CDC & Florida DOH Attribution

“We acknowledge the Centers for Disease Control and Prevention, for its support of the Florida Cancer Data System, and the printing and distribution of the materials for the 2017-2018 FCDS Webcast Series under cooperative agreement 1NU58DP006350 awarded to the Florida Department of Health. The findings and conclusions in this series are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention”.

FCDS would also like to acknowledge the Florida Department of Health for its support of the Florida Cancer Data System, including the development, printing and distribution of materials for the 2017-2018 FCDS Webcast Series under state contract CODJU. The findings and conclusions in this series are those of the author(s) and do not necessarily represent the official position of the Florida Department of Health.
FLCCSC LMS – CEU QUIZ – FCDS IDEA ACCESS

• Florida has changed how we track webcast attendance
• Florida has changed how we award CEUs for our webcast series
• Attendees must take and pass a 3-5 question CEU quiz to be awarded CEUs
• Only registered FLCCSC users will be given access to the CEU quiz
• Florida attendees must have a Florida FLCCSC account & pass the quiz to get CEUs
• South Carolina attendees must have a South Carolina FLCCSC account & pass the quiz to get CEUs
• Other attendees can attend the live webcasts but cannot receive CEUs for attendance at this time
• Please remember this is a new system with new requirements - some still being worked out

OUTLINE

• Introduction to WHO classification & basic anatomy
• Milestones in the classification of tumors of hematopoietic tissues
• Milestones in the classification of tumors of lymphoid tissues
• The 2010 hematopoietic MPH rules manual and database
• 2016 updates to WHO classification of myeloid neoplasms & acute leukemia
• 2016 updates to WHO classification of lymphoid neoplasms
• The 2019 hematopoietic MPH rules manual & database
• Staging myeloid neoplasms + 2018 myeloid SSDIs
• Staging lymphoid neoplasms + 2018 lymphoid SSDIs
• Questions
2016 WHO CLASSIFICATION OF TUMOURS OF
HAEMATOPOIETIC AND LYMPHOID TISSUES, 4TH ED.

4TH EDITION WHO CLASSIFICATION OF TUMOURS
• CENTRAL NERVOUS SYSTEM (2007)
• HEMATOPOIETIC AND LYMPHOID (2008)
• DIGESTIVE SYSTEM (2010)
• BREAST (2012)
• SOFT TISSUE AND BONE (2013)
• FEMALE REPRODUCTIVE ORGANS (2014)
• LUNG, PLEURA, THYMUS & HEART (2015)
• URINARY SYSTEM & MALE GENITAL (2016)
• CENTRAL NERVOUS SYSTEM (2016 REVISION)
• HEMATOPOIETIC & LYMPHOID (2016 REVISION)
• HEAD & NECK (2017)

2016 WHO CLASSIFICATION OF TUMOURS OF
HAEMATOPOIETIC AND LYMPHOID TISSUES, 4TH ED.

• WHO CLASSIFICATION OF TUMOURS, REVISED 4TH EDITION, VOLUME 2, LYON: IARC, 2017
• INTERNATIONAL STANDARD FOR PATHOLOGISTS AND ONCOLOGISTS
• DIAGNOSTIC CRITERIA
• PATHOLOGICAL FEATURES
• ASSOCIATED GENETIC ALTERATIONS
• NEW ICD-O CODES
• EPIDEMIOLOGY
• CLINICAL FEATURES
• MACROSCOPY
• PROGNOSTIC & PREDICTIVE FACTORS
2016 WHO CLASSIFICATION OF TUMOURS OF HAEMATOPOIETIC AND LYMPHOID TISSUES, 4TH ED.

• “CLASSIFICATION IS THE LANGUAGE OF MEDICINE: DISEASES MUST BE DESCRIBED, DEFINED AND NAMED BEFORE THEY CAN BE DIAGNOSED, TREATED AND STUDIED.”

• “A CONSENSUS ON DEFINITIONS AND TERMINOLOGY IS ESSENTIAL FOR BOTH CLINICAL PRACTICE AND INVESTIGATIONS.”

• THE 2016 EDITION REPRESENTS A REVISION OF THE PRIOR CLASSIFICATION RATHER THAN AN ENTIRELY NEW CLASSIFICATION AND ATTEMPTS TO INCORPORATE NEW CLINICAL, PROGNOSTIC, MORPHOLOGIC, IMMUNOPHENOTYPIC, AND GENETIC DATA THAT HAVE EMERGED SINCE THE LAST EDITION.

