Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Next generation sequencing for DLBCL classification (HTG EdgeSeq DLBCL Cell of Origin Assay)
Topic exploration report number:	TER220

Introduction and aims

The HTG EdgeSeq DLBCL Cell of Origin Assay is an in vitro diagnostic assay which is used to classify the tumours of people with diffuse large B-cell lymphoma (DLBCL) into activated B-cell like, germinal centre B-cell like or unclassified subtypes. This classification is known as cell of origin (COO) and provides information about likely prognosis and suitability of treatment strategies. HTG EdgeSeq uses a single 5µm section of formalin-fixed paraffin embedded tissue biopsy from the patient, and applies a classification algorithm to gene expression profiling data based on next-generation sequencing to classify tumours into the subtypes. The technology works in concert with an Illumina MiSeq sequencer for detection. The HTG Edge host system generates a digital report of the determined COO.

The manufacturer (HTG Diagnostics) notes that in current practice most laboratories use immunohistochemical panels, requiring 3-6 sections of formalin-fixed paraffin embedded tissue, to classify the DLBCL phenotype as there is not a routine alternative. A number of immunohistochemical algorithms have been proposed, including the Hans criteria, Colomo, Muris, Natkunam, Nyman, Choi, Tally and Visco. However, the prognostic value of COO established using immunohistochemistry has been shown to be inconsistent. In addition, immunohistochemistry algorithms do not recognise the 10%-15% of tumours that are unclassified by gene expression profiling. NICE guideline NG52 (*Non-Hodgkin's lymphoma: diagnosis and management*) recommends that immunohistochemical panels to determine COO are not used in people with DLBCL. Gene expression profiling to establish COO is not routinely used outside of the clinical trial setting. There are alternative methods for gene expression profiling, including conventional microarray gene expression profiling.

Health Technology Wales researchers searched for evidence on 'HTG EdgeSeq DLBCL Cell of Origin Assay EU' specifically, as well as more broadly for cell of origin subtype classification, gene expression profiling and next generation sequencing in DLBCL. The population of interest was people with diffuse large B-cell lymphoma (DLBCL) who are eligible for rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or similar therapy.

Summary of evidence

Health Technology Wales researchers identified relevant guidelines and systematic reviews, so did not search for primary studies for the purpose of this Topic Exploration Report.

HTG EdgeSeq DLBCL Cell of Origin Assay EU is a digital health technology and was determined to be a Tier 3b technology according to the Evidence Standards Framework for Digital Health Technologies**.** Technologies within this classification uses data to diagnose a condition in a patient, or to guide a diagnostic decision made by a healthcare professional. For technologies of this classification, it is recommended that, at a minimum, a high quality intervention study using a quasi-experimental or experimental design is produced to demonstrate effectiveness of the technology.

Guidelines

NICE guideline NG52 (*Non-Hodgkin's lymphoma: diagnosis and management*) was published in 2016 and makes the following relevant recommendation on the stratification of high grade B-cell lymphomas:

- Do not use immunohistochemistry to assess the prognostic value associated with cell of origin in people with DLBCL

The guideline states that this strong recommendation was made on the basis of a large body of moderate quality evidence which indicated that overall and progression free survival did not consistently differ between subtypes of DLBCL identified using immunohistochemistry, in contrast to the survival difference evident in gene expression profiling-based studies. The Guideline Committee felt that immunohistochemical panels are insufficiently reliable and reproducible, but were unable to make recommendations for gene expression profiling as the various available systems were not robust enough to be used in routine practice at the time, though the technology and analytical methods were said to be evolving rapidly and worked in research settings.

