Lymphoma Diagnosis

LYMPHOSIGN

LYMPHOTRANSCRIPT

CliniSciences

Introduction

Lymphomas are a group of cancers that affect the lymphatic system, which is part of the immune system. Lymphomas can be classified into two main types: Hodgkin's lymphoma and **non-Hodgkin's lymphoma**. Within these types, many subtypes have different clinical features, prognoses, and treatment options. Therefore, it is important to accurately diagnose and classify lymphomas based on their molecular characteristics.

One of the molecular features that can be used to identify and distinguish different types of lymphomas is gene expression signatures. Gene expression signatures are patterns of gene expression levels that reflect the biological state of a cell or a tissue. By comparing the gene expression signatures of normal and tumor samples, or between different tumor subtypes, it is possible to find genes that are differentially expressed or regulated in lymphomas. These genes can provide insights into the molecular mechanisms, pathways, and functions that are involved in lymphomagenesis and progression.

Another molecular feature that can be used to **identify** and characterize different types of lymphomas is **fusion transcripts**. Fusion transcripts are abnormal RNA molecules that result from the joining of two or more genes that are normally not connected. Fusion transcripts can be caused by chromosomal rearrangements, such as translocations, deletions, inversions, or amplifications, that bring together two gene loci. Fusion transcripts can also be caused by splicing errors, such as read-through events, that join two adjacent genes. Fusion transcripts can have various effects on the function and regulation of the fused genes, such as altering their expression levels, protein domains, interactions, or activities. Fusion transcripts can also create novel proteins that have new or enhanced functions that contribute to oncogenesis.

In this brochure will introduce two innovative products :
LymphoSign Kit and LymphoTranscript Kit, which classify non-Hodgkin's lymphomas, and detect fusion transcripts identified in lymphomas.

LymphoSign

For the classification of lymphomas

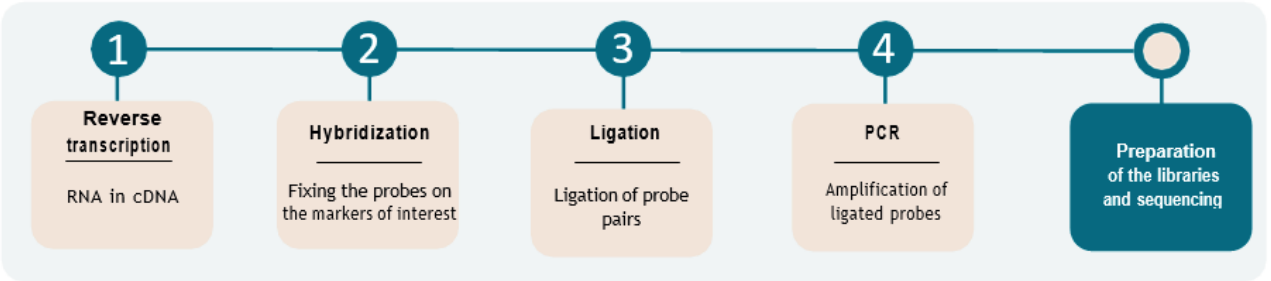
Genexpath's LymphoSign solution allows the characterization of non-Hodgkin lymphoma (NHL). It evaluates the degree of differentiation of tumor cells by analyzing the expression level of more than **130 relevant genetic markers**.

With an AI trained on a base of more than 3000 cases, the **RT-MIS** platform establishes the most probable classification between **13 subtypes of NHL B and T**.

RT-MLPSeq - a simple and fast technique

The **LymphoSign** test uses a semi-quantitative method: **RT-MLPSeq**.

The multi-step *in vitro* test simultaneously evaluates **genetic markers** (genes, mutations, chromosomal translocations, etc.) using pairs of specific oligo-nucleotide probes for each of them.



This *in vitro* test is associated with high-throughput sequencing that allows multiple samples and dozens of genes to be tested simultaneously.

Characteristics

- **1/2 day of manipulation**
- **Low RNA quantity needed**
- **Suitable for FFPE samples**
- **Sensitive thanks to short probes**
- **Sequencing with other libraries possible**
- **Increased specificity thanks to UMI**
- **100,000 reads are sufficient**
- **Bioinformatic analysis included**
- **Access to complete raw data**

Application domain	Gene expression		
Handling duration	≃4h before sequencing	Actual working time	≃1h-1h30
Type of samples	Fresh, frozen or fixed and paraffin-embedded tissue biopsies		
Input quantity	Between 50 and 500ng of RNA in a volume of 2µL		
Contents of the reagent kit	Probes targeting 137 markers of interest, barcodes, sequence primer		
Material compatibility	Sequencer Illumina®		

Categories	Cond.
GEP-LS08	8 reactions
GEP-LS16	16 reactions
GEP-LS24	24 reactions
GEP-LS48	48 reactions

For *in vitro* diagnostic use. For professional use only.
Please read the instructions carefully before use.

Frequently Asked Questions : Kit LymphoSign/RT-MIS

Table of contents :

1. What markers are present in the LymphoSign test?

ABC	GCB	PMBL	Doubles Expressors	Others markers
TACI	CD10	IL4I1	BCL2#1 (exon1-2)	EBER1
FOXP1	LMO2	CD23	BCL2#2 (exon1b-2b)	HTLV1
LIMD1	ASB13	CD30	MYC#1 (exon1-2)	KI67
IRF4	NEK6	MAL	MYC#2 (exon2-3)	CD68
PIM2	MYBL1	CD95		CD163
CCDC5O	MAML3	CD71		CCND1
CREB3L2	ITPKB	FGFR1		CCND2
CYB5R2	SERPINA9	JAK2		ZAP70
SH3BP5	S1PR2	TRAF1		ANXA1
RAB7L1	BCL6#1 (exon1-2)	STAT6		CRBN
	BCL6#2 (exon3-4)	PD-L1		APRIL
		PD-L2		BAFF
				BCMA