INTRODUCTION
ADULT MYELOID AND LYMPHOID NEOPLASMS

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2017 Estimates

<table>
<thead>
<tr>
<th>Site</th>
<th>Male Cases</th>
<th>Female Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>161,780</td>
<td>252,710</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>144,960</td>
<td>185,120</td>
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<tr>
<td>Colorectal</td>
<td>71,420</td>
<td>64,010</td>
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<tr>
<td>Uterine corpus</td>
<td>88,050</td>
<td>61,230</td>
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<tr>
<td>Thyroid</td>
<td>56,370</td>
<td>41,470</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>19,060</td>
<td>31,160</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>36,420</td>
<td>31,540</td>
</tr>
<tr>
<td>Lung &amp; intrahepatic bile duct</td>
<td>12,980</td>
<td>21,200</td>
</tr>
<tr>
<td>All sites</td>
<td>468,670</td>
<td>652,030</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site</th>
<th>Male Cases</th>
<th>Female Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>84,500</td>
<td>71,230</td>
</tr>
<tr>
<td>Colorectal</td>
<td>27,250</td>
<td>49,020</td>
</tr>
<tr>
<td>Prostate</td>
<td>30,530</td>
<td>23,100</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>22,930</td>
<td>20,790</td>
</tr>
<tr>
<td>Thyroid</td>
<td>16,890</td>
<td>14,590</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>14,300</td>
<td>30,920</td>
</tr>
<tr>
<td>Lung &amp; intrahepatic bile duct</td>
<td>12,700</td>
<td>33,200</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,400</td>
<td>9,530</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,520</td>
<td>7,850</td>
</tr>
<tr>
<td>All sites</td>
<td>285,420</td>
<td>281,000</td>
</tr>
</tbody>
</table>
INTRODUCTION

PEDIATRIC MYELOID AND LYMPHOID NEOPLASMS

Age-Adjusted and Age-Specific Cancer Incidence Rates for Patients Aged 0–14 Years (SEER 2009–2012)

- Leukemia
- CNS
- Lymphoma
- Soft tissue
- Neuroblastoma
- Renal
- Bone
- Epithelial
- Germ cell
- Retinoblastoma
- Liver
- Other

Source: NCI SEER

HEMATOPOIESIS AND "BLOOD CANCERS"

https://www.medicalnewstoday.com/articles/285666.php

https://HematologyOutlines.com
CELLULAR DIFFERENTIATION & REGULATORY FUNCTION

- 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

Blood Lines – Donald Metcalf, AlphaMED Press, 2005

Figure 3.2 The eight major hematopoietic lineages generated by self-renewing multipotential stem cells
Copyright © 2008 by AlphaMed Press http://www.alphamedpress.org
TWO CIRCULATORY SYSTEMS – BLOOD & LYMPHATIC

Source: http://www.gorhams.dk/html/the_lymphatic_system.htm

LYMPHATIC CIRCULATORY SYSTEM

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

LYMPHATIC ORGANS

• PRIMARY ORGANS
  • BONE MARROW
  • THYMUS

• 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
LYMPH NODE

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

LYMPH NODE CHAINS AND REGIONS

Source: AJCC Cancer Staging Form, 7th edition

Legend for colors:
- Blue = Regional
- Black = Distant
MILESTONES IN THE CLASSIFICATION OF TUMORS OF HEMATOPOIETIC TISSUES

- 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.
MILESTONES IN THE CLASSIFICATION OF TUMORS OF LYMPHOID TISSUES

- 1951 – DAMESHEK – CLINICAL PHENOTYPE
- 1960 – PHILADELPHIA (PH1) CHROMOSOME
- 1966 – RAPPAPORT CLASSIFICATION
- 1974 – KIEL CLASSIFICATION SYSTEM
- 1974 – LUKES AND COLLINS SYSTEM
- 1976 – REVISED RAPPAPORT CLASSIFICATION
- 1982 – WORKING FORMULATION
- 1994 – REVISED EUROPEAN-AMERICAN CLASSIFICATION OF LYMPHOID NEOPLASMS
- 2008 – WHO CLASSIFICATION OF TUMORS OF HEMATOPOIETIC AND LYMPHOID TISSUES, 4TH EDITION, OCTOBER 2008
- 2016 – REVISION TO 4TH EDITION, 2017

THE 2010 HEMATOPOIETIC MPH RULES MANUAL AND THE HEMATOPOIETIC DATABASE

- BASED ON THE 2008 WHO CLASSIFICATION OF HEMATOPOIETIC AND LYMPHOID TISSUES
- REPLACED ICD-O-3 FOR ANY HISTOLOGY CODE IN RANGE 9590-9992
- UPDATED IN 2012 – NO MAJOR CHANGES – DETAILS ADDED TO HEME DATABASE
- UPDATED IN 2014 – THE ORIGINAL 43 PRIMARY SITE AND HISTOLOGY CODING RULES WERE REDUCED TO 31 RULES. SOME RULES WERE DELETED, SOME COMBINED AND SOME CLARIFIED. AND, CLARIFIED THAT NO DESIGNATED OBSOLETE CODES ARE TO BE USED AS OF 1/1/2010.
- UPDATED IN 2015 – NO MAJOR CHANGES
THE 2010 HEMATOPOIETIC MPH RULES MANUAL
AND THE HEMATOPOIETIC DATABASE
HTTPS://SEER.CANCER.GOV/SEERTOOLS/HEMELYMPH/

