# 2022 Introduction to Lymphoid Neoplasms

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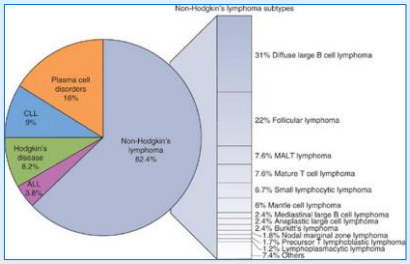
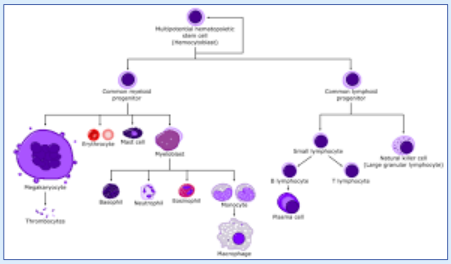
**FCDS VIRTUAL ANNUAL CONFERENCE**

**9/1/2022**

**STEVEN PEACE, CTR**







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# CDC & Florida DOH Attribution

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"Funding for this conference was made possible (in part) by the Centers for Disease Control and Prevention. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services, nor does the mention of trade names, commercial practices, or organizations imply endorsement by the US Government."

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# Outline

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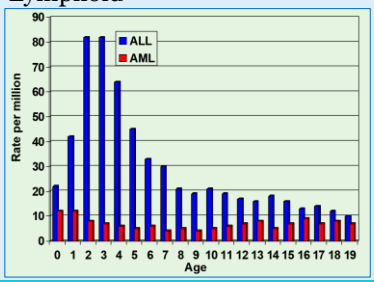
- Introduction to Lymphoid Neoplasms
- Pediatric versus Adult Lymphoid Neoplasms
- Inaugural WHO Classification of Pediatric Tumors
- Lymphatic System and Circulatory System - Anatomy
- Milestones in the Classification of Tumors of Lymphoid Tissues
- WHO Classification of Hematolymphoid Tumors, 5th ed
- The 2022 Hematopoietic Manual and Hematopoietic Data Base
- Demonstration Hematopoietic Manual and Hematopoietic Data Base - Lymphoid
- Diagnostic Confirmation for Lymphoid Neoplasms
- Molecular Genetics and Tumor Markers for Lymphoid Neoplasms
- Workup and Staging Lymphoid Neoplasms
- Treatment Guidelines for Lymphoid Neoplasms
- Bone Marrow/Stem Cell Transplant Procedures
- Documentation Needed for Lymphoid Neoplasms
- 2022 FCDS Audit of Lymphoid and Myeloid Neoplasms
- 2023 Lymphoid Neoplasms Webcast – 2/16/2023 – Post-Audit
- Questions

| LYMPHOID DISORDER | IMMUNOPHENOTYPE |
|---|---|
| CLL/SLL | CD5, 19,20,23, 43 (sometimes) |
| Follicular lymphoma | CD10,19, 20, bcl-2, |
| Marginal zone lymphoma | CD20, 79a |
| Mantle cell lymphoma | CD5, 19,20, cyclin D1 |
| Hairy cell leukemia | CD11c, 19, 20, 22, 25, 103 |
| Diffuse large B cell lymphoma | CD19, 20, bcl-6 |
| Burkitt lymphoma | CD19,20, CD10 (often) |
| Anaplastic large cell lymphoma | CD30 |
| Mycosis fungoides | CD2, 3, 4, 5 |
| Classical Hodgkin | CD15, 30 |
| Nodular lymphocyte predominate Hodgkin lymphoma | CD20 |
| Myeloid leukemias | CD13, 33 |

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# Introduction to Lymphoid Neoplasms

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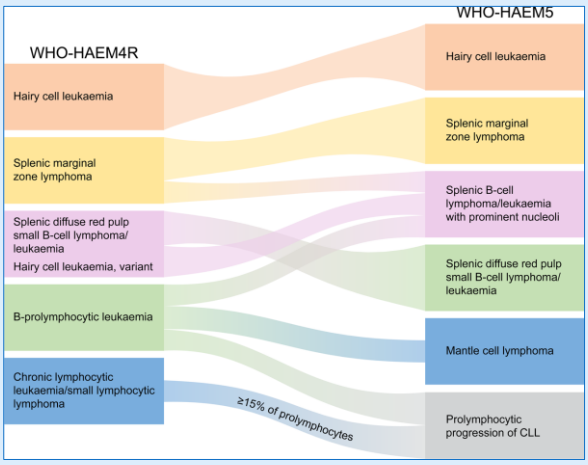


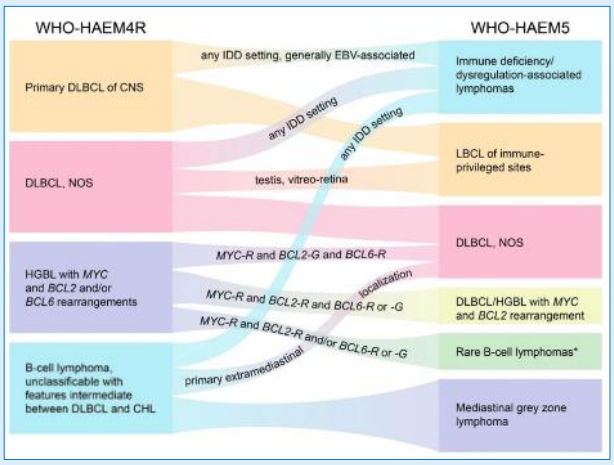


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# Pediatric versus Adult Lymphoid Neoplasms