B cells	Ig genes	Gene fusions	T cells	CCR4
CD19	Iα-Cα	BCL6-Cα	TCRα	CCR7
MS4A1 (CD20)	Iα-Cε	BCL6-Cε	TCRβ	CD56
CD22	Iα-Cγ	BCL6-Cγ	TCRγ	CD70
CD27	Iα-Cμ	BCL6-Cμ	TCRδ	DUSP22
CD38	Iε-Cα	Iγ-BCL6	CD3	MEF2B
CD138	Iε-Cε	Iε-BCL6	CD5	PRDM1
CD86	Iε-Cγ	Iα-BCL6	CD4	XBP1
CD80	Iε-Cμ	Iμ-BCL6	CD8	CARD11
CTLA4	Iγ-Cα	JH-BCL6	TBET	TCL1A
B2M	Iγ-Cε		INFγ	BANK
	Iγ-Cγ		GRB	
CSR / SHM	Iγ-Cμ	Mutations	PRF	
AID#I (exon2-3)	IGHD	XPO1 E571K	CD45RO	
AID#2 (exon4-5)	IGHM	MYD88 L265P	CXCR5	
CD40	Iμ-Cα	BRAF V600E	CXCL13	
CD40L#1(exon2-3)	Iμ-Cε	IDH2 R172K	GATA3	
CD40L#2(exon3-4)	Iμ-Cγ	IDH2 R172T	CD28	
	Iμ-Cμ	RHOA G17V	ICOS	
	JH-Cα	MYD88 (exon3-4)	FOXP3	
	JH-Cε	XPOWT	PD1	
	JH-Cγ		LAG3	
	JH-Cμ		ALK	

2. What method can I use to quantify my starting RNA?

The recommended method for quantifying RNA is fluorimetry. Other techniques can be used such as spectrometry or the determination of the RIN

3. What necessary quantity is recommended for a starting RNA? What quantity of RNA was extracted from an FFPE sample?

The quantity of RNA should be between 50 and 500 ng of RNA, even for FFPE samples. It is recommended to use the Promega Maxwell® RSC RNA FFPE kit (Promega, ref AS1440 and AS4500).

4. What is the effect of residual DNA contamination?

DNA contamination can induce an underestimated quantity of starting RNA. But contamination will have no impact on the technique since it is based on fixing the probes at the exon-exon junctions, except for mutation points.

5. How many kits are available and how many analyses can be performed?

Kit can contains :

	Reagent kit - U = number of analyses			
	8U	**16U**	**24U**	**48U**
GEP-LSPM probe mix	30 µL	48 µl	54 µl	108 µL
Barcodes **GEP-BC-xxx (from 001 to 032 depending on number of analyses purchased)** BC=barcode	8 BC	8 BC	12 BC	24 BC
	N°001 to 008	N°017 to 024	N°001 to 012	N°009 to 032
	5µL/BC	8µL/BC	6µL/BC	6µL/BC
GEP-SP-001 sequencing primers	96 µL	144 µL	180 µL	360 µL

6. How many barcodes are included in each kit?

For a kit of 8 analyses, 8 different barcodes are provided. For each kit of more than 8 analyses, each barcode will be used twice (for 2 different analyses).

7. What are the breakpoints in this protocol?

Breakpoints can be issued at the end of the following steps:

- Reverse transcription
- Ligation
- PCR
- Purification

They are indicated by the following symbols:

During breakpoint, samples must be stored between -30°C et -15°C.

8. How long does it take to obtain libraries before the purification step?

Libraries' obtention will go through different steps: Reverse transcription, probes hybridization, probes ligation, and PCR amplification. All these steps will last around 4 hours.

9. What is the recommended Library Read size?

The smallest recommended size is 120 pb.

10. On which sequencer can I use the obtained libraries with the in vitro test?

The tests are optimized for Illumina MiSeq et NextSeq 500/550 sequencer. During the PCR step, the Illumina technology-specific adapters are added to the ligation products.

11. What workflow is needed to create a sample sheet using Illumina Experiment manager?

NextSeq sequencer - Category: Other - Application: FASTQ only - Library Prep Workflow: Illumina DNA Prep - Index Read: 0 (None) - Read Type: Single Read - Cycles Read 1: 120 - Workflow-Specific Setting: - Check: Custom Primer for Read 1 - Uncheck: Use Adapter Trimming	NextSeq sequencer - Library Prep Workflow: Illumina DNA Prep - Index Read: 0 (None) - Read Type: Single Read - Cycles Read 1: 120 - WorkFlow-Specific Setting: Uncheck Use Adapter Trimming

12. What workflow is required to create a template with Local Run Manager?

After downloading the template, Fill in the file with the following information:

- IndexStrategy: NoIndex
- ReadType: Single
- DefaultReadLenght1: 120

13. What sequencing primers do you need?

The sequencing primer is included in the LymphoSign kit (GEP-SP-001).

14. What is the loading concentration of the libraries?

- Miseq: 8 to 10 pM
- NextSeq 500/550: 0.8-1 nM

15. Can I mix Genexpath libraries with others?

Yes, it is possible to mix Genexpath libraries with others as they are specifically built for our sequencing primers GEP-SPLM-001.

16. Do you always need to use PhiX? If yes, what percentage?

Illumina recommends phiX use for internal control in order to check the run functioning. We recommend at least the use given by Illumina (1% for most of the libraries).

17. What are the minimum reads required?

Only 100 000 reads per sample are necessary.

18. What software can analyze the LymphoSign test result?

The RT-MIS software enables rapid and comprehensive analysis of NGS data from the SarcomaFusion test. It determines the fusion(s) detected in the sample associated with sarcoma as well as the associated bibliography.
No other software can analyze the results.

19. Where can I find more details concerning my sample result?

RT-MIS can give us a different level of information on the realized analysis:
- Different information that allowed RT-MIS to predict a class according to the genetic profile of the sample.
- On the relative expression of the markers of a sample of interest compared to the entire database of one of two classes LNH_B or LNH_T or a sub-entity.

By clicking on the pencil associated with a barcode of interest, it is possible to select different information and generate a PDF summary.
The selected information is predefined for the following analyses.
You can download all CSV files associated with the used barcodes:
- The Excel file with the data of all samples analyzed according to the barcode, number of counts per read, informativeness, the amplification factor, the qscore (number of UMI), and the relative expression of all markers (format: full_gene_set_counts).
- An Excel file per sample with the raw data of this sample analyzed according to the name of the markers, the number of reads (raw_readCount), the number of UMIs (raw_UMIcount), the number of reads corrected for the hopping index (corrected_readCount), the number of corrected UMIs (corrected_UMIcount) (format: date-internal reference-number of BC_counts).

20. How is the classification by the AI algorithm?

From the normalized expression data, RT-MIS classifies the sample by Random Forest (or RF). This classification is based on the application of the expression data of 10 RF classification models derived from Machine Learning software from the database of nearly 3000 cases, covering the main subtypes of non-Hodgkin's lymphoma. The different probabilities of these classifiers allow identifying different signatures and classes.
The classification was validated on 146 cases as described in Figure 5 of the article Bobee et al., Blood Cancer Journal (2020).

