Florida Cancer Data System

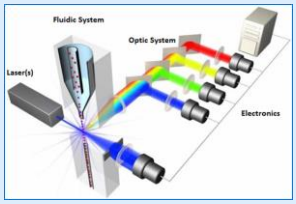
2023 Update to Lymphoid Neoplasms

1

2022-2023 FCDS EDUCATIONAL WEBCAST SERIES

2/16/2023

STEVEN PEACE, CTR



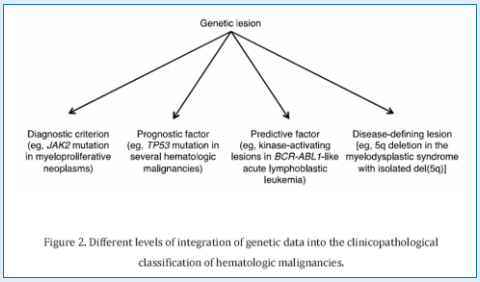
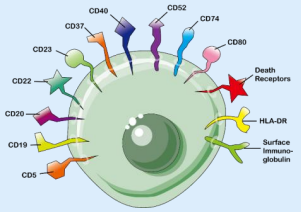


Figure 2. Different levels of integration of genetic data into the clinicopathological classification of hematologic malignancies.



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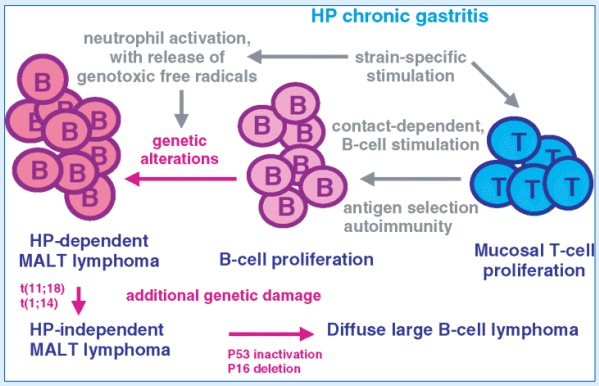
Risk Factors for Extranodal Marginal Zone B-cell Lymphomas of Mucosa-Associated Lymphoid Tissue (MALT Lymphomas)

2

TABLE 86.4 RISK FACTORS FOR EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMAS OF MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT LYMPHOMAS)

Site	Risk Factor	Reference
Stomach	*Helicobacter pylori*	177,178
Intestine	*Campylobacter jejuni*	179,180
Orbit	*Chlamydia psittaci*	181,182
alivary gland	Hepatitis C virus, autoimmunity (Sjögren syndrome)	183
Thyroid	Autoimmunity (Hashimoto's thyroiditis)	184
Skin	*Borrelia burgdorferi*	185,186 and 187



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CDC & Florida DOH Attribution

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FLccSC LMS – CEU Quiz –FCDS IDEA

FLccSC Fundamental Learning Collaborative for the Cancer Surveillance Community

NO CEU QUIZ FOR THIS WEBCAST

NCRA CEU# is 2022-163

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4

Outline

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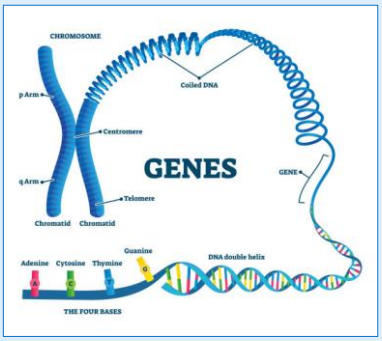
- Introduction to Lymphoid Neoplasms
- Lymphatic System and Circulatory System - Anatomy
- Extra-Lymphatic and Extra-Nodal Lymphomas
- Milestones in the Classification of Tumors of Lymphoid Tissues
- What is an “Integrated Diagnosis”?
- What are “Essential Criteria,” and “Desirable Criteria”?
- Flow Cytometry, IHC, PCR and Molecular Genetic Testing
- The Hematopoietic Manual and Hematopoietic Data Base
- Diagnostic Confirmation for Lymphoid Neoplasms
- Workup and Staging Lymphoid Neoplasms
- Treatment Guidelines for Lymphoid Neoplasms
- Coding Surgery for Lymphoma - Transplant Procedures
- Documentation Needed for Lymphoid Neoplasms
- 2022 FCDS Audit of Lymphoid and Myeloid Neoplasms
- Questions



Credit: VectorMine/Getty Images/iStockphoto

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Introduction to Lymphoid Neoplasms

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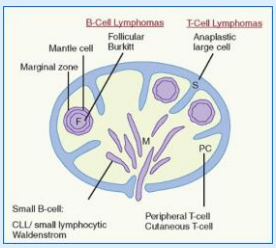
- Non-Hodgkin lymphomas are a group of related cancers involving lymphocytes
- They vary significantly in their rate of growth and response to treatment.
- The disease is usually already disseminated at the time of diagnosis.
- Molecular and genetic tests are essential for diagnosis and management.
- Limited indolent disease may be treated with radiation therapy.



- Treat more advanced disease (indolent or aggressive) with immunotherapy, chemotherapy, hematopoietic stem cell transplantation, or a combination depending on the type and stage of non-Hodgkin lymphoma.

https://www.merckmanuals.com/professional/hematology-and-oncology/lymphomas/non-hodgkin-lymphomas

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Introduction to Lymphoid Neoplasms

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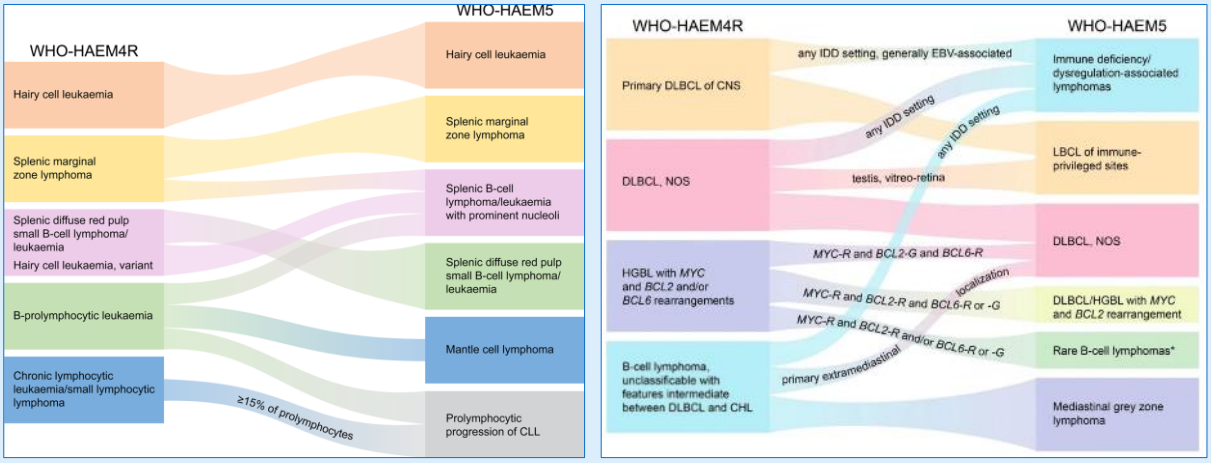

WHO Classification of Hematolymphoid Neoplasms, 5th edition – Chapter 1

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Hematopoiesis - Lymphoid

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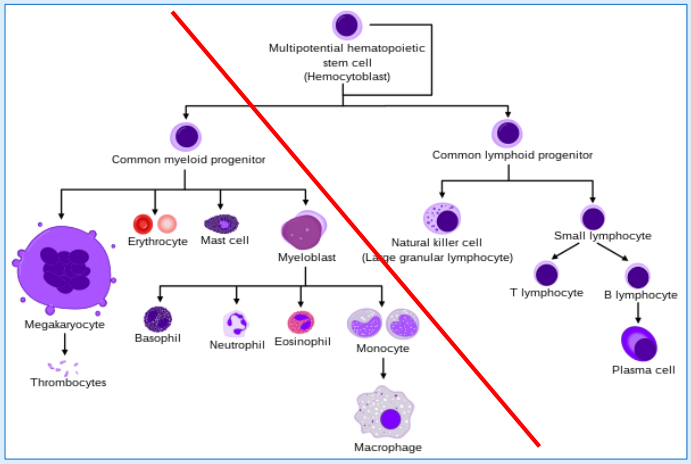
Myeloid



Lymphoid

Image:Hematopoiesis (human) diagram.png by A. Rad

8

Pediatric versus Adult Lymphoid Neoplasms

9

- Lymphoma is more common in adults but is the 3rd most common cancer in children representing about 15% of pediatric/young adult malignancies.
- The incidence of lymphoma varies from 3% in children younger than 5 years to 24% in 15 to 19 year olds.
- Non-Hodgkin lymphoma consists predominantly of mature aggressive B-cell lymphomas, with Burkitt lymphoma being most common in 5 to 14 year olds and diffuse large B-cell lymphoma more common in 15 to 19 year olds.
- Both Burkitt lymphoma and diffuse large B-cell lymphoma have better outcomes in children relative to adults, with survival rates greater than 90%
- The prognosis of adult diffuse large B-cell lymphoma is significantly worse than in children. It is not clear whether this is because children can better tolerate intensive treatment than adults or whether distinct pathogenetic mechanisms or distinct molecular genetics create different disease outcomes.
- Acute Lymphoblastic Leukemia occurs when 25% or more of cells in bone marrow are leukemic blasts of lymphoid origin (lymphoblasts). These are lymphoid leukemias as compared to the myeloid leukemias we discussed last hour. And yes, there are other lymphoid leukemias – so distinction of lymphoma from leukemia can be problematic.
- Acute Lymphoblastic Leukemia is a common malignancy in children. But, other lymphomas are not particularly common. Myeloid leukemia in children is much less common.

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Adult Myeloid and Lymphoid Neoplasms

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Figure 3. Leading Sites of New Cancer Cases and Deaths – 2022 Estimates

Estimated New Cases

Male			Female		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	983,160		All sites	934,870	

Estimated Deaths

Male			Female		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	322,090		All sites	287,270	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

2022 Cancer Facts & Figures – American Cancer Society

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Pediatric Myeloid and Lymphoid Neoplasms

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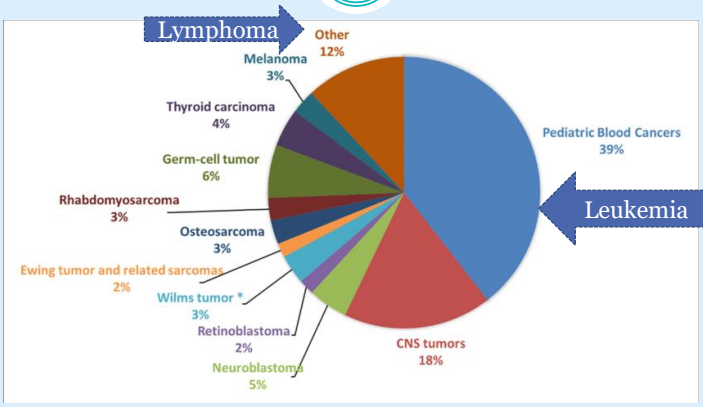

Frequency of pediatric cancers in patients younger than 19 years. The figure shows the prevalence of the main pediatric cancer types among patients younger than 19 years of age, calculated from Centers for Disease Control and Prevention (CDC) data (United States Cancer Statistics Data, https://wonder.cdc.gov/ cancer.html) and based on incidence in United States for the years 1999-2016.

Source: CDC NPCR United States Cancer Statistics

11

Inaugural WHO Classification of Pediatric Tumors

12

A Summary of the Inaugural WHO Classification of Pediatric Tumors: Transitioning from the Optical into the Molecular Era

Stefan M. Pfister[1,2,3], Miguel Reyes-Múgica[4,5], John K.C. Chan[6], Henrik Hasle[7], Alexander J. Lazar[8], Sabrina Rossi[9], Andrea Ferrari[10], Jason A. Jarzembowski[11], Kathy Pritchard-Jones[12], D. Ashley Hill[13], Thomas S. Jacques[14,15], Pieter Wesseling[16,17], Dolores H. López Terrada[18], Andreas von Deimling[19,20], Christian P. Kratz[21], Ian A. Cree[22], and Rita Alaggio[9]

ABSTRACT Pediatric tumors are uncommon, yet are the leading cause of cancer-related death in childhood. Tumor types, molecular characteristics, and pathogenesis are unique, often originating from a single genetic driver event. The specific diagnostic challenges of childhood tumors led to the development of the first World Health Organization (WHO) Classification of Pediatric Tumors. The classification is rooted in a multilayered approach, incorporating morphology, IHC, and molecular characteristics. The volume is organized according to organ sites and provides a single, state-of-the-art compendium of pediatric tumor types. A special emphasis was placed on "blastomas," which variably recapitulate the morphologic maturation of organs from which they originate.

Significance: In this review, we briefly summarize the main features and updates of each chapter of the inaugural WHO Classification of Pediatric Tumors, including its rapid transition from a mostly microscopic into a molecularly driven classification systematically taking recent discoveries in pediatric tumor genomics into account.

Cancer Discovery - https://doi.org/10.1158/2159-8290.CD-21-1094

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Inaugural WHO Classification of Pediatric Tumors

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Lymphoid neoplasms

Precursor lymphoid neoplasms

B-cell lymphoblastic leukemia/lymphomas

- B-LBLL with t(9;22)(q34.1;q11.2); *BCR::ABL1*
- B-LBLL with t(v;11q23.3); *KMT2A*-rearranged
- B-LBLL with t(12;21)(p13.2;q22.1); *ETV6::RUNX1*
- B-LBLL with hyperdiploidy, high
- B-LBLL with hypodiploidy, near-haploid
- B-LBLL with hypodiploidy, low
- B-LBLL with hypodiploidy, high
- B-LBLL with t(5;14)(q31.1;q32.3); *IGH::IL3*
- B-LBLL with t(1;19)(q23;p13.3); *TCF3::PBX1*
- B-LBLL, *BCR::ABL1*-like (Philadelphia-like B-ALL)
- B-LBLL with iAMP21

T-cell and natural killer (NK)–cell lymphoblastic leukemia/lymphoma

- T-lymphoblastic leukemia/lymphoma
- Early T-cell precursor lymphoblastic leukemia
- NK-lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms

- Primary mediastinal (thymic) large B-cell lymphoma
- Diffuse large B-cell lymphoma, NOS
- EBV-positive diffuse large B-cell lymphoma, NOS
- Large B-cell lymphoma with *IRF4* rearrangement
- Pediatric-type follicular lymphoma
- Pediatric nodal marginal zone lymphoma
- *ALK*-positive large B-cell lymphoma
- Lymphomatoid granulomatosis
- Plasmablastic lymphoma
- Grey-zone lymphoma
- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberration

Mature T/NK-cell neoplasms

- Peripheral T cell lymphoma
- Aggressive NK-cell leukemia
- Mycosis fungoides
- Anaplastic large cell lymphoma, *ALK*-positive
- Hepatosplenic T-cell lymphoma
- Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
- Systemic EBV$^+$ T-cell lymphoma of childhood
- Hydroa vacciniforme lymphoproliferative disorder
- Subcutaneous panniculitis-like T-cell lymphoma

Hodgkin lymphoma

- Classical Hodgkin lymphoma
- Nodular lymphocyte predominant Hodgkin lymphoma

Histiocytic and dendritic cell neoplasms

- Langerhans cell histiocytosis and other histiocytic/dendritic cell neoplasms

Immunodeficiency-associated lymphoproliferative disorders

- Primary immunodeficiency associated lymphoproliferative disorders
- Post-transplant lymphoproliferative disorders
- HIV-associated lymphoproliferative disorders

NOTE: Changes respect to fourth edition of the WHO Classification are highlighted in red (new). Molecularly defined entities are marked in green.

Mast cell neoplasia

- Mastocytosis

Cancer Discovery - https://doi.org/10.1158/2159-8290.CD-21-1094

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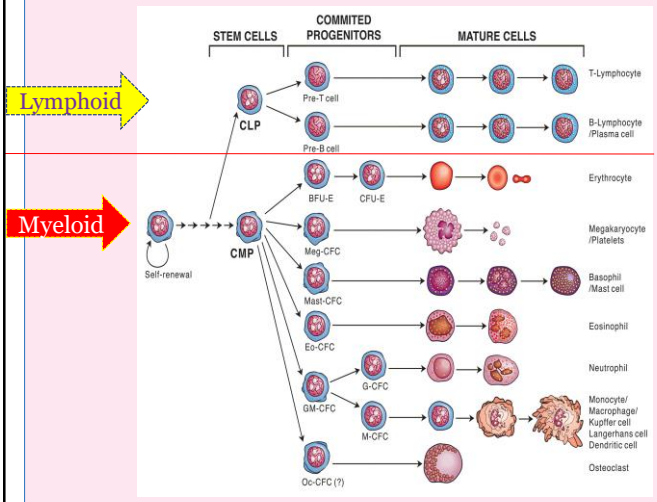
Blood, Bone Marrow, Circulatory System - Anatomy

14



- Cellular differentiation is the process by which an immature cell becomes a more mature cell
- Differentiation changes a cell's size, shape, membrane potential, metabolic activity, and responsiveness to signals or signal pathways
- Regulatory function of cells (regulates cell line proliferation and cell line differentiation) so you have right mix of different types of hematopoietic cells being produced by the bone marrow…and circulating in the blood and/or lymph.
- Over/Under Production by bone marrow of one cell line
- Too many/too few cells leads to chronic/acute disease

Blood Lines – Donald Metcalf, Alpha from MED Press, 2005

Figure 3.2 The eight major hematopoietic lineages generated by self-renewing multipotential stem cells

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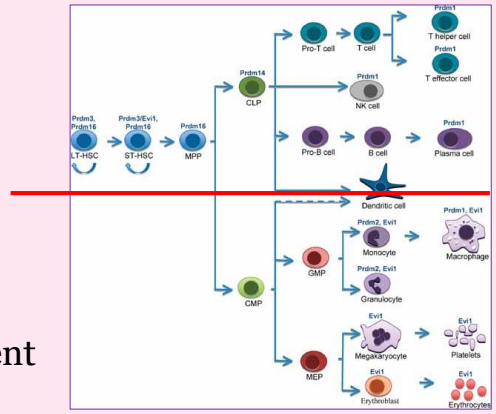
Blood, Bone Marrow, Circulatory System - Anatomy

15

- Cell differentiation
- Regulation of proliferation
- Regulation of differentiation
- Turn on/Turn off
  - Growth factors
  - Genes (including mutations)
  - Proteins
- Dysregulation disrupts normal development
- Oncogenesis – becoming malignant



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Why are cell line, proliferation, differentiation and function important?

