Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

Caracterización genética* de neoplasias linfoides, ¿qué estudiar y qué implicaciones tiene?

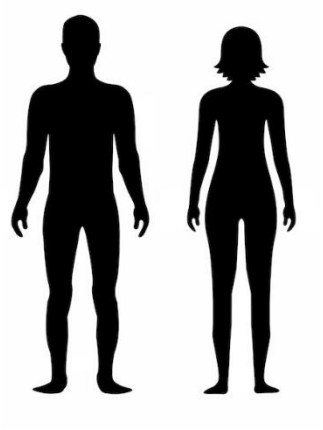
Blanca Espinet

Hospital del Mar, Barcelona

Outline

- **General considerations**
  - Guidelines and recommendations
  - Samples
  - Methods
- **Mature B-cell neoplasms**
  - General overview
  - Selected entities: CLL, MCL, HCL, LPL, MZL, FL, BL, DLBCL
- **Mature T-cell neoplasms**
  - General overview
  - Summarized recommendations
- **Final considerations and open questions**

The diagnostic work-up in lymphomas: an integrated process



Patients:
clinical information,
analytics, imaging tests

SUSPECTED DIAGNOSIS

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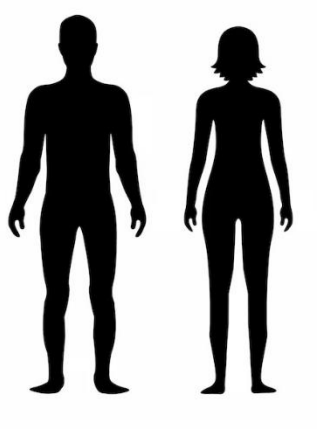

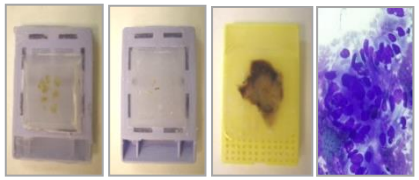

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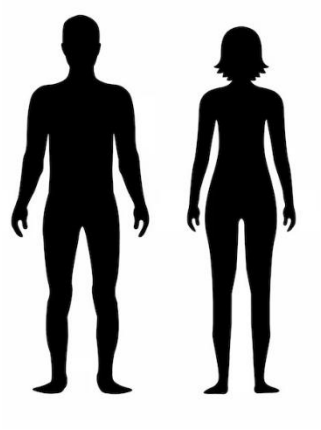

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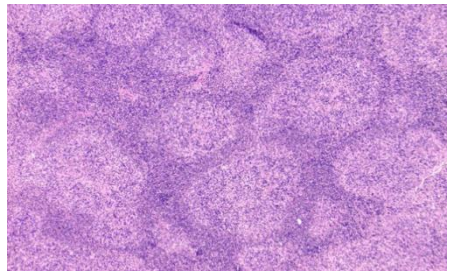
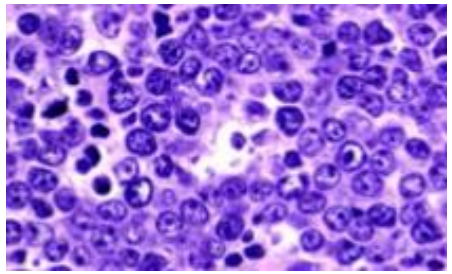
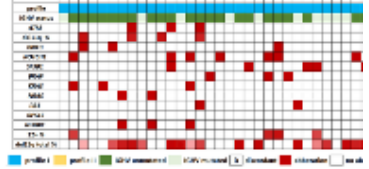


Histology, architecture



Cell morphology



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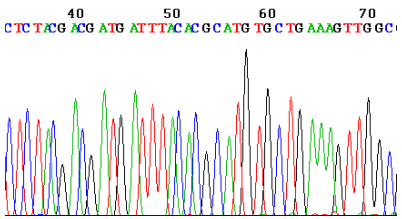

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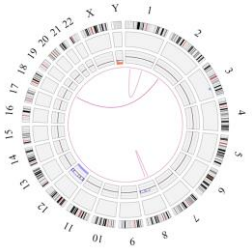

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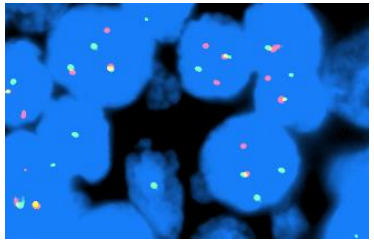

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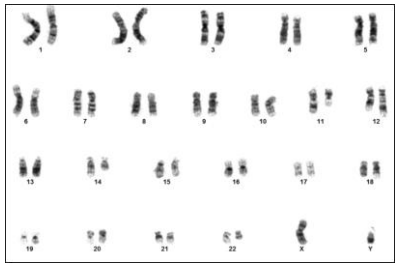
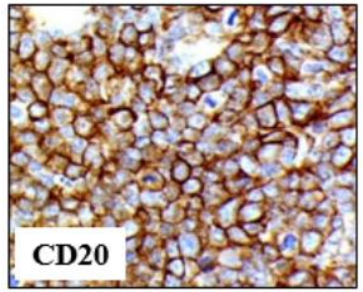
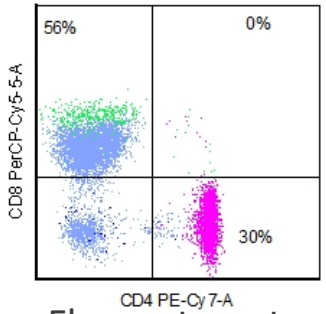


Karyotype



Immunohistochemistry



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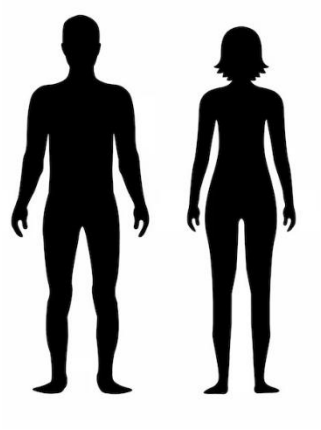

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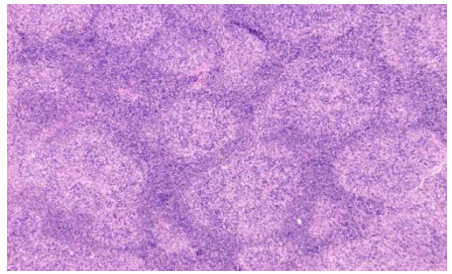
Samples



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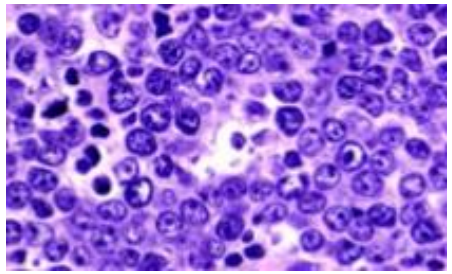

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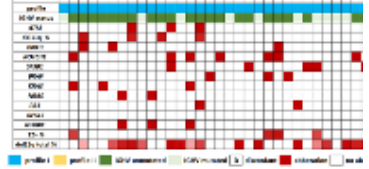

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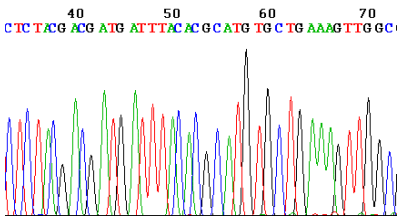

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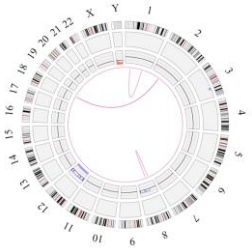

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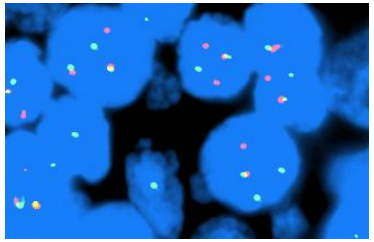

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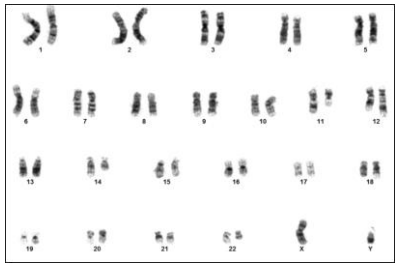
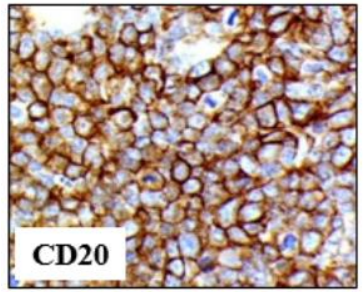


Karyotype



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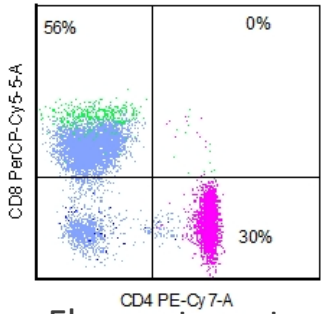

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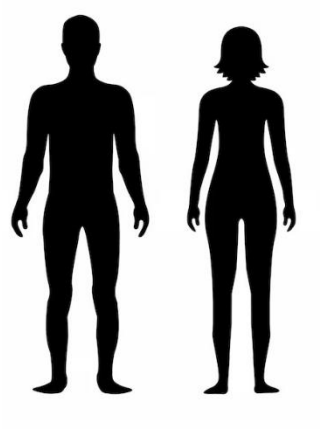

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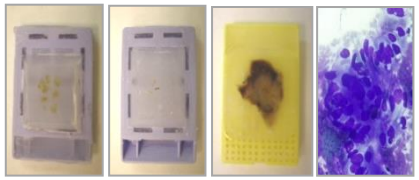
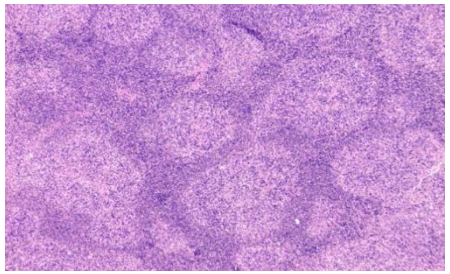


Samples



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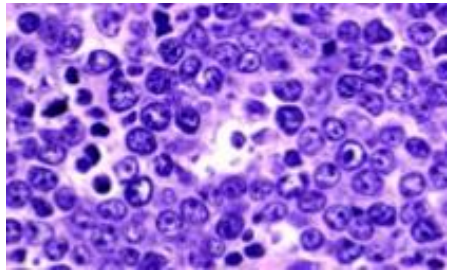

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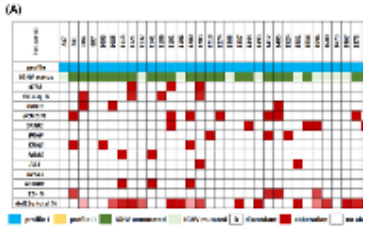

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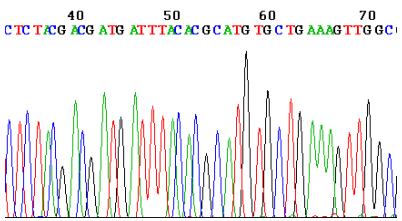

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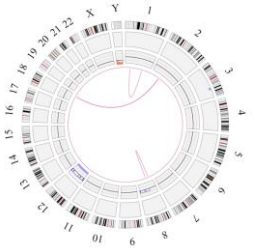
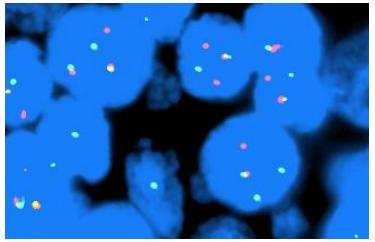


OGM

Diagnosis
Prognosis
Treatment



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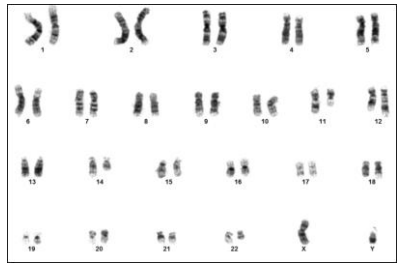

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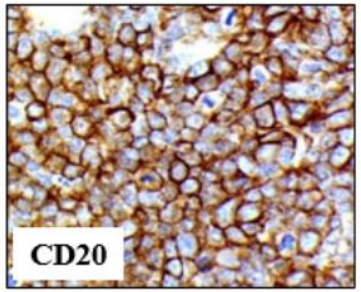

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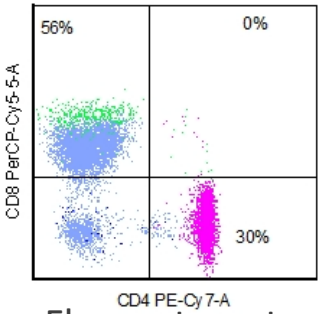

Flow cytometry

Guidelines and Recommendations: ICC and WHO-HAEM5 (2022)

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Special Report

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

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LYMPHOMA

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blood
24 NOVEMBER 2022 | VOLUME 140, NUMBER 21
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Genomic profiling for clinical decision making in lymphoid neoplasms

Laurence de Leval,[1,*] Ash A. Alizadeh,[2-5] P. Leif Bergsagel,[6] Elias Campo,[7] Andrew Davies,[8] Ahmet Dogan,[9] Jude Fitzgibbon,[10] Steven M. Horwitz,[11] Ari M. Melnick,[12] William G. Morice,[13] Ryan D. Morin,[14-16] Bertrand Nadel,[17] Stefano A. Pileri,[18] Richard Rosenquist,[19,20] Davide Rossi,[21] Itziar Salaverria,[22] Christian Steidl,[23] Steven P. Treon,[24] Andrew D. Zelenetz,[11,12] Ranjana H. Advani,[25] Carl E. Allen,[26] Stephen M. Ansell,[27] Wing C. Chan,[28] James R. Cook,[29] Lucy B. Cook,[30] Francesco d'Amore,[31] Stefan Dirnhofer,[32] Martin Dreyling,[33] Kieron Dunleavy,[34] Andrew L. Feldman,[13] Falko Fend,[35] Philippe Gaulard,[36,37] Paolo Ghia,[38] John G. Gribben,[10] Olivier Hermine,[39] Daniel J. Hodson,[40,41] Eric D. Hsi,[42] Giorgio Inghirami,[43] Elaine S. Jaffe,[44] Kennosuke Karube,[45] Keisuke Kataoka,[46,47] Wolfram Klapper,[48] Won Seog Kim,[49] Rebecca L. King,[13] Young H. Ko,[50] Ann S. LaCasce,[24] Georg Lenz,[51] José I. Martin-Subero,[52] Miguel A. Piris,[53] Stefania Pittaluga,[44] Laura Pasqualucci,[54-56] Leticia Quintanilla-Martinez,[35] Scott J. Rodig,[57] Andreas Rosenwald,[58] Gilles A. Salles,[11] Jesus San-Miguel,[59] Kerry J. Savage,[23] Laurie H. Sehn,[23] Gianpietro Semenzato,[60] Louis M. Staudt,[61] Steven H. Swerdlow,[62] Constantine S. Tam,[63] Judith Trotman,[64] Julie M. Vose,[65] Oliver Weigert,[33] Wyndham H. Wilson,[61] Jane N. Winter,[66] Catherine J. Wu,[24] Pier L. Zinzani,[67] Emanuele Zucca,[21] Adam Bagg,[68] and David W. Scott[23,*]

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LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Iguaracyra Barreto de Oliveira Araujo[5], Emilio Berti[6], Govind Bhagat[7], Anita Maria Borges[8], Daniel Boyer[9], Mariarita Calaminici[10], Amy Chadburn[11], John K. C. Chan[12], Wah Cheuk[12], Wee-Joo Chng[13], John K. Choi[14], Shih-Sung Chuang[15], Sarah E. Coupland[16], Magdalena Czader[17], Sandeep S. Dave[18], Daphne de Jong[19], Ming-Qing Du[20]✉, Kojo S. Elenitoba-Johnson[21], Judith Ferry[22]✉, Julia Geyer[11], Dita Gratzinger[23], Joan Guitart[24], Sumeet Gujral[25], Marian Harris[26], Christine J. Harrison[27], Sylvia Hartmann[28], Andreas Hochhaus[29], Patty M. Jansen[30], Kennosuke Karube[31], Werner Kempf[32], Joseph Khoury[33], Hiroshi Kimura[34], Wolfram Klapper[35], Alexandra E. Kovach[36], Shaji Kumar[37], Alexander J. Lazar[38], Stefano Lazzi[39], Lorenzo Leoncini[39], Nelson Leung[40], Vasiliki Leventaki[41], Xiao-Qiu Li[42], Megan S. Lim[21], Wei-Ping Liu[43], Abner Louissaint Jr.[22], Andrea Marcogliese[44], L. Jeffrey Medeiros[33], Michael Michal[45], Roberto N. Miranda[33], Christina Mitteldorf[46], Santiago Montes-Moreno[47], William Morice[48], Valentina Nardi[22], Kikkeri N. Naresh[49], Yasodha Natkunam[23], Siok-Bian Ng[50], Ilske Oschlies[35], German Ott[51]✉, Marie Parrens[52], Melissa Pulitzer[53], S. Vincent Rajkumar[54], Andrew C. Rawstron[55], Karen Rech[48], Andreas Rosenwald[3], Jonathan Said[56], Clémentine Sarkozy[57], Shahin Sayed[58], Caner Saygin[59], Anna Schuh[60], William Sewell[61], Reiner Siebert[62]✉, Aliyah R. Sohani[22], Reuben Tooze[63], Alexandra Traverse-Glehen[64], Francisco Vega[33], Beatrice Vergier[65], Ashutosh D. Wechalekar[66], Brent Wood[36], Luc Xerri[67] and Wenbin Xiao[53]

Guidelines and Recommendations: ICC and WHO-HAEM5 (2022)

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Genomic profiling for clinical decision making in lymphoid neoplasms

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LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

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medizinische genetik 2024; 36(1): 59–73

Cristina López[1,2,3]*, Anja Fischer[4], Andreas Rosenwald[5], Reiner Siebert[4], German Ott[6], Katrin S. Kurz[6]

Genetic alterations in mature B- and T-cell lymphomas – a practical guide to WHO-HAEM5

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Clinical and Translational Oncology (2024) 26:1043–1062
https://doi.org/10.1007/s12094-023-03307-1

REVIEW ARTICLE

A genetic profiling guideline to support diagnosis and clinical management of lymphomas

Margarita Sánchez-Beato[1,2] · Miriam Méndez[1,2,3] · María Guirado[2,4] · Lucía Pedrosa[1] · Silvia Sequero[2,5] · Natalia Yanguas-Casás[1] · Luis de la Cruz-Merino[2,6] · Laura Gálvez[2,7] · Marta Llanos[2,8] · Juan Fernando García[9] · Mariano Provencio[1,2,10]

Which aberrations should we study? Spanish recommendations (NGS ± FISH or other methods)

2023

Recomendaciones sobre el **estudio de secuenciación masiva**

NEOPLASIAS HEMATOLÓGICAS

Documento de consenso del
Grupo de Biología Molecular en Hematología (GBMH)

GBMH

SEHH
Sociedad Española de Hematología y Hemoterapia

2023-2024

Catálogo Común de Pruebas Genéticas

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Plan de Recuperación, Transformación y Resiliencia

2021
12/2024

Determinacions del perfil genètic de les malalties neoplàstiques hematològiques

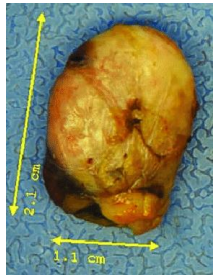
/Salut

Generalitat de Catalunya

Gómez-Casares et al, 2023; Abrisqueta et al, SCS 2024; https://cgen.sanidad.gob.es/#/

SAMPLES: Genetic analyses have to be done in the infiltrated tissue sample

Tissue biopsies: lymph node, extranodal



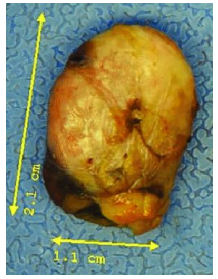
fresh

FFPE

10-20% tumor cells

SAMPLES: Genetic analyses have to be done in the infiltrated tissue sample

Tissue biopsies: lymph node, extranodal

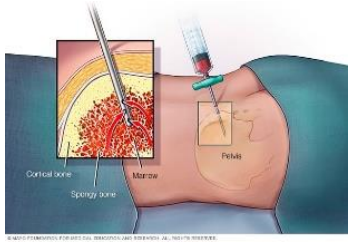


fresh

FFPE

10-20% tumor cells

Bone marrow aspirate



Heparin
(cytogen)