21. May I use another type of sample that is recommended in the user's manual?

For a result to be valid, the sample tested must be of the same nature as those of the training base. This database was made up of tissue fragments from non-Hodgkin's lymphoma tumor biopsies. The analysis of other types of samples (e.g. blood or bone marrow samples) or corresponding to tumors for which this algorithm has not been trained (e.g. Hodgkin's lymphomas, certain rare forms of nonHodgkin, other cancers, or non-tumor samples) can only lead to erroneous results.
It is therefore important to ensure the consistency of the result by taking into account the clinical and biological data, in particular the histopathological analysis.

22. What is the « additional features » section of the advanced interpretation?

The indications that may be returned in this section concern certain quantitative markers that are particularly important for the classification of lymphomas:

• Three correspond to somatic mutations:

- The MYD88L265P mutation, is recurrent in diffuse large cells lymphoma of the ABC type, in lymphoplasmacytic lymphomas, and in certain lymphomas in the marginal zone.
- The XPO1E571K, recurrent B-cell lymphomas of the médiastinum more rarely in the lymphocytics lymphomas. It is important to note that this mutation is also recurrent in Hodgkin's lymphomas but the sensitivity of the LymphoSign test is not sufficient to highlight it in this pathology where the percentage of tumoral cells is generally very low.
- The mutation RHOAG17V is found in a high percentage of angioimmunoblastic lymphomas as well as in other T lymphomas, most often T follicular helper origin.

• Two correspond to viral RNA:

- EBER1 RNA, expressed following infection by -Barr (EBV) virus. It is important to note that the expression of C markers does not necessarily imply that the tumor cells are infected by this virus but it can reflect the presence of EBV-positive cells in the tumor microenvironment.
- The HB2 RNA (noted HTLV1 in RT-MIS), expressed following infection by the HTLV1 virus. This virus is mostly associated with T lymphomas adult T-cell leukemia/lymphoma type.

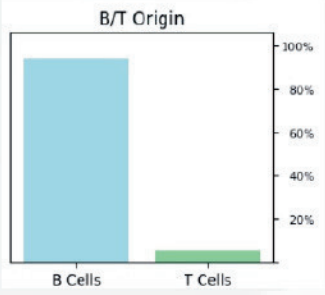
• two correspond to tumor markers overexpressed in very specific lymphoma subtypes:

- The RNA expressed/coded par the CCND1 gene, is very highly expressed in the majority of B lymphomas mantle cells.
- The Expressed/coded by the ALK gene, is strongly overexpressed in ALK-positive anaplastic T-cell lymphomas.

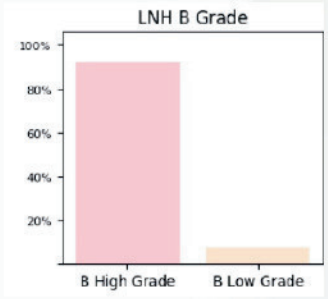
What is a Quality score?

The quality score is an important indicator of the success of the analysis. It corresponds to the total number of probes generated during the ligation step, i.e. the number of cDNA molecules detected. The threshold of 5000 ligations corresponds to the lower limit used to constitute the learning base of the classification algorithm. Below this threshold, the performance of this algorithm drops rapidly, and special care should be taken regarding the detection of quantitative markers (Additional Features), as the detection of only a few sequences can lead to false positives.

23. How can I interpret my advanced interpretation results?

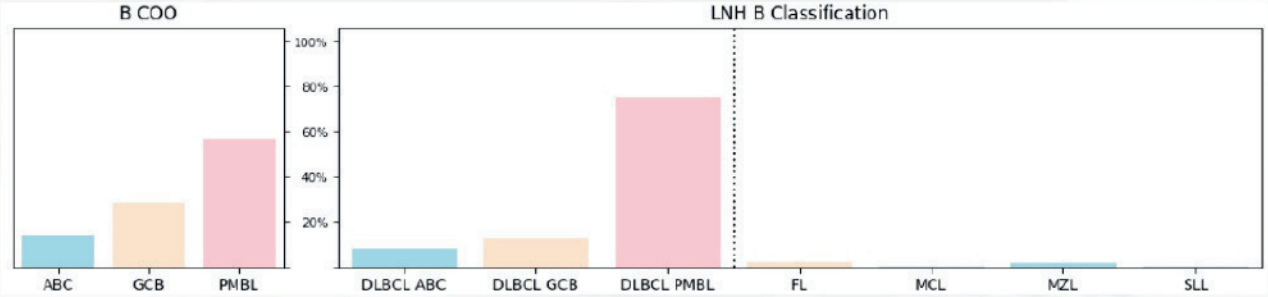


First Graphics: B/T Origin (B cells or T cells origin) allows us to visualize the results of a first Random Forest-type classification algorithm trained on all the B and T lymphomas in the learning base. The height of the histograms corresponds to the percentages of trees having voted in favor of one of the two classes tested.

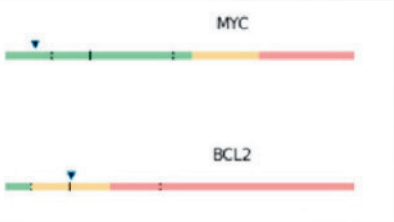


In the case when the result of the first algorithm indicates a cell origin of phenotype B, three additional graphs are displayed:

- NHL B grade graph: the classification result is given by an algorithm trained on all the high and low-grade B lymphomas of the training base.
- Graph B COO: the results are given by an algorithm trained on B lymphomas with phenotype B activity (ABC), B germinal center (GC), and primitive B of the mediastinum (PMBL)
- NHL B Classification graph: the results are given by an algorithm trained on the seven main B lymphoma subtypes present in the training database:
- The GC signature is mainly associated with follicular lymphomas (FL).
- The ABC signature is found in diffuse ABC-type lymphomas (DLBCLABC), mantle cell lymphomas (MCL), lymphocytic lymphomas (SLL), and in the majority of marginal zone lymphomas, and lymphoplasmacytic lymphomas (MZL).
- The PMBL signature is mainly associated with primary B-cell lymphoma of the mediastinum (PMBL) and is sometimes found in certain lymphomas with an intermediate phenotype between Hodgkin's lymphoma and PMBL (gray zone lymphoma).