THE 2010 HEMATOPOIETIC MPH RULES MANUAL
AND THE HEMATOPOIETIC DATABASE
HTTPS://SEER.CANCER.GOV/SEERTOOLS/HEMELYMPH/
THE 2010 HEMATOPOIETIC MPH RULES MANUAL AND THE HEMATOPOIETIC DATABASE
HTTPS://SEER.CANCER.GOV/SEERTOOLS/HEMELYMPH/
2016 REVISION OF THE WHO CLASSIFICATION
MYELOID NEOPLASMS & ACUTE LEUKEMIA

BLOOD, 19 MAY 2016 X VOLUME 127, NUMBER 20

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Daniel A. Arber,1 Attilo Orazi,2 Robert Haserjian,3 Jürgen Thiele,4 Michael J. Borowitz,5 Michelle M. Le Beau,6 Clara D. Bloomfield,7 Mario Cazzola,8 and James W. Vardiman9

1Department of Pathology, Stanford University, Stanford, CA; 2Department of Pathology, Weill Cornell Medical College, New York, NY; 3Department of Pathology, Massachusetts General Hospital, Boston, MA; 4Institute of Pathology, University of Cologne, Cologne, Germany; 5Department of Pathology, John Hopkins Medical Institutions, Baltimore, MD; 6Section of Hematology/Oncology, University of Chicago, Chicago, IL; 7Comprehensive Cancer Center, James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH; 8Department of Molecular Medicine, University of Pavia, and Department of Hematology/Oncology, Fondazione IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; and 9Department of Pathology, University of Chicago, Chicago, IL.

The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues was last updated in 2008. Since then, there have been numerous advances in the identification of unique biomarkers associated with some myeloid neoplasms and acute leukemias, largely derived from gene expression analysis and next-generation sequencing that can significantly improve the diagnostic criteria as well as the prognostic relevance of entities currently included in the WHO classification and that also suggest new entities that should be added. Therefore, there is a clear need for a revision to the current classification. The revisions to the categories of myeloid neoplasms and acute leukemia will be published in a monograph in 2016 and reflect a consensus of opinion of hematopathologists, hematologists, oncologists, and geneticists.

The 2016 edition represents a revision of the prior classification rather than an entirely new classification and attempts to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since the last edition. The major changes in the classification and their rationales are presented here. (Blood. 2016; 127(20):2391-2405)

INTEGRATING GENETIC DATA INTO CLASSIFICATION

![Diagram showing different levels of integration of genetic data into the clinicopathological classification of hematologic malignancies.](image)

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

- WHO SUPPORTS A ROBUST INTEGRATED APPROACH TO DISEASE CLASSIFICATION THAT INCLUDES HEMATOLOGIC, MORPHOLOGIC, CYTOGENETIC, AND MOLECULAR GENETIC FINDINGS
- THIS REVISION PROVIDES FOR A CLOSER INTEGRATION OF MORPHOLOGY AND GENETICS
  - IMPROVED CHARACTERIZATION AND STANDARDIZATION OF MORPHOLOGICAL FEATURES AIDING IN THE DIFFERENTIATION OF DISEASE GROUPS
  - DISCOVERY OF UNIQUE BIOMARKERS/MOLECULAR FEATURES THAT SIGNIFICANTLY IMPROVE DIAGNOSTIC CRITERIA FOR ENTITIES CURRENTLY INCLUDED IN THE WHO CLASSIFICATION
  - DISCOVERY OF UNIQUE BIOMARKERS/MOLECULAR FEATURES THAT IMPROVE PROGNOSTIC RELEVANCE OF ENTITIES CURRENTLY INCLUDED IN THE WHO CLASSIFICATION
  - DISCOVERY OF UNIQUE BIOMARKERS/MOLECULAR FEATURES THAT SUGGEST NEW ENTITIES SHOULD BE ADDED.
**CHRONIC MYELOID NEOPLASMS**

**MPN**
- MPN
- MPN/MDS
- MDS

**MYELOPROLIFERATIVE NEOPLASMS**

Myeloproliferative neoplasms
- Chronic myeloid leukemia, BCR-ABL positive
- Chronic neutrophilic leukemia
- Polycythemia vera
- Primary myelofibrosis
- Pre-fibrotic/early primary myelofibrosis
- Overt primary myelofibrosis
- Essential thrombocythaemia
- Chronic eosinophilic leukaemia, not otherwise specified
- Myeloproliferative neoplasm, undiagnostic

**Mastocytosis**— now has its own group
**MYELOPROLIFERATIVE NEOPLASMS**

![Diagram of myeloproliferative neoplasms]

**NEW ICD-10-CM DX CODES FOR MASTOCYTOSIS**

- C96.20 - MALIGNANT MAST CELL NEOPLASM, UNSPECIFIED
- C96.22 - AGGRESSIVE SYSTEMIC MASTOCYTOSIS
- C96.22 - MAST CELL SARCOMA
- D47.01 - CUTANEOUS MASTOCYTOSIS
- D47.02 - SYSTEMIC MASTOCYTOSIS
- D47.09 - OTHER MAST CELL NEOPLASMS OF UNCERTAIN BEHAVIOR