EDTA
(molecular)

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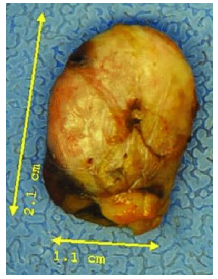

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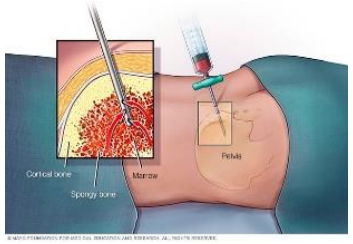
Bone marrow aspirate



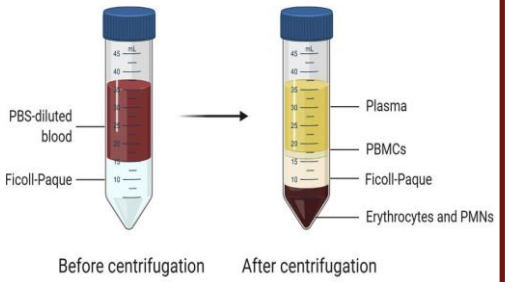
Heparin (cytogen)

EDTA (molecular)

Peripheral blood

Heparin (cytogen)

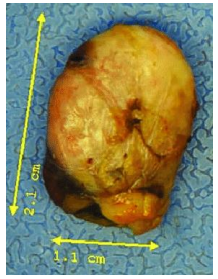
EDTA (molecular)



Isolation of mononuclear cells (Ficoll)

SAMPLES: Genetic analyses have to be done in the infiltrated tissue sample

Tissue biopsies: lymph node, extranodal

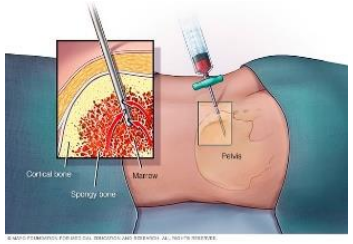


fresh

FFPE

10-20% tumor cells

Bone marrow aspirate



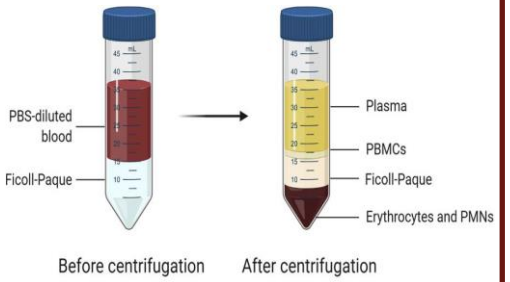
Heparin (cytogen)

EDTA (molecular)

Peripheral blood

Heparin (cytogen)

EDTA (molecular)

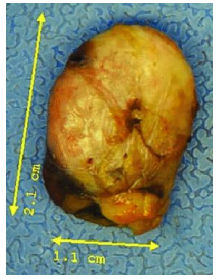


Isolation of mononuclear cells (Ficoll)

Other fluids: cerebrospinal, pleural, ascitic

SAMPLES: Genetic analyses have to be done in the infiltrated tissue sample

Tissue biopsies: lymph node, extranodal

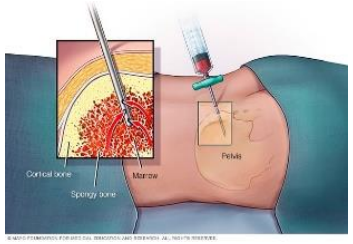


fresh

FFPE

10-20% tumor cells

Bone marrow aspirate



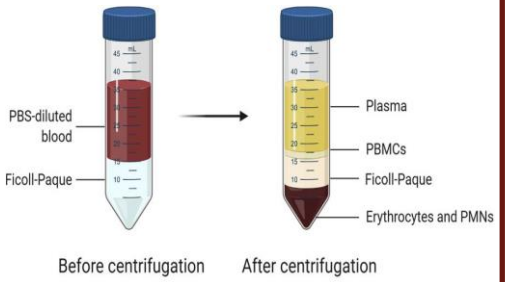
Heparin (cytogen)

EDTA (molecular)

Peripheral blood

Heparin (cytogen)

EDTA (molecular)



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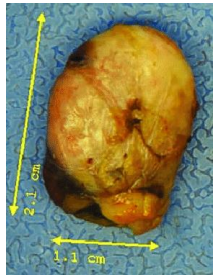

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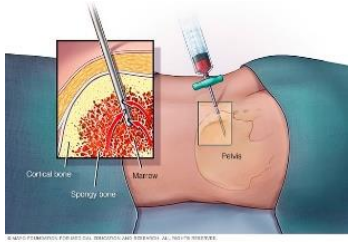

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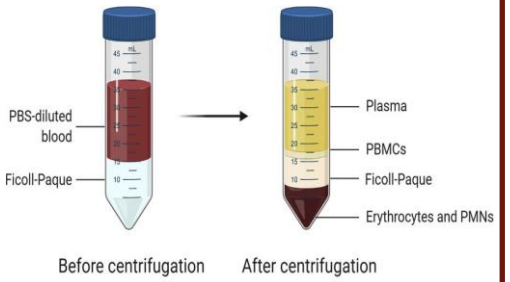
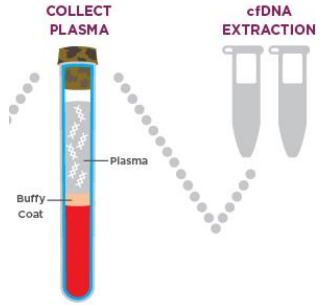


Isolation of mononuclear cells (Ficoll)

Other fluids: cerebrospinal, pleural, ascitic

Plasma: ctDNA (streck)



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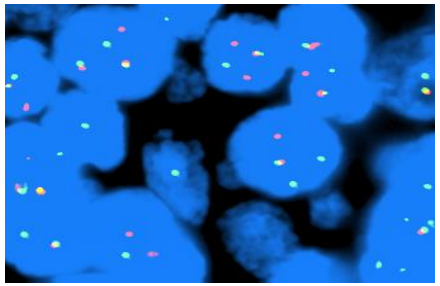

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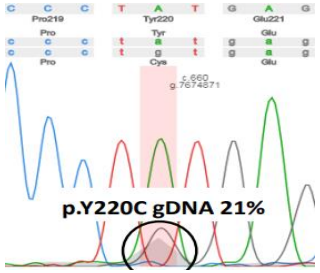

Sanger sequencing

NGS panels

Modified from De Leval et al, Blood 2022

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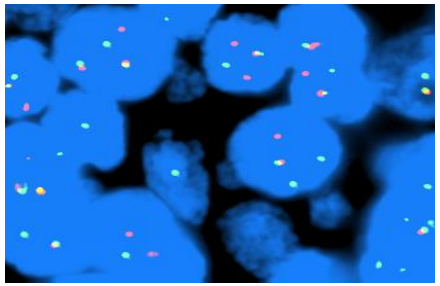

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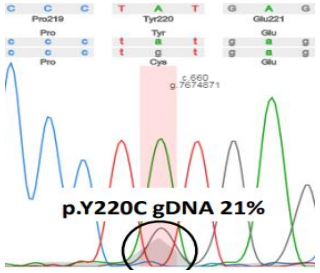

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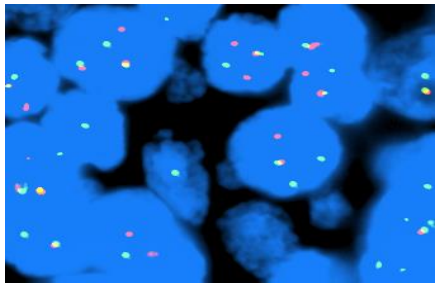

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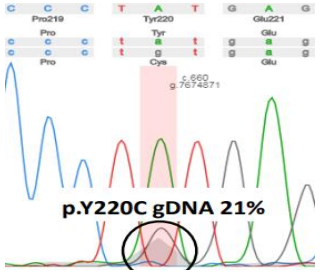

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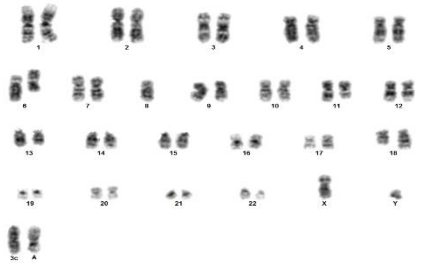

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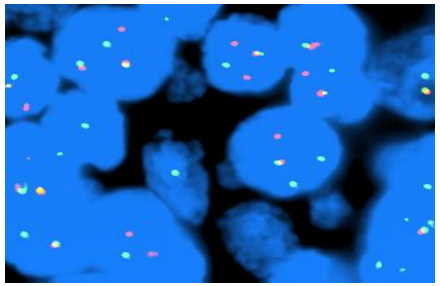

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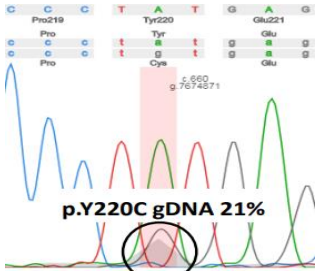

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NGS panels

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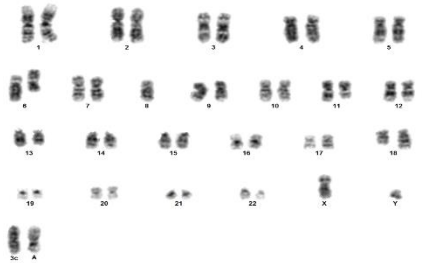

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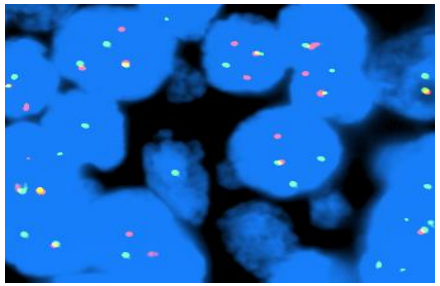

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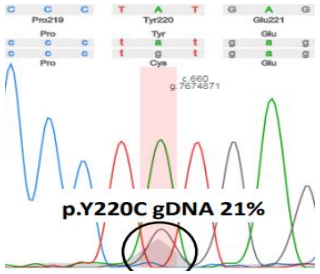

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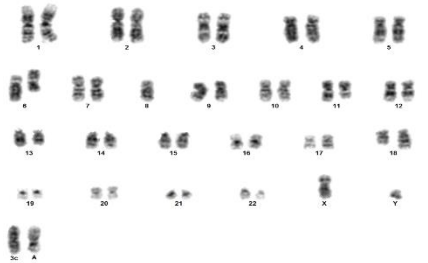

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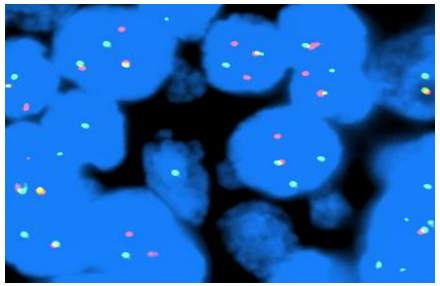

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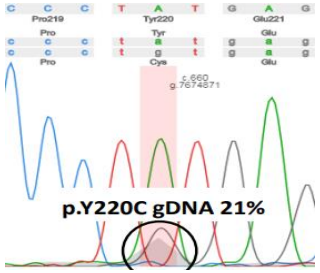

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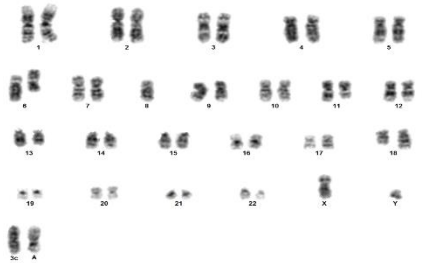


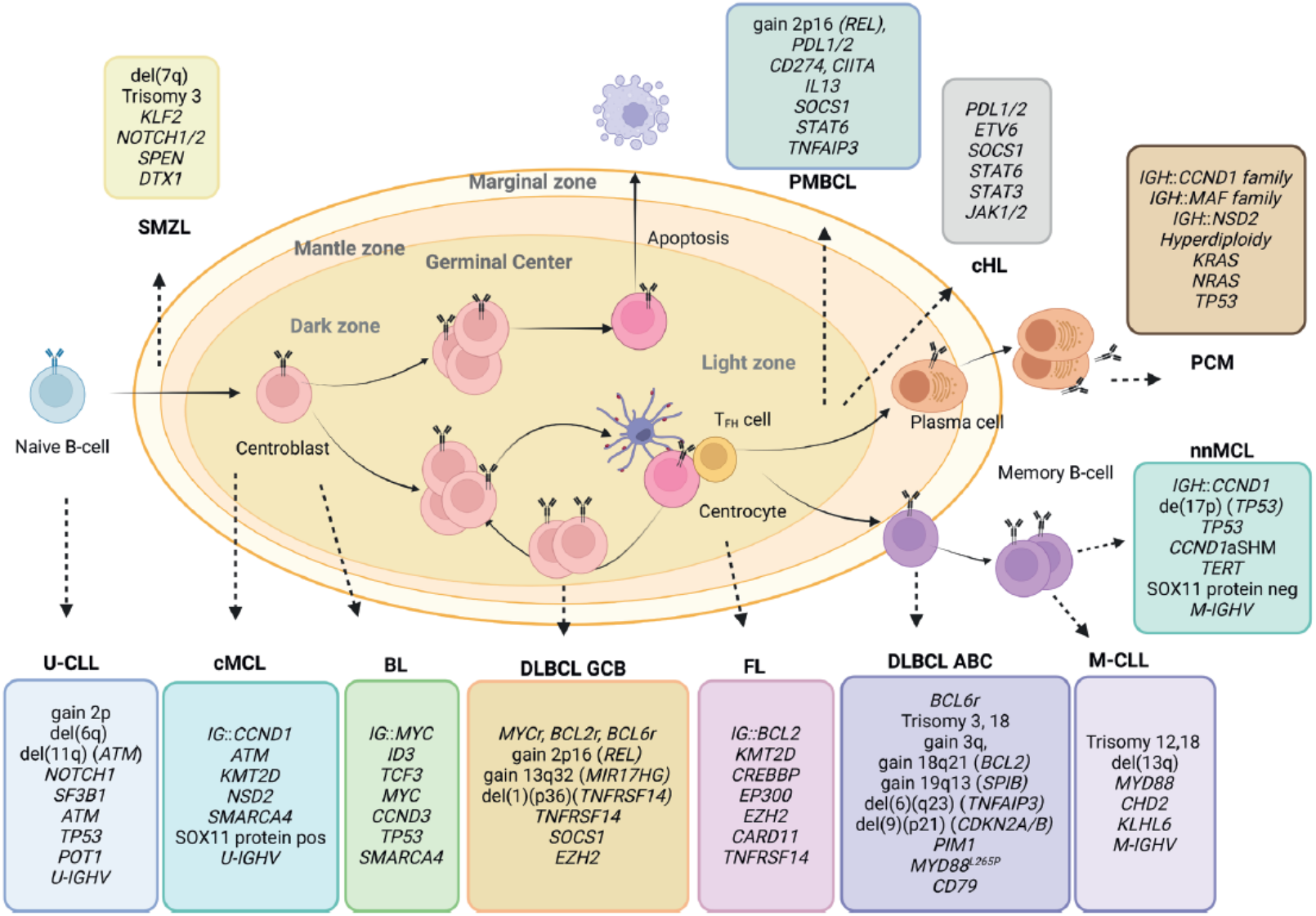
Karyotyping

ENAC Entidad Nacional de Acreditación

International Organization for Standardization ISO 15189

Modified from De Leval et al, Blood 2022

B-cell maturation process, and their derived B-cell lymphomas

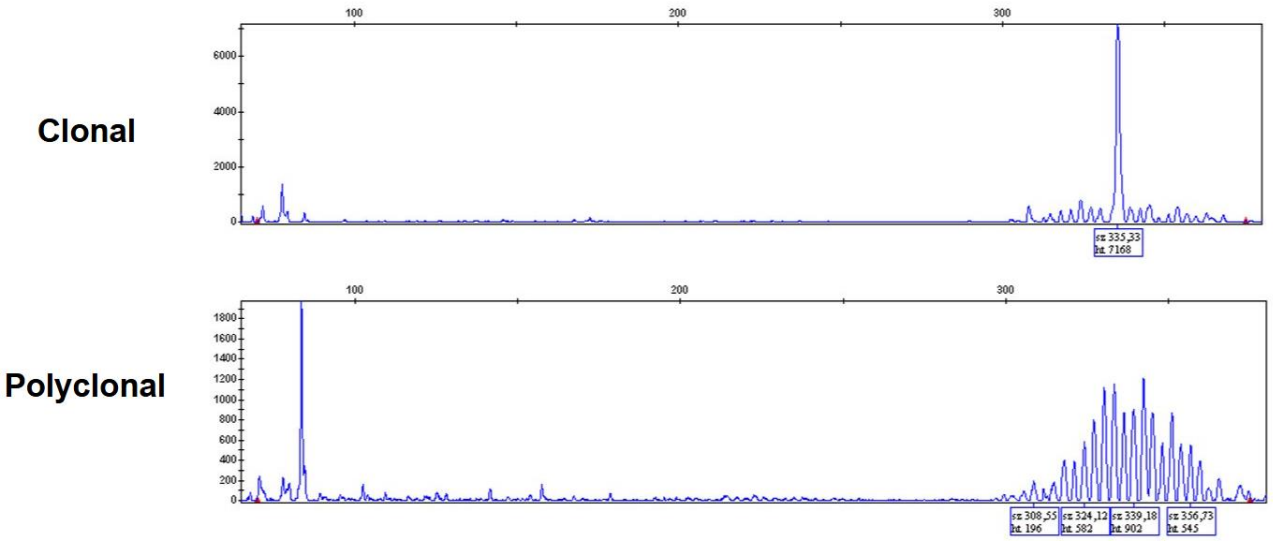


López et al, Medizinische Genetik 2024

B-cell clonality: The IG rearrangement/s

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
B-cell neoplasms	IG gene rearrangement: PCR-based assays with fragment analysis or HTS	Useful in certain circumstances to demonstrate monoclonality of B-cell lymphoproliferations to establish a diagnosis; mandatory in certain entities (eg, pediatric-type FL)		WGS for the detection of CNAs and SVs WTS to detect microenvironment signatures

EuroClonality/BIOMED-2



- To demonstrate B-cell monoclonality
- To demonstrate clonal relationship between entities (ie CLL and Richter)

Van Dongen et al, Leukemia 2003; Evans et al, Leukemia 2007; Langerak et al, Leukemia 2016; Stewart et al, Blood Adv 2021; De Leval et al, Blood 2022

Chronic lymphocytic leukemia (CLL)

Hallek et al, iwCLL Guidelines, Blood 2018 **CIT era**

Diagnostic test	General practice	Clinical trial
Additional tests before treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI*	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always

Hallek et al, Blood 2018; De Leval et al, Blood 2022; Medina et al, Med Clin 2025

