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B and T non-Hodgkin's lymphomas

For **B-NHL**, Eurofins Biomnis offers five NGS panels:

- the "LLC" NGS panel (see CLL panel data sheet, ref. DS119-INTGB),
- the "LLCTR" NGS panel (see CLL panel data sheet, ref. DS119-INTGB),
- the "LPWAL" NGS panel,
- the "BRAF" NGS panel,
- the "LNHB" NGS panel.

For T-NHL, Eurofins Biomnis offers one panel:

- the "LNHT" NGS panel.

Non-Hodgkin B lymphoma

▶ **The "LPWAL" NGS panel consists of an analysis of 10 genes:** *MYD88, CXCR4, ARID1A, CD79A, CD79B, NOTCH2, TP53, BTK, PLCG2* and *CARD11*. It must be combined with a bone marrow cytogenetic study.

It is used to diagnose lymphoplasmacytic lymphomas, principally Waldenström's disease. The *MYD88* mutation is reported in more than 90% of cases and can be used to rule out diagnosis of LZM, for example. In more than 40% of cases, a *CXCR4* mutation is observed, generally associated with a *MYD88* mutation. There are also cases with *CXCR4* mutation without MYD88 mutation. Mutations in the A*RID1A, CD79A, CD79B* and *NOTCH2* genes have also been reported in Waldenström disease and may contribute to the diagnostic approach.

This panel also provides a prognostic and therapeutic approach: The presence of a *CXCR4* mutation is associated with a poor prognosis and represents a resistance mutation, in the same way as secondary mutations in the *BTK* and *PLCG2* genes.

TP53 mutation, although rare (2%), is associated with a poor prognosis. The association of a *MYD88* mutation with the absence of a *CXCR4* mutation has a favourable prognosis under BTKi, unlike the association of both *MYD88* and *CXCR4* mutations, which is associated with a late response to BTKi. Absence of MYD88 mutation in Waldenström disease characterises a disease with a poor prognosis and a poor response to BTKIs or to a combination of bendamustine and rituximab.

The IPSSWM-R prognostic score does not currently include molecular data.

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« LPWAL » NGS Panel - Targeted genes

Gene	Transcript	Exon rank
ARID1A	NM_006015	Full Coding Region
BTK	NM_000061	Full Coding Region
CARD11	NM_032415	Full Coding Region
CD79A	NM_001783	Full Coding Region
CD79B	NM_000626	Full Coding Region
CXCR4	NM_003467	Full Coding Region
MYD88	NM_002468	Full Coding Region
NOTCH2	NM_024408	Full Coding Region
PLCG2	NM_002661	Full Coding Region
TP53	NM_000546	Full Coding Region

Test code: LPWAL

▶ The BRAF NGS panel involves mutational analysis of the *BRAF* gene. This mutation is reported in more than 95% of cases of Hairy Cell Leukaemia and represents a very useful diagnostic criterion in association with a targeted immunophenotypic analysis.

« BRAF » NGS Panel - Targeted genes

Gene	Transcript	Exon rank
BRAF	NM_004333	Full Coding Region

Test code: BRAF

▶ The B-NHL NGS panel consists of an analysis of 45 genes:

ARID1A/ATM/B2M/BAX/BCL2/BCOR/BIRC3/BRAF/BTK/CARD11/CD79A/CD79B/CREBBP/CXCR4/EGR2/EP300/EZH2/FBXW7/FOXO1A/GNA13/HRAS/KLF2/KRAS/MAP2K1/MCL1/MEF2B/MGA/MYC/MYD88/NFKBIE/NOTCH1/NOTCH2/NRAS/PIM1/PLCG2/POT1/RPS15/SAMHD1/SF3B1/SOCS1/STAT6/TNFAIP3/TNFRSF14/TP53/XPO1. It must be combined with a blood, bone marrow or lymph node cytogenetic analysis.

Note For CLL, Plasma cell lymphoma and Hairy Cell Leukaemia, see panel sheet DS119-INTGB and corresponding paragraphss.

It is used as a diagnostic aid to identify, in addition to histological, cytological and cytogenetic analyses, a type or subtype of B-NHL in the WHO and ICC 2022.