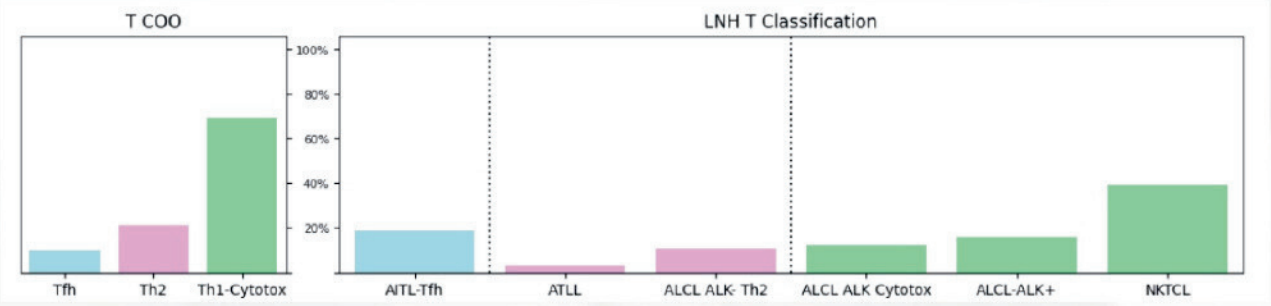


A study on the survival analysis of DLBCL demonstrated that the level of expression of the MYC and BLC2 genes obtained by the test is a good prognostic indicator and makes it possible to identify patients who can respond to targeted therapy (Bobee et al, Blood Cancer, 2020). RT-MIS represents the relationship between the level of expression of these two markers and the impact on the prognosis of patients from this study.



In case the first classification algorithm suggests a cellular origin of T phenotype, two additional graphs are displayed:

- T COO graph: it returns the results of an algorithm trained on T lymphomas with the T Follicular helper (Tfh), T helper type 2 (Th2), and T helper type 1/cytotoxic (Th1) phenotype
- LNH T Classification graph: it returns the results of an algorithm trained on the seven main subtypes of T-cell lymphoma present in the training database:
  - Tfh signature is mainly angioimmunoblastic type T-cell lymphoma (AITL)
  - The Th2 signature is mainly associated with adult T-cell leukemia/lymphoma (ATLL) and anaplastic ALK-negative T-cell lymphomas (ALCL ALK-Th2).
  - The Th1-cytotoxic signature is associated with cytotoxic ALK-negative anaplastic T-cell lymphoma (ALCL ALK-cytotoxic), ALK-positive anaplastic T-cell lymphoma (ALCL ALK+), and NK/T cell lymphoma (NKTCL).



24. What information can be extracted from raw and relative data present in CVS files?

For each analysis, 2 types of CVS files can be downloaded:

- A CVS file in the format date-internal reference-barcode number-sample name. The table contains 5 columns: the list of probes detected during the analysis, the raw count of reads and UMIs, the count of reads and UMIs after correction of the hopping index

probeset	raw_readCount	raw_UMIcount	corrected_readCount	corrected_readCount

A CVS file in full_gene_set_counts format. The table groups together all the samples of the same analysis with the following information: the barcode used, the total number of reads, the informativeness (percentage of sequences corresponding to those sought), the amplification factor, the quality score (number of IMUs detected) as well as the relative expression level of each of the markers (raw count data divided by the median of the counts of a fixed list of markers)

barcode	nReads	informativity	ampFactor	qScore

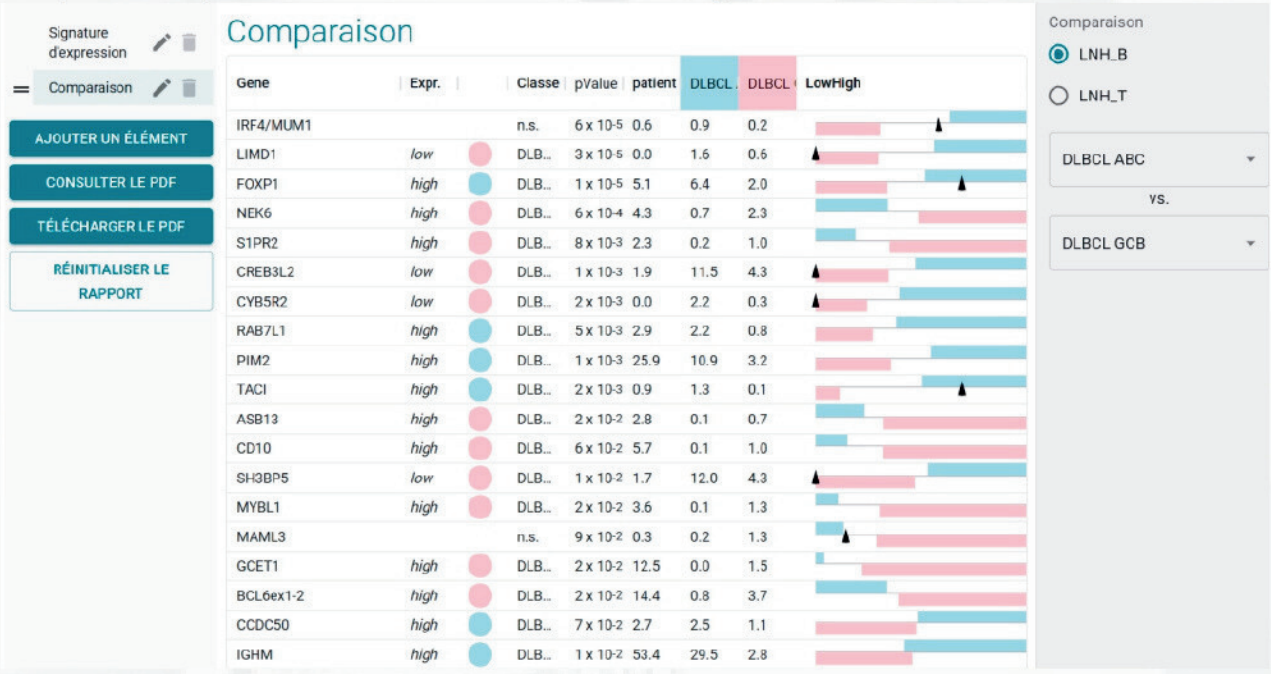
25. How to read the graphics?