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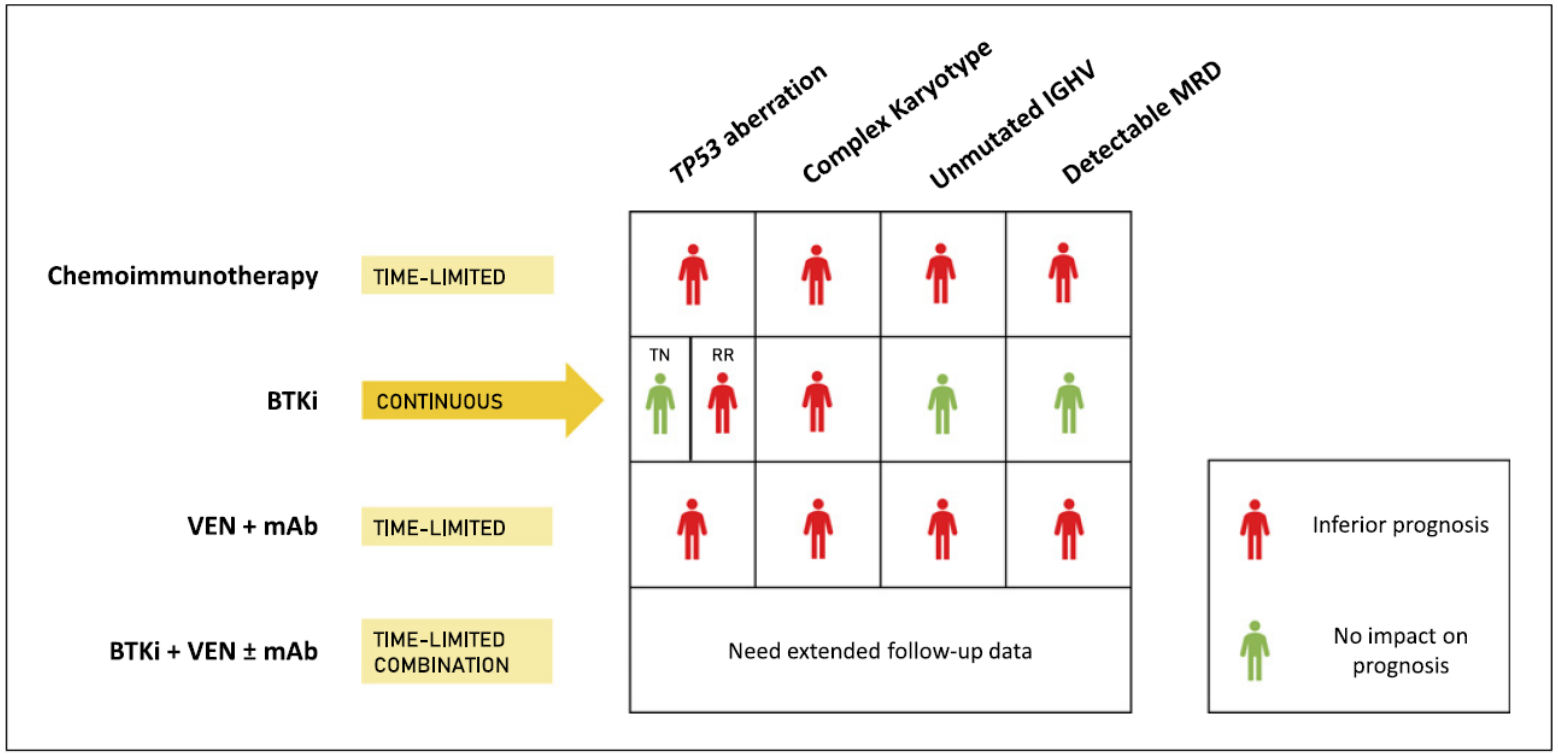
Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	IGHV mutation status*: IGHV sequencing		Prognostic and predictive. IGHV gene mutational status remains stable through the disease course and only needs to be performed once	Determining BcR stereotypy and IGLV3-21^{R110} mutation status for risk stratification; tracking of resistance mutations (*BTK*, *PLCG2*, and *BCL2*; supplemental Table 3) WGS for mutations, CNAs, SVs, and complex karyotype determination MRD testing using HTS to guide therapy decisions
	del(11q), +12, del(13q), del(17p)*: FISH		Prognostic and del(17p) is predictive. FISH testing should be performed before each new course of therapy	
	TP53 mutations*: HTS		Prognostic and predictive. *TP53* sequencing should be performed before each new course of therapy unless already demonstrated	
	Detection of complex karyotype (≥5 abnormalities): cytogenetics* or SNP arrays		Prognostic	

*Required/strongly recommended in the National Comprehensive Cancer Network 2022 guidelines.

Hallek et al, Blood 2018; De Leval et al, Blood 2022; Medina et al, Med Clin 2025

Chronic lymphocytic leukemia (CLL)

IMPACT OF PROGNOSTIC FACTORS BY TREATMENT REGIMENS



Kang and Ahn, Acta Haematologica 2024; Abrisqueta et al, SCS 2024

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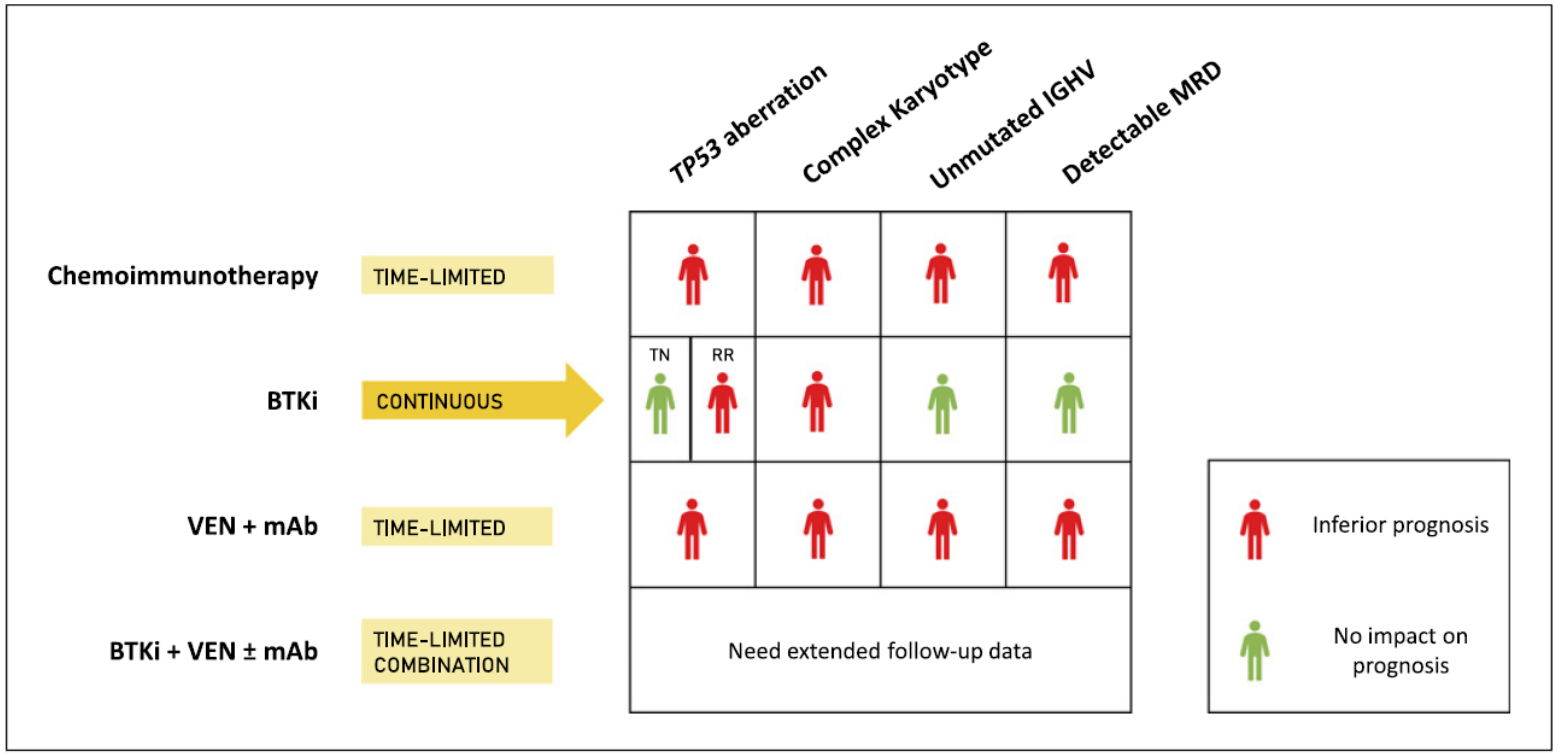

TP53 ***del/mut***

IGHV

CK? ***COMPLEX project***

Kang and Ahn, Acta Haematologica 2024; Abrisqueta et al, SCS 2024

Chronic lymphocytic leukemia (CLL)

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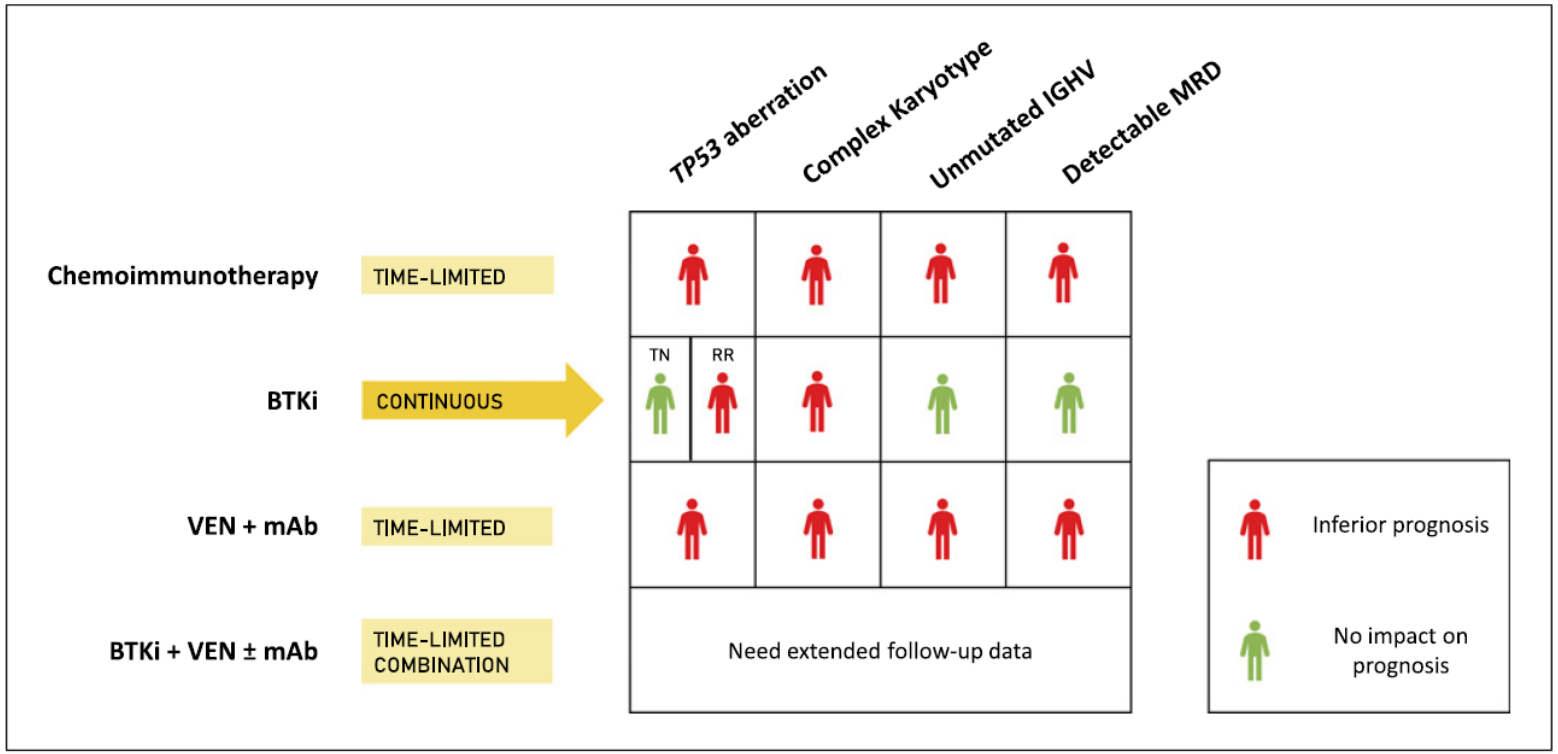

TP53 ***del/mut***

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CK? ***COMPLEX project***

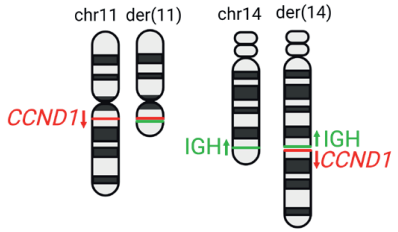
Gen	Transcrit referent	Regió específica d'interès	Indicació clínica *Diagnòstic*	Indicació clínica *Pronòstic*	Indicació clínica *Tractament: 1L*	Indicació clínica *Tractament: 2L*	Indicació clínica *Tractament: altres*
TP53	NM_000546.5	Exons 2-10		X	X	X	
IGHV	https://www.imgt.org/			X	X		
BTK	NM_000061.2	Exons 14-16				X	Fallida a ibrutinib
PLCG2	NM_002661.5	Exons 19-24				X	Fallida a ibrutinib
BCL2	NM_000633.2	Exons 2-3				X	Fallida a venetoclax

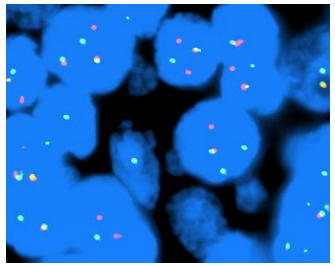
Kang and Ahn, Acta Haematologica 2024; Abrisqueta et al, SCS 2024

Mantle cell lymphoma (MCL)

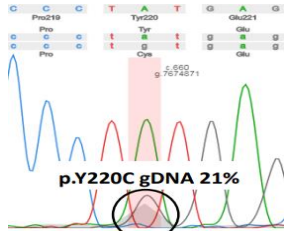
Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Mantle cell lymphoma	*CCND1* rearrangement†: FISH	Consider if CCND1 IHC is negative		MRD testing using HTS to guide treatment decisions WTS or targeted gene expression panel for proliferation and signatures of nnMCL vs cMCL
	CCND2 and *CCND3* rearrangement†: FISH	Consider in *CCND1*-R– negative tumors		
	TP53 mutation*: HTS‡		Prognostic and guide management[111]	

t(11;14)(q13;q32)/*CCND1*::*IGH*





FISH IGH::*CCND1*



***TP53* sequencing (Sanger or NGS)**

Eskelund et al, 2017, De Leval et al, 2022; López et al, 2024; Abrisqueta et al, SCS 2024

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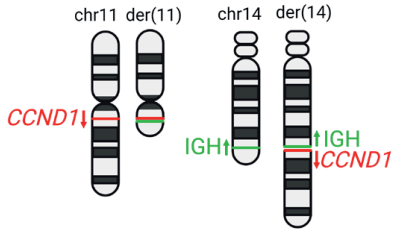
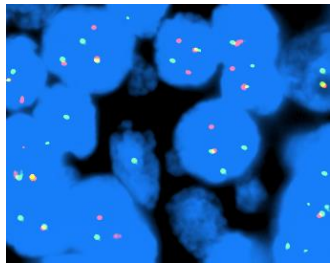
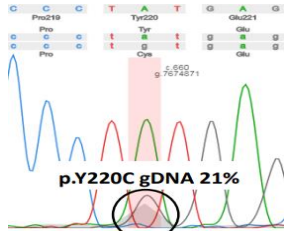
	TP53 mutation*: HTS‡		Prognostic and guide management[111]	

t(11;14)(q13;q32)/*CCND1*::*IGH*





FISH IGH::*CCND1*



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BTK	NM_000061.2	Exó 15				X	Fallida a ibrutinib
PLCG2	NM_002661.5	Exons 19-24				X	Fallida a ibrutinib
BIRC3	NM_001165.5	Exons 2-9				X	Abans d'ibrutinib
BCL2	NM_000633.2	Exons 2-3				X	Fallida a venetoclax

Eskelund et al, 2017, De Leval et al, 2022; López et al, 2024; Abrisqueta et al, SCS 2024

Mantle cell lymphoma (MCL): Identification and management of high-risk MCL

Table 1. High-risk prognostic features in patients with newly diagnosed or relapsed MCL

Features	Newly diagnosed MCL	R/R MCL*
Accepted ultra-high-risk features	De novo blastoid or pleomorphic histology with high-risk mutations[40] Ki-67% ≥50%† in involved tissue biopsy with blastoid or pleomorphic histology[12,41] ‡*TP53* mutation (R273) with other high-risk gene mutations (*KMT2D*, *NSD2*, *CCND1*, *NOTCH1*, *CDKN2A*, *NOTCH2*, or *SMARCA4* mutations) and extensive disease burden[42] CNS involvement with systemic disease[43]	Transformed blastoid or pleomorphic histology (transformed from classic histology; ie, disease resistant to BTKi, venetoclax, and anti-CD19 CART)[40] Primary BTKi-refractory disease [12] Refractory to ≥3 previous lines of standard therapy (including BTKi)[12] Triple-resistant MCL (disease resistant to BTKi, venetoclax, and anti-CD19 CART)[12,33]
Accepted high-risk features	Blastoid or pleomorphic histology[40] Ki-67 ≥50%† in involved tissues with classic histology[12,41] *TP53* mutation[14] and/or del(17p) by FISH, *TP53* overexpression by IHC, and/or non-*TP53* mutations (*NOTCH1/NOTCH2*, *KMT2D*, *NSD2*, and *SMARCA4* mutations)[44] CK[45] *MYC* rearrangement and/or amplification[46-50] *TP53* expression in >50% of cells or a high combined MIPI score Simplified MIPI score ≥6.2[51] Bulky disease‖	High-risk features for patients with newly diagnosed disease[12] ≤2 previous lines of standard therapy Progression within 24 months of first-line therapy[52] MRD$^+$ status after therapy§

Jain and Wang, Blood 2025

Mantle cell lymphoma (MCL): Identification and management of high-risk MCL

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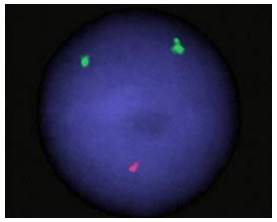
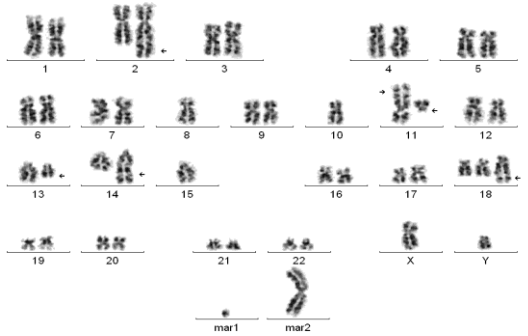
Accepted high-risk features	Blastoid or pleomorphic histology[40] Ki-67 ≥50%† in involved tissues with classic histology[12,41] *TP53* mutation[14] and/or del(17p) by FISH, *TP53* overexpression by IHC, and/or non-*TP53* mutations (*NOTCH1/NOTCH2, KMT2D, NSD2,* and *SMARCA4* mutations)[44] CK[45] *MYC* rearrangement and/or amplification[46-50] *TP53* expression in >50% of cells or a high combined MIPI score Simplified MIPI score ≥6.2[51] Bulky disease‖	High-risk features for patients with newly diagnosed disease[12] ≤2 previous lines of standard therapy Progression within 24 months of first-line therapy[52] MRD$^+$ status after therapy§