While the population is not relevant to this topic exploration report, in 2017 NICE produced a Medtech Innovation Briefing on the use of HTG EdgeSeq for ALK status testing in non-small cell lung cancer, which provides useful information. The Medtech Innovation Briefing notes that the automatic generation of a report which is interpretable by any clinician, without training or experience, is an innovative aspect of the test. Immunohistochemical testing is reported to take around two minutes and to cost £30 to £50 per test. NICE's Medtech Innovation Briefing reports that the HTG EdgeSeq ALKPlus Assay EU costs £250 to £300 (excluding VAT) and upkeep of the HTG EdgeSeq analyser costs £10,000 per year. The Medtech Innovation Briefing also highlights that laboratories also need to purchase a compatible Illumina MiSeq system.

An evidence-based guideline on the management of DLBCL was published in 2016 on behalf of the British Committee for Standards in Haematology. The guideline notes that "several immunohistochemistry algorithms (Hans, Choi and Meyer) have attempted to reproduce the GEP classification with good correlation, but the resultant prognostic value has been inconsistent in patients treated with rituximab in addition to chemotherapy" however, the guideline does not make a recommendation on the use of gene expression profiling. Both this guideline and NICE guideline NG52 make recommendations on other prognostic factors including age, International Prognostic Index and the use of fluorescence in situ hybridisation to identify MYC rearrangements.

The World Health Organization (WHO) 2016 revision of the classification of lymphoid neoplasms state that the use of immunohistochemistry algorithms is acceptable, as gene expression

profiling is still not a routine test. The WHO revision states that newer methods based on quantification of RNA transcripts may be a promising alternative to immunohistochemistry algorithms.

Alberta Health Services produced a clinical practice guideline for DLBCL (effective September 2019) which states that immunohistochemical panels used to determine COO have limitations regardless of the algorithm used, when compared with gene expression profiling. The guideline concedes that germinal centre B-cell like versus non germinal centre B-cell like COO as determined by immunohistochemical panels does correlate with survival rates following R-CHOP. The guideline states that Alberta haematopathologists currently use the Hans algorithm.

The 2015 European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow-up for DLBCL state that cell of origin determined by gene expression profiling is a major prognostic factor. The guideline considers that newer methods based on the evaluation of a limited set of genes rather than conventional gene expression profiling is being used in the setting of clinical trials. The guideline recommends that immunohistochemical techniques are not routinely used for the basis of clinical decisions. No recommendations are made on the use of gene expression profiling.

The European Society for Medical Oncology Consensus Conference recommendations for elderly patients with malignant lymphoma similarly recommended that in elderly people fit for curative treatment, "a cell of origin phenotype may be obtained based on immunohistochemistry, but that it is not recommended to base clinical decisions on these results".

Systematic reviews

One meta-analysis (Read et al, 2014) of gene expression profiling and immunohistochemistry algorithms included 24 studies, six of which considered gene expression profiling. The study concluded that there is a lack of evidence to support the use of the Hans and Choi algorithms and that gene expression profiling remains the gold standard for classifying DLBCL into subgroups to inform decisions on treatment options and provide a prognosis. The meta-analysis did not give detail on the types of gene expression profiling assay used in the six included studies, however it highlighted a study on the Lymph2Cx assay; a digital gene expression test by the Lymphoma/Leukemia Molecular Profiling Project. The Lymph2Cx assay uses 20 genes to assign DLBCL subtypes using formalin-fixed paraffin embedded tissue.

One systematic review (Hansen et al, 2017) on COO, MYC and BCL2 or BCL6 translocation status for prognostic information included 44 studies in total. It found that half of the studies on COO determined by gene expression profiling found that germinal centre B-cell like subtype is associated with better overall survival, while the remaining studies found no effect. The study found that COO determined by immunohistochemistry added no prognostic value in addition to the International Prognostic Index.

One study (Staiger et al, 2017) assessed COO using the Lymph2Cx assay across two randomised controlled trials. It found no significant difference between DLBCL subtypes for event-free survival, progression-free survival or overall survival in people treated with R-CHOP. In addition, the study found no differences in multivariable analyses when adjusting for International Prognostic Index factors in event-free survival, progression-free survival or overall survival.