**New WHO Classification Group**

<table>
<thead>
<tr>
<th>Mastocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous mastocytosis</td>
</tr>
<tr>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td>Mast cell sarcoma</td>
</tr>
</tbody>
</table>
MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND GENE REARRANGEMENT

Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement
- Myeloid/lymphoid neoplasms with PDGFRα rearrangement
- Myeloid/lymphoid neoplasms with PDGFRβ rearrangement
- Myeloid/lymphoid neoplasms with FGFR1 rearrangement
- Myeloid/lymphoid neoplasms with PCM1-JAK2

https://doi.org/10.3324/haematol.10328

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

Myelodysplastic/myeloproliferative neoplasms
- Chronic myelomonocytic leukaemia
- Atypical chronic myeloid leukaemia, BCR-ABL1-negative
- Juvenile myelomonocytic leukaemia
- Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable
MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes
Overview
Myelodysplastic syndrome with single lineage dysplasia
Myelodysplastic syndrome with ring sideroblasts
Myelodysplastic syndrome with multilineage dysplasia
Myelodysplastic syndrome with excess blasts
Myelodysplastic syndrome with excess blasts and erythroid predominance
Myelodysplastic syndrome with excess blasts and fibrosis
Myelodysplastic syndrome with isolated del(5q)
Myelodysplastic syndrome, unclassifiable
Childhood myelodysplastic syndrome
Refractory cytopenia of childhood

Myelodysplastic syndromes (MDS)

2016
• MDS with single lineage dysplasia
• MDS with multilineage dysplasia
• MDS with ring sideroblasts (MDS-RS)
  – MDS-RS and single lineage dysplasia
  – MDS-RS and multilineage dysplasia
• MDS with isolated del(5q)
• MDS with excess blasts
  – MDS-EB-1
  – MDS-EB-2
• MDS, unclassifiable
• Provisional entity: Refractory cytopenia of childhood

2008
• RCUD
• RCD
• RAEB-1
• RAEB-2

MYELOID DISEASE TRANSFORMATION

• Patients with myeloproliferative neoplasms (MPNS), including polycythemia vera, essential thrombocytemia, and primary myelofibrosis, have a propensity to develop acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).
• Blastic transformation represents a transformation of disease from indolent and chronic to acute and blastic life threatening disease (usually transform to AML).
• New targeted drugs like Gleevek treat pre-acute phase hoping for complete response.
• Many patients now diagnosed and treated at early phase of disease.
• Seldom see intermediate/accelerated phase.
• Acute phase is life-threatening.

A myeloid disease process will not transform to lymphoid or vice versa.
MYELOID NEOPLASMS WITH GERMLINE PREDISPOSITION

Myeloid neoplasms with germline predisposition
- Acute myeloid leukaemia with germline CEBPA mutation
- Myeloid neoplasms with germline DDX41 mutation
- Myeloid neoplasms with germline predisposition and pre-existing platelet disorders
- Myeloid neoplasms with germline RUNX1 mutation
- Myeloid neoplasms with germline ANKRD26 mutation
- Myeloid neoplasms with germline ETV6 mutation
- Myeloid neoplasms with germline predisposition associated with other organ dysfunction
- Myeloid neoplasms with germline GATA2 mutation
- Myeloid neoplasms with germline predisposition associated with inherited bone failure syndromes and telomere biology disorders

Somatic mutations
- Occur in nongermline tissues
- Cannot be inherited

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Mutation in tumor only (for example, breast)
Nonheritable

Mutation in egg or sperm
H eritable
All cells affected in offspring

ACUTE MYELOID LEUKEMIA AND RELATED (MYELOID) PRECURSOR NEOPLASMS

Acute myeloid leukaemia and related precursor neoplasms
- Acute myeloid leukaemia with recurrent genetic abnormalities
  - Introduction
  - Acute myeloid leukaemia with t(8;21)(q22;q22.1)
  - RUNX1-RUNX1T1
  - Acute myeloid leukaemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22), CBFβ-MYH11
  - Acute promyelocytic leukaemia with PML-RARA
  - Acute myeloid leukaemia with t(3;11)(q21.3;q23.3)
  - KMT2A-MLLT3
  - Acute myeloid leukaemia with t(6;9)(p23;q34.1)
  - DEK-NUP214
  - Acute myeloid leukaemia with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2), GATA2, MECOM
  - Acute myeloid leukaemia (megakaryoblastic) with t(1;22)(p13.3;q13.1), RBMI1-MKL1
  - Acute myeloid leukaemia with BCR-ABL1
  - Acute myeloid leukaemia with gene mutations
  - Acute myeloid leukaemia with mutated NPM1
  - Acute myeloid leukaemia with biallelic mutation of CEBPA
  - Acute myeloid leukaemia with mutated RUNX1