KMT2D
NOTCH1/NOTCH2
NSD2
SMARCA4
CCND1
CDKN2A

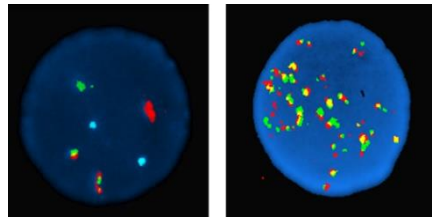
***Non-TP53* mutations**



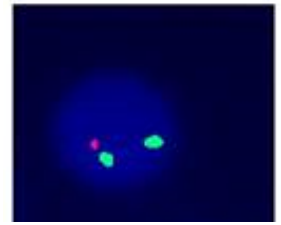
***TP53* (17p13) deletions**



Complex karyotype



***MYC* rearrangements**
***MYC* amplifications**

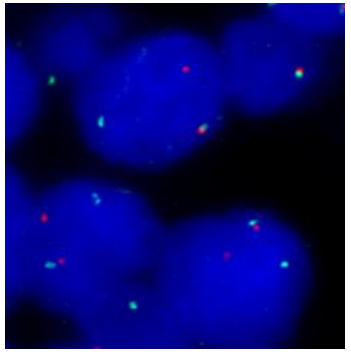


***CDKN2A* (9p21) deletions**

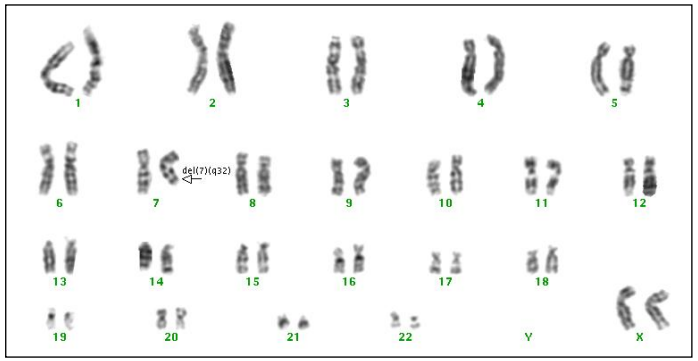
Jain and Wang, Blood 2025

Marginal zone lymphomas

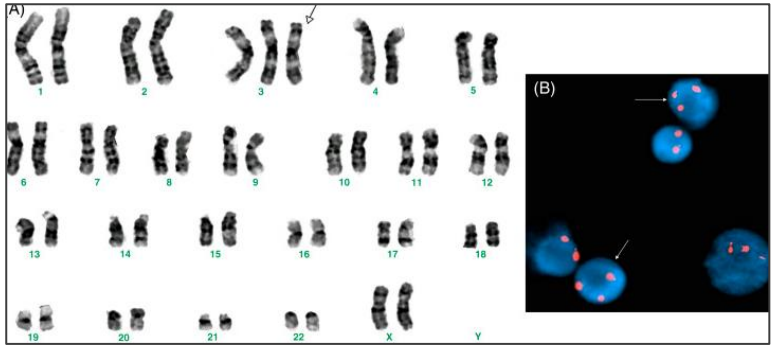
Entity	Genetic alteration: test	Diagnostic use	Clinical impact
Marginal zone lymphomas (MZL)	*BCL2* and *CCND1* rearrangements: FISH† *MYD88* L265 mutation†: AS-PCR or HTS	Detection prompts considering a diagnosis of other entities; see scenarios 1 and 2 in Table 3 and supplemental Figure 3	
Extranodal MZL of mucosa associated lymphoid tissue (MALT lymphoma)	*MALT1*, *BCL10*, *FOXP1* rearrangements†: FISH +3, +18[88]: cytogenetics and FISH	Detection is useful in certain circumstances to support the diagnosis	
	t(11;18) *BIRC3*::*MALT1**: FISH in *H pylori*–positive gastric MALT lymphoma		*MALT1* rearrangements are associated with lack of antibiotic response in *H pylori*–positive gastric MALT lymphoma[91]
Splenic MZL	del(7q)†, +3, +18[88]: cytogenetics and FISH *KLF2*, *NOTCH2* mutations[88]: HTS	Detection is useful in certain circumstances to support the diagnosis	
Nodal MZL	+3, +18[88]: cytogenetics and FISH *KLF2*, *NOTCH2*, *PTPRP*[88] mutations: HTS	Detection is useful in certain circumstances to support the diagnosis	



FISH *MALT1*



SMZL: Karyotypes in PB



Salido et al, Blood 2010; Solé et al, Haematologica 2011; De Leval et al, Blood 2022; Abrisqueta et al, 2024

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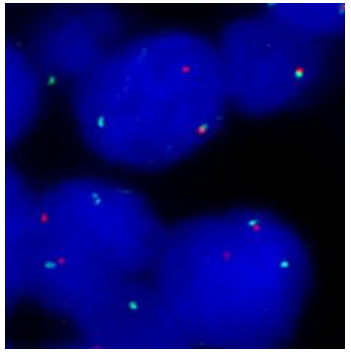
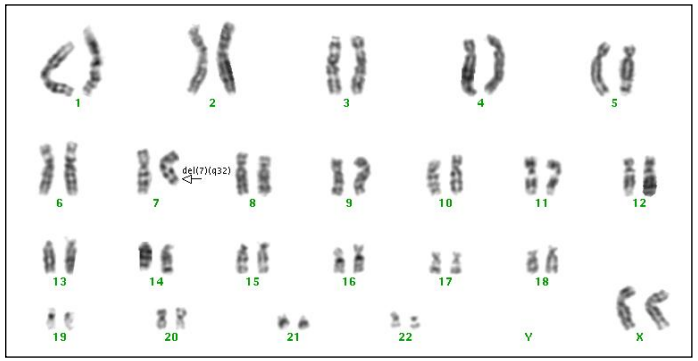
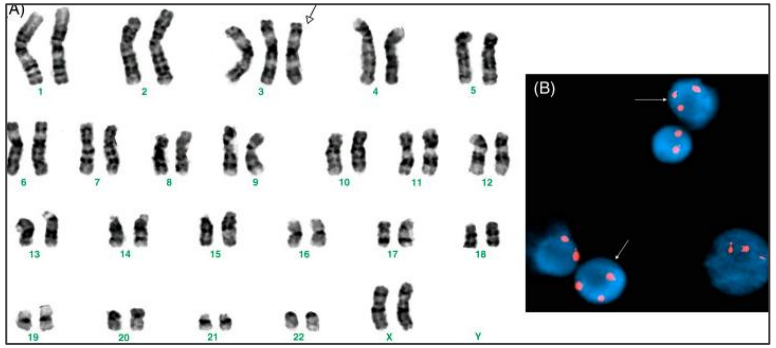


FISH *MALT1*



SMZL: Karyotypes in PB



Salido et al, Blood 2010; Solé et al, Haematologica 2011; De Leval et al, Blood 2022; Abrisqueta et al, 2024

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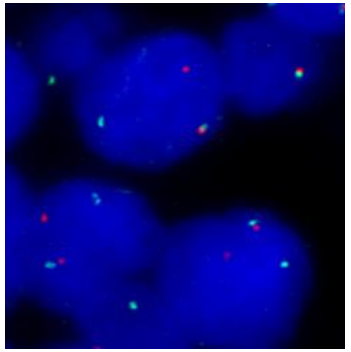
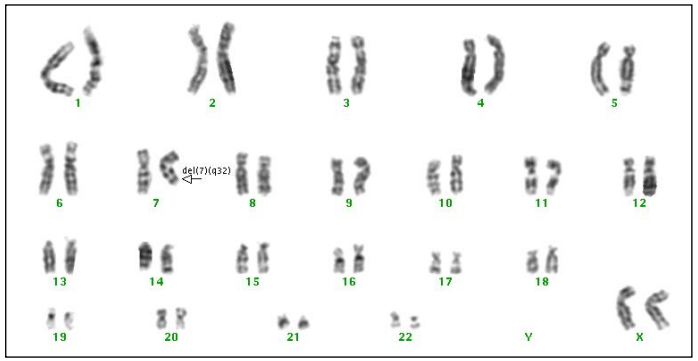
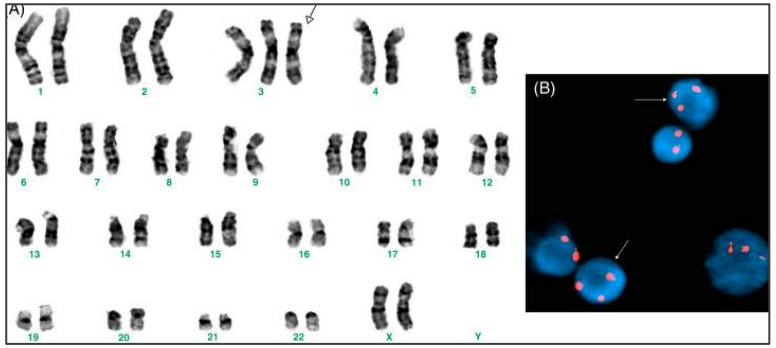


FISH *MALT1*



SMZL: Karyotypes in PB



Gen	Transcrit referent	Regió específica d'interès	Indicació clínica *Diagnòstic*	Indicació clínica *Pronòstic*	Indicació clínica *Tractament: 1L*	Indicació clínica *Tractament: 2L*	Indicació clínica *Tractament: altres*
KLF2	NM_016270.4	Regió codificant	Dx dubtós				
PTPRD	NM_002839.4	Exons 42-46	Dx dubtós				
TP53	NM_000546.5	Exons 2-10		X	X	X	
NOTCH2	NM_024408.4	Exó 34	Dx dubtós	X			
MYD88	NM_002468.5	Exons 3-5	Dx dubtós				
CCND3	NM_001760.4	Exó 5	Dx dubtós				

Salido et al, Blood 2010; Solé et al, Haematologica 2011; De Leval et al, Blood 2022; Abrisqueta et al, 2024

Hairy cell leukemia (HCL)

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Hairy cell leukemia	*BRAF* V600E mutation: sequencing or IHC	Useful to support the diagnosis on biopsy samples and in cases with uncommon presentations[463]		

Tiacci et al, NEJM 2011; De Leval et al, Blood 2022; Abrisqueta et al, SCS 2024

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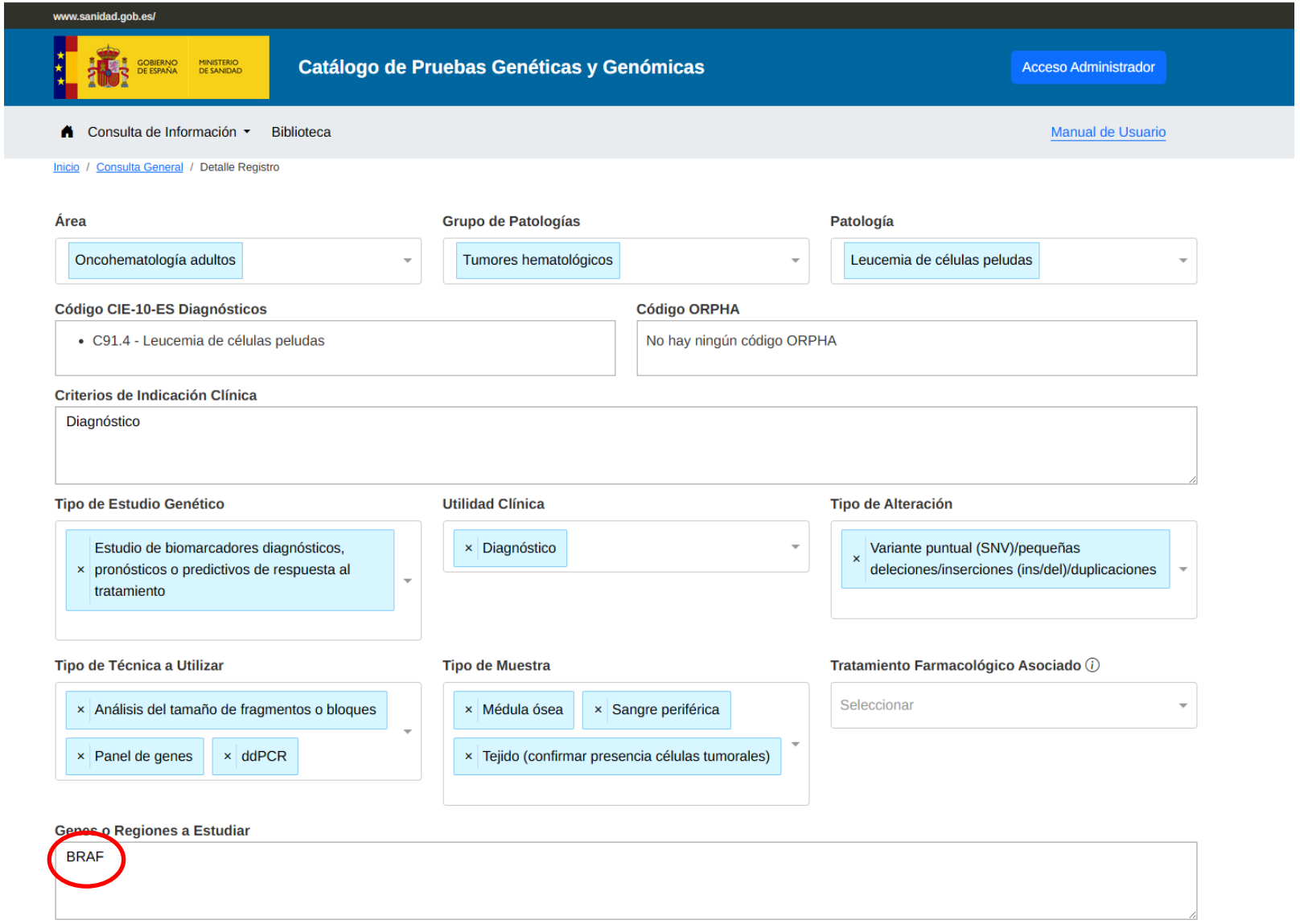
BRAF	NM_004333.6	Exons 11, 12, 15	X (casos dubtosos)	X		X	Vemurafenib
MAP2K1	NM_002755.3	Exons 1-11	X (HCLv)	X			
CCND3	NM_001760.4	Exó 5	X				
TP53	NM_000546.5	Exons 2-10		X		X	

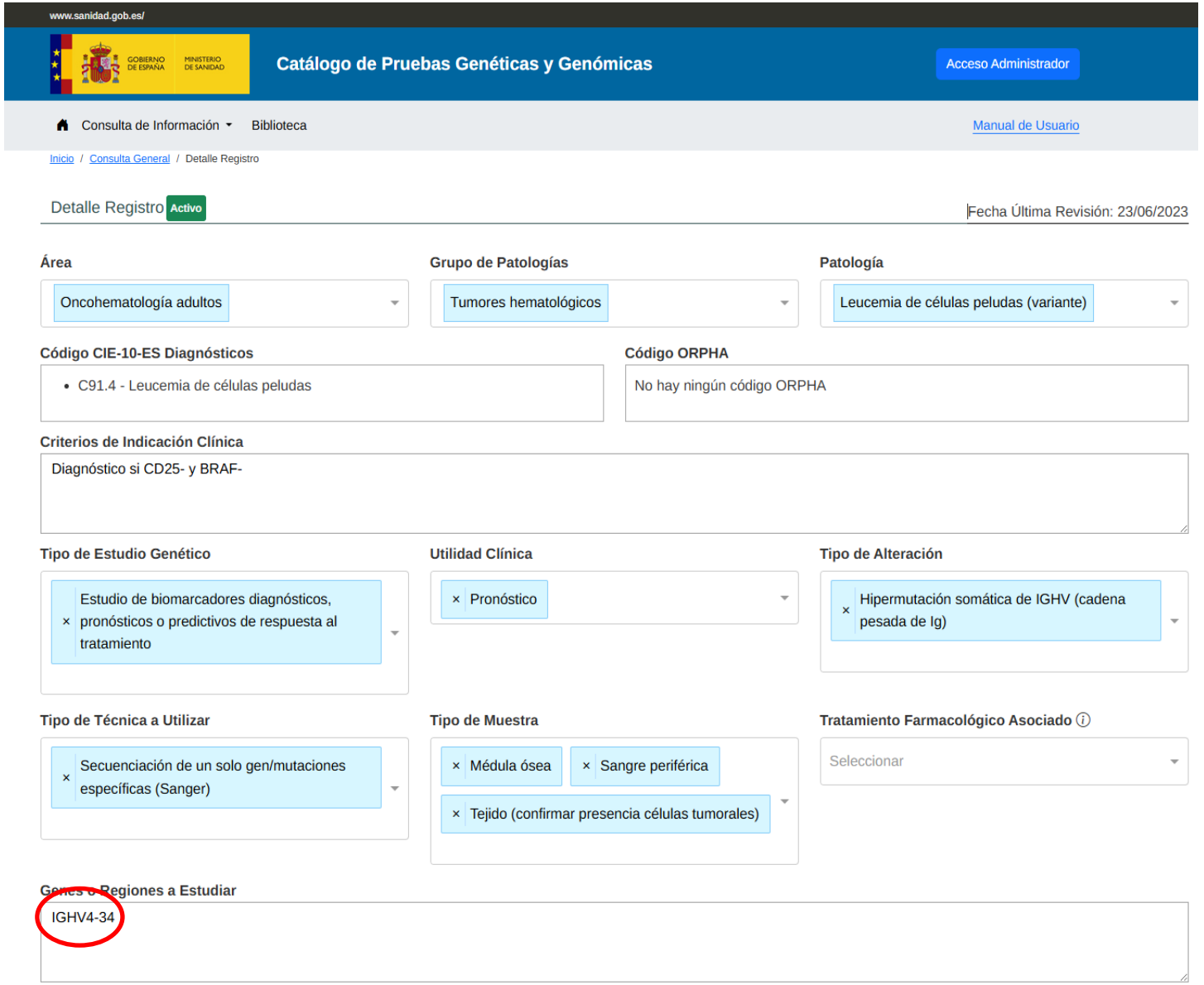
Tiacci et al, NEJM 2011; De Leval et al, Blood 2022; Abrisqueta et al, SCS 2024

Hairy cell leukemia (HCL)



https://cgen.sanidad.gob.es/#/

Hairy cell leukemia (HCL-variant)



https://cgen.sanidad.gob.es/#/

Lymphoplasmacytic lymphoma (LPL)

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Lymphoplasmacytic lymphoma	*MYD88* L265 mutation: AS-PCR testing on bone marrow* (or other highly sensitive HTS-based method: consider AS-PCR as a reflex test if negative)	Diagnostic. Aids in the differential with small B-cell lymphomas; see scenario 2A in Table 3		HTS methods for sensitive mutation detection
	CXCR4 mutations†: highly sensitive HTS-based method		Predictive of primary resistance to ibrutinib therapy[160]	

Treon et al, NEJM 2012; De Leval et al, Blood 2022; Abrisqueta et al, SCS 2024

Lymphoplasmacytic lymphoma (LPL)

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
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	CXCR4 mutations†: highly sensitive HTS-based method		Predictive of primary resistance to ibrutinib therapy[160]	

Gen	Transcrit referent	Regió específica d'interès	Indicació clínica *Diagnòstic*	Indicació clínica *Pronòstic*	Indicació clínica *Tractament: 1L*	Indicació clínica *Tractament: 2L*	Indicació clínica *Tractament: altres*
MYD88	NM_002468.5	Exons 3-5	X			X	Abans d'ibrutinib
CXCR4	NM_003467.3	Exons 1, 2		X		X	Abans d'ibrutinib
BTK	NM_000061.2	Exons 14-16				X	Fallida a ibrutinib
TP53	NM_000546.5	Exons 2-10	X	X	X	X	
PLCG2	NM_002661.5	Exons 19-24				X	Fallida a ibrutinib

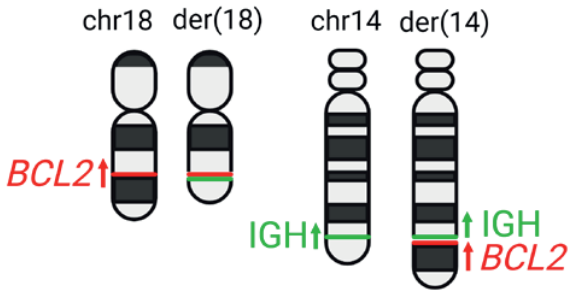
Treon et al, NEJM 2012; De Leval et al, Blood 2022; Abrisqueta et al, SCS 2024

Follicular lymphoma (FL)

Entity	Genetic alteration: test	Diagnostic use	Clinical impact
Follicular lymphoma (FL)	*BCL2* rearrangement†: FISH (or cytogenetics)	Consider if BCL2 IHC is negative. Further workup of *BCL2*-R–negative FL shown in scenario 1B in Table 3	
	EZH2 mutation†: HTS		*EZH2* mutation is predictive of response to EZH2 inhibition.[81] Tazemetostat is approved by the FDA for use in patients with *EZH2*-mutated FL

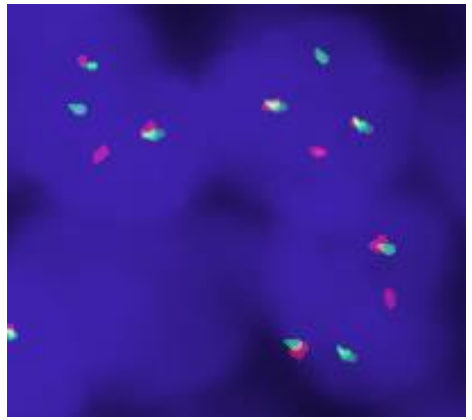
†Useful in certain circumstances in the National Comprehensive Cancer Network 2022 guidelines.