Some examples of **diagnostic** aids:

- For diffuse large cell lymphomas, the GC and ABC subtypes can be characterised by distinct mutational profiles: mutations in *EZH2*, *GNA13*, *MEF2B*, *TNFRSF14*, *B2M* and *CREBBP* genes for the GC type and *MYD88*, *CD79B*, *TNFAIP3*, *CARD11* and *PIM1* genes for the ABC type.
- The CD23+ «follicular lymphoma - non-rearranged BCL2» subtype is generally associated with a *STAT6* or *TNFRSF14* mutation.
- Primary mediastinal large B-cell lymphoma is characterised by mutations in the *STAT6*, *XPO1*, *NFKBIE*, *TNFAIP3*, *GNA13* or *B2M* genes.
- For marginal zone lymphomas, the mutational profile of the NGS panel makes it possible to differentiate extra-nodal forms (*TNFAIP3*, *TNFRSF14* or *TET2* mutations) from nodal or splenic forms (*KLF2* or *NOTCH2* mutations).

This panel also provides **prognostic** support:

- In follicular lymphoma, the m7-FLIPI score is used to assess prognosis using the mutation status of 7 genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP* and *CARD11*).
- In mantle cell lymphoma, the presence of mutations in *TP53*, *NOTCH1* or *NOTCH2* mutations is associated with a poor prognosis.
- In diffuse large cell lymphoma, new molecular subtypes (MCD, EZB, BN2, ST2, A53 and N1), defined by NGS, can also be used to establish a prognosis.
  This includes the analysis of new genes (*SOCS1*, *NOTCH1* for example). The *TP53* mutation also has a poor prognosis in this entity.

From a **therapeutic** point of view, in addition to research into BTKi resistance mutations (mutations in the *BTK* and *PLCG2* genes) in CLL, MCL, MZL and Hairy Cell Leukaemia, targeted therapies offer new therapeutic choices, for example, the *EZH2* target in follicular lymphoma.

« B-NHL» NGS Panel - Targeted gene

Gene	Transcript	Exon rank
ARID1A	NM_006015	Full Coding Region
ATM	NM_000051	Full Coding Region
B2M	NM_004048	Full Coding Region
BAX	NM_138761	Full Coding Region
BCL2	NM_000633	Full Coding Region
BCOR	NM_017745	Full Coding Region
BIRC3	NM_001165	Full Coding Region
BRAF	NM_004333	Full Coding Region
BTK	NM_000061	Full Coding Region
CARD11	NM_032415	Full Coding Region
CD79A	NM_001783	Full Coding Region
CD79B	NM_000626	Full Coding Region
CREBBP	NM_004380	Full Coding Region

Gene	Transcript	Exon rank
CXCR4	NM_003467	Full Coding Region
EGR2	NM_000399	Full Coding Region
EP300	NM_001429	Full Coding Region
EZH2	NM_004456	Full Coding Region
FBXW7	NM_033632	Full Coding Region
FOXO1A	NM_002015	Full Coding Region
GNA13	NM_006572	Full Coding Region
HRAS	NM_176795	Full Coding Region
KLF2	NM_016270	Full Coding Region
KRAS	NM_033360	Full Coding Region
MAP2K1	NM_002755	Full Coding Region
MCL1	NM_021960	Full Coding Region
MEF2B	NM_001145785	Full Coding Region

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Gene	Transcript	Exon rank
MGA	NM_001164273	Full Coding Region
MYC	NM_002467	Full Coding Region
MYD88	NM_002468	Full Coding Region
NFKBIE	NM_004556	Full Coding Region
NOTCH1	NM_017617	Full Coding Region
NOTCH2	NM_024408	Full Coding Region
NRAS	NM_002524	Full Coding Region
PIM1	NM_002648	Full Coding Region
PLCG2	NM_002661	Full Coding Region
POT1	NM_015450	Full Coding Region

Gene	Transcript	Exon rank
RPS15	NM_001018	Full Coding Region
SAMHD1	NM_015474	Full Coding Region
SF3B1	NM_012433	Full Coding Region
SOCS1	NM_003745	Full Coding Region
STAT6	NM_003153	Full Coding Region
TNFAIP3	NM_006290	Full Coding Region
TNFRSF14	NM_003820	Full Coding Region
TP53	NM_000546	Full Coding Region
XPO1	NM_003400	Full Coding Region

Test code: LNHB

Non-Hodgkin T lymphoma

▶ The "LNHT" NGS panel consists of an analysis of 19 genes: *ARID1A*, *ATM*, *BCOR*, *CARD11*, *CD28*, *DNMT3A*, *EP300*, *FBXW7*, *IDH2*, *JAK2*, *JAK3*, *MGA*, *NOTCH1*, *PLCG1*, *RHOA*, *STAT3*, *STAT5B*, *TET2* and *TP53*. It must be combined with a search for T clonality and a cytogenetic study.