The "comparison" page allows you to compare two probable classes of prediction. By default, RT-MIS compares the two most probable classes. The genes are displayed in descending order of the most discriminating genes from a statistical point of view between the two classes studied and the database of interest (LNH_B or LNH_T).

Each line corresponds to a gene with the following information:

- Gene name
- Level of expression (high, low)
- The color of the corresponding class
- The p-value = statistical difference between the two classes
- The numerical value of the relative level of expression of the patient
- The numerical value of the average relative level of expression for the class defined in blue
- The numerical value of the average relative level of expression for the class defined in pink
- A graphical representation with the expression levels of the two classes compared and the positioning of the patient (black triangle).

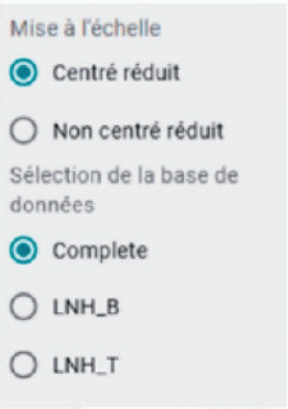
It is possible to compare according to the LNH_B or LNH_T database. By default, RT-MIS compares the predicted class vs the 2nd most likely class.



For the graphs "B vs T", "IG", "MUTS", "DLBCL", "PTCL", "Other", and "prognosis" to be personalized.

The level of expression of each of the markers corresponds to the raw data of the count is divided by the median of the counts of a fixed list of markers.

The data are represented as boxplots. They correspond for a given marker to the reference values of the database according to the entire database, of one of the two classes LNH_B or LNH_T or of a sub-entity.



Each boxplot is organized as follows:

- The central value of the graph is the median
- The edges of the rectangle are the quartiles (Q1 at the bottom and Q3 at the top)
- The endpoints of the boxplot are calculated using 1.5 times the interquartile space (the distance between the 1st and the 3rd quartile).

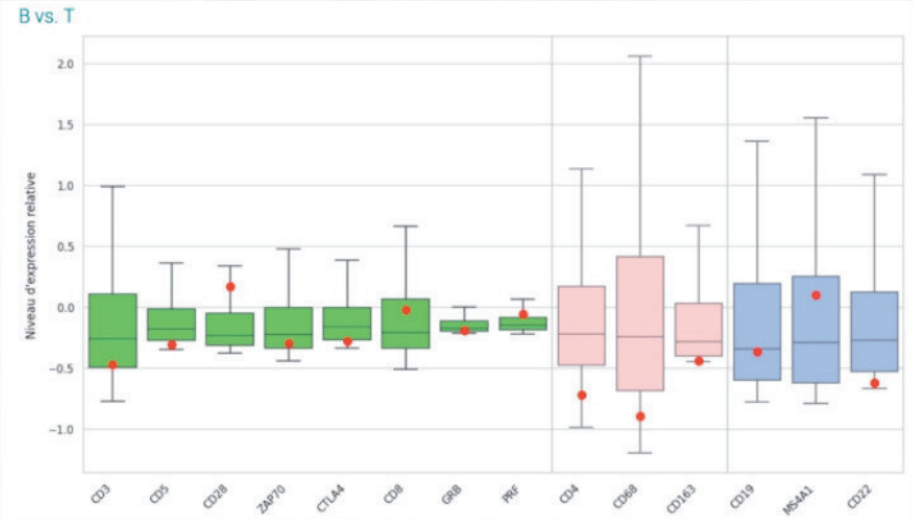
It is possible to observe the boxplots in a centered format are reduced or not.

The Redpoint corresponds to the relative value of the patient.

Page « B vs T »

It groups in predefined way markers for a type signature:

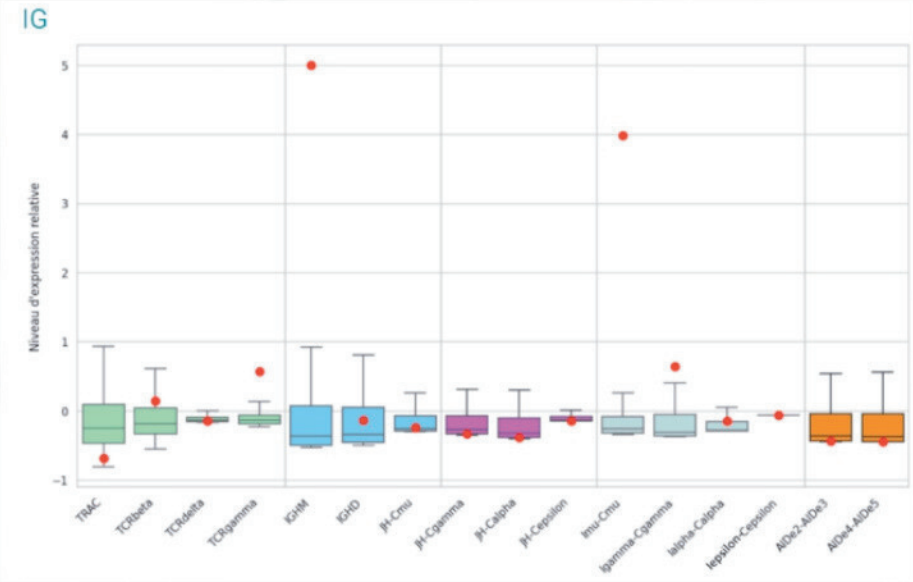
- T cells in green
- Macrophages in pink
- B cells in purple



Page « IG »

It groups together in a predefined way markers from:

- TCR in green
- BCR in blue and purple
- “switch transcripts” in light blue
- AID in orange

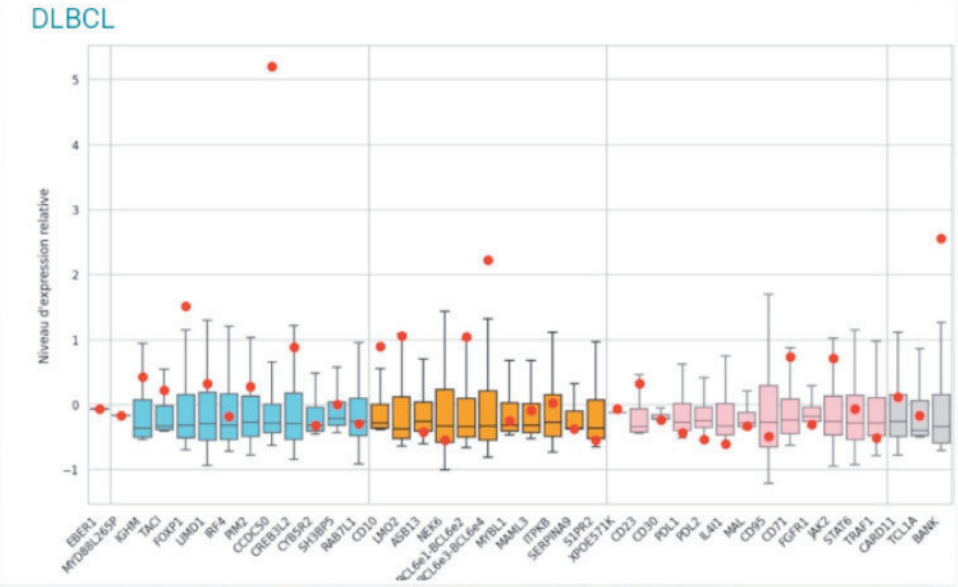


Page « DLBCL »