t(14;18)(q32;q21)/*IGH*::*BCL2*

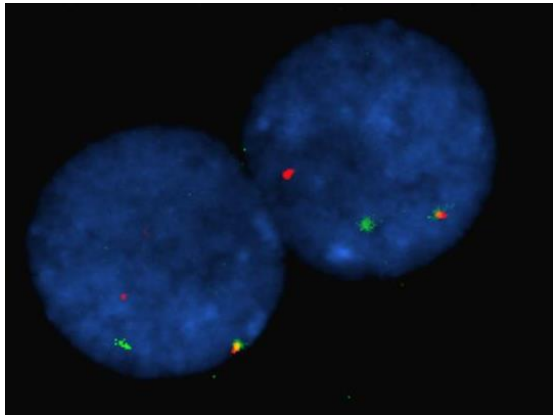


t(2;18)(p11;q21) - IGK::*BCL2*

t(18;22)(q21;q11) – IGL::*BCL2*



Dual Color Dual Fusion
IGH::*BCL2* probe



Break apart *BCL2* probe
Easier interpretation in tissue sections
Detects all *BCL2* rearrangements

De Leval et al, Blood 2022; López et al, Medizinische Genetik 2024

Follicular lymphoma (FL)

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EZH2	NM_004456.3	Exons 2-20		X		X	
TNFRSF14	NM_003820.3	Exons 1-6	Dx dubtós				
MAP2K1	NM_002755.3	Exons 1-11	Dx dubtós				
IRF4	NM_002460.4	Exons 2, 3, 9	Dx dubtós				
TP53	NM_000546.5	Exons 2-10		X		X	
STAT6	NM_003153.5	Exons 9-14	Dx dubtós				
IRF8	NM_002163.4	Regió codificant	Dx dubtós				
TNFAIP3	NM_006290	Exons 2-9	Dx diferencial				

Alcoceba et al, Guías NGS SEHH 2023; Abrisqueta et al, SCS 2024

Follicular lymphoma (FL)

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EZH2	NM_004456.3	Exons 2-20		X		X	
TNFRSF14	NM_003820.3	Exons 1-6	Dx dubtós				
MAP2K1	NM_002755.3	Exons 1-11	Dx dubtós				
IRF4	NM_002460.4	Exons 2, 3, 9	Dx dubtós				
TP53	NM_000546.5	Exons 2-10		X		X	
STAT6	NM_003153.5	Exons 9-14	Dx dubtós				
IRF8	NM_002163.4	Regió codificant	Dx dubtós				
TNFAIP3	NM_006290	Exons 2-9	Dx diferencial				

Genes más relevantes relacionados con linfoma folicular (LF) incluidos en el panel de secuenciación masiva (*next generation sequencing* -NGS-)

Genes	Valor clínico	Grado de evidencia
BCL2	Diagnóstico[a]	Recomendado
CREBBP[b]	Diagnóstico[a]	Recomendado
EZH2[b,c]	Pronóstico, tratamiento	Recomendado
FOXO1[b,c]	Pronóstico	Recomendado
KMT2D	Diagnóstico[a]	Recomendado
TP53	Pronóstico	Recomendado
ARID1A[b]	–	Opcional
CARD11[b]	–	Opcional
CTSS	–	Opcional
EP300[b,c]	–	Opcional
FAS	–	Opcional
HIST1H1 familia (B-E)	–	Opcional
MEF2B[b]	–	Opcional
SOCS1	–	Opcional
STAT6	Diagnóstico	Opcional
TNFAIP3	–	Opcional
TNFRSF14	Diagnóstico	Opcional

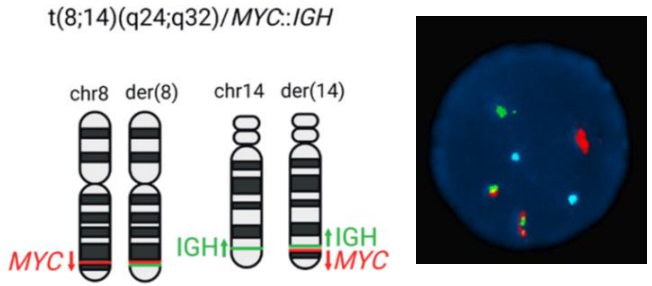
[a]Por su elevada incidencia en LF, podrían ser útiles en el diagnóstico diferencial con otros linfomas no Hodgkin de células B (LNH-B); [b] potencial pronóstico estudiados en conjunto dentro del m7-FLIPI; [c] potencial pronóstico estudiados en conjunto dentro del POD24-PI.

Alcoceba et al, Guías NGS SEHH 2023; Abrisqueta et al, SCS 2024

Burkitt lymphoma

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Burkitt lymphoma	*MYC*, *BCL2*, and/or *BCL6* rearrangement (latter two can be performed concurrently or only if *MYC* rearrangement is detected): FISH*	Required to exclude HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*		

70-80%	**t(8;14)(q24;q32) IGH*::MYC***
10-15%	t(2;8)(p11;q24) *IGK::MYC*
2-5%	t(8;22)(q24;q11) IGL*::MYC*
5-10%	absence r*MYC→11q gain/loss?*



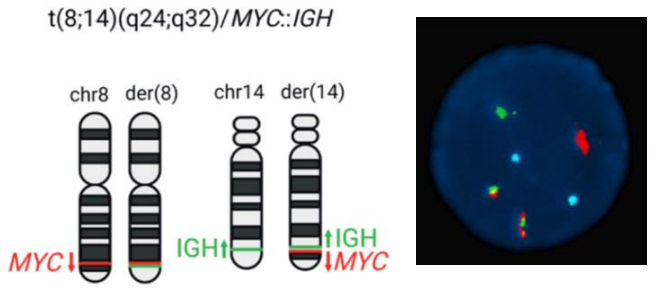
FISH

Angi et al, 2017; De Leval et al, 2022; López et al, 2024; Abrisqueta et al, SCS 2024

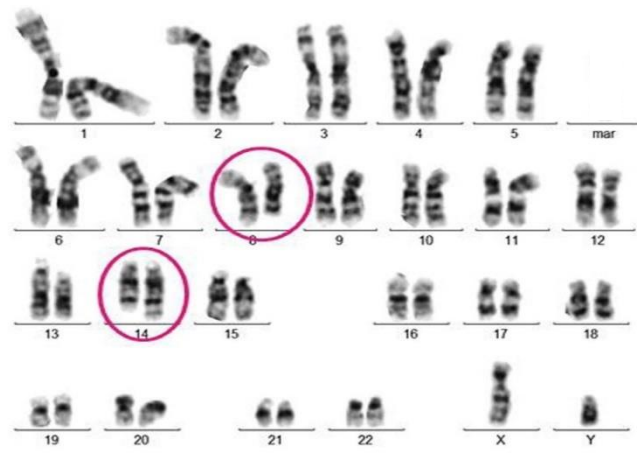
Burkitt lymphoma

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Burkitt lymphoma	*MYC*, *BCL2*, and/or *BCL6* rearrangement (latter two can be performed concurrently or only if *MYC* rearrangement is detected): FISH*	Required to exclude HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*		

70-80%	**t(8;14)(q24;q32) IGH*::MYC***
10-15%	t(2;8)(p11;q24) *IGK::MYC*
2-5%	t(8;22)(q24;q11) IGL*::MYC*
5-10%	absence r*MYC→11q gain/loss?*



FISH



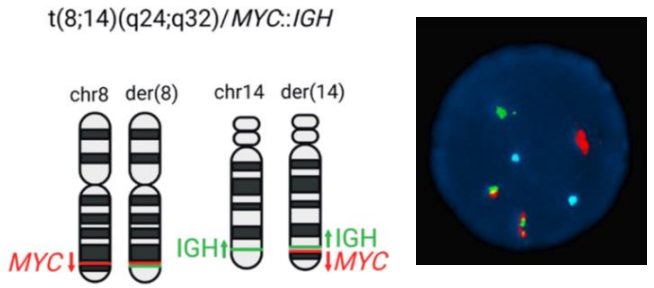
Cytogenetics cell cultures from PB or BM

Angi et al, 2017; De Leval et al, 2022; López et al, 2024; Abrisqueta et al, SCS 2024

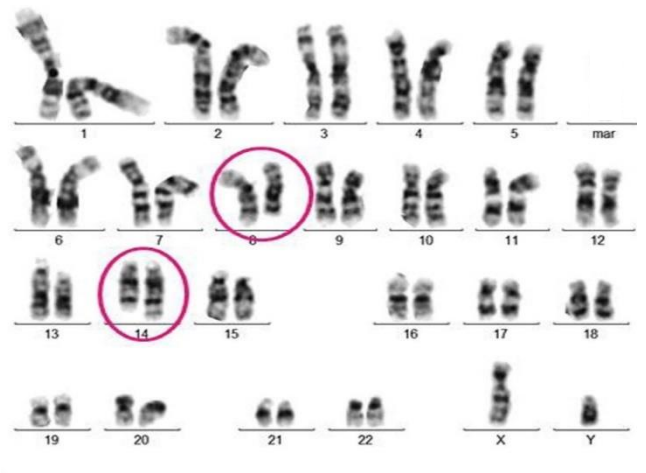
Burkitt lymphoma

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Burkitt lymphoma	*MYC*, *BCL2*, and/or *BCL6* rearrangement (latter two can be performed concurrently or only if *MYC* rearrangement is detected): FISH*	Required to exclude HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*		

70-80%	**t(8;14)(q24;q32) IGH*::MYC***
10-15%	t(2;8)(p11;q24) *IGK::MYC*
2-5%	t(8;22)(q24;q11) IGL*::MYC*
5-10%	absence r*MYC→11q gain/loss?*



FISH



Cytogenetics cell cultures from PB or BM

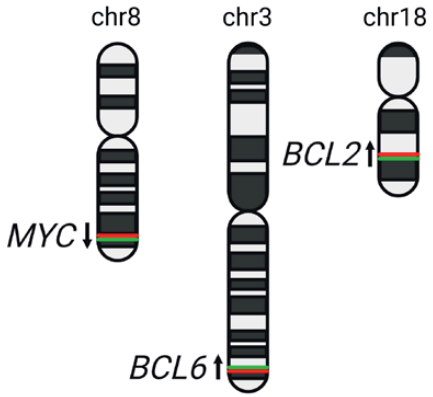
Gen	Transcrit referent	Regió específica d'interès	Indicació clínica *Diagnòstic*	Indicació clínica *Pronòstic*	Indicació clínica *Tractament: 1L*	Indicació clínica *Tractament: 2L*	Indicació clínica *Tractament: altres*
TP53	NM_000546.5	Exons 2-10		X		X	
ID3	NM_002167.5	Exons 1, 2	Dx diferencial				

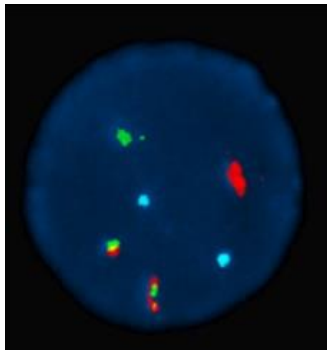
Angi et al, 2017; De Leval et al, 2022; López et al, 2024; Abrisqueta et al, SCS 2024

High-grade B-cell lymphomas (HGBCL)

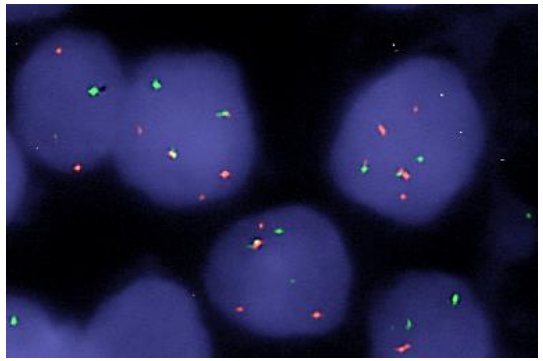
Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
High-grade B-cell lymphomas (HGBCL) HGBCL with *MYC* and *BCL2* rearrangement (HGBCL-DH-*BCL2*) *HGBCL with MYC and BCL6 rearrangement (HGBCL-DH-BCL6)* HGBCL, NOS	*MYC*, *BCL2*, and/or *BCL6* rearrangement (latter two can be performed concurrently or only if *MYC* rearrangement is detected): FISH*	Required for the diagnosis of HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*	Prognostic and predictive: HGBCL-DH-*BCL2* has poor prognosis with R-CHOP and likely benefits from treatment intensification[467]	Rearrangement detection and *MYC* partner determination by HTS HTS analysis of HGBCL, NOS tumors to assign these tumors to definitive disease categories

BCL6, *MYC* and *BCL2* rearrangements

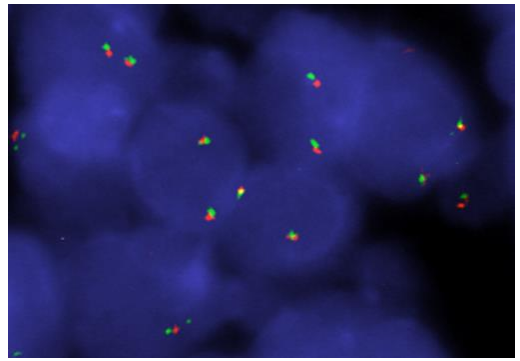




IGH::*MYC*, rearranged



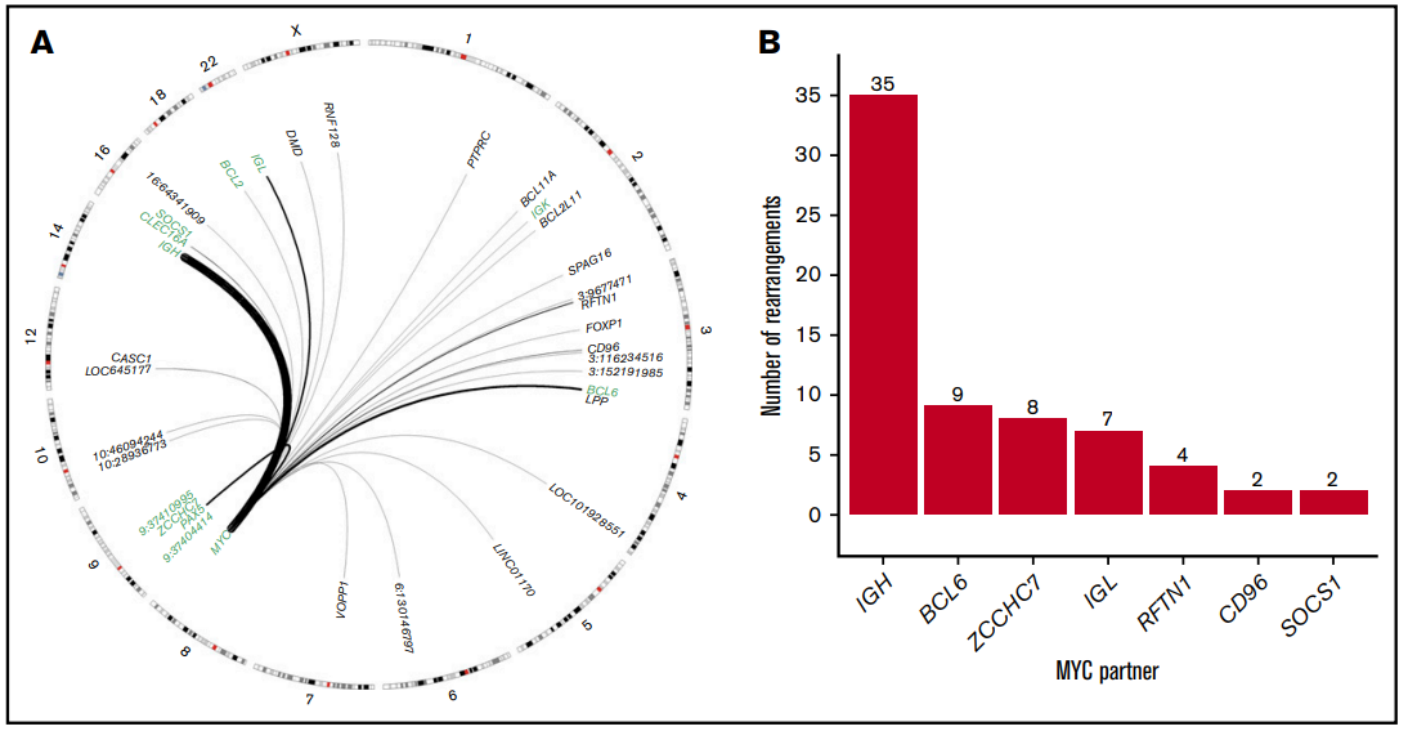
IGH::*BCL2*, rearranged
with 2xBCL2 extra copies



BCL6, not rearranged

De Leval et al, Blood 2022

High-grade B-cell lymphomas (HGBCL)



MYC partner gene (IG, non-IG) matters?

IG::*MYC* poorer outcomes?

Not really implemented in routine

Chong et al, Blood Adv 2018, Rosenwald et al, JCO 2019

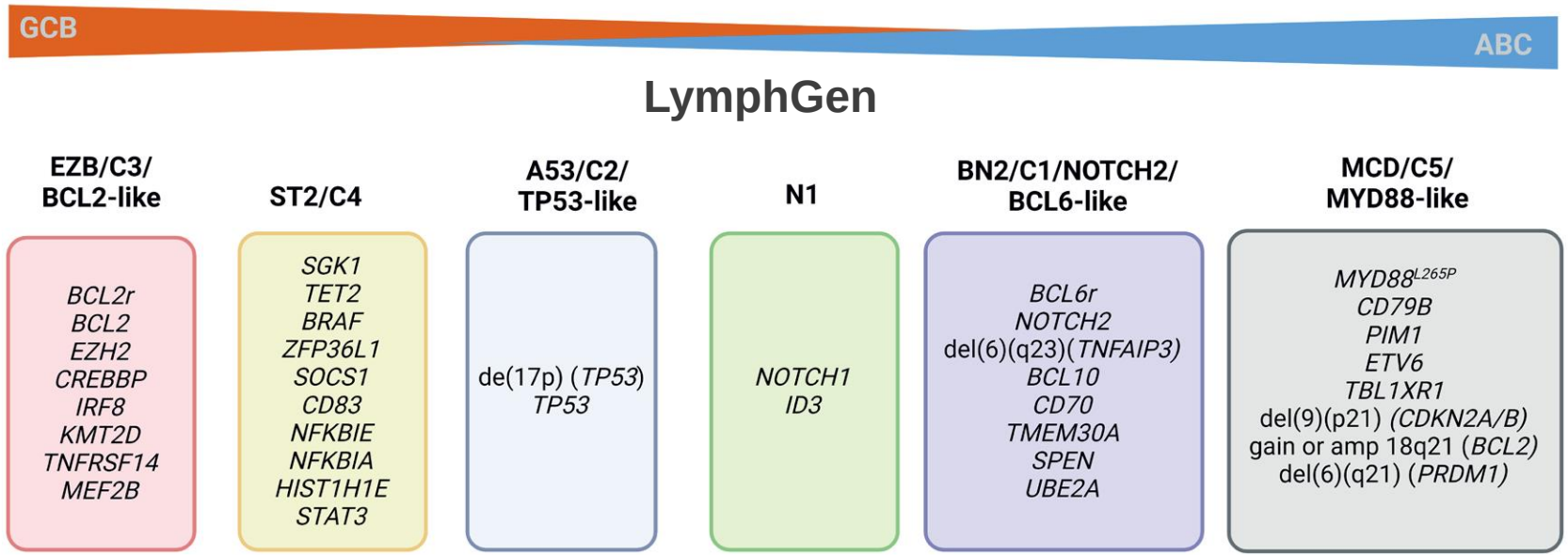
Diffuse large B-cell lymphoma (DLBCL), NOS

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Diffuse large B-cell lymphoma, NOS Germinal center B-cell subtype Activated B-cell subtype	*MYC*, *BCL2*, and/or *BCL6* rearrangement (latter two can be performed concurrently or only if *MYC* rearrangement is detected): FISH*	Required to exclude HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*	See "High-grade B-cell lymphoma"	Genetic subtype assignment (eg, LymphGen[187]) by panel, exome or WGS and *BCL2* and *BCL6* rearrangement detection and WTS or targeted gene expression panels (DHITsig[29]/MHG signature[199]) HTS-based ctDNA testing[465] for response-adapted management
	COO determination: GEP or widely used IHC surrogates* "Hans algorithm"	Required to assign DLBCL, NOS gene expression subtypes	Prognostic for outcomes following R-CHOP (GEP)[466]; predictive of response to treatment at relapse[177]	

Wright et al, Cancer Cell 2020; De Leval et al, Blood 2022; López et al, Medizinische Genetik 2024