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- 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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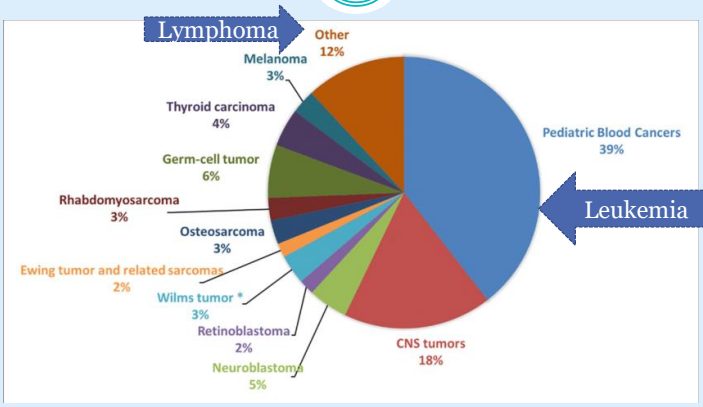


Frequency of pediatric cancers in patients younger than 19 years. The figure shows the prevalence of the main pediatric cancer types among patients younger than 19 years of age, calculated from Centers for Disease Control and Prevention (CDC) data (United States Cancer Statistics Data, https://wonder.cdc.gov/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

Source: CDC NPCR United States Cancer Statistics

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# Inaugural WHO Classification of Pediatric Tumors

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## 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.

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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

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# Inaugural WHO Classification of Pediatric Tumors

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**Li-Fraumeni syndrome***

**WILMS TUMOR**

- Beckwith-Wiedemann spectrum*
- Bohring-Opitz syndrome
- Mosaic variegated aneuploidy
- Mulibrey nanism
- Perlman syndrome
- Simpson-Golabi Behmel syndrome
- TRIM28 congenital predisposition to WT
- Trisomy 18
- *WT1*-associated syndromes*

**ENDOCRINE TUMORS**

- Hereditary pheochromocytoma/paraganglioma syndrome*
- Hyperparathyroidism jaw tumor syndrome
- Multiple endocrine neoplasia type 1
- Multiple endocrine neoplasia type 2
- Multiple endocrine neoplasia type 4
- Von Hippel-Lindau syndrome*

**HEMATOPOIETIC MALIGNANCIES**

- *ANKRD26*-related thrombocytopenia and myeloid malignancies*
- Ataxia telangiectasia
- Bloom syndrome
- *CEBPA*-associated familial AML*
- Congenital neutropenia*
- Down syndrome*
- Dyskeratosis congenita*
- *ETV6* susceptibility to ALL*
- Fanconi anemia*
- *GATA2*-deficiency*
- *IKZF1* susceptibility to ALL
- MIRAGE Syndrome*
- Nijmegen breakage syndrome
- Other immunodeficiency syndromes
- *PAX5* susceptibility to ALL*
- Ring chromosome 21
- Robertsonian translocation 15;21
- *RUNX1* familial platelet disorder with associated myeloid malignancies*
- *SAMD9L* ataxia-pancytopenia (ATXPC) syndrome*
- Shwachman-Diamond syndrome*

**Constitutional mismatch repair deficiency***

**GASTROINTESTINAL TUMORS**

- *APC*-associated polyposis syndromes*
- Lynch syndrome*
- *MUTYH*-associated polyposis
- Peutz-Jeghers syndrome

**NEURAL TUMORS**

- *ALK*-related neuroblastic tumor susceptibility
- Congenital central hypoventilation syndrome
- *ELP1* medulloblastoma syndrome*
- Gorlin syndrome*
- *GRP161* medulloblastoma syndrome
- Neurofibromatosis type 1*
- Neurofibromatosis type 2*
- Retinoblastoma predisposition syndrome*
- Rhabdoid tumor predisposition 1*
- Rhabdoid tumor predisposition 2*
- Schwannomatosis
- Tuberous sclerosis*

**OTHERS**

- *BAP1* tumor predisposition syndrome*
- *BRCA1/2*-associated hereditary breast and ovarian cancer syndrome
- Carney complex
- *DICER1* syndrome*
- Enchondromatosis
- Hereditary leiomyomatosis and renal cell cancer
- L-2-hydroxyglutaric aciduria
- Multiple osteochondromas
- NKX2-1 syndrome
- Ornithin transcarbamylase deficiency
- *POLE* deficiency
- *PTEN* hamartoma tumor syndrome
- Rasopathies*
- Rubinstein-Taybi syndrome
- Schinze-Giedion syndromel
- Sotos syndrome
- T (Brachyury) gene familial chordoma
- Tyrosinemia Type 1
- Weaver syndrome
- Werner syndrome
- Xeroderma pigmentosum*

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# Blood, Bone Marrow, Circulatory System - Anatomy