Acute myeloid leukaemia with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
  - Acute myeloid leukaemia, not otherwise specified
  - Acute myeloid leukaemia with minimal differentiation
  - Acute myeloid leukaemia without maturation
  - Acute myeloid leukaemia with maturation
  - Acute myelomonocytic leukaemia
  - Acute monocytic and monoblastic leukaemia
  - Pure erythroid leukaemia
  - Acute megakaryoblastic leukaemia
  - Acute basophilic leukaemia
  - Acute myelomonocytic leukaemia
  - Acute panmyelosis with myelofibrosis
  - Myeloid sarcoma

Myeloid proliferations associated with Down syndrome
- Transient abnormal myelopoiesis associated with Down syndrome
- Myeloid leukaemia associated with Down syndrome
BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

- "BLASTIC" IS THE KEY – LEUKEMIC PHASE

ACUTE LEUKEMIA OF AMBIGUOUS LINEAGE

Natural killer (NK) cell lymphoblastic leukemia/lymphoma
SUMMARY OF REVISIONS

- CLOSER INTEGRATION OF MORPHOLOGY AND GENETICS
- EXPLOSION OF PATHOLOGICAL AND GENETIC DATA FOR “SMALL B-CELL” LYMPHOMAS – CLL/SLL
- THERE ARE LYMPHOID PROLIFERATIONS THAT WE USED TO DIAGNOSE AS OVERT LYMPHOID NEOPLASMS BUT WHICH ARE NOT CONSIDERED AS SUCH IN 2016 IS FURTHER EMPHASIZED
- THERE ARE MAJOR CHANGES IN AGGRESSIVE B-CELL LYMPHOMAS THAT IMPACT HOW THESE CASES SHOULD BE EVALUATED AND DIAGNOSED THAT HAVE IMPORTANT THERAPEUTIC IMPLICATIONS IN ADDITION TO CHANGES RESULTING FROM BIOLOGICAL INTEREST.
- THE 2008 MONOGRAPH REPORTED THAT “NO CYTOGENETIC ABNORMALITY IS SPECIFIC FOR HAIRY CELL LEUKEMIA”, WE NOW KNOW THAT BRAF V600E MUTATIONS ARE FOUND IN ALMOST ALL CASES OF HAIRY CELL LEUKEMIA (HCL) BUT NOT IN HCL-VARIANT (HCL-V) OR OTHER SMALL B-CELL LYMPHOID NEOPLASMS
- THE 2008 MONOGRAPH ALSO NOTED THAT “NO SPECIFIC CHROMOSOMAL OR ONCOGENE ABNORMALITIES ARE RECOGNIZED” IN LYMPHOMAS MACCOTIC LYMPHOMA (LPL); HOWEVER, WE NOW KNOW THAT ABOUT 90% OF LPL OR WALDENSTROM MACROGLOBULINEMIA (LPL PLUS AN IMMUNOGLOBULIN M [IgM] PARAPROTEIN) HAVE MYD88 L265P MUTATIONS
- NEW CATEGORY OF HIGH-GRADE B-CELL LYMPHOMA (HGBL), WITH REARRANGEMENTS OF MYC AND BCL2 AND/OR BCL6
**PRECURSOR LYMPHOID NEOPLASMS**

- B-lymphoblastic leukaemia/lymphoma, not otherwise specified
- B-lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
  - B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34.1;q11.2), BCR-ABL1
  - B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3), KMT2A rearranged
  - B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1), ETV6-RUNX1
  - B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
  - B-lymphoblastic leukaemia/lymphoma with hypodiploidy
  - B-lymphoblastic leukaemia/lymphoma with t(6;14)(q31.1;q32.1), IGH-IGH3
  - B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3), TCF3-PBX1
  - B-lymphoblastic leukaemia/lymphoma, BCR-ABL1 t-like
  - B-lymphoblastic leukaemia/lymphoma with IAMP21
  - T-lymphoblastic leukaemia/lymphoma
  - Early T-cell precursor lymphoblastic leukaemia
  - NK-lymphoblastic leukaemia/lymphoma

**T-Lymphoblastic leukemia/lymphoma**

- Provisional entity: Early T-cell precursor lymphoblastic leukemia
- Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

---

**MATURE B-CELL NEOPLASMS**

- Chronic lymphocytic leukaemia
- Monoclonal B-cell lymphocytosis
- MALT lymphoma
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- Splenic B-cell lymphoma/leukaemia, unclassifiable
- Splenic diffuse red pulp small B-cell lymphoma
- Hairy cell leukaemia variant
- Lymphoplasmacytic lymphoma

- Heavy chain diseases
- Mu heavy chain disease
- Gamma heavy chain disease
- Alpha heavy chain disease
- Non-IgM monoclonal gammopathy of undetermined significance
- Plasma cell myeloma
- Plasma cell myeloma variants
- Smouldering (asymptomatic) plasma cell myeloma
- Non-secretory myeloma
- Primary amyloidosis
- Light chain and heavy chain deposition diseases
- Plasma cell neoplasms with associated paraneoplastic syndrome
- POEMS syndrome
- TEMT syndrome
MATURE B-CELL NEOPLASMS