Diffuse large B-cell lymphoma (DLBCL), NOS

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Diffuse large B-cell lymphoma, NOS Germinal center B-cell subtype Activated B-cell subtype	*MYC*, *BCL2*, and/or *BCL6* rearrangement (latter two can be performed concurrently or only if *MYC* rearrangement is detected): FISH*	Required to exclude HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*	See "High-grade B-cell lymphoma"	Genetic subtype assignment (eg, LymphGen[187]) by panel, exome or WGS and *BCL2* and *BCL6* rearrangement detection and WTS or targeted gene expression panels (DHITsig[29]/MHG signature[199]) HTS-based ctDNA testing[465] for response-adapted management
	COO determination: GEP or widely used IHC surrogates* "Hans algorithm"	Required to assign DLBCL, NOS gene expression subtypes	Prognostic for outcomes following R-CHOP (GEP)[466]; predictive of response to treatment at relapse[177]	



Wright et al, Cancer Cell 2020; De Leval et al, Blood 2022; López et al, Medizinische Genetik 2024

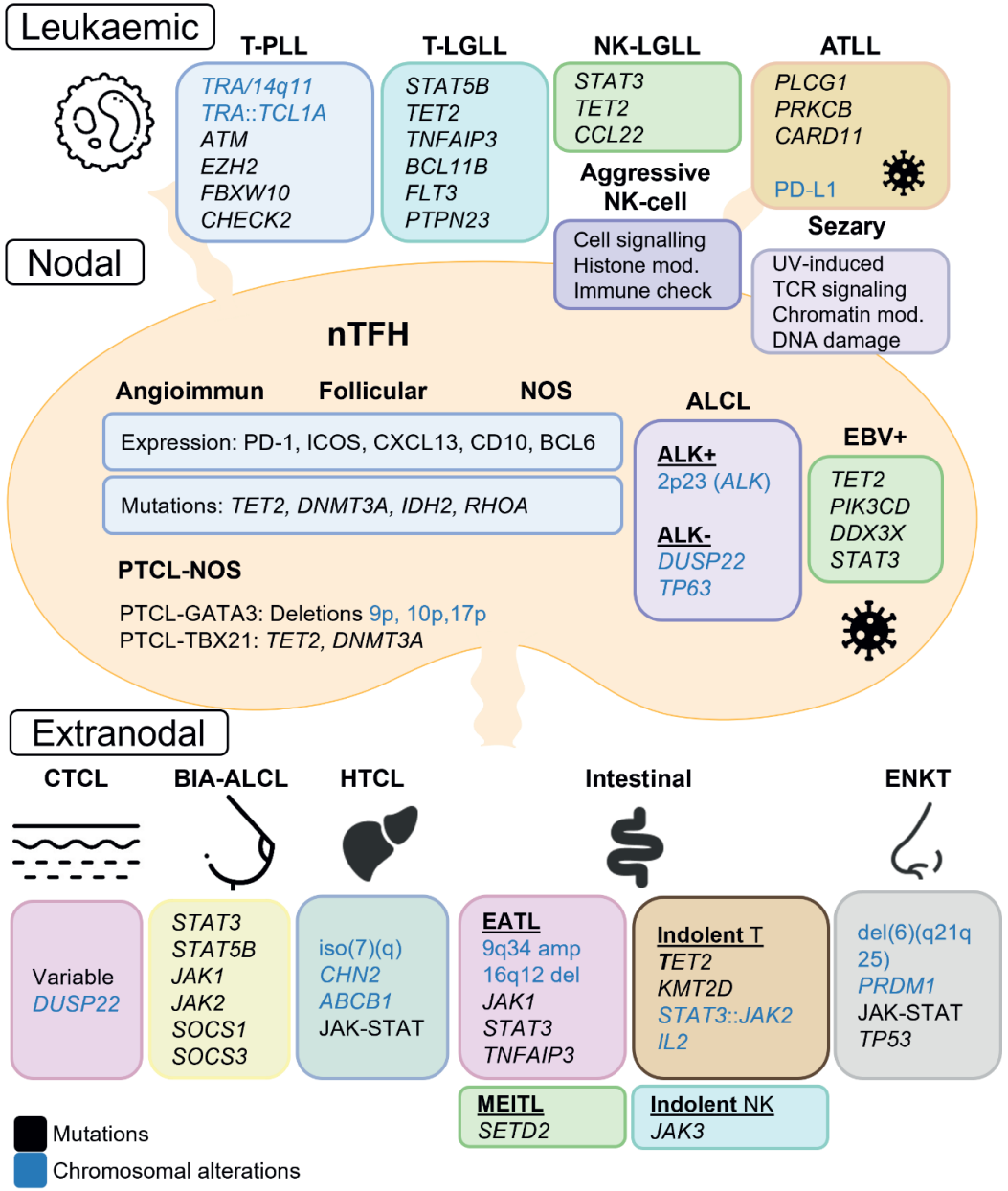
Diffuse large B-cell lymphoma (DLBCL), NOS

Gen	Transcrit referent	Regió específica d'interès	Indicació clínica *Diagnòstic*	Indicació clínica *Pronòstic*	Indicació clínica *Tractament: 1L*	Indicació clínica *Tractament: 2L*	Indicació clínica *Tractament: altres*
EZH2	NM_004456.3	Exons 2 - 20	Dx dubtós o transformats	X		X	X
TP53	NM_000546.5	Exons 2-10	Dx dubtós o transformats	X		X	X
CD79B	NM_000626.4	Exons 5-6	Dx dubtós o transformats	X		X	Ibrutinib
CARD11	NM_032415.6	Exons 3-25	Dx dubtós o transformats	X		X	Ibrutinib
MYD88	NM_002468.5	Exons 3-5	Dx dubtós o transformats	X		X	Ibrutinib
NOTCH2	NM_024408.4	Exó 34	Dx dubtós o transformats	X		X	
CD58	NM_017617.5	Exons 34, 3UTR	Dx dubtós o transformats	X		X	
BRAF	NM_004333.6	Exons 11 i 15	Dx dubtós o transformats	X		X	
RHOA	NM_001664.4	Exons 2-3	Dx dubtós o transformats	X		X	
NOTCH1	NM_017617.5	Exons 34, 3UTR	Dx dubtós o transformats	X		X	
CDKN2A	NM_000077.4	Exons 1, 2 i 3	Dx diferencial	X		X	
PIM1	NM_001243186.2	Exons 1 - 6	Dx diferencial	X		X	

Lymphoid gene panel

Abrisqueta et al, SCS 2024

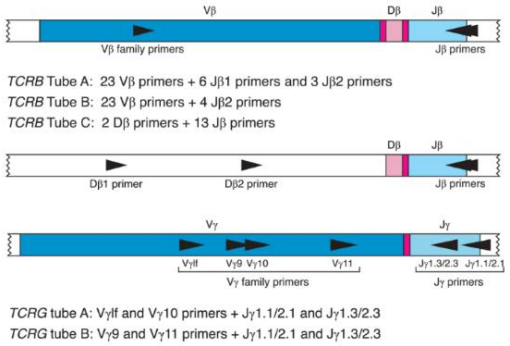
T/NK-cell mature malignancies are divided into leukemic, nodal and extranodal



López et al, 2024

Genetic tests in T-cell mature malignancies: clonality and FISH

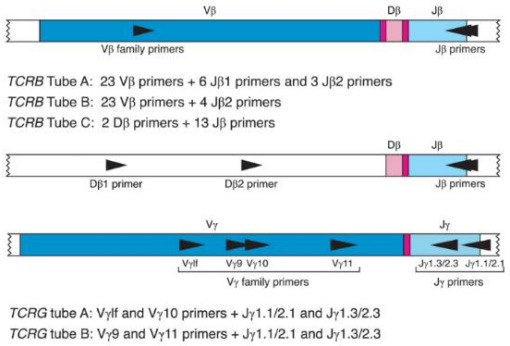
T-cell clonality



Stewart et al, 2021; López et al, 2024; https://atlasgeneticsoncology.org/

Genetic tests in T-cell mature malignancies: clonality and FISH

T-cell clonality



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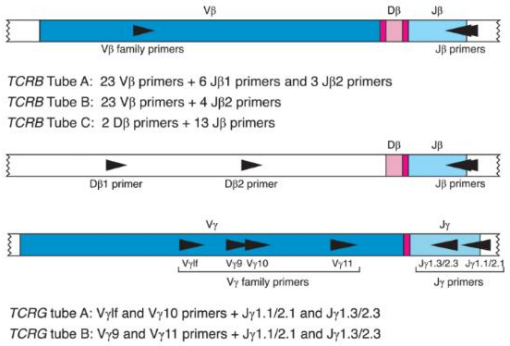
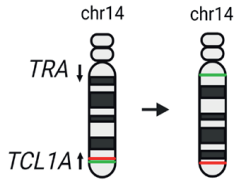
Genetic tests in T-cell mature malignancies: clonality and FISH

T-cell clonality

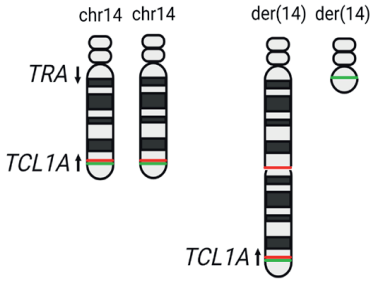


T-cell prolymphocytic leukaemia

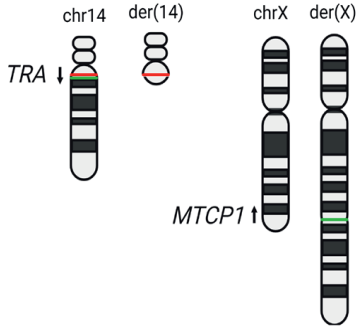
inv(14)(q11q32)/*TRA*::*TCL1A*



t(14;14)(q11;q32)/*TRA*::*TCL1A*



t(X;14)(q28;q11)/*MTCP1*::*TRA*

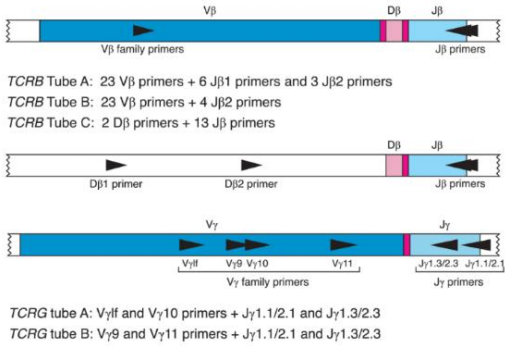


FISH: *TRA*

Stewart et al, 2021; López et al, 2024; https://atlasgeneticsoncology.org/

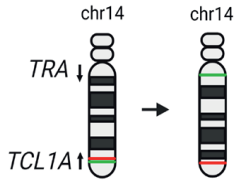
Genetic tests in T-cell mature malignancies: clonality and FISH

T-cell clonality

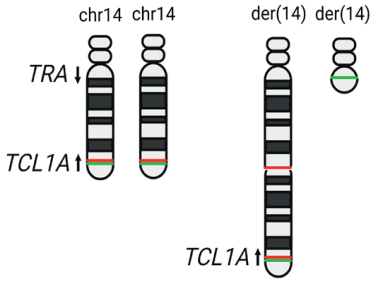


T-cell prolymphocytic leukaemia

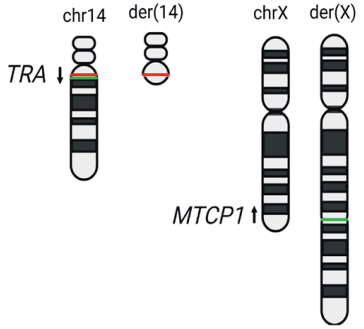
inv(14)(q11q32)/*TRA*::*TCL1A*



t(14;14)(q11;q32)/*TRA*::*TCL1A*



t(X;14)(q28;q11)/*MTCP1*::*TRA*

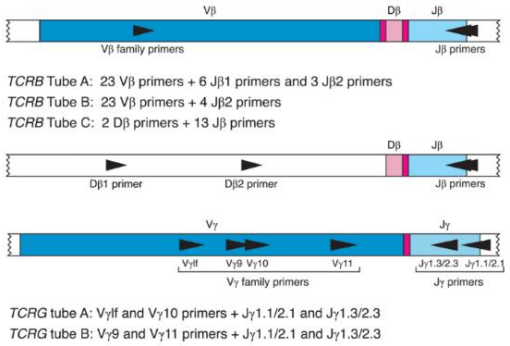


FISH: *TRA*

Stewart et al, 2021; López et al, 2024; https://atlasgeneticsoncology.org/

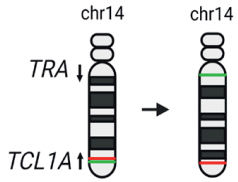
Genetic tests in T-cell mature malignancies: clonality and FISH

T-cell clonality

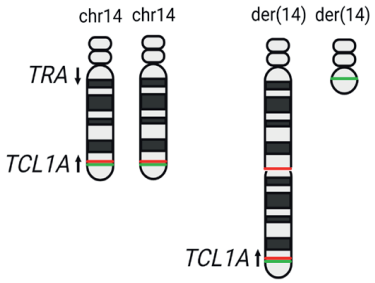


T-cell prolymphocytic leukaemia

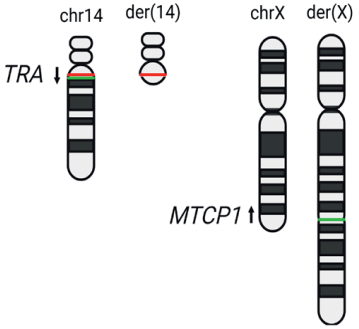
inv(14)(q11q32)/*TRA*::*TCL1A*



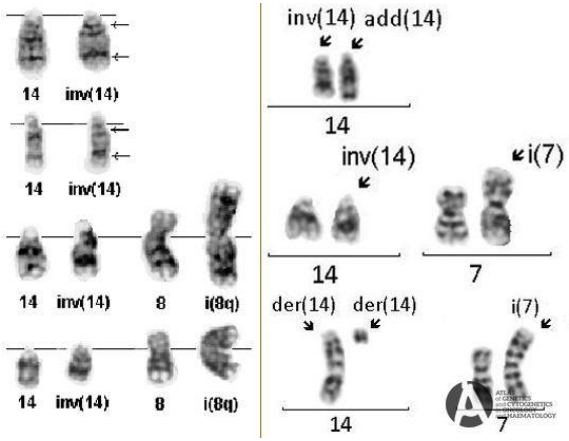
t(14;14)(q11;q32)/*TRA*::*TCL1A*



t(X;14)(q28;q11)/*MTCP1*::*TRA*



FISH: *TRA*

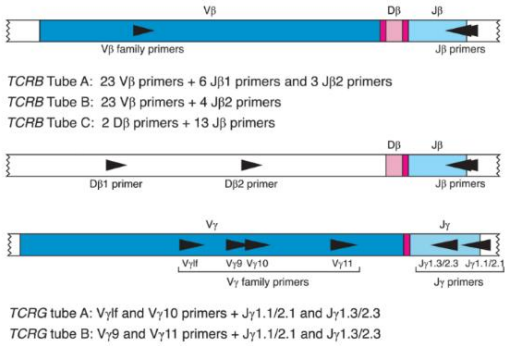


Cytogenetics from PB

Stewart et al, 2021; López et al, 2024; https://atlasgeneticsoncology.org/

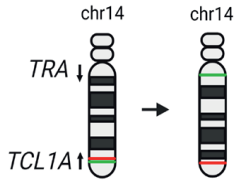
Genetic tests in T-cell mature malignancies: clonality and FISH

T-cell clonality

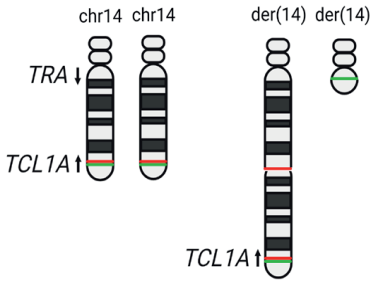


T-cell prolymphocytic leukaemia

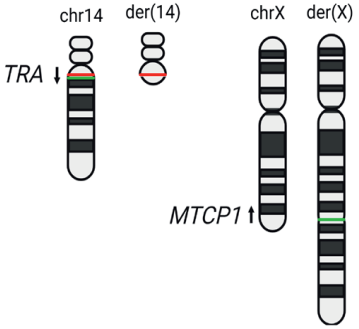
inv(14)(q11q32)/*TRA*::*TCL1A*



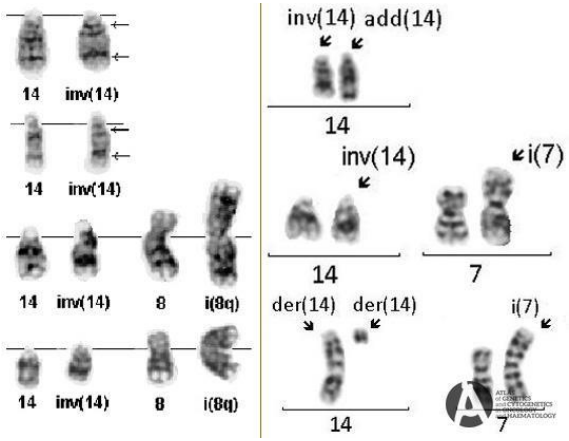
t(14;14)(q11;q32)/*TRA*::*TCL1A*



t(X;14)(q28;q11)/*MTCP1*::*TRA*



FISH: *TRA*



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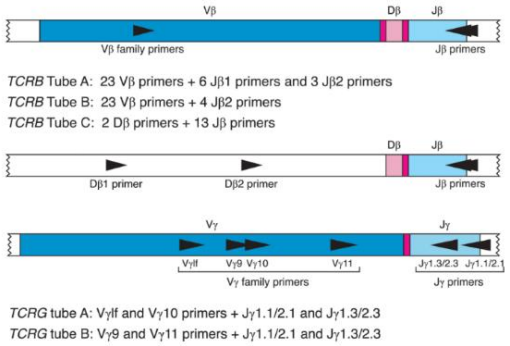
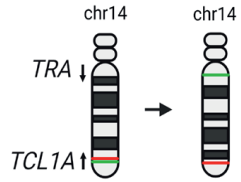
Genetic tests in T-cell mature malignancies: clonality and FISH

T-cell clonality

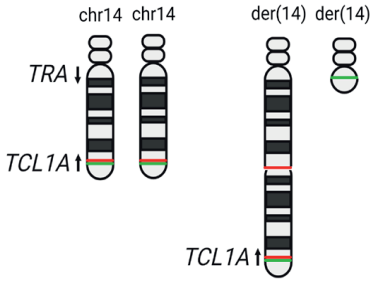


T-cell prolymphocytic leukaemia

inv(14)(q11q32)/*TRA*::*TCL1A*

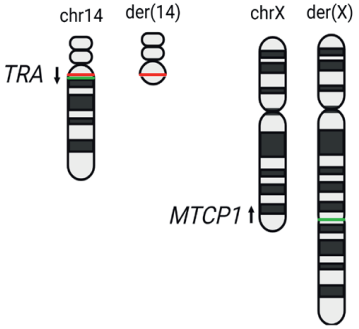


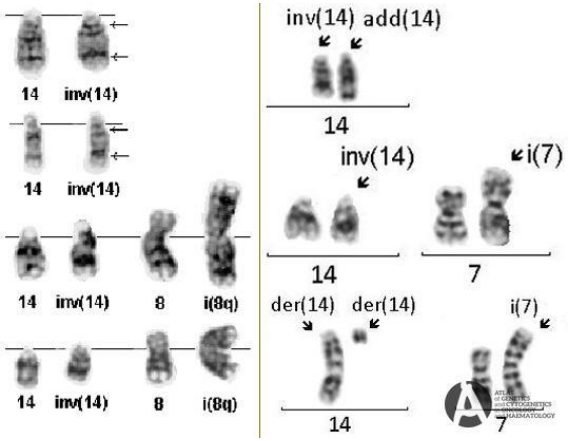
t(14;14)(q11;q32)/*TRA*::*TCL1A*



FISH: *TRA*

t(X;14)(q28;q11)/*MTCP1*::*TRA*

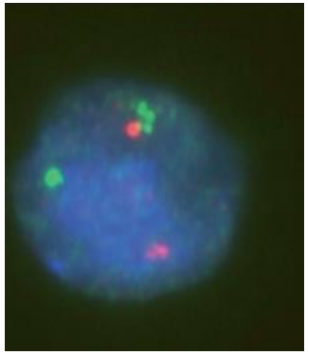




Cytogenetics from PB

ALK-positive anaplastic large cell lymphoma

Rearrangements of 2p23/*ALK*

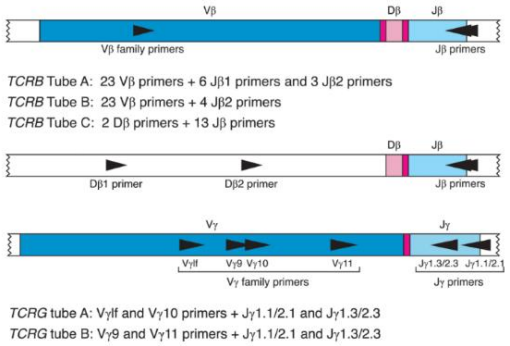


FISH: *ALK*

Stewart et al, 2021; López et al, 2024; https://atlasgeneticsoncology.org/

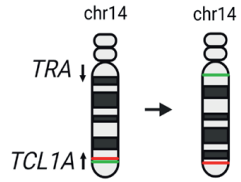
Genetic tests in T-cell mature malignancies: clonality and FISH