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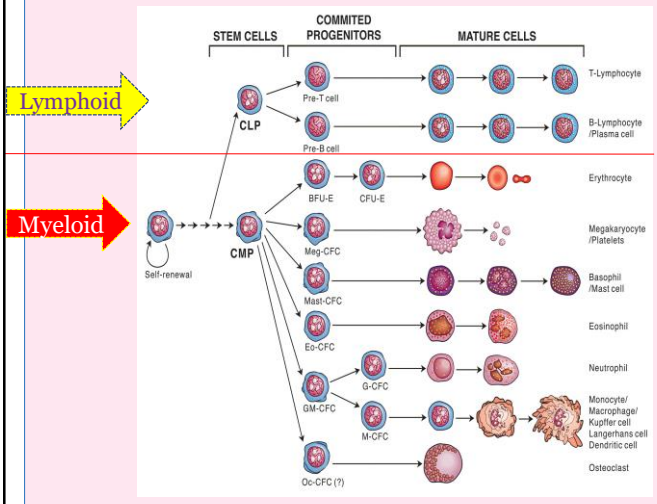



- Cellular differentiation is the process by which an immature cell becomes a more mature cell
- Differentiation changes a cell's size, shape, membrane potential, metabolic activity, and responsiveness to signals or signal pathways
- Regulatory function of cells (regulates cell line proliferation and 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

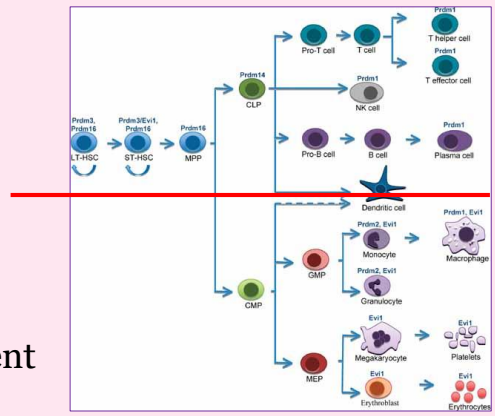
*Figure 3.2 The eight major hematopoietic lineages generated by self-renewing multipotential stem cells*

11

# Blood, Bone Marrow, Circulatory System - Anatomy

12

- 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?

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- 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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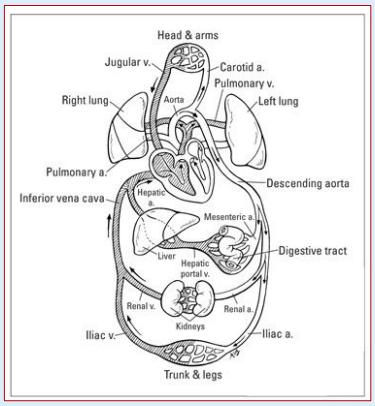


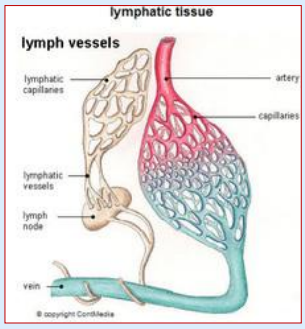


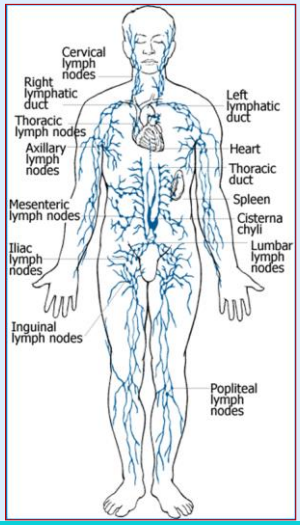


http://www.dummies.com/education/science/biology/the-path-of-blood-through-the-human-body http://www.gorhams.dk/html/the_lymphatic_system.htm

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# The Lymphatic System

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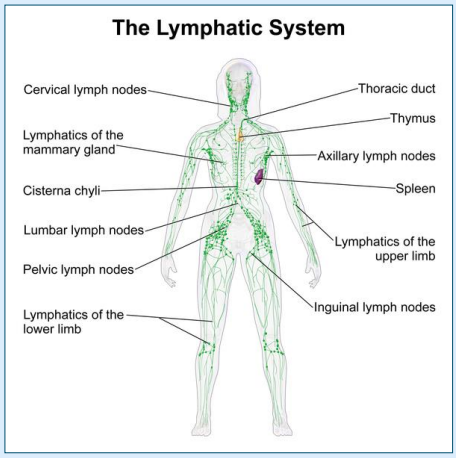


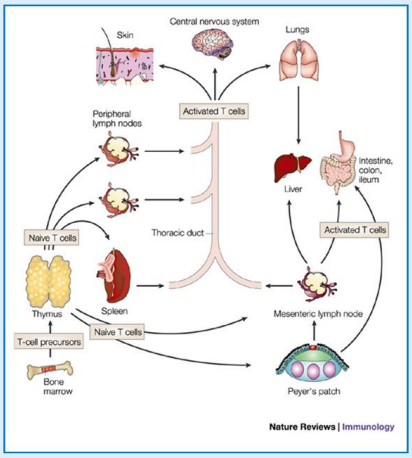


Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014".

