

New versatile genetic test for lymphoid neoplasms supports personalized management of patients

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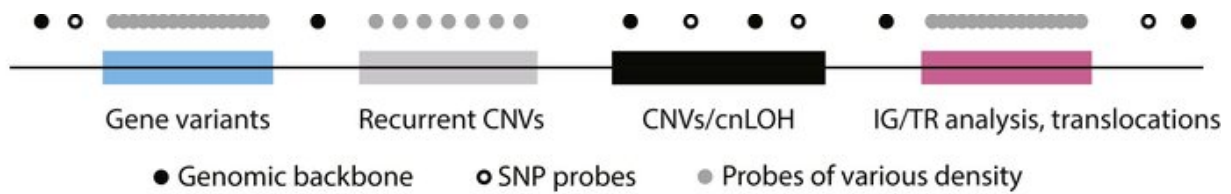
Increasing knowledge about genomic biomarkers has facilitated better monitoring and personalized management of patients with B-cell

malignant tumors. A new integrative, capture-based, next-generation sequencing (NGS) panel, LYmphoid NeXt-Generation Sequencing (LYNX), can detect and analyze standard and novel biomarkers in the most common lymphoid neoplasms simultaneously. This represents a crucial step towards more effective personalized treatment of these diseases and facilitates further research, report researchers in *The Journal of Molecular Diagnostics*.

Genomic profiling by NGS provides novel critical clinical information about prognostic and predictive biomarkers. NGS studies have identified several genomic alterations in hematologic malignant tumors, which have improved our understanding of the disease course as well as the evolution of these neoplasms.

"With a constantly growing number of genetic markers with evidenced or potential clinical impact in lymphoid neoplasms, a more comprehensive genomic test is highly desirable," explained lead investigator Prof. Dr. Sarka Pospisilova, from the Faculty of Medicine, Masaryk University and University Hospital Brno; and Central European Institute of Technology, Masaryk University, Brno, Czech Republic. "We therefore wanted to design, validate, and implement a new custom-designed NGS panel for the integrative analysis of diagnostic, prognostic, and predictive markers."

The investigators compiled a list of key genomic biomarkers in [chronic lymphocytic leukemia](#) (CLL), acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), [follicular lymphoma](#) (FL), and mantle cell lymphoma (MCL) from published and publicly available resources and established a comprehensive NGS panel for their analysis both in routine clinical practice and in [biomedical research](#).



List of genes

<i>ARID1A</i> ^{1,3}	<i>ASXL</i> ^{1,5}	<i>ATM</i> ^{1,2}	<i>BIRC3</i> ^{1,2}	<i>BRAF</i> ^{1,3-5}
<i>BTG1</i> ⁶	<i>CARD11</i> ¹⁻⁴	<i>CCND1</i> ²	<i>CD79A</i> ^{1,4}	<i>CD79B</i> ^{1,2,4}
<i>CDKN2A</i> ¹⁻⁵	<i>CDKN2B</i> ³⁻⁵	<i>CHD2</i> ¹	<i>CREBBP</i> ^{1,3-5}	<i>CRLF2</i> ⁵
<i>CSF2RA</i> ⁶	<i>EBF1</i> ⁶	<i>EGR2</i> ¹	<i>EP300</i> ^{1,3,4}	<i>EPOR</i> ⁶
<i>ETV6</i> ⁵	<i>EZH2</i> ³⁻⁵	<i>FBXW7</i> ¹	<i>FIGL1</i> ⁶	<i>FLT3</i> ⁵
<i>FOXO1</i> ³	<i>H1</i> ⁻⁴	<i>IKZF1</i> ⁵	<i>IKZF2</i> ⁶	<i>IKZF3</i> ^{1,6}
<i>IL2RB</i> ⁶	<i>IL3RA</i> ⁶	<i>IL7R</i> ⁵	<i>JAK1</i> ^{1,5}	<i>JAK2</i> ^{1,5}
<i>JAK3</i> ⁵	<i>KMT2A</i> ^{1,5}	<i>KMT2D</i> ¹⁻⁴	<i>KRAS</i> ^{1,5}	<i>MEF2B</i> ²⁻⁴
<i>MGA</i> ¹	<i>MYC</i> ^{3,5}	<i>MYD88</i> ¹⁻⁴	<i>NF1</i> ^{1,5}	<i>NFKBIE</i> ¹
<i>NOTCH1</i> ¹⁻⁴	<i>NOTCH2</i> ^{2,4}	<i>NRAS</i> ^{1,5}	<i>NSD2</i> ²	<i>P2RY8</i> ⁶
<i>PAG1</i> ⁵	<i>PAX5</i> ^{1,5}	<i>PIM1</i> ^{1,4}	<i>PTEN</i> ³⁻⁵	<i>PTPN11</i> ^{1,5}
<i>POT1</i> ¹	<i>RB</i> ^{1,5}	<i>RPS15</i> ¹	<i>RUNX1</i> ⁵	<i>SAMHD1</i> ¹
<i>SETD2</i> ^{1,5}	<i>SF3B1</i> ^{1,2}	<i>SH2B3</i> ⁶	<i>SHOX</i> ⁶	<i>TNFRSF14</i> ^{3,4}
<i>TP53</i> ¹⁻⁵	<i>TYK2</i> ⁶	<i>UBR5</i> ²	<i>XPO1</i> ¹	<i>ZMYM3</i> ¹

