are included in the model which is available from the corresponding author on request.

One way sensitivity analysis was also undertaken for the BL and PMBCL signatures (Online Resources). The BL result is most sensitive to the estimated effect of undertreating a BL case as a result of a false negative diagnosis. Table 3 explores this sensitivity further showing that the threshold hazard ratio for progression by eight years due to false negative diagnosis is around 1.2. If the hazards are below this value, then the test would not be cost-effective even at a zero price. The BL test result is not sensitive to any of the other parameters, including sensitivity and specificity as the room for improvement over the current diagnosis is assumed to be small in this analysis.

Table 3 Sensitivity to changes in the hazard due to false negative patients (patients classified as DLBCL when underlying disease is BL) being treated less intensively

HRs for progression	Incremental costs (GBP)	Incremental QALYs	Net monetary benefit (GBP)
1	338	(0.0001)	(340)
1.2	326	0.0107	(3)
2 (base case)	275	0.054	1,345
4	149	0.1621	4,175

BL – Burkitt Lymphoma, GBP – Great Britain Pound, QALY – quality adjusted life year. A hazard ratio of 1.2. represents an increase in probability of 20% of a patient progressing if a patient with BL is treated with R-CHOP. Brackets indicate a negative result.

The PMBCL result is sensitive to the impact of false positive results (see Online Resources). The base case assumes that there is no impact of false positive results on progression, so the impact is only positive if these hazard ratios are increased. The results are also sensitive to the proportion of DLBCL cases diagnosed as DLBCL (akin to the specificity of the diagnostic process with the addition of the PMBCL signature). The sensitivity analysis at its lowest range assumes that there is no additional benefit of adding the GEP signature, which predictably results in a negative net monetary benefit.

4. Discussion

The aims of this early exploratory economic evaluation were to inform developers about the potential impact of the tests on costs and health outcomes and to inform pricing and evidence generation strategies. We found that GEP signatures sub-typing DLBCL and aiding the differential diagnosis of BL and PMBCL versus DLBCL may be cost effective in the UK at a combined cost of GBP

15,352. The main value of the test, and the one supported by the most robust evidence is the sub-typing in DLBCL. The benefit comes as progression and mortality is reduced in patients with ABC and MHG sub-types if bortezomib is added to standard R-CHOP treatment. Improved progression-free and overall survival leads to additional QALYs and to a reduction in costs as less patients require expensive second and subsequent line treatments including stem cell transplants and CAR-T therapy. The BL and PMBCL tests both show small positive net monetary benefit but the supporting evidence base is very weak. In BL, introducing the test may increase costs as more patients may be treated intensively. However, the gain in QALYs offsets this additional cost as the improved accuracy leads to fewer patients dying during initial therapy or failing to respond to a less intensive treatment. For PMBCL, the addition of the signature may be cost saving overall, as more intensive chemotherapy and radiotherapy is avoided and this more than offsets the additional cost of testing. The QALY gains from both tests are small because the proportion of patients reclassified is low. However, the impact on the individual patients reclassified will be substantial, with an increased chance of long-term survival in BL and a reduction in the chances of suffering late adverse effects from radiotherapy in PMBCL.

The evidence supporting the DLBCL sub-typing model was sufficiently robust to allow us to perform probabilistic sensitivity analysis. This showed that in 82% of 1,000 simulations, assuming the cost price to be zero, the testing strategy would be cost-effective compared to treating all patients with R-CHOP, which is assumed to be current standard of care. One-way sensitivity analysis identified that the results were sensitive to the progression and mortality parameter estimates for some of the sub-types. This data was taken from a relatively large clinical trial (801 patients with sub-typing data) which has recently reported five-year follow up data [4]. Differences in progression and survival had not been found in earlier trial follow-up and it would be useful to see whether other research groups can repeat these findings [13]. The therapeutic environment is moving rapidly in DLBCL with Polatazumab vedotin in combination with rituximab, cyclophosamide, doxorubicin and prednisolone (pola-R-CHP) approved on 1 March 2023, by the National Institute of Health and Care Excellence (NICE) in the UK for the first line treatment of DLBCL [24]. This was based on the results of the POLARIX trial which found that pola-R-CHP improved progression free survival in intermediate and high-risk patients by approximately 6% compared to R-CHOP [25]. Pola-R-CHP, first line, in this population is likely to become standard of care [26]. This will likely require a reconsideration of the sequence of treatment in relapsed or refractory patients as Polatazumab vedotin has been used as salvage chemotherapy prior to stem cell transplant. The REMODL-A trial, which is currently recruiting, is looking at adding acalabrutinib to R-CHOP in DLBCL patients and will also gather information about DLBCL sub-type using gene expression profiles [27]. Given this therapeutic environment, the development of a test in this area is relatively high risk. This is because the clinical and cost-effectiveness of a test and treat strategy is impacted by both the therapeutic agent used in identified sub-types and the standard of care to which the test and treat strategy is compared.