It is primarily intended as a **diagnostic** aid for peripheral T lymphomas. Recurrent cytogenetic abnormalities are also reported for diagnostic purposes and must be investigated in association with these abnormalities. For example, the combination of *IDH2*, *RHOA* and *TET2* mutations confirms the diagnosis of angioimmunoblastic TFH lymphoma (the *IDH2* mutation being exclusive to this subtype of TFH lymphoma). The presence of a *STAT5B* and *JAK3* mutation helps in the differential diagnosis between a monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) (STAT5B mutation reported in more than 60% of cases) and an enteropathy-associated T-cell lymphoma (EATL), which tends to be associated with a *STAT3* mutation (20% of cases). Conversely, ALK+ anaplastic large cell lymphoma is associated with virtually no mutations in the classic T-cell lymphoma mutational spectrum.

In terms of **theranostics**, potential targeted therapies are currently being studied, targeting the *IDH2* or *RHOA* genes, for example.

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Gene mutation frequencies and mutations of high diagnostic interest in T-cell lymphomas

	T-PLL	T-LGLL	ATLL	SS	EATL	MEITL	HSTL	ALCL	TFHL-AI	ENTKL
ARID1A				X						X
ATM	X			X						
BCOR										X
CARD11			X	X					X	
CD28			X	X					X	
DNMT3A				X					X	
EP300				X						X
FBXW7			X							
IDH2									X	
JAK2										X
JAK3	X					X		X		X
MGA										X
NOTCH1			X							
PLCG1			X	X					X	
RHOA									X	
STAT3		X	X	X	X		X	X(ALK-)		X
STAT5B	X	X		X	X	X	X			X
TET2	X				X				X	X
TP53	X		X	X	X	X		X		X

Frequency of mutation:

X 5% < < 20%

X 20% < < 50%

X 50% < < 100%

Mutation of high diagnostic interest

Abbreviations:

T-PLL: T-prolymphocytic leukaemia

T-LGLL: T-large granular lymphocytic leukaemia

ATLL: Adult T-cell leukaemia/lymphoma

SS: Sezary syndrome

EATL: Enteropathy-associated T-cell lymphoma

MEITL: Monomorphic epitheliotropic intestinal T-cell lymphoma

HSTL: Hepatosplenic T-cell lymphoma

ALCL: Anaplastic large cell lymphoma

TFHL-AI: T-follicular helper (TFH) cell lymphoma, angioimmunoblastic-type

ENTKL: Extranodal NK/T-cell lymphoma

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« LNHT » NGS Panel - Targeted gene

Gene	Transcript	Exon rank
ARID1A	NM_006015	Full Coding Region
ATM	NM_000051	Full Coding Region
BCOR	NM_017745	Full Coding Region
CARD11	NM_032415	Full Coding Region
CD28	NM_006139	Full Coding Region
DNMT3A	NM_022552	Full Coding Region
EP300	NM_001429	Full Coding Region
FBXW7	NM_033632	Full Coding Region
IDH2	NM_002168	Full Coding Region
JAK2	NM_004972	Full Coding Region
JAK3	NM_000215	Full Coding Region
MGA	NM_001164273	Full Coding Region
NOTCH1	NM_017617	Full Coding Region
PLCG1	NM_002660	Full Coding Region
RHOA	NM_001664	Full Coding Region
STAT3	NM_139276	Full Coding Region
STAT5B	NM_012448	Full Coding Region
TET2	NM_001127208	Full Coding Region
TP53	NM_000546	Full Coding Region

Test code: LNHT

Pre-analytical requirements: EDTA whole blood or bone marrow

Turnaround time : 13 days (Results may require an extended turnaround time of one week, depending on the confirmation tests required by Sanger sequencing).

Contact

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