| Exon-proximal probes | 3' UTR region included | Introns included



Rearrangements¹⁻⁵

<i>IGH</i> locus	79 genes
<i>IGK</i> locus	45 genes
<i>IGL</i> locus	42 genes
<i>TRA</i> locus	96 genes
<i>TRB</i> locus	64 genes
<i>TRG</i> locus	13 genes
<i>TRD</i> locus	11 genes



Translocations²⁻⁴

<i>CCND1/IGH</i>	t(11;14)
<i>BCL2/IGH</i>	t(14;18)
<i>BCL6/IGH</i>	t(3;14)



Reccurent deletions^{1,2}

> 300 kb/1 Mb

Del17p	
Del11q	
Del13q	



Trisomy^{1,2}

Tri12	
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Genome-wide CNVs¹⁻⁶

> 6 MB across whole genome



cnLOH¹⁻⁶

According to SNP probe density

A schematic presentation of genomic targets and molecular markers integrated within the Lymphoid NeXt-generation sequencing (LYNX) panel design for the most common lymphoid malignant tumors (1 chronic lymphocytic leukemia, 2 mantle cell lymphoma, 3 follicular lymphoma, 4 diffuse large B-cell lymphoma, 5 acute lymphoblastic leukemia, and 6 Philadelphia chromosome-like acute lymphoblastic leukemia). cnLOH, copy neutral loss of heterozygosity; CNV, copy number variant; SNP, single-nucleotide polymorphism. Credit: *The Journal of Molecular Diagnostics*

"Such an all-in-one test covering a broad spectrum of crucial biomarkers in lymphoproliferative disorders represents a unique tool for obtaining relevant information about the patient-specific genetic background from just one biological sample," noted first author Veronika Navrkalova, Ph.D., from the Faculty of Medicine, Masaryk University and University Hospital Brno; and Central European Institute of Technology, Masaryk University, Brno, Czech Republic.

To ensure the accuracy of the test, researchers validated the reliability of the analytical procedure, which enabled an unbiased identification of various prognostic and predictive markers in a single test. In total, 84 DNA samples from 65 patients (30 with CLL, 13 with ALL, 9 with DLBCL, 6 with MCL, and 7 with FL) were sequenced in two validation rounds. The validation sample cohort was carefully selected to obtain a representative set of different mutation types, copy number variants, common lymphoma translocations, and immunoglobulin/T-cell receptor rearrangements.

A single LYNX test provides accurate detection of mutations in 70 lymphoma-related genes with high sensitivity, reliable identification of large genome-wide and recurrent chromosomal aberrations, the assessment of immunoglobulin and T-cell receptor gene rearrangements, and lymphoma-specific translocation detection.

"This represents a crucial step toward the effective management of hemato-oncological patients," commented Prof. Dr. Pospisilova.

"Because this assay is straightforward and can also be used in research, it warrants further prospective testing in close cooperation among researchers, clinical hemato-oncologists, and hematopathologists to demonstrate its clinical utility and benefit for patients with lymphoid malignant tumors."

The research team believes that the LYNX panel is suitable for routine

testing with research and clinical applicability and may assist in personalized management of patients with lymphoid malignancies. It enables an integrated analysis of clinically relevant genomic aberrations and markers into one test, monitors clonal evolution of the disease, and reveals various genetic architecture in different lymphoproliferative disorders. Furthermore, the results obtained by this test can guide clinical assessment of the patient diagnosis, prognosis, therapy selection and may lead to the revelation of patient-specific markers crucial for monitoring minimal residual disease.

More information: Veronika Navrkalova et al, LYmphoid NeXt-Generation Sequencing (LYNX) Panel, *The Journal of Molecular Diagnostics* (2021). [DOI: 10.1016/j.jmoldx.2021.05.007](https://doi.org/10.1016/j.jmoldx.2021.05.007)

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