It groups together in a predefined way markers from:

- ABC in blue
- GCB in orange
- PMBL in pink
- Markers not expressed in the PMBL (according to Rosenwald's signature) in gray

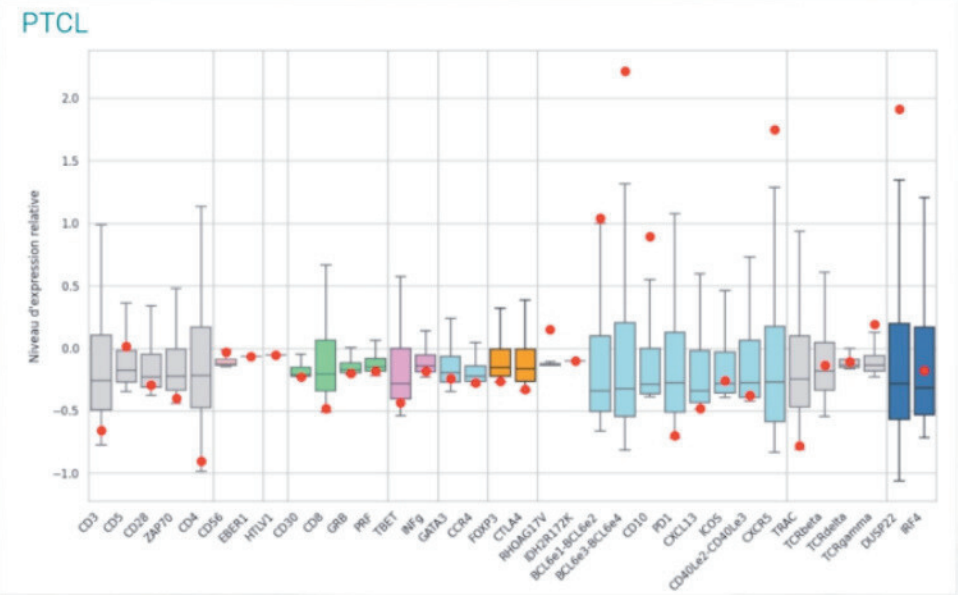
To the left of the page is the EBER1 marker.



Page « PTCL »

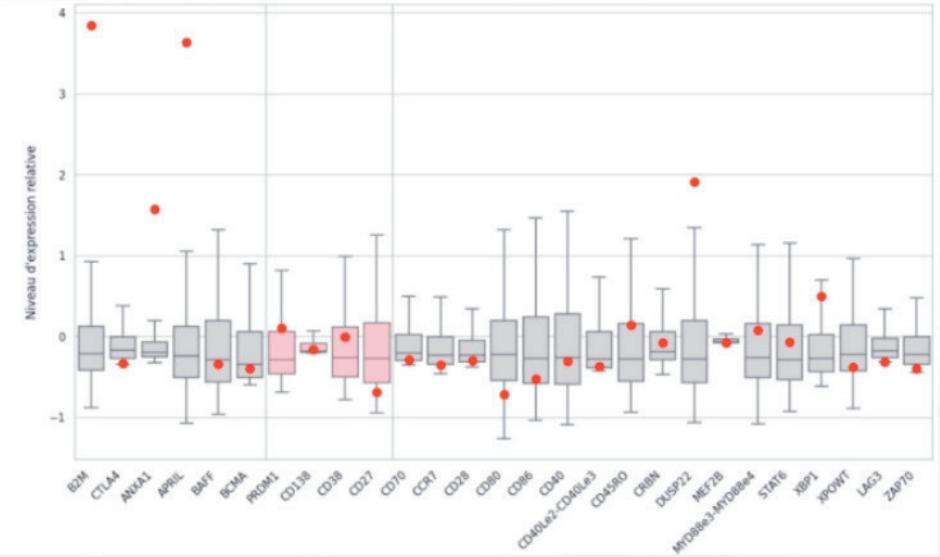
It groups together in a predefined way markers from:

- T cells in gray
- CD56+ NKT cells in pink
- Viral
- Of the ALCL ALK+ cytotoxic class in green
- Th1 in purple
- Th2 in light blue
- Treg in orange
- Tfh in blue
- TCR in light gray
- DUSP22-IRF4 rearrangement in dark blue



Page « Others »

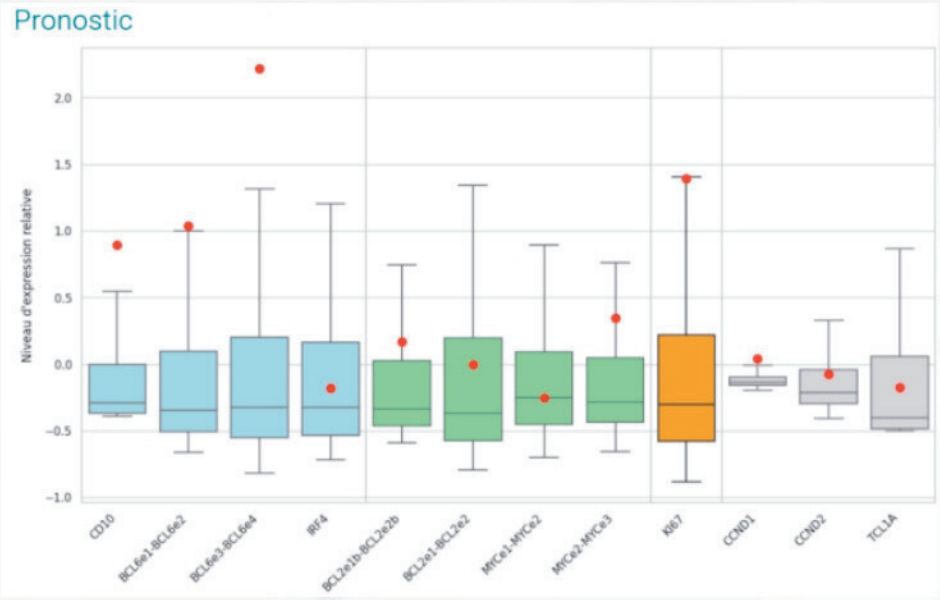
It groups various markers in a predefined way.