16

- All cells contain the full complement of biomolecules that are necessary for survival, proliferation, differentiation, cell death, and expression of many cell type–specific functions. These functions are controlled in normal cells and one or more of the functions operate out of control in cancer cells.
- Regulatory function of cells (proliferation and differentiation) ensure you have right mix/balance of hematopoietic cells produced by the bone marrow…and circulating in the blood and/or lymph.
- Failure to regulate the functions properly (dysregulation) results in an altered phenotype and cancer.
- Cell Lines show which major group of disease the malignancy occurs – lymphoid/myeloid
- Proliferation is the process when the body/bone marrow makes too many of a specific type of cells
- Differentiation is the process of an immature cell becoming a mature cell with a specific function.
- Mutations can occur during proliferation & differentiation – pathways to neoplastic development

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TWO Circulatory Systems – Blood & Lymphatic

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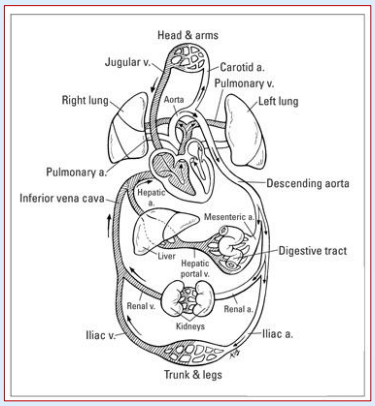

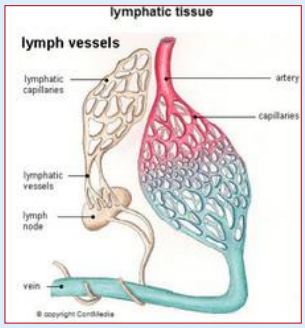

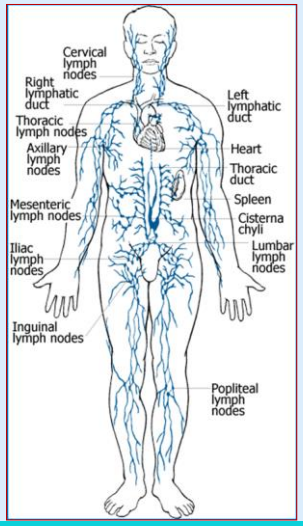

http://www.dummies.com/education/science/biology/the-path-of-blood-through-the-human-body http://www.gorhams.dk/html/the_lymphatic_system.htm

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The Lymphatic System

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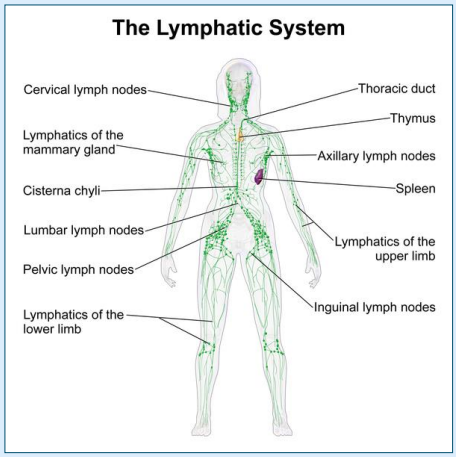

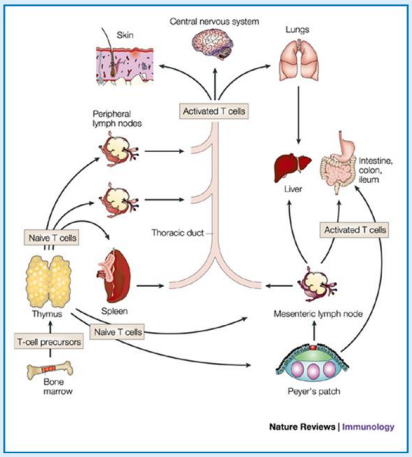

Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014".

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Lymphatic Circulatory System

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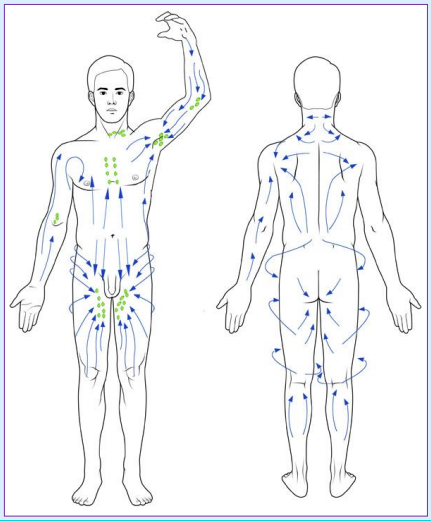

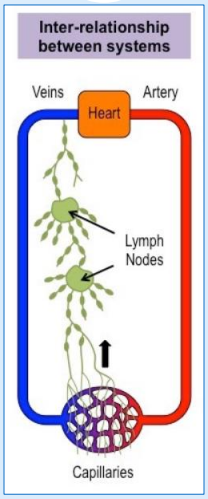

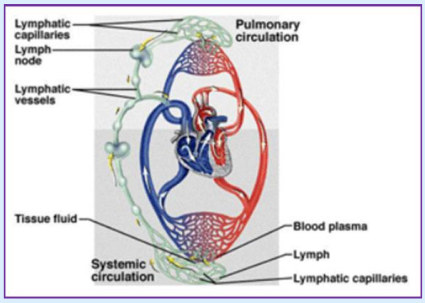

Source: Nature Reviews Immunology http://www.nature.com/nri/journal/v4/n5

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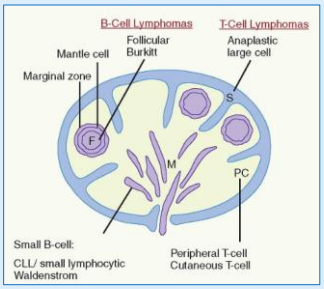
Lymph Node



Antibody Designation	Reactivity	Examples of Lymphoid Neoplasms
CD1a	Thymocytes, dendritic cells, and epidermal Langerhans cells	T lymphoblastic leukemia/lymphoma and Langerhans cell histiocytosis
CD2	T cells and natural killer cells	T-cell and natural killer cell lymphomas
CD3	T cells	T-cell lymphomas
CD4	Helper and inducer T cells, monocytes, and macrophages	T-cell lymphomas and diffuse large B-cell lymphoma with ALK expression (rare)
CD5	T-cells and B-cell subset	T-cell lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, and mantle cell lymphoma
CD7	T cells and natural killer cells	T-cell and natural killer cell lymphomas
CD8	Cytotoxic and suppressor cells T cells and natural killer cells	Cytotoxic T-cell lymphomas and natural killer cell lymphomas
CD10	Precursor B cells, B-cell subset (follicle center cells), and follicle center T-helper cells	B and some T lymphoblastic leukemias/lymphomas, follicular lymphoma, some diffuse large B-cell lymphomas, Burkitt lymphoma, and angioimmunoblastic T-cell lymphoma
CD15	Granulocytes, monocytes, Reed-Sternberg cells, activated lymphocytes, and some epithelial cells	Classical Hodgkin lymphomas
CD19	B cells	B-cell lymphomas
CD20	B cells	B-cell lymphomas and nodular lymphocyte predominant Hodgkin lymphoma
CD21	B-cell subset and follicular dendritic cells	Follicular dendritic cell sarcoma and follicular dendritic cell meshworks in angioimmunoblastic T-cell lymphoma
CD22	B-cell subset	Some B-cell lymphomas and hairy cell leukemia
CD23	Activated B cells, mantle B cells, and follicular dendritic cells	Chronic lymphocytic leukemia/small lymphocytic lymphoma and follicular dendritic cell meshworks in angioimmunoblastic T-cell lymphoma
CD25	Activated T- and B cells and activated macrophages	Adult T-cell leukemia/lymphoma, anaplastic large cell lymphoma, and hairy cell leukemia
CD30	Activated T- and B cells and Reed-Sternberg cells	Classical Hodgkin lymphomas, anaplastic large cell lymphoma, some peripheral T-cell lymphomas, NOS, and some large B-cell lymphomas
CD38	Plasma cells, thymocytes, and activated T cells	Plasma cell neoplasms, B-cell lymphomas with plasmacytic differentiation, and some chronic lymphocytic leukemias/small lymphocytic lymphomas
CD43	T cells, B cell subset, granulocytes, and monocytes and macrophages	T-cell lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, some marginal zone B-cell lymphomas, and Burkitt lymphoma
CD45	Leukocytes	Non-Hodgkin lymphomas and nodular lymphocyte predominant Hodgkin lymphoma
CD45RA	B cells, T-cell subset, granulocytes, and monocytes	B-cell lymphomas and some T-cell lymphomas
CD45RB	B cells, T-cell subset, granulocytes, and monocytes and macrophages	B-cell lymphomas and some T-cell lymphomas
CD45RO	T cells, B-cell subset, granulocytes, and monocytes and macrophages	Most T-cell lymphomas and some diffuse large B-cell lymphomas

Antibody Designation	Reactivity	Examples of Lymphoid Neoplasms
CD56	Natural killer cells and T-cell subset	Natural killer cell lymphomas, some cytotoxic T-cell lymphomas, and plasma cell neoplasms
CD57	Natural killer cells and T-cell subset	Natural killer cell lymphomas, some cytotoxic T-cell lymphomas, and diffuse large B-cell lymphoma with ALK expression (rare)
CD68	Monocytes and macrophages	Histiocytic sarcomas and reactive histiocytes in many lymphomas
CD79a	B cells	Most B-cell lymphomas and plasma cell neoplasms
CD103	Intestinal intraepithelial T cells	Enteropathy-associated T-cell lymphoma and hairy cell leukemia
CD138	Plasma cells	Plasma cell neoplasms and some B-cell lymphomas with plasmacytic differentiation
CD246 (ALK)	Neoplastic cells in anaplastic large cell lymphoma	Most anaplastic large cell lymphomas and diffuse large B-cell lymphoma with ALK expression (rare)
Bcl-2	B-cell subset and T cells	Follicular lymphoma and most other B-cell and T-cell lymphomas
Bcl-6	Follicle center B cells	Follicular lymphoma and some diffuse large B-cell lymphomas
Clusterin	Follicular dendritic cells	Follicular dendritic cell sarcoma, anaplastic large cel lymphoma, and follicular dendritic cell meshworks in angioimmunoblastic T-cell lymphoma
CXCL13	Follicle center T-helper cells	Angioimmunoblastic T-cell lymphoma and nodular lymphocyte predominant Hodgkin lymphoma
Cyclin D1	Neoplastic mantle cells	Mantle cell lymphoma, hairy cel leukemia, and some plasma cell neoplasms
Epithelial membrane antigen	Epithelial cells and plasma cells	Anaplastic large cell lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, plasmablastic lymphoma, and plasma cell neoplasms
Fascin	Follicular dendritic cells, histiocytes, Reed-Sternberg cells, and Epstein-Barr virus-infected immunoblasts	Classical Hodgkin lymphoma, Epstein -Barr virus-positive B-cell and T-cell lymphomas, follicular dendritic cell sarcoma
FoxP3	CD4+/CD25+ regulatory T cells	Adult T-cell leukemia/lymphoma
Granzyme A, B, and M	Natural killer cells and activated cytotoxic T cells	Natural killer cell and activated cytotoxic T-cell lymphomas
IgA, IgD, IgE, IgG, and IgM	Immunoglobulin heavy chains	B-cell lymphomas and plasma cell neoplasms
Kappa and Lambda	Immunoglobulin light chains	B-cell lymphomas and plasma cell neoplasms
Ki-67/mib-1	Nuclear proliferation antigens	
MUM-1	B cells in terminal phase of differentiation, plasma cells, activated T cells, and Reed-Sternberg cells	Lymphoplasmacytic lymphoma, some diffuse large B-cell lymphomas, plasma cell neoplasms, some T-cell lymphomas, and Hodgkin lymphomas
PAX-5	B cells and Reed-Sternberg cells	B-cell lymphomas and Hodgkin lymphomas
T-cell receptor α/β	α/β T cells	Most T-cell lymphomas
T-cell receptor γ/δ	γ/δ T cells	Few T-cell lymphomas
TdT	Lymphoblasts and some myeloblasts	B and T lymphoblastic leukemias/lymphomas
TIA-1	Natural killer cells and cytotoxic T cells	Natural killer cell and cytotoxic T-cell lymphomas

https://oncohemakey.com/diagnosis-and-classification-of-lymphomas/

20

Lymph Node

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Lymphoma Type	Growth Pattern	Cytology	CD5	CD10	CD23	Surface Ig	Genetics
Follicular lymphoma	Nodular (follicular)	Lymphocytes with irregular cleaved nuclei (centrocytes) and admixed large cells (centroblasts)	–	+	–	Bright	t(14;18)(q32; q21) in >85%
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Diffuse with proliferation centers	Small lymphocytes with round nuclei and scant cytoplasm	+	–	+	Weak IgM and IgD > IgG > IgA	Trisomy 12 20% to 30%
Lymphoplasmacytic lymphoma	Diffuse or interfollicular	Small lymphocytes, plasma cells, and plasmacytoid lymphocytes	–	–	–	Moderate IgM	MYD88 L265P mutation
Mantle cell lymphoma	Diffuse or vaguely nodular	Small lymphocytes with irregular nuclei, scant cytoplasm, and few admixed large cells	+	–	–	Moderate IgM and IgD; Lambda > kappa	t(11;14)(q13; q32)
Nodal marginal zone B-cell lymphoma	Interfollicular and perisinusoidal	Small lymphocytes with round, folded nuclei and abundant cytoplasm ± plasma cells	–	–	–	Moderate IgM	None
Splenic marginal zone B-cell lymphoma	Nodular	Biphasic: inner core of small lymphocytes with irregular nuclei and scant cytoplasm; outer core of medium-size lymphocytes with round nuclei and abundant clear cytoplasm +/- plasma cells	–	–	–	IgM +/- IgD	Del 7q
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue	Diffuse	Small lymphocytes with round, folded nuclei and abundant cytoplasm ± plasma cells	–	–	–	IgM	Trisomy 3 or t(11;18) (q21; q21)

https://oncohemakey.com/diagnosis-and-classification-of-lymphomas/

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Lymphatic Organs

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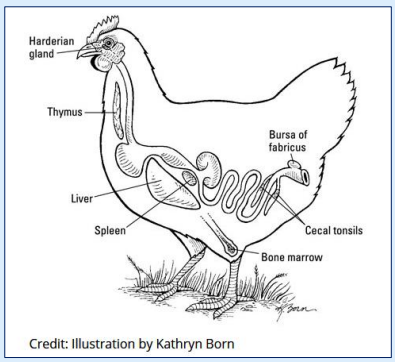
- **Primary Organs**
  - Bone Marrow
  - Thymus



Credit: Illustration by Kathryn Born

- **Secondary Organs**
  - Spleen – process blood
    - Red Pulp
    - White Pulp
  - Tonsils (Waldeyer's Ring)
  - Lymph Nodes – process extracellular fluids
  - MALT (mucosa-associated lymphoid tissue) – process mucosa
    - GALT (gut-associated lymphoid tissue)
    - Peyer's Patches
  - Skin

22

Lymphatic Organs

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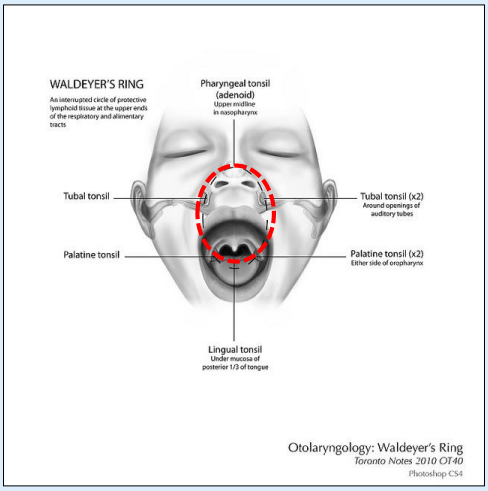

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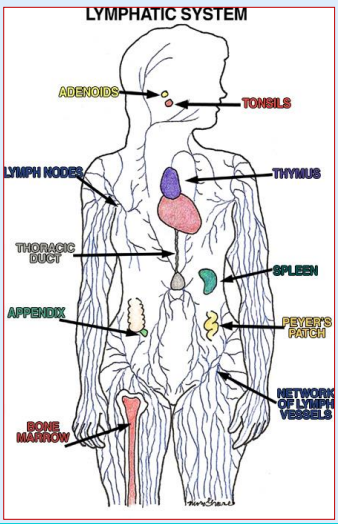
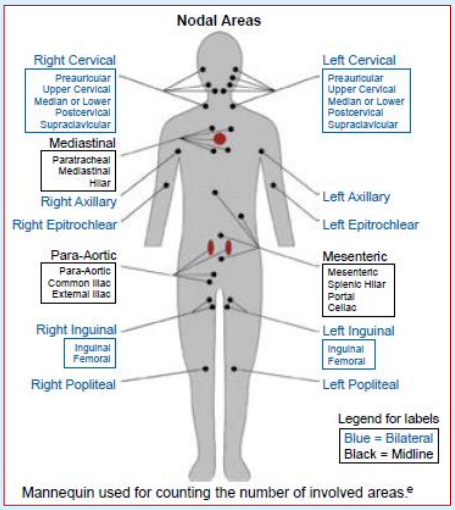
Lymphatic Organs vs Region

24



http://commonsensehealth.com



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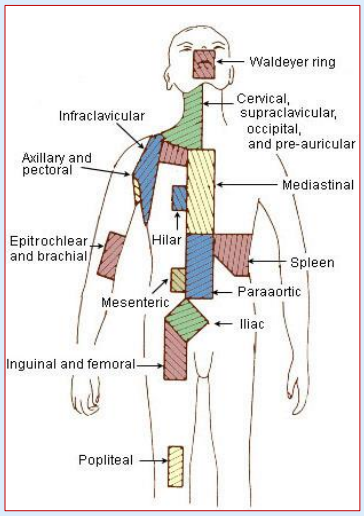
Lymph Node Chains and Regions

25

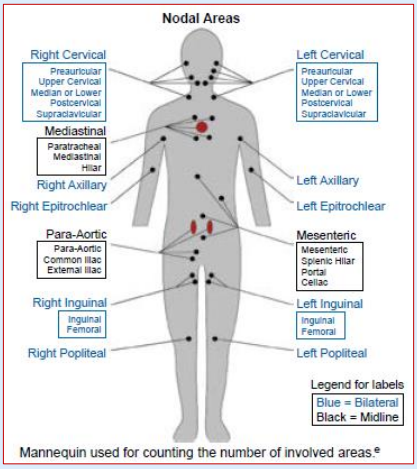


Lymph nodes above the diaphragm

1. Waldeyer's ring
2. Cervical, supraclavicular, occipital, and pre-auricular
3. Infraclavicular
4. Axillary and pectoral
5. Mediastinal
6. Hilar
7. Epitrochlear and brachial

Lymph nodes below the diaphragm

8. Spleen
9. Mesenteric
10. Paraaortic
11. Iliac
12. Inguinal and femoral
13. Popliteal



Source: Wikipedia – Ann Arbor Hodgkin's Lymphoma; Nodal Regions

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Appendix C
Lymph Node/Lymph Node Chain Reference Table

Use this table with the Primary Site and Histology Rules to determine whether involved lymph nodes are in a single ICD-O lymph node region or in multiple ICD-O lymph node regions.
This table contains the names of lymph nodes that have the capsule and sinus structure of true lymph nodes. Lymphoid tissue such as that in the GI tract, tonsils, etc., is not represented in this table.