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# Lymphatic Circulatory System

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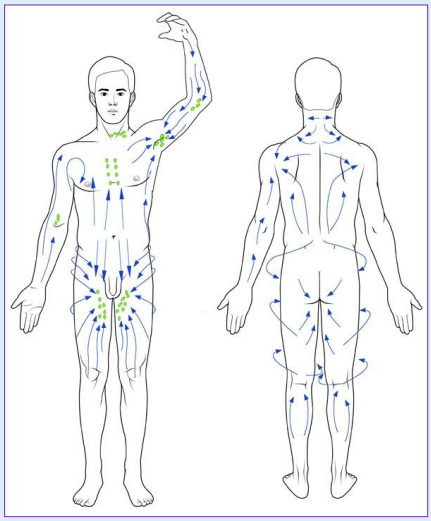

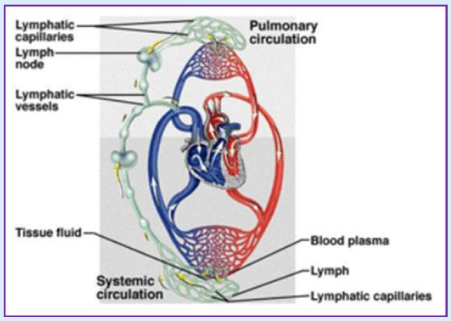


Source: Nature Reviews Immunology http://www.nature.com/nri/journal/v4/n5

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# Lymph Node

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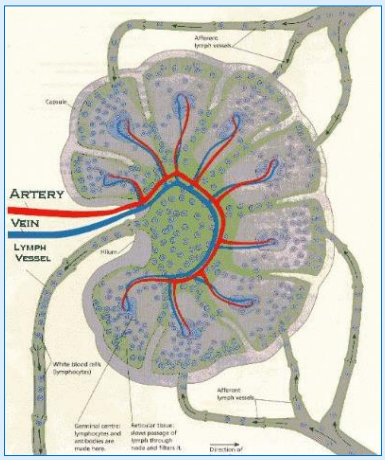


Source: http://www.bcb.uwc.ac.za/SCI_ED/grade10/manphys/plan.htm

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# Lymphatic Organs

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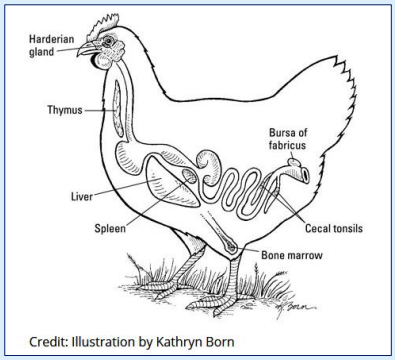
- **Primary Organs**
  - Bone Marrow
  - Thymus




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

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# Lymphatic Organs

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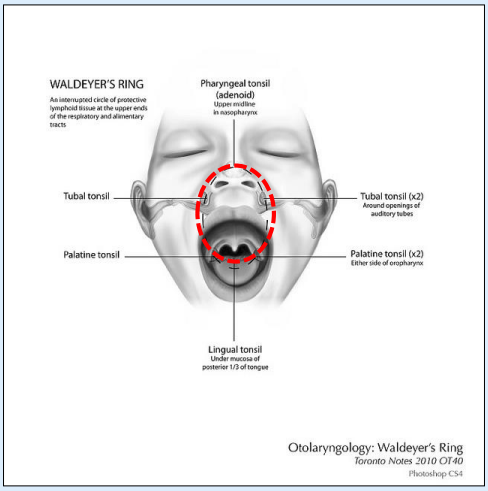


http://www.flickr.com/photos

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# Lymph Node Chains and Regions

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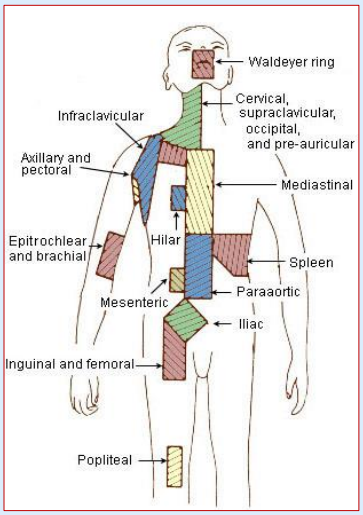
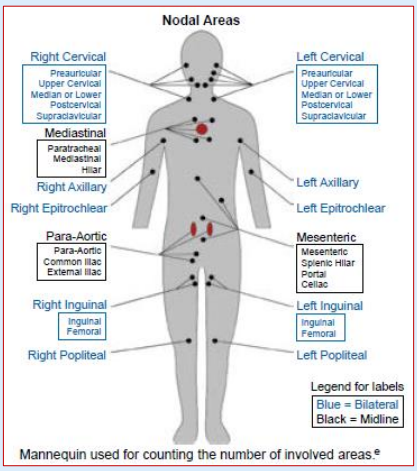



**Lymph nodes above the diaphragm**

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: AJCC Cancer Staging Form, 7th edition

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# Lymphatic Organs vs Region

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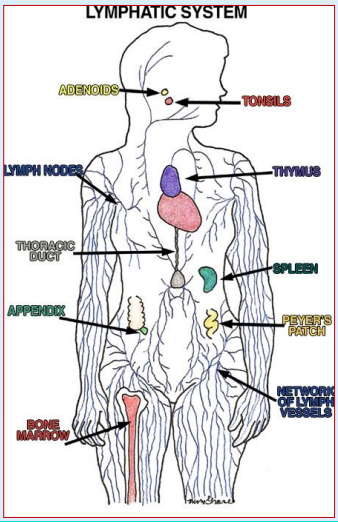


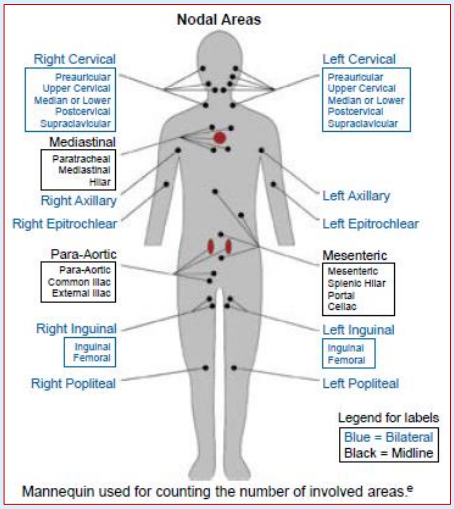


http://commonsensehealth.com

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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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# 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.