T-cell clonality

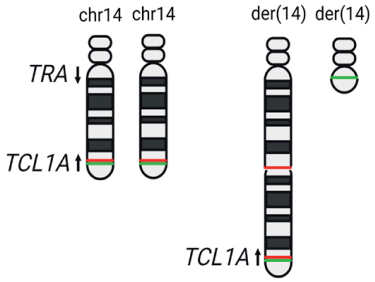


T-cell prolymphocytic leukaemia

inv(14)(q11q32)/*TRA*::*TCL1A*

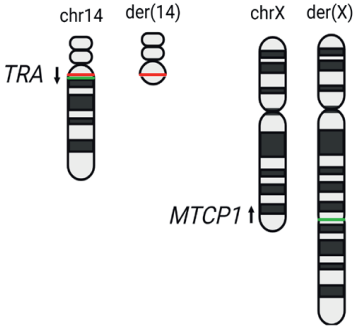


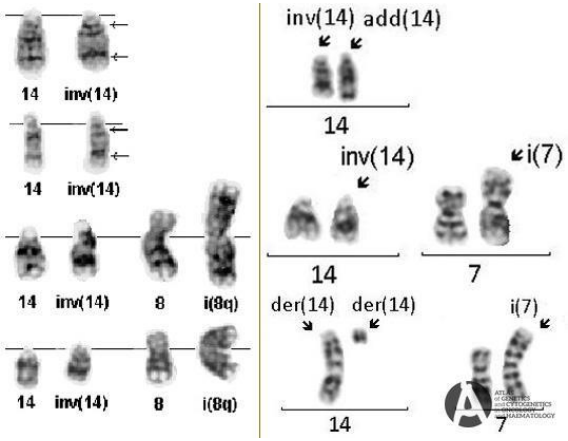
t(14;14)(q11;q32)/*TRA*::*TCL1A*



FISH: *TRA*

t(X;14)(q28;q11)/*MTCP1*::*TRA*

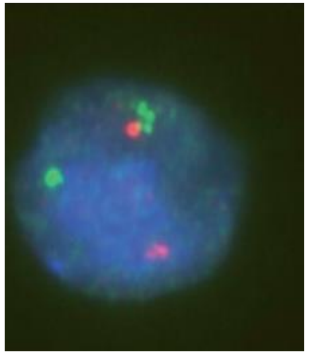




Cytogenetics from PB

ALK-positive anaplastic large cell lymphoma

Rearrangements of 2p23/*ALK*

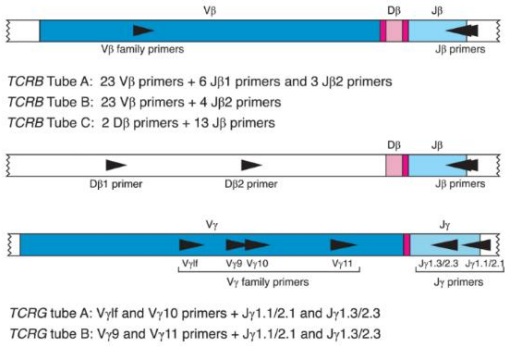


FISH: *ALK*

Stewart et al, 2021; López et al, 2024; https://atlasgeneticsoncology.org/

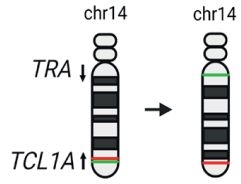
Genetic tests in T-cell mature malignancies: clonality and FISH

T-cell clonality

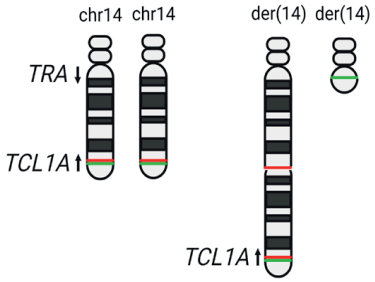


T-cell prolymphocytic leukaemia

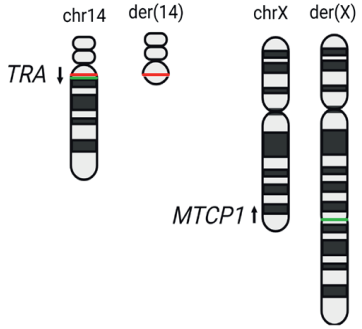
inv(14)(q11q32)/*TRA*::*TCL1A*



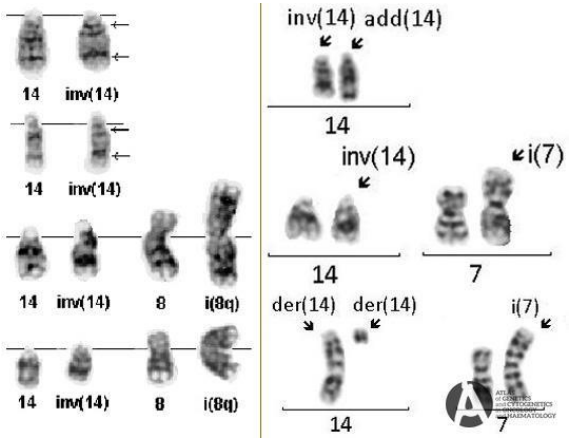
t(14;14)(q11;q32)/*TRA*::*TCL1A*



t(X;14)(q28;q11)/*MTCP1*::*TRA*



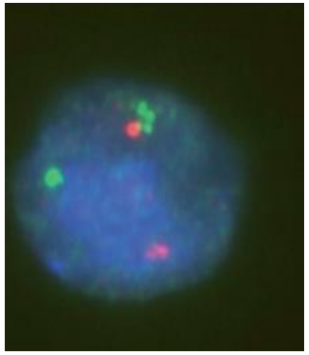
FISH: *TRA*



Cytogenetics from PB

ALK-positive anaplastic large cell lymphoma

Rearrangements of 2p23/*ALK*



FISH: *ALK*

ALK-negative anaplastic large cell lymphoma

Rearrangements of 3q28/*TP63*

Rearrangements of 6p25.3/*DUSP22*

FISH: *TP63 and DUSP22*

Stewart et al, 2021; López et al, 2024; https://atlasgeneticsoncology.org/

Genetic tests in T-cell mature malignancies: NGS

Gen	Transcrit referent	Regió específica d'interès	Indicació clínica *Diagnòstic*	Indicació clínica *Pronòstic*	Indicació clínica *Tractament: 1L*	Indicació clínica *Tractament: 2L*	Indicació clínica *Tractament: altres*
STAT3	NM_139276.2	Exons 19-22	X (LGL)				
STAT5B	NM_012448	Exons 14, 15, 16, 17, 18	X (LGL)				
RHOA	NM_001664.4	Exons 2-3	X				
TET2	NM_001127208.2	Exons 3-6	X				
IDH2	NM_002168.3	Exó 4	X				
DNMT3A	NM_175629.2	Exons 3 - 23	X				
TP53	NM_000546.5	Exons 2-10	X		X	X	
PLCG1	NM_182811.2	Exons 1, 11, 15-29	X				
NOTCH1	NM_017617.5	Exons 34, 3UTR	X				

Abrisqueta et al, SCS 2024

Panel NGS linfoide Hospital del Mar

- Panel de de amplicones dirigido a 44 genes (29 completos, 15 regiones seleccionadas)
- Mutaciones puntuales e indels
- No se estudian variantes estructurales (ni reordenamientos ni alteraciones del número de copias)

ARID1A	*CD58*	*KLF2*	*RRAGC*
ATM	*CD79B*	*MAP2K1*	*SF3B1* (E14-E16)
ATP6AP1	*CDKN2A*	*MYD88* (E2-E6)	*SOCS1*
ATP6AP2	*CTSS* (E4-E5)	*NFKBIE* (E4-E6)	*STAT3*
ATP6V1B2	*CXCR4*	*NOTCH1* (E11-E34 + 3'UTR)	*STAT5B*
BCL2	*DNMT3A*	*NOTCH2* (E34)	*STAT6* (E11-E17)
BIRC3	*EZH2* (E15-E19)	*PLCG1*	*TET2*
BRAF (E11+E15)	*IDH2* (E4)	*PLCG2*	*TNFAIP3*
BTK	*IKBKB* (E7-E8)	*PTPRD* (E35-E46)	*TNFRSF14*
CARD11 (E2-E10)	*IRF4*	*RHOA* (E2)	*TP53*
CCND3	*IRF8*	*RPS15*	*XPO1* (E13-E19)

Final considerations and open questions

- **Integrated diagnosis is essential in lymphoma management: joint committees with clinicians, pathologists, morphologists/cytometrists, and geneticists**
  - Suspected diagnosis: What are we looking for? And which type of genetic abnormality?
  - Which is best the sample and the most appropriate methodology?
  - When do we need to test? Diagnosis, before treatment, at relapse?
  - How we manage discordant cases?
  - Follow the guidelines and be updated

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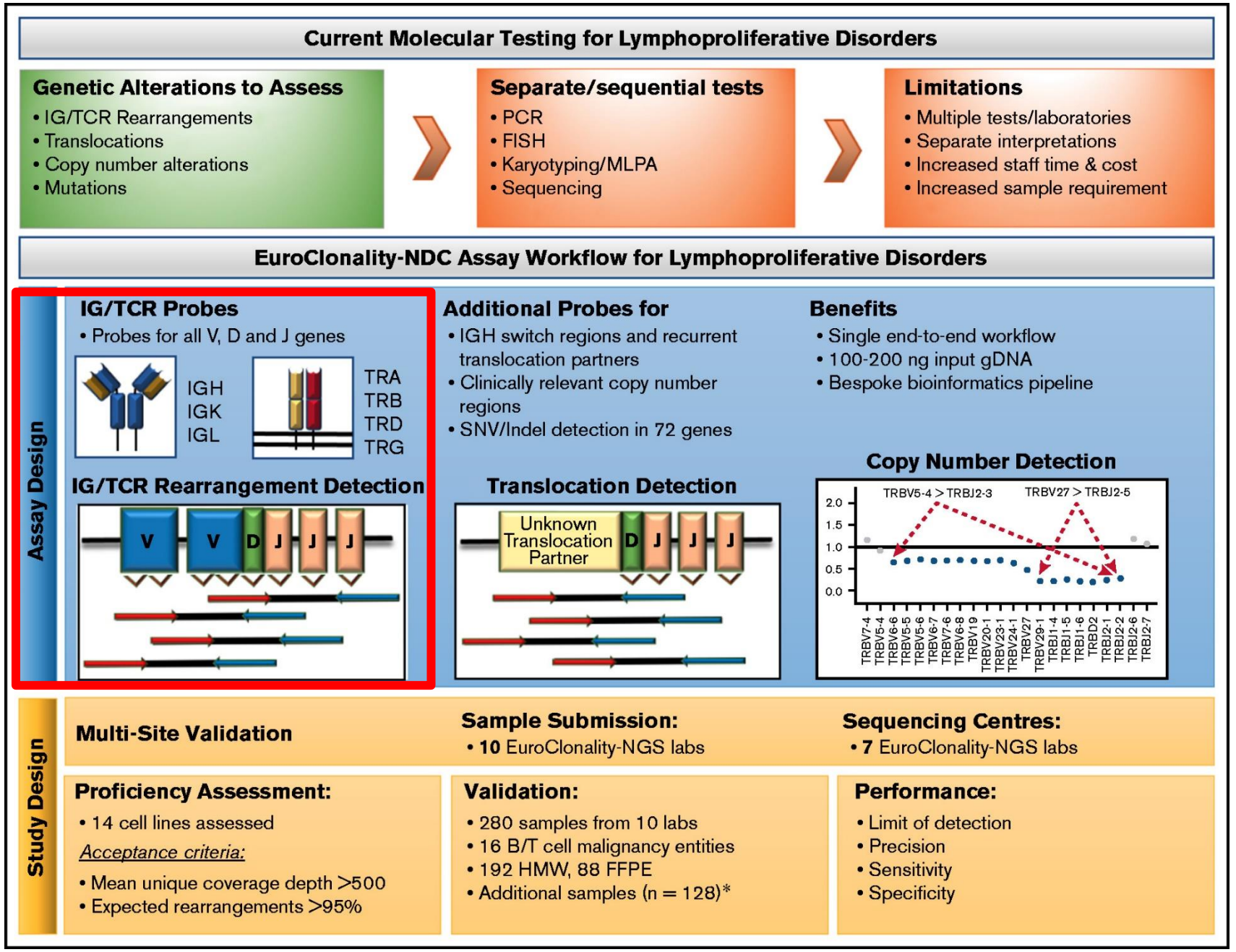
- **Some open questions:**
  - Does clonal percentage/VAF matter in prognosis/treatment? i.e. CLL with *TP53* mut 2% vs 90% is the same?
  - Are all mutations equal? Pathogenic vs Probably pathogenic vs Uncertain significance vs Probably benign vs Benign
  - Clonal hematopoiesis (myeloid) in lymphoid neoplasms?
  - Liquid biopsy in lymphoma?



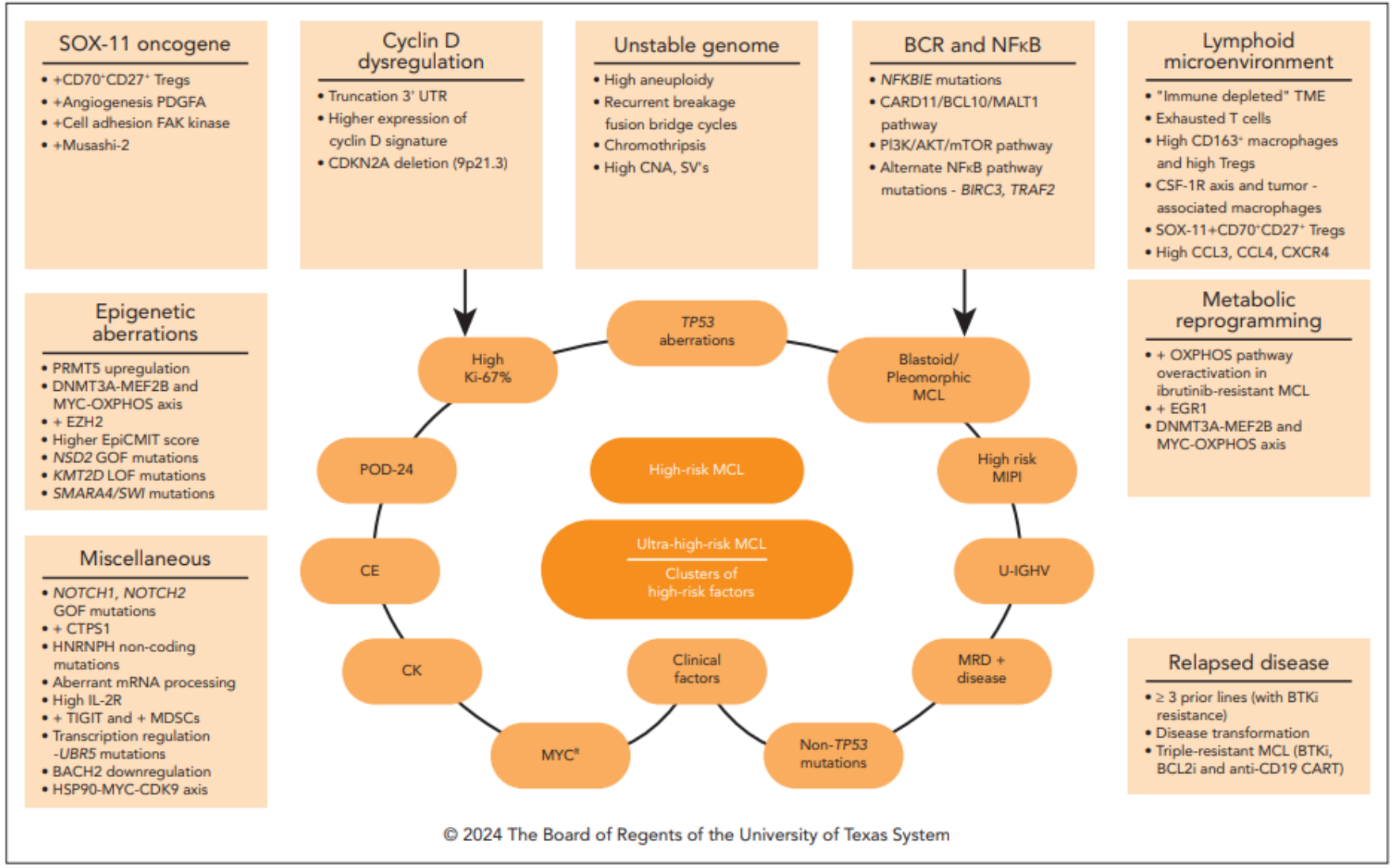
Stewart et al, Blood Adv 2021

Marginal zone lymphomas

Table 1. Anatomical Distribution of Predisposing Conditions and Molecular Features of Marginal-Zone Lymphomas (MZLs).*