Evidence from HealthTechConnect submission by manufacturer

One study (Schaffer et al, 2018) considered accordance between immunohistochemistry using the Hans algorithm, microarray gene expression profiling, a digital gene expression-based

Lymphoma Subtyping Test (Lymph2Cx, or NanoString) and a next-generation sequencing-based assay (HTG EdgeSeq DLBCL Cell of Origin Assay EU). For the purposes of the study, any samples that were subtyped as 'germinal centre B-cell' like remained so, while samples assigned 'unclassified' were considered 'non-germinal centre B-cell like'. The study found that the positive percent agreement of HTG EdgeSeq was 92% with the microarray gene expression profiling method against which it was calibrated, and 78.2% concordant with immunohistochemistry using the Hans algorithm.

Areas of uncertainty

The current standard of care in determining COO in people with DLBCL is uncertain. While NICE recommends that COO by immunohistochemistry is not used, the manufacturer noted that immunohistochemistry is the current standard of care due to the lack of a routine alternative. The HTG EdgeSeq DLBCL COO assay for COO classification is currently used in the context of clinical trials (e.g. to determine eligibility).

No studies were found which compared different methods for gene expression profiling for COO (e.g. conventional microarray, Lymph2Cx assay and HTG EdgeSeq DLBCL Cell of Origin Assay EU) with other prognostic variables, such as the MYC and BCL2 or BCL6 translocation status and the International Prognostic Index in the clinical setting.

No evidence was identified which assessed the influence of HTG EdgeSeq DLBCL Cell of Origin Assay EU, on downstream patient outcomes, or how these outcomes compare to use of other methods of determining COO. Furthermore, no evidence was identified that assessed the cost effectiveness of using next-generation sequencing to assess COO in people with DLBCL. However, we focussed on outcomes from systematic reviews and other sources of secondary evidence and did not carry out an exhaustive search for all relevant primary studies.

Conclusions

The guidelines identified in this topic exploration report focused on the limitations of immunohistochemical panels for determining COO. There is a need to establish the current standard of care for determining COO or otherwise stratifying patients with DLBCL.

NICE Guideline NG52 (published in 2016) did not make recommendations on the use of gene expression profiling to determine COO as the technology was rapidly evolving at the time and the guideline committee felt that the available systems were not yet robust enough for routine practice. There are no studies which address the clinical and cost effectiveness of the HTG EdgeSeq DLBCL Cell of Origin Assay compared with other methods for determining COO (such as the Lymph2Cx assay, or conventional microarray).

Two systematic reviews/meta-analyses considered different prognostic factors including gene expression profiling to determine COO, but did not compare different methods of gene expression profiling for determining COO (for example conventional microarray or next generation sequencing).

Evidence supplied by the manufacturer in the Health Tech Connect submission focused either on measures of agreement between the HTG EdgeSeq DLBCL Cell of Origin Assay EU and other available assays, or on the use of the assay to determine patient eligibility for clinical trials in DLBCL. No evidence was identified which considered the effect of using HTG EdgeSeq DLBCL

Cell of Origin Assay EU on patient outcomes (but a full search for this is beyond the scope of this report).