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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 4$^{th}$ edition, 2017
- 2022 – WHO Classification of Hematolymphoid Tumors, 5$^{th}$ ed

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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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# 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 |

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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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| 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) |

# 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* |

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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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# 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<br>Post–organ transplant lymphoma<br>Primary CNS diffuse large B cell lymphoma<br>Hodgkin's disease<br>Extranodal NK/T cell lymphoma, nasal type |
| *HTLV-I* | Adult T cell leukemia/lymphoma |
| *HIV* | Diffuse large B cell lymphoma<br>Burkitt's lymphoma |
| *Hepatitis C virus* | Lymphoplasmacytic lymphoma |
| *Helicobacter pylori* | Gastric MALT lymphoma |
| *HHV 8* | Primary effusion lymphoma<br>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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| 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<br>-POEMS syndrome<br>-TEMPI syndrome<br>-AESOP syndrome | (Same) Except AESOP syndrome *not previously included* |

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# "Overlap Lymphoid Syndromes" – Number of Primaries

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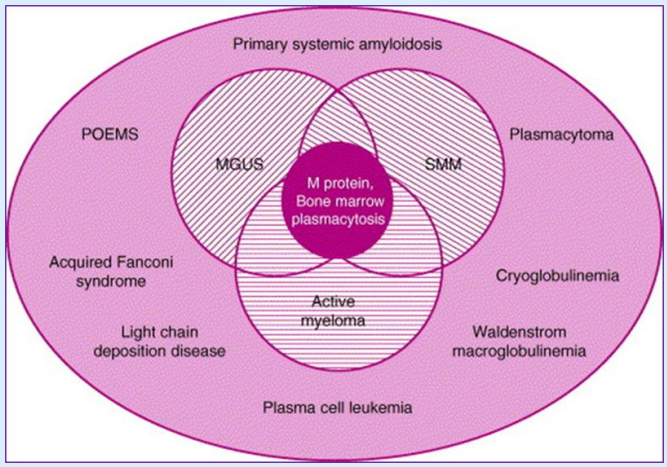


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# Demonstration Hematopoietic Manual and Hematopoietic Data Base

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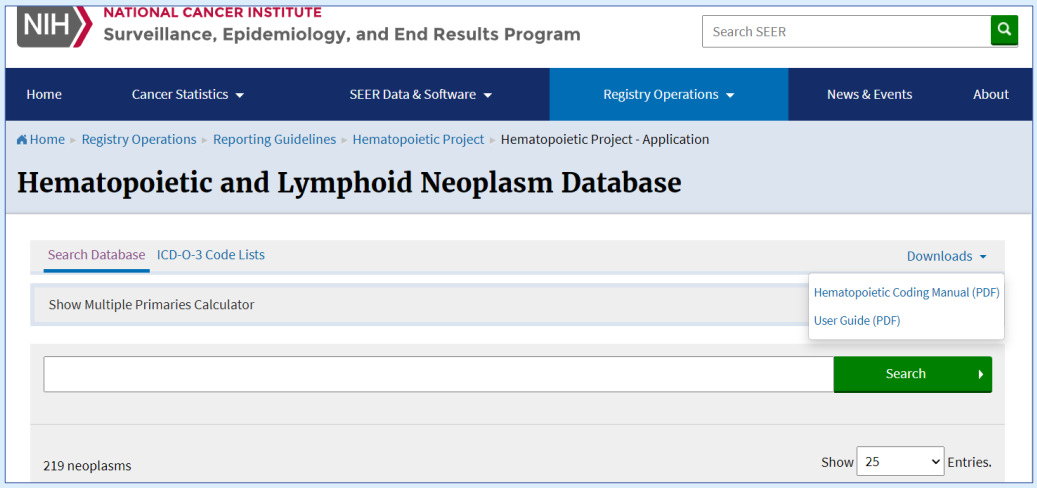


35

# Diagnostic Confirmation for Lymphoid Neoplasms

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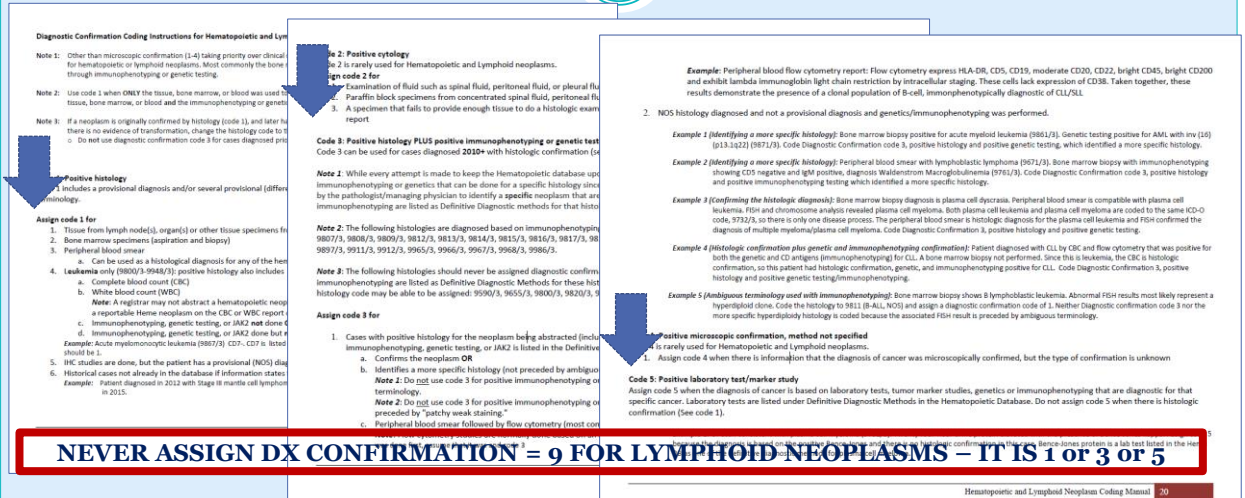