Note: Pathology reports may identify lymph nodes within most organs, the most common being breast, parotid gland, lung, and pancreas. The lymph nodes in these organs are called intra- (organ name) lymph nodes such as intramammary lymph nodes. We have included the most common intra-organ lymph nodes on this table. For an intra-organ lymph node not listed on the table, code to the ICD-O topography code for that organ's regional lymph node chain(s).

Table C1: Lymph Node/Lymph Node Chain Reference Table
*The right and left are separate regions per AJCC

Lymph Node/Lymph Node Chain	Use for Multiple Primaries in Heme	ICD-O Lymph Node Region(s)	TNM Staging
Abdominal	C772	Intra-abdominal	Mesenteric
Anorectal (pararectal)	C775	Pelvic	Pelvic, right and left*
Anterior axillary (pectoral)	C773	Axilla or arm	Axillary, right and left*
Anterior cecal (prececal)	C772	Intra-abdominal	Mesenteric
Anterior deep cervical (laterotracheal, recurrent laryngeal, recurrent pharyngeal)	C770	Head, face and neck	Cervical, right and left*
Anterior jugular	C770	Head, face and neck	Cervical, right and left*
Anterior mediastinal	C771	Intrathoracic	Mediastinal
Aortic (ascending, lateral, lumbar, subaortic, NOS)	C772	Intra-abdominal	Para-aortic
Aortico-pulmonary window (subaortic)	C772	Intra-abdominal	Para-aortic
Apical (subclavian)	C770	Head, face and neck	Cervical, right and left*
Appendiceal	C772	Intra-abdominal	Mesenteric
Apical axillary (deep axillary, Level III axillary)	C773	Axilla or arm	Axillary, right and left*
Aselli's glands (nodes near pancreas)	C772	Intra-abdominal	Para-aortic
Auricular (infraauricular, postauricular, preauricalar, retroauricular, NOS)	C770	Head, face and neck	Cervical, right and left*
Axillary (anterior, brachial, deep, lateral, superficial, NOS)	C773	Axilla or arm	Axillary, right and left*
Axillary (Level I [low axillary, superficial axillary], Level II, Level III [apical, deep)	C773	Axilla or arm	Infraclavicular, right and left*
Azygos (lower paratracheal)	C771	Intrathoracic	Mediastinal
Brachial (lateral axillary)	C773	Axilla or arm	Axillary, right and left*
Brachiocephalic	C773	Axilla or arm	Axillary, right and left*

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Extra-Lymphatic and Extra-Nodal Lymphomas

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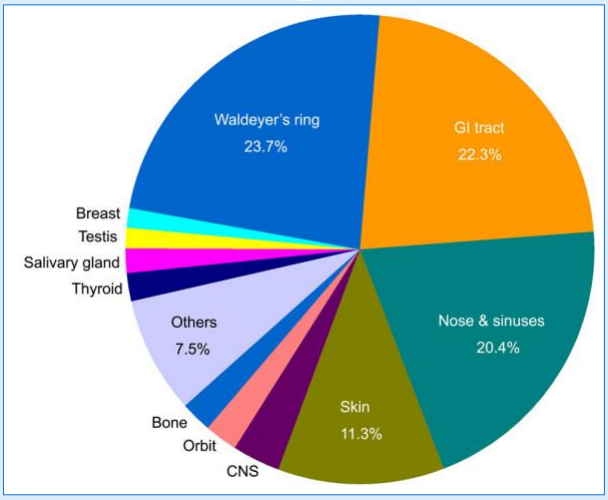

Source: Wen-yan Zhang – Research Gate

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Milestones - Classification of Hematopoietic Neoplasms

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- 1951 – Dameshek – clinical phenotype
- 1960 – Philadelphia (Ph1) chromosome
- 1966 – Rappaport Classification
- 1974 – Kiel Classification System
- 1974 – Lukes and Collins System
- 1976 – Revised Rappaport Classification
- 1976 – French/American/British (FAB) Classification
- 1982 – Working Formulation
- 1994 –Revised European-American Classification of Lymphoid Neoplasms
- 2001 – WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, 3rd edition, 2001
- 2008 – WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, 4th edition, October 2008
- 2016 – Revision to 4th edition, 2017
- 2022 – WHO Classification of Hematolymphoid Tumors, 5th ed

28

Milestones - Classification of Hematopoietic Neoplasms

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- 1951, William Dameshek described the concept of 'myeloproliferative disorders' by grouping together chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis and erythroleukemia
- 1960, Nowell and Hungerford discovered the Philadelphia (Ph) chromosome in CML.
- 1967, Fialkow and colleagues used X-linked polymorphisms to establish CML as a clonal stem cell disease.
- 1967, the PV Study Group was summoned by Louis Wasserman to study the natural history of Polycythemia Vera and conduct large-scale clinical trials.
- 1972, Janet Rowley deciphered the Ph chromosome as a reciprocal translocation between chromosomes 9 and 22, thus paving the way for its subsequent characterization as an oncogenic BCR–ABL mutation.
- 1996, Brian Druker discovered imatinib (Gleevec) —a small molecule ABL inhibitor with exceptional therapeutic activity in CML.
- 2005, a gain-of-function JAK2 mutation (JAK2V617F) was described in BCR–ABL-negative MPDs, raising the prospect of a CML-like treatment strategy in PV, ET and PMF.
- 2022, introduction of the concept of an 'integrated diagnosis' and 'essential diagnostic criteria'

29

Integrating genetic data into classification

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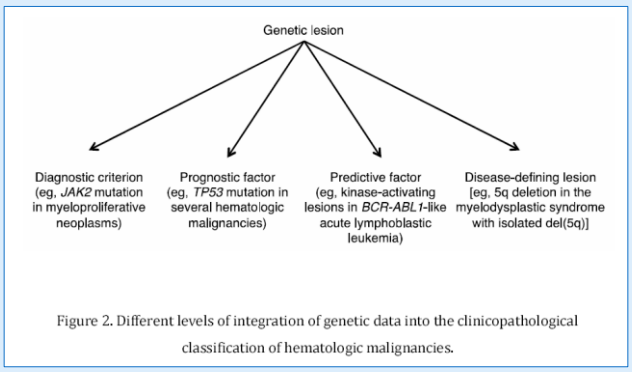

Figure 2. Different levels of integration of genetic data into the clinicopathological classification of hematologic malignancies.

National Cancer Institute

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Integrated Diagnosis, Essential & Desirable Diagnostic Criteria

31

- The definition and diagnosis of disease types continues to be based on multiple clinicopathologic parameters, but with refinement of diagnostic criteria and emphasis on therapeutically and/or prognostically actionable biomarkers. Using the classification to its fullest extent requires specialized techniques, which at a minimum should include immunophenotyping, conventional karyotyping, fluorescence in situ hybridization (FISH), and mutation profiling.
- **Diagnostic Integration or Integrated Diagnosis** - this classification is predicated on **integrating morphologic** (cytology and histology), **immunophenotypic**, **molecular and cytogenetic data**.
- The **essential and desirable diagnostic criteria** are intended to facilitate distilling the key diagnostic components needed to classify a particular disease type.
- **Essential diagnostic criteria** are considered must-have features
- **Desirable diagnostic criteria** are 'nice-to-have' features (they support a diagnosis but are not mandatory).

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Integrated Diagnosis, Essential & Desirable Diagnostic Criteria

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- Even the pathologists and oncologists are struggling with information overload from all of these tests – and their responsibility to interpret a complex set of literally hundreds of results from molecular testing while knowing only some of the results 'might' be important to Dx or Tx. So some Dx end up 'generic'.
- All of these new tests are new. It is not an exact science yet – and may never be…it is rapidly evolving.
- Not every case will fit neatly into a word-match like our traditional microscopic histology did
- Every case is individualized with some level of unique individual mutation(s)
- Cases will have some 'in common' mutations – but there is always something unique – that's what genetics is all about – molecular tests are drawing lines around 'families' of malignancies
- If each case required full interpretation of the entire set of mutations for each individual tumor we would have thousands of new histology codes to account for each tumor's unique genetic makeup
- That is why we have to rely on the pathologist and oncologist to give us the integrated diagnosis
- It is up to us to document the integrated diagnosis and which tests led the pathologist and/or oncologist to the conclusion that it was xyz lymphoma or 123 leukemia – but they still have to make the statement

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What Type of Test Do I Look for in Lymphoid Neoplasms?

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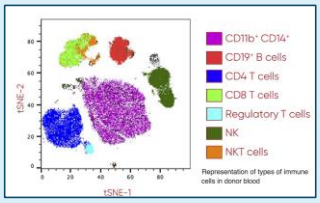
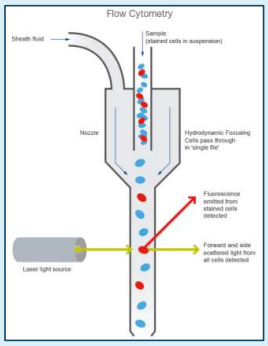
1. Did the patient have one or more of the following tests performed on blood, lymph, bone marrow or tissue biopsy or resection (traditional microscopic anatomic pathology)?

- Immunophenotype
  - Flow cytometry (cell sorting/counting) for cluster of designation or CD marker analysis,
  - IHC (immunohistochemistry) for CD marker analysis,
  - PCR testing (polymerase chain reaction) for CD marker analysis,
- Molecular pathology studies to analyze DNA or other genetic material using;
  - Single gene test,
  - Genetic panel test,
  - Multi-gene panel test,
  - DNA Microarray,
  - Biomolecular marker(s),
  - FISH (fluorescent in-situ hybridization),
  - Other Immunofluorescence testing,
  - Next-generation sequencing (NGS) gene panel, or
  - Other DNA/RNA/gene testing





2. Did any of the additional test results; confirm the diagnosis, clarify the type of neoplasm (histologic type or subtype), or identify a target drug or specific biological, molecular or immunotherapy (BRM)?

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Flow Cytometry – How it Works

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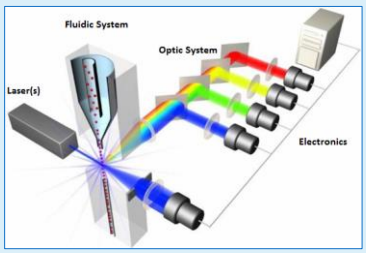

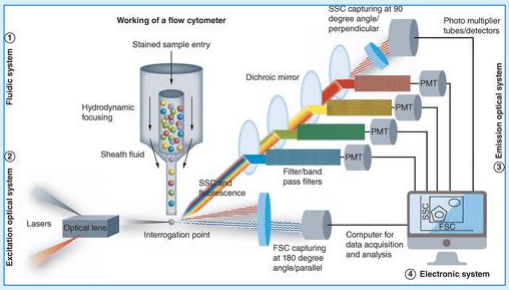

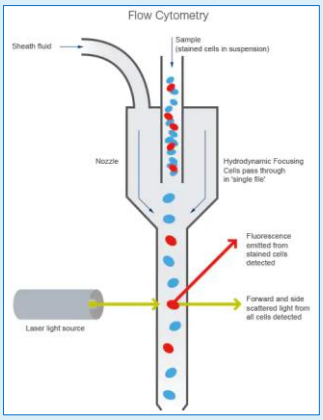

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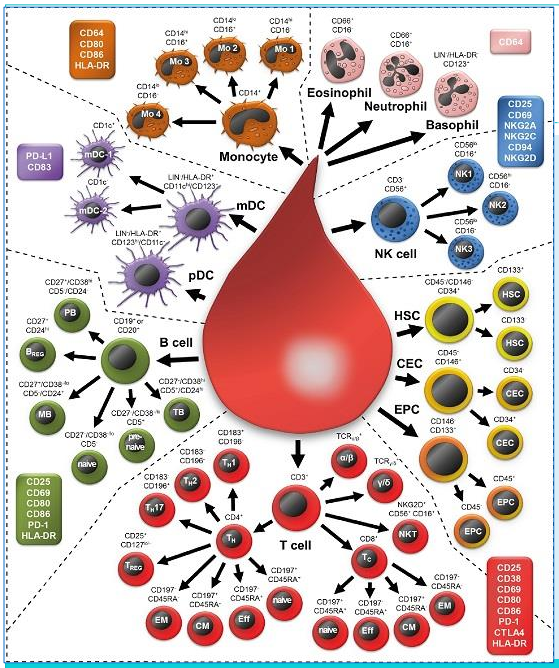

Flow Cytometry Assays and Reports

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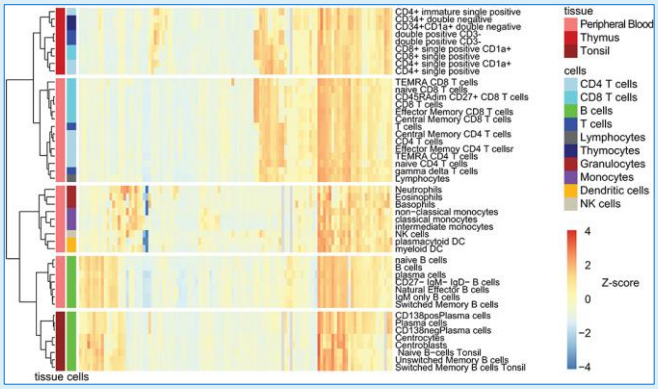

Int. J. Mol. Sci. **2016**, *17*(8), 1316; https://doi.org/10.3390/ijms17081316

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- **Histology** – Microscopy examines the microanatomy of cells, tissues, and organs as seen through a microscope – physical characteristics. It examines the correlation between structure and function.
- **Biologic Tumor Marker** – Immunoassay can be used to identify anything present in or produced by cancer cells or other cells from blood, urine and body fluids. Tumor Markers provide information about a cancer, aggressiveness, what kind of treatment it may respond to, or whether it is responding to treatment. Tumor markers can be proteins, conjugated proteins, peptides and carbohydrates.
- **Immunohistochemistry** – a microscopy-based technique that allows selective identification and localization of antigens in cells. IHC selectively identifies antigens (proteins) in cells from tissue by exploiting the principle of antibodies binding specifically to antigens in biological tissues. IHC uses light or fluorescent microscopy to analyze results. IHC is less expensive than flow cytometry.
- **Flow Cytometry** – a laser-based technique that detects and measures the physical and chemical characteristics of a cell population. Flow cytometry can be used to count and sort cells (identify proliferation of cells and type), determine cell characteristics, identify biomarkers and to diagnose/classify certain cancers. It is more precise metric for antigens than histology or IHC testing.
- **Cluster of Differentiation (CD) Molecules** – cell surface molecules used to classify white blood cells that are especially important for diagnosis of lymphomas and leukemias. CD marker antibodies have been widely used for cell sorting, phenotyping, and blood cancer diagnosis and for treatment.
- **Immunophenotype** – uses the CD system to define markers associated with specific cells or conditions
- **Proteomics** – provide valuable information on the identity, expression levels, and modification of proteins. For example, cancer proteomics unraveled key information in mechanistic studies on tumor growth and metastasis, which has contributed to the identification of clinically applicable biomarkers as well as therapeutic targets. Proteomics-based technologies have enabled the identification of potential biomarkers and protein expression patterns that can be used to assess tumor prognosis, prediction, tumor classification, and to identify potential responders for specific therapies
- **Cytogenetics** - involves testing samples of tissue, blood, or bone marrow in a laboratory to look for changes in chromosomes, including broken, missing, rearranged, or extra chromosomes. Changes in certain chromosomes may be a sign of a genetic disease or condition or some types of cancer. FISH is common cytogenetics test.
- **DNA Microarray** – used to study the extent to which certain genes are turned on or off in cells and tissues. It is used to identify the changes in gene sequences that are most often associated with a particular disease.
- **Next Generation Sequencing** – a large-scale DNA and RNA sequencing technology to determine the order of nucleotides in entire genomes or targeted regions of DNA or RNA in cells and tissues.