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Paediatric nodal marginal zone lymphoma
Follicular lymphoma
Testicular follicular lymphoma
In situ follicular neoplasia
Duodenal-type follicular lymphoma
Paediatric-type follicular lymphoma
Large B-cell lymphoma with IGHV4 rearrangement
Primary cutaneous follicle centre lymphoma
 Mantle cell lymphoma
 Leukaemic non-nodal mantle cell lymphoma
 In situ mantle cell neoplasia
 Diffuse large B-cell lymphoma (DLBCL), NOS
 T-cell/histiocyte-rich large B-cell lymphoma
 Primary diffuse large B-cell lymphoma of the CNS
 Primary cutaneous diffuse large B-cell lymphoma, leg type

EBV-positive diffuse large B-cell lymphoma, NOS
EBV-positive mucocutaneous ulcer
Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated diffuse large B-cell lymphoma
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK-positive large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8-associated lymphoproliferative disorders
Multicentric Castleman disease
HHV8-positive diffuse large B-cell lymphoma, NOS
HHV8-positive germinotropic lymphoproliferative disorder
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration
VIRUS-ASSOCIATED LYMPHOID NEOPLASMS

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Lymphoid Malignancy</th>
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</thead>
<tbody>
<tr>
<td>Epstein-Barr virus</td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>Post-organ transplant lymphoma</td>
</tr>
<tr>
<td></td>
<td>Primary CNS diffuse large B cell lymphoma</td>
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<tr>
<td></td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td></td>
<td>Extramedulmonary NKT cell lymphoma, nasal type</td>
</tr>
<tr>
<td>HTLV-I</td>
<td>Adult T cell leukemia/lymphoma</td>
</tr>
<tr>
<td>HIV</td>
<td>Diffuse large B cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Lymphoplasmacytoid lymphoma</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Gastric MALT lymphoma</td>
</tr>
<tr>
<td>HHV 8</td>
<td>Primary effusion lymphoma</td>
</tr>
<tr>
<td></td>
<td>Multicentric Castleman’s disease</td>
</tr>
</tbody>
</table>

MATURE B-CELL NEOPLASMS

High-grade B-cell lymphoma
- High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
- High-grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma

NEW

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Blastic</th>
<th>BL</th>
<th>DLBCL/LBL</th>
<th>DLBCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype &amp; cytogenetics</td>
<td>TdT+</td>
<td>TdT-, cyclin D1-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis: B-LBL, HGBL, NOS, BL, HGBL with MYC and BCL2 and/or BCL6, DLBCL, NOS
MATURE T- AND NK-CELL NEOPLASMS

**Mature T- and NK-cell neoplasms**
- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK-cell leukaemia
- EBV-positive T-cell and NK-cell lymphoproliferative diseases of childhood
- Systemic EBV+ T-cell lymphoma of childhood
- Chronic active EBV infection of T- and NK-cell type, systemic form
- Hydroa vacciniforme-like lymphoproliferative disorder
- Severe mosquito bite allergy
- Adult T-cell leukaemia/lymphoma
- Extramedullary NK/T-cell lymphoma, nasal type
- Intestinal T-cell lymphoma
- Enteropathy-associated T-cell lymphoma
- Monomorphic epithelioid/lymphoid intestinal T-cell lymphoma
- Intestinal T-cell lymphoma, NOS
- Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
- Hepatosplenic T-cell lymphoma

**Subcutaneous panniculitis-like T-cell lymphoma**
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous peripheral T-cell lymphomas, rare subtypes
- Introduction
- Primary cutaneous gamma delta T-cell lymphoma
- Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8-positive T-cell lymphoma
- Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T follicular helper (THF) cell origin
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with TPH phenotype
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative
- Breast implant-associated anaplastic large cell lymphoma

HODGKIN LYMPHOMAS

**Hodgkin lymphomas**
- Introduction
- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classic Hodgkin lymphoma
- Nodular sclerosing classic Hodgkin lymphoma
- Lymphocyte-rich classic Hodgkin lymphoma
- Mixed-cellularity classic Hodgkin lymphoma
- Lymphocyte-depleted classic Hodgkin lymphoma

Reed-Sternberg cell
IMMUNODEFICIENCY-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

CORRESPONDING MYELOID/ACUTE LEUKEMIA GROUP IS “BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM”
THE 2019 HEMATOPOIETIC MPH RULES & DATABASE

- ICD-O-3 UPDATES WORK GROUP DID NOT HAVE ENOUGH LEAD TIME FOLLOWING 2017 PUBLICATION OF THE REVISION TO THE WHO CLASSIFICATION FOR HEME/LYMPH TO INCORPORATE NEW HISTOLOGY CODES, NEW PREFERRED TERMS, OR NEW MPH OPTIONS.
- DELAYED UNTIL A 2019 RELEASE OF HEMATOPOIETIC MPH RULES & DATABASE
- ONLY A 1 YEAR DELAY WITH UNKNOWN RELEASE DATE IN 2019
- PLEASE STAND BY - CAN STILL PLAN FOR CHANGES
- KEEP EYE ON NEW TERMS
- PATHOLOGIST USE
- CLINICAL TRIALS