The diagnostic landscape in aggressive large B cell lymphoma is complex and there is no gold standard for diagnosis of any of the conditions under consideration. Disease classification is fluid as research continues to suggest different sub-divisions of disease. World Health Organisation reclassifications occurred in 2008 and 2016 and another reclassification is underway. Clinical studies often use a consensus panel approach to reach diagnosis, revisiting older cases when retrospective analysis is undertaken. To estimate the improvement which the introduction of GEP signatures would make, we assumed that the GEP status of disease was the true diagnosis and that the cases reclassified from current diagnosis represented the improvement in diagnostic performance expected from the introduction of the test. The number of patients reclassified was derived from small studies of GEP performance [2, 3]. This optimistic assumption was made as the studies

indicated that only a small proportion of patients would receive a different diagnosis and we aimed at this early stage to explore the full potential of the test in development. Should the developers take this test further, clinical studies will be required to arrive at an estimate of the number of patients reclassified as a result of the addition of a GEP test to the information available at diagnosis. QALY gains for the DLBCL sub-typing test may be generalisable outside the UK if treatment pathways are similar. For the BL and PMBCL tests QALY gains should be generalisable outside the UK assuming treatment pathways are similar, and the tests lead to the reclassifications shown in the small studies relied upon here [2,3]. The main influence on the BL and PMBCL results is from net movements of patients in and out of intensive first-line treatment regimens and the cost differences between them. These cost differences may not be replicated in other jurisdictions and good cost estimates are lacking, in particular for first line treatment in PMBCL.

A key aspect of the design of the test will be to determine which population will be tested and to ensure evidence is generated in this population. This is important as it impacts upon test performance and prevalence of DLBCL sub-types and BL/PMBCL in the population. In this study, we assumed that all patients with aggressive B cell lymphoma would be tested (approximately 5,000 per annum in the UK) but this assumption may not be appropriate for all contexts of use. The developers should engage with stakeholders, including hematopathologists and oncologists, in different settings to ascertain how the tests might be used. This should precede testing for analytical validity as it will impact on the samples to be tested. If the population to be tested is too small, this may result in it being unattractive as a commercial opportunity for the developers.

A previous cost-effectiveness analysis was published by Chen et al in 2019, looking at the potential cost effectiveness of a precision medicine treatment strategy for DLBCL [28]. This found that in a US setting a strategy which identified ABC sub-types of DLBCL and added lenalidomide to R-CHOP was cost effective compared to a treat all with R-CHOP strategy. As far as we are aware, this is the first economic evaluation to estimate the impact of introducing a GEP signature to determine sub-types of DLBCL and to distinguish between BL and DLBCL or PMBCL and DLBCL. We have built health economic models to cover the full life-course of aggressive B cell lymphoma, informed by evidence from population-wide observational studies. Our models have been validated by experienced clinicians working in the West of Scotland, UK.

The study has some significant limitations. The major limitation of this study is the paucity of evidence to inform estimates of key parameters in the BL and PMBCL models, in particular the impact of more intensive treatment for patients with DLBCL or less intensive treatment for those with BL and the number of patients likely to be reclassified by the addition of a GEP to the diagnostic pathway. Furthermore, disease progression in the models was informed by observational studies from settings other than the UK rather than individual level patient data in the UK setting. We, therefore, make the implicit assumption that the data in the observational studies (from the US, Netherlands and Belgium) are generalisable to the UK setting. If individual level data was available a simulation-based approach to modelling could account for time on treatment and time to relapse. In this complex disease area, if individual level data is available, simulation modelling may be more appropriate [12]. Observational studies also carry the risk that the diagnosis is not consistent across centres or time periods so that the data used may not represent the disease of interest. Utility data was taken from a 2004 health technology assessment [19] based on earlier studies. As both arms of each model used the same utility values and results were not found to be sensitive to utility values, it is unlikely that using more recent values would have a large impact on the findings of this study. Late adverse events of radiotherapy were based on estimates for Hodgkin's lymphoma and the data is, necessarily, based on radiotherapy treatments administered decades ago [17,18]. Our estimates