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Molecular Genetics and Tumor Markers for Lymphoid Neoplasms

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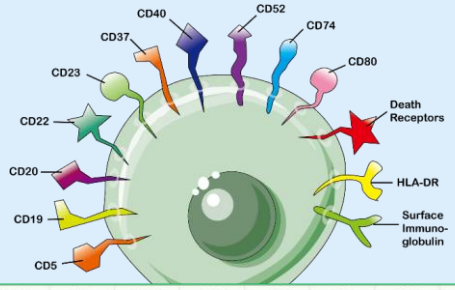

CD1A	CD2	CD3D	CD3E	CD4	CD5	CD8A	CD9
CD10	CD11A	CD11B	CD11C	CD13	CD14	CD15	CD16A
CD16B	CD19	CD22	CD24	CD25	CD27	CD28	CD29
CD31	CD32	CD33	CD34	CD38	CD40	CD41A	CD44
CD45	CD45RO	CD46	CD47	CD48	CD51/CD61	CD54	CD56
CD59	CD62E	CD62L	CD62P	CD64	CD69	CD73	CD80
CD83	CD85J	CD86	CD90	CD95	CD96	CD99	CD105
CD106	CD117	CD123	CD127	CD138	CD144	CD152	CD154
CD158Z	CD161	CD178	CD180	CD184	CD193	CD197	CD200
CD200R1	CD223	CD226	CD243	CD253	CD272	CD274	CD276
CD278	CD279	CD281	CD282	CD283	CD284	CD288	CD289
CD300E	CD319	CD338	CD357				

CD	Cell type
CD3	Pan T cell marker
CD4	T helper/inducer cell
CD5	Immature T cells; T-cell-ALL; B cell chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL); Mantle cell lymphoma
CD8	T suppressor/ cytotoxic cell
CD10	Acute lymphoblastic leukemia: CALLA antigen of early precursor B- and pre-B cell ALL; Follicular lymphoma
CD11c	Monocytes; Histiocytes; hairy cell leukemia
CD20	Mature B cell marker except plasma cells; B cell lymphomas; Lymphocyte predominant Hodgkin lymphoma (lympho-histocytic Red-Sternberg cell variant, aka L&H cells, popcorn cells)
CD25	Hairy cell leukemia
CD15, CD30	Hodgkin lymphoma: Classic Reed-Sternberg cells, Lacunar cells of nodular sclerosis type CD30-positive cells are seen with anaplastic large cell lymphoma
CD33	Myeloid progenitor cells and monocytes; acute myelogenous leukemia
CD41	Megakaryocytes: Acute megakaryocytic leukemia
CD55	Decay accelerating factor (DAF): loss is seen with paroxysmal nocturnal hemoglobinuria

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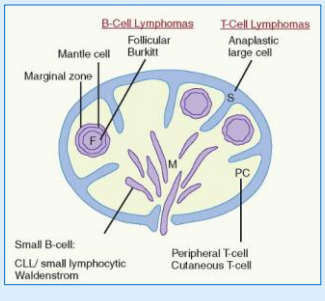
Lymph Node



Antibody Designation	Reactivity	Examples of Lymphoid Neoplasms
CD1a	Thymocytes, dendritic cells, and epidermal Langerhans cells	T lymphoblastic leukemia/lymphoma and Langerhans cell histiocytosis
CD2	T cells and natural killer cells	T-cell and natural killer cell lymphomas
CD3	T cells	T-cell lymphomas
CD4	Helper and inducer T cells, monocytes, and macrophages	T-cell lymphomas and diffuse large B-cell lymphoma with ALK expression (rare)
CD5	T-cells and B-cell subset	T-cell lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, and mantle cell lymphoma
CD7	T cells and natural killer cells	T-cell and natural killer cell lymphomas
CD8	Cytotoxic and suppressor cells T cells and natural killer cells	Cytotoxic T-cell lymphomas and natural killer cell lymphomas
CD10	Precursor B cells, B-cell subset (follicle center cells), and follicle center T-helper cells	B and some T lymphoblastic leukemias/lymphomas, follicular lymphoma, some diffuse large B-cell lymphomas, Burkitt lymphoma, and angioimmunoblastic T-cell lymphoma
CD15	Granulocytes, monocytes, Reed-Sternberg cells, activated lymphocytes, and some epithelial cells	Classical Hodgkin lymphomas
CD19	B cells	B-cell lymphomas
CD20	B cells	B-cell lymphomas and nodular lymphocyte predominant Hodgkin lymphoma
CD21	B-cell subset and follicular dendritic cells	Follicular dendritic cell sarcoma and follicular dendritic cell meshworks in angioimmunoblastic T-cell lymphoma
CD22	B-cell subset	Some B-cell lymphomas and hairy cell leukemia
CD23	Activated B cells, mantle B cells, and follicular dendritic cells	Chronic lymphocytic leukemia/small lymphocytic lymphoma and follicular dendritic cell meshworks in angioimmunoblastic T-cell lymphoma
CD25	Activated T- and B cells and activated macrophages	Adult T-cell leukemia/lymphoma, anaplastic large cell lymphoma, and hairy cell leukemia
CD30	Activated T- and B cells and Reed-Sternberg cells	Classical Hodgkin lymphomas, anaplastic large cell lymphoma, some peripheral T-cell lymphomas, NOS, and some large B-cell lymphomas
CD38	Plasma cells, thymocytes, and activated T cells	Plasma cell neoplasms, B-cell lymphomas with plasmacytic differentiation, and some chronic lymphocytic leukemias/small lymphocytic lymphomas
CD43	T cells, B cell subset, granulocytes, and monocytes and macrophages	T-cell lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, some marginal zone B-cell lymphomas, and Burkitt lymphoma
CD45	Leukocytes	Non-Hodgkin lymphomas and nodular lymphocyte predominant Hodgkin lymphoma
CD45RA	B cells, T-cell subset, granulocytes, and monocytes	B-cell lymphomas and some T-cell lymphomas
CD45RB	B cells, T-cell subset, granulocytes, and monocytes and macrophages	B-cell lymphomas and some T-cell lymphomas
CD45RO	T cells, B-cell subset, granulocytes, and monocytes and macrophages	Most T-cell lymphomas and some diffuse large B-cell lymphomas

Antibody Designation	Reactivity	Examples of Lymphoid Neoplasms
CD56	Natural killer cells and T-cell subset	Natural killer cell lymphomas, some cytotoxic T-cell lymphomas, and plasma cell neoplasms
CD57	Natural killer cells and T-cell subset	Natural killer cell lymphomas, some cytotoxic T-cell lymphomas, and diffuse large B-cell lymphoma with ALK expression (rare)
CD68	Monocytes and macrophages	Histiocytic sarcomas and reactive histiocytes in many lymphomas
CD79a	B cells	Most B-cell lymphomas and plasma cell neoplasms
CD103	Intestinal intraepithelial T cells	Enteropathy-associated T-cell lymphoma and hairy cell leukemia
CD138	Plasma cells	Plasma cell neoplasms and some B-cell lymphomas with plasmacytic differentiation
CD246 (ALK)	Neoplastic cells in anaplastic large cell lymphoma	Most anaplastic large cell lymphomas and diffuse large B-cell lymphoma with ALK expression (rare)
Bcl-2	B-cell subset and T cells	Follicular lymphoma and most other B-cell and T-cell lymphomas
Bcl-6	Follicle center B cells	Follicular lymphoma and some diffuse large B-cell lymphomas
Clusterin	Follicular dendritic cells	Follicular dendritic cell sarcoma, anaplastic large cell lymphoma, and follicular dendritic cell meshworks in angioimmunoblastic T-cell lymphoma
CXCL13	Follicle center T-helper cells	Angioimmunoblastic T-cell lymphoma and nodular lymphocyte predominant Hodgkin lymphoma
Cyclin D1	Neoplastic mantle cells	Mantle cell lymphoma, hairy cell leukemia, and some plasma cell neoplasms
Epithelial membrane antigen	Epithelial cells and plasma cells	Anaplastic large cell lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, plasmablastic lymphoma, and plasma cell neoplasms
Fascin	Follicular dendritic cells, histiocytes, Reed-Sternberg cells, and Epstein-Barr virus-infected immunoblasts	Classical Hodgkin lymphoma, Epstein -Barr virus-positive B-cell and T-cell lymphomas, follicular dendritic cell sarcoma
FoxP3	CD4+/CD25+ regulatory T cells	Adult T-cell leukemia/lymphoma
Granzyme A, B, and M	Natural killer cells and activated cytotoxic T cells	Natural killer cell and activated cytotoxic T-cell lymphomas
IgA, IgD, IgE, IgG, and IgM	Immunoglobulin heavy chains	B-cell lymphomas and plasma cell neoplasms
Kappa and Lambda	Immunoglobulin light chains	B-cell lymphomas and plasma cell neoplasms
Ki-67/mib-1	Nuclear proliferation antigens	
MUM-1	B cells in terminal phase of differentiation, plasma cells, activated T cells, and Reed-Sternberg cells	Lymphoplasmacytic lymphoma, some diffuse large B-cell lymphomas, plasma cell neoplasms, some T-cell lymphomas, and Hodgkin lymphomas
PAX-5	B cells and Reed-Sternberg cells	B-cell lymphomas and Hodgkin lymphomas
T-cell receptor α/β	α/β T cells	Most T-cell lymphomas
T-cell receptor γ/δ	γ/δ T cells	Few T-cell lymphomas
TdT	Lymphoblasts and some myeloblasts	B and T lymphoblastic leukemias/lymphomas
TIA-1	Natural killer cells and cytotoxic T cells	Natural killer cell and cytotoxic T-cell lymphomas

https://oncohemakey.com/diagnosis-and-classification-of-lymphomas/

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Lymph Node

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Lymphoma Type	Growth Pattern	Cytology	CD5	CD10	CD23	Surface Ig	Genetics
Follicular lymphoma	Nodular (follicular)	Lymphocytes with irregular cleaved nuclei (centrocytes) and admixed large cells (centroblasts)	–	+	–	Bright	t(14;18)(q32; q21) in >85%
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Diffuse with proliferation centers	Small lymphocytes with round nuclei and scant cytoplasm	+	–	+	Weak IgM and IgD > IgG > IgA	Trisomy 12 20% to 30%
Lymphoplasmacytic lymphoma	Diffuse or interfollicular	Small lymphocytes, plasma cells, and plasmacytoid lymphocytes	–	–	–	Moderate IgM	MYD88 L265P mutation
Mantle cell lymphoma	Diffuse or vaguely nodular	Small lymphocytes with irregular nuclei, scant cytoplasm, and few admixed large cells	+	–	–	Moderate IgM and IgD; Lambda > kappa	t(11;14)(q13; q32)
Nodal marginal zone B-cell lymphoma	Interfollicular and perisinusoidal	Small lymphocytes with round, folded nuclei and abundant cytoplasm ± plasma cells	–	–	–	Moderate IgM	None
Splenic marginal zone B-cell lymphoma	Nodular	Biphasic: inner core of small lymphocytes with irregular nuclei and scant cytoplasm; outer core of medium-size lymphocytes with round nuclei and abundant clear cytoplasm +/- plasma cells	–	–	–	IgM +/- IgD	Del 7q
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue	Diffuse	Small lymphocytes with round, folded nuclei and abundant cytoplasm ± plasma cells	–	–	–	IgM	Trisomy 3 or t(11;18) (q21; q21)

https://oncohemakey.com/diagnosis-and-classification-of-lymphomas/

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Molecular Genetics and Tumor Markers for Lymphoid Neoplasms

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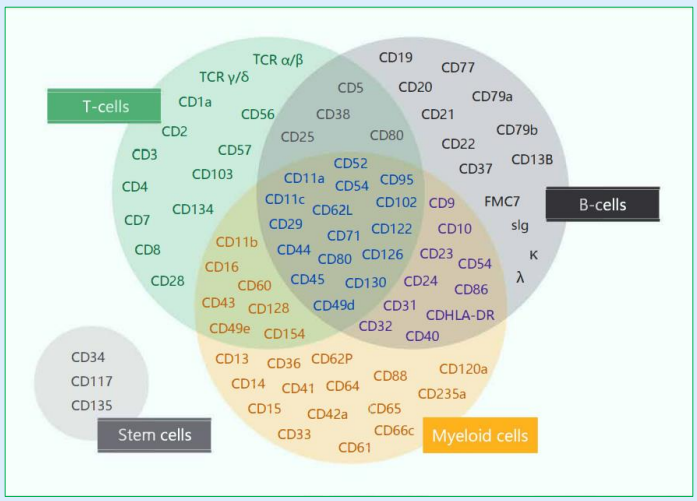

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What about Molecular Pathology

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	Early detection	Cancer diagnosis	Workup	Treatment	Monitoring recurrence	Relapse
Standard of care	Imaging, protein testing (i.e. PSA)	Tissue biopsy	Tissue testing	Late stage: systemic Early stage: curative	Imaging, protein testing (i.e. PSA)	Tissue biopsy
Liquid biopsy opportunity	Early detection of cancer in higher risk individuals		Therapy selection in advanced stage cancer patients		Minimal residual disease and recurrence detection in cancer survivors	
Market size	~ $18 billion (for higher risk individuals)		~$6 billion		~$15 billion	
# of Patients	35 million		0.7 million		15 million	
Products	LUNAR - 2		GUARDANT360 GUARDANTOMNI		LUNAR - 1	

https://www.guardantcomplete.com/guardant-portfolio/cdx

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What about Molecular Pathology

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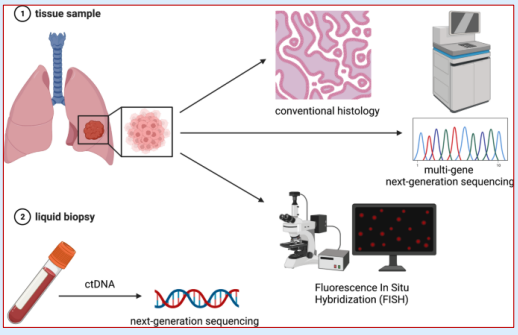

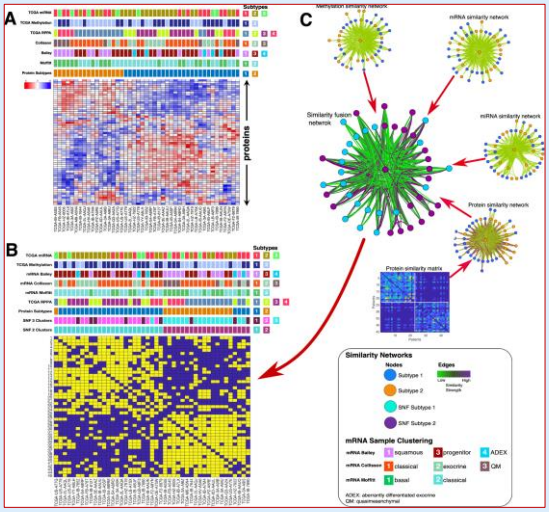

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What about Molecular Pathology

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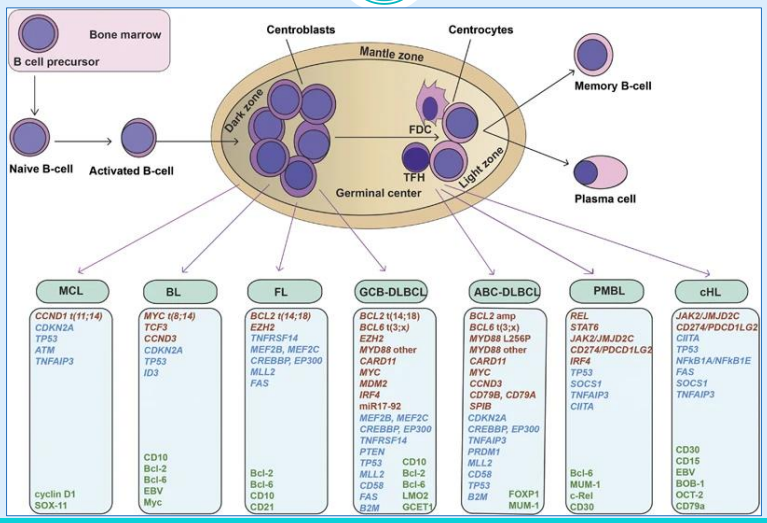

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What about Molecular Pathology

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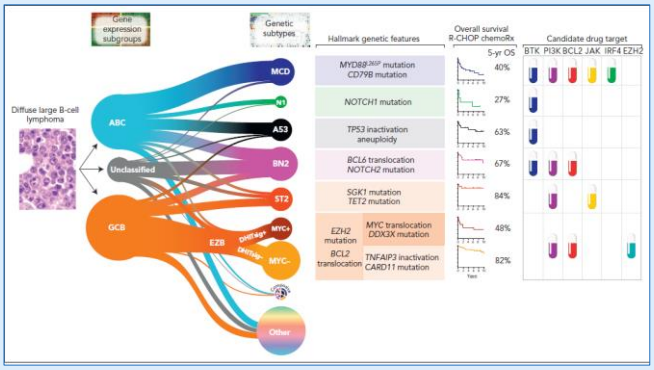
Precursor lymphoid neoplasms

B-cell lymphoblastic leukemia/lymphomas

- B-LBLL with t(9;22)(q34.1;q11.2); *BCR::ABL1*
- B-LBLL with t(v;11q23.3); *KMT2A*-rearranged
- B-LBLL with t(12;21)(p13.2;q22.1); *ETV6::RUNX1*
- B-LBLL with hyperdiploidy, high
- B-LBLL with hypodiploidy, near-haploid
- B-LBLL with hypodiploidy, low
- B-LBLL with hypodiploidy, high
- B-LBLL with t(5;14)(q31.1;q32.3); *IGH::IL3*
- B-LBLL with t(1;19)(q23;p13.3); *TCF3::PBX1*
- B-LBLL, *BCR::ABL1*-like (Philadelphia-like B-ALL)
- B-LBLL with iAMP21



WHO Classification of Pediatric Tumors and BLOOD, 24 NOVEMBER 2022 | VOLUME 140, NUMBER 21

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WHO Classification of Hematolymphoid Tumors, 5th ed

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

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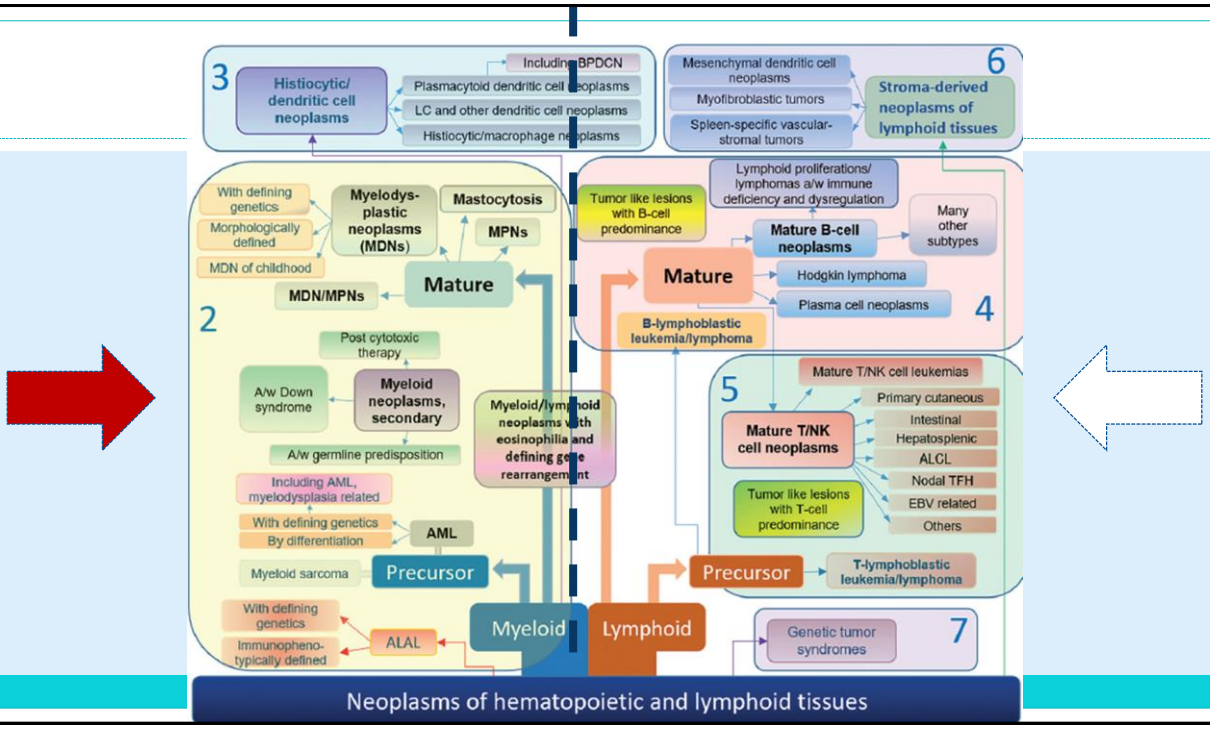

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WHO Classification of Hematolymphoid Tumors, 5th ed

