

Appendix A

Electronic search strategy

The literature search structured by the PICO approach was based on a research question [1].

Research question: How can alternatively spliced mRNAs or proteins be used as diagnostic, prognostic or predictive biomarkers in diffuse large B-cell lymphoma?

Relevant MeSH or Emtree terms and free-text words were selected according to the research question in the four categories: Population, intervention, comparison and outcome (Table A).

TABLE A

Structure of the PICO search strategy and terms used [1].

PICO search strategy		
AND		
OR	Population	MeSH/EMTREE: Lymphoma, Large B-Cell, Diffuse Free-text: Diffuse Large B-Cell Lymphoma*, Diffuse Large-Cell Lymphoma*, DLBCL
	Intervention	MeSH/EMTREE: RNA splicing, Protein isoforms Free-text: RNA splicing, Alternative splicing, Alternate splicing, Alternative RNA splicing, Alternate RNA splicing, Protein isoform*, mRNA isoform*, Splice variant*, Splicing variant*, Alternatively spliced, Alternative transcript*, Alternate transcript*
	Comparison Outcome	- MeSH/EMTREE: Biological markers, Diagnosis, Prognosis, Individualized medicine Free-text: Biological marker*, Biomarker*, Clinical marker*, Prognosis, Prognostic, Diagnosis, Diagnostic, Prediction, Predictive, Individualized medicine, Personalized medicine

Table B is used to combine the terms in a structured way in PubMed, Embase and Scopus.

TABLE B

Search results in PubMed.

#	Combinations of terms	Search result
#1	((((((((("Lymphoma, Large B-Cell, Diffuse"[Mesh]) OR DLBCL) OR diffuse large b-cell lymphoma) OR diffuse large b-cell lymphomas) OR diffuse large-cell lymphoma) OR diffuse large-cell lymphomas))	20,483
#2	((((((((((((((((("RNA Splicing"[Mesh]) OR "Protein Isoforms"[Mesh]) OR mrna isoform) OR mrna isoforms) OR rna splicing) OR alternative splicing) OR alternate splicing) OR alternative RNA splicing) OR alternate RNA splicing) OR protein isoform) OR protein isoforms) OR splice variant) OR splice variants) OR alternatively spliced) OR isoform) OR isoforms) OR alternative transcript) OR alternate transcript) OR alternative transcripts) OR alternate transcripts))	220,872
#3	((((((((((((((((("Biological Markers"[Mesh]) OR "Diagnosis"[Mesh]) OR "Prognosis"[Mesh]) OR "Individualized Medicine"[Mesh]) OR biological marker) OR biological markers) OR biomarker) OR biomarkers) OR clinical marker) OR clinical markers) OR prognosis) OR prognostic) OR prediction) OR predictive) OR diagnosis) OR diagnostic) OR individualized medicine) OR personalized medicine))))))	9,568,778
#4	#1 AND #2 AND #3	94

The results of each in search the databases are presented in Tables B, C and D.

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TABLE C

Search results in Embase.

	Combinations of terms	Search result
#1	'diffuse large b cell lymphoma'/exp OR 'diffuse large b cell lymphoma' OR 'diffuse large cell lymphoma'/exp OR 'diffuse large cell lymphoma' OR 'diffuse large cell lymphomas' OR 'diffuse large b-cell lymphomas' OR 'dlbel'/exp OR 'dlbcl'	25,739
#2	'rna splicing'/exp OR 'rna splicing' OR 'protein isoform'/exp OR 'protein isoform' OR 'protein isoforms'/exp OR 'protein isoforms' OR 'mrna isoform'/exp OR 'mrna isoform' OR 'mrna isoforms'/exp OR 'mrna isoforms' OR 'alternative splicing'/exp OR 'alternative splicing' OR 'alternate splicing' OR 'alternate RNA splicing' OR 'alternative RNA splicing'/exp OR 'alternative RNA splicing' OR 'splice variant' OR 'splice variants' OR 'splicing variants' OR 'splicing variant' OR 'alternatively spliced' OR 'alternate spliced' OR 'alternate transcript' OR 'alternative transcript' OR 'alternate transcripts' OR 'alternative transcripts'	76,755
#3	'biological markers'/exp OR 'biological markers' OR 'biological marker'/exp OR 'biological marker' OR 'biomarker'/exp OR 'biomarker' OR 'biomarkers'/exp OR 'biomarkers' OR 'clinical marker' OR 'clinical markers' OR 'diagnosis'/exp OR 'diagnosis' OR 'prognosis'/exp OR 'prognosis' OR 'prediction'/exp OR 'prediction' OR 'diagnostic' OR 'prognostic' OR 'predictive' OR 'individualised medicine'/exp OR 'individualised medicine' OR 'individualized medicine'/exp OR 'individualized medicine' OR 'personalised medicine'/exp OR 'personalised medicine' OR 'personalized medicine'/exp OR 'personalized medicine'	7,520,527
#4	#1 AND #2 AND #3	36

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TABLE D

Search results in Scopus.

	Combinations of terms	Search result
#1	(TITLE-ABS-KEY(diffuse large-cell lymphoma) OR TITLE-ABS-KEY(dlbcl) OR TITLE-ABS-KEY(diffuse large b-cell lymphoma) OR TITLE-ABS-KEY(diffuse large-cell lymphomas) OR TITLE-ABS-KEY(diffuse large b-cell lymphomas))	14,882
#2	(TITLE-ABS-KEY(rna splicing) OR TITLE-ABS-KEY(protein isoform) OR TITLE-ABS-KEY(protein isoforms) OR TITLE-ABS-KEY(mrna isoform) OR TITLE-ABS-KEY(mrna isoforms) OR TITLE-ABS-KEY(alternative splicing) OR TITLE-ABS-KEY(alternate rna splicing) OR TITLE-ABS-KEY(splice variant) OR TITLE-ABS-KEY(splice variants) OR TITLE-ABS-KEY(splicing variant) OR TITLE-ABS-KEY(splicing variants) OR TITLE-ABS-KEY(alternatively spliced) OR TITLE-ABS-KEY(alternative transcript) OR TITLE-ABS-KEY(alternative transcripts) OR TITLE-ABS-KEY(alternate transcript) OR TITLE-ABS-KEY(alternate transcripts))	159,548
#3	(TITLE-ABS-KEY(biological marker) OR TITLE-ABS-KEY(biological markers) OR TITLE-ABS-KEY(biomarker) OR TITLE-ABS-KEY(biomarkers) OR TITLE-ABS-KEY(clinical marker) OR TITLE-ABS-KEY(clinical markers) OR TITLE-ABS-KEY(diagnosis) OR TITLE-ABS-KEY(diagnostic) OR TITLE-ABS-KEY(prognosis) OR TITLE-ABS-KEY(prognostic) OR TITLE-ABS-KEY(prediction) OR TITLE-ABS-KEY(predictive) OR TITLE-ABS-KEY(individualized medicine) OR TITLE-ABS-KEY(personalized medicine))	5,603,516
#4	#1 AND #2 AND #3	30

The results of #4 in all databases were transferred to Mendeley where duplicates were removed. Titles and abstracts were reviewed before final inclusion.

LITERATURE

1. Schardt C, Adams MB, Owens T et al. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:16.