of the number of patients reclassified were based on small studies of other GEP signatures [2, 3]. However, this is the best evidence available at present until developers commission their own technology-specific studies. Cost information was derived from a variety of sources in the literature and was lacking for DA-EPOCH-R in the UK setting. We estimated the cost using the relative price difference between DLBCL and PMBCL from the US applied to DLBCL treatment costs from a UK paper [12,15]. A micro-costing for treatment regimens in BL and PMBCL in the UK setting would be useful particularly as R-CHOP21 is now being suggested as an alternative regimen for PMBCL [6].

This study has shown that there is potential for GEP signatures to aid the differential diagnosis of BL and PMBCL from DLBCL to be cost-effective and cost saving in the UK. Cost-effectiveness is driven primarily by improved progression-free and overall survival following DLBCL sub-typing and avoidance of expensive second and subsequent-line treatments. For BL and PMBCL cost-effectiveness is driven by the difference in first-line treatment costs and the net increase or decrease in the proportion of patients receiving an intensive treatment regimen. Next steps for the developers, should they decide that further development is commercially worthwhile, include comparing the results of their DLBCL sub-typing signature with the signature used in the REMODL-B trial, engaging with stakeholders to reduce uncertainty around the appropriate population to test for BL and PMBCL, further developing the signatures using samples from the appropriate population and generating evidence around the number of patients who would be reclassified as a result of the addition of the BL and PMBCL signatures. A later economic evaluation would benefit from individual level data from the UK, a micro-costing of intensive treatment regimens in the UK setting and adding data specific to the signatures in development regarding sub-typing and reclassification.

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Glossary

BFM – Berlin – Frankfurt – Munster protocol

DA-EPOCH-R – dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, rituximab

HOVON Hemato-Oncologie voor Volwassenen Nederland (HOVON – the Haemato Oncology Foundation for Adults in the Netherlands). cyclophosfamide, cytacarabine, methotrexate, adriamycine, etoposide, vincristine, prednisolone, rituximab, melphalan, carmustine, mitoxanatrone

LMB – Lymphome Malins B - cyclophosfamide, cytacarabine, methotrexate, adriamycine, etoposide, vincristine, prednisolone, hydroxycortison, rituximab

Pola-R-CHP – polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin hydrochloride and prednisone

R-ACVBP – rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone

R-CHOP14 – rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone given every 14 days

R-CHOP21 – rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone given every 21 days

R-CODOX-M/I-VAC - rituximab, cyclophosphamide, vincristine, methotrexate, cytarabine, ifosfamide, etoposide

Figure 1 – Cost-effectiveness plane for Diffuse Large B Cell Lymphoma sub-typing test

[Figure 1 here]

Blue dots indicate results from a 1,000 iterations Monte Carlo simulation for the costs and QALY impacts of comparing a sub-typing testing strategy for Diffuse Large B Cell Lymphoma. In the bottom right hand section of the plane, the test and treat strategy of introducing a GEP test then adding Bortezomib to R-CHOP for activated B-Cell (ABC) and molecular high grade (MHG) sub-types is both cheaper and more effective than the treat all with R-CHOP strategy. The black line shows a threshold for cost-effectiveness of GBP30,000 per QALY. In the simulation shown 82% of simulations show the testing strategy to be cost effective (to the right of the black line) and 92% cost saving (negative incremental costs). QALY – quality adjusted life year.

Figure 2 – One way sensitivity analysis for diffuse large B cell subtyping test and treat strategy compared with treat all with R-CHOP

[Figure 2 here]

Figure shows the sensitivity of the net monetary benefit (NMB) result (base case GBP 13,570) to changing a single parameter estimate. Probabilities/proportions/utilities are varied to the lower and upper limits of 95% confidence intervals, costs and life years are varied up and down by 20%. Results are insensitive to changes made in parameters not shown. Blue bar indicates the NMB at the lower limit, red bar indicates NMB at the higher limit.