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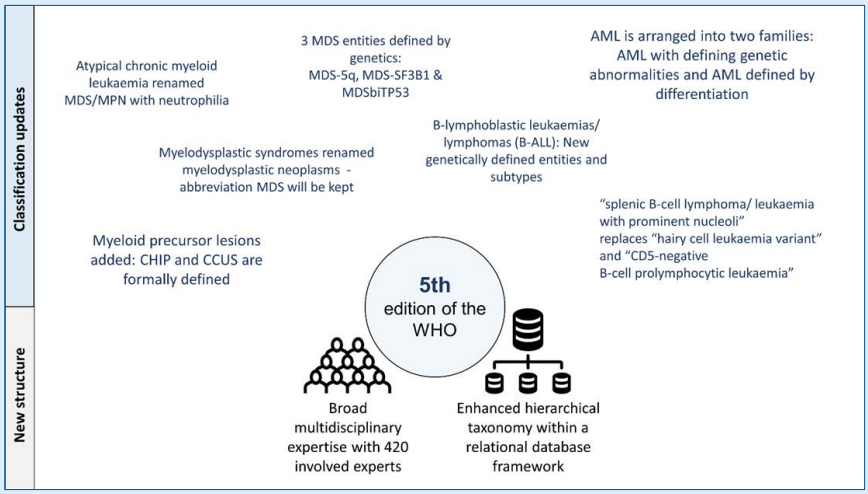

MLL Magazine – http://mll.com/en/the-new-who-classification-2022

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5th WHO Classification of Hematolymphoid Neoplasms

TABLE 4 Revised nomenclature and name changes of myeloid or mesenchymal neoplasms in the 5th edition compared with the revised 4th edition of WHO classification of hematolymphoid tumors

WHO classification, 5th edition	WHO classification, revised 4th edition
Myeloid proliferations and neoplasms	
Chronic myeloid leukemia	Chronic myeloid leukemia, *BCR-ABL1*–positive
Chronic eosinophilic leukemia	Chronic eosinophilic leukemia, not otherwise specified
Myeloproliferative neoplasm, not otherwise specified	Myeloproliferative neoplasm, unclassifiable
Myelodysplastic neoplasms (MDNs)	Myelodysplastic syndromes (MDSs)
MDN, with defining genetic abnormalities	MDS with single lineage dysplasia
MDN with low blasts and 5q deletion	MDS with ring sideroblasts
MDN with low blasts and *SF3B1* mutation	MDS with multilineage dysplasia
MDN with biallelic *TP53* inactivation	MDS with excess blasts
MDN, morphologically defined	MDS with excess blasts and erythroid predominance
MDN with low blasts	MDS with excess blasts and fibrosis
MDN, hypoplastic	MDS with isolated del(5q)
MDN with increased blasts	MDS, unclassifiable
MDNs of childhood	Childhood MDS
Childhood MDN with low blasts	Refractory cytopenia of childhood
Childhood MDN with increased blasts	

TABLE 5 Revised nomenclature and name changes of lymphoid neoplasms in the 5th edition compared with the revised 4th edition of WHO classification of hematolymphoid tumors

WHO classification, 5th edition	WHO classification, revised 4th edition
B-CELL lymphoid proliferations and lymphomas	
B-LBL/L with **high** hyperdiploidy	B-LBL/L with hyperdiploidy
B-LBL/L with *BCR::ABL1* fusion	B-LBL/L with t(9;22)(q34;q11.2); *BCR-ABL1*
B-LBL/L with *BCR::ABL1*-like features	B-LBL/L, *BCR-ABL1*-like
B-LBL/L with *KMT2A* rearrangement	B-LBL/L with t(v;11q23.3); *KMT2A*-rearranged
B-LBL/L with *ETV6:: RUNX1* fusion	B-LBL/L with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-LBL/L with *TCF3::PBX1* fusion	B-LBL/L with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-LBL/L with *IGH::IL3* fusion	B-LBL/L with t(5;14)(q31.1;q32.1); *IGH/IL3*
In situ follicular B-cell **neoplasm**	In situ follicular **neoplasia**
In situ mantle cell **neoplasm**	In situ mantle cell **neoplasia**
DLBCL/ HGBCL with *MYC* and *BCL2* rearrangements	HGBCL with *MYC* and *BCL2* **and/or** *BCL6* rearrangements
High-grade B-cell lymphoma with 11q aberrations	**Burkitt-like** lymphoma with 11q aberration
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, **NOS**
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Table 1. WHO Classification of Haematolymphoid Tumours, 5th edition: B-cell lymphoid proliferations and lymphomas.

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Tumour-like lesions with B-cell predominance	
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma	*Not previously included*
IgG4-related disease	*Not previously included*
Unicentric Castleman disease	*Not previously included*
Idiopathic multicentric Castleman disease	*Not previously included*
KSHV/HHV8-associated multicentric Castleman disease	Multicentric Castleman disease

Tumour like lesions with B-cell predominance

- Introduction
- Reactive B-cell rich lymphoid proliferations that can mimic lymphoma
- IgG4-related disease
- Unicentric Castleman disease
- Idiopathic multicentric Castleman disease
- KSHV/HHV8-associated multicentric Castleman disease

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WHO Classification of Hematolymphoid Tumors, 5th ed

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WHO Classification, 5th edition	WHO Classification, revised 4th edition
Precursor B-cell neoplasms	
B-cell lymphoblastic leukaemias/lymphomas	
B-lymphoblastic leukaemia/lymphoma, NOS	(Same)
B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy	B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
B-lymphoblastic leukaemia/lymphoma with hypodiploidy	(Same)
B-lymphoblastic leukaemia/lymphoma with iAMP21	(Same)
B-lymphoblastic leukaemia/lymphoma with *BCR::ABL1* fusion	B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*
B-lymphoblastic leukaemia/lymphoma with *BCR::ABL1*-like features	B-lymphoblastic leukaemia/lymphoma, *BCR-ABL1*-like
B-lymphoblastic leukaemia/lymphoma with *KMT2A* rearrangement	B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); *KMT2A*-rearranged
B-lymphoblastic leukaemia/lymphoma with *ETV6::RUNX1* fusion	B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukaemia/lymphoma with *ETV6::RUNX1*-like features	*Not previously included*
B-lymphoblastic leukaemia/lymphoma with *TCF3::PBX1* fusion	B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-lymphoblastic leukaemia/lymphoma with *IGH::IL3 fusion*	B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH/IL3*
B-lymphoblastic leukaemia/lymphoma with *TCF3::HLF* fusion	*Not previously included*
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities	(Same)

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Precursor B-cell neoplasms

B-lymphoblastic leukaemias/lymphomas

- Introduction
- B-lymphoblastic leukaemia/lymphoma
- B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy
- B-lymphoblastic leukaemia/lymphoma with hypodiploidy
- B-lymphoblastic leukaemia/lymphoma with iAMP21
- B-lymphoblastic leukaemia/lymphoma with BCR::ABL1 fusion
- B-lymphoblastic leukaemia/lymphoma with BCR::ABL1-like features
- B lymphoblastic leukaemia/lymphoma with KMT2A rearrangement
- B lymphoblastic leukaemia/lymphoma with ETV6::RUNX1 fusion
- B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1-like features
- B lymphoblastic leukaemia/lymphoma with TCF3::PBX1 fusion
- B lymphoblastic leukaemia/lymphoma with IGH::IL3 fusion
- B lymphoblastic leukaemia/lymphoma with TCF3::HLF fusion
- B-lymphoblastic leukaemia/lymphoma with other defined genetic alterations
- B-lymphoblastic leukaemia/lymphoma, NOS

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WHO Classification of Hematolymphoid Tumors, 5th ed

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Mature B-cell neoplasms	
Pre-neoplastic and neoplastic small lymphocytic proliferations	
Monoclonal B-cell lymphocytosis	(Same)
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	(Same)
(Entity deleted)	B-cell prolymphocytic leukaemia
Splenic B-cell lymphomas and leukaemias	
Hairy cell leukaemia	(Same)
Splenic marginal zone lymphoma	(Same)
Splenic diffuse red pulp small B-cell lymphoma	(Same)
Splenic B-cell lymphoma/leukaemia with prominent nucleoli	*Not previously included* (encompassing hairy cell leukaemia variant and some cases of B-cell prolymphocytic leukaemia)
Lymphoplasmacytic lymphoma	
Lymphoplasmacytic lymphoma	(Same)
Marginal zone lymphoma	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	(Same)
Primary cutaneous marginal zone lymphoma	*Not previously included* (originally included under "extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue")
Nodal marginal zone lymphoma	(Same)
Paediatric marginal zone lymphoma	(Same)
Follicular lymphoma	
In situ follicular B-cell neoplasm	In situ follicular neoplasia
Follicular lymphoma	(Same)
Paediatric-type follicular lymphoma	(Same)
Duodenal-type follicular lymphoma	(Same)

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Mature B-cell neoplasms

- Pre-neoplastic and neoplastic small lymphocytic proliferations
  - Introduction
  - Monoclonal B-cell lymphocytosis
  - Chronic lymphocytic leukaemia/small lymphocytic lymphoma
- Splenic B-cell lymphomas and leukaemias
  - Introduction
  - Hairy cell leukaemia
  - Splenic marginal zone lymphoma
  - Splenic diffuse red pulp small B-cell lymphoma
  - Splenic B-cell lymphoma/leukaemia with prominent nucleoli
- Lymphoplasmacytic lymphoma
  - Lymphoplasmacytic lymphoma
- Marginal zone lymphoma
  - Introduction
  - Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
  - Primary cutaneous marginal zone lymphoma
  - Nodal marginal zone lymphoma
  - Paediatric nodal marginal zone lymphoma
- Follicular lymphoma
  - Introduction
  - In situ follicular B-cell neoplasm
  - Follicular lymphoma
  - Paediatric-type follicular lymphoma
  - Duodenal-type follicular lymphoma
- Cutaneous follicle centre lymphoma
  - Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma
  - Introduction
  - In situ mantle cell neoplasm
  - Mantle cell lymphoma

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WHO Classification of Hematolymphoid Tumors, 5th ed

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WHO Classification, 5th edition	WHO Classification, revised 4th edition
Cutaneous follicle centre lymphoma	
Primary cutaneous follicle centre lymphoma	(Same)
Mantle cell lymphoma	
In situ mantle cell neoplasm	In situ mantle cell neoplasia
Mantle cell lymphoma	(Same)
Leukaemic non-nodal mantle cell lymphoma	(Same)
Transformations of indolent B-cell lymphomas	
Transformations of indolent B-cell lymphomas	*Not previously included*

Cutaneous follicle centre lymphoma

- Primary cutaneous follicle centre lymphoma

Mantle cell lymphoma

- Introduction
- In situ mantle cell neoplasm
- Mantle cell lymphoma
- Leukaemic non-nodal mantle cell lymphoma

Transformations of indolent B-cell lymphomas

- Introduction
- Transformations of indolent B-cell lymphomas

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WHO Classification of Hematolymphoid Tumors, 5th ed

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WHO Classification, 5th edition	WHO Classification, revised 4th edition
Large B-cell lymphomas	
Diffuse large B-cell lymphoma, NOS	(Same)
T-cell/histiocyte-rich large B-cell lymphoma	(Same)
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements	High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
ALK-positive large B-cell lymphoma	(Same)
Large B-cell lymphoma with *IRF4* rearrangement	(Same)
High-grade B-cell lymphoma with 11q aberrations	Burkitt-like lymphoma with 11q aberration
Lymphomatoid granulomatosis	(Same)
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS
Diffuse large B-cell lymphoma associated with chronic inflammation	(Same)
Fibrin-associated large B-cell lymphoma	*Not previously included* (Previously considered a subtype of diffuse large B-cell lymphoma associated with chronic inflammation)
Fluid overload-associated large B-cell lymphoma	*Not previously included*
Plasmablastic lymphoma	(Same)
Primary large B-cell lymphoma of immune-privileged sites	*Not previously included*, encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4th edition (*plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis*)
Primary cutaneous diffuse large B-cell lymphoma, leg type	(Same)
Intravascular large B-cell lymphoma	(Same)
Primary mediastinal large B-cell lymphoma	(Same)
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma
High-grade B-cell lymphoma, NOS	(Same)

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Large B-cell lymphomas
Introduction
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma / high grade B-cell lymphoma with MYC and BCL2 rearrangements
ALK-positive large B-cell lymphoma
Large B-cell lymphoma with IRF4 rearrangement
High grade B-cell lymphoma with 11q aberrations
Lymphomatoid granulomatosis
EBV-positive diffuse large B-cell lymphoma
Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated large B-cell lymphoma
Fluid overload-associated large B-cell lymphoma
Plasmablastic lymphoma
Primary large B-cell lymphoma of immune-privileged sites
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Primary mediastinal large B-cell lymphoma
Mediastinal grey zone lymphoma
High-grade B-cell lymphoma, NOS

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Virus-Associated Lymphoid Neoplasms

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Infectious Agents Associated with the Development of Lymphoid Malignancies	
Infectious Agent	**Lymphoid Malignancy**
Epstein-Barr virus	Burkitt's lymphoma Post–organ transplant lymphoma Primary CNS diffuse large B cell lymphoma Hodgkin's disease Extranodal NK/T cell lymphoma, nasal type
HTLV-I	Adult T cell leukemia/lymphoma
HIV	Diffuse large B cell lymphoma Burkitt's lymphoma
Hepatitis C virus	Lymphoplasmacytic lymphoma
Helicobacter pylori	Gastric MALT lymphoma
HHV 8	Primary effusion lymphoma Multicentric Castleman's disease

Harrison's Principles of Internal Medicine, 17th Edition

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WHO Classification of Hematolymphoid Tumors, 5th ed

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WHO Classification, 5th edition	WHO Classification, revised 4th edition
Burkitt lymphoma	
Burkitt lymphoma	(Same)
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas	
Primary effusion lymphoma	(Same)
KSHV/HHV8-positive diffuse large B-cell lymphoma	HHV8-positive diffuse large B-cell lymphoma, NOS
KSHV/HHV8-positive germinotropic lymphoproliferative disorder	HHV8-positive germinotropic lymphoproliferative disorder
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation	
Hyperplasias arising in immune deficiency/dysregulation	*Not previously included,* encompassing non-destructive post-transplant lymphoproliferative disorders, among others
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation	*Not previously included,* encompassing polymorphic posttransplant lymphoproliferative disorders, other iatrogenic immunodeficiency-associated lymphoproliferative disorders, among others
EBV-positive mucocutaneous ulcer	(Same)
Lymphomas arising in immune deficiency / dysregulation	*Not previously included,* encompassing monomorphic posttransplant lymphoproliferative disorders, classic Hodgkin lymphoma posttransplant lymphoproliferative disorders, lymphomas associated with HIV infection, among others
Inborn error of immunity-associated lymphoid proliferations and lymphomas	Lymphoproliferative diseases associated with primary immune disorders

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Hodgkin lymphoma	
Classic Hodgkin lymphoma	(Same)
Nodular lymphocyte predominant Hodgkin lymphoma	(Same)

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Burkitt lymphoma
Burkitt lymphoma

KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas
Introduction
Primary effusion lymphoma
KSHV/HHV8-positive diffuse large B-cell lymphoma
KSHV/HHV8-positive germinotropic lymphoproliferative disorder

Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation
Introduction
Hyperplasia arising in immune deficiency/dysregulation
Polymorphic lymphoproliferative disorders arising in immune deficiency / dysregulation
EBV-positive mucocutaneous ulcer
Lymphomas arising in immune deficiency / dysregulation
Inborn error of immunity-associated lymphoid proliferations and lymphomas

Hodgkin lymphoma
Introduction
Classic Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma

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WHO Classification of Hematolymphoid Tumors, 5th ed

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WHO Classification, 5th edition	WHO Classification, revised 4th edition
Plasma cell neoplasms and other diseases with paraproteins	
Monoclonal gammopathies	
Cold agglutinin disease	*Not previously included*
IgM monoclonal gammopathy of undetermined significance	(Same)
Non-IgM monoclonal gammopathy of undetermined significance	(Same)
Monoclonal gammopathy of renal significance	*Not previously included*
Diseases with monoclonal immunoglobulin deposition	
Immunoglobulin-related (AL) amyloidosis	Primary amyloidosis
Monoclonal immunoglobulin deposition disease	Light chain and heavy chain deposition disease
Heavy chain diseases	
Mu heavy chain disease	(Same)
Gamma heavy chain disease	(Same)
Alpha heavy chain disease	(Same)
Plasma cell neoplasms	
Plasmacytoma	(Same)
Plasma cell myeloma	(Same)
Plasma cell neoplasms with associated paraneoplastic syndrome -POEMS syndrome -TEMPI syndrome -AESOP syndrome	(Same) Except AESOP syndrome *not previously included*

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Plasma cell neoplasms and other diseases with paraproteins
- Introduction
- Monoclonal gammopathies
  - Cold agglutinin disease
  - IgM monoclonal gammopathy of undetermined significance
  - Non-IgM monoclonal gammopathy of undetermined significance
  - Monoclonal gammopathy of renal significance
- Diseases with monoclonal immunoglobulin deposition
  - Immunoglobulin-related (AL) amyloidosis
  - Monoclonal immunoglobulin deposition disease
- Heavy chain diseases
  - Introduction
  - Mu heavy chain disease
  - Gamma heavy chain disease
  - Alpha heavy chain disease
- Plasma cell neoplasms
  - Introduction
  - Plasmacytoma
  - Plasma cell myeloma / multiple myeloma
  - Plasma cell neoplasms with associated paraneoplastic syndrome

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"Overlap Lymphoid Syndromes" – Number of Primaries

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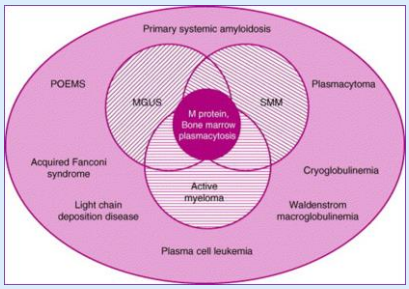

- Malignant plasma cells produce monoclonal immunoglobulin and invade and destroy bone.
- Expanding plasmacytomas and cytokine secretion cause multiple, discrete, osteolytic lesions (usually in the pelvis, spine, ribs, and skull) and diffuse osteoporosis; pain, fractures, and hypercalcemia are common.
- Anemia and renal failure are common.
- Amyloidosis develops in about 10%, typically patients who produce excess lambda light chains
- Do serum and urine protein electrophoresis followed by immunofixation, quantitative immunoglobulins, and measurement of serum free light chains.
- Do bone marrow aspiration and biopsy.
- Symptomatic patients and those with organ dysfunction should be treated with drug therapy, which may include corticosteroids, chemotherapy drugs, proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, selective inhibitors of nuclear export, histone deacetylase inhibitors, and cellular and antibody-based immune therapies targeting B-cell maturation antigen.
- Stem cell transplantation is an option for some patients, but newer, highly effective treatment options may make it unnecessary in others.

https://www.merckmanuals.com/professional/hematology-and-oncology/lymphomas/non-hodgkin-lymphomas

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Establishing a Diagnosis – Some are Easy

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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]		
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 (detected by an FDA	

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Establishing a Diagnosis – Some not as easy.