**NEVER ASSIGN DX CONFIRMATION = 9 FOR LYMPHOID NEOPLASMS – IT IS 1 or 3 or 5**

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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 are 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, 9871/3, 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.

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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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**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

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

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# Molecular Genetics and Tumor Markers for Lymphoid Neoplasms

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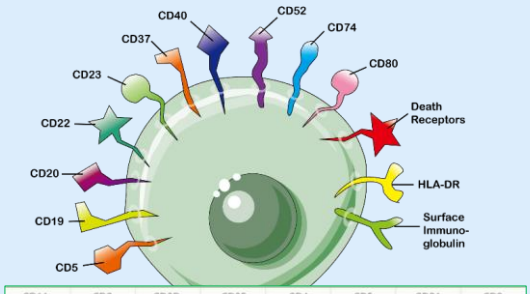


| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CD1A | CD2 | CD3D | CD3E | CD4 | CD5 | CD8A | CD9 |
| CD10 | CD11A | CD11B | CD11C | CD13 | CD14 | CD15 | CD16A |
| CD16B | CD19 | CD22 | CD24 | CD25 | CD27 | CD28 | CD29 |
| CD31 | CD32 | CD33 | CD34 | CD38 | CD40 | CD41A | CD44 |
| CD45 | CD45RO | 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<br>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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# Molecular Genetics and Tumor Markers for Lymphoid Neoplasms

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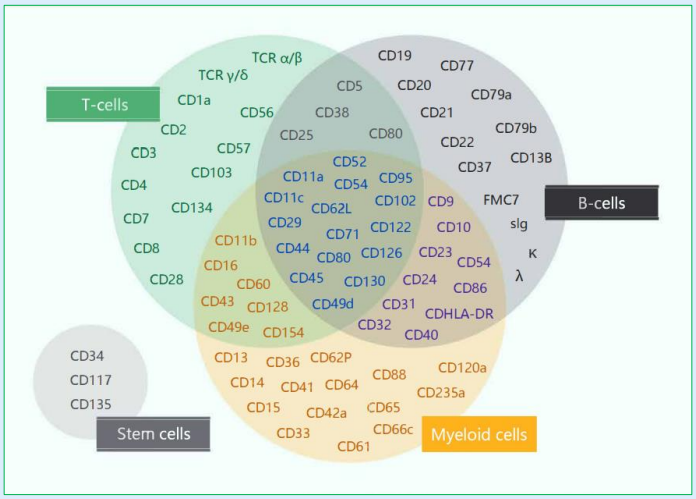


43

# Integrating genetic data into classification

44

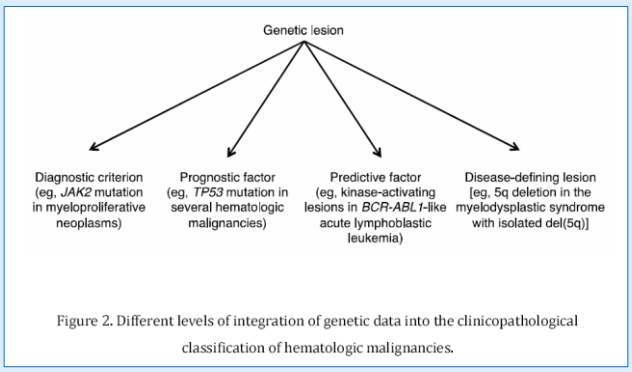


Figure 2. Different levels of integration of genetic data into the clinicopathological classification of hematologic malignancies.

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# Workup and Staging Lymphoid Neoplasms

45

- 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

45

- **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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# Staging Lymphoid Neoplasms

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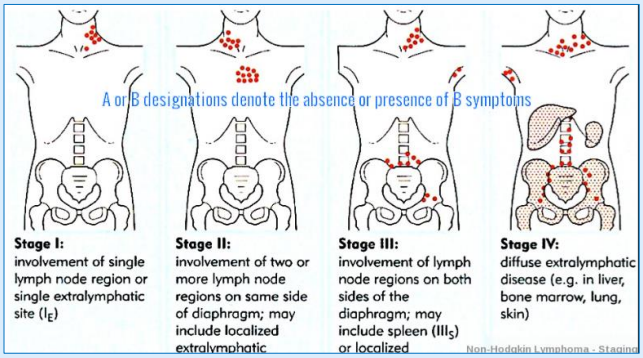
- Hodgkin Lymphoma
- Non-Hodgkin Lymphoma
- Extra-Nodal lymphoma
- Plasma Cell Neoplasms
- CLL/SLL
- ALL