Page « Pronostic »

It groups together in a predefined way markers from:

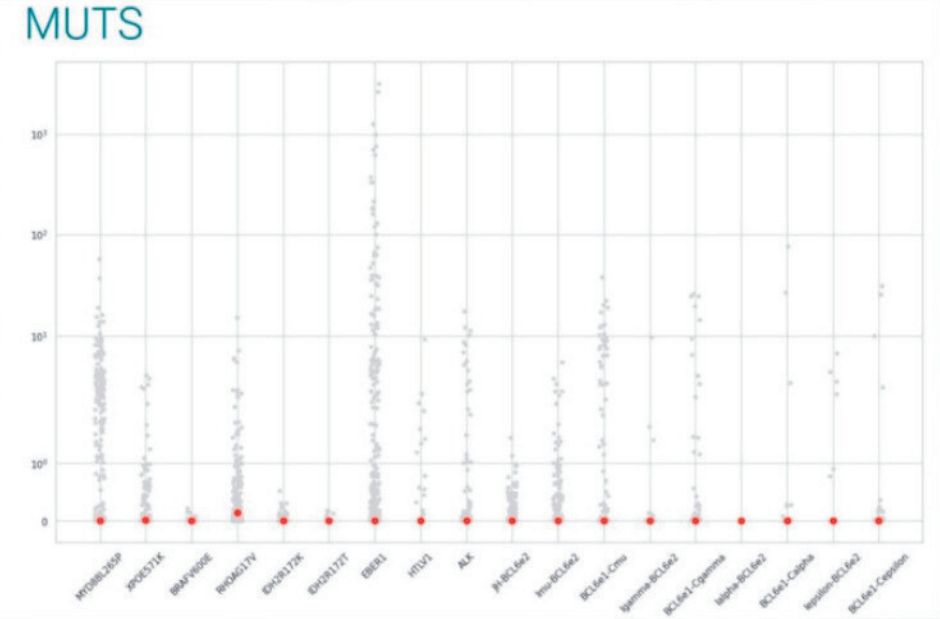
- The Hans-like algorithm
- MYC and BCL2
- Proliferation
- MCL



Page « Muts »

It displays the raw data count for:

- Point mutations,
- Viral markers
- Recombinations with BCL6-IGH@ (translocation t(3;14)(q27;q32)



The gray dots represent the data from the database and the red dot that of the patient

LymphoTranscript

For the detection of fusion transcripts

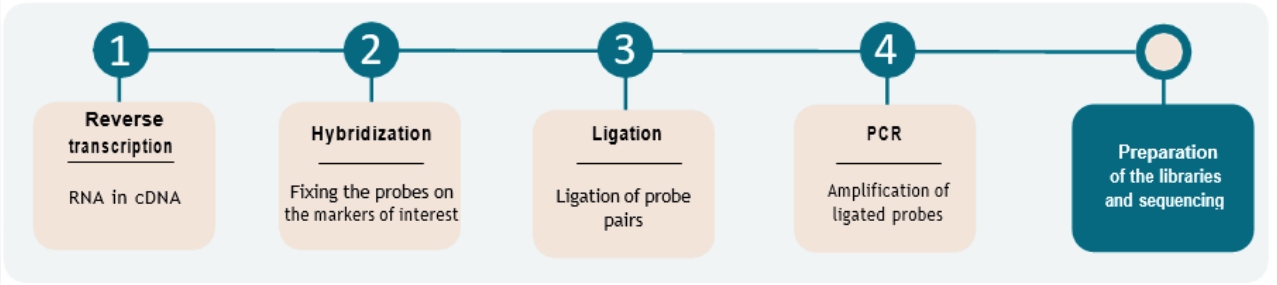
Genexpath's LymphoTranscript solution allows the identification of **fusion transcripts** associated with peripheral T-cell lymphomas.

The detection and quantification of these fusion transcripts are made possible by combining molecular biology and **high-throughput sequencing**. The data obtained is analyzed using our **RT-MIS** platform.

RT-MLPSeq - a simple and fast technique

The **LymphoTranscript** test uses the **RT-MLPSeq** method.

The multi-step in vitro test simultaneously evaluates a large number of **genetic markers** (chromosomal translocations and some mutations) using pairs of specific oligo-nucleotide probes for each of them.

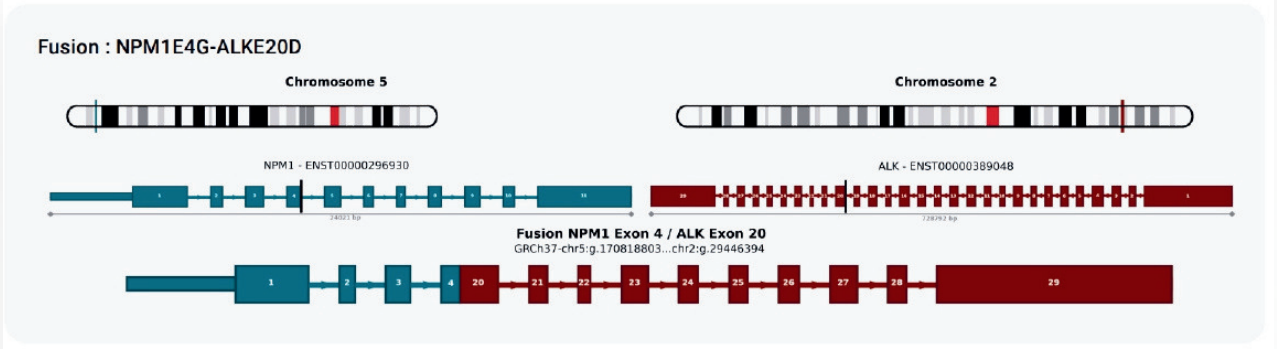


This *in vitro* test is associated to high-throughput sequencing that allows multiple samples and dozens of genes to be tested at the same time.