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant evidence from this source
Health Technology Assessment Group	We did not identify any relevant evidence from this source
Health Information and Quality Authority	We did not identify any relevant evidence from this source
EUnetHTA https://www.eunethta.eu/rapid-reas/	We did not identify any relevant evidence from this source
International HTA Database	We did not identify any relevant evidence from this source
UK guidelines and guidance	
SIGN	We did not identify any relevant evidence from this source
NICE	National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma: diagnosis and management. NICE guideline [NG52]. Published date: 20 July 2016. https://www.nice.org.uk/guidance/ng52 National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma diagnosis and staging. NICE Pathway. https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma#content=view-node%3Anodes-diagnosis-and-staging National Institute for Health and Care Excellence. HTG EdgeSeq ALKPlus Assay EU for ALK status testing in non-small-cell lung cancer. Medtech innovation briefing [MIB128]. Published date: 07 November 2017. https://www.nice.org.uk/advice/mib128
Secondary literature and economic evaluations	
https://www.epistemonikos.org/en/	We did not identify any relevant evidence from this source
https://www.tripdatabase.com/	Guidelines • Chaganti S, Illidge T, Barrington S, Mckay P, Linton K, Cwynarski K, McMillan A, Davies A, Stern S, Peggs K; British Committee for Standards in Haematology. Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol. 2016 Jul;174(1):43-56. https://doi.org/10.1111/bjh.14136 • Alberta Health Services. Clinical Practice Guideline LYHE-002 Version 12 LYMPHOMA. Effective Date: September 2019 https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lyhe002-lymphoma.pdf • Buske C, Hutchings M, Ladetto M, Goede V, Mey U, Soubeyran P, Spina M, Stauder R, Trněný M, Wedding U, Fields P; ESMO Lymphoma Consensus Conference Panel Members. ESMO Consensus Conference on malignant lymphoma: general perspectives and recommendations for the clinical management of the elderly patient with malignant lymphoma. Ann Oncol. 2018 Mar 1;29(3):544-562. https://doi.org/10.1093/annonc/mdx413 • Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Walewski J, André M, Johnson PW, Pfreundschuh M, Ladetto M; ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO

	Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v116-25. https://doi.org/10.1093/annonc/mdv304 Systematic reviews • Read JA, Koff JL, Nastoupil LJ, Williams JN, Cohen JB, Flowers CR. Evaluating cell-of-origin subtype methods for predicting diffuse large B-cell lymphoma survival: a meta-analysis of gene expression profiling and immunohistochemistry algorithms. Clin Lymphoma Myeloma Leuk. 2014 Dec;14(6):460-467.e2. Epub 2014 Jun 12. https://doi.org/10.1016/j.clml.2014.05.002 • Schmidt-Hansen M, Berendse S, Marafioti T, McNamara C. Does cell-of-origin or MYC, BCL2 or BCL6 translocation status provide prognostic information beyond the International Prognostic Index score in patients with diffuse large B-cell lymphoma treated with rituximab and chemotherapy? A systematic review. Leuk Lymphoma. 2017 Oct;58(10):2403-2418. https://doi.org/10.1080/10428194.2017.1287364 • Staiger AM, Ziepert M, Horn H, Scott DW, Barth TFE, Bernd HW, Feller AC, Klapper W, Szczepanowski M, Hummel M, Stein H, Lenze D, Hansmann ML, Hartmann S, Möller P, Cogliatti S, Lenz G, Trümper L, Löffler M, Schmitz N, Pfreundschuh M, Rosenwald A, Ott G; German High-Grade Lymphoma Study Group. Clinical Impact of the Cell-of-Origin Classification and the MYC/ BCL2 Dual Expresser Status in Diffuse Large B-Cell Lymphoma Treated Within Prospective Clinical Trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group. J Clin Oncol. 2017 Aug 1;35(22):2515-2526. https://doi.org/10.1200/jco.2016.70.3660
Cochrane library	We did not identify any relevant evidence from this source
Medline (via Ovid)	We did not find any additional evidence from this source
Ongoing primary or secondary research	
PROSPERO database	We did not identify any relevant evidence from this source
Other	
Evidence provided by the technology developer	• Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016 May 19;127(20):2375-90. https://doi.org/10.1182/blood-2016-01-643569 • Schaffer M, Chaturvedi S, Alvarez JD, Frans S, Aquino R, Hall B, Wildgust M, Balasubramanian S. Comparison of Immunohistochemistry Assay Results with Gene Expression Profiling Methods for Diffuse Large B-Cell Lymphoma Subtype Identification in Matched Patient Samples. Journal of Molecular Biomarkers & Diagnosis. 2018. 9(2). https://doi.org/10.4172/21559929.1000386

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Concepts used:	HTG EdgeSeq DLBCL Cell of Origin Assay, Cell of origin assay, cell of origin, gene expression profiling (GEP), next generation sequencing, quantitative nuclease protection