47

# Modified Ann Arbor Staging

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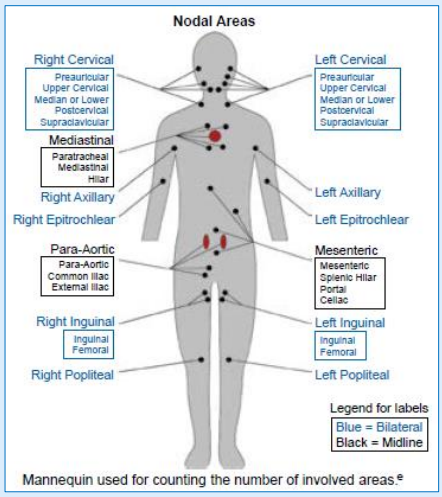


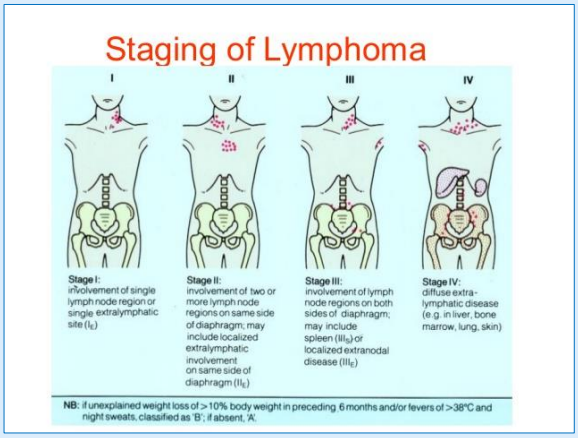


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# Extranodal Lymphoma – Modified Ann Arbor Staging

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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)

49

# Transformation or Progression

50

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

50

# Plasma Cell Neoplasms – R-ISS Staging

51

## Revised - International Staging System
## Plasma Cell Myeloma/Multiple Myeloma

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

51

# CLL/SLL – RAI Staging System

52

## 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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# Site-Specific Data Items – CAUTION – next slide

53

- 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


53

# PROBLEMS with Staging and SSDIs for Lymphomas

54

- 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

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# Treatment Guidelines for Lymphoid Neoplasms

55

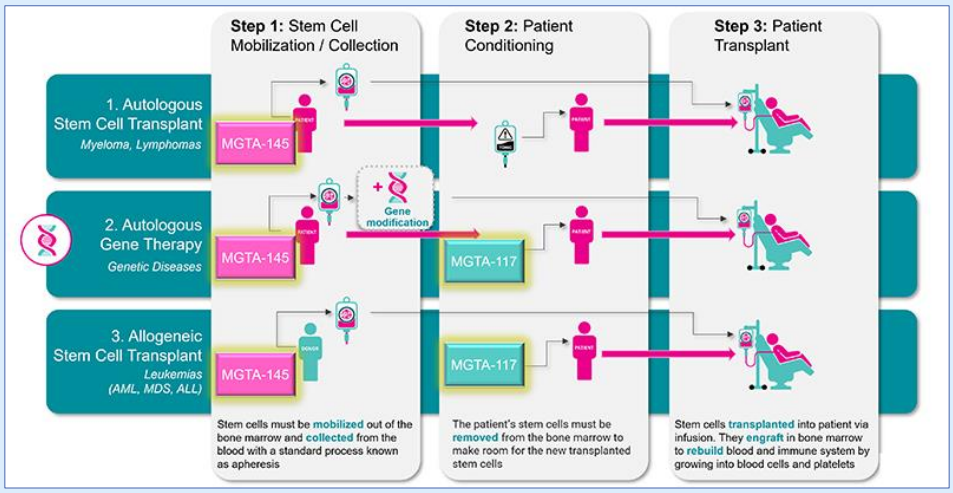
- NCCN Treatment Guidelines
  - Hodgkin Lymphoma
  - B-Cell Lymphomas
  - T-Cell Lymphomas
  - Primary Cutaneous Lymphoma
  - Hairy Cell Leukemia
  - Acute Lymphoblastic Leukemia
  - Systemic Light Chain Amyloidosis
  - Waldenstrom Macroglobulinemia
  - Lymphoplasmacytic Lymphoma
  - Multiple Myeloma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