STAGING MYELOID NEOPLASMS

Bone Marrow

Stem Cell

Circulation
2018 MYELOID NEOPLASMS – REQUIRED SSDI

| JAK2 | Chapter 83 | All Leukemia(C42.1) except CLL/SLL |

STAGING LYMPHOID NEOPLASMS

- HODGKIN LYMPHOMA
- NON-HODGKIN LYMPHOMA
- EXTRA-NODAL LYMPHOMA
- PLASMA CELL NEOPLASMS
- CLL/SLL
- ALL
HODGKIN AND NON-HODGKIN LYMPHOMA – MODIFIED ANN ARBOR STAGING

• WHAT ARE “B” SYMPTOMS
  • FEVERS
  • NIGHT SWEATS
  • WEIGHT LOSS > 10% OF BODY WEIGHT

• MINOR SYMPTOMS (NOT “B” SYMPTOMS)
  • MALAISE
  • FATIGUE
  • PRURITIS
  • ALCOHOL INTOLERANCE
  • FREQUENT INFECTIONS

• DO NOT CODE MINOR SYMPTOMS AS “B” SYMPTOMS
# Extranodal Lymphoma – Modified Ann Arbor Staging

## Staging of Gastrointestinal Lymphomas: Comparison of Different Systems

<table>
<thead>
<tr>
<th>Stage</th>
<th>Lugano Staging System for Gastrointestinal Lymphomas</th>
<th>Lugano Staging System for Modified Ann Arbor Staging System</th>
<th>TNM Staging System for Gastric Lymphoma</th>
<th>Tumor Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to GI tract</td>
<td>I</td>
<td>T1 NO M0</td>
<td>Mucosa/submucosa</td>
</tr>
<tr>
<td>Ia</td>
<td>Mucosa, submucosa</td>
<td>I</td>
<td>T2 NO M0</td>
<td>Muscular propria</td>
</tr>
<tr>
<td>Ib</td>
<td>Muscular propria, serosa</td>
<td>I</td>
<td>T3 NO M0</td>
<td>Serosa</td>
</tr>
<tr>
<td>II</td>
<td>Extending into abdomen</td>
<td>II</td>
<td>T1-3 N1 M0</td>
<td>Perigastric lymph nodes</td>
</tr>
<tr>
<td>IIa</td>
<td>Local nodal involvement</td>
<td>II</td>
<td>T1-3 N2 M0</td>
<td>More distant regional lymph nodes</td>
</tr>
<tr>
<td>IIb</td>
<td>Distant nodal involvement</td>
<td>II</td>
<td>T4 NO M0</td>
<td>Invasion of adjacent structures</td>
</tr>
<tr>
<td>III</td>
<td>Penetration of serosa to involve adjacent organs or tissues</td>
<td>III</td>
<td>T1-4 N3 M0</td>
<td>Lymph nodes on both sides of the diaphragm/ distant metastases (eg, bone marrow or additional extranodal sites)</td>
</tr>
<tr>
<td>IV</td>
<td>Disseminated extranodal involvement or concomitant splenopulmonary nodal involvement</td>
<td>IV</td>
<td>T1-4 N1-3 M1</td>
<td></td>
</tr>
</tbody>
</table>

---

# Plasma Cell Neoplasms – R-ISS Staging

## R-ISS -- The 2015 Revised International Staging System for Multiple Myeloma

**R-ISS I**
- Serum beta2-microglobulin level < 3.5 mg/L AND
- Serum albumin level of 3.5 g/dL or greater AND
- No high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)] AND
- Normal LDH level

**R-ISS II**
Includes all other possible combinations

**R-ISS III**
- Serum beta2-microglobulin level > 5.5 mg/L AND
- High-risk CA or
- High LDH level
CLL/SLL – RAI STAGING

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 1**: 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 2**: 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 3**: Lymphocytosis plus anemia (too few red blood cells), with or without enlarged lymph nodes, spleen, or liver. Platelet counts are near normal.
- **RAI stage 4**: 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.

2018 LYMPHOID NEOPLASMS – REQUIRED SSDI

1. ADENOPATHY
2. ANEMIA
3. B SYMPTOMS
4. HIGH RISK CYTOGENETICS
5. HIGH RISK HISTOLOGIC FEATURES
6. HIV STATUS
7. JAK2 – ACUTE LYMPHOID LEUKEMIA (EXCEPT CLL/SLL)
8. LYMPHOCYTOSIS
9. NCCN INTERNATIONAL PROGNOSTIC INDEX (IPI)
10. ORGANOMEGALY
11. PERIPHERAL BLOOD INVOLVEMENT
12. SERUM ALBUMIN PRETREATMENT LEVEL
13. SERUM BETA-2 MICROGLOBULIN PRETREATMENT LEVEL
14. SERUM LDH (LACTATE DEHYDROGENASE) PRETREATMENT LAB VALUE
15. THROMBOCYTOPENIA
### 2018 LYMPHOID NEOPLASMS – REQUIRED SSDI