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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]	
Multiple myeloma (MM) MM-NOS MM with recurrent genetic abnormality MM with CCND family translocation MM with MAF family translocation MM with *NSD2* translocation MM with hyperdiploidy	t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; t(11;14) *CCND1*::IGH;*,§ gain of odd numbered chromosomes: FISH on bone marrow plasma cells (CD138-positive selected sample strongly recommended)*	Diagnostic of the ICC subtypes of MM	t(11;14) predictive of response to venetoclax[134]	WGS for subtype assignment, risk stratification, and decision making MRD using HTS for decision making
	t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; amp(1q); del(1p), del(17p)*; *TP53* mutations[464] For SMM: t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; 1q gain/amplification; del(13)[145] and *MYC* rearrangement[139]: FISH and HTS	Risk stratification at diagnosis and relapse	The adverse prognosis of high-risk genetics is partially overcome by the addition of a proteasome inhibitor[131] and/or anti-CD38 MoAb[132] to first-line therapy	

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Establishing a Diagnosis – Even CLL has options now

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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	

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Establishing a Diagnosis – One more example

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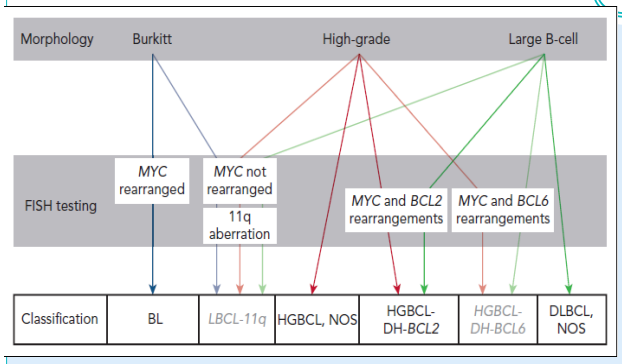

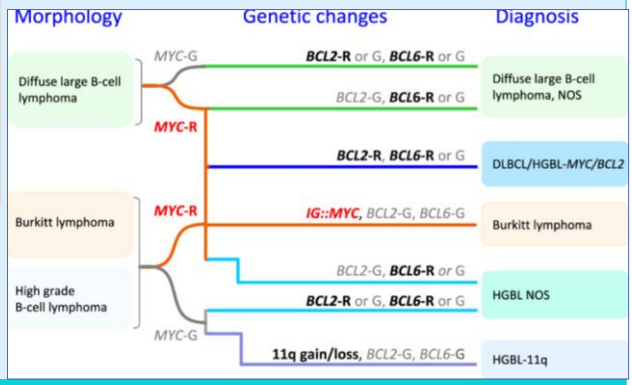

WHO Classification of Hematolymphoid Neoplasms, 5th edition – Chapter 1

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Demonstration Hematopoietic Manual and Hematopoietic Data Base

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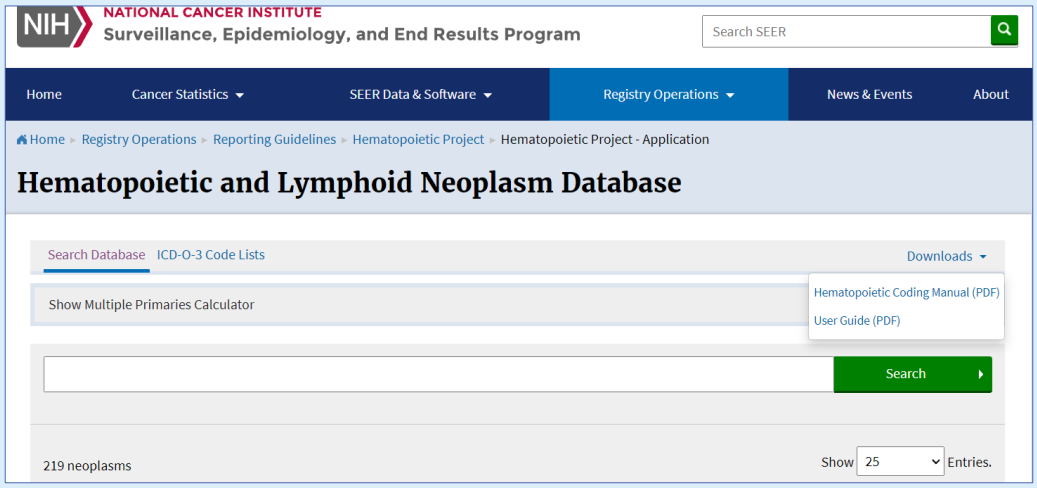

67

Diagnostic Confirmation for Lymphoid Neoplasms

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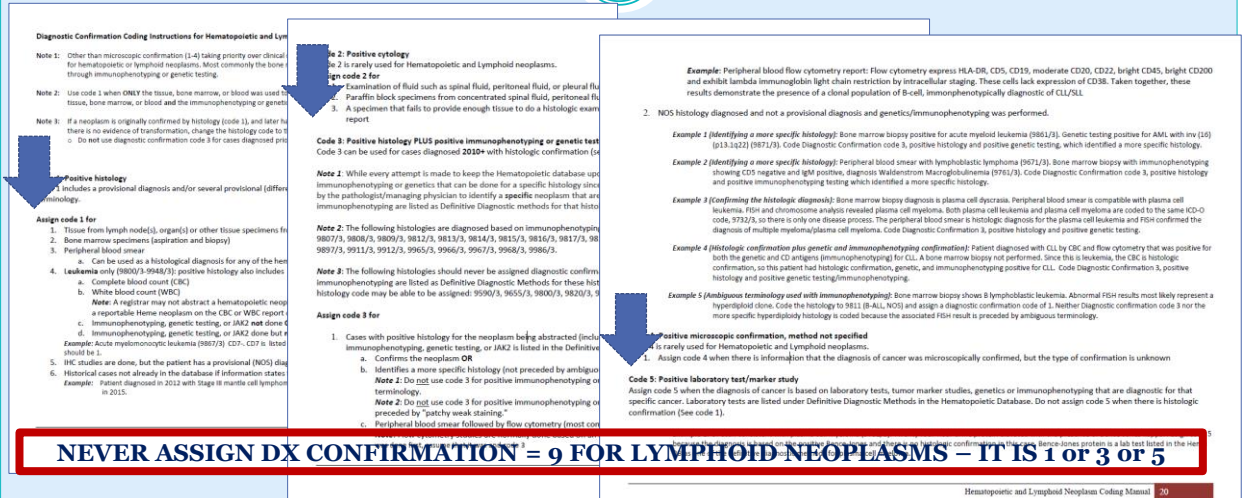

NEVER ASSIGN DX CONFIRMATION = 9 FOR LYMPHOID NEOPLASMS – IT IS 1 or 3 or 5

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Diagnostic Confirmation for Lymphoid Neoplasms

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- Note 1: Other than microscopic confirmation (1-4) taking priority over clinical diagnosis only (5-8), there is no priority order or hierarchy for coding the Diagnostic Confirmation for hematopoietic or lymphoid neoplasms. Most commonly the bone marrow provides several provisional diagnoses and the specific histologic type is determined through immunophenotyping or genetic testing.
- Note 2: Use code 1 when ONLY the tissue, bone marrow, or blood was used to diagnose the specific histology. Do not use code 1 if the provisional diagnosis was based on tissue, bone marrow, or blood and the immunophenotyping or genetic testing on that same tissue, bone marrow, or blood identified the specific disease (see Code 3).
- Note 3: If a neoplasm is originally confirmed by histology (code 1), and later has immunophenotyping, genetic testing or JAK2 which confirms a more specific neoplasm and there is no evidence of transformation, change the histology code to the more specific neoplasm and change the diagnostic confirmation to code 3.
- Do not use diagnostic confirmation code 3 for cases diagnosed prior to 1/1/2010.

NEVER ASSIGN DX CONFIRMATION = 9 FOR LYMPHOID NEOPLASMS – IT IS 1 or 3 or 5

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Diagnostic Confirmation for Lymphoid Neoplasms

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Assign code 1 for

1. Tissue from lymph node(s), organ(s) or other tissue specimens from biopsy, frozen section, surgery, or autopsy
2. Bone marrow specimens (aspiration and biopsy)
3. Peripheral blood smear
   a. Can be used as a histological diagnosis for any of the hematopoietic histologies (9590/3-9993/3)
4. **Leukemia** only (9800/3-9948/3): positive histology also includes
   a. Complete blood count (CBC)
   b. White blood count (WBC)
   Note: A registrar may not abstract a hematopoietic neoplasm based on a CBC or WBC with abnormal counts alone. There must be a diagnosis of a reportable Heme neoplasm on the CBC or WBC report or a subsequent physician diagnosis based on the WBC or CBC.
   c. Immunophenotyping, genetic testing, or JAK2 **not** done **OR**
   d. Immunophenotyping, genetic testing, or JAK2 done but **negative** (non-diagnostic) for the neoplasm being abstracted

   Example: Acute myelomonocytic leukemia (9867/3) CD7-. CD7 is listed under Immunophenotyping for this histology and this case is CD7-, so diagnostic confirmation should be 1.
5. IHC studies are done, but the patient has a provisional (NOS) diagnosis or one or more provisional diagnoses.
6. Historical cases not already in the database if information states that there was histologic confirmation

   Example: Patient diagnosed in 2012 with Stage III mantle cell lymphoma, diagnosed by LN biopsy. Mantle cell lymphoma not in the database. Now presents with DLBCL in 2015.

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Diagnostic Confirmation for Lymphoid Neoplasms

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Code 3: Positive histology PLUS positive immunophenotyping or genetic testing
Code 3 can be used for cases diagnosed **2010+** with histologic confirmation (see code 1) **AND** immunophenotyping, genetic testing, or JAK2 confirmation

Note 1: While every attempt is made to keep the Hematopoietic database updated, it is impossible to keep the Hematopoietic database updated with all the immunophenotyping or genetics that can be done for a specific histology since clinical medicine continues to evolve. If immunophenotyping or genetics is used by the pathologist/managing physician to identify a **specific** neoplasm that are not included in the Hematopoietic database, and genetic testing and/or immunophenotyping are listed as Definitive Diagnostic methods for that histology, go ahead and use these.

Note 2: The following histologies are diagnosed based on immunophenotyping or genetics and therefore should only be diagnostic confirmation 3: 9806/3, 9807/3, 9808/3, 9809/3, 9812/3, 9813/3, 9814/3, 9815/3, 9816/3, 9817/3, 9818/3, 9819/3, 9865/3, 9866/3, 9867/3, 9869/3, 9870/3, 9871/3, 9872/3, 9873/3, 9875/3, 9876/3, 9879/3, 9896/3, 9897/3, 9911/3, 9912/3, 9965/3, 9966/3, 9967/3, 9968/3, 9986/3.

Note 3: The following histologies should never be assigned diagnostic confirmation 3 since they are non specific codes and neither genetic testing or immunophenotyping are listed as Definitive Diagnostic Methods for these histologies. If there is immunophenotyping or genetics available, then a more specific histology code may be able to be assigned: 9590/3, 9655/3, 9800/3, 9820/3, 9860/3, 9863/3, 9980/3, 9982/3, 9989/3, 9991/3.

DO NOT USE DX CONFIRMATION = 3 FOR ANY SOLID TUMORS – ONLY MYELOID/LYMPHOID NEOPLASMS

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Diagnostic Confirmation for Lymphoid Neoplasms

Assign code 3 for

1. Cases with positive histology for the neoplasm being abstracted (including acceptable ambiguous terminology and provisional diagnosis) **AND** immunophenotyping, genetic testing, or JAK2 is listed in the Definitive Diagnosis in the Heme DB **AND** the testing
   a. Confirms the neoplasm **OR**
   b. Identifies a more specific histology (not preceded by ambiguous terminology)
      Note 1: Do not use code 3 for positive immunophenotyping or genetic testing identifying a more specific histology when preceded by ambiguous terminology.
      Note 2: Do not use code 3 for positive immunophenotyping or genetic testing identifying a more specific histology when the test result is preceded by "patchy weak staining."
   c. Peripheral blood smear followed by flow cytometry (most commonly done with CLL/SLL, 9823/3)
      Note: Flow cytometry studies are normally done based on an abnormal blood smear. If unable to find documentation that a peripheral blood smear was done first, assume that it was and code 3

   Example: Peripheral blood flow cytometry report: Flow cytometry express HLA-DR, CD5, CD19, moderate CD20, CD22, bright CD45, bright CD200 and exhibit lambda immunoglobin light chain restriction by intracellular staging. These cells lack expression of CD38. Taken together, these results demonstrate the presence of a clonal population of B-cell, immonphenotypically diagnostic of CLL/SLL

2. NOS histology diagnosed and not a provisional diagnosis and genetics/immunophenotyping was performed.

Example 1 (Identifying a more specific histology): Bone marrow biopsy positive for acute myeloid leukemia (9861/3). Genetic testing positive for AML with inv (16) (p13.1q22) (9871/3). Code Diagnostic Confirmation code 3, positive histology and positive genetic testing, which identified a more specific histology.

Example 2 (Identifying a more specific histology): Peripheral blood smear with lymphoblastic lymphoma (9671/3). Bone marrow biopsy with immunophenotyping showing CD5 negative and IgM positive, diagnosis Waldenstrom Macroglobulinemia (9761/3). Code Diagnostic Confirmation code 3, positive histology and positive immunophenotyping testing which identified a more specific histology.

Example 3 (Confirming the histologic diagnosis): Bone marrow biopsy diagnosis is plasma cell dyscrasia. Peripheral blood smear is compatible with plasma cell leukemia. FISH and chromosome analysis revealed plasma cell myeloma. Both plasma cell leukemia and plasma cell myeloma are coded to the same ICD-O code, 9732/3, so there is only one disease process. The peripheral blood smear is histologic diagnosis for the plasma cell leukemia and FISH confirmed the diagnosis of multiple myeloma/plasma cell myeloma. Code Diagnostic Confirmation 3, positive histology and positive genetic testing.

Example 4 (Histologic confirmation plus genetic and immunophenotyping confirmation): Patient diagnosed with CLL by CBC and flow cytometry that was positive for both the genetic and CD antigens (immunophenotyping) for CLL. A bone marrow biopsy not performed. Since this is leukemia, the CBC is histologic confirmation, so this patient had histologic confirmation, genetic, and immunophenotyping positive for CLL. Code Diagnostic Confirmation 3, positive histology and positive genetic testing/immunophenotyping.

Example 5 (Ambiguous terminology used with immunophenotyping): Bone marrow biopsy shows B lymphoblastic leukemia. Abnormal FISH results most likely represent a hyperdiploid clone. Code the histology to 9811 (B-ALL, NOS) and assign a diagnostic confirmation code of 1. Neither Diagnostic confirmation code 3 nor the more specific hyperdiploidy histology is coded because the associated FISH result is preceded by ambiguous terminology.

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Diagnostic Confirmation for Lymphoid Neoplasms

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DX CONFIRMATION = 5 CAN ONLY BE USED IN PLASMA CELL MYELOMA (9732/3)

Code 5: Positive laboratory test/marker study
Assign code 5 when the diagnosis of cancer is based on laboratory tests, tumor marker studies, genetics or immunophenotyping that are diagnostic for that specific cancer. Laboratory tests are listed under Definitive Diagnostic Methods in the Hematopoietic Database. Do not assign code 5 when there is histologic confirmation (See code 1).

Example 1: CT scan consistent with plasma cell myeloma (9732/3). Twenty-four-hour urine protein elevated with the presence of Bence-Jones kappa. Assign code 5 because the diagnosis is based on the positive Bence-Jones and there is no histologic confirmation in this case. Bence-Jones protein is a lab test listed in the Heme DB as one of the definitive diagnostic methods for plasma cell myeloma.

Note: Do not use this code when a peripheral blood smear is done (which qualifies for a code 1) or a peripheral blood smear followed by flow cytometry (which qualifies for a code 3). Flow cytometry studies are normally done based on an abnormal peripheral blood smear. If unable to find documentation that a peripheral blood smear was done first, assume that it was and code 3

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Case Example One

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Patient has elevated WBC. Workup shows lymphocytosis. Pt just had Covid infection. Further workup shows nodes above and below diaphragm and splenomegaly. Then BX and Immunophenotype Panel shows CD5 positive B-cell lymphoma – gives some information but not enough to subclassify further than B-cell lymphoma.

The expression of CD5 on B-cell neoplasms is classically indicative of either chronic lymphocytic leukemia (CLL), an indolent neoplasm, or mantle cell lymphoma (MCL), a usually aggressive lymphoma. Further testing needs to be done to rule out low grade indolent or high grade aggressive CD5 positive B-cell lymphoma. Knowing the difference determines treatment plan.

The path actually had listed more than just CD5 positive B-cell lymphoma. It also included LARGE MONOCLONAL B CELLS POSITIVE FOR CD5, CD19, CD20 (DIM), CD22, CD23, FMC 7, HLA-DR AND KAPPA DIM).

Using the Heme DB. How to do LookUp. You can cut off the CD numbers and just enter them into the Heme DB or just into Google and it pulls up – CLL/SLL – and the path says immunophenotypically suggestive of CLL/SLL (78%). And, they decided to just follow the patient with close observation (active surveillance) – it should be low grade.

So, this clears up the histology code - it is CLL/SLL, not a new type or genetic variant of mature b-cell neoplasms – but, it does differentiate between low/high grade & tx planning for stage III lymphoma.

- CLL/SLL is positive for CD5, CD19, CD23, CD43, and CD200, with dim expression of CD20, CD22, CD79b.
- MCL is positive for CD5, CD19, CD20, CD22, CD79b, kappa, and negative for CD23, CD43, and CD200.

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Case Example Two

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Patient has right groin node enlarge growing larger with no response to antibiotics. CT Scans not available. PET Scan shows update along right ilium and right pelvic soft tissue. Right inguinal large mass SUV of 33.2. Uptake concerning for malignancy involving ileum and adjacent soft tissue as well as adenopathy extending to superficial inguinal regional and along posterior pelvic soft tissues & fat.

Biopsy 3cm inguinal node shows B-CELL LYMPHOMA, CD10 POSITIVE DIFFUSE LARGE B-CELL LYPHOMA COMMENT: THE CD10 POSITIVITY FAVORS A DIFFUSE FOLLICULAR CENTER CELL LYMPHOMA. Bone marrow and flow cytometry show no monoclonal lymphoid population, no population w/aberrant immunophenotype and no increased plasma cells – no involvement by Non-Hodgkin Lymphoma. Peripheral blood – no circulating blasts.