55

# Blood & Marrow Stem Cell Transplant Procedures

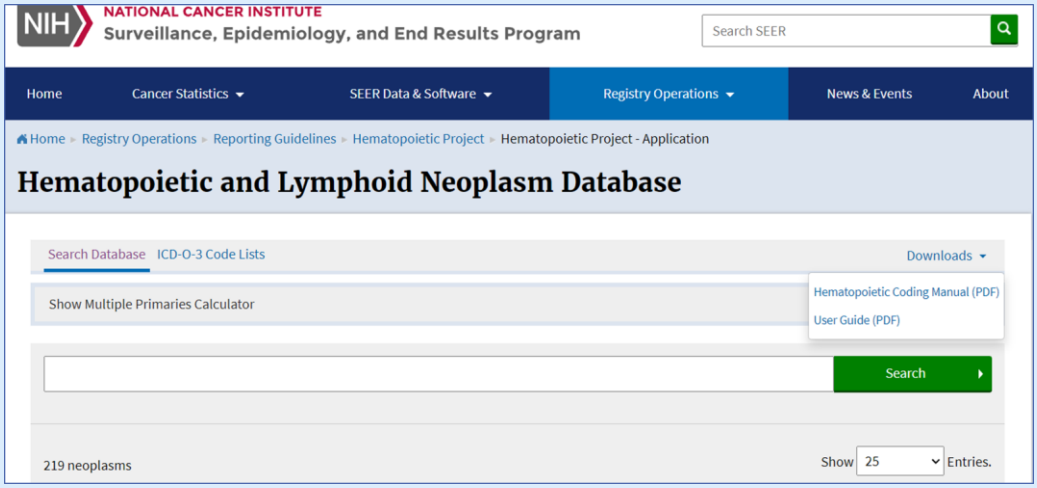
56




56

# Documentation Needed for Lymphoid Neoplasms

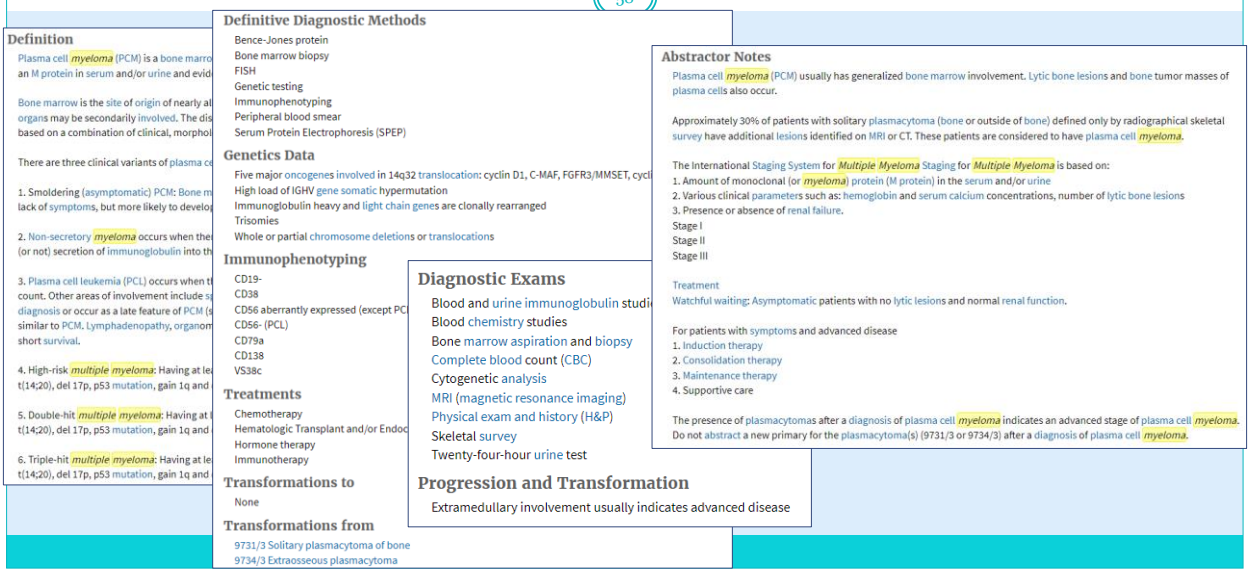
57




57

# Documentation Needed for Lymphoid Neoplasms

58

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# 2022 FCDS Audit of Lymphoid and Myeloid Neoplasms

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**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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# 2023 Lymphoid Neoplasms Webcast – 2/16/2023 – Post-Audit

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| Date | 2022-2023 FCDS Webcast Series - Topics |
|---|---|
| 9/22/2022 | FCDS Annual Conference Summary – 2022 Requirements |
| 10/20/2022 | Lung & Thoracic Neoplasms – WHO 5th edition Classification, Volume 5; 2021 |
| 11/17/2022 | Brain & CNS Neoplasms (includes pediatric) – WHO 5th ed Classification, Volume 6; 2021 |
| 12/15/2022 | Common Registrar Technical Questions and Clarifications from Visual Editing |
| 1/19/2023 | Myeloid Neoplasms – 2022 Updates & 2022 Audit Findings |
| 2/16/2023 | Lymphoid Neoplasms – 2022 Updates & 2022 Audit Findings |

Post Introduction – Post Audit – Audit Findings – More on 5th Edition – Updates to Heme DB
More Detailed Information and More Time – 2 hours – for each topic.

60

# References and Resources

61


- A Summary of the Inaugural WHO Classification of Pediatric Tumors: Transitioning from the Optical into the Molecular Era; AACR: Cancer Discover, February 2022
- WHO Classification of Tumours – Online – Haematolymphoid -5th ed. https://whobluebooks.iarc.fr/structures/haematolymphoid/
- The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms; Leukemia (2022) 36:1703–1719; https://doi.org/10.1038/s41375-022-01613-1
- 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 2016 revision of the World Health Organization classification of lymphoid neoplasms; BLOOD, 19 MAY 2016 x VOLUME 127, NUMBER 20
- 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
- 2021 Update on Diffuse large B cell lymphoma: A review of current data and potential applications on risk stratification and management; Susanibar-Adaniya; Am J Hematol. 2021 May 01; 96(5): 617–629. doi:10.1002/ajh.26151


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# Questions

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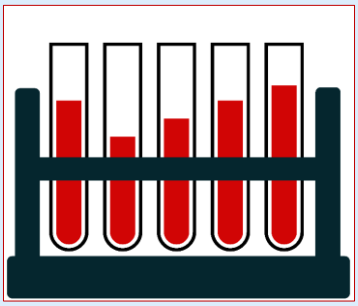

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