<table>
<thead>
<tr>
<th>B Symptoms</th>
<th>Chapters 79, 80</th>
<th>All Lymphoma</th>
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<tbody>
<tr>
<td>HIV Status</td>
<td>Chapters 79, 80</td>
<td>All Lymphoma</td>
</tr>
<tr>
<td>NCCN International Prognostic Index (IPI)</td>
<td>Chapters 79, 80</td>
<td>All Lymphoma</td>
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</tbody>
</table>

### 2018 CUTANEOUS LYMPHOMA – REQUIRED SSDI

| Peripheral Blood Involvement | Chapter 81: Primary Cutaneous Lymphomas: MF/SS  
Required for Staging | P Site: C44.9, C51, C60, C63.2  
Histology: 9597, 9680, 9700, 9701, 9708, 9709, 9712, 9718, 9719, 9726, 9727 |
|-----------------------------|-------------------------------------------------|-------------------------------------------------|
**2018 PLASMA CELL NEOPLASMS – REQUIRED SSDI**

**R-ISS STAGING**

**R-ISS -- THE 2015 REVISED INTERNATIONAL STAGING SYSTEM FOR MULTIPLE MYELOMA**

<table>
<thead>
<tr>
<th>High Risk Cytogenetics</th>
<th>Chapter 82: Plasma Cell Myeloma Required for Staging (R-ISS)</th>
<th>9731, 9732, 9734 Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Albumin Pretreatment Level</td>
<td>Chapter 82: Plasma Cell Myeloma Required for Staging (R-ISS)</td>
<td>9731, 9732, 9734 Only</td>
</tr>
<tr>
<td>Serum Beta-2 Microglobulin Pretreatment Level</td>
<td>Chapter 82: Plasma Cell Myeloma Required for Staging (R-ISS)</td>
<td>9731, 9732, 9734 Only</td>
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<tr>
<td>Serum LDH (Lactate Dehydrogenase) Pretreatment Lab Value</td>
<td>Chapter 82: Plasma Cell Myeloma Required for Staging (R-ISS)</td>
<td>9731, 9732, 9734 Only</td>
</tr>
</tbody>
</table>

**High Risk Cytogenetics:** several cytogenetic abnormalities such as t(4;14), del(17q17p), t(14;16), t(14;20), nonhyperdiploidy, and gain(1q) were identified that confer poor prognosis.

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**2018 CLL/SLL – REQUIRED SSDI**

**RAI STAGING SYSTEM FOR CLL/SLL – 1968**

- **Rai stage 0:** Lymphocytosis and no enlargement of the lymph nodes, spleen, or liver, and with 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 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 normal.
- **Rai stage III:** Lymphocytosis plus anemia (too few red blood cells), with or without enlarged lymph nodes, spleen, or liver. Platelet counts are 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.
2018 CLL/SLL – REQUIRED SSDI RAI STAGING

<table>
<thead>
<tr>
<th>Condition</th>
<th>Source</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Chapter 79: CLL/SLL only (AJCC ID 79.5) Required for staging (RAI)</td>
<td>9823 Only</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>Chapter 79: CLL/SLL only (AJCC ID 79.5) Required for staging (RAI)</td>
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<tr>
<td>Adenopathy</td>
<td>Chapter 79: CLL/SLL only (AJCC ID 79.5) Required for staging (RAI)</td>
<td>9823/3 Only</td>
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<tr>
<td>Anemia</td>
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<td>Lymphocytosis</td>
<td>Chapter 79: CLL/SLL only (AJCC ID 79.5) Required for staging (RAI)</td>
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<tr>
<td>Organomegaly</td>
<td>Chapter 79: CLL/SLL only (AJCC ID 79.5) Required for staging (RAI)</td>
<td>9823/3 Only</td>
</tr>
</tbody>
</table>

ADDITIONAL RESOURCES

- WHO CLASSIFICATION OF TUMOURS OF HAEMATOPOIETIC AND LYMPHOID TISSUES, 4TH ED, 1ST REV, 2017
- 2016 REVISION OF THE WHO CLASSIFICATION MYELOID NEOPLASMS & ACUTE LEUKEMIA
  BLOOD, 19 MAY 2016 X VOLUME 127, NUMBER 20
- 2016 REVISION OF THE WHO CLASSIFICATION LYMPHOID NEOPLASMS
  BLOOD, 19 MAY 2016 X VOLUME 127, NUMBER 20
- REVISED INTERNATIONAL STAGING SYSTEM FOR MULTIPLE MYELOMA: A REPORT FROM INTERNATIONAL MYELOMA WORKING GROUP; VOLUME 33 NUMBER 26 SEPTEMBER 10 2015
- NCCN CLINICAL PRACTICE GUIDELINES – B-CELL LYMPHOMAS V5.2017
- BLOOD FIRST EDITION PAPER, APRIL 11, 2016; DOI 10.1182/BLOOD-2016-03-657379
- NAACCR 2018 SSDI REQUIRED ITEMS FOR HEME/LYMPH NEOPLASMS BY CHAPTER - AJCC STAGING MANUAL, 8TH ED
QUESTIONS