DX Confirmation = 3
Primary site C77.8 multiple lymph node regions
Histology – DLBCL is the most common B-cell lymphoma. Diffuse follicular center cell is more specific in CD10-positive. So we code to 9698/3 follicular lymphoma, grade 3 as high-grade subtype of DLBCL
Stage IV – distant - involves ileum and adjacent soft tissue, superficial inguinal node, pelvic soft tissue
Treatment – R-CHOP and proton beam radiation to pelvis 45 CGY

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Case Example Three

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MRI right hip: diffuse osseous metastasis involving imaged bones, most pronounced in rt iliac wing w/ associated extraosseous soft tissue component.
PET/CT: multifocal osseous malignancy suggestive of diffuse metastatic disease. Likely pathologic fracture T8 with paraspinal soft tissue mass.
Bone marrow Bx: normocellular marrow w/ trilineage hematopoiesis, and marked involvement by plasma cell myeloma (PCM)(~50% involvement).

COMMENT: flow cytometry with no monoclonal B cells, aberrant T cells or increase in blasts.
Cytogenetic Study with no female karyotype.
FISH myeloma studies positive for hyperdiploidy, gains of 1q, deletion of 13q or monosomy 13, and atypical signals suggestive of IgH rearrangement or partial IgH gain.

Final Synoptic DX: Chest wall bx shows features compatible with plasmacytoma.

Treatment with Velcade, Revlimid, Dexamethasone and XRT photon beam to T-spine.
Recommend Stem Cell Transplant post high dose chemo to increase potential for durable response

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Case Example Four

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Bone Survey: Multiple lytic lesions are seen in the calvarium consistent with the diagnosis of multiple myeloma.

Bone Marrow BX - plasma cell myeloma; high risk cytogenetics - normal female karyotype

Where are the cytogenetics test results? Including the phrase 'high-risk cytogenetics' is no help at all.

We must have the details even when you have the bone marrow dx and the bone survey dx of MM.

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Workup and Staging Lymphoid Neoplasms

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- Physical Exam
- Complete blood cell (CBC) count & Serum Chemistry
- Serum beta2-microglobulin
- Immunoglobulins Test – IgG, IgM, IgA
- Immunoelectrophoresis
- Bence-Jones protein – serum or urine
- Chest radiography
- Bone Survey – osteolytic bone lesions
- CT scan of the neck, chest, abdomen, and pelvis
- Positron emission tomography (PET) - PET/CT or FDG/PET
- Excisional lymph node biopsy
- Bone marrow aspirate and biopsy
- Hepatitis B testing in patients in whom rituximab therapy is planned
- Histology – biopsy or resection
- Flow Cytometry – lineage and clonality
- Immunophenotypic Analysis - lineage and clonality
- Molecular Analysis – FISH test samples of tissue, blood, or bone marrow in a laboratory to look for changes in chromosomes, including broken, missing, rearranged, or extra chromosomes.
- Staging – Stage I-IV
- Extra-lymphatic Involvement
  - Lung
  - Liver
  - Pleura
  - Bone
  - Bone Marrow
  - Skin
- Extranodal Lymphoid Malignancy
- IPI and FLIPI – International Prognostic Indices

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Staging Lymphoid Neoplasms

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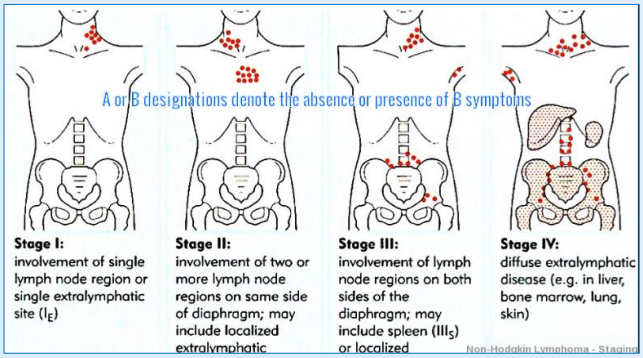
- Hodgkin Lymphoma
- Non-Hodgkin Lymphoma
- Extra-Nodal lymphoma
- Plasma Cell Neoplasms
- CLL/SLL
- ALL



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Modified Ann Arbor Staging

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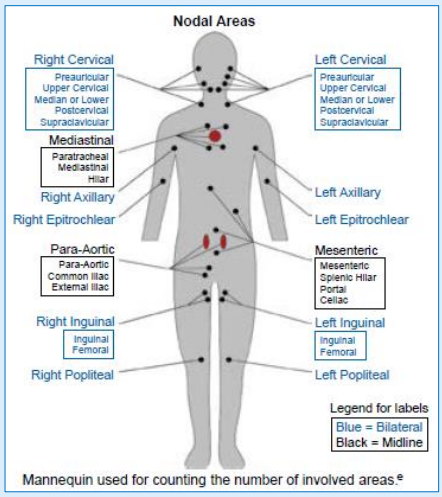

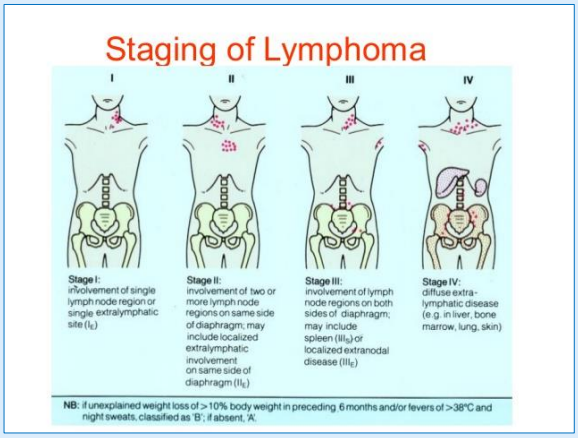

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CLL/SLL – RAI Staging System

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RAI Staging System for CLL/SLL – 1968

- **Rai stage 0:** Lymphocytosis and no enlargement of the lymph nodes, spleen, or liver, and with near normal red blood cell and platelet counts.
- **Rai stage I:** Lymphocytosis plus enlarged lymph nodes. The spleen and liver are not enlarged and the red blood cell and platelet counts are near normal.
- **Rai stage II:** Lymphocytosis plus an enlarged spleen (and possibly an enlarged liver), with or without enlarged lymph nodes. The red blood cell and platelet counts are near normal.
- **Rai stage III:** Lymphocytosis plus anemia (too few red blood cells), with or without enlarged lymph nodes, spleen, or liver. Platelet counts are near normal.
- **Rai stage IV:** Lymphocytosis plus thrombocytopenia (too few blood platelets), with or without anemia, enlarged lymph nodes, spleen, or liver.

- Stage 0 is considered low risk.
- Stages I and II are considered intermediate risk.
- Stages III and IV are considered high risk.

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Staging Extra-Nodal/Extra-Lymphatic Lymphoid Neoplasms

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SUMMARY STAGE

1 Localized only

Nodal Lymphomas

- Single lymph node region involved
- Involvement of multiple contiguous lymph node regions in the SAME lymph node region

Extranodal Lymphomas

- Single extralymphatic site
  - WITHOUT nodal involvement (see code 2 for WITH nodal involvement)
- Multifocal involvement of one extralymphatic organ/site (EXCEPT multifocal lung involvement or any liver involvement, see code 7)
  - WITHOUT nodal involvement (see code 7 for WITH nodal involvement)

2 Regional by direct extension only

Bulky disease present

Nodal Lymphomas

- Two or more lymph node regions involved SAME side of diaphragm
- Contiguous extension between extralymphatic sites and regional nodes
  - WITH or WITHOUT involvement of other nodal regions on SAME side of diaphragm

Extranodal Lymphomas

- Localized involvement of a single extralymphatic organ/site
  - WITH involvement of its regional lymph node(s) OR
  - WITH involvement of other lymph node(s) on the SAME side of the diaphragm

7 Distant site(s)/lymph node(s) involved

- Distant involvement
  - Diffuse or disseminated involvement of ONE OR MORE extralymphatic organ(s)/site(s) WITH or WITHOUT nodal involvement
  - Involvement of isolated extralymphatic organ in absence of involvement of adjacent lymph nodes, but in conjunction with disease in distant sites
  - Involvement of lymph node regions on BOTH sides of the diaphragm WITH or WITHOUT spleen involvement
  - Involvement of lymph node regions ABOVE the diaphragm WITH spleen involvement
  - Multifocal involvement of one extralymphatic organ/site WITH nodal involvement
  - Noncontiguous extralymphatic organ involvement in conjunction with nodal disease (two or more sites involved)
- Distant metastasis, NOS
  - Blood/peripheral blood
  - Bone marrow
  - Cerebrospinal fluid (CSF)
  - Liver
  - Lung (other than by direct extension in code 2)

9 Unknown if extension or metastasis

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Staging Extra-Nodal/Extra-Lymphatic Lymphoid Neoplasms

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Table 1: Ann Arbor staging system for extranodal lymphomas

Stage	*Area of involvement*
IE	One extralymphatic site involvement
IIE	One extralymphatic organ and one or more lymph node regions involvement on the same side of the diaphragm
IIIE	One extralymphatic organ and lymph node regions involvement on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extralymphatic organs, including any involvement of the liver, bone marrow or nodular involvement of the lungs

Adapted Ann Arbor System[1]	Lugano System[2]	Paris System[3]	Areas Involved*
IE1	I_1	T1 N0 M0	Mucosa to submucosa
IE2	I_2	T2 N0 M0	To muscularis propria or subserosa
		T3 N0 M0	To serosa
	IIE	T4 N0 M0	To adjacent organs
IIE1	II_1	T1-4 N1 M0	Regional lymph nodes†
IIE2	II_2	T1-4 N2 M0	Non-regional abdominal lymph nodes
IIIE	IV	T1-4 N3 M0	Extra-abdominal lymph nodes
IV		T1-4 N0-3 M1 B1	Distant organs Bone marrow

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Gastric MALT Lymphoma – Modified Ann Arbor Staging

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STAGING OF GASTRIC MALT LYMPHOMA: COMPARISON OF DIFFERENT SYSTEMS

Lugano Staging System for Gastrointestinal Lymphomas		Lugano Modification of Ann Arbor Staging System	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension
Stage I_E	Confined to GI tract[a]			
	I_{E1} = mucosa, submucosa	I_E	T1 N0 M0	Mucosa, submucosa
	I_{E2} = muscularis propria, serosa	I_E	T2 N0 M0	Muscularis propria
		I_E	T3 N0 M0	Serosa
Stage II_E	Extending into abdomen			
	II_{E1} = local nodal involvement	II_E	T1-3 N1 M0	Perigastric lymph nodes
	II_{E2} = distant nodal involvement	II_E	T1-3 N2 M0	More distant regional lymph nodes
Stage II_E	Penetration of serosa to involve adjacent organs or tissues	II_E	T4 N0 M0	Invasion of adjacent structures
Stage IV[b]	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement		T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/ distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

Zucca E, Bertoni F, Yahalom J, Isaacson P. Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT lymphoma) in Armitage et al eds. Non-Hodgkin's Lymphomas. Philadelphia: Lippincott, 2010:242. (http://lww.com)

84

Staging Mycosis Fungoides

85

SUMMARY STAGE

1 Localized only (localized, NOS)

- MFCG Stage I
  - Less than 10% of skin surface, no tumors
  - Limited to patches, papules, or plaques
- MFCG Stage II
  - Greater than or equal to 10% of skin surface, no tumors
  - Generalized patches, papules, or plaques
- Not stated whether patches, papules, or plaques
  - % of body surface not stated, no tumors
  - Skin involvement, NOS: extent not stated, no tumors

2 Regional by direct extension only

- MFCG Stage III
  - Cutaneous tumor, size not stated
  - Generalized erythroderma (confluence of erythemia)
    - (greater than 50% of body involved with diffuse redness)
  - One or more tumors equal to 1 cm or greater
  - Sezary syndrome
  - Skin lesion described as tumor less than 1 cm

3 Regional lymph node(s) involved only

- Both clinically enlarged palpable lymph node(s) (adenopathy) AND
  - pathologically positive nodes
- Clinically enlarged palpable lymph node(s) (adenopathy) AND
  - either pathologically negative nodes or no pathological statement
- No clinically enlarged palpable lymph node(s) (adenopathy) BUT
  - pathologically positive lymph node(s)
- Dutch grade 1-4 OR NCI LN 0-4
  - Clone positive, negative or unknown
- Regional lymph node(s), NOS
  - Lymph node(s), NOS

4 Regional by BOTH direct extension AND regional lymph node(s) involved

- Codes (2) + (3)

7 Distant site(s) involved

- Distant site(s) (including further contiguous extension)
  - MFCG Stage IV
    - Bone marrow
    - Involvement by at least one organ outside the skin, nodes, blood, or bone marrow
    - Liver
    - Spleen
    - Visceral (non-cutaneous, extranodal) involvement, pathologically confirmed
- Distant metastasis, NOS
  - Carcinomatosis

9 Unknown if extension or metastasis

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Staging Primary Cutaneous Lymphoma

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SUMMARY STAGE

1 Localized only

- Solitary lesion
- Solitary skin involvement

2 Regional by direct extension only

- Multiple lesions confined to one or two contiguous body regions
- Multiple lesions, NOS
- Regional skin involvement

3 Regional lymph node(s) involved only

- Central
- Peripheral node region that drains an area of current or prior skin involvement
- Regional lymph node(s), NOS
  - Lymph node(s), NOS

4 Regional by BOTH direct extension AND regional lymph node(s) involved

- Codes (2) + (3)

7 Distant site(s)/lymph node(s) involved

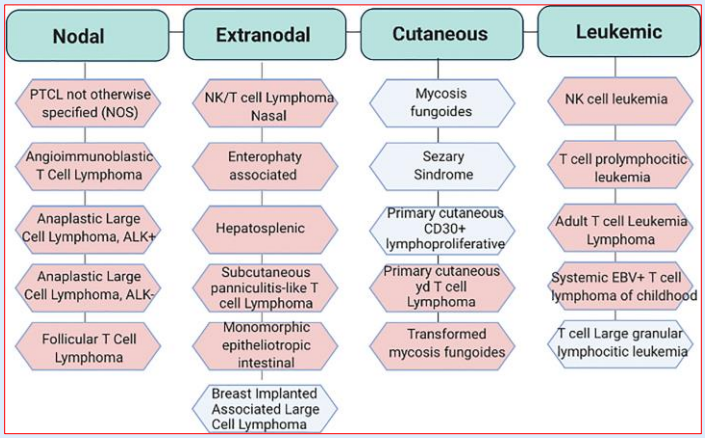
- Distant site(s) (including further contiguous extension)
  - Blood/peripheral blood
  - Bone marrow
  - Extracutaneous non-lymph node disease present
  - Generalized skin involvement
  - Multiple lesions confined to discontiguous body regions
  - Multiple lesions confined to three or more contiguous body regions
  - Visceral (non-cutaneous) metastasis
- Distant lymph node(s), NOS
- Distant metastasis, NOS
  - Carcinomatosis
  - Distant metastasis WITH or WITHOUT distant lymph node(s)

9 Unknown if extension or metastasis

86

Peripheral T-cell Lymphoma – not always skin

87



87

Staging Myeloma and Plasma Cell Disorders

88

1 Localized only

- Single plasmacytoma occurring in bone (osseous or medullary) (9731)
  - WITH or WITHOUT soft tissue extension
- Single plasmacytoma, NOS (9734)
  - Single plasmacytoma occurring outside of bone (extraosseous or extramedullary) (9734)

3 Regional lymph node(s) involved only

- Extraosseous plasmacytomas only (9734)
  - Regional lymph node(s), NOS
    - Lymph node(s), NOS

7 Distant site(s)/lymph node(s) involved

- Lymphoplasmacytic lymphoma (9671)
- Plasma cell myeloma (9732)
  - Multiple myeloma
  - Myeloma, NOS
  - Multiple extraosseous or extramedullary plasmacytomas
  - Multiple osseous or medullary plasmacytomas
  - Multiple plasmacytomas, NOS
- Waldenstrom Macroglobulinemia (9761)

9 Unknown if extension or metastasis (applicable for 9731 and 9734 only)

Revised International Staging System

The Revised International Staging System (R-ISS) is now used more commonly to classify multiple myeloma. It defines the factors that affect a person's survival of the disease. The R-ISS is based on data collected from people with multiple myeloma from around the world. The system has 3 stages based on the measurement of serum albumin, LDH, and serum β2-M and whether high-risk chromosomes are found using the FISH test (see **Diagnosis**).

Recent efforts have been made to further classify myeloma based on patterns of gene expression in myeloma cells. This is an ongoing area of research.

Stage I: All of the following apply:

- β2-M less than 3.5 mg/L
- Serum albumin of 3.5 g/dL or more
- Normal LDH
- No high-risk chromosome changes in myeloma cells found by FISH test

Stage II: Not stage I or stage III.

Stage III: β2-M is more than 5.5 mg/L, plus one of the following:

- Myeloma cells have high-risk chromosome changes found by FISH test
- High LDH

The R-ISS is most commonly used to predict prognosis. Higher blood levels of LDH indicate a poorer prognosis.

Recurrent or relapsed myeloma. Myeloma that returns after a period of being in control after treatment is called recurrent myeloma or relapsed myeloma. If there is a recurrence, the cancer may need to be staged again (called re-staging) using one of the systems above.

88

Plasma Cell Neoplasms – R-ISS Staging

89

Revised - International Staging System
Plasma Cell Myeloma/Multiple Myeloma

Stage	Criteria
I	Sβ2M < 3.5 mg/l Serum albumin ≥ 3.5 g/dl Standard-risk chromosomal abnormalities (CA) by iFISH Normal LDH
II	Not R-ISS stage I or III
III	Sβ2M ≥ 5.5 mg/L and either High-risk CA by FISH OR High LDH

89

Is it a Transformation or Disease Progression?

90

When a Myeloid Disease (MPN, MDS, Chronic Myeloid Leukemia) Transforms to Acute Myeloid Leukemia – See Heme DB for Transformations

Acute Leukemia
The phase of leukemia in which 20% or more of the cells in the blood or bone marrow are blast cells. Lymphoblasts or Leukemic Blasts.