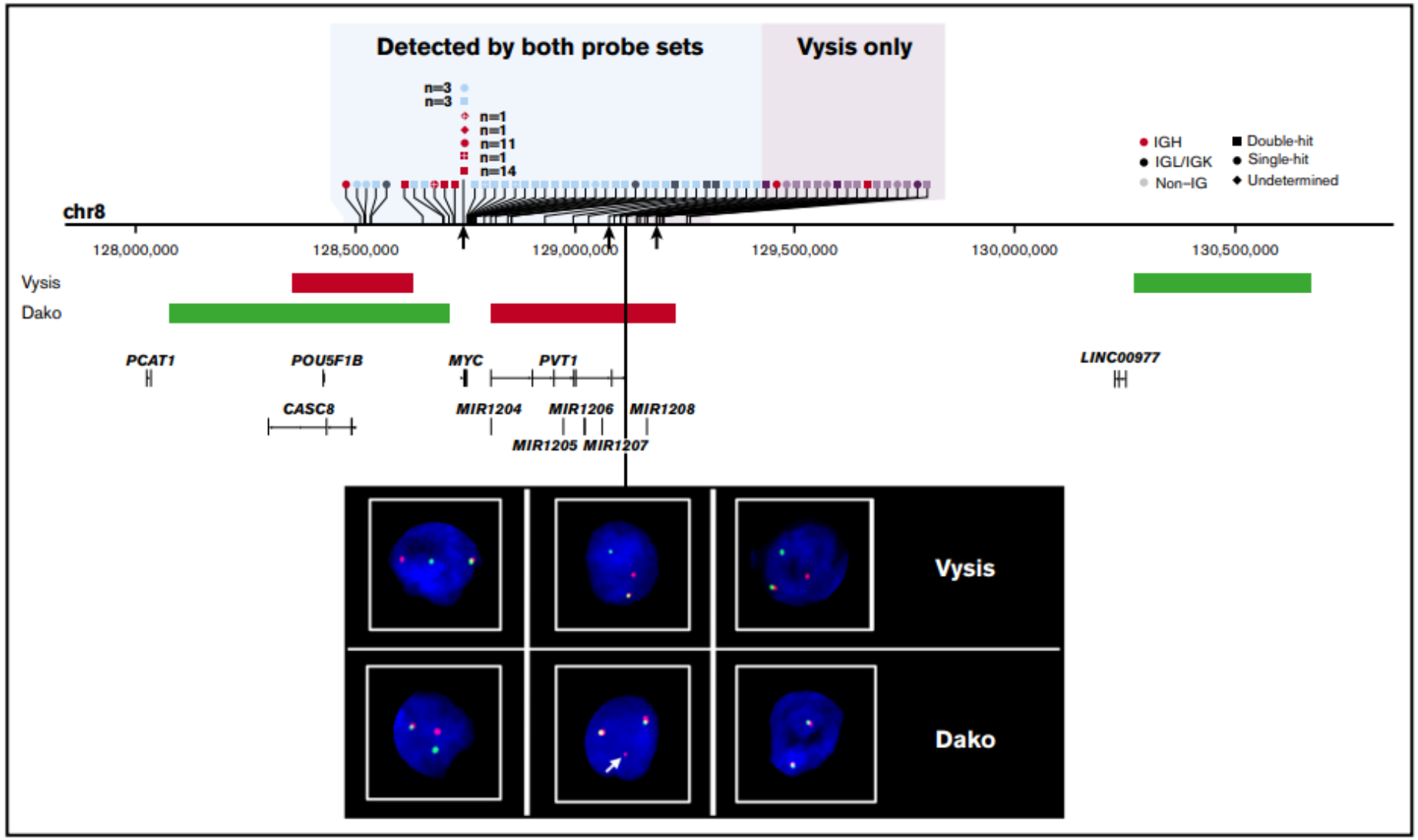
Site of Disease	Infectious Agent	Autoimmune Condition	Biased Immunoglobulin-Gene Usage†	Recurrent Translocations	Recurrent Copy-No. Aberrations	Site-Specific Gene Mutations
Stomach	*Helicobacter pylori*	—	IGHV3–23	t(11;18)(q21;q21) *BIRC3/MALT1* t(14;18)(q32;q21) *IGH/MALT1* t(1;14)(p22;q32) *BCL10/IGH*	+3, +18	—
Ocular adnexa	*Chlamydia psittaci*	Sjögren's syndrome (in lacrimal gland MZL)	IGHV4–34	t(14;18)(q32;q21) *IGH/MALT1* t(3;14)(p14.1;q32) *FOXP1/IGH*	+3, +18	*TNFAIP3*
Lung	*Achromobacter xylosoxidans*	Lymphocytic interstitial pneumonia	—	t(11;18)(q21;q21) *BIRC3/MALT1* t(14;18)(q32;q21) *IGH/MALT1*	+3, +18	—
Intestine	*Campylobacter jejuni*	—	—	t(11;18)(q21;q21) *BIRC3/MALT1* t(1;14)(p22;q32) *BCL10/IGH*	+3, +18	—
Skin	*Borrelia burgdorferi*	—	—	t(14;18)(q32;q21) *IGH/MALT1* t(3;14)(p14.1;q32) *FOXP1/IGH*	+3, +18	—
Salivary gland	—	Sjögren's syndrome	IGHV1–69	t(14;18)(q32;q21) *IGH/MALT1*	+3, +18	*TBL1XR1*, *GPR34*
Thyroid	—	Hashimoto's thyroiditis	IGHV3–23	t(14;18)(q32;q21) *IGH/MALT1* t(3;14)(p14.1;q32) *FOXP1/IGH*	+3, +18	*TET2*, *TNFRSF14*, *CD274*
Lymph node	Hepatitis C virus	—	IGHV4–34	—	+3, +18	*KLF2*, *NOTCH2*, *PTPRD*
Spleen	Hepatitis C virus	—	IGHV1–2*04	t(2;7)(p11;q21) *IGK/CDK6*	+3, +18, del(7q31–32)	*KLF2*, *NOTCH2*

Rossi et al, NEJM 2022



Jain and Wang, Blood 2025

MYC rearrangements in DLBCL: FISH probes



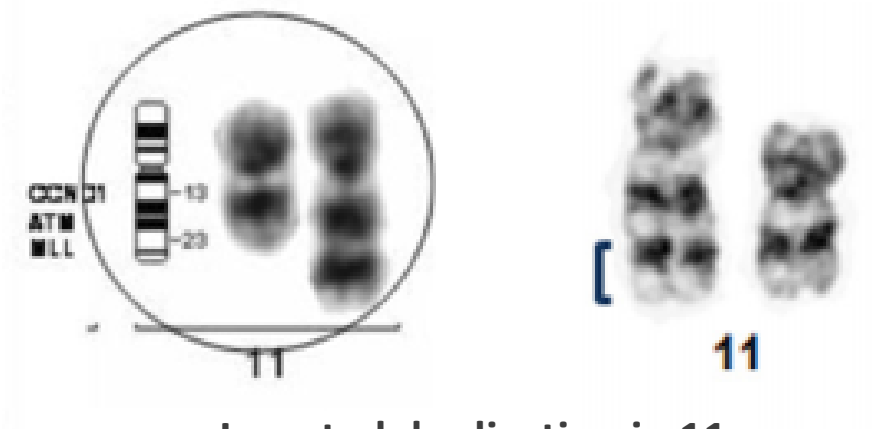
Chong et al, Blood Adv 2018

Pediatric and young adults lymphomas

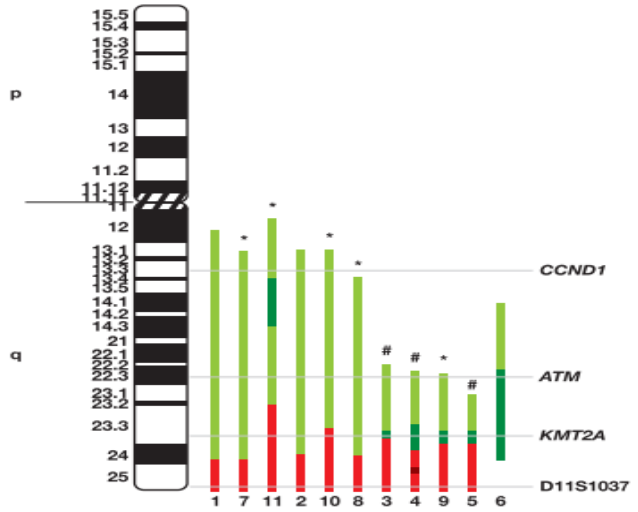
Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Pediatric lymphomas				Detection of CNAs and SVs using HTS
Pediatric-type FL **Pediatric nodal MZL**	*BCL2* or *BCL6* rearrangements†: FISH *IRF8, MAP2K1 TNFRSF14* mutations†: HTS B-cell clonality testing	Useful in certain circumstances for diagnosis; see also scenario 3A in Table 3. Of note, pediatric-type FL and pediatric nodal MZL are not readily distinguishable by genomic features		
Large B-cell lymphoma with 11q aberration	11q aberration: SNP array or FISH	Required for diagnosis of *LBCL-11q*		
Large B-cell lymphoma with *IRF4* rearrangement	*IRF4* rearrangement: FISH *CARD11*, *IRF4* mutations†: HTS	FISH required for diagnosis of LBCL-*IRF4* rearrangement Useful in certain circumstances for diagnosis; see also scenario 3A in Table 3.		

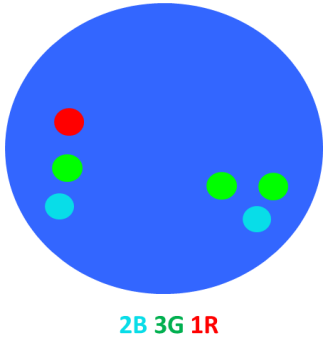
Large B-cell lymphoma/high grade B cell lymphoma with 11q aberration (LBCL/HGBCL-11q)

Presence of 11q22-q23.3 gain /11q24.1-qter loss

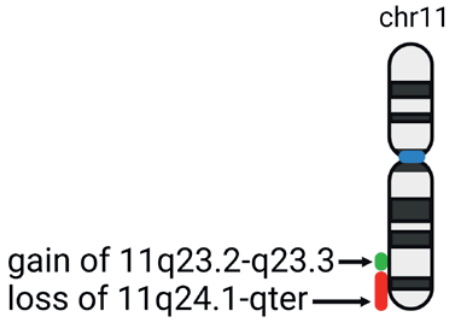


Inverted duplication in 11q





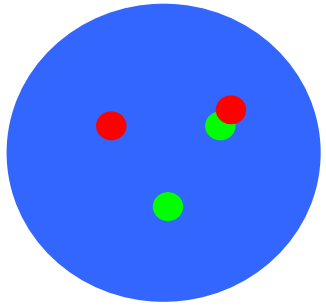
3 or more green signals



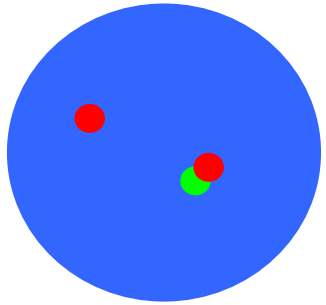
- **New entity in WHO, provisional entity in ICC**
- **Test all *MYC-R* negative cases with Burkitt or Burkitt-like morphology**
- **11q alterations also found in *MYC-R* BL and *MYC-R* HGBCL, NOS**
- **Best test: genomic microarrays (or OGM, WGS)**

Provided by S. Beà; Pienkowska-Grela et al, 2011; Grygalewicz, 2017; López et al, 2024

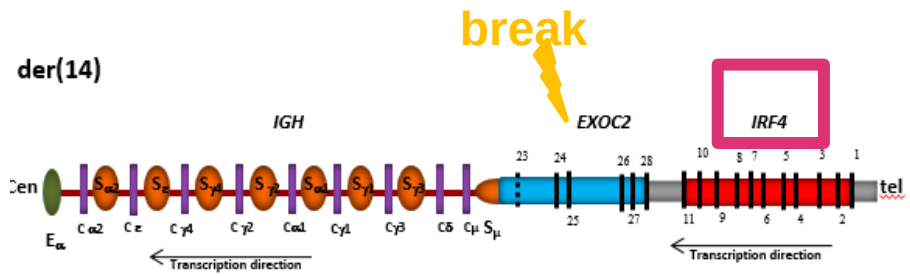
Large B-cell lymphoma with *IRF4* rearrangement (LBCL-IRF4)



Split signal
1F1R1G

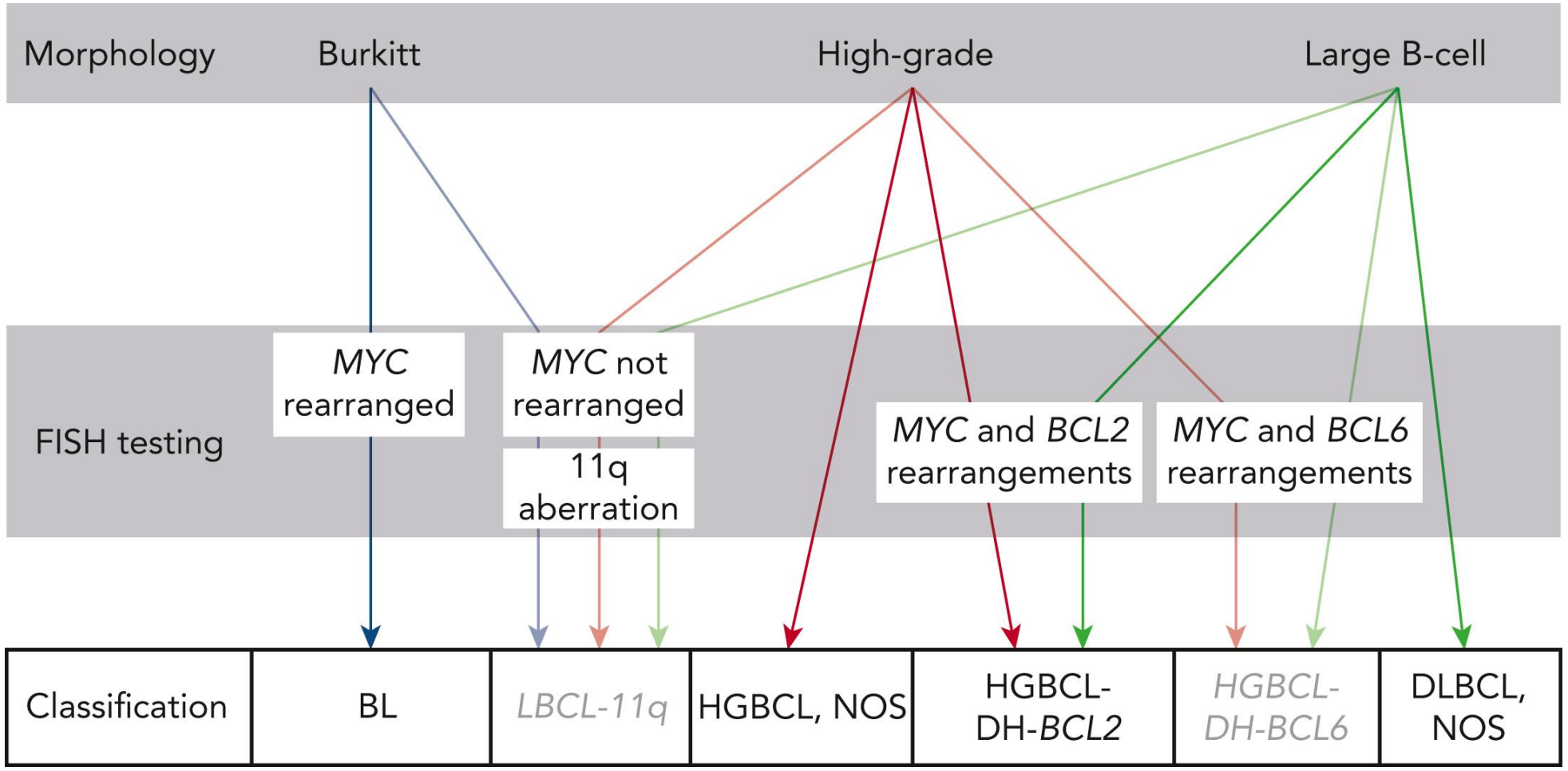


Loss of 3' signal
1F1R
Atypical signal pattern
Consistent with *IRF4* mechanism
Possible unbalanced transloc



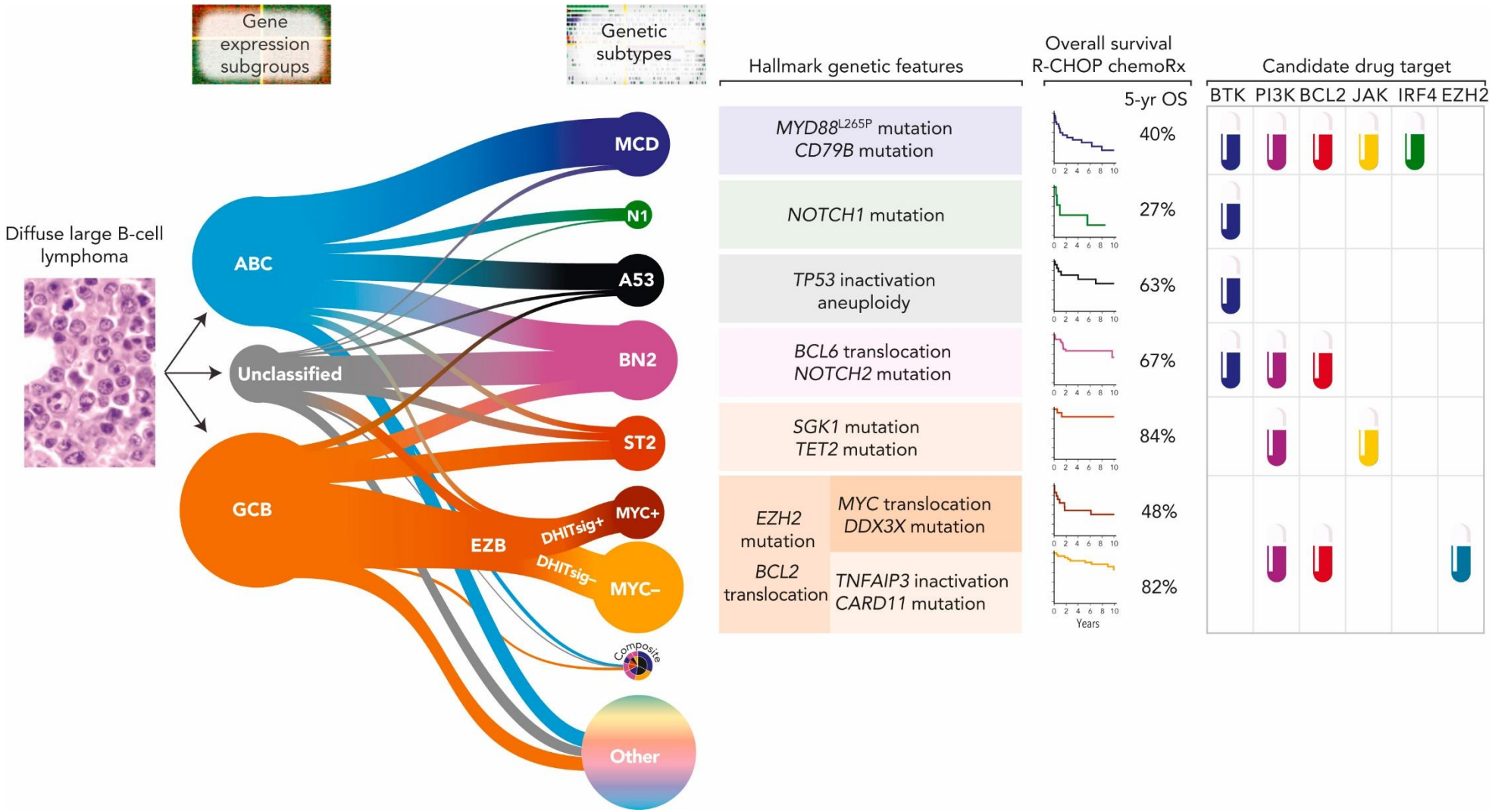
- ***IRF4* gene lies in a complex/polymorphic region** (potential false positive and negative results)
- **The partner is usually *IGH*** (very few with *IGK* and *IGL,* one non-IG reported in chr21 by RNAseq)
- **10% false negative cases by FISH approach using an *IRF4 BA* probe**
- **No commercial *IGH::IRF4* fusion probe**
- **Presence of *IRF4*** mutations in the highly conserved N-terminal DNA-binding domain in exon 2, in the correct context (aSHM), might be used as **a surrogate marker for the presence of *IRF4-R***
- ***IRF4*-R is not exclusive of LBCL-IRF4,** can be found in LBCL with *BCL2-R*. Need of integrated diagnosis

Provided by S. Beà



De Leval et al, Blood 2022

Diffuse large B-cell lymphoma (DLBCL), NOS



De Leval et al, Blood 2022

A reflection/thinkin

Table 2. Categorization of gene mutations based on current evidence levels.

Category	Gene mutations
1. Immediate impact on patient care	*TP53* mutations (exons 4-10) in CLL
2. Diagnostic impact	$MYD88^{L265P}$ mutation in WM/LPL $BRAF^{V600E}$ mutation in HCL *KLF2* mutations in SMZL *ID3* and *TCF3* mutations in BL *STAT3* mutations in LGLL *RHOA*, *TET2*, *IDH2* and DNMT3A mutations in AITL and other T_{FH}-derived PTCL
3. Prognostic impact	*CLL*: *TP53*, *ATM*, *BIRC3*, *NFKBIE*, *NOTCH1*, *SF3B1* MCL: *TP53*, *NOTCH1*, *NOTCH2* mutations SMZL: *NOTCH2*, *TP53* mutations DLBCL: *TP53* mutation & MYC translocation NKTCL: *DDX3X* mutations
4. Potential clinical impact in the near future	Therapy response to BcR inhibitors: WM: *MYD88*, *CXCR4* mutations DLBCL: *CD79B* mutations (responsive) *CARD11*, MYD88 mutations (non-responsive) Resistance to BcR inhibitors: BTK^{C481S}, PCLG2 mutations New inhibitors under development: *EZH2*, *SF3B1* & *NOTCH1*

[a]*Based on references listed in Table 1. CLL: chronic lymphocytic leukemia; WM: Waldenström's Macroglobulinemia; LPL: lymphoplasmacytic lymphoma; HCL: hairy-cell leukemia; BL: Burkitt lymphoma; AITL: angioimmunoblastic T-cell lymphoma; MCL: mantle cell lymphoma; SMZL: splenic marginal zone lymphoma; DLBCL: diffuse large B-cell lymphoma; NKTCL: NK T-cell lymphoma.*

Rosenquist et al, Haematologica 2016