Post sequencing analysis using dedicated software

After sequencing, the **FASTQ** file is loaded into the **RT-MIS platform** which carries out demultiplexing, identification and quantification of any fusion transcripts.

RT-MIS delivers a report in just a few minutes including the detected fusion transcripts and the associated bibliography.



Characteristics

- **1/2 day of manipulation**
- **Low RNA quantity needed**
- **Suitable for FFPE samples**
- **Sensitive thanks to short probes**
- **Sequencing with other libraries possible**
- **Increased specificity thanks to UMI**
- **100,000 reads are sufficient**
- **Bioinformatic analysis included**
- **Access to complete raw data**

Application domain	Fusion transcript detection		
Handling duration	≃4h before sequencing	Actual working time	≃1h-1h30
Type of samples	Fresh, frozen or fixed and paraffin-embedded tissue biopsies		
Input quantity	Between 50 and 500ng in a volume of 2µL		
Contents of the reagent kit	Probes targeting fusion transcripts, somatic mutations and HTLV1 virus, barcodes, sequencing primers		
Material compatibility	Sequencer Illumina®		

Categories	Cond.
GEP-LT08	8 reactions
GEP-LT16	16 reactions
GEP-LT24	24 reactions

RUO *For research only.*

cliniSciences

Austria
Company: CliniSciences GmbH
Address: Sternwartestrasse 76, A-1180 Wien - Austria
Telephone: +43 720 115 580
Fax: +43 720 115 577
Email: oesterreich@clinisciences.com
Web: https://www.clinisciences.com

Belgium
Company: CliniSciences S.R.L
Address: Avenue Stalingrad 52, 1000 Brussels - Belgium
Telephone: +32 2 31 50 800
Fax: +32 2 31 50 801
Email: belgium@clinisciences.com
Web: https://www.clinisciences.com

Denmark
Company: CliniSciences ApS
Address: Oesterbrogade 226, st. 1, Copenhagen, 2100 - Denmark
Telephone: +45 89 888 349
Fax: +45 89 884 064
Email: danmark@clinisciences.com
Web: https://www.clinisciences.com

Finland
Company: CliniSciences ApS
Address: Oesterbrogade 226, st. 1, Copenhagen, 2100 - Denmark
Telephone: +45 89 888 349
Fax: +45 89 884 064
Email: suomi@clinisciences.com
Web: https://www.clinisciences.com

France
Company: CliniSciences S.A.S
Address: 74 Rue des Suisses, 92000 Nanterre- France
Telephone: +33 9 77 40 09 09
Fax: +33 9 77 40 10 11
Email: info@clinisciences.com
Web: https://www.clinisciences.com

Germany
Company: Biotrend Chemikalien GmbH
Address: Wilhelm-Mauser-Str. 41-43, 50827 Köln - Germany
Telephone: +49 221 9498 320
Fax: +49 221 9498 325
Email: info@biotrend.com
Web: https://www.biotrend.com

Iceland
Company: CliniSciences ApS
Address: Oesterbrogade 226, st. 1, Copenhagen, 2100 - Denmark
Telephone: +45 89 888 349
Fax: +45 89 884 064
Email: island@clinisciences.com
Web: https://www.clinisciences.com

Ireland
Company: CliniSciences Limited
Address: Ground Floor, 71 lower Baggot street Dublin D02 P593 - Ireland
Telephone: +353 1 6971 146
Fax: +353 1 6971 147
Email: ireland@clinisciences.com
Web: https://www.clinisciences.com

Italy
Company: CliniSciences S.r.l
Address: Via Maremmana inferiore 378 Roma 00012 Guidonia Montecelio - Italy
Telephone: +39 06 94 80 56 71
Fax: +39 06 94 80 00 21
Email: italia@clinisciences.com
Web: https://www.clinisciences.com

Netherlands
Company: CliniSciences B.V.
Address: Gaetano Martinolaan 85, 6229 GS Maastricht - Netherlands
Telephone: +31 85 2082 351
Fax: +31 85 2082 353
Email: nederland@clinisciences.com
Web: https://www.clinisciences.com

Norway
Company: CliniSciences
Address: 74 Rue des Suisses, 92000 Nanterre - France
Email: norge@clinisciences.com
Web: https://www.clinisciences.com

Poland
Company: CliniSciences sp.Z.o.o.
Address: ul. Rotmistrza Witolda Pileckiego 67 lok. 200 - 02-781 Warszawa -Poland
Telephone: +48 22 307 0535
Fax: +48 22 307 0532
Email: polska@clinisciences.com
Web: https://www.clinisciences.com

Portugal
Company: Quimigen Unipessoal LDA
Address: Rua Almada Negreiros, Lote 5, Loja 14, 2615-275 Alverca Do Ribatejo - Portugal
Telephone: +351 30 8808 050
Fax: +351 30 8808 052
Email: info@quimigen.com
Web: https://www.quimigen.pt

Spain
Company: CliniSciences Lab Solutions
Address: C/ Hermanos del Moral 13 (Bajo E), 28019, Madrid - Spain
Telephone: +34 91 269 40 65
Fax: +34 91 269 40 74
Email: espana@clinisciences.com
Web: https://www.clinisciences.com

Sweden
Company: CliniSciences ApS
Address: Oesterbrogade 226, st. 1, Copenhagen, 2100 - Denmark
Telephone: +45 89 888 349
Fax: +45 89 884 064
Email: sverige@clinisciences.com
Web: https://www.clinisciences.com

Switzerland
Company: CliniSciences Limited
Address: Marktgasse 18 8302 Kloten - Switzerland
Telephone: +41 (044) 805 76 81
Fax: +41 (044) 805 76 75
Email: switzerland@clinisciences.com
Web: https://www.clinisciences.com

UK
Company: CliniSciences Limited
Address: 11 Progress Business center, Whittle Parkway, SL1 6DQ Slough- United Kingdom
Telephone: +44 (0)1753 866 511
or +44 (0) 330 684 0982
Fax: +44 (0)1753 208 899
Email: uk@clinisciences.com
lWeb: https://www.clinisciences.com

USA
Company: Biotrend Chemicals LLC
Address: c/o Carr Riggs Ingram, 500 Grand Boulevard, Suite 210 Miramar Beach, FL 32550- USA
Telephone: +1 850 650 7790
Fax: +1 850 650 4383
Email: info@biotrend-usa.com
Web: https://www.biotrend-usa.com

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