Lymphoma does not have Transformation

Some lymphoma progresses to Stage IV lymphoma that involves bone marrow

Other lymphomas begin in bone marrow as lymphoid leukemia

Leukemia/Lymphoma is always Distant Stage/Systemic Disease

Chronic Leukemia is always Distant Stage/Systemic Disease

Acute Leukemia is always Distant Stage/Systemic Disease

Plasma Cell Myeloma is always Distant Stage/Systemic Disease

90

Site-Specific Data Items – CAUTION – next slide

91

- Adenopathy
- Anemia
- B Symptoms
- High Risk Cytogenetics
- High Risk Histologic Features
- HIV Status
- JAK2
- Lymphocytosis
- NCCN International Prognostic Index (IPI)
- Organomegaly
- Peripheral Blood Involvement
- Serum Albumin Pretreatment Level
- Serum Beta-2 Microglobulin Pretreatment Level
- Serum LDH (Lactate Dehydrogenase) Pretreatment Lab Value
- Thrombocytopenia

91

PROBLEMS with Staging and SSDIs for Lymphomas

92

- AJCC and EOD Schema ID are Primarily Designed to be compatible with the AJCC TNM Staging Criteria.
- AJCC TNM Staging is designed for Solid Tumors – not Lymphoma, Leukemia, Plasma Cell Myeloma
- There are a few POORLY Designed Schema for Mycosis Fungoides, Plasma Cell Myeloma, and Hematologic Malignancies – only of lymph nodes or blood/marrow – not extra-lymphatic/marrow sites
- Therefore, they are primarily organized by solid organ primary site NOT histology-based malignancies
- Lymphoid and Myeloid Neoplasms are ALL organized by Histology
- Extra-Nodal Lymphomas (UNFORTUNATELY) are still assigned to the solid organ schema ID
- Therefore, the Grade, Staging, SSDIs and Surgery are all Tied to the Solid Organ Requirements
- Why is this a problem?
- When you have a lymphoid or myeloid malignancy of a solid organ – the SSDIs do not apply at all.
  - Lymphoma of H&N asks for H&N SSDIs – none apply to lymphoma/leukemia
  - Lymphoma of Tonsil asks for Nasopharynx SSDIs
  - Lymphoma of Brain – asks for IDH and Brain Markers or Benign/Borderline Tumor Status
  - Lymphoma of GI Tract asks for GE Junction, Tumor Epicenter, CEA, MSI, KRAS – none apply
- You CANNOT Code Lymphoid/Myeloid SSDIs when extra-nodal or extra-marrow

92

Treatment Guidelines for Lymphoid Neoplasms

93

- NCCN Treatment Guidelines
  - Hodgkin Lymphoma
  - B-Cell Lymphomas
  - T-Cell Lymphomas
  - Primary Cutaneous Lymphoma
  - Hairy Cell Leukemia
  - Acute Lymphoblastic Leukemia
  - Systemic Light Chain Amyloidosis
  - Waldenstrom Macroglobulinemia
  - Lymphoplasmacytic Lymphoma
  - Multiple Myeloma
  - Pediatric Hodgkin Lymphoma
  - Pediatric B-Cell Lymphoma
  - Pediatric Acute Lymphocytic Leukemia

- NCCN Treatment Guidelines
  - Detailed Description of Diseases
  - Descriptions of Genetic Mutations
  - Evaluation of Disease at Diagnosis – Staging
  - Non-Bulky or Bulky Disease
  - Risk Stratification by Genetics
    - Criteria for Favorable Risk
    - Criteria for Intermediate Risk
    - Criteria for Unfavorable Risk
  - Non-Genetic Risk Stratification Factors
  - Treatment Strategies by Risk Group
    - Induction Therapy
    - Consolidation Therapy
    - Maintenance Therapy
    - BMT/SCT Transplant Criteria
    - Monitoring Post-Treatment
    - Relapsed/Refractory Disease
  - Response Criteria

93

Treatment Options for Lymphoid Neoplasms

94

- Watch and wait (for indolent, largely asymptomatic lymphomas)
- Chemotherapy
- Radiation therapy (most common in patients with limited-stage disease and sometimes in those with advanced-stage disease)
- Immunotherapy (eg, monoclonal antibodies targeting CD20, CD19, or CD79, or chimeric antigen receptor T cells [CAR T cells])
- Targeted drugs (eg, BTK [Bruton tyrosine kinase] inhibitors, PI3K [phosphoinositide 3-kinase] inhibitors, cereblon inhibitors)
- Sometimes hematopoietic stem cell transplantation (autologous or allogeneic)

https://www.merckmanuals.com/professional/hematology-and-oncology/lymphomas/non-hodgkin-lymphomas

94

Lymphoma – one node removed – Biopsy or Surgery?

95

LYMPH NODES
C77.0–C77.9

Codes

00 None; no surgery of primary site; autopsy ONLY

19 Local tumor destruction or excision, NOS

Unknown whether a specimen was sent to pathology for surgical events coded to 19 (principally for cases diagnosed prior to January 1, 2003).

15 Local tumor destruction, NOS

No specimen sent to pathology from surgical event 15.

25 Local tumor excision, NOS

~~Less than a full chain, includes an excisional biopsy of a single lymph node.~~

ASK YOURSELF: Is this procedure a cancer treatment or only a biopsy to make a diagnosis? A single lymph node is always just for diagnosis.

Item #	Length	Column #	Allowable Values	Required Status	Date Revised
1350	2	2235-2236	00–07, 09	All Years	09/06, 09/08, 01/12, 01/15

Description

Identifies the positive surgical procedure(s) performed to diagnose and/or stage disease.

Rationale

This data item is used to track the use of surgical pr… ources that are not considered treatment.

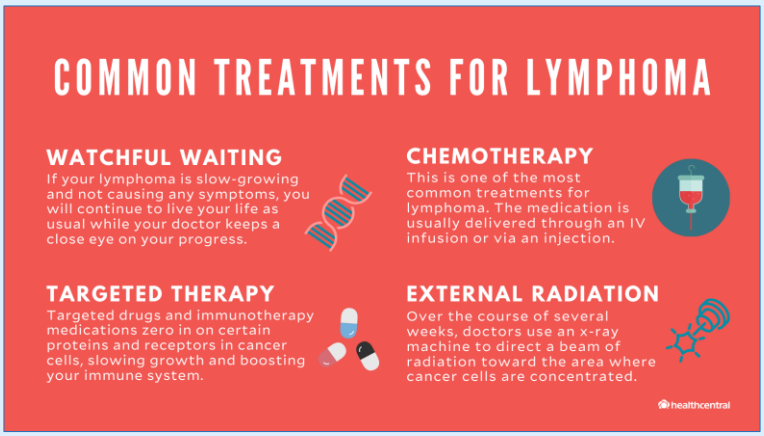
Coding Instructions

- Record the type of procedure performed as … initial diagnosis and workup, whether this is done at your institution or another f…
- Only record positive procedures. For benig… e reportable tumors, report the biopsies positive for those conditions. For malignant t… report procedures if they were positive for malignancy.
- If both an incisional biopsy of the primary site and an incisional biopsy of a metastatic site are done, use code 02 (incisional biopsy of primary site).
- If a lymph node is biopsied or removed to diagnose or stage lymphoma, and that node is NOT the only node involved with lymphoma, use code 02. If there is only a single lymph node involved with lymphoma, use the data item Surgical Procedure of Primary Site [1290] to code these procedures.
- Do not code surgical procedures which aspirate, biopsy, or remove regional lymph nodes in an effort to diagnose lymph node disease in this data item. Use the data item Scope of Regional Lymph Node Surgery [1292] to code these procedures. Do not record the date of surgical procedures which aspirate, biopsy, or remove regional lymph nodes in the data item Date of Surgical Diagnostic and Staging Procedure [1280]. See instructions for Scope of Regional Lymph Node Surgery [1292].

95

Surgical Treatment for Nodal Lymphoid Neoplasms

96



96

Chemotherapy and Immunotherapy

97

- R-CHOP
  - Rituximab (Rituxan) – Immune TX
  - Cyclophosphamide
  - Doxorubicin
  - Vincristine
  - Prednisone – Hormone

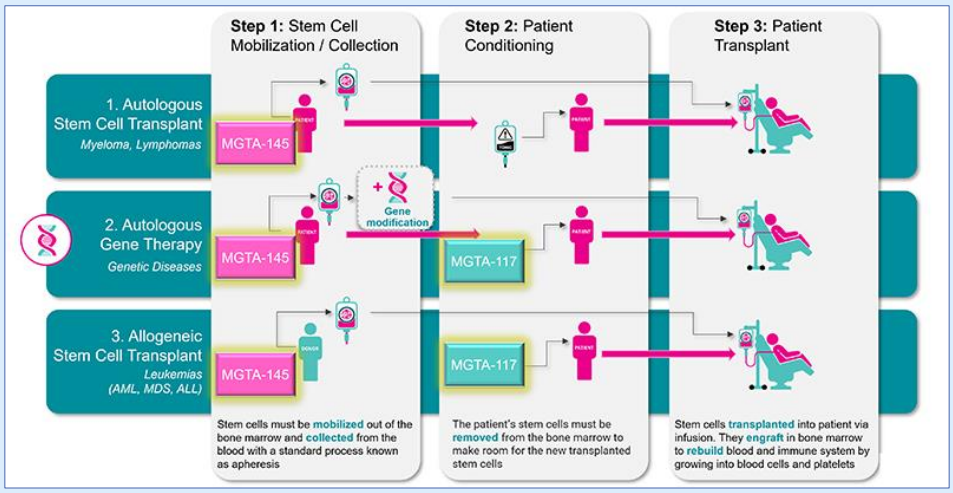
  Multi-Agent chemotherapy
- Maxi-CHOP
  - High-dose cytarabine
  - Carmustine
  - Etoposide
  - Ara-C
  - Melphalan
- Autologous Stem Cell Transplant

- Since the advent of rituximab as the first successful immunotherapy for B-cell non-Hodgkin lymphoma over two decades ago, a plethora of new immunotherapeutic approaches to treat lymphoma has ensued.
- Four of the most exciting classes of immunotherapies include: chimeric antigen receptor T-cells (CAR-T cells), bi-specific antibodies, immune checkpoint inhibitors, and vaccines.

97

Blood & Marrow Stem Cell Transplant Procedures

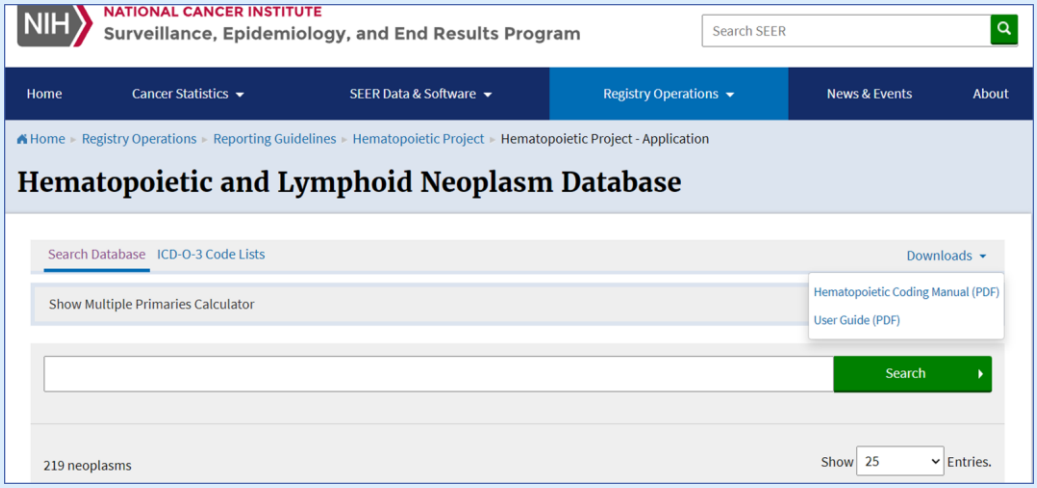
98



98

Documentation Needed for Lymphoid Neoplasms

99



99

Documentation Needed for Lymphoid Neoplasms

100

Definition

Plasma cell *myeloma* (PCM) is a bone marro
an M protein in serum and/or urine and evid

Bone marrow is the site of origin of nearly al
organs may be secondarily involved. The dis
based on a combination of clinical, morpholo

There are three clinical variants of plasma ce

1. Smoldering (asymptomatic) PCM: Bone m
lack of symptoms, but more likely to develo

2. Non-secretory *myeloma* occurs when the
(or not) secretion of immunoglobulin into th

3. Plasma cell leukemia (PCL) occurs when t
count. Other areas of involvement include s
diagnosis or occur as a late feature of PCM (s
similar to PCM. Lymphadenopathy, organom
short survival.

4. High-risk *multiple myeloma*: Having at le
t(14;20), del 17p, p53 mutation, gain 1q and

5. Double-hit *multiple myeloma*: Having at
t(14;20), del 17p, p53 mutation, gain 1q and

6. Triple-hit *multiple myeloma*: Having at le
t(14;20), del 17p, p53 mutation, gain 1q and

Definitive Diagnostic Methods

Bence-Jones protein
Bone marrow biopsy
FISH
Genetic testing
Immunophenotyping
Peripheral blood smear
Serum Protein Electrophoresis (SPEP)

Genetics Data

Five major oncogenes involved in 14q32 translocation: cyclin D1, C-MAF, FGFR3/MMSET, cycli
High load of IGHV gene somatic hypermutation
Immunoglobulin heavy and light chain genes are clonally rearranged
Trisomies
Whole or partial chromosome deletions or translocations

Immunophenotyping

CD19-
CD38
CD56 aberrantly expressed (except PC
CD56- (PCL)
CD79a
CD138
VS38c

Treatments

Chemotherapy
Hematologic Transplant and/or Endoc
Hormone therapy
Immunotherapy

Transformations to

None

Transformations from

9731/3 Solitary plasmacytoma of bone
9734/3 Extraosseous plasmacytoma

Diagnostic Exams

Blood and urine immunoglobulin studi
Blood chemistry studies
Bone marrow aspiration and biopsy
Complete blood count (CBC)
Cytogenetic analysis
MRI (magnetic resonance imaging)
Physical exam and history (H&P)
Skeletal survey
Twenty-four-hour urine test

Progression and Transformation

Extramedullary involvement usually indicates advanced disease

Abstractor Notes

Plasma cell *myeloma* (PCM) usually has generalized bone marrow involvement. Lytic bone lesions and bone tumor masses of plasma cells also occur.

Approximately 30% of patients with solitary plasmacytoma (bone or outside of bone) defined only by radiographical skeletal survey have additional lesions identified on MRI or CT. These patients are considered to have plasma cell *myeloma*.

The International Staging System for *Multiple Myeloma* Staging for *Multiple Myeloma* is based on:
1. Amount of monoclonal (or *myeloma*) protein (M protein) in the serum and/or urine
2. Various clinical parameters such as: hemoglobin and serum calcium concentrations, number of lytic bone lesions
3. Presence or absence of renal failure.
Stage I
Stage II
Stage III

Treatment
Watchful waiting: Asymptomatic patients with no lytic lesions and normal renal function.

For patients with symptoms and advanced disease
1. Induction therapy
2. Consolidation therapy
3. Maintenance therapy
4. Supportive care

The presence of plasmacytomas after a diagnosis of plasma cell *myeloma* indicates an advanced stage of plasma cell *myeloma*. Do not abstract a new primary for the plasmacytoma(s) (9731/3 or 9734/3) after a diagnosis of plasma cell *myeloma*.

100

2022 FCDS Audit of Lymphoid and Myeloid Neoplasms

101

FCDS DATA VALIDATION AUDIT with E-PATH VERIFICATION

Diagnosis Year: 2020

Cancer Site: Adult & Pediatric Lymphoid and Myeloid Neoplasms

Includes;

Any Lymphoma (Nodal/Extra-Nodal), Any Plasma Cell Neoplasm,

Myelodysplastic Syndrome (MDS), Myeloproliferative Neoplasm (MPN),

Acute Leukemia (myeloid/lymphoid), Chronic Leukemia (myeloid/lymphoid)

Any ICD-O-3 Histology Code 9590-9993

Hospital Analytic Cases Only

- ALL Option 2-5 Facilities will be included in this audit. The audit will include both adult and pediatric lymphoid and myeloid neoplasms of any type. The number of cases will be stratified by 2020 reporting year caseload for any primary site with histology 9590-9992 – analytic cases only (see below Class of Case).
- A facility may be selected for more than 1 audit during the 5-year cycle using the enhanced facility select criteria.
- A facility may have more than 1 reported cancer selected for this audit.
- Case Selection will be based upon the following criteria:
  - Date of Diagnosis 01/01/2020-12/31/2020
  - Primary Site(s) = Any

Histology-Driven Case Selection	# Cases
Histology Codes 9590-9992	1000
TOTAL	**1000**

  - Behavior = 3 (malignant)
  - Central Sequence = 00 (only 1 cancer ever reported)
  - ICD-O-3 Histology – 9590-9992
  - Class of Case = 10, 11, 12, 13, 14, 20, 21, 22 (hospital analytic – diagnosed and/or treated at facility)
- Case Selection will be stratified by 2020 reporting year caseload for combined lymphoid/myeloid neoplasms.
- Pathology Selection will be based on any e-pathology report(s) with Date of Specimen within 30 days of the original Date of Diagnosis (plus or minus 30 days) as documented/coded on the original case abstract.

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2022 FCDS Audit of Lymphoid and Myeloid Neoplasms

102

176 Hospitals – 1500 cases/750 e-path

Audit Timeline

12/2022	1/2023	1/2023	2/2023	3/2023	4/2023	6/2023
Final Protocol						
	Software Updates					
	Identify Audit Team	Auditor Orientation Webcast				
		Audit	Audit	Audit		
				Audit Reconciliation Webcast		
				Reconciliation	Reconciliation	
					Final Review	Final Review
						Final Audit Report
						Update FCDS Record

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References and Resources

103

- WHO Classification of Tumours – Online – Haematolymphoid -5th ed. https://whobluebooks.iarc.fr/structures/haematolymphoid/
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- Diagnosis and Classification of Lymphoma: Impact of Technical Advances; ES Jaffe: Semin Hematol. 2019 January ; 56(1): 30–36. doi:10.1053/j.seminhematol.2018.05.007
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- The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee; Blood 15 SEPTEMBER 2022 | VOLUME 140, NUMBER 11
- SEER Hematopoietic and Lymphoid Neoplasm Database – https://seer.cancer.gov/seertools/hemelymph/
- Hematopoietic and Lymphoid Neoplasm Coding Manual (Effective 1/1/2010); Release date: August 2021
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) – ALL, B-Cell Lymphoma, T-Cell Lymphoma, Hairy Cell Leukemia, Hodgkin Lymphoma, Multiple Myeloma, Pediatric ALL, Pediatric B-Cell Lymphoma, Pediatric Hodgkin Lymphoma, Primary Cutaneous Lymphoma, Waldenstrom macroglobulinemia, Amyloidosis– http://nccn/org
- NCI Physician Data Query – Adult ALL, Childhood ALL, HD, NHL, Multiple Myeloma, AIDS-Related Lymphoma, Primary CNS Lymphoma, Burkitt Lymphoma, CLL, Lymphoma, Hairy Cell Leukemia, Mycosis Fungoides, NHL, Myeloproliferative Neoplasms, Chronic– http://cancer.gov
- American Cancer Society – About Cancer – NHL, HL, ALL, CLL, Lymphoma of Skin, Multiple Myeloma, Waldenstrom Macroglobulinemia– http://cancer.org
- The WHO Classification of Haematolymphoid Tumours (editorial); Leukemia (2022) 36:1701 – 1702

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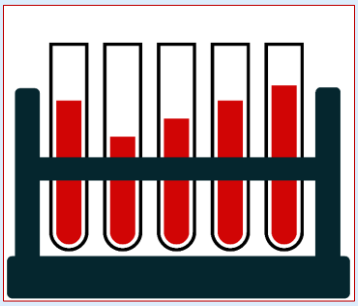
Questions

104



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